7-29-2021 1:00 PM

Cognitive Neuroscience of Schizophrenia: Stochastic Modelling of Cognitive-Process Latencies and Nonlinear Dynamics of Neuro-signals

Colleen D. Cutler, *The University of Western Ontario*

Supervisor: Neufeld, Richard W. J., *The University of Western Ontario*
Co-Supervisor: Tremblay, Paul F., *The University of Western Ontario*
A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Psychology

Abstract

We study known and potential numerical earmarks of schizophrenia through mathematical methods. One known numerical characteristic of schizophrenia is that of prolonged encoding latencies in response to cognitive stimuli. Motivated by the need to explain interaction patterns in 2×2 factorial data where one factor is encoding load and the other is diagnostic status, we define a class of general serial mixture models based on the number of encoding subprocesses executed and the speed at which they are executed. Mathematical derivations performed on these models yield closed form expressions for the mean encoding latency and average intertrial variance, which in turn yield expressions for the mean interaction contrast and variance interaction contrast. Different interaction signatures correspond to different members of the model class. A wealth of examples are provided linking various potential physical and neurophysiological encoding mechanisms to members of the model class. We also derive results for a specific subset of the general model class where only the number of subprocesses is allowed to vary over factorial cells. Our development includes a numerical test (verified by theory and simulation methods) to determine if the number of encoding subprocesses varies over trials. Theoretical results are then developed for the case where the speed of encoding subprocesses is allowed to vary. Secondly, by means of an exhaustive literature search and application of contingency tables, we investigate whether a collection of numerical indices, called nonlinear indices or complexity indices, can be utilized to support or refute a conjecture in the literature which states that complexity in EEG recordings tends to be higher in schizophrenia

patients than controls with this tendency being dampened (and even inverted) by medication, increasing age, and decreasing symptomatology. Our analysis indicates only weak effects due to age and medication, and suggests that symptomatology may play a greater role. Moreover, we observe a strong "study effect" which suggests that laboratory procedures may also play a role. Our systematic review of nonlinear indices does, however, indicate that heart rate variability is reduced in schizophrenia and bipolar disorder.

Keywords: schizophrenia, stimulus encoding, mixture models, mean interaction contrast, nonlinear dynamics, complexity, EEG, heart rate variability, bipolar disorder

Summary

Schizophrenia is a mental disorder which is usually described in behavioural terms. A person with schizophrenia will often exhibit symptoms of delusions (strongly-held false beliefs) or hallucinations (the experience of sensations or perceptions without supporting stimulus events accessible to others). Other symptoms may include incoherent speech and disorganized thought. This thesis, however, focuses on characteristics of schizophrenia that can be quantified numerically. One such characteristic is that of prolonged encoding times. Encoding is the process by which a person mentally transforms an observed event or object into a format which facilitates the task at hand, e.g., transforms a word into a picture for comparison with another picture. Experimental evidence has shown that schizophrenia patients require longer encoding times than normal controls or even other psychiatric controls. This thesis develops a family of mathematical models which can be used to describe and investigate the possible physical and psychological mechanisms that underlie the encoding process. These models are constrained to fit known experimental data in which encoding load and diagnostic status are manipulated. Secondly, the thesis investigates whether a collection of numerical indices, called nonlinear indices or complexity indices, can be used to differentiate schizophrenia (and bipolar disorder) patients from normal controls in EEG and ECG studies. In particular, we examine the question of whether there is a tendency toward greater complexity in the EEG of schizophrenia patients, with this tendency dampened or even reversed with medication, increasing age, and reduced symptomatology. This analysis was spurred by a large literature with contra-

dictory findings. We found only weak effects due to age and medication, and noted that symptomatology as well as laboratory procedures may play a greater role in outcomes. On the other hand, nonlinear indices seem to consistently indicate lower complexity in the heart rate of both schizophrenia and bipolar patients.

Co-authorship statement

C. D. Cutler carried out all the work of Chapter 2, including the literature review, conception of all theory and development of all theorems and their subsequent corollaries, construction of all examples and their interpretations, the writing of the **R** code for the simulations, performing and analyzing the simulations, and writing the chapter. This material is under preparation for publication as two articles. Dr. R. W. J. Neufeld will be second author on these papers for having contributed by providing generous feedback as the work developed and by providing inspiration due to his earlier developments in the field. The authorship split will be 95%-5%.

Chapter 3 of the thesis has been published with C. D. Cutler as first author and Dr. R. W. J. Neufeld as second author. The authorship split was 98%-2%. C. D. Cutler carried out the literature search, conceived of and carried out the statistical analysis, and wrote the article. Dr. Neufeld contributed by reading the manuscript and providing feedback.

To my family

Acknowledgments

I have been fortunate enough to have two dedicated and kind supervisors, Dr. R. W. J. (Jim) Neufeld and Dr. Paul Tremblay, who have guided me throughout the thesis process. Jim, thank you for your unwavering interest in this work and your generous availability and advice even with being so far away in B. C. I must also thank you especially for the inspiration your work (and dedication to it) gives to me. Paul, your command of the administrative details of thesis matters and your patient insistence that I make my work as readable as possible has been invaluable in production of the final document. A heartfelt thanks to you as well.

Finally I would like to thank my family for their forbearance throughout this journey with me.

Table of Contents

List of Tables

List of Appendices

List of Abbreviations, Symbols, and Nomenclature

Chapter 2:

CRT: Choice Reaction Time

expo(v): exponential distribution with rate v

FCPR: fixed capacity parallel model with reallocation

Gam(u, r): a gamma distribution with shape parameter u and rate parameter r

$\Gamma(x)$: gamma function evaluated at x. If x is a positive integer then $\Gamma(x) = (x-1)!$

gen-CN: generalized Cutler-Neufeld model

iff: if and only if

i.i.d. : independent and identically distributed

IG(μ, λ): inverse Gaussian distribution with mean μ and shape parameter λ

K_i: number of subprocesses executed by participant i

ℓ_{ij}: encoding time of j^{th} encoding subprocess for participant i

LN(μ, σ^2): lognormal distribution with associated normal parameters μ and σ^2

MIC: mean interaction contrast

$\mu(\theta)$: $E(\ell(\Theta) \,|\, \Theta = \theta)$ first-order moment function evaluated at $\Theta = \theta$

pdf: probability density function

Pois(m): Poisson distribution with mean m

RT: reaction time

$\sigma^2(\theta)$: Var$(\ell(\Theta) \,|\, \Theta = \theta)$ second-order moment function evaluated at $\Theta = \theta$

Θ: vector parameter governing the speed of execution of subprocesses

$\triangle$: symbol indicating end of a proof

VIC: variance interaction contrast

Wei(a, b): Weibull distribution with shape parameter a and scale parameter b

$\overset{\mathcal{D}}{\sim}$: symbol indicating that two quantities follow the same distribution

Chapter 3:

ANS: autonomic nervous system

ApEn: approximate entropy (randomness index)

ECG: electrocardiogram

CFNN: Cao false nearest neighbours (embedding method)

EEG: electroencephalogram

D_2: correlation dimension (spatial clustering index)

DS: deficit schizophrenia

FNN: false nearest neighbours (embedding method)

GP algorithm: Grassberger-Procaccia algorithm (embedding method)

Hc: compression entropy (compressibility index)

HFD: Higuchi fractal dimension (graph roughness index)

HRV: heart rate variability

KFD: Katz fractal dimension (graph roughness index)

KSE: Kolmogorov-Sinai entropy (information index)

λ_1: largest Lyapunov exponent (predictability index)

LZC: Lempel-Ziv complexity (pattern index)

Methods I and II: symbolic dynamics (symbol complexity)

MED = medicated (antipsychotics)

MSE: multiscale entropy (multiple scales SampEn indices)

NDS: nondeficit schizophrenia

NMF = never-medicated first episode schizophrenia

PANSS: Positive and Negative Syndrome Scales for schizophrenia

pNN50: proportion of successive normal-to-normal RR-intervals differing by at least 50 ms

RBFD: real box fractal dimension (graph roughness index)

RMSSD: square root of the mean summed squared differences between normal-to-normal RR-intervals

RR-interval: interval between two consecutive beats in a heart rate (ECG) series

SampEn: sample entropy (randomness index)

SDNN: standard deviation of normal-to-normal RR-intervals

UM: unmedicated

UMx: unmedicated for at least x months

UNMED: unmedicated at time of study

Chapter 1

Introduction to the Thesis

In the study of clinical psychology, the earmarks of psychopathology are of particular interest – those identifying characteristics which may allow us to distinguish a disordered state from that of a healthy one. In this thesis we bring rigorous mathematical methods to bear on a suite of *numerically quantifiable* potential earmarks, seen, for specificity, primarily through the lens of schizophrenia, yet demonstrably applicable to certain other disorders (see, for example, the sections on bipolar disorder in Chapter 3). The potential earmarks we consider can largely be subsumed under the rubric of the cognitive neuroscience of schizophrenia, with the chiefly studied numerical characteristics either taking the form of cognitive-processing latencies (in particular, encoding times) or nonlinear functions of reactive electroencephalogram (EEG) signals in response to cognitive stimuli. However, further potential earmarks that are studied are nonlinear functions of heart rate variability (HRV), the latter which is governed by neuro-signals through the autonomic nervous system (ANS) and may be measured easily in a noninvasive fashion.

One broad goal of the thesis is to illustrate the value and utility of mathematics as a tool to describe, model, investigate, quantify, and validate (or invalidate)

potential earmarks of psychopathology (in this case the pathology of schizophrenia). This theme is omnipresent throughout the thesis. In Chapter 2, we focus specifically on the earmark of prolonged encoding latencies which are observed in schizophrenia (R. W. J. Neufeld and coauthors; for details see Chapter 2 and the references therein). Encoding is the mental process by which a person transforms cognitive stimuli into a task-facilitative format (for example, transforms a word into a picture for comparison with another picture). Neufeld and coauthors have determined experimentally that the encoding process requires more time for schizophrenia patients than it does for normal controls or other psychiatric controls (such as persons exhibiting major depression), thus rendering its prolongation a verified earmark of the disorder. In Sec 2.1.1 we review the literature on 2×2 factorial experimental paradigms (with encoding load as one factor and diagnostic status as the other) which have given rise to the above conclusions. These results are accompanied by the observation that the mean interaction contrast (MIC) is always found to be zero whereas the variance interaction contrast (VIC) may be zero or nonzero depending on the experiment. In Sec 2.1.2 we review some early models for encoding latencies which satisfy the constraint VIC $= 0$ if and only if MIC $= 0$ and are sufficient to explain certain experimental paradigms. These early models act as a springboard to the definition of a general class of serial mixture models in Sec 2.2, which is the first original contribution of the thesis. (Material in Chapter 2 from Sec 2.2 onward is original work by the thesis author.) This class of serial mixture models features two key components: K, the number of encoding subprocesses being executed on a trial, and Θ, a vector which governs the speed at which each subprocess is encoded. Each serial mixture model also

features a base distribution which can essentially be any continuous positive right-tailed probability distribution. The broad generality in the definition of this class of models allows it to be potentially applicable to a wide range of cognitive-processing latencies (where encoding subprocesses are replaced by the relevant components of the cognitive process under consideration). In Theorem 1 we further illustrate the flexibility of this model class by demonstrating that each instantiation can also be interpreted in parallel form as well as serial form; specifically, each instantiation has a representation as a fixed capacity parallel model with reallocation. Mathematical derivations performed on this model class then lead to Theorem 2 which provides closed form formulae for mean encoding latencies $E(T)$ and average intertrial variances $E(\mathrm{Var}(T))$ (calculations which heretofore had to be computed by integrals on a case-by-case basis). These closed form expressions are a highlight of the thesis, as they in turn yield expressions for MIC and VIC which can be developed for any member of the model class. In Sec 2.3 we study a specific subset of the model class which we call generalized Cutler-Neufeld (gen-CN) models as they are extensions of the earlier models developed by Neufeld and Cutler and Neufeld reviewed in Sec 2.1.2. These models have the feature that only the number of subprocesses K can vary over factorial cells whereas the distribution of Θ remains the same from cell to cell. Thus these models correspond to encoding mechanisms where changes in $E(T)$ and $E(\mathrm{Var}(T))$ over cells can be explained by changes in the number of subprocesses executed. The structure of gen-CN models allows for simple elegant expressions for MIC and VIC (Theorem 3) and for mathematical derivation of numerous examples which feature various MIC-VIC signatures, some of which satisfy VIC = 0 if MIC =

0 and some of which satisfy VIC $\neq 0$ if MIC $= 0$. The potential underlying physical and/or neurophysiological encoding mechanisms corresponding to each of these examples is also discussed. It would seem that gen-CN models have the potential for wide applicability, given the number of encoding mechanisms that can be put in this format and given the fact that converging experimental evidence has indicated that in many cases changes in encoding latencies can be explained by changes in the number of subprocesses executed (see Sec 2.1.2). In Sec 2.4 we consider the problem of distinguishing gen-CN models *with variation* from gen-CN models *without variation*. A gen-CN model has variation if K varies over trials for a participant in addition to possibly varying over participants, whereas in a gen-CN model without variation K can only vary over participants. Variation over trials can occur for a number of reasons, but one specific cause of particular interest to experimenters is (unwanted) variability of the stimulus input sequence of the experiment. We show that VIC $\neq 0$ implies variability over trials (Theorem 4) which in many cases will be a quick sufficient method to establish variation. However, it is possible for variation to occur even in the presence of VIC $=$ MIC $= 0$ so an alternative method to Theorem 4 required development. In Theorem 5 and Corollary 5.1 we develop a ratio statistic (based on the sample variances and means of the cell encoding latencies) and show that if this ratio differs over cells then variation over trials must be present. Extensive simulation studies are carried out to illustrate both the use and limitations of this ratio statistic. Finally, in Sec 2.5, we turn our attention to the case where Θ, rather than K, varies over cells. This amounts to explaining changes in $E(T)$ and $E(\mathrm{Var}(T))$ across cells by changes in the encoding speed of subprocesses rather than

by changes in the number of subprocesses. Although there is less experimental evidence supporting this paradigm where encoding is involved, it is possible that it may describe some encoding situations as well as being applicable to cognitive-processing latencies other than encoding. Since the definition of Θ depends explicitly on the base distribution, one must choose a particular base and derive results on a case-by-case basis. Theorems 6-8 (along with attendant corollaries) develop MIC-VIC expressions for different choices of base distribution and different choices of varying component in the Θ vector. The section is rounded out with a number of examples illustrating various MIC-VIC signatures. The chapter closes with the section Discussion and Future Directions.

Chapter 2 saw us focus attention on the goal of developing mathematical models for a numerical characteristic (encoding latency) which has been verified experimentally as an earmark of schizophrenia. In Chapter 3 we turn our attention to a different goal – specifically, that of attempting to ascertain whether a certain collection of (or subset of) numerical characteristics can be utilized as earmarks of schizophrenia. The numerical characteristics we consider are called *nonlinear indices* and are often referred to as *complexity indices*, in spite of the fact that the term "complexity", although ubiquitous in the nonlinear science literature, is actually an ill-defined concept. At least some authors regard a complex state as one falling somewhere between a completely ordered state and a completely random state, but this intuitive idea is complicated by the fact that the various nonlinear indices do not all measure the same quantity, and in fact some of these indices, such as entropy indices, actually reach their maximum value in the case of completely random states.

Chapter 3 has been published as the article Cutler and Neufeld (2019)[1] but here we provide a version of this article with slightly expanded introductory material (Secs 3.1-3.3) which gives concise but precise definitions of the various nonlinear indices and the methods used to obtain them since these are typically not well-known quantities or methodologies outside of nonlinear science. In Sec 3.4 we proceed to examine the potential utility of nonlinear indices in distinguishing the EEG of schizophrenia patients from that of normal controls. A vast array of authors have attempted to utilize nonlinear indices in this way – specifically, to ascertain if a particular nonlinear index (or group of indices) can indicate whether EEG recordings, in response to cognitive stimuli, are more complex or less complex in schizophrenia patients compared to those of normal controls. The resulting literature has provided numerous contradictory findings in this regard. The centerpiece of this chapter and its chief unique contribution (presented as Section 3.4.1), is an exhaustive quantitative analysis of the existing literature on this topic. In particular, we attempt to determine whether a certain hypothesis put forward in the literature by some authors (a hypothesis which we call the L-F proposal) appears to have merit based on the totality of studies that have been done. The L-F proposal, paraphrased, is the claim that "complexity tends to be higher in the EEG of schizophrenia patients, especially first episode patients, than that of controls, but this tendency is dampened or even inverted by antipsychotic medication, increasing age, and reduced symptomatology". Obviously such a proposal implies a delicate interplay between several factors, and can be used to

[1]Cutler, C. D., & Neufeld, R. W. J. (2019). Nonlinear indices with applications to schizophrenia and bipolar disorder. *Nonlinear Dynamics, Psychology, and Life Sciences, 23,* 17-56.

explain the various contradictory and perplexing results found in the literature. We utilize chi-square contingency tables in our quantitative analysis and find only weak effects due to age and medication, and propose that symptomatology may be the most important of the suggested L-F factors. However, it should be noted that the most consistent and significant finding yielded by our analysis was that of a pronounced "study effect", i.e., the observation that, in most cases, each study showed similar EEG outcomes in the patients over a range of cognitive stimuli. This is of course not inconsistent with the suggestion that symptomatology of the patients is the most important factor, but it also does not preclude the possibility that the different EEG procedures and analyses used by different laboratories were contributing factors in the outcomes. In Sec 3.5 we carry out a systematic review of nonlinear indices applied to heart rate variability in both schizophrenia and bipolar disorder; here we find much more consistent results, with nonlinear indices suggesting lower complexity (greater regularity) in heart rate in both these disorders. It is known that greater regularity in heart rate creates a predisposition toward cardiac disease and sudden cardiac events. Sec 3.6 reviews the limited literature applying nonlinear indices to mood data in bipolar disorder, and the chapter closes out with Sec 3.7 Discussion and Future Directions. Chapter 4 consists of Concluding Remarks which summarize the key points of the thesis.

Chapter 2

Encoding Latencies in Schizophrenia and Psychopathology

2.1 Introduction to Chapter 2

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the American Psychiatric Association (2013) provides categorical descriptions of mental disorders, generally focusing on the observed behavioural symptoms of a disorder. For example, schizophrenia is characterized by an individual displaying two or more of the following features: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behviour, and negative symptoms (with at least one among the first three features being present) (DSM-5, p. 99). In this chapter, however, we focus our attention on a *quantitative* characteristic of schizophrenia (specifically, prolonged encoding latencies – see below) which may be modelled analytically, thereby rendering insight into the nature of the underlying disease process. The general family of models we develop (Sec 2.2 and onward), while explicated here in the context of encoding times in schizophrenia, can be applied in principle to other cognitive-process latencies in

both healthy individuals and those exhibiting various psychopathologies.

Cognitive deficits have long been recognized to play a significant role in the presentation of schizophrenia (see, e.g., American Psychiatric Association, 2013; Andreasen, 1999; Bleuler, 1950; Friston, 1999). The cognitive deficit we focus on here is that of the prolongation of *encoding latencies* or *encoding times* (the two terms to be used interchangeably). *Stimulus encoding* (encoding, for short), is the mental process by which an individual transforms a cognitive stimulus into a format which facilitates carrying out the task at hand. As a concrete example, consider the classic memory search Choice Reaction Time (CRT) task as described in Sternberg (1966, 1975). Here the participant is first presented with a set of alphanumeric items (memory set), then later presented with an item (probe item) which may or may not have been a member of the memory set. The participant must determine, as quickly and accurately as possible, whether the probe item was a member of the memory set, indicating a decision by pressing a button with a "yes" or "no" response. In order to achieve this, the participant must first encode the probe item, that is, extract its salient physical features, such as lines, curves, and intersections, to facilitate subsequent comparison with the members of the memory set. The total *response latency* or *reaction time* (to be denoted RT) is the time measured from onset of presentation of the probe item to completion of the "yes" or "no" response. This may be expressed mathematically (e.g., Townsend & Ashby, 1983) as

$$RT = T_{\text{encoding}} + Y + W \tag{2.1.1}$$

where T_{encoding} represents the time spent encoding the probe item, Y represents the ad-

ditional time required to complete the mental task, such as making comparisons with members of the memory set to render a decision, and W represents the additional time required for the physical yes-no response. Although in some experimental paradigms it is possible that these three steps are carried out sequentially in a nonoverlapping manner, (2.1.1) allows them to overlap, permitting behaviour such as the cascade model of McClelland (1979) in which encoding and comparisons operate simultaneously. The results of Neufeld (1978), combined with those of Neufeld (1977), in a more complex sentence-verification CRT task, provide evidence that in some experiments, at least for patients with schizophrenia, the ability to continuously access the probe item (what we call, somewhat imprecisely, as "ongoing encoding") improves performance in making comparisons. Highgate-Maynard and Neufeld (1986) deliberately kept the probe item in view throughout their entire experiment to permit ongoing encoding.

In a variety of CRT tasks, the memorial comparison times, as exemplified by Y in (2.1.1), have been shown to be equivalent between normal controls and schizophrenia patients (Boksman, 2006; Checkosky, cited in Sternberg, 1975; Highgate-Maynard & Neufeld, 1986; Marusarz & Koh, 1980; Neufeld, 1977; Wishner, Stein, & Paestrel, 1978). This is seen by examining the plot of the RT vs. the size of the memory set (typically 1-4 items) or vs. the complexity of the comparison task quantified in some suitable way (see Neufeld (1977, 1978) for an example of a sentence-verification CRT task of varying complexity). The slope of the RT vs. memory set size (or complexity) is the same for both normal controls and schizophrenia patients, indicating that they are making comparisons at equivalent rates. However, the RTs differ in their

intercept values, with those of the schizophrenia patients being elevated above those of the controls. The intercept value accounts for the encoding time plus the physical response time, as exemplified by $T + W$ in (2.1.1). These elevated intercepts cause the RTs of schizophrenia patients to be elongated as compared to those of controls.

Converging evidence has indicated that both Y and the physical response time W are spared in schizophrenia, and the elevation in RT intercepts is due solely to a prolonged encoding time T. Neufeld (1978) designed an experiment where encoding was arranged to take place first, then the probe item was removed, followed by the commencement of timing. Under these circumstances the differences in intercepts disappeared. Moreover, Carter and Neufeld (1999, 2007) found that estimates of the time engaged in memory search, decision-making, and physical response did not differ between schizophrenia patients and controls. Intercept inequalities also remained after accounting for memorial comparisons and physical response time in Neufeld, Vollick, and Highgate (1993). These results point to the conclusion that encoding is the process chiefly affected in schizophrenia.

It is worthy of note that the elongation of RTs is also more pronounced among schizophrenia patients compared to other psychiatric control groups (such as patients with major depression) and that schizophrenia patients with paranoid symptoms (delusions and hallucinations) generally exhibit the most prolonged RTs of all (George & Neufeld, 1987; Highgate-Maynard & Neufeld, 1986; Neufeld, 2007a; Neufeld & Williamson, 1996).

The potential consequences of protracted encoding times are numerous. We provide a summary of some of these here, and refer the reader to Neufeld (2021) for

an excellent and thorough review. A direct link has been posited between elongated encoding times and thought-content disorder (thematic delusions) in schizophrenia (Neufeld, 2007a; Neufeld, 2021; Neufeld, Boksman, Vollick, George, & Carter, 2010). Given a fixed small window of time available to encode a situation (e.g., a passing conversation) it is possible that a person who requires considerably more time for satisfactory encoding may fail to properly transform several of the less salient but nonetheless important contextual features of the situation, thus coming away with a false impression of what transpired. A natural need to contextualize the situation may lead the person to attribute persecutory or grandiose elements to the circumstances, considering that such attribution may have a self-protective element to it. Prolonged encoding times can also be used to explain the compromised coherence of judgments that depend on execution of multiple stimulus dimensions (Carter & Neufeld, 1999). Moreover, schizophrenia patients, particularly those with paranoid features, exhibit increased numbers of rapid eye-movement saccades when visually tracking a slow moving target. The increased number of saccades are believed to be due to inefficient encoding of the spatial stimulus properties required for smooth tracking (Adams, Huys, & Rosier, 2016; Collewijn & Tamminga, 1982; Neufeld & Williamson, 1996). Finally, protracted encoding impacts negatively on the successful navigation of environmental stressors (Morrison, Neufeld, & Lefebvre, 1988; Neufeld & Grant, 2018; Shanahan & Neufeld, 2010).

In this chapter we will be looking at mathematical models applied to encoding times and designed to explain patterns in mean interaction contrast (MIC) and average intertrial variance contrast (VIC) (see below) arising in certain 2×2 factorial

CRT experimental paradigms. We describe these paradigms, with specific examples, in the subsection below.

2.1.1 2×2 Factorial Paradigms

Here we will consider 2×2 factorial experiments where one factor to be manipulated is *encoding load* (designated to be low (L) or high (H)) and the second factor to be manipulated is *diagnostic status* (designated to be normal health (N) or schizophrenia (S)). The format is that of a 2×2 mixed model ANOVA where the between-subjects factor is diagnostic status and the within-subjects factor is encoding load. We perform a CRT task and obtain the RTs for all participants in the four factorial cells (LN, LS, HN, and HS). The experiments we consider all have the feature that memorial comparisons Y and physical response times W behave the same way for both controls and schizophrenia patients (as discussed in the Introduction to Chapter 2) but encoding times T depend on both encoding load and diagnostic status. Specifically, T tends to increase as the encoding load moves from low to high (which is intuitively credible) and, as we have discussed earlier, T also tends to increase as diagnostic status changes from normal to schizophrenia. Thus we can replace the general RT model (2.1.1) here by the specific factorial RT model

$$RT_{\text{load, diagnosis}} = T_{\text{load, diagnosis}} + Y + W \tag{2.1.2}$$

We now describe some specific examples of such experiments. Highgate-Maynard and Neufeld (1986) asked participants to decide, "yes" or "no", whether a probe item (an object or animal) was similar in real-life size to any member of a memory set of objects (e.g., an airplane and a coffee pot are not similar in real-life size). Encoding load was

manipulated by either presenting both probe item and memory set in pictures (low encoding load; see Paivio (1975, 1979)) or presenting both probe item and memory set in words (high encoding load, as this requires transformation to visual imagery; again see Paivio (1975, 1979)). For the sake of the factorial design, only trials on which there were no matches were considered. George and Neufeld (1987) conducted a CRT task where participants were briefly shown a four-letter word in the central visual field (memory set), followed by a probe item. The probe item consisted of two words, one presented in the right visual field and one presented in the left visual field. Participants were asked to indicate, "yes" or "no", whether either one of the two words matched the memory set. For the sake of the factorial design, only the case of matched trials was considered. The encoding load was appraised to be low if the matching word was presented in the right visual field (left hemispheric superiority for processing of verbal stimuli) and high if the matching word was presented in the left visual field. Boksman (2006) considered a CRT task where participants were asked to determine if a probe item (a consonant) belonged to a previously memorized set of consonants. Encoding load was manipulated by presenting the probe item either in the same font as the memory set (low encoding load) or in a different font (high encoding load). Kieffaber et al.(2006) provided participants with a pre-trial auditory cue ("shape" or "size"), then asked them to decide, "yes" or "no", whether a presented pair of items were the same in terms of the cue. Trials were divided as either "stay" trials (where the cue was the same as on the previous trial) or "switch" trials (where the cue changed from the previous trial). Stay trials can be designated as low encoding load and switch trials as high encoding load (see Schneider & Logan (2005)) and indeed

results showed a marked increase in the length of correct-response RTs for switch trials compared to stay trials. Finally, Taylor, Théberge, Williamson, Densmore, and Neufeld (2016, 2017) considered the Stroop cognitive task where the congruent case (colour of name matching the name of colour) comprised the low encoding load, and the incongruent case (colour of name not matching name of colour) comprised the high encoding load.

We now define the *mean interaction contrast* (MIC) as

$$\begin{aligned} \text{MIC} &= (E(RT)_{HS} - E(RT)_{HN}) - (E(RT)_{LS} - E(RT)_{LN}) \\ &= (E(T)_{HS} - E(T)_{HN}) - (E(T)_{LS} - E(T)_{LN}) \end{aligned} \tag{2.1.3}$$

where equality between the two lines of (2.1.3) comes about because the expectations $E(Y)$ and $E(W)$ are the same over the four factorial combinations (see (2.1.2)). Thus we may express MIC in terms of the second-order differences of either the raw RTs or the implicit encoding times T. We will utilize the encoding times because those are the particular cognitive processes we wish to model; however, in practice it is the RTs which are readily available from data. Rough estimates of encoding times can be determined by employing the method of subtraction (Donders, 1969) as illustrated in Neufeld et al. (2010) after estimating $E(Y)$ and replacing $E(W)$ by an estimated experimental quantity (Woodworth & Schlossberg, 1954, p. 36). However, these estimates of encoding times can be too crude to be useful in some cases (Cutler & Neufeld, 2017) although Neufeld et al. (2010) was able to exploit them profitably. However, due to the equality of the two lines in (2.1.3), we can continue to express MIC in terms of second order differences of mean encoding times while in practice computing it by second order differences of estimated mean RTs.

The case MIC = 0 of course corresponds to the case where there is no interaction between the two factors encoding load and diagnostic status. Perhaps surprisingly, this feature was observed in all five of the experiments described in this subsection; mean reaction times in schizophrenia patients and normal controls increased by the same amount as the encoding load moved from low to high (factorial additivity of means). Although some caution must be applied in accepting this conclusion (since testing for interactions favours the null hypothesis) the replication of this result over a variety of experimental paradigms suggests it is a genuine phenomenon. It appears that schizophrenia and encoding load operate separately and independently to alter encoding times. Thus any models we utilize for encoding times should easily accommodate this phenomenon; see the discussion in Neufeld (2021) and Neufeld et al. (2010) and Sec 2.2 onward of this chapter.

Another quantity which can be used to augment our ability to model is the *average intertrial variance contrast* VIC. In order to define VIC, first note that, under the assumption that T, Y, and W act independently of one another, from (2.1.2) we have, for any random trial on any participant in a particular cell

$$\mathrm{Var}(RT)_{\text{load, diagnosis}} = \mathrm{Var}(T)_{\text{load, diagnosis}} + \mathrm{Var}(Y) + \mathrm{Var}(W) \tag{2.1.4}$$

and hence, taking expectations over all participants in each cell:

$$\begin{aligned}\mathrm{VIC} &= (E(\mathrm{Var}(RT))_{HS} - E(\mathrm{Var}(RT))_{HN}) - (E(\mathrm{Var}(RT))_{LS} - E(\mathrm{Var}(RT))_{LN}) \\ &= (E(\mathrm{Var}(T))_{HS} - E(\mathrm{Var}(T))_{HN}) - (E(\mathrm{Var}(T))_{LS} - E(\mathrm{Var}(T))_{LN})\end{aligned} \tag{2.1.5}$$

where the two lines in (2.1.5) are equal because $E(\mathrm{Var}(Y))$ and $E(\mathrm{Var}(W))$ are the same over each of the four cells. Thus, as in the case of MIC, VIC can be de-

fined in terms of either second order differences of average intertrial variances of RTs or of second order differences of average intertrial variances of encoding times. $E(\mathrm{Var}(RT))_{\text{load, diagnosis}}$ can be estimated from the data in a cell by computing the sample variance of the RTs of each cell participant, then averaging these sample variances over all participants in the cell. The case VIC = 0 indicates factorial additivity in the variances.

George and Neufeld (1987) (see Neufeld et al. (2007) and Neufeld et al. (2010) for discussion) as well as Taylor et al. (2016, 2017) found results compatible with MIC = VIC = 0. However, factorial additivity of variances is not as universal as factorial additivity of means; the Highgate-Maynard and Neufeld (1986) data, as cited in Neufeld and Williamson (1993), found factorial superadditivity in the variances, i.e., VIC > 0 in company with MIC = 0.

This chapter is devoted to developing a class of models that spawn various examples which, when MIC = 0, provide different outcomes for VIC; more specifically, for these different examples we are able to compute the exact form of VIC for MIC = 0. The physical mechanisms underlying these examples are also discussed. This provides a collection of templates against which an experimenter can compare theoretical mechanisms and factorial data to choose or eliminate certain models.

Earlier models considered by Neufeld (2021), Neufeld et al. (2010), and Cutler and Neufeld (2017) provide a springboard to the general class of models we develop in Sec 2.2 and onward. We review these earlier models in the next subsection.

2.1.2 The Neufeld and Cutler-Neufeld Models

The encoding process overall can be viewed as the execution of a collection of component *subprocesses*; e.g., in a basic Sternberg memory search CRT task (Sternberg, 1975), the alphanumeric probe item is encoded as a collection of lines, curves, and intersections (subprocesses) for comparison against the memory set. In a more complex CRT language-verification task (Neufeld, 1977, 1978), sentences needed to be encoded as an abstract set of negative vs. affirmative components for comparison against a visual display. It has been shown (Townsend & Nozawa, 1995; Townsend & Wenger, 2004) that MIC = 0 (factorial additivity of means as discussed in the previous subsection) is a signature of constituent subprocesses being carried out in serial. To this end, Neufeld et al. (2007), Neufeld et al. (2010), and Neufeld (2021) used the simple standard serial model as a starting point to model encoding times T. This model has the exponential distribution as its base. The time to complete each individual component encoding subprocess ℓ_j is assumed to follow an exponential distribution with the same rate parameter v and probability density function (pdf)

$$\phi(\ell) = ve^{-v\ell} \quad \text{for } \ell > 0 \tag{2.1.6}$$

We can then express T as the sum of its k individual subprocess encoding times

$$T = \ell_1 + \cdots + \ell_k \tag{2.1.7}$$

which, under the assumption the $\ell_j s$ also act independently of one another (independent intercompletion times) leads to T following an Erlang distribution with param-

eters k and v with pdf given by

$$f(t) = \frac{v^k t^{k-1}}{(k-1)!}\, e^{-vt} \quad \text{for } t > 0 \tag{2.1.8}$$

The Erlang is a special case of the gamma distribution (see Appendix B). Here the parameter k is interpreted as the number of encoding subprocesses and v is interpreted as the rate at which each subprocess can be completed (elemental workload capacity). The serial model as described above in (2.1.7) is intuitively appealing but it should be noted that it can be mimicked by a fixed capacity parallel model with reallocation (FCPR model); see Townsend and Ashby (1983, p. 138) for a discussion focusing on the exponential case, as well as Sec 2.2 of this chapter for details and a general equivalence between such models even in the non-exponential case. In fact Neufeld et al. (2010) presented the Erlang model as an FCPR model. It can be seen that the Erlang (whether interpreted in its serial or parallel form) easily accommodates the signature VIC = 0 if MIC = 0, and that MIC = 0 is achieved by appropriately varying the number of subprocesses k across cells while holding v fixed; see Sec 2.2 and onward where more general models are considered. Taylor et al. (2016, 2017) were able to utilize the Erlang model profitably in fitting their Stroop factorial data.

It should be noted that Neufeld et al. (2010) and Neufeld (2021) considered two other models for T which can easily accommodate the signature MIC = 0; one is the independent parallel model with moderately limited capacity, and the other is a first stage unlimited capacity model. In both these cases the distribution of T is seen to have a general gamma distribution (McGill & Gibbon, 1965) in which the pdf of T is a weighted combination of exponential distributions with different rates.

In particular, the intercompletion times are not identically-distributed. We will not expand on these two models because in this chapter we focus on developing a class of models where the intercompletion times are independent and identically-distributed (i.i.d.) on any given trial, thus extending the Erlang model.

In some cases the Erlang model can explain factorial data well (e.g., Taylor et al. (2016, 2017)). However, other data may display extra variation or "over dispersion" which degrades the model fit. A novel approach to account for over dispersion in encoding latencies, given by Neufeld, Vollick, Carter, Boksman, and Jetté (2002), Neufeld et al. (2007), and Neufeld et al. (2010), was to expand the Erlang model to a Bayesian mixture model (Batchelder & Riefer, 2007; Berger, 1985; Neufeld, 2016). In a mixture model extension of the Erlang model[1], each participant i is assigned their own values k_i and v_i representing, respectively, the number of subprocesses they require to encode the stimulus and the rate at which they encode them. This extension is quite natural as we would not generally expect two individuals to behave in identical fashion in the course of an experiment. The differences between the $k_i s$ and the $v_i s$, ranging over participants, can account for the variation previously dismissed as exogenous "noise". Moreover, this variation, now captured within the model itself as a meaningful and elucidated feature, can itself be modelled in terms of distributions (called Bayesian priors or Bayesian mixing distributions) over the four cells. In the specific mixture model we call the *Neufeld model*, specific choices for prior distributions were made on the number of subprocesses k and the rate v. The number of subprocesses k, distributed across participants in cell *, was assumed to

[1] in this case the Erlang may be considered as the "skeleton" of the mixture model

follow a Poisson distribution with mean m_* (abbreviated $k \overset{\mathcal{D}}{\sim} \text{Pois}(m_*)$), whereas v was assumed distributed across participants in each cell according to a gamma distribution with constant shape parameter u and constant rate parameter r (abbreviated $v \overset{\mathcal{D}}{\sim} \text{Gam}(u, r)$) (see Appendices A and B for distributions). In this context, m_*, u, r are called *hyperparameters*. These hyperparameters can take on specific psychological meanings within an experiment (Neufeld, 2007b). The hyperparameter m_* of course represents the average number of subprocesses required for encoding by participants in cell *. The hyperparameter u is a competence-based parameter, where higher values of u reflect greater participant competence (owing, for example, to practice effects), and r is a stress-related hyperparameter, where larger r detracts from the performance of the participants.

The reason in the Neufeld model for allowing m_* to vary with the cell * while keeping u and r fixed over the cells was to easily satisfy the signature VIC = MIC = 0; this was profitably utilized in fitting the George and Neufeld (1987) factorial data (Neufeld et al., 2007; Neufeld et al., 2010). Note that allowing m_* to vary over cells while keeping the distribution of v fixed over cells proclaims that the increase in mean encoding latencies seen in moving diagnostic status from normal health to schizophrenia, or from low encoding load to high encoding load, is due to an increase in the *number of subprocesses* being executed rather than any change in the rate at which they are being executed. Thus this model posits a hypothesis about the neurophysiological mechanism behind prolonged encoding times in schizophrenia patients. It is intuitively credible that the number of required subprocesses would increase when shifting from a low encoding load to a high encoding load, but it is less obvious why the

schizophrenia disease process should produce additional encoding operations above those of a control. Nonetheless, converging evidence suggests that the mechanism posited by the Neufeld model is indeed accurate for a class of factorial experimental paradigms. Russell and Knight (1977) noted that elevated preparatory activity (described as "process system priming") appeared to take place in schizophrenia patients at the inception of a cognitive task. A wealth of results from neuroimaging studies and related paradigms support the notion of an atypical resting state default-mode network of neurocircuitry in schizophrenia patients (Bluhm et al., 2007; Hare et al., 2019; Lee, Doucet, Leibu, & Frangou, 2018; Murphy, Birn, Handwerker, & Bandettini, 2000; Orliac et al., 2013; Penner et al., 2018; Williamson & Allman, 2012). Braver and Barch (2006) note that atypical default-system connectivity in schizophrenia may negatively impact the efficient implementation of encoding steps once encoding is initiated. Failure to implement may arise from a variety of sources, e.g., failing to successfully navigate an encoding step and therefore being required to repeat it, or failing to tag a step as completed and thus unnecessarily repeating it (Hemsley, 1993, 1994; Steffy & Galbraith, 1980; Steffy & Waldman, 1993). There may also be failure to aggregate redundant elements of a subprocess into a single Gestalt (Treisman, 1996).

As successful as the Neufeld model has been in modelling some factorial experiments, it has also exhibited one particular flaw. Specifically, estimates of the average number m_{LN} of subprocesses required to be executed by participants in the LN (Low-Normal) cell were considerably below one; in Neufeld et al. (2010) it was observed that $m_{LN} = .0971$ and in Highgate-Maynard and Neufeld (1986) it was observed that

$m_{LN} = .00001$. Assuming these estimates are all based on valid encoding trials (i.e., the participants did not disengage from the task or respond based on some other cue) this implies that some participants were encoding instantaneously. In other words, they were encoding without executing any subprocesses, which is unsatisfactory both conceptually and mathematically. Cutler and Neufeld (2017) managed this situation by introducing a task parameter $\alpha > 0$ (smaller α implies the task is easier) and replacing the exponential base (2.1.6) with the following gamma base

$$\phi(\ell) = \frac{v^{\alpha}\ell^{\alpha-1}}{\Gamma(\alpha)}e^{-v\ell} \tag{2.1.9}$$

Once again a random encoding time T can be represented in serial form by the sum of the $\ell_j s$ as in (2.1.7), only now T follows a $\text{Gam}(k\alpha, v)$ distribution rather than an Erlang distribution. We further cast it in the form of a mixture model by allowing k_i and v_i to vary with the participant i as in the Neufeld model. However, we further stipulate that the distribution of k over participants in each cell must follow a distribution which takes mass only on positive integers, thereby disallowing the Poisson distribution as a mixing distribution. Thus, the Cutler-Neufeld model differs from the Neufeld model only in two fundamental ways; one in the choice of base distribution on the subprocesses (gamma rather than exponential) and second in a restriction on the legitimate mixing distributions for subprocesses. Both models accommodate VIC = MIC = 0 but the Cutler-Neufeld model allows for arbitrarily small (but nonzero) estimates of m_{LN}, recast now as being estimates of the product αm_{LN} (Cutler & Neufeld, 2017) rather than that of the mean itself. This provides one motivation and justification for considering base distributions other than the

exponential, as we do in Sec 2.2. Allowing a wide range of base distributions not only permits a flexible range of modelling for encoding times, it allows extension of modelling to other cognitive-processing latencies which may suit a particular base distribution. In Sec 2.2 we also relax our restriction on requiring mixing distributions on k to be restricted to positive integers, instead interpreting cases where $k = 0$ as "faulty trials" where the participant has disengaged or responded based on some other cue. This provides a convenient mathematical and conceptual bookend to possible outcomes. (In practice the experimenter would likely identify and remove faulty trials from consideration before analysis.)

In this chapter we will be focusing on the development and analysis of models (nested within a large class of mixture models) yielding examples with specific values of VIC given the constraint MIC = 0 and thereby extending the work of Neufeld and Williamson (1996) and Neufeld (2021). Having said that, it is worth noting that mixture models have an enormous range of applicability beyond the scope in which we consider them here. Examples range from obtaining accurate personal parameter estimates (e.g., k_i, v_i) based on a relatively small samples of encoding latencies from a participant to estimating the probabilities of illness severity (group membership) again based on a relatively small sample of encoding latencies compared against a population (Neufeld, 2021; Neufeld et al., 2010).

Other sources on applications of modelling include Ahn and Busemeyer (2016), Chechile (2020), Neufeld (2007b, 2015, 2016, 2021), Neufeld and Cutler (2019), Neufeld and Shanahan (2021), and Townsend, Fifić, and Neufeld (2007).

2.2 A Class of General Serial Mixture Models

The Cutler-Neufeld model can be considered as an extension of the Neufeld model in the sense that the former allows for a general gamma base (2.1.9) of which the exponential base (2.1.6) is the special case $\alpha = 1$. Neufeld and Williamson (1996), Neufeld et al. (2010), and especially Neufeld (2021), have considered extensions of the Neufeld model which retain the exponential base but deviate from the Neufeld model in other ways; for example, by allowing the number of subprocesses k or the rate v to vary over encoding trials (rather than, or in addition to, varying over participants) according to a Poisson or gamma distribution respectively. We will see that these Neufeld extensions are specific examples of the class of models we develop now. This class is a general extension of the standard serial model (2.1.7). We allow any continuous positive infinite-tailed distribution to act as the base distribution for an encoding latency, subject to the mild constraint that it have finite first and second moments. The parameters that govern the base distribution are allowed to vary over both trials and participants (and cells), and the number of subprocesses is also allowed to vary over both trials and participants (and cells). Note that the *form* of the base distribution (i.e., its probability distribution, with the exception of the values of its parameters) is kept the same for all participants in all four cells. This is a simplifying assumption in keeping with the observation of Neufeld et al. (2010) and Neufeld (2021) that seldom is a change in overall model architecture required for different participants within a given experimental paradigm; any necessary changes can generally be accommodated by tweaking distributional parameters.

Definition 1: the general serial mixture model: Let T_i denote a random encoding trial for participant i. We may express this in serial form as

$$T_i = \begin{cases} 0 & \text{if } K_i = 0 \\ \ell_{i1}(\Theta_i) + \cdots + \ell_{iK_i}(\Theta_i) & \text{if } K_i \geq 1 \end{cases} \tag{2.2.1}$$

where the number of subprocesses K_i is a nonnegative integer-valued random variable (that is, its values may vary over trials within a participant, and it may also vary across participants) and the $\ell_{i1}(\Theta_i), \ldots, \ell_{iK_i}(\Theta_i)$ are independently and identically-distributed (i.i.d.) continuous positive infinite-tailed random variables with the simplifying assumption that, for each participant, the distributional form of $\ell_{ij}(\Theta_i)$ is the same except possibly for the values of the governing parameters Θ_i. The Θ_i are random vectors which may vary over trials within a participant as well as across participants. In other words, for all participants, the individual subprocess encoding times $\ell_{ij}(\Theta_i)$ share a common base distribution but the parameters of that distribution on a particular trial for participant i depend on the value $\Theta_i = \theta_i$ for that trial. We further define the first and second-order moment functions

$$\mu(\theta) = E(\ell(\Theta) \,|\, \Theta = \theta) \quad \text{and} \quad \sigma^2(\theta) = \text{Var}(\ell(\Theta) \,|\, \Theta = \theta) \tag{2.2.2}$$

and make the assumption that $\mu(\theta)$ and $\sigma^2(\theta)$ are finite for all possible values of θ. The mappings $i \rightarrow K_i$ and $i \rightarrow \Theta_i$ can be considered as measure-valued random processes (Kallenberg, 2017) over the individuals in each cell * with respective distributions $\mathbb{P}_*(K)$ and $\mathbb{Q}_*(\Theta)$. It is assumed that the processes $\mathbb{P}_*(K)$ and $\mathbb{Q}_*(\Theta)$ act independently.

Notes Attendant to Definition 1: The capital letter notation K_i is used to indicate the possibility that the number of subprocesses varies over trials for the i^{th} participant;

the capital Θ_i is used for similar reasons. The lower case letters k_i and θ_i will be reserved for two situations, the first being the case where there may be variation across participants but none across trials (in which case $K_i = k_i$ and $\Theta_i = \theta_i$ are constants for participant i) or, secondly, when we are conditioning on the observed outcome of a given trial, yielding $K_i = k_i$ and $\Theta_i = \theta_i$ for that trial. The case $K_i = 0$ represents the situation where, on the specified trial, participant i does not encode at all but either disengages from the task or responds based on some other cue ("faulty trial"). Variability in K_i across trials can have a number of sources, such as variability in the experimental input sequence from trial to trial, variability in the participant's attention from trial to trial, and instances of "partial encoding" (needing or choosing to encode only parts of the stimulus before executing a response). Variability in K_i across participants is of course due to differences between participants. Note that changes in the vector parameter Θ_i (whether it be over trials or participants) represent changes in the encoding speed of the subprocesses (thus Θ may be seen as a generalization of the rate V associated with the exponential distribution) and we may well envisage situations in which the nature of the input sequence or state of mind of the participant may affect encoding speed of individual components.

Below we delineate a small number of potential base distributions. We refer the reader to Appendix B for details, properties, and abbreviations concerning these distributions. The reader can find information about these distributions in Hogg, McKean, and Craig (2005), Johnson, Kotz, and Balakrishnan (1994), and Van Zandt (2000). Note that, in practice, any continuous positive right-tailed distribution

would be a valid candidate provided it satisfied the finite moment constraints on $\mu(\theta)$ and $\sigma^2(\theta)$.

examples of base distributions:

1. **exponential base:** Here $\Theta_i = V_i$ and $\ell_{ij} \overset{\mathcal{D}}{\sim} \text{expo}(V_i)$. It follows that $\mu(\Theta_i) = 1/V_i$ and $\sigma^2(\Theta_i) = 1/V_i^2$. For observed $K_i = k_i$ and $V_i = v_i$ on a trial, we obtain $T_i = \ell_{i1}(v_i) + \cdots + \ell_{ik_i}(v_i) \overset{\mathcal{D}}{\sim} \text{Gam}(k_i, v_i)$ which is the Erlang distribution.

2. **gamma base:** Here $\Theta_i = (A_i, V_i)$ and $\ell_{ij} \overset{\mathcal{D}}{\sim} \text{Gam}(A_i, V_i)$. It follows that $\mu(\Theta_i) = A_i/V_i$ and $\sigma^2(\Theta_i) = A_i/V_i^2$. For observed $K_i = k_i$, $A_i = a_i$, and $V_i = v_i$ on a trial, we obtain $T_i = \ell_{i1}(a_i, v_i) + \cdots + \ell_{ik_i}(a_i, v_i) \overset{\mathcal{D}}{\sim} \text{Gam}(k_i a_i, v_i)$

3. **inverse Gaussian base:** Here $\Theta_i = (M_i, \Lambda_i)$ and $\ell_{ij} \overset{\mathcal{D}}{\sim} \text{IG}(M_i, \Lambda_i)$. It follows that $\mu(\Theta_i) = M_i$ and $\sigma^2(\Theta_i) = M_i^3/\Lambda_i$. For observed $K_i = k_i$, $M_i = \mu_i$, and $\Lambda_i = \lambda_i$, we obtain $T_i = \ell_{i1}(\mu_i, \lambda_i) + \cdots + \ell_{ik_i}(\mu_i, \lambda_i) \overset{\mathcal{D}}{\sim} \text{IG}(k_i\mu_i, k_i^2\lambda_i)$.

4. **Weibull base:** Here $\Theta_i = (A_i, B_i)$ and $\ell_{ij} \overset{\mathcal{D}}{\sim} \text{Wei}(A_i, B_i)$. It follows that $\mu(\Theta_i) = B_i\,\Gamma(1{+}1/A_i)$ and $\sigma^2(\Theta_i) = B_i^2\{\Gamma(1{+}2/A_i) - (\Gamma(1{+}1/A_i))^2\}$. For given values $K_i = k_i$, $A_i = a_i$ and $B_i = b_i$ we obtain $T_i = \ell_{i1}(a_i, b_i) + \cdots + \ell_{ik_i}(a_i, b_i)$. In the case of the Weibull, a closed form expression for the distribution of T_i is not known.

5. **lognormal base:** Here $\Theta_i = (M_i, \Sigma_i^2)$ and $\ell_{ij} \overset{\mathcal{D}}{\sim} \text{LN}(M_i, \Sigma_i^2)$. It follows that $\mu(\Theta_i) = e^{M_i + \Sigma_i^2/2}$ and $\sigma^2(\Theta_i) = e^{2M_i + \Sigma_i^2}\,(e^{\Sigma_i^2} - 1)$.For given values $K_i = k_i$, $M_i = \mu_i$ and $\Sigma_i^2 = \sigma_i^2$ we obtain $T_i = \ell_{i1}(\mu_i, \sigma_i^2) + \cdots + \ell_{ik_i}(\mu_i, \sigma_i^2)$. In the case of the log normal, a closed form expression for the distribution of T_i is not

known.

We now show that the general serial mixture model can be mimicked distributionally by a fixed capacity parallel model with reallocation (FCPR model) as first discussed in Sec 2.1.2. In an FCPR model, all subprocesses begin executing simultaneously at time $t = 0$; as soon as one subprocess finishes executing, its workload capacity is reallocated over the remaining $k_i - 1$ subprocesses and these remaining subprocesses are "restarted" simultaneously with this new capacity. This procedure is repeated until all subprocesses have finished executing. We make this precise in the following (see also Atkinson, Holmgren, and Juola (1969), Townsend (1972, 1990), Townsend and Ashby (1983), and more recently Houpt, Townsend, and Jefferson (2018) and Townsend, Wenger, and Houpt (2018)).

Theorem 1: Suppose the encoding latency T_i can be represented by the general serial mixture model in Definition 1. Then T_i has an equivalent (up to a random ordering of the subprocesses) representation as an FCPR model.

proof: Condition on the outcome $K_i = k_i$ and $\Theta_i = \theta_i$ for a given trial. In the cases $k_i = 0$ or $k_i = 1$ there is nothing to prove as the parallel process is the same as the serial process. Therefore assume $k_i \geq 2$. Let $S_i(t)$ denote the survivor function of $\ell_{ij}(\theta_i)$, i.e., $S_i(t) = P(\ell_{ij}(\theta_i) > t)$. At time $t = 0$ simultaneously start k_i parallel i.i.d. processes $\ell_1^{(1)}, \ldots, \ell_{k_i}^{(1)}$ where each $\ell_j^{(1)}$ has survivor function $S^{(1)}(t) = (S_i(t))^{1/k_i}$. That is, $S^{(1)}(t)$ is the k_i^{th} root of $S_i(t)$. Note that $S^{(1)}(t)$ is itself a survivor function because $S^{(1)}(t)$ is decreasing, $S^{(1)}(0) = 1$, and $S^{(1)}(\infty) = 0$. Let m_1 be the time of

finishing of the fastest process, i.e., $m_1 = \min(\ell_1^{(1)}, \ldots, \ell_{k_i}^{(1)})$. Then

$$\begin{aligned} P(m_1 > t) = P(\min(\ell_1^{(1)}, \ldots, \ell_{k_i}^{(1)}) > t) &= P(\ell_1^{(1)} > t) \cdots P(\ell_{k_i}^{(1)} > t) \\ &= (S^{(1)}(t))^{k_i} \\ &= \left(S_i(t))^{1/k_i}\right)^{k_i} \\ &= S_i(t) \\ &= P(\ell_{i1} > t) \end{aligned} \tag{2.2.3}$$

Thus m_1 has the same distribution as ℓ_{i1}, i.e., $m_1 \overset{\mathcal{D}}{\sim} \ell_{i1}$. Now at time m_1 simultaneously speed up and independently restart the remaining $k_i - 1$ processes to produce new parallel i.i.d. processes $\ell_1^{(2)}, \ldots, \ell_{k_i-1}^{(2)}$ which have survivor function $S^{(2)}(t) = (S_i(t))^{1/(k_i-1)}$. (This amounts to redistributing capacity over the remaining $k_i - 1$ processes and restarting them from time m_1.) Let $m_2 = \min(\ell_1^{(2)}, \ldots, \ell_{k_i-1}^{(2)})$ which is the fastest finishing time of the restarted processes. Note that m_2 represents the intercompletion time between the first finishing time m_1 and the second overall finishing time $m_1 + m_2$. Moreover

$$\begin{aligned} P(m_2 > t) = P(\min(\ell_1^{(2)}, \ldots, \ell_{k_i-1}^{(2)}) > t) &= P(\ell_1^{(2)} > t) \cdots P(\ell_{k_i-1}^{(2)} > t) \\ &= (S^{(2)}(t))^{k_i-1} \\ &= \left(S_i(t))^{1/(k_i-1)}\right)^{k_i-1} \\ &= S_i(t) \\ &= P(\ell_{i2} > t) \end{aligned} \tag{2.2.4}$$

and, from independence of the restarting process, $m_1 + m_2 \overset{\mathcal{D}}{\sim} \ell_{i1} + \ell_{i2}$. If $k_i \geq 3$ we can continue on in this manner, independently restarting and speeding up the

remaining $k_i - 2$ processes to produce new parallel i.i.d. processes $\ell_1^{(3)}, \ldots, \ell_{k_i-2}^{(3)}$ which have survivor function $S^{(3)}(t) = (S_i(t))^{1/(k_i-2)}$ and intercompletion time $m_3 \overset{\mathcal{D}}{\sim} \ell_{i3}$. Carrying on in this way we have an overall parallel process with k_i subprocesses and independent intercompletion times $m_1, \ldots, m_{k_i}$ where $m_j \overset{\mathcal{D}}{\sim} \ell_{ij}$ and

$$m_1 + \cdots + m_{k_i} \overset{\mathcal{D}}{\sim} \ell_{i1} + \cdots + \ell_{ik_i} \tag{2.2.5}$$

The parallel and serial models are equivalent up to an ordering of the execution of the subprocesses. The serial model may (or may not) specify a specific ordering of execution of the subprocesses whereas the order of completion of the subprocesses in this FCPR model is uniformly at random. However, they are distributionally equivalent in the sense that they lead to the same distribution of the overall encoding time T_i for given values $K_i = k_i$ and $\Theta_i = \theta_i$. $\triangle$

Thus the ability to consider the distribution of T_i as the result of a serial or parallel process provides flexibility to the model architecture.

We now wish to derive general closed-form expressions for the mean encoding latency $E(T)_*$ and average intertrial variance $E(\mathrm{Var}(T))_*$ in cell * for the general serial mixture model. Although we will continue to use the convenient notation $E(T)_*$ and $E(\mathrm{Var}(T))_*$ to denote these quantities, we will be more careful with the notation in the computational formulas, since they will require computing moments over both trials and participants. Before we take this step, we will summarize some standard known formulas for calculating moments.

Lemma 1: standard calculation formulas: Suppose X and Y are two random

variables. Then

$$E(X) = E_Y[E(X \mid Y)] \tag{2.2.6}$$

$$\mathrm{Var}(X) = \mathrm{Var}_Y[E(X \mid Y)] + E_Y[\mathrm{Var}(X \mid Y)] \tag{2.2.7}$$

and if X and Y are independent, then

$$\mathrm{Var}(XY) = \mathrm{Var}(X)\mathrm{Var}(Y) + E(X)^2\mathrm{Var}(Y) + E(Y)^2\mathrm{Var}(X) \tag{2.2.8}$$

proof: see Ross (2007) for (2.2.6) and (2.2.7). The expression (2.2.8) follows from elementary properties of the variance and independence. $\triangle$

We now derive closed form expressions for $E(T)_*$ and $E(\mathrm{Var}(T))_*$. We note that this notation is somewhat careless, in that we should precisely express these quantities as

$$E(T)_* = E^i_*[E(T_i)] \quad \text{and} \quad E(\mathrm{Var}(T))_* = E^i_*[\mathrm{Var}(T_i)] \tag{2.2.9}$$

where $E(T_i)$ and $\mathrm{Var}(T_i)$ denote the mean and variance, respectively, of the encoding latencies of the i^{th} participant *over trials*, and E^i_* denotes the subsequent averaging of those quantities over all participants in cell *. For convenience we will continue to employ the casual notation $E(T)_*$ and $E(\mathrm{Var}(T))_*$ with the understanding that they represent (2.2.9), but in the following computational formulas we will be very precise with notation in order to avoid any confusion.

Theorem 2: general formulas for cell means and cell variances: Suppose we have a general serial mixture model where, for the i^{th} participant, T_i has associated subprocess number K_i and random vector Θ_i. Let $\mu(\Theta_i)$ and $\sigma^2(\Theta_i)$ be the moment

functions defined in (2.2.2). Then

$$E(T)_* = E^i_*[E(K_i)]E^i_*[E(\mu(\Theta_i))] \tag{2.2.10}$$

and

$$\begin{aligned} E(\mathrm{Var}(T))_* = \big\{ & E^i_*[\mathrm{Var}(K_i)]E^i_*[\mathrm{Var}(\mu(\Theta_i))] + E^i_*[E(K_i)^2]E^i_*[\mathrm{Var}(\mu(\Theta_i))] \\ & + E^i_*[E(\mu(\Theta_i))^2]E^i_*[\mathrm{Var}(K_i)]\big\} + E^i_*[E(K_i)]E^i_*[E(\sigma^2(\Theta_i))] \end{aligned} \tag{2.2.11}$$

proof: We first precisely define the notation on the right hand side of both (2.2.10) and (2.2.11) and ask the reader to compare with (2.2.9). The outer expectations E^i_* refer to expectations being taken *across all participants* in cell *. The inner moments (either expectations E or variances Var) are taken *across trials* within a participant within a cell. These inner moments are computed first. Conditioning on $K_i = k_i$ and $\Theta_i = \theta_i$ for participant i we obtain

$$(T_i \,|\, K_i = k_i, \Theta_i = \theta_i) \;=\; \ell_{i1}(\theta_i) + \cdots + \ell_{ik_i}(\theta_i) \quad \text{i.i.d. sum}$$

so

$$\begin{aligned} E(T_i \,|\, K_i = k_i, \Theta_i = \theta_i) \;&=\; E(\ell_{i1}(\theta_i)) + \cdots + E(\ell_{ik_i}(\theta_i)) \\ &= k_i\mu(\theta_i) \end{aligned} \tag{2.2.12}$$

and similarly

$$\begin{aligned} \mathrm{Var}(T_i \,|\, K_i = k_i, \Theta_i = \theta_i) \;&=\; \mathrm{Var}(\ell_{i1}(\theta_i)) + \cdots + \mathrm{Var}(\ell_{ik_i}(\theta_i)) \\ &= k_i\sigma^2(\theta_i) \end{aligned} \tag{2.2.13}$$

Expressed in functional form these become

$$E(T_i \,|\, K_i, \Theta_i) = K_i\mu(\Theta_i) \quad \text{and} \quad \mathrm{Var}(T_i \,|\, K_i, \Theta_i) = K_i\sigma^2(\Theta_i) \tag{2.2.14}$$

Applying the standard calculation formulas in Lemma 1 and the independence of K_i and Θ_i we obtain

$$E(T_i) = E(K_i)E(\mu(\Theta_i)) \tag{2.2.15}$$

and

$$\begin{aligned}
\mathrm{Var}(T_i) &= \mathrm{Var}(E(T_i \,|\, K_i, \Theta_i)) + E(\mathrm{Var}(T_i \,|\, K_i, \Theta_i)) \\
&= \mathrm{Var}(K_i\mu(\Theta_i)) + E(K_i\sigma^2(\Theta_i)) \\
&= \left\{\mathrm{Var}(K_i)\mathrm{Var}(\mu(\Theta_i)) + E(K_i)^2\mathrm{Var}(\mu(\Theta_i)) + E(\mu(\Theta_i))^2\mathrm{Var}(K_i)\right\} \\
&\quad + E(K_i)E(\sigma^2(\Theta_i))
\end{aligned} \tag{2.2.16}$$

Now averaging over all participants in cell * (that is, applying E^i_*) and using (2.2.9) and the fact that the random measures K and Θ are independent of one another, we obtain (2.2.10) and (2.2.11). $\triangle$

Note: When applying expectations in (2.2.10) and (2.2.11), care must be taken to apply expectations in the correct manner over the correct quantities. As noted at the beginning of the proof of Theorem 2, inner moments, such as $E(K_i)^2$ and $\mathrm{Var}(\mu(\Theta_i))$, are computed *across trials* for the i^{th} participant. Thus, if $K_i = k_i$ and $\Theta_i = \theta_i$ are constant over trials for the i^{th} participant, we obtain $E(K_i)^2 = k_i^2$ and $\mathrm{Var}(\mu(\Theta_i)) = \mathrm{Var}(\mu(\theta_i)) = 0$. On the other hand, the outer expectations E^i_* are taken *across all participants* in cell *.

Theorem 2 yields general closed form solutions to $E(T)_*$ and $E(\mathrm{Var}(T))_*$ for any base distribution with any admissible choice of distributions $\mathbb{P}_*(K)$ and $\mathbb{Q}_*(\Theta)$. In the following we apply Theorem 2 to the exponential base.

Corollary 2.1: exponential base: Suppose we have a general serial mixture model

with an exponential base and distributions $\mathbb{P}_*(K)$ and $\mathbb{Q}_*(V)$. (Recall $\Theta = V$, the exponential rate, in the case of an exponential base.) Then

$$E(T)_* = E^i_*[E(K_i)]E^i_*[E(1/V_i)] \tag{2.2.17}$$

and

$$\begin{aligned} E(\mathrm{Var}(T))_* = \big\{ & E^i_*[\mathrm{Var}(K_i)]E^i_*[\mathrm{Var}(1/V_i)] + E^i_*[E(K_i)^2]E^i_*[\mathrm{Var}(1/V_i)] \\ & + E^i_*[E(1/V_i)^2]E^i_*[\mathrm{Var}(K_i)]\big\} + E^i_*[E(K_i)]E^i_*[E(1/V_i^2)] \end{aligned} \tag{2.2.18}$$

proof: Here $\ell_{ij} \overset{\mathcal{D}}{\sim} \mathrm{expo}(V_i)$ and hence $\mu(V_i) = 1/V_i$ and $\sigma^2(V_i) = 1/V_i^2$ (see Appendix B). Plugging these values into (2.2.10) and (2.2.11) yields the desired results. $\triangle$

We now apply Corollary 2.1 to a collection of examples considered by Neufeld (2021). The examples fall under the umbrella of Corollary 2.1, each exhibiting an exponential base, accompanied by a Poisson distribution over K (either over participants or trials) and a gamma distribution over V (either over participants or trials). Thus these examples represent extensions of the Neufeld model. The purpose of examining these examples is to show how easily $E(T)_*$ and $E(\mathrm{Var}(T))_*$ can be calculated by utilizing known related distributional moments (see Appendix A and Appendix B for moments and notation) and plugging into (2.2.17) and (2.2.18). This contrasts with Neufeld (2021) where it was necessary to calculate integrals on a case-by-case basis.

Example 1: This is the Neufeld model, and corresponds to example 5 of Neufeld (2021). Here $k \sim \mathrm{Pois}(m_*)$ across participants in cell * and $v \overset{\mathcal{D}}{\sim} \mathrm{Gam}(u, r)$ across participants in each cell where $u > 2$. There is no variation over trials, and so all three terms

within the braces of (2.2.18) vanish. This yields

$$E(T)_* = E^i_*[k_i]E^i_*[1/v_i] = m_*\left[\frac{r}{u-1}\right] = \frac{m_* r}{u-1}$$

and

$$E(\mathrm{Var}(T))_* = E^i_*[k_i]E^i_*[1/v_i^2] = m_*\left[\frac{r^2}{(u-1)(u-2)}\right] = \frac{m_* r^2}{(u-1)(u-2)}$$

Example 2: This corresponds to example 6 of Neufeld (2021). Here $K_i \overset{\mathcal{D}}{\sim} \mathrm{Pois}(m_*)$ across trials for each participant in cell * whereas $v \overset{\mathcal{D}}{\sim} \mathrm{Gam}(u, r)$ across participants in each cell where $u > 2$. Applying (2.2.17) yields

$$E(T)_* = E^i_*[E(K_i)]E^i_*[1/v_i] = E^i_*[m_*]E^i_*[1/v_i] = m_* E^i_*[1/v_i] = \frac{m_* r}{u-1}$$

Now because K_i is a random variable over trials whereas v_i is constant over trials, we see from (2.2.18) that the first two terms inside the braces vanish whereas the last term inside the braces does not, and we obtain

$$\begin{aligned} E(\mathrm{Var}(T))_* &= E^i_*[1/v_i^2]E^i_*[\mathrm{Var}(K_i)] + E^i_*[E(K_i)]E^i_*[1/v_i^2] \\ &= E^i_*[1/v_i^2]\big(E^i_*[\mathrm{Var}(K_i)] + E^i_*[E(K_i)]\big) \\ &= E^i_*[1/v_i^2]\, 2m_* \quad \text{since } \mathrm{Var}(K_i) = E(K_i) = m_* \\ &= \frac{2m_* r^2}{(u-1)(u-2)} \end{aligned} \tag{2.2.19}$$

Example 3: This corresponds to example 7 of Neufeld (2021). Here $K_i \overset{\mathcal{D}}{\sim} \mathrm{Pois}(m_i)$ over trials for participant i, and then $m \overset{\mathcal{D}}{\sim} \mathrm{Gam}(w_*, z_*)$ across participants in cell *. (Thus K_i varies over both trials and participants.) As in the previous two examples, $v \overset{\mathcal{D}}{\sim} \mathrm{Gam}(u, r)$ over participants in each cell where $u > 2$. Applying (2.2.17) yields

$$E(T)_* = E^i_*[E(K_i)]E^i_*[1/v_i] = E^i_*[m_i]E^i_*[1/v_i] = \left[\frac{w_*}{z_*}\right]\left[\frac{r}{u-1}\right] = \frac{r w_*}{z_*(u-1)}$$

As in Example 2, the first two terms inside the braces of (2.2.18) vanish whereas the third does not, yielding

$$E(\mathrm{Var}(T))_* = E^i_*[1/v_i^2]E^i_*[m_i] + E^i_*[m_i]E^i_*[1/v_i^2] = 2\left[\frac{w_*}{z_*}\right]\left[\frac{r^2}{(u-1)(u-2)}\right] = \frac{2r^2w_*}{z_*(u-1)(u-2)} \tag{2.2.20}$$

Example 4: This corresponds to example 9 of Neufeld (2021). Here $K_i \overset{\mathcal{D}}{\sim} \mathrm{Pois}(m_*)$ over trials for each participant in cell * and also $V_i \overset{\mathcal{D}}{\sim} \mathrm{Gam}(u_*, r_*)$ over trials for each participant in cell * where $u_* > 2$. Applying 2.2.17 yields

$$E(T)_* = E^i_*[m_*]E^i_*[r_*/(u_*-1)] = \frac{m_*r_*}{u_*-1}$$

Now since both K_i and V_i are random variables over trials here, all terms within the braces of (2.2.18) are nonzero. Noting that $E(K_i) = \mathrm{Var}(K_i) = m_*$ and that $E(1/V_i) = r_*/(u_*-1)$, $E(1/V_i^2) = r_*^2/[(u_*-1)(u_*-2)]$ and $\mathrm{Var}(1/V_i) = r_*^2/[(u_*-1)^2(u_*-2)]$ (see Appendices A and B), we can plug into (2.2.18) to obtain

$$\begin{aligned} E(\mathrm{Var}(T))_* &= \left\{\frac{m_*r_*^2}{(u_*-1)^2(u_*-2)} + \frac{m_*^2r_*^2}{(u_*-1)^2(u_*-2)} + \frac{r_*^2m_*}{(u_*-1)^2}\right\} + \frac{r_*^2m_*}{(u_*-1)(u_*-2)} \\ &= \frac{m_*r_*^2[m_*+2(u_*-1)]}{(u_*-1)^2(u_*-2)} \end{aligned} \tag{2.2.21}$$

Example 5: This corresponds to example 10 of Neufeld (2021). $V_i \overset{\mathcal{D}}{\sim} \mathrm{Gam}(u_*, r_*)$ across trials for each participant in cell * where $u_* > 2$ (as in previous example) but here $K_i \overset{\mathcal{D}}{\sim} \mathrm{Pois}(m_i)$ across trials for participant i where $m \overset{\mathcal{D}}{\sim} \mathrm{Gam}(w_*, z_*)$ across participants in cell *. Applying (2.2.17) gives

$$E(T)_* = E^i_*[m_i]E^i_*[r_*/(u_*-1)] = \left[\frac{w_*}{z_*}\right]\left[\frac{r_*}{u_*-1}\right] = \frac{r_*w_*}{z_*(u_*-1)}$$

Again all terms inside the braces of (2.2.18) are nonzero. Since $E(K_i) = \mathrm{Var}(K_i) = m_i$ we obtain $E_*^i[E(K_i)^2] = E_*^i[m_i^2] = [(w_*+1)w_*]/z_*^2$ and $E_*^i[\mathrm{Var}(K_i)] = E_*^i[m_i] = w_*/z_*$. Plugging into (2.2.18) yields

$$\begin{aligned} E(\mathrm{Var}(T))_* &= \left[\frac{w_*}{z_*}\right]\left[\frac{r_*^2}{(u_*-1)^2(u_*-2)}\right] + \left[\frac{w_*(w_*+1)}{z_*^2}\right]\left[\frac{r_*^2}{(u_*-1)^2(u_*-2)}\right] \\ &\quad + \left[\frac{r_*^2}{(u_*-1)^2}\right]\left[\frac{w_*}{z_*}\right] + \left[\frac{w_*}{z_*}\right]\left[\frac{r_*^2}{(u_*-1)(u_*-2)}\right] \\ &= \frac{r_*^2 w_*}{z_*^2}\left[\frac{2z_*(u_*-1)+w_*+1}{(u_*-1)^2(u_*-2)}\right] \end{aligned} \tag{2.2.22}$$

Below we apply Theorem 2 to a gamma base distribution.

Corollary 2.2: gamma base: Suppose we have a general serial mixture model with a gamma base and distributions $\mathbb{P}_*(K)$ and $\mathbb{Q}_*(\Theta)$. Recall $\Theta = (A, V)$, the shape and rate parameters, respectively, in the case of a gamma base. Further assume that the distributions of A and V act independently over both trials and participants. Then

$$E(T)_* = E_*^i[E(K_i)]E_*^i[E(A_i)]E_*^i[E(1/V_i)] \tag{2.2.23}$$

and

$$\begin{aligned} E(\mathrm{Var}(T))_* &= E_*^i[E(K_i^2)]\big\{E_*^i[\mathrm{Var}(A_i)]E_*^i[\mathrm{Var}(1/V_i)] + E_*^i[E(A_i)^2]E_*^i[\mathrm{Var}(1/V_i)] \\ &\quad + E_*^i[E(1/V_i)^2]E_*^i[\mathrm{Var}(A_i)]\big\} + E_*^i[E(A_i)^2]E_*^i[E(1/V_i)^2]E_*^i[\mathrm{Var}(K_i)] \\ &\quad + E_*^i[E(K_i)]E_i^*[E(A_i)]E_*^i[E(1/V_i^2)] \end{aligned} \tag{2.2.24}$$

proof: For the gamma base $\mu(\Theta_i) = A_i/V_i$ and $\sigma^2(\Theta_i) = A_i/V_i^2$. Plugging into (2.2.10) and using the assumed independence of A and V yields (2.2.23). Now as direct application of (2.2.11) will produce a very lengthy algebraic expression, we shorten it first by noting that $\mathrm{Var}(K_i) + E(K_i)^2 = E(K_i^2)$ and thus (2.2.11) can

equivalently be written in the more compact asymmetric form

$$E(\mathrm{Var}(T))_* = \big\{E^i_*[E(K_i^2)]E^i_*[\mathrm{Var}(\mu(\Theta_i))] + E^i_*[E(\mu(\Theta_i))^2]E^i_*[\mathrm{Var}(K_i)]\big\} + E^i_*[E(K_i)]E^i_*[E(\sigma^2(\Theta_i))] \tag{2.2.25}$$

Now expanding $\mathrm{Var}(\mu(\Theta_i)) = \mathrm{Var}(A_i/V_i)$ according to (2.2.8) and plugging into (2.2.25) and using independence yields (2.2.24). $\triangle$

Corollary 2.3: the Cutler-Neufeld base: This is a special case of the gamma base where the shape parameter $A_i = \alpha$ is a constant; hence $\mathrm{Var}(A_i) = 0$. Plugging into (2.2.23) and replacing $E(K_i^2)$ with $\mathrm{Var}(K_i) + E(K_i)^2$ in (2.2.24) yields

$$E(T)_* = \alpha E^*_i[E(K_i)]E^*_i[E(1/V_i)] \tag{2.2.26}$$

and

$$E(\mathrm{Var}(T))_* = \alpha^2\big\{E^i_*[\mathrm{Var}(K_i)]E^i_*[\mathrm{Var}(1/V_i)] + E^i_*[E(K_i)^2]E^i_*[\mathrm{Var}(1/V_i)] + E^i_*[E(1/V_i)^2]E^i_*[\mathrm{Var}(K_i)]\big\} + \alpha E^i_*[E(K_i)]E^i_*[E(1/V_i^2)] \tag{2.2.27}$$

Corollary 2.4: inverse Gaussian base: Suppose we have a general serial mixture model with an inverse Gaussian base and distributions $\mathbb{P}_*(K)$ and $\mathbb{Q}_*(\Theta)$. Recall $\Theta = (M, \Lambda)$, the mean and shape parameters, respectively, in the case of an inverse Gaussian base. Further assume that the distributions of M and Λ act independently over both trials and participants. Then

$$E(T)_* = E^i_*[E(K_i)]E^i_*[E(M_i)] \tag{2.2.28}$$

and

$$E^i_*[\mathrm{Var}(T_i)] = \big\{E^i_*[\mathrm{Var}(K_i)]E^i_*[\mathrm{Var}(M_i)] + E^i_*[E(K_i)^2]E^i_*[\mathrm{Var}(M_i)] + E^i_*[E(M_i)^2]E^i_*[\mathrm{Var}(K_i)]\big\} + E^i_*[E(K_i)]E^i_*[E(M_i^3)]E^i_*[E(1/\Lambda_i)] \tag{2.2.29}$$

proof: This follows directly by plugging $\mu(\Theta_i) = M_i$ and $\sigma^2(\Theta_i) = M_i^3/\Lambda_i$ into (2.2.10) and (2.2.11) and utilizing independence. $\triangle$

Note: In Corollary 2.2 and 2.4 we assumed that the components of the vector Θ acted independently of one another; i.e., A and V were independent in the case of the gamma, and M and Λ in the case of the inverse Gaussian. This assumption was made simply in order to allow us to calculate the cell means and variances in terms of the moments of the individual components of Θ. If the components of Θ are not independent, this in no way invalidates (2.2.10) and (2.2.11); however, these expressions must then be calculated using the joint distribution of Θ.

Example 6: Here we consider an inverse Gaussian base where the mean $m \overset{\mathcal{D}}{\sim} \text{Gam}(u, r)$ across participants in each cell and the shape parameter $\lambda \overset{\mathcal{D}}{\sim} \text{Gam}(w, z)$ across participants in each cell with $w > 1$ (there is no variation over trials for either m or λ). Assume m and λ act independently over participants. In addition, assume K_i varies over trials according to a geometric distribution with parameter p_i (i.e., $K_i \overset{\mathcal{D}}{\sim} \text{geom}(p_i)$; see Appendix A) and p follows a beta distribution across participants in cell * with pdf $f(p) = \beta_* \, p^{\beta_* - 1}$ for $0 < p < 1$ and some $\beta_* > 2$. Then

$$E(T)_* = E_*^i[E(K_i)]E_*^i[E(M_i)] = E_*^i[1/p_i]E_*^i[m_i] \tag{2.2.30}$$

and the first two terms inside the braces of (2.2.29) vanish, yielding

$$E_*^i[\text{Var}(T_i)] = E_*^i[m_i^2]E_*^i[(1-p_i)/p_i^2] + E_*^i[1/p_i]E_*^i[m_i^3]E_*^i[1/\lambda_i] \tag{2.2.31}$$

Applying the gamma distributions $\text{Gam}(u, r)$ and $\text{Gam}(w, z)$ yields

$$E_*^i[m_i] = \frac{u}{r}, \quad E_*^i[m_i^2] = \frac{u(u+1)}{r^2}, \quad E_*^i[m_i^3] = \frac{u(u+1)(u+2)}{r^3}, \quad E_*^i[1/\lambda_i] = \frac{z}{w-1}$$

and applying the beta distribution yields

$$E_*^i[E(K_i)] = E_*^i[1/p_i] = \int_0^1 \frac{1}{p}\,\beta_*\,p^{\beta_*-1}\,dp \;=\; \frac{\beta_*}{\beta_*-1}$$

and

$$E_*^i[\mathrm{Var}(K_i)] = E_*^i[(1-p_i)/p_i^2] = \int_0^1 \left(\frac{1-p}{p^2}\right)\beta_*\,p^{\beta_*-1}\,dp \;=\; \frac{\beta_*}{(\beta_*-1)(\beta_*-2)}$$

Plugging in to (2.2.30) and (2.2.31) produces

$$E(T)_* = \left[\frac{\beta_*}{\beta_*-1}\right]\left[\frac{u}{r}\right] = \frac{\beta_* u}{r(\beta_*-1)} \tag{2.2.32}$$

and

$$\begin{aligned} E(\mathrm{Var}(T))_* = &\left[\frac{u(u+1)}{r^2}\right]\left[\frac{\beta_*}{(\beta_*-1)(\beta_*-2)}\right] \\ &+ \left[\frac{\beta_*}{\beta_*-1}\right]\left[\frac{u(u+1)(u+2)}{r^3}\right]\left[\frac{z}{w-1}\right] \end{aligned} \tag{2.2.33}$$

Thus we have seen by numerous examples that Theorem 2 allows us to compute $E(T)_*$ and $E(\mathrm{Var}(T))_*$ for various continuous positive infinite-tailed base distributions with different choices for $\mathbb{P}_*(K)$ and $\mathbb{Q}_*(\Theta)$. This in turn will allow us to compute MIC and VIC by plugging into (2.1.3) and (2.1.5). However, in taking our first steps toward calculating MIC and VIC, we first consider a particular subset of the class of general serial mixture models, a subset we call *generalized Cutler-Neufeld models*. These models have the feature that MIC and VIC take particularly simple forms.

2.3 Generalized Cutler-Neufeld Models

Definition 2: Generalized Cutler-Neufeld Model: This is a specific subset of the class of general serial mixture models in Definition 1 with unspecified base and

having the properties that (a) $\Theta_i = \theta_i$ for each participant i (i.e., $\Theta_i = \theta_i$ does not vary over trials although it may vary across participants) and (b) the distribution of θ over participants is the same in each cell. Note that (a) and (b) can be summarized by stating that there exists a distribution $Q(\theta)$ such that $\mathbb{Q}_*(\Theta) = Q(\theta)$ in each cell *. On the other hand, K_i may vary over both trials and participants, and its distribution $\mathbb{P}_*(K)$ depends on the cell *. In the case K_i varies over trials for some participants, we say it is a generalized Cutler-Neufeld model *with variation*. In the case $K_i = k_i$ is constant for each participant i, we say it is a generalized Cutler-Neufeld model *without variation,* in which case the notation $\mathbb{P}_*(K)$ can be replaced by the notation $P_*(k)$ describing the distribution of k across participants in cell *. Both the Neufeld and Cutler-Neufeld models are examples of generalized Cutler-Neufeld models without variation. For convenience, we use the abbreviation gen-CN model to denote generalized Cutler-Neufeld models.

There are three motivations behind defining gen-CN models. First, they describe a large flexible subset of the class of general serial mixture models that includes the Neufeld model, the Cutler-Neufeld model, as well as Examples 1, 2, 3, and 6 given above. Second, specific cases of such models have proven useful in modelling factorial experiment encoding latencies (see Neufeld et al. (2002), Neufeld, Vollick, et al. (2007), Neufeld et al. (2010), Taylor et al. (2016, 2017)) in which the changes in $E(T)_*$ and $E(\mathrm{Var}(T))_*$ over cells have been satisfactorily explained by shifting the distribution of the number of subprocesses K over cells while keeping the distribution of all other parameters constant. Third, the gen-CN models permit particularly succinct and aesthetic expressions for MIC and VIC.

Theorem 3: MIC and VIC for gen-CN models: Suppose we have a gen-CN model with moment functions $\mu(\theta)$ and $\sigma^2(\theta)$. Since the distribution of θ over participants in a cell is the same for each cell, we can reflect this by writing $E^i_*[\mu(\theta_i)] = E^i[\mu(\theta_i)]$ and $E^i_*[\sigma^2(\theta_i)] = E^i[\sigma^2(\theta_i)]$. Define

$$\text{KMIC} = (E^i_{HS}[E(K_i)] - E^i_{HN}[E(K_i)]) - (E^i_{LS}[E(K_i)] - E^i_{LN}[E(K_i)]) \tag{2.3.1}$$

and

$$\text{KVIC} = (E^i_{HS}[\text{Var}(K_i)] - E^i_{HN}[\text{Var}(K_i)]) - (E^i_{LS}[\text{Var}(K_i)] - E^i_{LN}[\text{Var}(K_i)]) \tag{2.3.2}$$

Then

$$\text{MIC} = E^i[\mu(\theta_i)]\text{KMIC} \tag{2.3.3}$$

and

$$\text{VIC} = E^i[\mu(\theta_i)^2]\text{KVIC} + E^i[\sigma^2(\theta_i)]\text{KMIC} \tag{2.3.4}$$

proof: It follows from the assumptions of the theorem and (2.2.10) that

$$E(T)_* = E^i_*[E(K_i)]E^i[\mu(\theta_i)] \tag{2.3.5}$$

and since $\text{Var}(\mu(\theta_i)) = 0$, leading to a vanishing of the first two terms in (2.2.11), we obtain

$$E(\text{Var}(T))_* = E^i[\mu(\theta_i)^2]E^i_*[\text{Var}(K_i)] + E^i_*[E(K_i)]E^i[\sigma^2(\theta_i)] \tag{2.3.6}$$

Thus applying (2.1.3) and the above, we obtain

$$\begin{aligned}\text{MIC} &= E^i[\mu(\theta_i)]\left\{(E^i_{HS}[E(K_i)] - E^i_{HN}[E(K_i)]) - (E^i_{LS}[E(K_i)] - E^i_{LN}[E(K_i)])\right\} \\ &= E^i[\mu(\theta_i)]\text{KMIC}\end{aligned} \tag{2.3.7}$$

whereas applying (2.1.5) and the above yields

$$\begin{aligned}
\text{VIC} &= \big\{(E^i[\mu(\theta_i)^2]E^i_{HS}[\text{Var}(K_i)] + E^i_{HS}[E(K_i)]E^i[\sigma^2(\theta_i)]) \\
&\qquad - (E^i[\mu(\theta_i)^2]E^i_{HN}[\text{Var}(K_i)] + E^i_{HN}[E(K_i)]E^i[\sigma^2(\theta_i)])\big\} \\
&\quad - \big\{(E^i[\mu(\theta_i)^2]E^i_{LS}[\text{Var}(K_i)] + E^i_{LS}[E(K_i)]E^i[\sigma^2(\theta_i)]) \\
&\qquad - (E^i[\mu(\theta_i)^2]E^i_{LN}[\text{Var}(K_i)] + E^i_{LN}[E(K_i)]E^i[\sigma^2(\theta_i)])\big\} \\
&= E^i[\mu(\theta_i)^2]\left\{(E^i_{HS}[\text{Var}(K_i)] - E^i_{HN}[\text{Var}(K_i)]) - (E^i_{LS}[\text{Var}(K_i)] - E^i_{LN}[\text{Var}(K_i)])\right\} \\
&\quad + E^i[\sigma^2(\theta_i)]\left\{(E^i_{HS}[E(K_i)] - E^i_{HN}[E(K_i)]) - (E^i_{LS}[E(K_i)] - E^i_{LN}[E(K_i)])\right\} \\
&= E^i[\mu(\theta_i)^2]\text{KVIC} + E^i[\sigma^2(\theta_i)]\text{KMIC}
\end{aligned} \tag{2.3.8}$$

as claimed. $\triangle$

Note: We see that the base distribution itself plays no role in the form of (2.3.3) and (2.3.4) except for the specific values that $E^i[\mu(\theta_i)], E^i[\mu(\theta_i)^2]$, and $E^i[\sigma^2(\theta_i)]$ attain. Moreover, we see that MIC = 0 if and only if (iff) KMIC = 0. Thus these models will exhibit factorial additivity over means iff KMIC = 0.

We now note that the situation becomes even simpler in the case of gen-CN models without variation.

Corollary 3.1: MIC and VIC in gen-CN models without variation: Assume the gen-CN model is without variation, i.e., K_i does not vary over trials for any participant. Then

$$\text{MIC} = E^i[\mu(\theta_i)]\text{KMIC} \tag{2.3.9}$$

and

$$\text{VIC} = E^i[\sigma^2(\theta_i)]\text{KMIC} \tag{2.3.10}$$

Thus VIC = 0 iff MIC = 0 which in turn occurs iff KMIC = 0.

proof: Since there is no variation over trials, $K_i = k_i$ and $\mathrm{Var}(k_i) = 0$ for all i and hence KVIC = 0. The result then follows from (2.3.4) and (2.3.3). $\triangle$

Corollary 3.2: alternate expression of Corollary 3.1: In the case of a gen-CN model without variation, we have $K_i = k_i$ and can express

$$E^i_{LN}[k_i] = m,\ E^i_{HN}[k_i] = m + h,\ E^i_{LS}[k_i] = m + g,\ E^i_{HS}[k_i] = m + f \tag{2.3.11}$$

Thus KMIC $= f - (h + g)$ and it follows from Corollary 3.1 that

$$\mathrm{MIC} = E^i[\mu(\theta_i)][f - (h + g)] \tag{2.3.12}$$

and

$$\mathrm{VIC} = E^i[\sigma^2(\theta_i)][f - (h + g)] \tag{2.3.13}$$

Thus VIC = 0 iff MIC = 0 which in turn occurs iff $f = h + g$. $\triangle$

Note: In the experimental paradigms we are considering, $E(T)_*$ is shortest in the LN cell, increasing as we shift into any of the other three cells. This combined with (2.3.5) implies that, for all practical purposes, $h > 0, g > 0$, and $f > 0$. Although this positivity constraint is not necessary for most mathematical expressions to be valid, it will simplify things going forward (especially when evaluating the sign of VIC) to assume related definitions of such quantities are positive. We will call attention to this as the situation arises.

Note: The value of Corollary 3.2 is as follows. For a given outcome of a specific experiment, we may observe the equality $f = h+g$ as the result of serendipity. However, if repeated manipulations of the encoding load (perhaps over a series of increasing

loads) and repeated manipulations of diagnostic status (perhaps by considering patients of increasing levels of illness) always result in $f = h + g$, this suggests that the observed additivity is a real phenomenon. In this case the additional subprocesses due to increases in encoding load (represented by h) and the additional subprocesses due to schizophrenia diagnostic status (represented by g) act independently of one another, producing $f = h + g$ and the result VIC = MIC = 0.

In the case of gen-CN models with variation, we may or may not obtain the signature VIC = 0 iff MIC = 0. Below we present an assortment of gen-CN models that permit a variety of different explicit MIC-VIC signatures.

Example 7: Poisson over trials: Consider a gen-CN model where, for participant i in cell *, K_i follows a Poisson distribution over trials with mean m_i which in turn may vary over participants in the cell according to some positive distribution $P_*(m)$. Since $m_i = E(K_i) = \mathrm{Var}(K_i)$ for the Poisson, then setting $E^i_*[m_i] = \lambda_*$ yields

$$\begin{aligned} \mathrm{KMIC} = \mathrm{KVIC} &= (E^i_{HS}[m_i] - E^i_{HN}[m_i]) - (E^i_{LS}[m_i] - E^i_{LN}[m_i]) \\ &= (\lambda_{HS} - \lambda_{HN}) - (\lambda_{LS} - \lambda_{LN}) \end{aligned} \tag{2.3.14}$$

where the boundary conditions $0 < \lambda_{LN} < \lambda_{HN}, \lambda_{LS} < \lambda_{HS}$ hold in order to satidy (2.3.5) and the factorial outcomes of $E(T)_*$ in Sec 2.1.1. Hence VIC = 0 iff MIC = 0 and there is a wide range of admissible choices of λ_* which will permit this outcome . Thus this is an example of a gen-CN model *with variation* that satisfies the signature VIC = 0 iff MIC = 0. Note that Example 7 also embraces the special subcase where there is no variation in m_i across participants in the cell, in which case $P_*(m)$ is just a point mass at λ_* and K_i only varies over trials.

Example 8: a simple negative binomial model: Consider a gen-CN model where

we assume that, for each participant i, K_i has a negative binomial distribution across trials with parameters r_* and p_* in cell * (see Appendix A). There is no variation across participants. We interpret r_* as the number of steps that must be encoded in cell * in order for successful encoding of the entire stimulus to occur, and p_* represents the probability of successful encoding of a step on any one try. Thus K_i represents the total number of tries (subprocesses) required to successfully encode the stimulus on a trial. It follows that $E(K_i) = r_*/p_*$ and $\mathrm{Var}(K_i) = r_*(1-p_*)/p_*^2$ in cell *. Assume further that the required number of steps r_* is the same in cells LN and LS and can be denoted by r_L. Similarly assume that the required number of steps r_* is the same in cells HN and HS and can be denoted by r_H. (Note this assumption is very reasonable as it implies the same set of stimuli are presented to both normal controls and schizophrenia patients, but that there is a difference in number of steps between the low and high encoding loads.) Assume that the probability of successful encoding of a step on any try is p_N for a normal control and p_S for a schizophrenia patient (and this does not vary with encoding load, which also is reasonable). Make the assumption that the experiment satisfies $r_L < r_H$ and $p_S < p_N$ in order to be consistent with observed outcomes $E(T)_*$ in the factorial experiments described in Sec 2.1.1. Then

$$\begin{aligned} \mathrm{KMIC} &= \left(\frac{r_H}{p_S} - \frac{r_H}{p_N}\right) - \left(\frac{r_L}{p_S} - \frac{r_L}{p_N}\right) \\ &= (r_H - r_L)\left(\frac{1}{p_S} - \frac{1}{p_N}\right) \\ &> 0 \end{aligned} \tag{2.3.15}$$

and

$$\text{KVIC} = \left(\frac{r_H(1-p_S)}{p_S^2} - \frac{r_H(1-p_N)}{p_N^2}\right) - \left(\frac{r_L(1-p_S)}{p_S^2} - \frac{r_L(1-p_N)}{p_N^2}\right)$$

$$= (r_H - r_L)\left(\frac{1-p_S}{p_S^2} - \frac{(1-p_N)}{p_N^2}\right) \tag{2.3.16}$$

$$> 0$$

It follows that both MIC > 0 and VIC > 0 always in this simple negative binomial model. Thus this model, while appealing in its explanatory physical mechanism, is *not* a candidate for modelling the experimental paradigms considered in Sec 2.1.1 because those experiments always produced MIC $= 0$.

Example 9: an alternative negative binomial model: In Example 8 above a specific negative binomial model was considered where the number of successful steps required to encode under the low encoding condition was r_L whereas the number of successful steps required to encode under the high encoding condition was r_H. These steps may be considered to be determined by the physical complexity of the input stimulus sequence (e.g., consider encoding a 3-letter word as opposed to a 6-letter word). An alternative model which may be more appropriate in some cases is when the complexity of the input sequence physically stays the same (e.g., always present a 6-letter word) but some quality in the presentation results in a differential encoding load (e.g., present the word in bold face vs. faded) which leads to a differential probability of successfully encoding a step on any try. The diagnostic status of the participant also affects this probability. In this case the number of required encoding steps r remains the same from cell to cell but the probability p_* of successfully encoding a

step on any one try depends on the cell. The number of subprocesses K_i required to encode follows a negative binomial distribution over trials with parameters r and p_*. Hence $E(K_i) = r/p_*$ and $\mathrm{Var}(K_i) = r(1-p_*)/p_*^2$. In order to be consistent with the factorial outcomes of Sec 2.1.1 we have the boundary conditions

$$0 < p_{HS} < p_{HN}, p_{LS} < p_{LN} < 1$$

These boundary conditions imply that there exists $p > 0$, $h > 0$, $g > 0$, and $f > 0$ such that

$$\frac{1}{p_{LN}} = \frac{1}{p}, \;\; \frac{1}{p_{HN}} = \frac{1}{p} + h, \;\; \frac{1}{p_{LS}} = \frac{1}{p} + g, \;\; \frac{1}{p_{HS}} = \frac{1}{p} + f$$

It follows that

$$\begin{aligned} \mathrm{KMIC} &= \left[\left(\frac{r}{p_{HS}} - \frac{r}{p_{HN}}\right) - \left(\frac{r}{p_{LS}} - \frac{r}{p_{LN}}\right) \right] \\ &= r \left[\left(\frac{1}{p} + f\right) - \left(\frac{1}{p} + h\right) - \left\{ \left(\frac{1}{p} + g\right) - \frac{1}{p} \right\} \right] \\ &= r[f - (h+g)] \end{aligned} \tag{2.3.17}$$

so here MIC $= 0$ iff $f = h + g$, which is a possible scenario. We will show that MIC $= 0$ always implies VIC > 0 for this model. First note that

$$p_* = \frac{p}{1 + p x_*} \quad \text{where } x_* = 0, h, g \text{ or } f \text{ depending on the cell } *$$

and furthermore

$$1 - p_* = \frac{1 + p x_* - p}{1 + p x_*}$$

Then it follows that

$$\begin{aligned}
\text{KVIC} &= r\left[\frac{1-p_{HS}}{p_{HS}^2} - \left(\frac{1-p_{HN}}{p_{HN}^2}\right)\right] - r\left[\frac{1-p_{LS}}{p_{LS}^2} - \left(\frac{1-p_{LN}}{p_{LN}^2}\right)\right] \\
&= r\left[\left(\frac{1+pf}{p}\right)^2\left(\frac{1+pf-p}{1+pf}\right) - \left(\frac{1+ph}{p}\right)^2\left(\frac{1+ph-p}{1+ph}\right)\right] \\
&\qquad - r\left[\left(\frac{1+pg}{p}\right)^2\left(\frac{1+pg-p}{1+pg}\right) - \frac{(1-p)}{p^2}\right] \\
&= \frac{r}{p^2}\big\{(1+pf)(1+pf-p) - (1+ph)(1+ph-p) \\
&\qquad - [(1+pg)(1+pg-p) - (1-p)]\,\big\} \\
&= \frac{r}{p^2}\left\{2p[f-(h+g)] - p^2[f-(h+g)] + p^2[f^2-(h^2+g^2)]\right\}
\end{aligned} \tag{2.3.18}$$

Substituting in the restriction $f = h + g$ corresponding to MIC $= 0$ yields

$$\text{KVIC} = r[(h+g)^2 - (h^2+g^2)] = 2rhg \;>\; 0 \tag{2.3.19}$$

so MIC $= 0$ yields

$$\text{VIC} = 2rE^i[\mu(\theta_i)^2]hg \;>\; 0 \tag{2.3.20}$$

Thus this alternative negative binomial model is a candidate for modelling experiments that yield factorial additivity of means and factorial superadditivity of variances.

Example 10: a binomial model: Suppose we have a gen-CN model and assume that there exists $n \geq 1$ such that for each individual there is a set of n underlying subprocesses which could be activated on any encoding trial and, in cell *, p_* is the probability that any one of these subprocesses is activated. We let K_i = number of activated subprocesses for participant i, and assume that this does not depend on i but only the cell probabilities p_*. If the subprocesses are activated independently

of one another then K_i follows a binomial distribution over trials with parameters n and p_* with $E(K_i) = np_*$ and $\text{Var}(K_i) = np_*(1-p_*)$. In order to accommodate the factorial data outcomes $E(T)_*$ we have the boundary conditions

$$0 < p_{LN} < p_{HN}, p_{LS} < p_{HS} < 1$$

We obtain

$$\text{KMIC} = n[(p_{HS} - p_{HN}) - (p_{LS} - p_{LN})] \tag{2.3.21}$$

and

$$\text{KVIC} = n[(p_{HS}(1-p_{HS}) - p_{HN}(1-p_{HN})) - (p_{LS}(1-p_{LS}) - p_{LN}(1-p_{LN}))] \tag{2.3.22}$$

There are many admissible solutions rendering KMIC = 0 and hence MIC = 0; for example, select any $0 < x < 1/4$ and set $p_{LN} = x$, $p_{HN} = 2x$, $p_{LS} = 3x$, and $p_{HS} = 4x$. Then KMIC = 0 and KVIC $= -4nx^2 < 0$ so VIC < 0. In fact we can show that in this model, MIC = 0 always implies VIC < 0. Note that if KMIC = 0 then there must exist x, y, and d such that $p_{LN} = x$, $p_{LS} = x + d$, $p_{HN} = y$, and $p_{HS} = y + d$. Under the usual factorial data outcomes we will have $x < y$ and $d > 0$. Now

$$\begin{aligned}
\text{KVIC} &= n\left[(y+d)(1-(y+d)) - y(1-y) - \{(x+d)(1-(x+d)) - x(1-x)\}\right] \\
&= n\left[(y+d) - (y+d)^2 - y(1-y) - \{(x+d) - (x+d)^2 - x(1-x)\}\right] \\
&= n\left[y + d - y^2 - 2dy - d^2 - y + y^2 - \{x + d - x^2 - 2dx - d^2 - x + x^2\}\right] \\
&= n\left[d - 2dy - d^2 - \{d - 2dx - d^2\}\right] \\
&= -n\left[2d(y-x)\right] \; < \; 0
\end{aligned} \tag{2.3.23}$$

Thus here we always have MIC = 0 implying VIC < 0. Therefore the binomial model is a candidate for modelling those factorial experiments exhibiting factorial additivity of means but factorial subadditivity of variances.

The next model can exhibit VIC < 0 or VIC > 0 depending on the situation when MIC = 0.

Example 11: the truncated Poisson: Assume we have a gen-CN model where, in cell *, K_i follows a truncated Poisson distribution over trials (see Appendix A) with parameter $m_* > 0$. The truncated Poisson can be described as a Poisson distribution conditional on having at least one observation (i.e., at least one subprocess occurs), so the range of K is $k = 1, 2, 3, \ldots$. It follows that

$$E(K_i) = \frac{m_*}{1 - e^{-m_*}} \quad \text{and} \quad \text{Var}(K_i) = \frac{m_*}{1 - e^{-m_*}} - \left(\frac{m_*}{1 - e^{-m_*}}\right)^2 e^{-m_*} \tag{2.3.24}$$

Note that $E(K_i)$ and $\text{Var}(K_i)$ converge rapidly to m_* as m_* increases, and that since the function $f(v) = v/(1 - e^{-v})$ is a 1-1 increasing function over $(0, \infty)$ we have the boundary conditions

$$0 \; < \; m_{LN} \; < \; m_{HN}, m_{LS} \; < \; m_{HS}$$

We obtain

$$\begin{aligned} \text{KMIC} &= (E^i_{HS}[E(K_i)] - E^i_{HN}[E(K_i)]) - (E^i_{LS}[E(K_i)] - E^i_{LN}[E(K_i)]) \\ &= \left(\frac{m_{HS}}{1 - e^{-m_{HS}}} - \frac{m_{HN}}{1 - e^{-m_{HN}}}\right) - \left(\frac{m_{LS}}{1 - e^{-m_{LS}}} - \frac{m_{LN}}{1 - e^{-m_{LN}}}\right) \end{aligned} \tag{2.3.25}$$

so KMIC = 0 is equivalent to the constraint

$$\frac{m_{HS}}{1 - e^{-m_{HS}}} \; = \; \frac{m_{HN}}{1 - e^{-m_{HN}}} + \frac{m_{LS}}{1 - e^{-m_{LS}}} - \frac{m_{LN}}{1 - e^{-m_{LN}}} \tag{2.3.26}$$

which for notational convenience we will rewrite as

$$\frac{z}{1 - e^{-z}} \; = \; \frac{w}{1 - e^{-w}} + \frac{y}{1 - e^{-y}} - \frac{x}{1 - e^{-x}} \tag{2.3.27}$$

Note that the above constraint is invariant under an interchange of w and y. Note that since $f(v) = v/(1 - e^{-v})$ is increasing over $(0, \infty)$ then, given $0 < x < w, y$, there is a unique solution $z > w, y$ to (2.3.27) which can be computed by numerical iteration, thereby rendering MIC = KMIC = 0. Note also that as, $v \to \infty$, $f(v)$ is asymptotic to v, and this asymptotic behaviour is achieved rapidly. Thus, once x is modestly large, the exact constraint (2.3.27) can be approximated well by the easily computable linear constraint

$$z = w + y - x \quad \text{where} \quad w, y > x \tag{2.3.28}$$

which corresponds to the solution to MIC = 0 for the original (non-truncated) Poisson

distribution. Now

$$\begin{aligned}
\text{KVIC} &= (E^i_{HS}[\text{Var}(K_i)] - E^i_{HN}[\text{Var}(K_i)]) - (E^i_{LS}[\text{Var}(K_i)] - E^i_{LN}[\text{Var}(K_i)]) \\
&= \left[\left(\frac{m_{HS}}{1-e^{-m_{HS}}} - \left(\frac{m_{HS}}{1-e^{-m_{HS}}}\right)^2 e^{-m_{HS}}\right)\right. \\
&\qquad \left. - \quad \frac{m_{HN}}{1-e^{-m_{HN}}} - \left(\frac{m_{HN}}{1-e^{-m_{HN}}}\right)^2 e^{-m_{HN}}\right)\Bigg] \\
&\quad - \left[\left(\frac{m_{LS}}{1-e^{-m_{LS}}} - \left(\frac{m_{LS}}{1-e^{-m_{LS}}}\right)^2 e^{-m_{LS}}\right)\right. \\
&\qquad \left. - \quad \frac{m_{LN}}{1-e^{-m_{LN}}} - \left(\frac{m_{LN}}{1-e^{-m_{LN}}}\right)^2 e^{-m_{LN}}\right)\Bigg] \\
&= \text{KMIC} + \left[\left(\frac{m_{HN}}{1-e^{-m_{HN}}}\right)^2 e^{-m_{HN}} - \left(\frac{m_{HS}}{1-e^{-m_{HS}}}\right)^2 e^{-m_{HS}}\right] \\
&\qquad - \left[\left(\frac{m_{LN}}{1-e^{-m_{LN}}}\right)^2 e^{-m_{LN}} - \left(\frac{m_{LS}}{1-e^{-m_{LS}}}\right)^2 e^{-m_{LS}}\right] \\
&= \text{KMIC} + \left[\left(\frac{w}{1-e^{-w}}\right)^2 e^{-w} - \left(\frac{z}{1-e^{-z}}\right)^2 e^{-z}\right] \\
&\qquad - \left[\left(\frac{x}{1-e^{-x}}\right)^2 e^{-x} - \left(\frac{y}{1-e^{-y}}\right)^2 e^{-y}\right]
\end{aligned} \tag{2.3.29}$$

Now $\text{MIC} = 0$ implies $\text{KMIC} = 0$ and so then KVIC reduces to

$$\text{KVIC} = \left[\left(\frac{w}{1-e^{-w}}\right)^2 e^{-w} - \left(\frac{z}{1-e^{-z}}\right)^2 e^{-z}\right] - \left[\left(\frac{x}{1-e^{-x}}\right)^2 e^{-x} - \left(\frac{y}{1-e^{-y}}\right)^2 e^{-y}\right] \tag{2.3.30}$$

where $0 < x < w, y < z$ and (2.3.27) holds. (Note that this expression is invariant to interchange of w and y.) Now for fixed $x > 0$ with $0 < x < w, y < z$ we see that (2.3.27) implies $z \to \infty$ if either $w \to \infty$ or $y \to \infty$ and we obtain

$$\lim_{w,y\to\infty} \text{KVIC} = -\left(\frac{x}{1-e^{-x}}\right)^2 e^{-x} \; < \; 0 \tag{2.3.31}$$

Thus MIC = 0 implies VIC < 0 for sufficiently large w and y. Of course VIC $\to 0$ as $x \to \infty$ and this limit coincides with the original (non-truncated) Poisson distribution where VIC = 0 iff MIC = 0. Moreover the convergence of KVIC to 0 is rapid. Consider the example $x = 5$, $w = 6$, and $y = 8$. Solving (2.3.27) for z yields $z = 8.9825$ (compare this with the value $z = 9$ from the linear approximation (2.3.28)), and we obtain KVIC $= -0.0697$. However, we end this example by noting that VIC is not always negative for MIC = 0. The sign flips to positive for some very small values near the origin. Letting $x = 0.05$, $w = 0.1$, and $y = 0.15$ (this would correspond to a high probability of zero subprocesses occurring for the original (non-truncated) Poisson), we solve (2.3.27) numerically to obtain $z = 0.19845$. This yields KVIC $= 0.000788 > 0$.

We now consider a special type of gen-CN model.

Definition 3: hybrid gen-CN models: These are gen-CN models in which we can partition $K_i = n_i + R_i$ where n is distributed across participants in cell * according to some nonnegative discrete distribution $P_*(n)$ (no variation over trials) and R_i is a nonnegative discrete random variable. The quantity n_i can be interpreted as a minimum on the number of subprocesses that must be executed by participant i (may encompass resting-state subprocesses plus possibly particular task-related subprocesses) and R_i represents additional subprocesses that may arise trial to trial due to a variety of reasons, such as variability of the stimulus input sequence or failure to tag subprocesses as completed.

Corollary 3.3: Suppose we have a hybrid gen-CN model where $K_i = n_i + R_i$. Define

$$\text{nMIC} = (E^i_{HS}[n_i] - E^i_{HN}[n_i]) - (E^i_{LS}[n_i] - E^i_{LN}[n_i]) \tag{2.3.32}$$

$$\text{RMIC} = (E^i_{HS}[E(R_i)] - E^i_{HN}[E(R_i)]) - (E^i_{LS}[E(R_i)] - E^i_{LN}[E(R_i)]) \tag{2.3.33}$$

and

$$\text{RVIC} = (E^i_{HS}[\text{Var}(R_i)] - E^i_{HN}[\text{Var}(R_i)]) - (E^i_{LS}[\text{Var}(R_i)] - E^i_{LN}[\text{Var}(R_i)]) \tag{2.3.34}$$

Then $\text{KMIC} = \text{nMIC} + \text{RMIC}$ and $\text{KVIC} = \text{RVIC}$, and applying Theorem 3 yields

$$\text{MIC} = E^i[\mu(\theta_i)](\text{nMIC} + \text{RMIC}) \tag{2.3.35}$$

and

$$\text{VIC} = E^i[\mu(\theta_i)^2]\text{RVIC} + E^i[\sigma^2(\theta_i)](\text{nMIC} + \text{RMIC}) \tag{2.3.36}$$

proof: Substituting $E(n_i + R_i) = n_i + E(R_i)$ for $E(K_i)$ in (2.3.1) yields KMIC = nMIC+RMIC, whereas noting that $\text{Var}(K_i) = \text{Var}(n_i + R_i) = \text{Var}(R_i)$ yields KVIC = RVIC. Now apply Theorem 3. $\triangle$

The simplest example of a hybrid gen-CN model is a translated Poisson distribution (see Appendix A).

Example 12: translated Poisson: Suppose we have a hybrid gen-CN model where there exists an integer $n \geq 1$ such that $K_i = n + R_i$ and R_i is Poisson over trials with mean m_i where m is distributed across participants in cell * according to some distribution with mean $E^i_*[m_i] = \lambda_*$. Thus K_i follows a translated Poisson distribution with translation factor n. It follows that nMIC = 0 and since $m_i = E(R_i) = \text{Var}(R_i)$

for the Poisson, we obtain

$$\begin{aligned} \text{RMIC} &= (E^i_{HS}[m_i] - E^i_{HN}[m_i]) - (E^i_{LS}[m_i] - E^i_{LN}[m_i]) \\ &= (\lambda_{HS} - \lambda_{HN}) - (\lambda_{LS} - \lambda_{LN}) \\ &= \text{RVIC} \end{aligned} \tag{2.3.37}$$

Thus applying Corollary 3.3 it follows that VIC $= 0$ iff MIC $= 0$ here.

Example 13: Suppose we have a hybrid gen-CN model $K_i = n_i + R_i$ where n is distributed across participants according to some distribution $P_*(n)$ in cell *, and the random variables R_i have the property that the distribution of R across participants in cell LN is the same as that of R across participants in cell HN, and the distribution of R across participants in cell LS is the same as that of R across participants in cell HS. (This assumption describes a model that implies that the number of random additional subprocesses R is driven by diagnostic status alone, a model which would likely posit that individuals with schizophrenia tend to incur more additional "incidental" subprocesses (interpreted here as "errors") above their baseline level n_i than do normal controls.) Thus we obtain $E^i_{LN}[E(R_i)] = E^i_{HN}[E(R_i)]$, $E^i_{LS}[E(R_i)] = E^i_{HS}[E(R_i)]$, $E^i_{LN}[\text{Var}(R_i)] = E^i_{HN}[\text{Var}(R_i)]$, $E^i_{LS}[\text{Var}(R_i)] = E^i_{HS}[\text{Var}(R_i)]$, and consequently RMIC $= 0$ and RVIC $= 0$. Thus Corollary 3.3 yields

$$\text{MIC} = E^i[\mu(\theta_i)]\,\text{nMIC} \quad \text{and} \quad \text{VIC} = E^i[\sigma^2(\theta_i)]\,\text{nMIC} \tag{2.3.38}$$

which coincides with the expressions for MIC and VIC in the gen-CN model *without variation* (i.e., where we remove R_i from the model and simply consider $k_i = n_i$ distributed across participants; see Corollary 3.1). However, despite this equivalence in the final expressions for MIC and VIC, these two models are not equivalent. The

hybrid model allows for more variation in T_i over trials (by varying the number of subprocesses executed on a trial) and also captures a possible qualitative difference between patients and controls.

Example 14: Here we present a variation on Example 13 but with a very different interpretation. Assume $K_i = n_i + R_i$ where the distribution of R_i does not depend on i and moreover, the distribution of R_i over trials is the same in both cells LN and LS (denoted in shorthand by $R_{LN} \overset{\mathcal{D}}{\sim} R_{LS}$), as is the distribution of R_i over trials in cells HN and HS (denoted $R_{HN} \overset{\mathcal{D}}{\sim} R_{HS}$). Recall that the same set of stimuli is presented to all participants in cells LN and LS (low encoding load) whereas a different set of stimuli is presented to all participants in cells HN and HS (high encoding load). Thus this model can be used to describe the situation where there is a certain amount of variability over items in the stimulus input sequence (leading to variability in the number of subprocesses required for encoding on a trial) with that degree of variability potentially depending on the encoding load set. As in Example 13 we obtain RMIC = RVIC = 0, yielding (2.3.38) here as well. However, just as in Example 13, this hybrid model is not equivalent to the corresponding gen-CN model without variation, and indeed an experimenter might be very concerned about a high degree of variability among items in a stimulus set.

Finally we close out this section by presenting a detailed example of a hybrid model.

Example 15: Suppose we have a hybrid gen-CN model $K_i = n_i + R_i$ where n_i follows a translated Poisson distribution (with translation factor $m \geq 1$) across participants in cell $*$ with $E^i_*[n_i] = m + \lambda_*$. Suppose $R_i \overset{\mathcal{D}}{\sim} \text{geom}(p_i)$ over trials where p is distributed

over $(0,1)$ according to a beta distribution with pdf $f(p) = \beta_* p^{\beta_*-1}$ with $\beta^* > 2$ in cell * (see Example 6 for details and calculations). It follows that

$$\text{nMIC} = (\lambda_{HS} - \lambda_{HN}) - (\lambda_{LS} - \lambda_{LN}) \tag{2.3.39}$$

whereas

$$\text{RMIC} = \left[\frac{\beta_{HS}}{\beta_{HS}-1} - \frac{\beta_{HN}}{\beta_{HN}-1}\right] - \left[\frac{\beta_{LS}}{\beta_{LS}-1} - \frac{\beta_{LN}}{\beta_{LN}-1}\right] \tag{2.3.40}$$

and

$$\begin{aligned}\text{RVIC} = &\left[\frac{\beta_{HS}}{(\beta_{HS}-1)(\beta_{HS}-2)} - \frac{\beta_{HN}}{(\beta_{HN}-1)(\beta_{HN}-2)}\right] \\ &- \left[\frac{\beta_{LS}}{(\beta_{LS}-1)(\beta_{LS}-2)} - \frac{\beta_{LN}}{(\beta_{LN}-1)(\beta_{LN}-2)}\right]\end{aligned} \tag{2.3.41}$$

Thus from Corollary 3.3 it follows that

$$\text{MIC} = E^i[\mu(\theta_i)]\,(\text{nMIC} + \text{RMIC}) \tag{2.3.42}$$

and

$$\text{VIC} = E^i[\mu(\theta_i)^2]\,\text{RVIC} + E^i[\sigma^2(\theta_i)]\,(\text{nMIC} + \text{RMIC}) \tag{2.3.43}$$

and the signs of MIC and VIC will depend on the particular values of λ_* and β_*.

In the next section we consider the problem of distinguishing between gen-CN models with and without variation.

2.4 Testing for Variation in Generalized Cutler-Neufeld Models

In the previous section we have seen that gen-CN models without variation always yield the signature VIC = 0 iff MIC = 0 whereas gen-CN models with variation can

also yield that signature or a variety of other MIC-VIC signatures, depending on the specific model. Variation in K_i over trials can be explained by the physical mechanism driving the encoding process (see Examples 7-12) or be due to other sources, such as attentional errors associated with diagnostic status (Example 13) or to variability over items in the stimulus encoding set (Example 14). There is probably no real-world case where there is absolutely no variation in K_i over trials, but it is of interest to detect cases where this variation is substantial enough to be informative. Detecting this variation may give us insight into the physical mechanism guiding the encoding process or, if the source of variation is the stimulus set of the experiment, it may lead the experimenter to modify and more tightly control the input sequence.

The following theorem provides a simple test for the presence of variation in some cases.

Theorem 4: Suppose we have a gen-CN model in which MIC $= 0$ and VIC $\neq 0$. Then this is a gen-CN model *with variation*.

proof: Since MIC $= 0$ implies VIC $= 0$ in gen-CN models without variation (see Corollary 3.1) the observation of MIC $= 0$ with VIC $\neq 0$ implies we have a model with variation. Another way to see this is to note that MIC $= 0 \Rightarrow$ KMIC $= 0$ and thus VIC $\neq 0 \Rightarrow E^i[\mu(\theta_i)^2]$KVIC $\neq 0$, which in turn implies $E^i_*[\mathrm{Var}(K_i)] > 0$ for some cell. Thus $\mathrm{Var}(K_i) > 0$ for at least some participants.

Theorem 4 is so useful because we often have factorial additivity of means (i.e., MIC $= 0$) and given the sample variances of reaction times we can do a test for interaction to determine potential factorial additivity of variances. If we reject additivity of variances, i.e., conclude VIC $\neq 0$, then we have strong evidence that

there is variation over trials.

However, as earlier examples have shown, it is possible to observe MIC = VIC = 0 even when there is variation over trials (see Examples 7 and 12, and also Examples 13 and 14 when nMIC = 0). Thus, observation of MIC = VIC = 0 is not in itself sufficient evidence of no variation. In the following we develop a technique which can aid in elucidating whether variation exists which may be applied in general, even when VIC = 0. In order to apply this technique, however, we need to assume that we have obtained the actual encoding times of each participant. We discuss this further after stating and proving the following theorem.

Theorem 5: Suppose we have a gen-CN model. If the ratio $E(\mathrm{Var}(T))_*/E(T)_*$ varies depending on the cell *, then we have a gen-CN model with variation.

proof: From (2.3.5) and (2.3.6) of Theorem 3 we obtain

$$E(\mathrm{Var}(T))_* = E^i[\mu(\theta_i)^2]E^i_*[\mathrm{Var}(K_i)] + E^i_*[E(K_i)]E^i[\sigma^2(\theta_i)] \tag{2.4.1}$$

and

$$E(T)_* = E^i_*[E(K_i)]E^i[\mu(\theta_i)] \tag{2.4.2}$$

and thus the ratio

$$\begin{aligned} \frac{E(\mathrm{Var}(T))_*}{E(T)_*} &= \frac{E^i[\mu(\theta_i)^2]E^i_*[\mathrm{Var}(K_i)] + E^i_*[E(K_i)]E^i[\sigma^2(\theta_i)]}{E^i_*[E(K_i)]E^i[\mu(\theta_i)]} \\ &= b\,\frac{E^i_*[\mathrm{Var}(K_i)]}{E^i_*[E(K_i)]} \;+\; c \end{aligned} \tag{2.4.3}$$

where for convenience here we set

$$b = \frac{E^i[\mu(\theta_i)^2]}{E^i[\mu(\theta_i)]} \quad \text{and} \quad c = \frac{E^i[\sigma^2(\theta_i)]}{E^i[\mu(\theta_i)]} \tag{2.4.4}$$

Obviously, if there is no variation over trials, then $\mathrm{Var}(K_i) = 0$ for each participant and the ratio (2.4.3) is a constant over cells (and specifically equals c). Thus if (2.4.3)

differs over at least two cells, this implies there must be variation over trials for at least some participants. $\triangle$

Now, in terms of applying Theorem 5 using sample data, we assume that for each participant i we have their actual encoding times $t_{i1}, \ldots, t_{iN}$ based on N trials. Over these N trials we compute the sample mean $\bar{t}_i$ and sample (intertrial) variance s_i^2 for each participant i. We then estimate $E(T)_*$ by $\bar{t}_* = (\sum_{i=1}^{M} \bar{t}_i)/M$ and $E(\mathrm{Var}(T))_*$ by $\bar{s_*^2} = (\sum_{i=1}^{M} s_i^2)/M$, where M is the number of participants per cell. Then we have the following:

Corollary 5.1: Suppose we have a gen-CN model. Define the sample ratio r_* by $r_* = \bar{s_*^2}/\bar{t}_*$. Then

$$\lim_{M\to\infty} \lim_{N\to\infty} r_* = \frac{E(\mathrm{Var}(T))_*}{E(T)_*} \quad \text{with probability 1} \tag{2.4.5}$$

provided $0 < E(T)_* < \infty$ and $E(\mathrm{Var}(T))_* < \infty$. If r_* differs in a statistically significant fashion over at least two cells, then we have strong evidence that this is a gen-CN model with variation.

proof: see Appendix C. $\triangle$

In the following examples we fix the sample sizes at $N = 200$ and $M = 100$ for an individual experiment, regarding these as feasible experimental values, and then repeat the experiment 500 times. This enables us to calculate the average ratio $\bar{r_*}$ in each cell over the 500 repetitions, as well as calculate the sample standard deviation sd_* of the 500 ratios for each cell. This will provide an idea, in a single experiment, of the extent to which differences between ratios in various cells are due to genuine differences or due to statistical error. We will see that the choice of base distribution

significantly affects the statistical error, and the conclusion is, not surprisingly, that N and M should be made as large as possible to reduce this unwanted error.

In all of the following examples, models and parameter values have been chosen so that MIC = VIC = 0 so that Theorem 4 cannot be applied to assess the presence of variation over trials. All numerical work was carried out using the **R** statistical programming language (**R**(2013)). We examined two base distributions – the exponential(θ) in which a rate parameter θ was generated randomly from a Gam$(30, 10)$ distribution for each participant, and a lognormal distribution LN(θ, Σ^2) in which we fixed $\Sigma = 1$ and generated θ randomly from a normal $N(0, 1)$ distribution for each participant. In the case of the exponential base with the above parameter values, the statistical error was generally small and Corollary 5.1 worked well; in the case of the lognormal base with the above parameter values, the statistical variation was large, and greater values of M and N would be required to draw reliable conclusions from a single experiment. This is likely due to the thicker tail of the lognormal distribution.

Note that in the case of the exponential base with rate $\theta \overset{\mathcal{D}}{\sim}$ Gam$(30, 10)$ and in the case of a lognormal base LN$(\theta, 1)$ where $\theta \overset{\mathcal{D}}{\sim} N(0, 1)$, it is possible to explicitly calculate the theoretical constants b and c in (2.4.4), yielding

$$b_{\text{expo}} = c_{\text{expo}} = .35714 \quad \text{and} \quad b_{\text{lognorm}} = 7.389,\ c_{\text{lognorm}} = 12.696 \tag{2.4.6}$$

Thus, for any chosen distribution on the number of subprocesses K, it is then possible to explicitly calculate the theoretical ratios

$$\frac{E(\text{Var}(T))_*}{E(T)_*} = b\,\frac{E_*^i[\text{Var}(K_i)]}{E_*^i[E(K_i)]} \ + \ c \tag{2.4.7}$$

for our two chosen base distributions. These can then be compared with the obtained simulated average ratios $\bar{r_*}$ in each cell. In the following tables, the first row of numbers consist of the simulated average ratios $\bar{r_*}$ in each cell, accompanied by the sample standard deviation over the 500 repetitions in that cell. The second row of numbers consists of the (true) theoretical ratios (2.4.7) in each cell.

Example 16: Here we used the exponential base, and there is no variation over trials; k varied only over participants with parameter λ_* depending on the cell. We actually used a translated Poisson $k = 1 + x$ where $x \overset{\mathcal{D}}{\sim} \text{Pois}(\lambda_*)$ with parameters $\lambda_{LN} = 2, \lambda_{HN} = 5, \lambda_{LS} = 20$, and $\lambda_{HS} = 23$. (These parameter choices yield MIC = VIC = 0.) The reason for using the translated Poisson was simply to avoid the possibility of an entire vector of 0s and hence a zero encoding time. The results are presented in Table 2.1.

Table 2.1: k Poisson without variation over trials (exponential base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
.357	.0097	.357	.0090	.356	.0085	.358	.0087
.357		.357		.357		.357	

Example 17: Here we used the exponential base, and there is no variation over trials; k followed a geometric distribution over participants with parameter p_* depending on the cell. We employed $p_{LN} = 1/2, p_{HN} = 1/6, p_{LS} = 1/20$, and $p_{HS} = 1/24$ (these parameter values result in MIC = VIC = 0). The results are presented in Table 2.2. Note that the standard deviations are very small in both Examples 16 and 17, and that accurate results would likely be obtained with a single experiment. The stability of the sample ratios across cells is suggestive of a model without variation in both

Table 2.2: k geometric without variation over trials (exponential base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
.357	.0112	.358	.0120	.356	.0115	.358	.0115
.357		.357		.357		.357	

examples. Also note that the sample ratios in both examples yield approximately the same value .357, which is the common value c_{expo} in (2.4.7) (the theoretical ratio here).

Example 18: This is Example 16 (Poisson without variation over trials) repeated with the lognormal base in place of the exponential base. The results are presented in Table 2.3.

Table 2.3: k Poisson without variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
12.3	6.00	12.3	5.61	12.2	6.00	12.1	5.96
12.7		12.7		12.7		12.7	

Example 19: This is Example 17 (geometric without variation over trials) repeated with the lognormal base. The results are presented in Table 2.4.

Table 2.4: k geometric without variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
12.0	9.72	11.5	5.84	11.9	7.09	12.2	9.34
12.7		12.7		12.7		12.7	

Note that for both Examples 18 and 19 the average cell ratios (computed over 500 repetitions of the experiment) yield an approximate value of 12 (which provide a slight underestimate of the true value c_{lognorm} in (2.4.7)). However, the standard

deviations are comparatively large, and a single experiment (with the given values of $N = 200$ and $M = 100$) might give the appearance of significant differences between ratios in cells and produce misleading results.

We now consider some examples where K_i is varying over trials. The first point to note is that the Poisson distribution is in a special position because it satisfies $\mathrm{Var}(K_i) = E(K_i)$ and hence the ratios will not vary over cells. In fact any integer multiple $X_i = nK_i$ of a Poisson distribution K_i will share this property, since $\mathrm{Var}(X_i) = \mathrm{Var}(nK_i) = n^2\mathrm{Var}(K_i) = n^2E(K_i) = nE(nK_i) = nE(X_i)$. Thus Theorem 5 will not pick up variation over trials in the case of a Poisson or any of its integer multiples. We illustrate this with the following.

Example 20: Here K_i follows a Pois(λ_*) distribution over trials with no variation over participants, and the exponential base is used. The cell parameters are $\lambda_{LN} = 2, \lambda_{HN} = 5, \lambda_{LS} = 20$, and $\lambda_{HS} = 23$, yielding MIC = VIC = 0. The results are presented in Table 2.5. Note that the standard deviations are very small and the ratios very stable across cells. The simulated mean cell ratios of approximately .714 exactly match the theoretical ratio $b_{\text{expo}} + c_{\text{expo}}$ of (2.4.7).

Table 2.5: K Poisson with variation over trials (exponential base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
.714	.0176	.715	.0178	.714	.0178	.715	.0170
.714		.714		.714		.714	

Example 21: Translated Poisson distributions do not share the special position of the Poisson and its integer multiples. Specifically, if K_i is a translated Poisson distribution varying over trials, then Theorem 5 may pick up this variation provided the standard

deviations are small. Here we consider the exponential base and $K_i = 5 + X_i$ where $X_i \overset{\mathcal{D}}{\sim} \text{Pois}(\lambda_*)$ over trials with cell parameters λ_* identical to those of Example 20. The results are presented in Table 2.6. Note that the cell ratios are small, but the difference between the largest ratio and the smallest ratio is well outside twice the standard deviations, indicating that a single experiment will pick up genuine differences. Note the close match with the theoretical ratios (2.4.7).

Table 2.6: K translated Poisson with variation over trials (exponential base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
.459	.0111	.536	.0125	.642	.0154	.652	.0170
.459		.536		.643		.651	

Example 22: Here we consider the case where K_i follows a geometric(p_*) distribution over trials with the exponential base and no variation over participants. The parameter values are $p_{LN} = p_{LS} = .5$ and $p_{HN} = p_{HS} = .05$ (representing the situation where successful encoding depends only on encoding load) which yields MIC = VIC = 0. The results are presented in Table 2.7. Note the sharp deviations between the cell ratios, well outside the scope of the standard deviations, and the close match with the theoretical ratios.

Table 2.7: K geometric with variation over trials (exponential base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
.715	.018	7.15	.194	.715	.020	7.15	.198
.714		7.14		.714		7.14	

Example 23: Here we consider the case where K_i follows a binomial distribution over trials (no variation over participants) with the exponential base. We assume there

are a maximum of $n = 100$ subprocesses which could be activated, with schizophrenia patients activating a subprocess with probability $p_{LS} = p_{HS} = .8$ and normal controls activating a subprocess with probability $p_{LN} = p_{HN} = .2$, yielding MIC = VIC = 0. The results are presented in Table 2.8.

Table 2.8: K binomial with variation over trials (exponential base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
.644	.0154	.643	.0148	.428	.0100	.429	.0100
.643		.643		.429		.429	

Note that the difference between the largest and smallest cell ratios is well outside the range of the standard deviations, indicating that a single experiment would pick up genuine differences. Also note the close match with the theoretical ratios.

Example 24: Here we consider a hybrid model (see Definition 3) where K_i varies over both trials and participants. We express $K_i = n_i + R_i$ where n varies over participants according to a Poisson distribution with parameters $\lambda_{LN} = 2, \lambda_{HN} = 5, \lambda_{LS} = 20, \lambda_{HS} = 23$, and R_i follows a geometric distribution over trials with $p_{LN} = p_{LS} = .7$ and $p_{HN} = p_{HS} = .2$. The exponential base is assumed. The results are presented in Table 2.9.

Table 2.9: K hybrid Poisson-geometric with variation over trials (exponential base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
.421	.012	1.07	.032	.367	.009	.612	.016
.421		1.07		.367		.612	

Again we have a close match with the theoretical ratios and see that standard deviations are sufficiently small that a single experiment would pick up genuine dif-

ferences between the cell ratios. However, as noted in Examples 18 and 19, this need not be true if we alter the base distribution. Changing the base distribution can lead to differences that are purely the result of statistical error. We illustrate this further with the following example.

Example 25: Here we repeat Example 20 (K_i Poisson over trials) with the lognormal base. The results are presented in Table 2.10. We see that, whereas the cell mean

Table 2.10: K Poisson with variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
18.6	7.49	19.0	7.03	19.4	10.88	20.4	11.78
20.1		20.1		20.1		20.1	

ratios (over 500 repetitions) are stable at about a value of 19 (representing a slight underestimate of the theoretical value $b_{\text{lognorm}} + c_{\text{lognorm}} = 20.1$ in (2.4.7)), the sample standard deviations are large so that a single experiment might return highly variable ratios over cells, leading the experimenter to conclude there is variation over trials. Ironically such an occurrence would lead to the correct conclusion (since there *is* variation over trials) even though theoretically this technique should actually fail at detecting the case of random Poisson trials.

We now repeat Examples 21-24 using the lognormal base in place of the exponential base. We see that the mean cell ratios correctly pick up the variation over trials (which can be verified by comparing with the standard errors of these means, given by $sd_{\text{mean}*} = sd_*/\sqrt{500}$) but that the individual cell standard deviations sd_* are so large in some cases as to possibly blur these differences on a single experiment. We also note that the simulated cell ratios consistently slightly underestimate the true

theoretical ratios in the case of the lognormal base.

Example 26: Here we repeat Example 21 (K_i translated Poisson over trials) using the lognormal base. The results are presented in Table 2.11. Note that the mean cell ratios reveal some differences (as they should) but their actual values on a single experiment would probably be blurred by the large standard deviations. Nonetheless the conclusion based on a single experiment would likely be that variation over trials exists.

Table 2.11: K translated Poisson with variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
14.1	5.33	15.9	9.95	18.3	14.37	17.9	8.76
14.8		16.4		18.6		18.8	

Example 27: Here we repeat Example 22 (K_i geometric over trials) with a lognormal base, and the results are presented in Table 2.12.

Table 2.12: K geometric with variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
19.7	11.82	148.7	68.62	19.7	11.41	150.1	76.47
20.1		153.1		20.1		153.1	

The cell mean ratios differ sharply here, correctly indicating variation over trials, and these marked differences would almost certainly be observed by a single experiment, although a blurring of the actual values due to the standard deviations might occur.

Example 28: Here we repeat Example 23 (K_i binomial over trials) with the lognormal base. The results are presented in Table 2.13. The cell mean ratios correctly

Table 2.13: K binomial with variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
17.8	8.87	18.1	8.78	13.6	5.95	13.5	5.62
18.6		18.6		14.2		14.2	

pick up the differences and hence the variation over trials but the standard deviations may blur the actual values in the outcome of a single experiment.

Example 29: Here we repeat Example 24 (K_i hybrid Poisson-geometric) with the lognormal base, and the results are presented in Table 2.14.

Table 2.14: K hybrid Poisson-geometric with variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
13.5	9.11	27.1	15.44	11.9	4.37	17.1	6.33
14.0		27.5		12.9		18.0	

Again we see marked mean cell differences but large standard deviations.

Note: We have seen that the choice of base distribution can introduce considerable variability into the individual cell ratios, so that a single experiment may produce incorrect or inconclusive results. The most significant effect of large standard deviations is to create the appearance of differences between cell ratios even when there is none (leading the experimenter to erroneously conclude there is variation over trials when such is not the case). The experimenter is less likely to erroneously conclude that there is no variation over trials when such variation is in fact present, although large standard deviations can blur the differences between cells and lead to incorrect estimates of cell ratios. The most effective method of reducing error is to increase the number of trials N per participant as well as the number of participants M per

cell to the greatest degree possible, since obviously repeating the experiment hundreds of times is not possible. However, considerable increases in N and M may be necessary to reduce the standard deviations to suitable levels. By way of illustrating that this method works in principle, we increased N and M to the values $N = 1000$ and $M = 500$ in Examples 18 and 19. Note the reduced (yet still large) standard deviations presented below:

Example 30: This is Example 18 (Poisson without variation over trials) repeated for $N = 1000$ and $M = 500$. The results are presented in Table 2.15. Contrast this with Table 2.3.

Table 2.15: k Poisson without variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
12.6	3.50	12.7	4.50	12.6	3.44	12.4	2.56
12.7		12.7		12.7		12.7	

Example 31: This is Example 19 (geometric without variation over trials) repeated for $N = 1000$ and $M = 500$. The results are presented in Table 2.16. Contrast this with Table 2.4.

Table 2.16: k geometric without variation over trials (lognormal base)

$\bar{r}_{LN}$	sd_{LN}	$\bar{r}_{HN}$	sd_{HN}	$\bar{r}_{LS}$	sd_{LS}	$\bar{r}_{HS}$	sd_{HS}
12.3	4.02	12.7	5.61	12.3	3.98	12.4	4.31
12.7		12.7		12.7		12.7	

Note that, in addition to the reduced standard deviations, Examples 30 and 31 exhibit improved convergence of the simulated mean ratios to the theoretical ratios; specifically, the downward bias of the simulated values seen in Examples 18 and 19 is

noticeably decreased. Further increases in N and M would result in further improved convergence and further reduction in the standard deviations.

2.5 Results for Models with Varying Θ

In Secs 2.3 and 2.4 we focused attention on generalized Cutler-Neufeld (gen-CN) models which are specific members of the class of general serial mixture models (Sec 2.2) having the special property that the only quantity whose distribution differs depending on the cell * is the number of subprocesses K. In various factorial experiments involving schizophrenia patients and controls, gen-CN models have seemed sufficient to capture the changes across cells in mean encoding times $E(T)_*$ and average intertrial variances $E(\mathrm{Var}(T))_*$. However, many other models might be selected from the class of general serial mixture models (not just for modelling encoding times in schizophrenia, but potentially other cognitive processes as well). In particular, we might question the favoured position being delegated to K in gen-CN models, and wonder whether changes in the distribution of the vector Θ over cells might better describe observed data. This changes the focus from the number of subprocesses K to the encoding speed (governed by Θ) of individual subprocesses. However, the definition of Θ depends explicitly on the choice of base distribution; thus to work with Θ we must first select a particular base distribution (which was not the case for gen-CN models). Having to choose a base distribution is not a barrier to obtaining results; however, it does mean that results need to be derived on a case-by-case basis.

We now proceed to determine MIC-VIC signatures for a variety of serial mixture models with different choices of base and Θ. Throughout these derivations we

make the assumption that $K_i = k_i$ does not vary over trials, and that the distribution of k across participants is the same in every cell. Instead it will be Θ that is allowed to vary across trials, participants, and cells. This amounts to a reversal of the roles of K and Θ from that of gen-CN models.

2.5.1 Gamma Base with Varying Rate Parameter V

Here we choose a gamma base (see Appendix B) with accompanying vector $\Theta = (A, V)$ where A denotes the shape parameter and V denotes the rate parameter. It will be too complex to cope with both A and V varying over trials and cells, so in this subsection we assume it is only V which is allowed to vary in that manner. This leads to the following:

Theorem 6: Let ℓ_{ij} follow a gamma base distribution with $\Theta_i = (a_i, V_i)$ where the rate parameter V_i is allowed to vary over trials and participants within a cell as well as to vary across cells. The shape parameter a_i can vary over participants within a cell but not over trials, and moreover must follow the same distribution in each cell. We also assume that the number of subprocesses k_i can vary over participants in a cell but not over trials, and must follow the same distribution in each cell. Further assume that the random processes a_i, V_i, and k_i act independently of each other over participants and trials. Define

$$\text{IVMIC} = (E^i_{HS}[E(1/V_i)] - E^i_{HN}[E(1/V_i)]) - (E^i_{LS}[E(1/V_i)] - E^i_{LN}[E(1/V_i)]) \quad (2.5.1)$$

and

$$\text{IVVIC} = (E^i_{HS}[\text{Var}(1/V_i)] - E^i_{HN}[\text{Var}(1/V_i)]) - (E^i_{LS}[\text{Var}(1/V_i)] - E^i_{LN}[\text{Var}(1/V_i)]) \quad (2.5.2)$$

and

$$\text{IVSQMIC} = (E^i_{HS}[E(1/V_i^2)] - E^i_{HN}[E(1/V_i^2)]) - (E^i_{LS}[E(1/V_i^2)] - E^i_{LN}[E(1/V_i^2)]) \tag{2.5.3}$$

Then

$$\text{MIC} = E^i[k_i]E^i[a_i]\text{IVMIC} \tag{2.5.4}$$

and

$$\text{VIC} = E^i[k_i^2]E^i[a_i^2]\text{IVVIC} \ + \ E^i[k_i]E^i[a_i]\text{IVSQMIC} \tag{2.5.5}$$

note: The prefactor "IV" in the notation above stands for "Inverse of V".

proof: For the gamma base distribution $\mu(\Theta_i) = a_i/V_i$ and $\sigma^2(\Theta_i) = a_i/V_i^2$. Plugging into (2.2.10) and using the independence of the processes we obtain

$$\begin{aligned} E(T)_* &= E^i_*[E(K_i)]E^i_*[E(a_i/V_i)] \\ &= E^i[k_i]E^i_*[a_iE(1/V_i)] \\ &= E^i[k_i]E^i[a_i]E^i_*[E(1/V_i)] \end{aligned} \tag{2.5.6}$$

so

$$\begin{aligned} \text{MIC} &= (E(T)_{HS} - E(T)_{HN}) - (E(T)_{LS} - E(T)_{LN}) \\ &= E^i[k_i]E^i[a_i]\text{IVMIC} \end{aligned} \tag{2.5.7}$$

Similarly, plugging into (2.2.11), we obtain

$$\begin{aligned} E(\text{Var}(T))_* &= E^i[k_i^2]E^i_*[\text{Var}(a_i/V_i)] + E^i[k_i]E^i_*[E(a_i/V_i^2)] \\ &= E^i[k_i^2]E^i_*[a_i^2\text{Var}(1/V_i)] + E^i[k_i]E^i_*[a_iE(1/V_i^2)] \\ &= E^i[k_i^2]E^i[a_i^2]E^i_*[\text{Var}(1/V_i)] + E^i[k_i]E^i[a_i]E^i_*[E(1/V_i^2)] \end{aligned} \tag{2.5.8}$$

Then

$$\begin{aligned} \text{VIC} &= (E(\text{Var}(T))_{HS} - E(\text{Var}(T))_{HN}) - (E(\text{Var}(T))_{LS} - E(\text{Var}(T))_{LN}) \\ &= E^i[k_i^2]E^i[a_i^2]\text{IVVIC} \ + \ E^i[k_i]E^i[a_i]\text{IVSQMIC} \quad \text{as claimed. } \triangle \end{aligned} \tag{2.5.9}$$

In the corollary below we consider the subcase where $V_i = v_i$ does not vary over trials.

Corollary 6.1: Suppose the premise of Theorem 6 holds. Further suppose v_i varies only over participants and cells with no variation over trials. Then $\text{Var}(1/V_i) = \text{Var}(1/v_i) = 0$ for each participant, yielding $\text{IVVIC} = 0$. Thus

$$\text{MIC} = E^i[k_i]E^i[a_i]\text{IVMIC} \tag{2.5.10}$$

and

$$\text{VIC} = E^i[k_i]E^i[a_i]\text{IVSQMIC} \quad \triangle \tag{2.5.11}$$

The following two examples illustrate the application of Corollary 6.1.

Example 32: Assume the premises of Theorem 6 and Corollary 6.1 both hold. Consider the case where v follows a $\text{Gam}(u, r_*)$ distribution across participants in cell *, i.e., the shape parameter $u > 2$ stays the same for each cell but the rate parameter r_* varies. Then we know that

$$E^i_*[1/v_i] = \frac{r_*}{u-1} \quad \textit{and} \quad E^i_*[1/v_i^2] = \frac{r_*^2}{(u-1)(u-2)}$$

Let r, h, g, f be defined by $r_{LN} = r,\ r_{HN} = r + h,\ r_{LS} = r + g$, and $r_{HS} = r + f$. Note that (2.5.6) plus the usual factorial data assumptions implies $h > 0, g > 0$, and $f > 0$. Then

$$\begin{aligned} \text{IVMIC} &= (E^i_{HS}[1/v_i] - E^i_{HN}[1/v_i]) - (E^i_{LS}[1/v_i)] - E^i_{LN}[1/v_i]) \\ &= \left[\frac{r_{HS}}{u-1} - \frac{r_{HN}}{u-1}\right] - \left[\frac{r_{LS}}{u-1} - \frac{r_{LN}}{u-1}\right] \\ &= \frac{1}{u-1}[f - (h+g)] \end{aligned} \tag{2.5.12}$$

and

$$\begin{aligned}\text{IVSQMIC} &= (E^i_{HS}[1/v_i^2] - E^i_{HN}[1/v_i^2]) - (E^i_{LS}[1/v_i^2] - E^i_{LN}[1/v_i^2]) \\ &= \left[\frac{r^2_{HS}}{(u-1)(u-2)} - \frac{r^2_{HN}}{(u-1)(u-2)}\right] - \left[\frac{r^2_{LS}}{(u-1)(u-2)} - \frac{r^2_{LN}}{(u-1)(u-2)}\right] \\ &= \frac{1}{(u-1)(u-2)}\left[(r+f)^2 - (r+h)^2 - \{(r+g)^2 - r^2\}\right] \\ &= \frac{1}{(u-1)(u-2)}\left[2r[f-(h+g)] + f^2 - (h^2+g^2)\right]\end{aligned} \tag{2.5.13}$$

Since IVMIC $= 0$ iff $f = h + g$, substituting this constraint into IVSQMIC yields

$$\text{IVSQMIC} = \frac{2hg}{(u-1)(u-2)} \;>\; 0 \tag{2.5.14}$$

so MIC $= 0$ implies VIC > 0 always in this model.

note: Consider the case of the Erlang model, which has the exponential base (a special case of the gamma where $a_i = 1$ for all participants) and the two parameters k and v. The Neufeld model extends the Erlang to the case where k and v are both allowed to vary over participants in each cell. One can then make a choice – attempt to explain changes in $E(T)_*$ and $E(\text{Var}(T))_*$ by changes in k over cells, or attempt to explain changes in $E(T)_*$ and $E(\text{Var}(T))_*$ by changes in v over cells. The first choice (which was the choice made by Neufeld) leads to the signature VIC $= 0$ iff MIC $= 0$ (see Corollary 3.1) whereas the second choice, when assigning v a $\text{Gam}(u, r_*)$ distribution (recall Neufeld used a fixed gamma distribution to describe v in each cell) leads to VIC > 0 whenever MIC $= 0$ (Example 32). This shows that, if we assume the premise of a basic Neufeld model, factorial data which supports additivity in both means and variances suggests that neurophysiological changes due to schizophrenia and encoding load are explained by increases in the number of subprocesses k required

for encoding, whereas factorial data which supports additivity in means but super-additivity of variances suggests that neurophysiological changes due to schizophrenia and encoding load are explained by decreases in the rate v at which subprocesses are executed.

The above note describes the possible choice between two models and the resulting interpretation of neurophysiological processes, but it is also important to realize that Example 32 specifically assumed a $\text{Gam}(u, r_*)$ distribution on v. The conclusions of that example can be altered by changing the behaviour of v, as we do in the next example. There we retain a gamma distribution on v but introduce a relationship between the rate parameter r_* and the shape parameter u_*.

Example 33: Consider a modification of Example 32 where $v \overset{\mathcal{D}}{\sim} \text{Gam}(u_*, r_*)$ and there exists some $\beta > 0$ such that $r_* = \beta(u_* - 2)$. The shape parameter u_* can vary over $(2, \infty)$ which results in r_* varying over $(0, \infty)$. The connection between the parameters introduces a linear relationship between $E^i_*[1/v_i^2]$ and $E^i_*[1/v_i]$; specifically $E^i_*[1/v_i^2] = \beta E^i_*[1/v_i]$. To see this, note that

$$E^i_*[1/v_i] = \frac{r_*}{u - 1} = \frac{\beta(u_* - 2)}{u_* - 1} \tag{2.5.15}$$

and

$$E^i_*[1/v_i^2] = \frac{r_*^2}{(u_* - 1)(u_* - 2)} = \frac{\beta^2(u_* - 2)^2}{(u_* - 1)(u_* - 2)} = \beta\left(\frac{\beta(u_* - 2)}{u_* - 1}\right) = \beta E^i_*[1/v_i] \tag{2.5.16}$$

Applying this yields

$$\begin{aligned}\text{IVSQMIC} &= (E^i_{HS}[1/v_i^2] - E^i_{HN}[1/v_i^2]) - (E^i_{LS}[1/v_i^2] - E^i_{LN}[1/v_i^2]) \\ &= (\beta E^i_{HS}[1/v_i] - \beta E^i_{HN}[1/v_i]) - (\beta E^i_{LS}[1/v_i] - \beta E^i_{LN}[1/v_i]) \qquad (2.5.17) \\ &= \beta\,\text{IVMIC}\end{aligned}$$

Thus IVSQMIC $= 0$ iff IVMIC $= 0$, yielding VIC $= 0$ iff MIC $= 0$.

Note: There are some restrictions to the applicability of Example 33. Note from (2.5.15) that $E^i_*[1/v_i]$ is an increasing function of u_* but is bounded above by an asymptote at β, i.e., $0 < E^i_*[1/v_i] < \beta$. Applying (2.5.6), this in turn implies the restriction $0 < E(T)_* < E^i[k_i]E^i[a_i]\,\beta$ which must be considered when applying the model to data. Moreover, the asymptote at β for $E^i_*[1/v_i]$ sometimes precludes the possibility of a solution to MIC $= 0$. In order to see this, for convenience in this example let $c_* = E^i_*[1/v_i]$. Now suppose we have $0 < c_{LN} < c_{LS} < c_{HN} < c_{HS} < \beta$ where $c_{LS} - c_{LN} > \beta/2$. This forces $c_{LS} > \beta/2$ and thus $c_{HS} - c_{HN} < \beta - \beta/2 = \beta/2$. This results in IVMIC < 0 whenever this pattern arises. However, there are other circumstances which produce solutions to IVMIC $= 0$. For example, suppose $0 < c_{LN} < c_{LS} < c_{HN} < \beta/2$. Then $c_{LS} - c_{LN} = b < \beta/2$ and it follows that $c_{HN} + b < \beta/2 + \beta/2 = \beta$ which implies that $c_{HN} + b$ is an admissible value for c_{HS}. Setting $c_{HS} = c_{HN} + b$ yields IVMIC $= 0$. Similarly, if $0 < c_{LN} < c_{HN} < c_{LS} < \beta/2$ then once again $c_{LS} - c_{LN} = b < \beta/2$ and setting $c_{HS} = c_{HN} + b$ yields a solution to IVMIC $= 0$.

In the next two examples, V_i varies over trials rather than participants.

Example 34: Assume the premise of Theorem 6 holds. Suppose the rate parameter V_i follows an inverse Gaussian distribution over trials (no variation over participants)

in each cell, with the assumption that the shape parameter λ is fixed in each cell whereas the mean μ_* shifts from cell to cell, i.e., $V_i \overset{\mathcal{D}}{\sim} \mathrm{IG}(\mu_*, \lambda)$ in cell *. For convenience let $\phi_* = 1/\mu_*$ and $\psi = 1/\lambda$. It follows that

$$E(1/V_i) = \phi_* + \psi, \quad \mathrm{Var}(1/V_i) = \psi\phi_* + 2\psi^2, \quad E(1/V_i^2) = \phi_*^2 + 3\psi\phi_* + 3\psi^2 \tag{2.5.18}$$

Then, setting $m = \phi_{LN}$ and defining h, g, f by $\phi_{HN} = m + h$, $\phi_{LS} = m + g$, and $\phi_{HS} = m + f$, yields

$$\begin{aligned} \mathrm{IVMIC} &= (E^i_{HS}[E(1/V_i)] - E^i_{HN}[E(1/V_i)]) - (E^i_{LS}[E(1/V_i)] - E^i_{LN}[E(1/V_i)]) \\ &= (\phi_{HS} - \phi_{HN}) - (\phi_{LS} - \phi_{LN}) \\ &= f - (h + g) \end{aligned} \tag{2.5.19}$$

and also

$$\begin{aligned} \mathrm{IVVIC} &= (E^i_{HS}[\mathrm{Var}(1/V_i)] - E^i_{HN}[\mathrm{Var}(1/V_i)]) - (E^i_{LS}[\mathrm{Var}(1/V_i)] - E^i_{LN}[\mathrm{Var}(1/V_i)]) \\ &= \psi[(\phi_{HS} - \phi_{HN}) - (\phi_{LS} - \phi_{LN})] \\ &= \psi[f - (h + g)] \end{aligned} \tag{2.5.20}$$

Therefore IVVIC $= 0$ iff IVMIC $= 0$. However

$$\begin{aligned} \mathrm{IVSQMIC} &= (E^i_{HS}[E(1/V_i^2)] - E^i_{HN}[E(1/V_i^2)]) - (E^i_{LS}[E(1/V_i^2)] - E^i_{LN}[E(1/V_i^2)]) \\ &= [(\phi_{HS}^2 + 3\psi\phi_{HS}) - (\phi_{HN}^2 + 3\psi\phi_{HN})] - [(\phi_{LS}^2 + 3\psi\phi_{LS}) - (\phi_{LN}^2 + 3\psi\phi_{LN})] \\ &= 2m[f - (h + g)] + f^2 - (h^2 + g^2) + 3\psi[f - (h + g)] \end{aligned} \tag{2.5.21}$$

so substituting in $f = h + g$ always yields

$$\mathrm{IVSQMIC} = 2hg \ > \ 0 \tag{2.5.22}$$

so MIC $= 0$ always implies VIC > 0.

Note: We can impose different relationships between μ_* and λ_* to produce other results; for example, if the mean and shape parameter are identical in each cell but change from cell to cell, then it can easily be seen that IVMIC $= 0$ implies both IVVIC > 0 and IVSQMIC > 0 as illustrated below:

Example 35: Assume the premise of Theorem 6 holds. Suppose the rate parameter V_i follows an inverse Gaussian distribution over trials (no variation over participants) in each cell, with the assumption that the mean and shape parameters coincide in each cell and shift from cell to cell, i.e., $V_i \overset{\mathcal{D}}{\sim} \text{IG}(\lambda_*, \lambda_*)$ in cell *. For convenience let $\phi_* = 1/\lambda_*$. It follows that

$$E(1/V_i) = 2\phi_*, \quad \text{Var}(1/V_i) = 3\phi_*^2, \quad E(1/V_i^2) = 7\phi_*^2 \tag{2.5.23}$$

Then

$$\begin{aligned} \text{IVMIC} &= (E^i_{HS}[E(1/V_i)] - E^i_{HN}[E(1/V_i)]) - (E^i_{LS}[E(1/V_i)] - E^i_{LN}[E(1/V_i)]) \\ &= 2[(\phi_{HS} - \phi_{HN}) - (\phi_{LS} - \phi_{LN})] \\ &= 2[f - (h + g)] \end{aligned} \tag{2.5.24}$$

where we define m, h, g, f as in Example 34. Then also

$$\begin{aligned} \text{IVVIC} &= (E^i_{HS}[\text{Var}(1/V_i)] - E^i_{HN}[\text{Var}(1/V_i)]) - (E^i_{LS}[\text{Var}(1/V_i)] - E^i_{LN}[\text{Var}(1/V_i)]) \\ &= 3[(\phi^2_{HS} - \phi^2_{HN}) - (\phi^2_{LS} - \phi^2_{LN})] \\ &= 3\left[2m[f - (h + g)] + f^2 - (h^2 + g^2)\right] \end{aligned} \tag{2.5.25}$$

and similarly

$$\begin{aligned}\text{IVSQMIC} &= (E^i_{HS}[E(1/V_i^2)] - E^i_{HN}[E(1/V_i^2)]) - (E^i_{LS}[E(1/V_i^2)] - E^i_{LN}[E(1/V_i^2)]) \\ &= 7\,[2m[f-(h+g)] + f^2 - (h^2+g^2)]\end{aligned} \tag{2.5.26}$$

so substituting in $f = h + g$ always yields

$$\text{IVVIC} = 6hg \;>\; 0 \quad \text{and} \quad \text{IVSQMIC} = 14hg \;>\; 0 \tag{2.5.27}$$

so MIC $= 0$ always implies VIC > 0.

2.5.2 Gamma Base with Varying Shape Parameter A

Here we assume ℓ_{ij} follows a gamma base distribution with vector $\Theta_i = (A_i, v_i)$, i.e., $\ell_{ij} \overset{\mathcal{D}}{\sim} \text{Gam}(A_i, v_i)$, where A_i may vary across participants, trials, and cells, whereas v_i can only vary across participants with the same distribution in each cell. Thus we are simply reversing the rules for A_i and v_i from the previous subsection. This yields the following:

Theorem 7: Here we assume $\ell_{ij} \overset{\mathcal{D}}{\sim} \text{Gam}(A_i, v_i)$ where the shape parameter A_i is allowed to vary over trials and participants within a cell as well as vary across cells. The rate parameter v_i can vary over participants within a cell but not over trials, and moreover must follow the same distribution in each cell. We also assume that the number of subprocesses k_i can vary over participants in a cell but not over trials, and must follow the same distribution in each cell. Further assume that the random processes A_i, v_i, and k_i act independently of each other over participants and trials. Define

$$\text{AMIC} = (E^i_{HS}[E(A_i)] - E^i_{HN}[E(A_i)]) - (E^i_{LS}[E(A_i)] - E^i_{LN}[E(A_i)]) \tag{2.5.28}$$

and

$$\text{AVIC} = (E^i_{HS}[\text{Var}(A_i)] - E^i_{HN}[\text{Var}(A_i)]) - (E^i_{LS}[\text{Var}(A_i)] - E^i_{LN}[\text{Var}(A_i)]) \quad (2.5.29)$$

Then

$$\text{MIC} = E^i[k_i]E^i[1/v_i]\text{AMIC} \quad (2.5.30)$$

and

$$\text{VIC} = E^i[1/v_i^2]\left\{E^i[k_i^2]\text{AVIC} + E^i[k_i]\text{AMIC}\right\} \quad (2.5.31)$$

Therefore if MIC = 0 the sign of VIC depends on the sign of AVIC.

proof: For the gamma base distribution $\mu(\Theta_i) = A_i/v_i$ and $\sigma^2(\Theta_i) = A_i/v_i^2$. Plugging into (2.2.10) and using the independence of the processes we obtain

$$\begin{aligned} E(T)_* &= E^i_*[E(K_i)]E^i_*[E(A_i/v_i)] \\ &= E^i[k_i]E^i_*[(1/v_i)E(A_i)] \\ &= E^i[k_i]E^i[1/v_i]E^i_*[E(A_i)] \end{aligned} \quad (2.5.32)$$

so

$$\begin{aligned} \text{MIC} &= (E(T)_{HS} - E(T)_{HN}) - (E(T)_{LS} - E(T)_{LN}) \\ &= E^i[k_i]E^i[1/v_i]\text{AMIC} \end{aligned} \quad (2.5.33)$$

Similarly, plugging into (2.2.11), we obtain

$$\begin{aligned} E(\text{Var}(T))_* &= E^i[k_i^2]E^i_*[\text{Var}(A_i/v_i)] + E^i[k_i]E^i_*[E(A_i/v_i^2)] \\ &= E^i[k_i^2]E^i_*[(1/v_i^2)\text{Var}(A_i)] + E^i[k_i]E^i_*[(1/v_i^2)E(A_i)] \\ &= E^i[k_i^2]E^i[1/v_i^2]E^i_*[\text{Var}(A_i)] + E^i[k_i]E^i[1/v_i^2]E^i_*[E(A_i)] \\ &= E^i[1/v_i^2]\left\{E^i[k_i^2]E^i_*[\text{Var}(A_i)] + E^i[k_i]E^i_*[E(A_i)]\right\} \end{aligned} \quad (2.5.34)$$

Then

$$\begin{aligned}
\text{VIC} &= (E(\text{Var}(T))_{HS} - E(\text{Var}(T))_{HN}) - (E(\text{Var}(T))_{LS} - E(\text{Var}(T))_{LN}) \\
&= E^i[1/v_i^2]E^i[k_i^2]\left\{(E^i_{HS}[\text{Var}(A_i)] - E^i_{HN}[\text{Var}(A_i)])\right. \\
&\qquad \left. - (E^i_{LS}[\text{Var}(A_i)] - E^i_{LN}[\text{Var}(A_i)])\right\} \\
&+ E^i[1/v_i^2]E^i[k_i]\left\{(E^i_{HS}[E(A_i)] - E^i_{HN}[E(A_i)]) - (E^i_{LS}[E(A_i)] - E^i_{LN}[E(A_i)])\right\} \\
&= E^i[1/v_i^2]\left\{E^i[k_i^2]\text{AVIC} + E^i[k_i]\text{AMIC}\right\} \quad \text{as claimed. } \triangle
\end{aligned} \tag{2.5.35}$$

Corollary 7.1: Suppose the premise of Theorem 7 holds. Further suppose A_i varies only over participants with no variation over trials. Then $\text{Var}(A_i) = 0$ for each participant, yielding AVIC = 0. Thus VIC reduces to VIC $= E^i[1/v_i^2]E^i[k_i]$AMIC and so VIC = 0 iff MIC = 0. $\triangle$

Corollary 7.1 shows that the signature VIC = 0 iff MIC = 0 is obtained in the case of a gamma base distribution where a_i, v_i, and k_i vary only over participants, and the shifting in $E(T)_*$ across cells is explained by shifting the distribution of a_i. Thus this model is a competitor for a gen-CN model without variation (using a gamma base, e.g., the Cutler-Neufeld model) where the shifting in $E(T)_*$ across cells is explained by shifting the distribution of k_i (see Corollary 3.1). Here the two models mimic each other.

We now consider a series of examples with a gamma base where A_i varies only over trials. We employ different positive distributions for A_i since, as a shape parameter, A_i must satisfy $A_i > 0$. We have chosen to model A_i with continuous distributions (as would most likely be done in practice) but there is no reason discrete distributions could not be employed. The quantities m, h, g, and f that are defined

in some of these examples (whose values depend on the example) are always positive due to (2.5.32) and the shifting values of $E(T)_*$ in our factorial models.

Example 36: $\mathbf{A_i}$ follows a gamma distribution over trials with shifting shape parameter and fixed rate parameter: Assume the premise of Theorem 7 holds. Suppose that, in cell *, A_i follows a gamma distribution over trials (no variation over participants) with shape parameter a_* and fixed rate parameter b, i.e., $A_i \overset{\mathcal{D}}{\sim} \text{Gam}(a_*, b)$. Then

$$E(A_i) = \frac{a_*}{b} \quad \text{and} \quad \text{Var}(A_i) = \frac{a_*}{b^2} \tag{2.5.36}$$

Thus

$$\begin{aligned} \text{AMIC} &= (E^i_{HS}[E(A_i)] - E^i_{HN}[E(A_i)]) - (E^i_{LS}[E(A_i)] - E^i_{LN}[E(A_i)]) \\ &= (1/b)[(a_{HS} - a_{HN}) - (a_{LS} - a_{LN})] \end{aligned} \tag{2.5.37}$$

and

$$\begin{aligned} \text{AVIC} &= (E^i_{HS}[\text{Var}(A_i)] - E^i_{HN}[\text{Var}(A_i)]) - (E^i_{LS}[\text{Var}(A_i)] - E^i_{LN}[\text{Var}(A_i)]) \\ &= (1/b^2)[(a_{HS} - a_{HN}) - (a_{LS} - a_{LN})] \\ &= (1/b)\text{AMIC} \end{aligned} \tag{2.5.38}$$

Thus AVIC = 0 iff AMIC = 0 and so VIC = 0 iff MIC = 0.

Note that Example 36, where A_i is varying over trials, produces the same MIC-VIC signature as the case where a_i varies only over participants (Corollary 7.1) but these models are not equivalent as the former produces more variability in the trials T_i.

Example 37: $\mathbf{A_i}$ follows a gamma distribution over trials with fixed shape parameter and shifting rate parameter: Assume the premise of Theorem 7 holds. In cell *, let A_i follow a gamma distribution over trials (no variation over participants)

with fixed shape parameter a and shifting rate parameter b_*, i.e., $A_i \overset{\mathcal{D}}{\sim} \text{Gam}(a, b_*)$ in cell *. Then

$$E(A_i) = \frac{a}{b_*} \quad \text{and} \quad \text{Var}(A_i) = \frac{a}{b_*^2} \tag{2.5.39}$$

and setting $m = \frac{1}{b_{LN}}$, $\frac{1}{b_{HN}} = m+h$, $\frac{1}{b_{LS}} = m+g$, and $\frac{1}{b_{HS}} = m+f$ yields

$$\begin{aligned} \text{AMIC} &= (E^i_{HS}[E(A_i)] - E^i_{HN}[E(A_i)]) - (E^i_{LS}[E(A_i)] - E^i_{LN}[E(A_i)]) \\ &= a[(1/b_{HS} - 1/b_{HN}) - (1/b_{LS} - 1/b_{LN})] \\ &= a[f - (h+g)] \end{aligned} \tag{2.5.40}$$

and

$$\begin{aligned} \text{AVIC} &= (E^i_{HS}[\text{Var}(A_i)] - E^i_{HN}[\text{Var}(A_i)]) - (E^i_{LS}[\text{Var}(A_i)] - E^i_{LN}[\text{Var}(A_i)]) \\ &= a[(1/b^2_{HS} - 1/b^2_{HN}) - (1/b^2_{LS} - 1/b^2_{LN})] \\ &= a[((m+f)^2 - (m+h)^2) - ((m+g)^2 - m^2)] \\ &= a[2m[f - (h+g)] + f^2 - (h^2 + g^2)] \end{aligned} \tag{2.5.41}$$

Now AMIC $= 0$ iff $f = h + g$ and substituting this constraint into AVIC yields

$$\text{AVIC} = 2ahg > 0 \tag{2.5.42}$$

Thus MIC $= 0$ always implies VIC > 0 here.

Example 38: $\mathbf{A_i}$ follows an inverse Gaussian distribution over trials with shifting mean and fixed shape parameter: Assume the premise of Theorem 7 holds. Here we assume that, in cell *, A_i follows an inverse Gaussian distribution over trials (no variation over participants) with mean a_* and fixed shape parameter b, i.e., $A_i \overset{\mathcal{D}}{\sim} \text{IG}(a_*, b)$ in cell *. Then

$$E(A_i) = a_* \quad \text{and} \quad \text{Var}(A_i) = \frac{a_*^3}{b} \tag{2.5.43}$$

so

$$\begin{aligned}\text{AMIC} &= (E^i_{HS}[E(A_i)] - E^i_{HN}[E(A_i)]) - (E^i_{LS}[E(A_i)] - E^i_{LN}[E(A_i)]) \\ &= (a_{HS} - a_{HN}) - (a_{LS} - a_{LN}) \\ &= f - (h + g)\end{aligned} \tag{2.5.44}$$

where we set $m = a_{LN}$ and $a_{HN} = m + h$, $a_{LS} = m + g$, and $a_{HS} = m + f$. Then

$$\begin{aligned}\text{AVIC} &= (E^i_{HS}[\text{Var}(A_i)] - E^i_{HN}[\text{Var}(A_i)]) - (E^i_{LS}[\text{Var}(A_i)] - E^i_{LN}[\text{Var}(A_i)]) \\ &= \frac{1}{b}[(a^3_{HS} - a^3_{HN}) - (a^3_{LS} - a^3_{LN})] \\ &= \frac{1}{b}[((m+f)^3 - (m+h)^3) - ((m+g)^3 - m^3)] \\ &= \frac{1}{b}[3m^2[f - (h+g)] + 3m[f^2 - (h^2 + g^2)] + f^3 - (h^3 + g^3)]\end{aligned} \tag{2.5.45}$$

Since AMIC $= 0$ iff $f = h + g$, substituting this constraint into AVIC yields

$$\begin{aligned}\text{AVIC} &= \frac{1}{b}[3m[(h+g)^2 - (h^2 + g^2)] + (h+g)^3 - (h^3 + g^3)] \\ &= \frac{1}{b}[3m(2hg) + 3(h^2 g + hg^2)] \\ &= \frac{1}{b}(3hg)[2m + h + g] > 0\end{aligned} \tag{2.5.46}$$

Thus MIC $= 0$ always implies VIC > 0.

Note: We do not consider the case of the inverse Gaussian where we hold the mean fixed and only shift the shape parameter, since in this case $E(A_i) = a$ is the same in all four cells, rendering $E(T)_{HS} = E(T)_{HN} = E(T)_{LS} = E(T)_{LN}$ which is not of any practical interest.

Example 39: $\mathbf{A_i}$ follows a lognormal distribution over trials with shifting associated normal mean and fixed associated normal variance: Assume the premise of Theorem 7 holds. In cell *, let A_i follow a lognormal distribution over trials

(no variation over participants) with an associated normal mean a_* and associated normal variance b^2, i.e., $A_i \overset{\mathcal{D}}{\sim} \text{LN}(a_*, b^2)$ in cell *. Then

$$E(A_i) = e^{a_* + \frac{b^2}{2}} = e^{a_*} e^{\frac{b^2}{2}} \quad \text{and} \quad \text{Var}(A_i) = e^{2a_* + b^2}(e^{b^2} - 1) = e^{2a_*} e^{b^2}(e^{b^2} - 1) \tag{2.5.47}$$

Setting $m = e^{a_{LN}}$ and defining h, g, f by $e^{a_{HN}} = m + h$, $e^{a_{LS}} = m + g$, and $e^{a_{HS}} = m + f$, we obtain

$$\begin{aligned} \text{AMIC} &= (E^i_{HS}[E(A_i)] - E^i_{HN}[E(A_i)]) - (E^i_{LS}[E(A_i)] - E^i_{LN}[E(A_i)]) \\ &= e^{\frac{b^2}{2}}[(e^{a_{HS}} - e^{a_{HN}}) - (e^{a_{LS}} - e^{a_{LN}})] \\ &= e^{\frac{b^2}{2}}[f - (h + g)] \end{aligned} \tag{2.5.48}$$

and

$$\begin{aligned} \text{AVIC} &= (E^i_{HS}[\text{Var}(A_i)] - E^i_{HN}[\text{Var}(A_i)]) - (E^i_{LS}[\text{Var}(A_i)] - E^i_{LN}[\text{Var}(A_i)]) \\ &= e^{b^2}(e^{b^2} - 1)[(e^{2a_{HS}} - e^{2a_{HN}}) - (e^{2a_{LS}} - e^{2a_{LN}})] \\ &= e^{b^2}(e^{b^2} - 1)[((m + f)^2 - (m + h)^2) - ((m + g)^2 - m^2)] \\ &= e^{b^2}(e^{b^2} - 1)[2m[f - (h + g)] + f^2 - (h^2 + g^2)] \end{aligned} \tag{2.5.49}$$

Since MIC $= 0$ iff $f = h + g$, substituting this constraint into AVIC yields

$$\text{AVIC} = 2e^{b^2}(e^{b^2} - 1)hg > 0 \tag{2.5.50}$$

so MIC $= 0$ always implies VIC > 0.

Example 40: $\mathbf{A_i}$ follows a lognormal distribution over trials with fixed associated normal mean and shifting associated normal variance: Assume the premise of Theorem 7 holds. In cell *, let A_i follow a lognormal distribution over trials (no variation over participants) with an associated normal mean a and associated normal variance b_*^2, i.e., $A_i \overset{\mathcal{D}}{\sim} \text{LN}(a, b_*^2)$ in cell *. Then

$$E(A_i) = e^{a + \frac{b_*^2}{2}} = e^a e^{\frac{b_*^2}{2}} \quad \text{and} \quad \text{Var}(A_i) = e^{2a + b_*^2}(e^{b_*^2} - 1) = e^{2a} e^{b_*^2}(e^{b_*^2} - 1) \tag{2.5.51}$$

Setting $m = e^{\frac{b_{LN}^2}{2}}$ and $e^{\frac{b_{HN}^2}{2}} = m + h$, $e^{\frac{b_{LS}^2}{2}} = m + g$, and $e^{\frac{b_{HS}^2}{2}} = m + f$, we obtain

$$\begin{aligned}
\text{AMIC} &= (E^i_{HS}[E(A_i)] - E^i_{HN}[E(A_i)]) - (E^i_{LS}[E(A_i)] - E^i_{LN}[E(A_i)]) \\
&= e^a[(e^{\frac{b_{HS}^2}{2}} - e^{\frac{b_{HN}^2}{2}}) - (e^{\frac{b_{LS}^2}{2}} - e^{\frac{b_{LN}^2}{2}})] \qquad (2.5.52) \\
&= e^a[f - (h + g)] \qquad \text{and}
\end{aligned}$$

$$\begin{aligned}
\text{AVIC} &= e^{2a}[(e^{b_{HS}^2}(e^{b_{HS}^2} - 1) - e^{b_{HN}^2}(e^{b_{HN}^2} - 1)) - (e^{b_{LS}^2}(e^{b_{LS}^2} - 1) - e^{b_{LN}^2}(e^{b_{LN}^2} - 1))] \\
&= e^{2a}[(m + f)^2[(m + f)^2 - 1] - (m + h)^2[(m + h)^2 - 1]] \\
&\quad - e^{2a}[(m + g)^2[(m + g)^2 - 1] - m^2[m^2 - 1]] \\
&= e^{2a}\left\{((m + f)^4 - (m + h)^4) - ((m + g)^4 - m^4)\right. \\
&\quad \left. - (m + f)^2 + (m + h)^2 + (m + g)^2 - m^2\right\} \\
&= e^{2a}[4m^3[f - (h + g)] + 6m^2[f^2 - (h^2 + g^2)] + 4m[f^3 - (h^3 + g^3)] \\
&\quad + e^{2a}[f^4 - (h^4 + g^4)] - 2m[f - (h + g)] - [f^2 - (h^2 + g^2)]] \\
&= e^{2a}[(4m^3 - 2m)[f - (h + g)] + (6m^2 - 1)[f^2 - (h^2 + g^2)]] \\
&\quad + e^{2a}[4m[f^3 - (h^3 + g^3)] + f^4 - (h^4 + g^4)] \qquad (2.5.53)
\end{aligned}$$

Since MIC $= 0$ iff $f = h + g$, substituting this constraint into AVIC yields

$$\begin{aligned}
\text{AVIC} &= e^{2a}[(6m^2 - 1)[(h + g)^2 - (h^2 + g^2)] + 4m[(h + g)^3 - (h^3 + g^3)] \\
&\quad + e^{2a}[(h + g)^4 - (h^4 + g^4)] \qquad (2.5.54) \\
&= e^{2a}[(6m^2 - 1)[2hg] + 12m[h^2g + hg^2] + 4[h^3g + hg^3] + 6h^2g^2] \\
&= e^{2a}(2hg)[(6m^2 - 1) + 6m(h + g) + 2(h^2 + g^2) + 3hg] \ > \ 0
\end{aligned}$$

so MIC $= 0$ always implies VIC > 0. (Note that $m > 1$ always in this example.)

Example 41: $\mathbf{A_i}$ follows a Weibull distribution over trials with shifting scale parameter and fixed shape parameter: Assume that the premise of Theorem 7 holds. Suppose that, in cell *, A_i follows a Weibull distribution over trials (no variation over participants) with shape parameter a and scale parameter b_*, i.e., $A_i \overset{\mathcal{D}}{\sim} \text{Wei}(a, b_*)$ in cell *. Then

$$E(A_i) = b_*\Gamma(1+1/a) \quad \text{and} \quad \text{Var}(A_i) = b_*^2\left\{\Gamma(1+2/a) - (\Gamma(1+1/a))^2\right\} \tag{2.5.55}$$

Set $m = b_{LN}$ and define h, g, f by $b_{HN} = m+h$, $b_{LS} = m+g$, and $b_{HS} = m+f$. Then

$$\begin{aligned}\text{AMIC} &= (E^i_{HS}[E(A_i)] - E^i_{HN}[E(A_i)]) - (E^i_{LS}[E(A_i)] - E^i_{LN}[E(A_i)]) \\ &= \Gamma(1+1/a)[(b_{HS} - b_{HN}) - (b_{LS} - b_{LN})] \\ &= \Gamma(1+1/a)[f - (h+g)]\end{aligned} \tag{2.5.56}$$

Now

$$\begin{aligned}\text{AVIC} &= (E^i_{HS}[\text{Var}(A_i)] - E^i_{HN}[\text{Var}(A_i)]) - (E^i_{LS}[\text{Var}(A_i)] - E^i_{LN}[\text{Var}(A_i)]) \\ &= \left\{\Gamma(1+2/a) - (\Gamma(1+1/a))^2\right\}[((m+f)^2 - (m+h)^2) - ((m+g)^2 - m^2)] \\ &= \left\{\Gamma(1+2/a) - (\Gamma(1+1/a))^2\right\}[2m[f - (h+g)] + f^2 - (h^2+g^2)]\end{aligned} \tag{2.5.57}$$

Now AMIC $= 0$ iff $f = h + g$ and substituting this constraint into AVIC yields

$$\text{AVIC} = 2\left\{\Gamma(1+2/a) - (\Gamma(1+1/a))^2\right\} hg > 0 \tag{2.5.58}$$

Thus MIC $= 0$ always implies VIC > 0.

Note: So far we have seen, in the case of a gamma base with a varying shape parameter, and with the the notable and important exceptions of Corollary 7.1 and Example 36 where the signature VIC $= 0$ iff MIC $= 0$ is obtained, in all other

examples MIC $= 0$ implied VIC > 0. The latter tends to occur because of the definition of AVIC and the fact that variances tend to skew concave upward because of the squaring operation. However, in the case where A_i follows a Weibull distribution with fixed scale parameter but shifting shape parameter, it can be shown that whereas many cases with MIC $= 0$ do result in VIC > 0, this is not universally true; there exist specific solutions where MIC $= 0$ yields VIC < 0. One is illustrated below.

Example 42: $\mathbf{A_i}$ follows a Weibull distribution over trials with fixed scale parameter and specific varied shape parameter values: Assume the premise of Theorem 7 holds. Suppose that, in cell *, A_i follows a Weibull distribution over trials (no variation over participants) with scale parameter b and specific shape parameters a_*, i.e., $A_i \overset{\mathcal{D}}{\sim} \text{Wei}(a_*, b)$ in cell *. Then

$$E(A_i) = b\,\Gamma(1+1/a_*) \quad \text{and} \quad \text{Var}(A_i) = b^2\left\{\Gamma(1+2/a_*) - (\Gamma(1+1/a_*))^2\right\} \tag{2.5.59}$$

For convenience we define $x_* = 1/a_*$ and set $x_{LN} = 0.46$, $x_{HN} = 0.56$, and $x_{LS} = 0.66$. Then define $m_{LN} = \Gamma(1.46) = 0.8856$, $m_{HN} = \Gamma(1.56) = 0.8896$, and $m_{LS} = \Gamma(1.66) = 0.9017$. Now the result MIC $= 0$ is equivalent to the constraint

$$m_{HS} = m_{HN} + m_{LS} - m_{LN} = 0.8896 + 0.9017 - 0.8856 = 0.9057 \tag{2.5.60}$$

Solving numerically yields $\Gamma(1.684) = 0.9057$ so $x_{HS} = 0.684$ corresponds to MIC $= 0$ here. We can then compute

$$\begin{aligned}\text{AVIC} &= (E^i_{HS}[\text{Var}(A_i)] - E^i_{HN}[\text{Var}(A_i)]) - (E^i_{LS}[\text{Var}(A_i)] - E^i_{LN}[\text{Var}(A_i)]) \\ &= b^2[(0.3965 - 0.2654) - (0.3678 - 0.1845)] \\ &= -b^2(0.0522) \;<\; 0\end{aligned} \tag{2.5.61}$$

Thus the possibility VIC < 0 when MIC $= 0$ does arise here.

2.5.3 Inverse Gaussian Base with Varying Mean M

Here we choose an inverse Gaussian base (see Appendix B) with accompanying vector $\Theta = (M, \Lambda)$ where M denotes the mean of the distribution and Λ denotes the shape parameter. We will restrict consideration to the case where only M is allowed to vary over cells. This leads to the following

Theorem 8: Here we assume ℓ_{ij} follows an inverse Gaussian base distribution with $\Theta_i = (M_i, \lambda_i)$ where the mean M_i is allowed to vary over trials and participants within a cell as well as vary across cells. The shape parameter λ_i can vary over participants within a cell but not over trials, and moreover must follow the same distribution in each cell. We also assume that the number of subprocesses k_i can vary over participants in a cell but not over trials, and must follow the same distribution in each cell. Further assume that the random processes M_i, λ_i, and k_i act independently of each other over participants and trials. Define

$$\text{MMIC} = (E^i_{HS}[E(M_i)] - E^i_{HN}[E(M_i)]) - (E^i_{LS}[E(M_i)] - E^i_{LN}[E(M_i)]) \quad (2.5.62)$$

and

$$\text{MVIC} = (E^i_{HS}[\text{Var}(M_i)] - E^i_{HN}[\text{Var}(M_i)]) - (E^i_{LS}[\text{Var}(M_i)] - E^i_{LN}[\text{Var}(M_i)]) \quad (2.5.63)$$

and

$$\text{MCUMIC} = (E^i_{HS}[E(M_i^3)] - E^i_{HN}[E(M_i^3)]) - (E^i_{LS}[E(M_i^3)] - E^i_{LN}[E(M_i^3)]) \quad (2.5.64)$$

Then

$$\text{MIC} = E^i[k_i]\text{MMIC} \quad (2.5.65)$$

and

$$\text{VIC} = E^i[k_i^2]\text{MVIC} + E^i[k_i]E^i[1/\lambda_i]\text{MCUMIC} \tag{2.5.66}$$

proof: For the inverse Gaussian distribution $\mu(\Theta_i) = M_i$ and $\sigma^2(\Theta_i) = M_i^3/\lambda_i$. Using (2.2.10) we obtain

$$E(T)_* = E^i[k_i]E^i_*[E(M_i)] \tag{2.5.67}$$

and using (2.2.11) we obtain

$$E(\text{Var}(T))_* = E^i[k_i^2]E^i_*[\text{Var}(M_i)] + E^i_*[k_i]E^i[1/\lambda_i]E^i_*[E(M_i^3)] \tag{2.5.68}$$

from which the results follow. $\triangle$

The following two examples are illustrations of Theorem 8.

Example 43: Assume the premise of Theorem 8 holds. Suppose M_i does not vary over trials but does vary over participants in cell * according to a $\text{Gam}(a_*, b)$ distribution. Then $\text{Var}(M_i) = 0$ so $\text{MVIC} = 0$ and we have $M_i = m_i$ with

$$E^i_*[m_i] = \frac{a_*}{b} \quad \text{and} \quad E^i_*[m_i^3] = \frac{(a_*+2)(a_*+1)a_*}{b^3} \tag{2.5.69}$$

Setting $m = a_{LN}$ and defining h, g, f by $a_{HN} = m+h$, $a_{LS} = m+g$, and $a_{HS} = m+f$ (note $h > 0, g > 0, f > 0$ as usual using (2.5.67)), we obtain

$$\text{MMIC} = \frac{1}{b}[f - (h+g)] \tag{2.5.70}$$

and

$$\begin{aligned}\text{MCUMIC} &= \frac{1}{b^3}\{[(m+f+2)(m+f+1)(m+f) - (m+h+2)(m+h+1)(m+h)] \\ &\qquad - [(m+g+2)(m+g+1)(m+g) - (m+2)(m+1)m]\} \\ &= \frac{1}{b^3}\big\{f^3 - (h^3+g^3) + (3m+3)[f^2 - (h^2+g^2)] \\ &\qquad + (3m^2+6m+2)[f-(h+g)]\big\}\end{aligned} \tag{2.5.71}$$

Substituting in $f = h + g$ yields

$$\text{MCUMIC} = \frac{3}{b^3}hg(h+g+2m+2) \ > \ 0 \tag{2.5.72}$$

so MIC $= 0$ implies VIC > 0.

Example 44: Assume the premise of Theorem 8 holds. Suppose M_i varies over trials according to an exponential distribution with rate c_i, i.e., $M_i \overset{\mathcal{D}}{\sim} \text{expo}(c_i)$. For convenience let $a_i = 1/c_i$ and suppose a varies over participants in cell * according to a gamma distribution where $a \overset{\mathcal{D}}{\sim} \text{Gam}(\alpha, b_*)$. Then

$$E(M_i) = a_i, \quad \text{Var}(M_i) = a_i^2, \quad E(M_i^3) = 6a_i^3$$

and setting $d_* = 1/b_*$ yields

$$E_*^i[E(M_i)] = E_*^i[a_i] = \alpha d_*\,, \qquad E_*^i[\text{Var}(M_i)] = E_*^i[a_i^2] = \alpha(\alpha+1)d_*^2$$

and

$$E_*^i[E(M_i^3)] = E_*^i[6a_i^3] = 6\alpha(\alpha+1)(\alpha+2)d_*^3$$

Set $m = d_{LN}$ and define h, g, f by $d_{HN} = m + h\,, d_{LS} = m + g$, and $d_{HS} = m + f$. Note that $h > 0, g > 0, f > 0$ as usual by (2.5.67). Then

$$\text{MMIC} = \alpha[(d_{HS} - d_{HN}) - (d_{LS} - d_{LN})] = \alpha[f - (h+g)] \tag{2.5.73}$$

and

$$\begin{aligned} \text{MVIC} &= \alpha(\alpha+1)[(d_{HS}^2 - d_{HN}^2) - (d_{LS}^2 - d_{LN}^2)] \\ &= \alpha(\alpha+1)[2m[f-(h+g)] + f^2 - (h^2+g^2)] \end{aligned} \tag{2.5.74}$$

whereas

$$\begin{aligned} \text{MCUMIC} &= 6\alpha(\alpha+1)(\alpha+2)[(d_{HS}^3 - d_{HN}^3) - (d_{LS}^3 - d_{LN}^3)] \\ &= 6\alpha(\alpha+1)(\alpha+2)\big\{f^3 - (h^3+g^3) + 3m[f^2-(h^2+g^2)] \\ &\qquad + 3m^2[f-(h+g)]\big\} \end{aligned} \tag{2.5.75}$$

Substituting in $f = h + g$ yields both

$$\text{MVIC} = 2\alpha(\alpha+1)hg \ > \ 0 \tag{2.5.76}$$

and

$$\text{MCUMIC} = 18\alpha(\alpha+1)(\alpha+2)(hg)(h+g+2m) \ > \ 0 \tag{2.5.77}$$

Thus MIC $= 0$ always implies VIC > 0 here.

Note that expressions for MIC and VIC can always be developed for other base distributions and varying choices of Θ simply by employing the general expressions for cell means and variances given by (2.2.10) and (2.2.11). Here in Sec 2.5 we have attempted to produce relatively simple expressions for MIC and VIC by holding the distribution of k and that of at least one component of the vector Θ constant over trials and cells. For example, in Theorem 8, only M_i was allowed to vary over trials and cells. However, if one is willing to accept more complicated expressions for MIC and VIC, then one can allow other quantities to vary over trials and/or cells as well, and simply plug into (2.2.10) and (2.2.11).

2.6 Discussion and Future Directions

Encoding is the mental process by which a cognitive task is transformed into an internal representation which facilitates carrying out the task at hand. In this chapter we observed that, for patients with schizophrenia, encoding latencies are prolonged as compared to those of normal controls whereas other mental operations, such as making comparisons with memory sets, and executing a response time, are spared by the disease process. Moreover, the prolonged encoding times in schizophrenia are even seen in comparison to other psychiatric controls (such as patients with major depressive disorder) with the greatest increase found among schizophrenia patients with paranoid symptoms (delusions and hallucinations). Thus prolonged encoding times appear to be an earmark of the schizophrenia disease process.

In this chapter we also reviewed the outcomes of 2×2 factorial experiments in which encoding load (low vs. high) and health diagnostic status (normal vs. schizophrenia) were manipulated. These experiments were always seen to feature factorial additivity of means (MIC = 0) whereas we might observe factorial additivity of variances (VIC = 0) or factorial nonadditivity of variances (VIC $\neq$ 0) depending on the experiment. The persistent observation of MIC = 0 suggests that the total encoding time can be broken down into a sum of encoding times of individual subprocesses (a serial model). Previously developed models (the Erlang model, Neufeld model, and Cutler-Neufeld model) were in fact examples of such serial models which featured the signature VIC = 0 if and only if (iff) MIC = 0, and were suitable to describe the outcomes of certain factorial experiments. The goal of this chapter was

to develop a much broader class of serial models which could address a variety of factorial experimental paradigms with differing MIC-VIC signatures. The general serial mixture models of Sec 2.2 are the class that emerged from this pursuit. This class allows the individual subprocess encoding times to be distributed according to any continuous positive infinite-tailed distribution (called the base distribution) whereas the Erlang and Neufeld models both utilized an exponential base. This new flexibility in base distribution is not only potentially useful for modelling encoding times but for application to modelling other cognitive processes which may follow different distributions. The serial mixture models of Sec 2.2 also feature the innovation of the Neufeld model whereby parameter values are allowed to vary according to participant (thus incorporating heretofore "exogenous model noise" into the model itself, leading to Bayesian mixture models) but extend beyond this to further allow parameter values to vary from trial to trial. The value of the latter is particularly seen when considering the number of subprocesses K_i executed by the i^{th} participant on any given trial. It is easy to posit physical (and neurophysiological) mechanisms which would lead to K_i varying from trial to trial. One such mechanism is the stimulus set of the experiment itself, where there may be variability in the encoding requirements of individual items in the set. Sec 2.3 presents examples of other mechanisms which can lead to variability in K_i over trials. Sec 2.5 focuses on cases where the parameter Θ of the base distribution itself varies over trials, representing the situation in which the encoding speed of a subprocess increases or decreases depending on the trial.

One main sequela of the development of the general serial mixture models of Sec 2.2 was the derivation of general closed-form expressions for the mean encoding

time $E(T)_*$ and average intertrial variance $E(\mathrm{Var}(T))_*$ in each cell. These expressions allow us to derive the form of MIC and VIC for any general serial mixture model. Of course under many circumstances these expressions can be quite complicated, so in Secs 2.3 and 2.5 we focus on special cases where particularly elegant and simple expressions for MIC and VIC can be obtained. In Sec 2.3 we consider the special case of what we call generalized Cutler-Neufeld (gen-CN) models. These models are general serial mixture models where the base distribution is arbitrary and the only variable which can vary over trials and cells is the number of subprocesses K_i. These models, which are an extension of the Cutler-Neufeld model of Sec 2.1.2, not only provide simple concise expressions for MIC and VIC but allow for a variety of MIC-VIC signatures which are explored through a series of examples. Moreover, the models themselves are supported by experimental evidence that has suggested that the changes in $E(T)_*$ across cells can be explained by shifts in the distribution of K_i across cells. Thus these models may have wide applicability. Note that one particularly significant result in this section is that if K_i does not vary over trials (what we call gen-CN models without variation) then we always obtain the signature VIC $= 0$ iff MIC $= 0$. Thus observation of VIC $\neq 0$ implies there is some variation in subprocess number over trials. However, various examples also illustrate the fact that VIC $=$ MIC $= 0$ can be obtained in some situations where variation is present. Sec 2.4 addresses the problem of determining, using factorial data, whether variation is present in a gen-CN model. As noted earlier, Sec 2.5 considers special cases of the general serial mixture model where the parameter Θ of the base distribution is allowed to vary across participants, trials, and cells. (In a sense, this is the reverse of the set-

up in Sec 2.3.) The results here are dependent on the choice of base distribution. It is worth noting that the signature VIC = 0 iff MIC = 0 can be obtained here as well in some special cases, e.g., Corollary 7.1 and Example 36.

Note that although throughout this chapter we have been focusing on the sign of VIC when MIC = 0, we have actually derived explicit expressions for VIC in each example. Most of these expressions involve constants unknown to the experimenter, so it would be difficult to match any of these signatures against one set of experimental data, i.e., against a single estimated value for VIC. However, this situation may change if we are able to manipulate the encoding load and health status and obtain a second value of VIC. For example, consider the case of a gamma base where we are trying to decide between the shape parameter A following a gamma distribution with shifting rate parameter (Example 37) or A following an inverse Gaussian distribution with shifting mean (Example 38). Now for both these examples, when MIC = 0, we have

$$E(T)_* = c\, E^i_*[E(A_i)] \quad \text{and} \quad \text{VIC} = d\, \text{AVIC} \tag{2.6.1}$$

where $c > 0$ and $d > 0$ are constants unknown to the experimenter. Define the quantities $h' > 0$ and $g' > 0$ by $E(T)_{HN} = E(T)_{LN} + h'$ and $E(T)_{LS} = E(T)_{LN} + g'$. Note that h' and g' can easily be estimated from the estimates of $E(T)_{LN}, E(T)_{HN}$, and $E(T)_{LS}$ based on factorial data. In Example 37, the quantities $E(T)_{LN}, E(T)_{HN}$, and $E(T)_{LS}$, can be represented respectively by $acm, ac(m+h)$, and $ac(m+g)$, so $h' = ach$ and $g' = acg$ in this example. (Note in this example that $m = 1/b_{LN}$.) It

then follows from (2.5.42) and (2.6.1) that there exists $d' > 0$ such that

$$\text{VIC} = d'h'g' \qquad \text{for Example 37}$$

Similarly, in Example 38, the quantities $E(T)_{LN}, E(T)_{HN}$, and $E(T)_{LS}$, can be represented respectively by $cm, c(m+h)$, and $c(m+g)$, so $h' = ch$ and $g' = cg$ in this example. (Here $m = a_{LN} = E(T)_{LN}/c$.) Plugging into (2.5.46) and (2.6.1) yields existence of a constant $d'' > 0$ such that

$$\text{VIC} = d''(h'g')[2E(T)_{LN} + h' + g'] \qquad \text{for Example 38}$$

Note in particular that, in Example 38, VIC is a function of the mean encoding latency in the first cell as well as the differences h' and g' between cells, whereas in Example 37, VIC is only a function of the differences between cells. In theory, repetitions of the experiment that yield different choices for h' and g' would allow us to distinguish between the above two expressions for VIC and thus between the two models. Numerical studies in this area would be a fruitful avenue to explore for future work.

Another area for future work would be the development of the distribution of the ratio statistic $r_* = \bar{s}_*^2/\bar{t}_*$ proposed in Sec 2.4 as a method for testing for variation in generalized Cutler-Neufeld models. As noted in that section, the standard deviation of r_* is highly dependent on the underlying base distribution, so it would be useful to have distributional results for different choices of base. A related problem, possibly more easily accomplished in the short term, would be numerical work determining the required sample sizes necessary to obtain desired standard deviations for different base distributions. Experimenters could then choose sample sizes according to the

base distribution believed to be applicable to their problem or, more likely, according to a "worst case scenario" choice for base distribution.

It would also be desirable to develop explicit expressions for MIC and VIC for at least some general serial mixture models where more than one quantity is varying over trials and/or cells. Of course term-by-term expressions for MIC and VIC can always be obtained by plugging into (2.2.10) and(2.2.11) (see Examples 4 and 5 where both K and V are varying over trials) and then applying (2.1.3) and (2.1.5). However, such expressions (at least for VIC) are bound to be complicated and unwieldy. It would be of interest to determine if there is a subset of models with at least two quantities varying over trials and/or cells for which somewhat concise and elegant expressions can be obtained for MIC and VIC.

Finally, a core assumption made in the definition of the general serial mixture model (Definition 1) was that the process that governed the number of subprocesses K was independent of the process that governed the random vector Θ. This permitted factoring in several expressions and led to the simplicity of many of the obtained results, in particular (2.2.10) and (2.2.11). However, one can easily envisage situations where K_i and Θ_i are linked for participant i. Such cases might need to be solved on a case-by-case basis, but exploration of this area would be of interest.

References for Chapter 2

Adams, R. A., Huys, Q. J. M., & Rosier, J. P. (2016). Computational psychiatry: Towards a mathematically informed understanding of mental illness. *Journal of Neurology, Neurosurgery and Psychiatry, 87,* 153-163.

Ahn, W. & Busemeyer, J. R. (2016). Challenges and promises for translating computational tools into clinical practice. *Current Opinion in Behavioral Science, 11,* 1-7.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, (5^{th} Ed.).* Arlington, VA: American Psychiatric Publishing.

Andreasen, N. C. (1999). A unitary model of schizophrenia: Bleuler's "fragmented phrene" as schizencephaly. *Archives of General Psychiatry, 56,* 781-787.

Atkinson, R. C., Holmgren, J. E., & Juola, J. F. (1969). Processing time as influenced by the number of elements in a visual display. *Pereception & Psychophysics, 6,* 321-326.

Batchelder, W.H., & Riefer, D.M. (2007). Using multinomial processing tree models to measure cognitive deficits in clinical populations. In R. W. J. Neufeld (Ed.), *Advances in clinical cognitive science: Formal modeling of processes and symptoms* (pp. 19-50). Washington, D.C: American Psychological Association.

Berger, J. O. (1985). *Statistical decision theory and Bayesian analysis, 2nd Ed.* New York: Springer

Bleuler, E. (1950). *Dementia praecox or the group of schizophrenias.* (J. Kinkin, translator). New York: International Universities Press.

Bluhm, R. L., Miller, J., Lanius, R. A., Osuch, E. A., Boksman, K., & Neufeld, R. W. J. (2007). Spontaneous low frequency fluctuations in the BOLD signal in schizophrenia patients: Anomalies in the default network. *Schizophrenia Bulletin, 33,* 1004-1012.

Boksman, K. (2006). *Investigation of effective connectivity in schizophrenia using functional magnetic resonance imaging and Sternberg item recognition tasks.* Unpublished doctoral thesis. Faculty of Graduate Studies. University of Western Ontario, London, ON.

Braver, T. S., & Barch, D. M. (2006). Extracting core components of cognitive control. *Trends in Cognitive Science, 10,* 529-532.

Carter, J. R., & Neufeld, R. W. J. (1999). Cognitive processing of multidimensional stimuli in schizophrenia: Formal modeling of judgment speed and content. *Journal of Abnormal Psychology, 108,* 633-654.

Carter, J. R., & Neufeld, R. W. J. (2007). Cognitive processing of facial affect: Neuro-connectionist modeling of deviations in schizophrenia. *Journal of Abnormal Psychology, 166,* 290-305.

Chechile, R. A. (2020). *Bayesian statistics for experimental scientists: A general introduction using distribution-free methods.* Cambridge, MA: MIT Press.

Collewijn, H., & Tamminga, E. P. (1982). Human smooth and saccadic eye movements during voluntary pursuit of different target motions on different backgrounds. *Journal of Physiology, 351,* 217-250.

Cutler, C. D., & Neufeld, R. W. J. (2017). Addressing very short stimulus encoding times in modeling schizophrenia cognitive deficit. *Journal of Mathematical Psychology, 79,* 53-63.

Donders, F. C. (1969). Over die snelheid van psychische processen. [On the rapidity of mental processes] (W. G. Koster, Trans.) *Acta Psychologica, 30*, 412-431. (Originally published in 1868).

Friston, K. J. (1999). Schizophrenia and the disconnection hypothesis. *Acta Psychiatrica Scandinavica, 99, (Suppl. 395),* 68-79.

George, L., & Neufeld, R. W. J. (1987). Attentional resources and hemispheric functional asymmetry in schizophrenia. *British Journal of Clinical Psychology, 26,* 35-45.

Hare, S. M., Ford, J. M., Mathalon, D. H., Damaraju, E., Bustillo, J., Belger, A., Lee, H. J., Mueller, B., A., Lim, K. O., Brown, G. G., Preda, A., van Erp, T. G., Potkin, S. G., Calhoun, V. D., & Turner, J. A. (2019). Salience-default mode functional network connectivity linked to positive and negative symptoms in schizophrenia. *Schizophrenia Bulletin, 45,* 821-901. doi: 10.1093/schbul/sby112

Hemsley, D. R. (1993). Perception and cognition in schizophrenia. In R. L. Cromwell & C. R. Snyder (Eds.), *Schizophrenia: Origins, processes, treatment and outcome* (pp. 135-150). New York: Oxford University Press.

Hemsley, D. R. (1994). Perceptual and cognitive normality as the bases for schizophrenic symptoms. In A. S. David & J. Cutting (Eds.), *The neuropsychology of schizophrenia* (pp. 97-116). Hillsdale, NJ: Erlbaum.

Highgate-Maynard, S., & Neufeld, R. W. J. (1986). Schizophrenic memory-search performance involving nonverbal stimulus properties. *Journal of Abnormal Psychology, 95,* 67-73.

Hogg, R. V., McKean, J. W., & Craig, A. T. (2005). *Introduction to mathematical statistics, 6th Ed.* Upper Saddle River, NJ: Pearson Prentice Hall.

Houpt, J. W., Townsend, J. T., & Jefferson, B. (2018). Stochastic foundations of elementary mental architectures. In W. H. Batchelder, H. Colonius, & E. N. Dzhafarov (Eds.), *New handbook of mathematical psychology, Volume 2: Modeling and measurement* (pp. 104-127). Cambridge: Cambridge University Press.

Johnson, N. L., Kotz, S., & Balakrishnan, N. (1994). *Continuous univariate distributions (Vol. 1, 2nd Ed.)* New York: Wiley.

Kallenberg, O. (2017). *Random measures, theory and applications.* New York: Springer.

Kieffaber, P. D., Kappenman, E. S., Bodkins, M., Shekhar A., ODonnell, B. F., & Hetrick, W.P. (2006). Switch and maintenance of task set in schizophrenia. *Schizophrenia Research, 84,* 345358.

Lee, W. H., Doucet, Leibu, E., & Frangou, S. (2018). Resting-state network connectivity and metastability predict clinical symptoms in schizophrenia. *Schizophrenia Research, 201,* 208-216.

Marusarz, T. Z., & Koh, S. D. (1980). Contextual effects on short-term memory retrieval of schizophrenic young adults. *Journal of Abnormal Psychology, 89,* 683-696.

McClelland, J. (1979). On the time relation of mental processes: An examination of systems of processes in cascade. *Psychological Review, 86,* 287-330.

McGill, W. J., & Gibbon, J.(1965).The general gamma distribution and reaction times. *Journal of Mathematical Psychology, 2,* 1-18. doi:10.1016/0022-2496(65)90014-3

Morrison, M. S., Neufeld, R. W. J., & Lefebvre, L. A. (1988). The economy of probabilistic stress: Interplay of controlling activity and threat reduction. *British Journal of Mathematical and Statistical Psychology, 41,* 155-177.

Murphy, K., Birn, R. M., Handwerker, D. A., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: Are anti-correlated networks introduced? *Neuroimage, 44,* 893-905.

Neufeld, R.W.J. (1977). Components of processing deficit among paranoid and nonparanoid schizophrenics. *Journal of Abnormal Psychology, 86,* 60-64.

Neufeld, R.W.J. (1978). Paranoid and nonparanoid schizophrenics' deficit in the interpretation of sentences: An information-processing approach. *Journal of Clinical Psychology, 34,* 333-339.

Neufeld, R. W. J. (2007a). On the centrality and significance of encoding deficit in schizophrenia. *Schizophrenia Bulletin, 33,* 982-983.

Neufeld, R. W. J. (2007b). Composition and uses of formal clinical cognitive science. In B. Shuart, W. Spaulding, & J. Poland (Eds.), *Modeling complex symptoms: Nebraska symposium on motivation: Vol 52* (pp. 1-83). Lincoln, Nebraska: University of Nebraska.

Neufeld, R. W. J. (2015). Mathematical modeling applications in clinical psychology. In J. R Busemeyer, J. R., J.T. Townsend, Z. Wang, & A. Eidels (Eds.), *Oxford handbook of computational and mathematical psychology* (pp. 341-368). Oxford, U. K.: Oxford University Press.

Neufeld, R. W. J. (2016). Modeling stress effects on coping-related cognition. In J. W. Houpt & L. Blaha (Eds.), *Mathematical modeling of perception and cognition: Essays in honor of James T. Townsend* (pp. 172-195). New York: Taylor & Francis.

Neufeld, R. W. J. (2021). A mathematically disciplined theory of thought-content disorder in schizophrenia, to be submitted.

Neufeld, R. W. J., Boksman, K., Vollick, D., George, L., & Carter, J. R. (2010). Stochastic dynamics of stimulus encoding in schizophrenia: Theory, testing, and application. *Journal of Mathematical Psychology, 54,* 90-108.

Neufeld, R. W. J., & Cutler, C. D. (2019). Potential contributions of clinical mathematical psychology to robust modeling in cognitive science. *Computational Brain and Behavior, 2*, 251-254. DOI 10.1007/s42113-019-00044-z

Neufeld, R. W. J. & Grant, B. (2018). Quantitative modeling in stress and coping. In K. Harkness & E. Hayden (Eds.), *Oxford handbook of stress, coping and mental health* (pp. 75-96). New York: Oxford University Press.

Neufeld, R. W. J., & Shanahan, M. J. (2021). Formal innovations to clinical cognitive science and assessment. To appear in *Current Directions in Psychological Science.*

Neufeld, R. W. J., Vollick, D., Carter, J. R., Boksman, K., & Jetté, J. (2002). Applications of stochastic modelling to the assessment of group and individual differences in cognitive functioning. *Psychological Assessment, 14,* 279-298.

Neufeld, R. W. J., Vollick, D., Carter, J. R., Boksman, K., Levy, L. R., George, L., & Jetté, J. (2007). A mathematical process account of group and individual differences in memory-search facilitative stimulus encoding, with application to schizophrenia. In R. W. J. Neufeld (Ed.), *Advances in clinical cognitive science: Formal modeling of processes and symptoms* (pp. 147-177). Washington, DC: American Psychological Association.

Neufeld, R. W. J., Vollick, D., & Highgate, S. (1993). Stochastic modelling of stimulus encoding and memory search in paranoid schizophrenia: clinical and theoretical implications. In R. L. Cromwell & C. R. Snyder (Eds.), *Schizophrenia:*

Origins, processes, treatment, and outcome (pp. 176-198). New York: Oxford University Press.

Neufeld, R. W. J., & Williamson, P. C. (1996). Neuropsychological correlates of positive symptoms: Delusions and hallucinations. In C. Pantelis, H. E. Nelson, & T. R. E. Barnes (Eds.), *Schizophrenia: A neuropsychological perspective* (pp. 205-235). New York: John Wiley & Sons Ltd.

Orliac, F., Naveau, M., Joliot, M., Delcroix, N., Razafimandimby, A., Brazo, P., Dollfus, S. & Delamilleure, P. (2013). Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia. *Schizophrenia Research, 148,* 74-80.

Paivio, A. (1975). Perceptual comparisons through the mind's eye. *Memory and Cognition. 3,* 635-647.

Paivio, A. (1979). *Imagery and verbal processes.* Hillsdale, NJ: Lawrence Erlbaum and Associates.

Penner, J., Osuch, E. A., Schaefer, B., Théberge, J., Neufeld, R. W. J., Menon, R., Rajakumar, N., Bourne, J. A., & Williamson, P. (2018). Higher order thalamic nuclei resting network connectivity in early schizophrenia and major depressive disorder. *Psychiatry Research: Neuroimaging, 272,* 7-16.

R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org

Ross, S. M. (2007). *Introduction to probability models,* 9^{th} *Ed.* Burlington, MA: Academic Press.

Russell, P. N., & Knight, R. G. (1977). Performance of process schizophrenics on tasks involving visual search. *Journal of Abnormal Psychology, 86,* 16-26.

Schneider, D. W., & Logan, G. D. (2005). Modeling task switching without switching tasks: A short-term priming account of explicitly cued performance. *Journal of Experimental Psychology: General,* 134, 343-367.

Shanahan, M. J., & Neufeld, R. W. J. (2010). Coping with stress through decisional control: Quantification of negotiating the environment. *British Journal of Mathematical and Statistical Psychology, 63,* 575-601.

Steffy, R. A., & Galbraith, K. (1980). Relation between latency and redundancy-associated deficit in schizophrenic reaction time performance. *Journal of Abnormal Psychology, 89,* 419-427.

Steffy, R. A., & Waldman, I. (1993). Schizophrenics' reaction time: North star or shooting star? In R. L. Cromwell & C. R. Snyder (Eds.), *Schizophrenia: Origins, processes, treatment and outcome* (pp. 111-134). New York: Oxford University Press.

Sternberg, S. (1966). High-speed scanning in human memory. *Science, 153,* 652-654.

Sternberg, S. (1975). Memory and scanning: New findings and current controversies. *Quarterly Journal of Experimental Psychology, 27,* 1-32.

Taylor, R., Théberge, J., Williamson, P., Densmore, M., & Neufeld, R. W. J. (2016). ACC neuro-over-connectivity is associated with mathematically modeled additional encoding operations of Schizophrenia Stroop-Task performance. *Frontiers in Quantitative Psychology and Measurement,* 1-23, doi:10.3389/fpsyg.2016.01295.

Taylor, R., Théberge, J., Williamson, P., Densmore, M., & Neufeld, R. W. J. (2017). Systems-factorial technology-disclosed stochastic dynamics of Stroop processing in the cognitive neuroscience of schizophrenia. In M. Fific, N. Altieri, and D. Little (Eds.), *Systems factorial technology: A theory-driven methodology for the identification of perceptual and cognitive mechanisms*(pp. 351-380). New York: Taylor & Francis.

Townsend, J. T. (1972). Some results on the identifiability of parallel and serial processes. *British Journal of Mathematical and Statistical Psychology, 25,* 168-199.

Townsend, J. T. (1990). Serial vs. parallel processing: Sometimes they look like Tweedledum and Tweedledee but they can (and should) be distinguished. *Psychological Science, 1*, 46-54.

Townsend, J. T., & Ashby, F. G. (1983). *Stochastic modelling of elementary psychological processes.* Cambridge, England: Cambridge University Press.

Townsend, J. T., Fifić, M. & Neufeld, R. W. J. (2007). Assessment of mental architecture in clinical/cognitive research. In T.A. Treat, R.R. Bootzin, & T.B. Baker, (Eds.), *Psychological clinical science: Papers in honor of Richard M. McFall* (pp. 223-258). Hillsdale, N.J.: Erlbaum.

Townsend, J. T., & Nozawa, G. (1995). Spatio-temporal properties of elementary perception. An investigation of parallel, serial and coactive theories. *Journal of Mathematical Psychology, 39,* 321-359.

Townsend, J. T., & Wenger, M. J. (2004). The serial-parallel dilemma: A case study in a linkage of theory and method. *Psychonomic Bulletin & Review, 11*(3), 391-418.

Townsend, J. T., Wenger, M. J. & Houpt, J. W. (2018). Uncovering mental architecture and related mechanisms in elementary human perception, cognition and action. In J. T. Wixted (Ed.), *Stevens handbook of experimental psychology and cognitive neuroscience, 5* (pp. 1-30). New York: Wiley.

Triesman, A. (1996). The binding problem. *Current Opinion in Neurobiology, 6,* 330-354.

Van Zandt, T. (2000). How to fit a response time distribution. *Psychonomic Bulletin & Review, 7,* 424-465.

Williamson, P. C, & Allman, J. M. (2012). Framework for interpreting functional networks in schizophrenia. *Frontiers in Human Neuroscience, 6,* 184. doi: 10.3389/fnhum.2012.00184

Wishner, J., Stein, M. K., & Paestrel, A. L. (1978). Stages of information processing in schizophrenia: Sternberg's paradigm. In L. Wynne, R. L. Cromwell, & S. Matthysse (Eds.), *The nature of schizophrenia: New approaches to research and treatment* (pp. 233-243). New York: Wiley & Sons.

Woodworth, R. S., & Schlossberg, H. (1954). *Experimental psychology.* New York: Holt, Rinehart & Winston.

Chapter 3

Nonlinear Indices in Schizophrenia and Bipolar Disorder

3.1 Introduction to Chapter 3

The idea that the human brain operates as a series of interacting nonlinear processes initially generated considerable enthusiasm about potential applications to the study of schizophrenia and bipolar disorder (Ehlers, 1995; Globus & Arpaia, 1994; Heiby, 1995; Melançon, Joanette, & Bélair, 2000; Schmid, 1991). It seems natural to consider schizophrenia and bipolar disorder together as they represent the two major psychoses and share some commonalities in both symptoms and genetics (Demjaha, MacCabe, & Murray, 2012; Murray et al., 2004). Schizophrenia research moved more quickly to meet this interest in nonlinear dynamics, and more recent articles (Breakspear, 2006; Paulus & Braff, 2003) have argued vigorously for continuing exploration of this area. Nonlinear research in bipolar disorder is now emerging as well. A wealth of nonlinear techniques exist, and we refer the reader to Heath, Kelly, and Longstaff (2000), Guastello (2009), Guastello and Gregson (2011), and Heath (2014) for general overviews of these techniques, especially as they are applied to psychological and

biological data.

In this chapter[1] we focus on applications of *nonlinear indices* to univariate time series X_t arising from electroencephalogram (EEG) studies, electrocardiogram (ECG) studies, and mood studies. A nonlinear index is a numerical value that either quantifies some aspect of nonlinearity about a system (the indices we have called the *phase space indices*) or is inspired by nonlinear concepts such as fractal dimension and entropy (the indices we have called the *time domain indices*). Evaluating phase space indices requires embedding procedures to reconstruct the underlying system dynamics whereas evaluating time domain indices does not. A summary of the indices we consider is given in Table 3.1. This list is by no means exhaustive, but for space constraints it was necessary to limit the number of indices. Nonlinear indices stand apart from linear quantities such as the mean, variance, and power spectrum of a time series.

Table 3.1: Summary of Nonlinear Indices

	Phase Space Indices	
symbol	name	description
λ_1	largest Lyapunov exponent	predictability index
KSE	Kolmogorov-Sinai entropy	information index
D_2	correlation dimension	spatial clustering index
	Time Domain Indices	
symbol	name	description
ApEn	approximate entropy	randomness index
SampEn	sample entropy	randomness index
MSE	multiscale entropy	multiple scales SampEn indices
LZC	Lempel-Ziv complexity	pattern index
Hc	compression entropy	compressibility index
KFD	Katz fractal dimension	graph roughness index
HFD	Higuchi fractal dimension	graph roughness index
RBFD	Real box fractal dimension	graph roughness index
Methods I and II	symbolic dynamics	symbol complexity indices

[1] A slightly modified version of this chapter has been published as Cutler and Neufeld (2019)

Nonlinear indices are frequently referred to as *complexity indices* in the literature (Fernández, Gómez, Hornero, & López-Ibor, 2013; Takahashi, 2013). However, the notion of "complexity" is an ill-defined one (Kantz & Schreiber, 1997, p. 91) although the recent article by Yang and Tsai (2013) has described complexity as occupying a position intermediate between order and randomness. The different nonlinear indices actually measure somewhat different quantities (possibly one reason for the many contradictory findings in the literature) and entropy indices typically reach their maximum for totally random series, not complex ones (however, see Heath (2015) for an index which reaches its maximum at the edge of chaos).

The purpose of this chapter is threefold. The first is to provide an accessible self-contained description of the nonlinear indices and techniques under consideration. The second is to discuss the ways in which nonlinear indices and techniques have been applied to EEG data, ECG data, and mood data in schizophrenia and bipolar disorder. The third involves a lengthy quantitative investigation (Section 3.4) into a hypothesis put forward by Lee, Choo, Im, and Chae (2008) and Fernández et al. (2013) which can be paraphrased as "higher complexity in EEG tends to be the default condition in symptomatic unmedicated schizophrenia (especially first-episode patients) with this tendency being dampened or even inverted by medication (antipsychotics), increasing age, and decreasing symptomatology". For brevity, we will call this the *L-F proposal*. We find only weak quantitative evidence to support individual aspects of this proposal, but suggest that the underlying symptomatology of the patients may provide the key to untangling apparent contradictions.

For the purpose of identifying the research studies for this systematic review

and quantitative analysis, we searched PsychInfo, PubMed, Scopus, and Google Scholar for all combinations of the words nonlinear, correlation dimension, Lyapunov, chaos, fractal, entropy, and symbolic dynamics coupled with each of the terms schizophrenia, bipolar disorder, mania, manic depression, and bipolar depression.

3.2 Phase Space Indices

3.2.1 Dynamical Systems, Attractors, and Time Series

The definitions of phase space indices are predicated on the assumption that the observed time series X_t is a univariate measurement on an underlying multivariate dynamical system φ_t evolving in N dimensions. The N-dimensional space is typically called state space or *phase space*. If $\mathbf{y}_0$ is the starting position of the system in phase space (called the *initial condition*) then $\varphi_t(\mathbf{y}_0)$ denotes the position of the system in phase space after t units of time have passed. The curve $\{\varphi_t(\mathbf{y}_0) \,|\, t \geq 0\}$ is called the *trajectory* of the system with initial condition $\mathbf{y}_0$.

A dynamical system is called *linear* if $\varphi_t(c_1\mathbf{y}_1 + c_2\mathbf{y}_2) = c_1\varphi_t(\mathbf{y}_1) + c_2\varphi_t(\mathbf{y}_2)$; otherwise it is called *nonlinear*. The long-run behaviours of linear systems are relatively simple. Depending on the initial condition, the trajectory may become unbounded over time, or settle onto an attracting fixed point, limit cycle (e.g., an ellipse), or torus (Hirsch & Smale, 1974). Accordingly, the behaviour of the measured time series X_t is simple as well. However, in the nonlinear case, the long-run behaviour of φ_t can be very complex if $N \geq 3$. In such a situation, it is possible that, for a collection of initial conditions, the trajectories exhibit chaotic behaviour (see Sec 3.2.3 below) and settle onto a complicated fractal attractor (a set so structurally intricate that

it has a noninteger dimension; see Mandelbrot (1977, 1982)). When the underlying dynamics are chaotic, the measured time series X_t will be so irregular as to appear random (also called *stochastic*) even though a latent determinism is generating the series.

Phase space indices can be used to identify and quantify aspects of nonlinearity and chaos. However, before we define these indices, it is necessary to cope with the fact that in practice we usually do not know the actual dynamical system. All we have available to us is the univariate time series X_t. The next section considers reconstruction of the underlying dynamics from knowledge of X_t alone.

3.2.2 Reconstruction of Dynamics from the Time Series

It may seem evident that having only a univariate measurement on a multivariate system will yield only partial information about the underlying dynamics of the multivariate system. However, if the measurement function is sensitive to changes in all the variables (as is typically the case) following one measurement over time will reveal information about the entire system. This is done by the method of time-delay embeddings, first introduced by Packard, Crutchfield, Farmer, and Shaw (1980), which we describe below. At this point we will simplify our presentation by noting that the continuous-time realization X_t is, in practice, sampled only at discrete time steps, say with step size Δt. Thus the sampled data takes the form $X_{\Delta t}, X_{2\Delta t}, \ldots, X_{n\Delta t}$. For convenience we will represent this as $X_1, X_2, \ldots, X_n$. Let $L \geq 1$ and $M \geq 1$ be integers and define the vector $\mathbf{X}_j^{(M)}$ by

$$\mathbf{X}_j^{(M)} = (X_j, X_{j+L}, X_{j+2L}, \ldots, X_{j+(M-1)L}) \tag{3.2.1}$$

Thus $\mathbf{X}_j^{(M)}$ is a vector in M-space which consists of M points of the original time series separated by L units in time. L is called the *lag* or delay, and should be chosen so that consecutive elements of the vector are neither too correlated nor too uncorrelated. The sequence of vectors $\mathbf{X}_j^{(M)}$, $j = 1, 2, \ldots, n-(M-1)L$, sketches out a curve in M-space. Celebrated reconstruction theorems (Takens, 1981; Sauer, Yorke, and Casdagli, 1991) state that, under "most" typical conditions, if M is large enough, the curve sketched out by the vectors (3.2.1) will mimic (with perhaps some minor distortions) the trajectory of the underlying dynamical system as it moves around its attractor. In the case that this mimicking occurs, we refer to (3.2.1) as a *time-delay embedding* of the system and M as the *embedding dimension*. Since the required embedding dimension M is unknown apriori, an approach to determining it has been given by Kennel, Brown, and Abarbanel (1992), called the method of *false nearest neighbours* (FNN). Cao (1997) modified the FNN method to be less subjective and more efficient, an algorithm we will denote CFNN. The methods FNN and CFNN seem to be the most popular ways of determining M in papers after the year 2000. Prior to that the Grassberger-Procaccia (GP) algorithm (Sec 3.2.5 below) was generally used. It is important to note that different choices of lag and embedding method can produce different answers, and these differences can affect estimates of the phase space indices.

3.2.3 Lyapunov Exponents (λ_1) and Chaos

For a dynamical system φ_t evolving in N-space, a spectrum of numbers can be obtained that indicate the long-run rate of divergence (or convergence) of two initially

close trajectories along N principal axes of motion. These are called the *Lyapunov exponents* of the system and are typically ordered largest to smallest

$$\lambda_1 \geq \lambda_2 \geq \ldots \geq \lambda_N \tag{3.2.2}$$

Positive exponents indicate directions of expansion whereas negative exponents indicate directions of contraction. The existence of at least one positive exponent (i.e., $\lambda_1 > 0$) implies that any two nearby trajectories diverge exponentially fast. In this case, if $\Delta\mathbf{y}_0$ denotes a very small perturbation so that the starting points of two nearby trajectories are given by $\mathbf{y}_0$ and $\mathbf{y}_0 + \Delta\mathbf{y}_0$, respectively, then the distance between the two trajectories at time t is:

$$||\varphi_t(\mathbf{y}_0 + \Delta\mathbf{y}_0) - \varphi_t(\mathbf{y}_0)|| \approx e^{\lambda_1 t}||\Delta\mathbf{y}_0|| \tag{3.2.3}$$

This rapid exponential expansion of an originally small perturbation is known as *sensitivity to initial conditions*. A dynamical system is called *chaotic* if it stays bounded over time, has no stable periodic cycles (in practice this means that if you select an initial condition at random then the trajectory will never repeat itself numerically) and the system displays sensitivity to initial conditions (i.e., has at least one positive Lyapunov exponent). Chaotic systems are of such great interest because they are deterministic and may involve a small number of variables (the Lorenz system has only three) and yet, because of the sensitivity to initial conditions, behave almost as unpredictably as a random process. Much of the search for chaos from data has centred on a search for a positive Lyapunov exponent. We call the phase space index λ_1 a *predictability index* since greater positive values of λ_1 imply faster separation of trajectories and greater unpredictability of the system. It is possible to estimate

λ_1 using only the time-delay reconstructions of the previous section; a variety of algorithms exist (Kantz & Schreiber, 1997; Kreindler & Lumsden, 2007; Rosenstein, Collins, & De Luca, 1993; Wolf, Swift, Swinney, & Vastano, 1985).

3.2.4 Kolmogorov-Sinai Entropy (KSE)

The Kolmogorov-Sinai entropy index (KSE) is closely tied to the notion of Lyapunov exponents and can be defined as

$$\text{KSE} = \sum_{\lambda_i > 0} \lambda_i \tag{3.2.4}$$

The sum of the positive Lyapunov exponents governs the rate at which new information comes into the system. Chaotic systems create information as they evolve because trajectories that are initially so close that we cannot tell them apart will become separate and distinct under the stretching actions of the system. Thus KSE is called an *information index*.

3.2.5 Correlation Dimension and the GP Algorithm

The indices λ_1 and KSE measure active dynamical properties of the underlying system. Another value of interest is a static quantity, which is the number of distinct dimensions that characterize the system attractor $\mathcal{A}$. A higher number of dimensions is generally viewed as reflecting greater system complexity. In the chaotic case $\mathcal{A}$ typically has a fractional dimension, and thus verification of a fractional dimension for $\mathcal{A}$ has been used as an identifier of chaos. One difficulty here is that the trajectories of the system typically visit different regions of $\mathcal{A}$ with unequal probabilities, so it may require enormous sample sizes to get an accurate picture of $\mathcal{A}$. Thus experimen-

talists turned their attention to dimension quantities associated with the probability distribution over the attractor. The most popular of these has been the correlation dimension.

Correlation Dimension (D_2)

Let P denote the probability distribution describing the relative frequency with which the trajectories visit different regions of $\mathcal{A}$. Suppose $\mathbf{X}$ and $\mathbf{Y}$ are two vectors drawn randomly and independently from the phase space according to P. For each $r > 0$ the *spatial correlation integral* is defined to be the probability that those two vectors are no more than distance r apart, i.e.,

$$C(r) \;=\; \text{Probability}(||\mathbf{X} - \mathbf{Y}|| \leq r) \tag{3.2.5}$$

As $r \to 0$ this quantity is believed to scale as r^{D_2}, i.e.,

$$C(r) \sim r^{D_2} \tag{3.2.6}$$

where the exponent D_2 is called the *correlation dimension*. It turns out that D_2 is a lower bound on the dimension of $\mathcal{A}$ (Cutler, 1991) and is often viewed as a measure of complexity, although really it is a measure of the spatial clustering of points over $\mathcal{A}$. Given a sample of time-delay embedded vectors $\mathbf{X}_1, \ldots, \mathbf{X}_n$, Grassberger and Procaccia (1983a) introduced the *sample correlation integral*

$$C_n(r) \;=\; \frac{2}{n(n-1)} \sum_i \sum_{j>i} I_{[||\mathbf{X}_j - \mathbf{X}_i|| \leq r]} \tag{3.2.7}$$

where $I_{[||\mathbf{X}_j - \mathbf{X}_i|| \leq r]} = 1$ if $||\mathbf{X}_j - \mathbf{X}_i|| \leq r$ and is otherwise 0. Thus $C_n(r)$ is simply the proportion of pairs of vectors in the sample that are no more than r units apart.

$C_n(r)$ is the natural estimator of the correlation integral $C(r)$ defined in (3.2.5). In order to estimate D_2, Grassberger and Procaccia (1983a) proposed that $\log C_n(r)$ should be plotted versus $\log r$ and a suitable scaling region (a region of linear slope) determined. The estimate of D_2 is then the slope of this scaling region. Various difficulties with and improvements of this procedure have been discussed (Denker & Keller, 1986; Eckmann & Ruelle, 1992; Theiler, 1986, 1990). Accurate estimates of D_2 require long time series of stationary noise-free data.

The Grassberger-Procaccia (GP) Algorithm

As noted in Sec 3.2.2, the required embedding dimension M can be determined by methods such as FNN or CFNN. Historically, the Grassberger-Procaccia (GP) algorithm (Grassberger & Procaccia, 1983a, 1983b) has been used, as will be seen in some of the earlier papers we review. For each embedding dimension $M = 1, 2, \ldots$ the embedded M-vectors are constructed and an estimate $\hat{D}_2$ is obtained by plotting $\log C_n(r)$ versus $\log r$. The value of M at which the estimates $\hat{D}_2$ stop changing (assuming this occurs) is taken as the embedding dimension. Moreover, the final value of $\hat{D}_2$ is taken to be the estimate of D_2. When this occurs, the correlation dimension estimates are said to *converge*. If the estimates fail to converge, this suggests that the underlying system is very high-dimensional or maybe even stochastic. A problem with this algorithm is that coloured noise with a $1/f^{\alpha}$ power-law spectrum can produce (false) convergence of the D_2 estimates (Osborne & Provenzale, 1989). Coloured noise actually has infinite correlation dimension but the rate at which the trajectory "fills out" this infinite-dimensional space can be so slow that the GP algorithm appears to

converge to a finite value (Cutler, 1994; Theiler, 1991).

3.2.6 Surrogate Data Tests for Nonlinearity

The phase space indices λ_1, KSE, and D_2 directly capture some qualities of a noise-free dynamical system. However, they can also be used in another way. If the original univariate time series X_t is stochastic (i.e., noisy) it will appear irregular and unpredictable (like a chaotic process) whether it is a linear or nonlinear process. The phase space indices (as well as other discriminating statistics) can be used to detect the presence of nonlinearity in X_t. The null hypothesis H_0 that is assumed is that X_t is a linear Gaussian stochastic process. A statistical test is carried out by constructing B independent *surrogate series*. The surrogate series are obtained by a method which retains the linear properties of X_t but destroys any nonlinear structure. The linear properties of X_t are contained in its autocorrelation function (equivalently, its Fourier transform or power spectrum). Thus each surrogate series is created to have the same mean, variance, and autocorrelation function as X_t by computing the fast Fourier transform of the original series, randomizing the phases, then inverting the transform to obtain the surrogate series (Chan & Tong, 2001; Kantz & Schreiber, 1997; Kugiumtzis, 2000; Theiler, Eubank, Longtin, Galdrikian, & Farmer, 1992). The randomization of the phases destroys any nonlinear structure in the surrogate series. A discriminating statistic is then used to see if there is a difference between the original series and the collection of surrogate series. Very often D_2 is used. If we set the size of the test to be $\alpha = .05$ we would construct 40 independent surrogate series, calculate $\hat{D}_2$ for the original series, and $\hat{D}_2^{(1)}$, $\hat{D}_2^{(2)}$, $\ldots$ $\hat{D}_2^{(40)}$ for the surrogate series.

We would only reject H_0 and conclude there was some nonlinear structure in X_t if $\hat{D}_2$ was either smaller or larger than all 40 surrogate D_2 estimates, since $\text{Prob}(D_2 \leq \min(\hat{D}_2^{(1)}, \hat{D}_2^{(2)}, \ldots \hat{D}_2^{(40)}) = \text{Prob}(D_2 \geq \max(\hat{D}_2^{(1)}, \hat{D}_2^{(2)}, \ldots \hat{D}_2^{(40)}) < 1/40 = .025$ which yields a two-sided hypothesis test at $\alpha = .05$.

3.3 Time Domain Indices

These are indices based directly on X_t and do not require phase space reconstruction.

3.3.1 Approximate Entropy (ApEn) and Sample Entropy (SampEn)

Pincus (1991, 1995) developed an index which could rank time series in order of their degree of randomness. Pincus (and others) use the term "order of complexity" but it should be understood that Pincus' index, called *approximate entropy* ApEn, assigns its highest values to completely random series. It has received wide use in the analysis of EEG signals and heart rate series as well as other psychological, physiological, and biological processes; see Pincus (2006) for a review of applications.

We now describe the ApEn index. Let $X_1, \ldots, X_n$ be the time series, let $m \geq 1$, and create the m-vectors $\mathbf{X}_i^{(m)} = (X_i, X_{i+1}, \ldots, X_{i+(m-1)})$ for $i = 1, \ldots, n-(m-1)$. Let the "tolerance limit" $r > 0$ be fixed. $\mathbf{X}_j^{(m)}$ is considered a "match" to $\mathbf{X}_i^{(m)}$ if $||\mathbf{X}_j^{(m)} - \mathbf{X}_i^{(m)}|| \leq r$. Using the simplifying notation of Richman, Lake, and Moorman (2004), the index $\text{ApEn}(m, r, n)$ can be defined as

$$\text{ApEn}(m, r, n) \;=\; -\frac{1}{n-m} \sum_{i=1}^{n-m} \log\left(\frac{A_i}{B_i}\right) \tag{3.3.1}$$

where B_i denotes the number of matches with $\mathbf{X}_i^{(m)}$, and A_i denotes the number

of matches with $\mathbf{X}_i^{(m+1)}$. Note that the ratio A_i/B_i is an estimate of the conditional probability that a vector of length $m+1$ matches $\mathbf{X}_i^{(m+1)}$ given that the vector of length m matches $\mathbf{X}_i^{(m)}$. When these conditional probabilities are close to 1, ApEn(m, r, n) is close to zero. Pincus (1991, 1995) found that he could effectively distinguish between the degree of randomness for many series using as few as $n = 75 - 1000$ observations, with $m = 1$ or 2, and r selected to be 0.1·SD or 0.2·SD, where SD is the standard deviation of $X_1, \ldots, X_n$.

The counts in A_i and B_i in (3.3.1) include "self-matches" which has been criticized by Richman and Moorman (2000) and Richman et al. (2004). The self-matches cause a downward bias in the ApEn index. Richman and colleagues also claim that ApEn is dependent on series length and has problems with relative consistency. In order to remedy these problems, they modified the definition of ApEn to create an index they called *sample entropy* SampEn. This index is defined as

$$\text{SampEn}(m, r, n) \;=\; -\log\left(\frac{A}{B}\right) \tag{3.3.2}$$

where B is the number of matches among vectors of length m and A is the number of matches among vectors of length $m + 1$. Self-matches are not included in the counts for A and B. Note that the ratio A/B can be viewed as an estimate of the conditional probability of a match of length $m + 1$ given a match of length m.

3.3.2 Multiscale Entropy (MSE)

Multiscale entropy (MSE) is actually a family of indices derived from SampEn for different scaling factors τ. Let $X_1, \ldots, X_n$ be the original time series, and for each

$\tau = 1, 2, \ldots, n$ define a new time series X^τ whose elements are given by

$$X_j^\tau = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} X_i \quad \text{for } 1 \leq j \leq [n/\tau] \tag{3.3.3}$$

The MSE values are generated by calculating SampEn for each of the series X^τ (Costa, Goldberger, & Peng, 2005). Note that $\tau = 1$ reproduces the original time series and yields the usual SampEn value. SampEn(τ) provides information about short-range temporal irregularity when τ is small and information about long-range temporal irregularity when τ is large.

3.3.3 Lempel-Ziv Complexity (LZC) and Compression Entropy (Hc)

Here the time series X_t is coarse-grained into a sequence of 0's and 1's by setting $s(t) = 1$ if $X_t > m$ and $s(t) = 0$ if $X_t \leq m$ where m is the median of the time series. Lempel and Ziv (1976) developed a measure of pattern complexity that begins by scanning the sequence $s(1), \ldots, s(n)$ left to right and updating the counter $c(k)$ each time a new pattern is observed. For example, if the sequence was 0101101 then $c(7) = 3$ since the new patterns are 0, 1, 011. Usually $c(n)$ is then normalized to account for the length of the original sequence, producing a value known as the *Lempel-Ziv complexity* (LZC); see Li et al. (2008) for detailed discussion.

Ziv and Lempel (1977) developed an algorithm for compressing data strings. The *compression entropy* Hc is defined to be $\text{Hc} = \frac{\text{length of compressed string}}{\text{length of string}}$. See Baumert et al. (2004) for discussion and application to heart rate series.

3.3.4 Fractal Dimension of the Graph (KFD, HFD, and RBFD)

Here measures of the fractal dimension (FD) of the graph $G = \{(t, X_t) \,|\, t \geq 0\}$ are considered. The FD of a graph falls between 1 and 2, where FD is higher when the graph is rougher. (A smooth line would have FD = 1.) There are three popular algorithms which are employed to estimate FD, one due to Katz (1988), a second due to Higuchi (see Bahrami, Seyedsadjadi, Babadi, & Noroozian (2005) for the algorithm), and a "real" box-counting algorithm which has a long history (see Cutler (1993, p. 74) for discussion). The Katz fractal dimension (KFD) is given simply by

$$\text{KFD} = \frac{\log_{10}(n)}{\log_{10}(n) + \log_{10}(d/L)} \tag{3.3.4}$$

where n is the number of data points, d is the planar extent of the observed graph, and L is the length of the linearly-interpolated observed graph. In the Higuchi method, successive linear approximations with step size $r = 1, 2, \ldots, r_{\max}$ are constructed with a computed vertical length $L(r)$. If $L(r)$ scales as $r^{-\text{HFD}}$, i.e.,

$$L(r) \sim r^{-\text{HFD}} \tag{3.3.5}$$

then the exponent HFD is taken as the Higuchi fractal dimension. In the real box-counting method, for each small $\epsilon > 0$, a "real" box count is computed

$$N_\epsilon = \sum (\max X_t - \min X_t)(1/\epsilon) \tag{3.3.6}$$

where the differences between the max and min of the graph are computed and then summed across nonoverlapping strips of width ϵ. If

$$N_\epsilon \sim \epsilon^{-\text{RBFD}} \tag{3.3.7}$$

then the exponent RBFD is taken as the real box-counting fractal dimension. These algorithms need not always yield the same answer (and in particular the estimated KFD can sometimes exceed 2), although HFD and RBFD should be closely related.

3.3.5 Symbolic Dynamics

Another way of assessing the regularity of a time series is through the method of *symbolic dynamics*. Symbolic dynamics have increasingly been used in the analysis of heart rate variability (HRV) (Voss et al., 1996; Voss, Baier, Schulz, & Bär, 2006) so we describe it in this context. A heart rate series is generated by an electrocardiogram (ECG) recording, and the times between successive beats are computed, called the RR-intervals. Specifically, $\mathrm{RR}_i = T_i - T_{i-1}$ is the time between the $(i-1)^{th}$ and i^{th} beat. (Usually only normal-to-normal beats are considered.) There are two basic methods of generating a symbol sequence $a_0, a_1, \ldots$ from the RR series.

Method I: Choose a threshold parameter c (e.g., $c = 10$ ms) and set $a_i = 0$ if $\mathrm{RR}_i - \mathrm{RR}_{i-1} \leq c$ and $a_i = 1$ if $\mathrm{RR}_i - \mathrm{RR}_{i-1} > c$. The sequence of 0's and 1's is often analyzed for its regularity in two basic ways. One is to calculate *plvar* (which is based on the number of occurrences of six consecutive 0's) and *phvar* (which is based on the number of occurrences of six consecutive 1's). A large value of plvar indicates low variability in the RR series and is often indicative of cardiac disease, whereas a large value of phvar indicates high variability and is typical of healthy persons. Another way the sequence is analyzed is to concatenate successive symbols into 3-letter "words" $a_i a_{i+1} a_{i+2}$ and calculate the Shannon entropy (see (3.3.9) below) of the frequency distribution of the words, usually corrected for sample size. A higher

value for the entropy indicates greater randomness in the sequence.

Method II: This is more sophisticated. Here we choose a 4-letter alphabet $\{0, 1, 2, 3\}$, let $\mu =$ the mean of the RR-series, and let c be a parameter (often $c = 0.1$). Then set

$$a_i \;=\; \begin{cases} 0 & \mu < \mathrm{RR}_i \le (1+c)\mu \\ 1 & (1+c)\mu < \mathrm{RR}_i < \infty \\ 2 & (1-c)\mu < \mathrm{RR}_i \le \mu \\ 3 & 0 < \mathrm{RR}_i \le (1-c)\mu \end{cases} \tag{3.3.8}$$

Concatenating three successive symbols generates a 3-letter word $a_i a_{i+1} a_{i+2}$ which can take on one of $4^3 = 64$ values. The frequency distribution of the 3-letter words (over the 64 possible bins) can be evaluated by Shannon entropy (see (3.3.9) below). Other statistics that are sometimes considered are Word Count (WC) which is the percentage of different words encountered out of the possible 64, as well as the number of "forbidden" words (words that occur with probability $p < .001$). Voss et al. (1996) and Voss et al. (2006) note that a high percentage of words consisting only of 0's and 2's indicates abnormal regularity and tends to categorize serious cardiac patients.

Shannon entropy: Consider K bins with probabilities $p_1, p_2, \ldots, p_K$ where $\sum_{i=1}^{K} p_i = 1$. The *Shannon entropy* H is defined to be

$$H \;=\; -\sum_{i=1}^{K} p_i \log p_i \tag{3.3.9}$$

where $0 \cdot \log 0 = 0$. Note that H reaches a maximum of $\log K$ if the probabilities are uniformly distributed over the K bins (maximum randomness) and reaches a minimum of 0 if $p_i = 1$ for some i (minimum randomness).

3.4 Applications to EEG

Pritchard, Duke, and Krieble (1995), Theiler and Rapp (1996), and Palus (1996) studied several EEG data sets obtained from healthy adults and concluded, based on surrogate data techniques, that there was evidence of nonlinearity in the EEG but not low-dimensional chaos. The EEG likely combines some nonlinear properties with nonstationary stochastic elements. As such, the actual specific values of nonlinear index estimates (contaminated by choice of algorithm and stochastic noise) probably do not reflect meaningful characteristics in themselves. However, comparisons of these values between groups (e.g., patients vs. healthy controls) may provide useful information. Ideally we would hope to be able to distinguish between groups, at least under certain conditions.

EEG recordings are carried out with varying numbers and placements of electrodes. The placement of an electrode can significantly alter the value of the index being estimated (often this is the purpose of the study, e.g., the difference between patients and controls might be statistically significant at frontal electrodes but non-significant at parietal electrodes). Very early papers have featured analysis at just a few electrodes (often one or two) whereas now most (although not all) papers use a multiplicity of electrodes encompassing the entire scalp. Generally articles calculate indices for patients and controls from an EEG segment at each electrode and present those electrodes at which a statistically significant difference ($p < .05$) is obtained. In terms of deriving overall conclusions for a given paper, this situation is simplified by the fact that in the papers we have studied, differences at individual electrodes

are either statistically nonsignificant (ns) or significant in the same direction, so that one may make a global statement such as "this index was higher in the patients". This statement does not mean it was true at every electrode, but that it was true at those which were found to be statistically significant. It should be noted that seldom is a mixed ANOVA (with patients and controls as between-groups and electrodes and/or conditions as within-subjects) or corrections for multiple comparisons between electrodes (e.g., Bonferroni corrections) carried out (some exceptions include Akar, Kara, Latifoğlu,& Bilgiç, 2015a, and Carlino et al., 2012). Whereas this can be considered a weakness in some studies (if 20 electrodes are compared and uncorrected statistically significant differences ($p < .05$) are found at one or two, is it surprising or meaningful?) it can also be argued that different regions of the brain deserve to be evaluated separately and an observed difference at even one electrode may signify important information about that brain location. Finally we note that, whereas the above electrode-by-electrode analysis is most common, a few authors appear to have compared averages over all electrodes (e.g., Chen et al., 2013, Sabeti, Katebi, & Boostani, 2009), and yet others have included comparisons by electrode groups (e.g., comparisons among frontal, temporal, and occipital lobes such as those presented by Thilakavathi, Shenbaga, Bhanu, & Malaippan, 2017).

3.4.1 EEG in Schizophrenia

There have been a multitude of nonlinear index EEG studies comparing schizophrenia patients to healthy controls, often producing contradictory results. Fernández et al. (2013) give an excellent discussion of the situations in which these various contra-

dictions arise and provide an argument, derived from the disconnection hypothesis of Friston (1996) and Friston and Frith (1995), for the notion that nonlinear indices should be higher in schizophrenia patients than controls. Building on an insight of Lee et al. (2008), they sought to explain the observation that this was frequently not the case as the result of the interplay of symptoms, medication (antipsychotics), and age. Specifically, recall the L-F proposal that higher complexity tends to be the default condition in symptomatic unmedicated schizophrenia (especially first-episode patients) with this tendency being dampened or even inverted by medication (antipsychotics), increasing age, and decreasing symptoms. Fernández et al. (2011) provide empirical support for the proposed effect of aging by noting that, in a magnetoencephalography study, LZC decreased with age in schizophrenia patients, a phenomenon they attributed to a possible "progressive defect".

The present authors began this work with three notions in mind. The first was that more studies have been done since the Fernández et al. (2013) article and perhaps sufficient data now existed for a quantitative analysis of the L-F proposal. The second was that perhaps enough data existed that it could be determined if the actual condition under which the EEG data was collected (e.g., resting eyes-closed vs. counting or visual stimulation) also played a consistent role in the outcome. We believed that condition could play a role since various other authors have noticed a change in outcome (increase or decrease) when moving from one condition to another (e.g., Kirsch, Besthorn, Klein, Rindfleisch, & Olbrich, 2000). Finally we hoped that enough data existed that perhaps differences in behaviour between nonlinear indices could be discerned. Unfortunately, neither a clear difference between nonlinear in-

dices nor a clear consistency within conditions emerged from the data. However, the decision to include all conditions permitted us to inflate our data set (allowing a quantitative analysis of aspects of the L-F proposal) and to make the observation that, in many cases, the outcome was a statistically nonsignificant (ns) difference between schizophrenia patients and controls. This is true even in papers that report a significant difference; for example, the authors may have collected data under three conditions of which only one was statistically significant. This raises the possibility of a serious "file drawer" problem, involving papers that were shelved because they did not obtained statistically significant differences.

In the presentation that follows we have accepted the statistical conclusions of the authors of each paper at face value provided that they have indicated that a statistical test has been carried out and that the statistical data they offer does not contradict their conclusions. In the latter respect, we note that Sabeti et al. (2009) conclude that ApEn, LZC, and HFD are lower in schizophrenia patients than controls, but the error bars (standard deviations) they present on their graph lead to a statistically nonsignificant conclusion for their sample size of 20. (Thus we have entered "ns" for their paper in Table 3.6). Similarly, Katebi and Sabeti (2012) report that D_2, HFD, and KFD are lower in schizophrenia patients than controls, but electrode-by-electrode independent-sample t-tests of the means and standard deviations presented in their table produce ns results. It should be noted that in the case of HFD, the use of a paired t-test (with electrodes acting as "blocks" and ignoring the individual standard deviations) does produce a globally significant result, but other authors do not use this approach and there is some conceptual question as to whether

it is appropriate. Thus we have entered "ns" in Tables 3.2 and 3.6. At times we have also used data provided by other authors to augment their results; for example, Carlino et al. (2012) provide means and standard deviations at each electrode for each of their four conditions, enabling us to carry out independent-sample t-tests at each electrode for each condition. We note that their entry at the F_{p2} electrode for controls in the resting eyes-open condition appears to be a typographical error, and we have ignored it, assigning that electrode a "ns" value in keeping with other electrodes in that condition.

Quantitative Analysis of Correlation Dimension in Schizophrenia

Sufficient data has been collected on D_2 that a quantitative analysis can be carried out on it alone. (It is desirable to separate the nonlinear indices if possible in order to reduce confounds.) The outcomes are listed in Table 3.2 by year of publication, where "higher" implies that D_2 was higher in the schizophrenia patients than controls. We divide patients into four groups and retain the following notation throughout: MED = medicated, NMF = never-medicated first episode, UM = unmedicated (which includes the possibility of prior medication), and UMx = unmedicated for at least x months. Medication, in the context of schizophrenia patients, always refers to antipsychotics.

The paper of Lee et al. (2001b) is often cited as an example of UM patients yielding a lower correlation dimension than controls but they utilized a spatial embedding (rather than time delay embeddings) to calculate a global dimension D_S whose interpretation and relation to D_2 is controversial (Pezard, Lachaux, Thomasson, & Martinerie, 1996; Pritchard, 1999; Pritchard, Krieble, & Duke, 1996). Hence we have

not included it in Table 3.2 or our analysis. We have also omitted a commonly cited paper by Elbert, Lutzenberger, Rockstroh, Berg, and Cohen (1992) since they actually computed pointwise dimension D_1, a related but distinct quantity that provides an upper bound on D_2.

Table 3.2: Outcome of D_2 in EEG of schizophrenia patients vs. controls by condition

authors	N	mean age	patient status	condition	result
Koukkou et al. (1993)	15	27.6	NMF	initial resting	ns
				rest eyes closed	ns
				before audio #1	higher
				after audio #1	higher
				before audio #2	higher
				after audio #2	ns
Koukkou et al. (1993)	12	27.3	remitted UM3	initial resting	ns
				rest eyes closed	ns
				before audio #1	ns
				after audio #1	ns
				before audio #2	ns
				after audio #2	ns
Röschke et al. (1994)	11	28	acute UM3	sleep stage II	lower
				sleep stage III	ns
				sleep stage IV	ns
				REM sleep	lower
Lutzenberger et al. (1995)	18	34.4	chronic MED	count backwd	ns
				observe pendulum	higher
				imagine pendulum	ns
Hoffman et al. (1996)	12	33.9	UM1 or NMF	passive visual	lower
Jeong et al. (1998)	13	27.3	MED	rest eyes closed	lower
Saito et al. (1998)	9	20.7	NMF	rest eyes closed	higher
Kirsch et al. (2000)	87	26.9	remitted MED	rest eyes open	ns
				task CPT1	higher
				task CPT2	higher
Lee et al. (2001a)	18	30.6*	UM	rest eyes closed	higher
Jin et al. (2003)	10	35.8*	chronic MED	rest eyes closed	lower
				sound & light	lower
Katebi et al. (2012)	10	?	?	rest eyes open	ns
Carlino et al. (2012)	17	34.7	stable MED	rest eyes closed	higher
				rest eyes open	ns
				count forward	ns
				count backward	higher
Zhao et al. (2012)	31	25.9	MED	rest eyes closed	higher

(table continued next page)

MED = medicated (antipsychotics)
UM = unmedicated; UMx = unmedicated for at least x months
NMF = never medicated first-episode

sample sizes for controls similar or identical to those of patients so omitted from table

* controls are not age-matched with patients, otherwise age-matched

Table 3.2 (continued):

authors	N	mean age	patient status	condition	result
Chen et al. (2013)	45	31	NMF	rest eyes closed	ns
				rest eyes open	ns
				count backward	lower
				memory test	ns
				number cancel	lower
Akar et al. (2015a)	22	34.6	neg symps MED	rest eyes closed	ns
				white noise	ns
				music	higher
				after music	ns

From Table 3.2 we see that out of the 43 reported conditions (each condition within each study is counted as a separate condition, even if that condition is also examined in another study), D_2 is higher in patients in 12 conditions and lower in patients in 8 conditions. This is a 3:2 ratio. Moreover, we calculated the effect sizes (Hedge's g) for the statistically significant results for those papers for which such data was available, and most effect sizes were large ($g > 0.8$) and all were at least medium-large ($g > 0.6$), regardless of whether D_2 was higher or lower. This suggests that statistically significant results (whether higher or lower) are reporting a meaningful effect, and further suggests that something distinctly different is occurring in studies that yield higher rather than lower results (and conversely).

From Table 3.2 we also see that the greatest number (23) of outcomes are in fact ns. An ns outcome actually has an important role to play here. For example, if there is a propensity toward higher D_2 in UM patients and medication reduces this propensity (a tenet of the L-F proposal) then we may see a shift from higher D_2 toward ns differences in MED patients.

We also note from Table 3.2 that there appears to be a strong "study effect", i.e., within any given study, we do not see "higher" appear in one condition and "lower" appear in another. Rather, the outcomes of any one study are all of the same

type (higher or lower) with perhaps some ns outcomes mixed in for some conditions. This suggests that the "study effect" (possibly due to the fact that repeated measures are carried out on the same group of patients) is more important than the conditions under which the study is carried out. This in itself lends support for something like an L-F proposal which suggests that patient characteristics are the dominating factor in outcome. However, laboratory procedures (which may differ from laboratory to laboratory) may also contribute to this pattern of outcomes.

In order to quantitatively test aspects of the L-F proposal, we will utilize contingency tables (chi-square tests of independence). For example, Table 3.3 tests whether medication status is independent of outcome. UNMED combines all those conditions in which the patients are NMF, UM, or UMx (in other words, it comprises all conditions in which patients were unmedicated at the time of the study). The observed number of conditions, with the expected number (under the hypothesis of independence) alongside in brackets, is given in each cell. The observed chi-square statistic and its p-value is given at the base of the table. As we can see, there is no evidence of an association between medication status and outcome.

Table 3.3: Contingency Table Medication Status vs. Outcome for D_2

	higher	lower	ns
UNMED	$5_{[6.86]}$	$5_{[4.57]}$	$14_{[12.57]}$
MED	$7_{[5.14]}$	$3_{[3.43]}$	$8_{[9.43]}$

$\chi^2_{\text{obs},2} = 1.651$, $p = .438$

Two caveats must be made here. First, it is typical to require expected cell frequencies of at least 5 to validate the chi-square approximation. However, this

requirement can be relaxed, as discussed in Lawal and Upton (1984). It is sufficient if the minimum expected frequency exceeds $5s/rc$ where s is the number of cells having expected frequency < 5 and r and c are, respectively, the number of rows and columns in the table. Here we require min > 1.67 which is clearly satisfied. The second caveat we must make is to acknowledge again that, within studies, outcomes are repeated measures on the same group of patients, possibly contributing to what we have already noted is a "study effect". However, it is important to realize that it is the conditions (not the patients) which are actually being slotted into the contingency tables. To use an analogy, if we regard a condition as being a geographical region being evaluated for independence of its agricultural yield and rainfall, there is no difficulty in seeing widely-separated geographical regions (conditions from different laboratories) as unrelated entities, while we might expect physically close but distinct geographical regions (different conditions evaluated in the same laboratory) to potentially have similarities in rainfall and yield. This does not prevent us from classifying these regions into a table, and we expect that strong trends within the data would be picked up by the chi-square statistic.

We carried out a similar analysis to look for an age effect. It was decided to partition the data into those in which the mean age of the sample was under 30 and those in which the mean age was over 30. This division was not arbitrary. It permitted the division into two groups of roughly equal size, and resulted in a 2-year age gap between the oldest in the younger group and the youngest in the older group. Moreover, since the first-time onset of schizophrenia is usually prior to age 30, we expected to catch most of such patients in the first group. The results are displayed

in Table 3.4. No association between age and D_2 outcome is observed.

Table 3.4: Contingency Table Age vs. Outcome for D_2

	higher	lower	ns
under 30	$7_{[6.29]}$	$3_{[4.19]}$	$12_{[11.52]}$
over 30	$5_{[5.71]}$	$5_{[3.81]}$	$10_{[10.48]}$

$\chi^2_{\text{obs},2} = 0.920$, $p = .631$

It can be argued that the L-F proposal really suggests an interplay between age, medication, and symptomatology, so we present a contingency table which examines UNMED and Under Age 30 vs. MED and Over Age 30. The expected cell frequencies of this reduced data set are too low to carry out a chi-square analysis but we present the table for visual inspection. Unfortunately too little is known about the actual symptomatology of patients in most studies to include this in any meaningful way.

Table 3.5: Contingency Table Medication Status × Age vs. Outcome for D_2

	higher	lower	ns
UNMED and under 30	$4_{[4.53]}$	$2_{[2.27]}$	$11_{[10.20]}$
MED and over 30	$4_{[3.47]}$	$2_{[1.73]}$	$7_{[7.80]}$

In the next subsection we augment our data set by including outcomes from other nonlinear indices.

Quantitative Analysis of All Indices in Schizophrenia

It could be argued that the data set in Table 3.2 is too small for the chi-square statistic to pick up moderate associations. In Table 3.6 we compile data from all other nonlinear indices. Our procedure will be to repeat the analysis of the preceding

subsection, using all the nonlinear indices together (including D_2 from Table 3.2, although, for the sake of parsimony, we have not re-entered those values in Table 3.6). This makes the basic (and questionable) assumption that all nonlinear indices behave the same way with respect to medication, age, and symptomatology.

For the reader's convenience, in Table 3.6 we have grouped papers together by index, so that the reader may see how outcomes differ even within the same index. Some authors have studied more than one index in the same paper so their paper appears multiple times on the table, once for each index. For example, Thilakvathi et al. (2017) have studied LZC, ApEn, and HFD, so their paper appears thrice. Once again we notice a very strong "study effect" that in fact extends to all indices measured within the same study. By that we mean not only do we observe the same result (or ns) for a given index measured over different conditions, if authors measure one index as lower in patients then they will also measure other indices as lower in patients. There are only two exceptions to this rule. Akar et al. (2015a) found D_2 to be higher in patients in the music condition (see Table 3.2) while finding λ_1 to be lower in patients in all conditions (see Table 3.6). Thilakvathi et al. (2017) found both LZC and ApEn to be ns in the resting eyes-closed condition but HFD to be higher in patients in that condition. Totalling over both Tables 3.2 and 3.6, we observe 29 conditions in which the index is higher in patients than controls and 19 in which it is lower, maintaining the same 3:2 ratio observed for D_2 alone.

Table 3.6: Outcome of index in EEG of schizophrenia patients vs. controls by condition

authors	index	N	mean age	patient status	condition	result
Röschke et al. (1995)	λ_1	13	28	acute UM3	sleep stage I	ns
					sleep stage II	ns
					sleep stage III	ns
					sleep stage IV	ns
					REM sleep	higher
Kim, & Jeong et al. (2000)	λ_1	25	25.1	MED	rest eyes closed	lower
Keshavan et al. (2004)	λ_1	10	20.5	NMF	rest eyes closed	ns
					sleep stage I-II	ns
					sleep stage III-IV	ns
					REM sleep	lower
Akar et al. (2015a)	λ_1	22	34.6	MED	rest eyes closed	lower
					white noise	lower
					music	lower
					after music	lower
Fritzsche et al. (2006)	KSE	22	32.2	stable MED	rest eyes closed	higher
					count backward	higher
Zhao et al. (2012)	KSE	31	25.9	MED	rest eyes closed	higher
Li et al. (2008)	LZC	62	34.8	NMF	rest eyes closed	higher
					count backward	higher
Sabeti et al. (2009)	LZC	20	33.4	MED	rest eyes open	ns
Zhao et al. (2012)	LZC	31	25.9	MED	rest eyes closed	higher
Akar et al. (2016)	LZC	22	41.1	chronic MED	rest eyes closed	lower
Cerquera et al. (2017)	LZC	9	42.2	deficit MED	rest eyes open	ns
	LZC	10	40.3	nondeficit MED	rest eyes open	ns
Thilakvathi et al. (2017)	LZC[1]	55	40.3	MED	rest eyes closed	ns
					visual stimulus 1	higher
					visual stimulus 2	higher
Sabeti et al. (2009)	ApEn	20	33.4	MED	resting eyes open	ns
Taghavi et al. (2011)	ApEn	10	36.5	remitted MED	rest eyes open	lower
Akar et al. (2016)	ApEn	22	41.1	chronic MED	rest eyes closed	lower
Thilakvathi et al. (2017)	ApEn	55	40.3	MED	rest eyes closed	ns
					visual stimulus 1	higher
					visual stimulus 2	higher

(table continued next page)

[1]Thilakvathi et al. (2017) call this Kolmogorov complexity but in fact they have defined LZC

Table 3.6 (continued):

authors	index	N	mean age	patient status	condition	result
Takahashi et al. (2010)	MSE	22	25.6	NMF	resting	higher
		15	25.7	post MED	resting	ns
Raghavendra et al. (2009)	HFD	18	?	NMF	rest eyes closed	lower
Sabeti et al. (2009)	HFD	20	33.3	MED	rest eyes open	ns
Katebi et al. (2012)	HFD	10	?	?	rest eyes open	ns
Thilakvathi et al. (2017)	HFD	55	40.3	MED	rest eyes closed	higher
					visual stimulus 1	higher
					visual stimulus 2	higher
Katebi et al. (2012)	KFD	10	?	?	rest eyes open	ns
Akar et al. (2015b)	KFD	22	41.1	chronic MED	rest eyes closed, noisy	ns
					rest eyes closed, denoised	lower
Yu et al. (2016)	RBFD	17	28	NMF	Tower of Hanoi	ns
					TMT-A	higher
					TMT-B	higher

The contingency tables (computed for those articles for which mean age and/or medication status are known as required) are:

Table 3.7: Contingency Table Medication Status vs. Outcome for All Indices

	higher	lower	ns
UNMED	$11_{[13.33]}$	$7_{[8.74]}$	$22_{[17.93]}$
MED	$18_{[15.67]}$	$12_{[10.26]}$	$17_{[21.07]}$

$\chi^2_{\text{obs},2} = 3.105$, $p = .212$

Table 3.8: Contingency Table Age vs. Outcome for All Indices

	higher	lower	ns
under 30	$13_{[13.15]}$	$5_{[8.16]}$	$21_{[17.69]}$
over 30	$16_{[15.85]}$	$13_{[9.84]}$	$18_{[21.31]}$

$\chi^2_{\text{obs},2} = 3.375$, $p = .185$

Tables 3.7 and 3.8 show no evidence for an association between medication status and outcome, or between age and outcome, although in the latter case we see that younger patients are about 2.5 times more likely to have a higher than a lower outcome, whereas older patients are almost equally likely to have either outcome. Adding in the other indices has not only increased the sample size but increased the available age status in the pool (e.g., we now have some samples in which the average age exceeds 40). This time we have enough data to compare UNMED and Under 30 vs. MED and Over 30.

Table 3.9: Contingency Table Medication Status × Age vs. Outcome for All Indices

	higher	lower	ns
UNMED and under 30	$8_{[9.26]}$	$3_{[5.74]}$	$19_{[15]}$
MED and over 30	$13_{[11.74]}$	$10_{[7.26]}$	$15_{[19]}$

$\chi^2_{\text{obs},2} = 4.557$, $p = .102$

In Table 3.9 we see a weak trend suggesting that age and medication factors may combine to create some sort of effect on outcome. Younger unmedicated patients appear about 2.5 times more likely to have a higher index than a lower one relative to controls; older medicated patients are about equally likely to have higher or lower indices. Perhaps what is most striking from Table 3.9 is the observation that the

UNMED and Under 30 group are almost twice as likely to have an ns outcome rather than any other outcome; this may be partly accounted for by the inclusion in Table 3.9 of the young unmedicated remitted patients of Koukkou, Lehmann, Wackermann, Dvorak, and Henggeler (1993) who were ns under six conditions (Table 3.2). Table 3.9 suggests that medication may produce a slight shift from higher to lower or ns results in older patients.

Missing in the above analysis is the role of symptomatology as most papers do not supply details of this. However, the next subsection deals with some results and hypotheses concerning the role of symptoms.

The Role of Symptomatology in Index Outcome in Schizophrenia

Even the extreme ends of the L-F proposal do not always hold true, as can be seen in Keshavan, Cashmere, Miewald, and Yeragami (2004) who found lower λ_1 in very young NMF patients (Table 3.6), and in Thilakvathi et al. (2017) who found higher LZC, ApEn, and HFD in MED patients whose average age exceeded 40 (Table 3.6). This, combined with the mixture of results from Tables 3.2 and 3.6, the strong "study effect", and weak, at best, evidence of association provided by the chi-square analyses, suggests that other factors beyond age and medication status must be in play. The L-F proposal does suggest that symptomatology plays a role, favouring higher indices for NMF patients (who are highly symptomatic with positive symptoms almost by definition) and lower indices for chronic patients, who are dominated by negative and cognitive symptoms. In this section, we propose that recent work by Cerquera, Gjini, Bowyer, and Boutros (2017) sheds some light on this subject, explaining why young

UNMED patients may score lower and older MED patients may score higher. Specifically, Cerquera et al. (2017) studied two separate groups of schizophrenia patients. One group was defined to have deficit schizophrenia (DS), a syndrome characterized by severe primary and persistent negative symptoms, poor psychosocial premorbid functioning, and worse prognosis than their nondeficit (NDS) counterparts (Kirkpatrick & Galderisi, 2008). To qualify as DS, a patient must meet criteria on the Scale for the Deficit Syndrome (Kirkpatrick, Buchanan, McKenny, Alphs, & Carpenter, 1989). There is some question in the literature as to whether DS may even be a separate disease entity from NDS. Cerquera et al. 's patients were medicated, were not young, and sample sizes were small (mean age of DS = 42.2, N = 9; mean age of NDS = 40.3, N = 10). They found the LZC of DS patients to be statistically significantly lower than that of NDS patients with a large effect size (Cohen's $d = 1.539$). The controls fell in between the two groups, with the DS being lower than the controls with a trend ($p < .1$) toward statistical significance and a large effect size ($d = 1.002$). The LZC of NDS patients was higher than that of controls with a medium effect size ($d = 0.428$) although not statistically different. It is easily argued that with such small sample sizes there was insufficient power to separate all three groups, and we propose that replication with sufficient power might show the NDS patients to have higher LZC than controls, and the controls to have higher LZC than the DS patients. The authors also found that LZC was positively correlated with general psychopathology scores on the PANSS (Kay, Fiszbein, & Opler, 1987), explained partially by the emotional component subscale, which comprises anxiety, guilt feelings, depression, and active social avoidance. Kirkpatrick and Galderisi (2008) point out that DS pa-

tients are "less distressed" than their NDS counterparts, and it is reasonable to posit that DS patients might therefore score lower on the emotional component, thereby suppressing their LZC scores.

We therefore propose that the outcome in index studies may be governed in part by the predominance of the type of patient (DS vs. NDS) in that particular study. It may be that NDS patients, governed more by positive symptoms and emotional reactivity, tend to score as high or even higher than controls. Medication may temper some of this response; Takahashi et al. (2010) apparently performed the first study to compare never medicated patients before initiation of medication and after 2-8 weeks of medication. They used MSE as a discriminator, and found that for high scaling frequencies τ ($10 \leq \tau \leq 40$ depending on electrode location) MSE was significantly higher in pre-treatment patients than controls in the fronto-central-temporal regions. These differences became nonsignificant in the fronto-central regions post-treatment, but the differences in the temporal regions did not vanish.

Koukkou et al. (1993) were the first to consider that symptomatology could play a role in outcome. They included a group of fully remitted UM3 patients in their study along with a group of NMF patients and a group of controls. In Koukkou, Lehmann, Federspiel, and Merlo (1995) they more fully describe the patients in Koukkou et al. (1993), stating that the NMF patients had such severe positive symptoms that they required hospitalization, and the UM3 patients had achieved "complete clinical and social remission" from which we can conclude the remitted patients were remitted NDS. The D_2 values for the remitted patients fell between those of the NMF patients and the controls, but were not significantly different from either

of them, although the NMF patients were significantly higher than the controls.

Raghavendra, Dutt, Halahalli, and John (2009) also noted that the type of symptomatology was relevant. They calculated HFD in NMF patients under the resting eyes closed condition, and whereas they found HFD to be significantly lower generally in patients than controls (suggesting to us that perhaps they had several DS patients) they found that among those patients with prominent positive symptoms and an absence of negative symptoms, HFD appeared higher than that of controls in the temporal regions. .

3.4.2 EEG in Bipolar Disorder

Very little work has been done in applying nonlinear indices to EEG in bipolar patients. There seem to have been three papers investigating bipolar disorder or mania. Thomasson, Pezard, Boyer, Renault, and Martinerie (2002) followed one rapid-cycling bipolar II patient with a pronounced predictable 48-hour cycle, alternating between one day of hypomania and one day of depression. They collected mood data twice daily, and performed a 31-channel EEG (using a motor task response) on each of six consecutive days. They used the multiple channels to construct a 31-dimensional spatial embedding and computed KSE for each day. Their main result was that high values of KSE were correlated with depressed days and low values of KSE were correlated with hypomanic days. Bahrami, Seyedsadjadi, Babadi, and Noroozian (2005) noted that computer simulations have suggested that increased HFD of the graph of the EEG is due to "asynchronous co-activation of multiple neuronal populations in the cortex" (p. 190). Using 19-electrode EEG recordings, they were able to establish

that HFD of the EEG in acute manic inpatients was significantly greater than that of controls. (Patients were on a variety of medications). They concluded that brain complexity is greater during mania, in the sense that the brain is dominated by an increasing number of independently and asynchronously firing neural assemblies. In contrast, Bhattacharya (2000) reported that persons with mania exhibited similar EEG profiles to those of controls.

We were unable to locate any articles examined EEG in bipolar depression. Articles are now starting to appear on EEG in major unipolar depression. With the important caveat that behaviour in unipolar depression may not be the same as in bipolar depression, we note that an (inexhaustive) search of unipolar depression has revealed a general consensus that nonlinear indices seem to be higher in depression than in controls. Ahmadlou, Adeli, and Adeli (2012) founder higher HFD (but not KFD) in unmedicated depressive patients than controls. Akar, Kara, Agambayev, & Bilgiç (2015a,b) found both higher HFD and higher KFD in medicated depressive patients, not only in resting conditions but in audio conditions (being subjected to music and noise). Bachmann, Lass, Suhhova, and Hinrikus (2013) also found higher HFD in depressive patients. Li et al. (2008) found not only that LZC was higher in NMF psychotic depression patients compared to controls but that it was even higher in depression than in schizophrenia. Akar et al. (2015a) as well as Bachmann, Kalev, Suhhova, Lass, and Hinrikus (2015) also observed higher LZC in depression patients compared to controls. Thomasson and Pezard (1999) did not use controls but followed a single recurrent depression patient over the course of treatment and found KSE to be highly correlated with self-report measures of depression symptoms. Specifically,

KSE was high at the start of treatment and decreased as health improved.

In a recent article, Jaworska et al. (2018) were able to use pre-treatment MSE to predict response to antidepressant medication.

3.5 Applications to Heart Rate Variability (HRV)

Persons with schizophrenia or bipolar disorder are at increased risk of cardiovascular disease and death (Brown, Inskip, & Barraclough, 2000; Enger et al., 2004, Kessing, Vradi, & Andersen, 2015). Among other factors such as lifestyle habits, this has been linked to changes in the Autonomic Nervous System (ANS) controlling the rhythms of the heart. Psychotropic medication is also known to adversely affect the ANS, and part of the focus of current research is teasing apart the effects of disease from the effects of medication. Voss et al. (2006) makes the important point that the field has historically suffered from serious confounding effects, such as having patients on differing types of medication, having patients with differing degrees of illness, and featuring a lack of properly matched controls. However, recent studies have made inroads toward addressing these issues.

A common noninvasive tool is to study the heart rate variability (HRV) of the RR series (Sec 3.3.5). Reduced HRV is a known risk factor for cardiac illness and death (Klieger, 1995). It is postulated that greater HRV offers a protective effect, allowing the heart rhythm to adapt to environmental perturbations and return to normal functioning (Levy, 1990). Standard linear indices for studying HRV include SDNN (the standard deviation of the normal-to-normal RR-intervals), RMSSD (the square root of the mean sum of squared differences between successive normal-to-

normal RR intervals), and pNN50 (the proportion of successive normal-to-normal RR intervals that differ by more than 50 ms). A lower value of SDNN, RMSSD, or pNN50 is indicative of a reduction in some aspect of HRV. It is also typical to analyze the RR series in the frequency domain, reporting on the power in the low and high regions of the spectrum, in order to examine the balance between the sympathetic and parasympathetic (vagal) forces on the heart. HRV is also investigated using nonlinear indices, the most popular being the time domain indices as they are better suited to the shorter and noisy RR series arising from ECG data. Typical choices include symbolic dynamics, Hc, ApEn, SampEn, MSE, and KFD. Lower values for these quantities are indicative of a reduction in the complexity (more precisely, an increase in the regularity) of the RR series. Voss et al. (1996) point out that a synthesis of both linear and nonlinear indices can aid in discriminating between persons at risk for sudden cardiac events.

As will be seen below, HRV analysis leads to much more consistent results than those obtained in the EEG analyses of the preceding section. In general, patients with schizophrenia exhibit reduced HRV and reduced RR complexity compared to healthy controls. Much less work has been done on bipolar disorder, but results there also point toward reduced HRV and reduced complexity.

3.5.1 HRV in Schizophrenia

The tendency in schizophrenia toward parasympathetic withdrawal and sympathetic predominance in heart rate modulation as well as the reduction in HRV, as measured by linear and spectral indices, has been documented by Montaquila, Trachik, and

Bedwell (2015) and Clamor, Lincoln, Thayer, and Koenig (2016). Thus we focus on articles that have employed nonlinear indices. A number of studies have provided evidence that RR series from unmedicated (UM) schizophrenia patients result in significantly lower nonlinear scores than those from healthy matched controls. Compression entropy Hc has been repeatedly evaluated and found to be lower in such patients (Bär et al., 2007; Bär, Boettger, et al., 2008; Bär, Koschke, et al., 2008; Schulz, Bär, & Voss, 2015). ApEn and KFD were found to be significantly reduced in Bär et al. (2007) and Bär, Koschke, et al. (2008). SampEn was found to be lower in Chang et al. (2009) and Schulz, Bär, and Voss (2015), and only failed to reach statistical significance after Bonferroni correction in Chang et al. (2010). Various versions of symbolic dynamics (methods I or II) have also revealed reduced complexity in UM patients (Bär et al., 2007; Bär, Boettger, et al., 2008; Mujica-Parodi, Yeragani, & Malaspina, 2005; Schulz, Bär, & Voss, 2008; Schulz, Bär, & Voss, 2015). Thus the evidence that RR complexity is reduced due to schizophrenia itself is compelling.

Antipsychotics can also have an impact on HRV and carry an increased risk of cardiac death, even for persons without schizophrenia (Silke, Campbell, & King, 2002; Strauss et al., 2004). Thus research has also focussed on the effects of antipsychotics on HRV in schizophrenia. The results have suggested that in general antipsychotics tend to further reduce HRV and complexity. Schulz, Bär, and Voss (2008) examined 46 acute hospitalized patients split into two groups, medicated (MED) and unmedicated (UM). They calculated the Shannon entropy as well as the forbidden words of the symbolic dynamics Method II words. The Shannon entropy was lower and the number of forbidden words higher in the MED group, indicating lower complexity.

They also calculated plvar and phvar from symbolic dynamics Method I. The former was higher and the latter lower in the MED group, again indicating lower complexity in the MED group. Schulz, Bär, and Voss (2009) extended this study to include Hc, also finding it lower in the MED group. One shortcoming of their analysis, as noted by the authors, is that patients were on a variety of antipsychotics, so differences due to antipsychotic choice could not be ascertained. Mujica-Parodi et al. (2005), comparing UM patients with patients treated with either clozapine or olanzapine, found that the percentage word count from symbolic dynamics Method II exhibited a trend toward lower values among MED patients. Bär, Koschke, et al. (2008) calculated ApEn, KFD, and Hc in patients before and after seven days of treatment with olanzapine, and found Hc to be significantly lower after treatment. Chang et al. (2010), however, who studied patients before and after six weeks of risperidone treatment, did not find a significant change in SampEn or the Shannon entropy of words constructed from symbolic dynamics Method I. The article by Kim, Yi, Lee, and Kim (2013) is a particularly important paper because it illustrates the point that the effect of antipsychotics on HRV may be more subtle than simply one of suppression. Kim, Yi, et al. obtained baseline Positive and Negative Syndrome Scales (PANSS) scores as well as baseline ApEn and SampEn scores on 42 treatment-resistant patients. These quantities were re-evaluated after four weeks and again after eight weeks of monotherapy with clozapine. As a group, the patients exhibited significantly lower ApEn and SampEn at four weeks than at baseline, with slightly higher (but still suppressed with respect to baseline) values at eight weeks. However, based on changes in PANSS scores from baseline to eight weeks, Kim, Yi, et al. retrospectively classified

patients as responders (37.5%) or non-responders (62.5%). They observed that both ApEn and SampEn decreased from baseline through week four through week eight for the non-responders. However, for the responders, ApEn and SampEn decreased through week four, but then increased to slightly above baseline values at week eight. The difference in ApEn and SampEn values between responders and non-responders at week eight was statistically significant. In our view this suggests that patients having a good response to an antipsychotic may be less compromised by deleterious effects of the medication, possibly because their ANS responds to the improvement in symptoms. The paper also illustrates the importance of the time frame over which treatment response is evaluated; the rise in ApEn and SampEn values in responders was not seen until week eight.

The aforementioned article by Kim, Yi, et al. (2013) suggests that there may be a relationship between HRV and degree of psychopathology symptoms, and this has in fact been investigated by a few authors. Kim et al. (2004) compared 50 clozapine-treated patients with 50 controls, using RMSSD, pNN50, ApEn, SampEn and the Shannon entropy of words constructed from symbolic dynamics Method I. All these indices were significantly lower in the patient group, but what was new was an observed significant negative correlation between SampEn and both the total scores and positive symptoms subscales of the PANSS, even after controlling for clozapine dose. Chang et al. (2010), who compared PANSS scores before and after six weeks of risperidone treatment in a small sample ($N = 16$), found a significant negative correlation between changes in SDNN and changes in the PANSS positive symptoms subscale as well as a significant negative correlation between changes in RMSSD and

changes in both the PANSS total score and positive symptom subscales. SampEn was not correlated with these changes. Kim, Ann, and Lee (2011) compared SDNN, RMSSD, and ApEn with PANSS scores of 21 patients on risperidone monotherapy. Although ApEn was reduced in the patients compared to the controls, ApEn did not correlate with the PANSS scores. However, similar to what was obtained by Chang et al., Kim et al. found (after controlling for risperidone dose) a significant negative correlation between PANSS total scores and both SDNN and RMSSD. In addition, they found a significant negative correlation between the PANSS cognitive/disorganization factor and both SDNN and RMSSD. Chung et al. (2013) ran a much larger study (94 medicated patients, 51 healthy controls) and evaluated SDNN, RMSSD, pNN50, ApEn, and MSE, where an overall score for this last quantity was calculated by summing the SampEn values over all scaling factors $1 \leq \tau \leq 20$. SDNN, RMSSD, and pNN50 were all negatively correlated with the PANSS positive subscale. MSE was negatively correlated with the PANSS general psychopathology scale, and both MSE and ApEn were negatively correlated with the equivalent haloperidol dose of the patients. A unique aspect of this study was that metabolic profiles of the participants were also examined, and both ApEn and MSE showed some correlation with aspects of metabolic syndrome, e.g., they both were negatively correlated with amount of high-density lipoprotein. Thus the HRV indices, especially the linear indices, seem to be sensitive to degree of psychopathology, particularly the positive symptoms.

Two recent papers have investigated the possible role of HRV indices in evaluating side effects of antipsychotic medication. Kim, Ann, Lee, Kim, and Han (2013) studied ApEn in the context of Antipsychotic Induced Subjective Restlessness (AISR)

which can be an unpleasant side effect of antipsychotics and interfere with treatment compliance. They found that the severity of AISR was significantly negatively correlated with ApEn. Chang et al. (2015) studied a number of linear and nonlinear HRV indices in the context of subjective self-reports on side effects of antipsychotics. While they found correlations between side effects and various indices, they pointed out that SampEn seemed to be more sensitive than the linear indices and exhibited a significant negative correlation with extrapyramidal and anticholinergic side effects.

In summary, nonlinear (and linear) indices of HRV have been shown to differ between schizophrenia patients and healthy controls, and to further differentiate between medicated and unmedicated patients in a number of areas. The ultimate goal would be to do be able to use these indices clinically to predict (and prevent) adverse cardiac events and adverse responses to certain antipsychotics.

3.5.2 HRV in Bipolar Disorder

There have been comparatively few studies done on bipolar disorder involving nonlinear indices, so we first report on articles involving only linear indices in order to present evidence that HRV, as measured by linear indices, is reduced in bipolar patients regardless of clinical mood state. Cohen et al. (2003) analyzed euthymic medicated bipolar patients and found SDNN to be lower in patients than controls. The patients were on a variety of medications, but an ANOVA did not reveal any difference in SDNN between medication groups, so the authors proposed that the reduced HRV was due to the disease and not the medications. Voggt et al. (2015) also found reduced SDNN in medicated euthymic bipolar patients and argued that

medication was not likely the sole cause of the reduction. Lee, Kim, Hong, and Joo (2012) analyzed medicated bipolar patients who were in a subsyndromal depressive state and found both SDNN and pNN50 (althought not RMSSD) significantly reduced compared to controls. The proposal that the disease itself (apart from medication) carries a risk for reduced HRV has now been supported by recent work of Chang et al. (2014) and Chang, Chang, Kuo, and Huang (2015). Chang et al. (2014) compared 61 patients during an acute manic episode with 183 matched controls. Participants were carefully selected to have no physical condition or smoking history that could impact HRV; moreover, patients could have no comorbid psychiatric diagnosis and had to be unmedicated for at least one month (UM1). Chang et al. found SDNN significantly lower in patients than controls. Furthermore, SDNN was inversely correlated with scores on the Young Mania Rating Scale. Chang et al. (2015) then carried out a study comparing UM1 depressed bipolar II patients to UM1 depressed unipolar patients and controls (again carefully selecting for physical health, smoking history, and lack of comorbidities). They found that SDNN was significantly lower in the bipolar patients than in both the unipolar patients and controls. Since the two patient groups were matched on severity of symptoms, the authors suggested that their results may indicate that bipolar II depression and unipolar depression are two distinct diseases. The most important point to be drawn from these studies, however, is that HRV, at least as measured by SDNN, appears to be reduced regardless of the clinical state (manic, depressed, euthymic) of a bipolar patient. A recent meta-analysis (Faurholt-Jepsen, Kessing, & Munkholm, 2017) concludes that there is evidence for reduced HRV in bipolar disorder but makes an argument for stricter methodology in studies.

Most work that has been done in evaluating nonlinear indices in the context of HRV has focused on SampEn. It was first proposed by Migliorini, Mendez, and Bianchi (2012) that SDNN and RMSSD might be useful in discriminating between a bipolar patient and a healthy control (which is consistent with our discussion above) whereas SampEn (and LZC) might be more sensitive to the actual mood state of the patient. Migliorini et al. ran a very small study where they computed normal ranges ($5^{th} - 95^{th}$ percentile) of various indices based on sleep ECG from eight healthy controls. They then determined these same indices for one bipolar patient over four nights (at least one week apart) who was in a different clinical state during each night. The different clinical states were different levels of depression (mild or severe) and different levels of anxiety (low or high). On the fourth night only she was euthymic with low anxiety. SDNN and RMSSD for the patient fell below the normal 5^{th} percentile on all four nights. SampEn, on the other hand, while much below the normal 5^{th} percentile on the first three nights, increased into the normal range on the fourth night. Interestingly, LZC was slightly *elevated* above the normal 95^{th} percentile for the first three nights, dropping into the normal range on the fourth night. The idea that SampEn might be exploited to predict onset of euthymia (and hence response to treatment) has been studied further by Nardelli, Valenza, Gentili, Lanata, and Scilingo (2014) and Lanata, Valenza, Nardelli, Gentili, and Scilingo (2015). The second paper is essentially an extension of the first with a larger sample size. Ten hospitalized patients (either experiencing acute depression or an acute mixed depressive/hypomanic episode) were followed from the initiation of treatment or a change of treatment until remission. In each case SampEn increased almost linearly with

time, with mixed states exhibiting the lowest SampEn and euthymia exhibiting the highest. The authors opined that measuring early changes in SampEn might be an objective way of determining whether a particular treatment protocol was going to be effective for a given patient. It should be noted that data was obtained using very long ECG recordings obtained by having patients wear a comfortable textile T-shirt (with embedded electrodes) as they went about their day. The authors see a future in such personal monitoring systems in providing patients and physicians with feedback on multiple indices of HRV and perhaps predicting mood relapses as well as treatment response. Levy (2014) divided medicated remitted bipolar I patients into two groups, those with high illness severity (HIS) and those with low illness severity (LIS). Patients were considered to be HIS if they had ever had a psychotic episode, otherwise they were classified as LIS. Levy calculated SDNN and SampEn. He found that SDNN could distinguish between HIS patients, LIS patients, and controls, with the first group exhibiting the lowest SDNN and the last group exhibiting the highest SDNN. SampEn, on the other hand, could only distinguish between the HIS group and the controls, assigning lower value to the first. This again suggests that within a fixed mood state (in this case euthymia) SampEn is less sensitive to differences in diagnostic status. Valenza, Nardelli, Bertschy, Lanata, and Scilingo (2014) further studied the discriminatory power of SampEn by considering MSE at different scales τ. They utilized a small sample of six depression recordings, five hypomanic recordings, and five euthymic recordings. MSE was not discriminatory when the standard parameters $m = 2$, $r = 0.15 \cdot \text{SDNN}$ were used in calculating SampEn on each series. However, by changing r to be optimal for each series (in the sense that it maximized

approximate entropy for that series) MSE became discriminatory at most values of $1 \leq \tau \leq 20$. In particular it could distinguish the hypomanic sample from the euthymic sample at $\tau = 1, 2$ and $\tau = 4 - 20$. Moreover, the hypomanic sample could be distinguished from the depressive sample at $\tau = 1, 9, 10$. (The hypomanic MSE scores were the lowest and the euthymic MSE scores the highest.) Since $\tau = 1$ is just SampEn, this is further evidence of the discriminatory power of SampEn among mood states even when samples are small (at least when r is optimal).

A few papers have examined other nonlinear indices. Todder, Bersudsky, and Cohen (2005) re-analyzed the euthymic data of Cohen et al. (2003) using λ_1 as well as symbolic dynamics (Method II) where they computed the Shannon entropy of the word distribution. They found no difference between patients and controls on either index. Thus the lowered HRV that was picked up by SDNN was not buttressed by a reduction in complexity as reflected by these indices. The reasons are unknown and could range from a lack of sensitivity within a fixed mood state (similar to SampEn) to the (unknown) length of the RR series, to which nonlinear indices (especially λ_1) are sensitive. Henry, Minassian, Paulus, Geyer, and Perry (2010) compared bipolar inpatients who were in an actively manic state with schizophrenia inpatients and healthy controls. The majority of all patients were on medication. Henry et al. used symbolic dynamics (Method I) and SampEn along with the linear indices. The manic patients scored significantly lower than the controls on both nonlinear indices as well as RMSSD (interestingly, SDNN was reduced but did not reach statistical significance). There was also a trend toward reduced HRV in the schizophrenia patients (across both linear and nonlinear indices) but these did not reach statistical signifi-

cance. However, the sample size of the schizophrenia patients was about half that of the manic patients. Moon, Lee, Kim, and Huang (2013) investigated differences in HRV in a variety of psychiatric disorders, using more than double the sample sizes of Henry et al. (2010). ECG recordings were taken 0-7 days after starting medication. The only nonlinear index used was ApEn which did not reach statistical significance for any disorder. However, the bipolar patients exhibited significantly reduced SDNN and RMSSD whereas the schizophrenia patients just exhibited reduced SDNN; moreover, the reductions in bipolar disorder were accentuated compared to schizophrenia.

3.6 Applications to Mood Data in Bipolar Disorder

The application of nonlinear indices to the RR series generated by bipolar patients was considered in the previous section. Here we consider applications to mood data generated by self-report measures. Bipolar disorder, as measured by mood data over time, shows some evidence of cyclical behaviour between manic and depressive states, but for almost all individuals these cyclicities are too irregular and unpredictable to be considered truly periodic. This fact was noted almost 100 years ago by Kraepelin (as discussed and cited by Woyshville, Lackamp, Eisengart, and Gilliland, 1999). As such, bipolar mood data presents a natural example of a situation ripe for investigation for the possibility of underlying nonlinear dynamics. In spite of this, there has been relatively little application of nonlinear indices to the analysis of mood data, possibly because of the difficulty of collecting sufficiently long time series to produce reliable estimates. A notable exception is the article by Gottschalk, Bauer, and Whybrow

(1995) who applied estimates of D_2 to distinguish between patients and controls. Gottschalk et al. followed seven rapid-cycling bipolar patients and 28 healthy controls over a period of 1-2.5 years. All patients and controls completed daily mood logs (the controls actually reported mood twice daily, but for the purpose of comparison with the patients one of the daily reports was later dropped). The mood log utilized was a 100-mm continuous analogue scale ranked from "Very Worst I Felt" to "Very Best I Felt" with the midpoint designated as "Normal". Patients placed a mark on the scale indicating their average mood over the preceding 24 hours. A slightly different but similar recording procedure was used for controls. Time series lengths ranged from $n = 358$ to $n = 922$ for the patients, which are short compared to the lengths of time series usually considered in the physical sciences. Plots of the time series revealed clear distinctions between patients and controls; the latter appeared much more irregular or "rougher", whereas the patients' series seemed to suggest more structure with the occasional appearance of cyclical features. In the following discussion we omit Patient 7 who was identified by Gottschalk et al. as the "healthiest" of the patients and who produced data closer to that of the controls. Spectral analysis (which is equivalent to analysis of the autocorrelation function) suggested that both patients and controls had power spectra consistent with a $1/f^{\alpha}$ power spectrum (up to the "noise floor" of the data) where $\hat{\alpha} = 2.24$ for patients and $\hat{\alpha} = 0.57$ for controls. The difference between these two α values was statistically significant. The lack of "peaks" in the spectra (for both patients and controls) indicates the absence of well-defined periodicities in the time series, thus validating the observations of Kraepelin. The higher value of α for the patients is also indicative of a greater degree of short-term correlation in the

patients' data, which is suggested from the time series plots. The key result of the paper, however, was that the Grassberger-Procaccia (GP) algorithm converged for each of the patients (producing surprisingly low finite values for the estimates of D_2) whereas the algorithm failed to converge for the controls. The quantitative validity of the finite D_2 estimates cannot be known, as linear correlations in the data may play a role in the convergence, but the difference in the behaviour of the algorithm between patients and controls certainly suggests a qualitative difference in dynamics. In particular, as Gottschalk et al. noted, the time series of the patients is much more organized than those of the controls. Gottschalk et al. went on to construct three surrogate series for each patient, and found that the GP algorithm failed to converge for the surrogate series. This suggests that the patients' original time series probably do include nonlinear features, and that the finite D_2 values were not simply the result of strongly-correlated linear noise. However, it was not clear why Gottschalk et al. did not carry out a full surrogate analysis as described in Sec 2.2.6. This could have been done by selecting a significance level, generating B or more surrogate series for each patient, and choosing an embedding dimension M for which the GP algorithm had converged for that patient. The values of the estimates of D_2 for the surrogate series (using the chosen value of M) could then be compared to the estimate of D_2 for the original series. Gottschalk et al. concluded that their results implied evidence of chaotic dynamics in the bipolar mood data, but in view of the short lengths of the time series, absence of estimates of Lyapunov exponents, and form of power spectra (see paragraph below) the best that can be firmly concluded from their analysis is that bipolar patients exhibit qualitatively more organized dynamics than controls

with a possibility of nonlinearity.

Krystal and Greenside (1998) provided a short critique of Gottschalk et al. (1995) where they pointed out that chaotic deterministic dynamics should show power spectra that decay *exponentially* fast (not as power laws) in the high frequency range (Sigeti, 1995a,b). Gottschalk et al. (1998) responded that their spectral data was also consistent with an exponential decay; statistically neither the exponential model nor the power-law model fit better (which calls into question the interpretation of the α estimates mentioned in the original article; see also the comment regarding Woyshville et al. (1999) below). It may simply be that there is too much noise in the patients' data to see a clear exponential decay. However, Gottschalk et al. (1998) do point out that, for the controls, the power law model fits the data significantly better than the exponential model.

Woyshville et al. (1999) carried out a shorter study where similar daily mood data was collected only over a period of 90 days. (In this case patients were identified as exhibiting affective instability and were not limited to bipolar diagnoses; they had a variety of Axis I mood disorders). Woyshville et al. did not have enough data to carry out a GP algorithm analysis, but they did calculate the power spectra of participants as well as the fractal dimension (FD) of the graph of the mood series data, using a coastline algorithm (Mandelbrot, 1977). They fit power law models to the spectra, and found the α ratio of patients to controls to be approximately 2, which is roughly the same ratio as obtained by Gottschalk et al. (1995). Woyshville et al. made the intriguing suggestion that this ratio was perhaps an invariant characteristic between patients and controls. However, in view of Gottschalk et al. (1998), these α

values must be viewed with caution. Moreover, in a very brief recent report, Kreindler and Munshi (2015) did not find any significant difference in α between groups consisting of bipolar patients, patients with affective instability, and healthy controls; nor did Ribeiro and Lourenço (2016). However, Woyshville et al. also found that FD was significantly lower in patients than controls, which quantitatively supports the observation that mood series in controls appear rougher than those in patients.

Heiby, Pagano, Blaine, Nelson, and Heath (2003) carried out hourly mood measurements (using a 7-point Likert scale) 10 times daily on one depressed female patient and one female control, obtaining a time series of length 1,840 for each. They found a periodic component in each woman's power spectrum (stronger in the patient) which they attributed as possibly being due to the participants' menstrual cycles. Using the GP algorithm, Heiby et al. found a D_2 estimate of 2.7 for the patient and a D_2 estimate of 4 for a single surrogate series constructed for the patient. (The GP algorithm did not converge for the control). The D_2 estimates for the patient and the surrogate series are mentioned here only to indicate how potentially indistinguishable the two may be; a proper analysis using a full set of surrogate series might have revealed whether the patient's D_2 value was reflecting nonlinear structure or was the result of strong linear correlations in the time series. The latter is quite possible since we can expect hourly mood measurements to be highly correlated in a person with persistent low mood. Katerndahl, Ferrer, Best, and Wang (2007) obtained mood data from three depressed patients and four controls. Mood data here was also recorded hourly (while participants were awake) on a 100-mm analogue scale for 30 days. The authors report D_2, λ_1, KSE, and the results of surrogate data testing (based on 20

surrogate series) for each participant. These results were produced by a software package and the authors do not provide details as to how they selected the final values. Critically, unlike Gottschalk et al. (1995) or Heiby et al., they claim finite correlation dimensions for the controls (which are not distinguishable from those of the patients; this is also true of λ_1 and KSE). The authors do not offer an explanation for the lack of distinction. Moreover, they indicate that surrogate data testing indicates nonlinearity for all participants. However, there is insufficient information to evaluate their results.

It is important to note that techniques that do not involve embedding methods have been utilized to evaluate possible nonlinearity in bipolar mood series. Bonsall, Wallace-Hadrill, Geddes, Goodwin, and Holmes (2012) obtained weekly mood data from 23 bipolar patients for a period ranging 46-220 weeks; unlike Gottschalk et al. (1995), however, they used only depression score ratings (the Quick Inventory of Depressive Symptomatology QIDS-SR). An interesting aspect of their approach is that, based on the first six months of data, they classified patients as either *stable* ($n = 11$) or *unstable* ($n = 12$). Using the Akaike Information Criterion, they fit various models, and found that distinct nonlinear models best fit the two different groups. The stable group was best described by a threshold autoregressive model of order one (TAR(1)) whereas the unstable group was best described by a threshold autoregressive model of order two (TAR(2)). In both cases the threshold was the mean score of the individual patient's mood data. Moore, Little, McSharry, Goodwin, and Geddes (2014) were critical of the rather large in-sample errors of the TAR models in Bonsall et al., although the latter indicated that some of this error was

probably due to runs of missing data. Moore et al. used 100 weekly mood ratings from eight bipolar patients (employing the same QIDS-SR scale as Bonsall et al.) and constructed surrogate series for each patient. Comparing the original and surrogate series using two discriminating statistics, first the ratio of linear vs. nonlinear in-sample forecast errors, and then a time-reversal asymmetry statistic, Moore et al. concluded that there was no distinction between the original and surrogate time series. Thus they found no evidence for nonlinearity in the original mood series. Moreover, a comparison of various linear and nonlinear out-of-sample forecasts showed little difference between methods. The authors acknowledged that their conclusion of lack of nonlinearity in the original series could be due to insensitivity of the discriminating statistics, short length of the time series, or the sampling frequency. It is worth noting that Ortiz, Bradler, Garnham, Slaney, and Alder (2015) found that mood ratings of both healthy controls and *euthymic* bipolar patients could be modelled by a linear stochastic process in the form of an autoregressive integrated moving average (ARIMA(1,1,0)) process. This means that after the original mood series X_t is differenced to create $Z_t = X_t - X_{t-1}$ (this is done in order to render the series stationary) then Z_t can be expressed as an AR(1) process $Z_t = cZ_{t-1} + a_t$. However, Ortiz et al. point out that a model for medicated euthymic patients may not fit unmedicated patients or patients experiencing active episodes (recall that the patients in Gottschalk et al. (1995) were rapid-cycling). The question of linear vs. nonlinear models remains open.

There have been a few studies using time space indices in bipolar mood data. Bauer et al. (2011) expanded on a pilot study by Glenn et al. (2006) where they used

approximate entropy ApEn to see if pre-episode states could be distinguished from pre-remission states in bipolar patients. They followed 98 patients over a period of one year, collecting daily mood data (rapid-cycling patients were excluded from the study). A pre-hypomanic state was defined to be the 60 days before an episode of hypomania, a pre-depressive state was defined to be the 60 days before an episode of depression, and a pre-remission state was defined to be the 60 days before a month (30 days) of euthymia. Thus the time series to be compared were only of length $n = 60$. The ApEn parameters used were $m = 1$ and $r = 0.2 \cdot \text{SD}$ for each patient. The key result of the paper is that ApEn(1, r, 60) could distinguish between all three states, yielding ApEn(pre-hypomanic)> ApEn(pre-depression) > ApEn(pre-remission), with all differences being statistically significant using t-tests. In contrast, mean mood could not distinguish between pre-hypomanic and pre-depressive states, or between pre-hypomanic and pre-remission states. The mood SD was more sensitive to changes in the time series but still could not distinguish pre-hypomanic states from pre-depressive states. This points not only to the utility of ApEn as a tool for distinguishing patterns in data, but to the notion that prodromal changes in bipolar mood may begin and be detected in longer time periods (e.g., 60 days) before the onset of an episode. Yeragani, Pohl, Mallavarapu, and Balon (2003) also showed that ApEn could distinguish between mood in healthy controls (also using $n = 60$).

Kreindler and Munshi (2015) reported on a study in which they did not find a significant difference in SampEn on mood ratings between bipolar patients, affectively unstable patients, and healthy controls. However, Ribeiro and Lourenço (2016) did a more involved analysis where they examined SampEn for different parameter choices

m and r over five different 110-mm visual analogue daily mood scales (VAS) (e.g., "very worst I ever felt" to "very best I ever felt" was one scale, "very tired/slow" to "very energetic/excited" was another scale). There were 17 patients with active affective instability (71% bipolar) and 10 matched controls. Two-way ranked ANOVA revealed a difference in SampEn between the patient and control groups over the five VAS, although post hoc Mann-Whitney multiple comparisons did not reveal a significant difference between the patients and controls on any particular VAS. There was a second part to the analysis, however, where the authors looked at the relationship between SampEn and the "load of bad days" which, for each participant, was defined as the proportion of days in the "very worst – very best" VAS that fell beneath one standard deviation below the mean score of the VAS. The load of bad days was seen as a proxy for the amount of daily strain on the affective system. The authors predicted that, in controls, mood complexity (as measured by SampEn) would increase as load of bad days increased (indicating a resilient response to strain) and that this response would be compromised in patients. This hypothesis was born out; SampEn increased with load of bad days in general, but the relationship was much stronger in controls, with patients showing on average up to 25% lower complexity of mood variation than controls for the same load of bad days. The authors conclude that the healthy response to adversity involves activation of processes of emotion regulation that lead to increases of complexity in mood variability, and that this response is impaired in patients with affective disorders. They state that the main clinical implication of their findings is that "interventions aimed at increasing flexibility of emotion regulation and complexity of mood variation may be effective

treatments for people with affective disorders" (p. 43).

3.7 Discussion and Future Directions

In this chapter we began by reviewing the definitions of the main nonlinear indices employed in the study of EEG, HRV, and mood data for persons with schizophrenia or bipolar disorder. This list of indices is not exhaustive, but due to space constraints we isolated these as the indices receiving most frequent attention. An important point to be taken from these various definitions is that these indices are generally measuring different quantities and there is no unique definition of the term "complexity". In our view it may be better to avoid that term altogether, but we have sometimes used it because it is so ubiquitous in the literature.

In the study of EEG in schizophrenia (Section 3.4.1), we performed an exhaustive literature search and investigated the L-F proposal. We saw that if D_2 was used as the index, there was no observable medication or age effect (in contradiction to the L-F proposal). When all nonlinear indices were combined (requiring the assumption that they all behave the same way with respect to age and medication) we obtained only weak evidence of age and medication effects. Based on recent work of Cerquera et al. (2017) we proposed that patient symptomatology (a specific component of the L-F proposal) may be the most important determinant of outcome relative to healthy controls. It would also be important to determine the extent to which laboratory techniques are contributing to the apparent "study effect". Resolving this conundrum may be part of unravelling the observed patterns and ultimately the neurobiology of schizophrenia.

Future directions may lie in the area of determining if in fact there are any key elements of conditions (or tasks) that partly determine the outcome of an index (i.e., other than patient symptoms). Results from the present review appear to indicate elevated D_2 in schizophrenia samples for certain tasks. Further scrutiny indicates that these tasks evidently share requirements for stimulus encoding, meaning the cognitive translating of presenting stimuli into a format facilitating performance (e.g., sentence representation for possible later recall, Koukkou et al., 1993; input of continuously presented items, of the continuous-performance task, Kirsch et al., 2000; and visual tracking of a pendulum, Lutzenberger et al., 1995; see Cutler and Neufeld (2017) and Chapter 2 for a discussion of stimulus encoding in schizophrenia.)

Linear and nonlinear indices have consistently pointed toward reduced complexity (increased regularity) of the RR series in schizophrenia with similar conclusions now being reached for bipolar disorder. Studies have shown that antipsychotic effects on HRV can also be detected via these indices, and it is possible that they might be employed to predict both adverse and positive responses to treatment. One of the more intriguing suggestions is that SampEn can be used to differentiate between mood states in bipolar disorder, and that personalized wearable monitoring systems might utilize HRV indices to predict both mood relapses and response to treatment. Since such wearable systems are already in the testing stage, this seems a possibility in the near future.

There have been few studies of mood data using phase space indices likely because of the difficulty in obtaining sufficiently long time series. Now that attention is turning more toward time domain indices (which are more applicable to relatively

short and even noisy time series) we can expect more advances in this area. The fact that Bauer et al. (2011) found that ApEn could distinguish between pre-manic, pre-depressive, and pre-remission mood states (while linear measures could not) was particularly interesting. It suggests that applying nonlinear indices to mood records might aid in predicting both the onset and nature of relapses. This might become a particularly powerful tool if it was coupled with prediction methods from HRV data as discussed in the preceding paragraph.

The focus above has been on EEG and ECG. Future directions will include applying nonlinear concepts to MEG and fMRI data, the latter offering spatial resolution that may reveal new information.

. **Acknowledgments**

Salary support for the second author was provided by the Joey and Toby Tannenbaum Schizophrenia Research Distinguished Scientist Award, as well as a Senior Research Fellowship from the Ontario Mental Health Foundation. Also supported by operating grants from the Canadian Social Sciences and Humanities Research Council, the Canadian Medical Research Council, and the Canadian Institutes of Health Research (RWJN principal investigator; coinvestigator).

References for Chapter 3

Abhishekh, H. A., Thirthalli, J., Manjegowda, A., Phutane, V. H., Muralidharan, K., & Gangadhar, B. N. (2013). Ictal EEG fractal dimension in ECT predicts outcome at 2 weeks in schizophrenia. *Psychiatry Research, 209,* 155-159.

Ahmadlou, M., Adeli, H., & Adeli, A. (2012). Fractality analysis of frontal brain in major depressive disorder. *International Journal of Psychopharmacology, 85,* 206-211.

Akar, S. A., Kara, S., Agambayev, S., & Bilgiç, V. (2015a). Nonlinear analysis of EEGs of patients with major depression during different emotional states. *Computers in Biology and Medicine, 6,* 49-60.

Akar, S. A., Kara, S., Agambayev, S., & Bilgiç, V. (2015b). Nonlinear analysis of EEG in major depression with fractal dimensions. *37th Annual International Conference of the IEEE Engineering and Biology Society,* 7410-7413.

Akar, S. A., Kara, S., Latifoğlu, F., & Bilgiç, V. (2015a). Estimation of nonlinear measures of schizophrenia patients' EEG in emotional states. *IRBM, 36,* 250-258.

Akar, S. A., Kara, S., Latifoğlu, F., & Bilgiç, V. (2015b). Investigation of the noise effect on fractal dimension of EEG in schizophrenia patients using wavelet and SSA-based approaches. *Biomedical Signal Processing and Control, 18,* 42-48.

Akar, S. A., Kara, S., Latifoğlu, F., & Bilgiç, V. (2016). Analysis of the complexity measures in the EEG of schizophrenia patients. *International Journal of Neural Systems, 26*(2), 1-13.

Bachmann, M., Kalev, K., Suhhova, A., Lass, J.,& Hinrikus, H. (2015). Lempel Ziv complexity of EEG in depression. *6th European Conference of the International Federation for Medical and Biological Engineering, IFMBE Proceedings, 45,* 58-61.

Bachmann, M., Lass, J., Suhhova, A., & Hinrikus, H. (2013). Spectral asymmetry and Higuchi's fractal dimension measures of depression encephalogram. *Computational and Mathematical Models in Medicine,* 1-8.

Bahrami, B., Seyedsadjadi, R., Babadi, B., & Noroozian, M. (2005). Brain complexity increases in mania. *Clinical Neuroscience and Neuropathology, 16*(2), 187-191.

Bär, K-J., Boettger, M. K., Koschke, M., Schulz, M., Chokka, P., Yeragani, V. K., & Voss, A. (2007). Non-linear complexity measures of heart rate variability in acute schizophrenia. *Clinical Neurophysiology, 118,* 2009-2015.

Bär, K.-J., Boettger, M. K., Schulz, S., Harzendorf, C., Agelink, M. W., Yeragani, V. K., ... Voss, A. (2008). The interaction between pupil function and cardiovascular regulation in patients with acute schizophrenia. *Clinical Neurophysiology, 119,* 2209-2213.

Bär, K.-J., Koschke, M., Berger, S., Schulz, S., Tancer, M., Voss, A., & Yeragani, V. K. (2008). Influence of olanzapine on QT variability and complexity measures of heart rate in patients with schizophrenia. *Journal of Clinical Psychopharmacology, 28*(6), 694-698.

Bauer, M., Glenn, T., Alda, M., Grof, P., Sagduyu, K., Bauer, R.,... Whybrow, P. C. (2011). Comparison of pre-episode and pre-remission states using mood ratings from patients with bipolar disorder. *Pharmacopsychiatry, 44(Suppl. 1),* S49-S53.

Bhattacharya, J. (2000). Complexity analysis of spontaneous EEG. *Acta Neurobiologiae Experimentaus, 60,* 495-501.

Bonsall, M. B., Wallace-Hadrill, S. M. A., Geddes, J. R., Goodwin, G. M., & Holman, E. A. (2012). Nonlinear time-series approaches in characterizing mood stability and mood instability in bipolar disorder. *Proceedings of the Royal Society B, 279,* 916-924.

Breakspear, M. (2006). The nonlinear theory of schizophrenia. *Australian and New Zealand Journal of Psychiatry, 40,* 20-35.

Brown, S., Inskip, H., & Barracough, B. (2000). Causes of excess mortality of schizophrenia. *British Journal of Psychiatry, 177,* 212-217.

Cao, L. (1997). Practical method for determining the minimum embedding dimension of a scalar time series. *Physica D, 110,* 43-50.

Carlino, E., Siguado, M., Pollo, A., Benedetti, F., Mongini, T., Castagna, F.,... Rocca, P. (2012). Nonlinear analysis of electroencephalogram at rest and during cognitive tasks in patients with schizophrenia. *Journal of Psychiatry Neuroscience, 37*(4), 259-266.

Cerquera, A., Gjini, K., Bowyer, S. M., & Boutros, N. (2017). Comparing EEG nonlinearity in deficit and nondeficit schizophrenia patients: Preliminary report. *Clinical EEG and Neuroscience, 48*(6), 376-382.

Chan, K.-S., & Tong, H. (2001). *Chaos: A statistical perspective.* New York, NY: Springer-Verlag.

Chang, H.-A., Chang, C.-C., Kuo, T. B. J., & Huang, S.-Y. (2015). Distinguishing bipolar II depression from unipolar major depressive disorder: Differences in heart rate variability. *World Journal of Biological Psychiatry, 16*(5), 351-360.

Chang, H.-A., Chang, C.-C., Tzeng, N.-S., Kuo, T. B. J., Lu, R.-B., & Huang, S.-Y. (2014). Heart rate variability in unmedicated patients wih bipolar disorder in the manic phase. *Psychiatry and Clinical Neurosciences, 68,* 674-682.

Chang, J. S., Hwang, S. S.-H., Yi, S. H., Kim, Y., Lee, Y.-S., Kim, Y. S., & Jung, H.-Y. (2015). Evauating subjective domains of antipsychotic-induced adverse effects using heart rate variability. *Psychiatry and Clinical Neurosciences, 69,* 283-291.

Chang, J. S., Yoo, C. S., Yi, S. H., Hong, K. H., Lee, Y.-S., Oh, H. S., ... Ahn, Y. M. (2010). Changes in heart rate dynamics of patients with schizophrenia treated with risperidone. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 34,* 924-929.

Chang, J. S., Yoo, C. S., Yi, S. H., Hong, K. H., Oh, H. S., Hwang, J. Y., ... Kim, Y. S. (2009). Differential pattern of heart rate variability in patients with schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 33,* 991-995.

Chen, X., Xu, Y., Tang, Y., Fang, Y., Zhang, C., Zhang, M., ... Cui, Y. (2013). Nonlinear dynamics of electroencephalography study in schizophrenic patients. *Chinese Medical Journal, 126*(15), 2886-2889.

Chung, M.-S., Yang, A. C., Li, Y.-C., Lin, C.-N., Chang, F.-R., Shen, S., ... Chiu, H.-J. (2013). Association of altered cardiac autonomic function with psychopathology and metabolic profiles in schizophrenia. *Psychiatry Research, 210,* 710-715.

Clamor, A., Lincoln, T. M., Thayer, J. F., & Koenig, T. (2016). Resting vagal activity in schizophrenia: Meta-analysis of heart rate variability as a potential endophenotype. *British Journal of Psychiatry, 208,* 9-16.

Cohen, H., Kaplan, Z., Kotler, M., Mittelman, I., Osher, Y., & Bersudsky, Y. (2003). Impaired heart rate variability in euthymic bipolar patients. *Bipolar Disorders, 5,* 138-143.

Costa, M., Goldberger, A.L., & Peng, C. K. (2005). Multiscale entropy analysis of biological signals. *Physical Review E, 71,* 021906, 1-18.

Cutler, C. D. (1991). Some results on the behavior and estimation of the fractal dimensions of distributions on attractors. *Journal of Statistical Physics, 62,* 651-708. Errata and Addenda (1991), *65,* 417-418.

Cutler, C. D. (1993). A review of the theory and estimation of fractal dimension. In H. Tong (Ed.), *Dimension estimation and models* (pp. 1–107). Singapore: World Scientific.

Cutler, C. D. (1994). A theory of correlation dimension for stationary time series. *Philosophical Transactions of the Royal Society of London, Series A, 348,* 343-355.

Cutler, C. D., & Neufeld, R. W. J. (2017). Addressing very short stimulus encoding times in modeling schizophrenia cognitive deficit. *Journal of Mathematical Psychology, 79,* 53-63.

Cutler, C. D., & Neufeld, R. W. J. (2019). Nonlinear indices with applications to schizophrenia and bipolar disorder. *Nonlinear Dynamics, Psychology, and Life Sciences, 23,* 17-56.

Demjaha, A., MacCabe, J. H., & Murray, R. M. (2012). How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. *Schizophrenia Bulletin, 38*(2), 209-214.

Denker, M., & Keller, G. (1986). Rigorous statistical procedures for data from dynamical systems. *Journal of Statistical Physics, 44,* 67-93.

Eckmann, J.-P., & Ruelle, D. (1992). Fundamental limitations for estimating dimensions and Lyapunov exponents for dynamical systems. *Physica D, 56,* 185-187.

Ehlers, C. L. (1995). Chaos and complexity: can it help us understand mood and behavior? *Archives of General Psychiatry, 52*(11), 960-964.

Elbert, T., Lutzenberger, W., Rockstroh, B., Berg, P., & Cohen, R. (1992). Physical aspects of the EEG in schizophrenics. *Biological Psychiatry, 32,* 595-606.

Enger, C., Weatherby, L., Reynolds, R. F., Glasser, D. B., & Walker, A. H. (2004). Serious cardiovascular events and mortality among patients with schizophrenia. *Journal of Nervous and Mental Disease, 192*(1), 19-27.

Faurholt-Jepsen, M., Kessing, L. V., & Munkholm, K. (2017). Heart rate variability in bipolar disorder: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 73,* 68-80.

Fernández, A., Gómez, C., Hornero, R., & López-Ibor, J. J. (2013). Complexity and schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 45,* 267-276.

Fernández, A., López-Ibor, M.-I., Turrero, A., Santos, J.-M., Morón, M.-D., Hornero, R., ... López-Ibor, J. J. (2011). Lempel-Ziv complexity in schizophrenia; A MEG study. *Clinical Neurophysiology, 122,* 2227-2235.

Friston, K. J. (1996). Theoretical neurobiology and schizophrenia. *British Medical Bulletin, 52,* 644-655.

Friston, K. J., & Frith, C. D. (1995). Schizophrenia: A disconnection syndrome? *Clinical Neuroscience, 3,* 89-97.

Fritzche, M., Fritzche, L. N., Kosidubova, S. M., Prognimak, A. B., & Mayorov, O. Y. (2006). Asymmetric information-processing in development, evolution, and psychopathology. *Cognition, Brain & Behavior, X*(2), 311-342.

Guastello, S. J. (2009). Chaos as a psychological construct: Historical roots, principal findings, and current growth directions. *Nonlinear Dynamics, Psychology, and Life Sciences, 13*(3), 289-310.

Guastello, S. J., & Gregson, R. A. M. (2011). *Nonlinear dynamical systems analysis for the behavioral sciences using real data.* Boca Raton, FL: CRC Press.

Glenn, T., Whybrow, P. C., Rasgon, N., Grof, P., Alda, M., Baethge, C., & Bauer, M. (2006). Approximate entropy of self-reported mood prior to episodes in bipolar disorder. *Bipolar Disorders, 8,* 424-429.

Globus, G. G., & Arpaia, J. P. (1994). Psychiatry and the new dynamics. *Biological Psychiatry, 35,* 352-364.

Gottschalk, A., Bauer, M. S., & Whybrow, P. C. (1995). Evidence of chaotic mood variation in bipolar disorder. *Archives of General Psychiatry, 52*(11), 947-959.

Gottschalk, A., Bauer, M. S., & Whybrow, P. C. (1998). In reply to "low-dimensional chaos in bipolar disorder?" *Archives of General Psychiatry, 55,* 275-276.

Grassberger, P., & Procaccia, I. (1983a). Characterization of strange attractors. *Physical Review Letters, 50*(5), 346-349.

Grassberger, P., & Procaccia, I. (1983b). Measuring the strangeness of strange attractors. *Physica D, 9,* 189-208.

Heath, R. A. (2014). *Nonlinear dynamics: Techniques and applications in psychology.* New York, NY: ψ Psychology Press.

Heath, R. A. (2015). Detecting nonlinearity and edge-of-chaos phenomena in ordinal data. *Nonlinear Dynamics, Psychology, and Life Sciences, 19*(3), 229-248.

Heath, R. A., Kelly, A., & Longstaff, M. (2000). Detecting nonlinearity in psychological data: Techniques and applications, *Behavior Research Methods, Instruments, & Computers, 32*(2), 280-289.

Heiby, E. M. (1995). Chaos theory, nonlinear dynamical models, and psychological assessment. *Psychological Assessment, 7*(1), 5-9.

Heiby, E. M., Pagano, I. S., Blaine, D. D., Nelson, K., & Heath, R. A. (2003). Modeling unipolar depression as a chaotic process. *Psychological Assessment, 15*(3), 426-434.

Henry, B. L., Minassian, A., Paulus, M. P., Geyer, M. A., & Perry, W. (2010). Heart rate variability in bipolar mania and schizophrenia. *Journal of Psychiatric Research, 44,* 168-176.

Hirsch, M. W., & Smale, S. (1974). *Differential equations, dynamical systems, and linear algebra.* Orlando, Florida: Academic Press.

Hoffman, R. E., Buchsbaum, M. S., Jensen, R. V., Guich, S. M., Tsai, K., & Nuechterlein, K. (1996). Dimensional complexity of EEG waveforms in neuroleptic-free schizophrenic patients and normal control subjects. *Journal of Neuropsychiatry and Clinical Neuroscience, 8,* 436-441.

Jaworska, N., Wang, H., Smith, D. M., Blier, P., Knott, V., & Protzner, A. B. (2018). Pre-treatment EEG signal variability is associated with treatment success in depression. *NeuroImage: Clinical, 17,* 368-377.

Jeong, J., Kim, D.-J., Chae, J.-H., Kim, S. Y., Ko, H.-J., & Paik, I.-H. (1998). Nonlinear analysis of the EEG of schizophrenics with optimal embedding dimension. *Medical Engineering & Physics, 20,* 669-676.

Jin, S.-H., Na S. H., Kim, S. Y., Ham, B.-J., Lee, D. H., Lee, J. H., & Lee, H. (2003). Hemispheric laterality and dimensional complexity in schizophrenia under sound and light stimulation. *International Journal of Psychophysiology, 49,* 1-15.

Kantz, H., & Schreiber, T. (1997). *Nonlinear time series analysis.* Cambridge, U.K.: Cambridge University Press.

Katebi, S. D., & Satebi, M. (2012). Complexity measures as a feature to classify schizophrenic and healthy participants. *2012 14th International Conference on Modelling and Simulation,* IEEE Computer Society, 337-382. doi: 10.1109/UKSim2012.61

Katerndahl, D., Ferrer, R., Best, R., & Wang, C.-P. (2007). Dynamic patterns in mood among newly diagnosed patients with major depressive episode or panic disorder and normal controls. *Primary Care Companion Journal of Clinical Psychiatry, 9,* 183-187.

Katz, M. J. (1988). Fractals and the analysis of waveforms. *Computers in Biology and Medicine, 18*(3), 145-146.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261-276.

Kennel, M. B., Brown, R., & Abarbanel, H. D. I. (1992). Determining embedding dimension for phase-space reconstruction using a geometrical construction. *Physical Review A, 45,* 3403-3411.

Keshavan, M. S., Cashmere, J. D., Miewald, J., & Yeragani, V. K. (2004). Decreased nonlinear complexity and chaos during sleep in first episode schizophrenia : a preliminary report. *Schizophrenia Research, 71,* 263-272.

Kessing, L. V., Vradi, E., & Andersen, P. K. (2015). Life expectancy in bipolar disorder. *Bipolar Disorders, 17,* 543-548.

Kim, J.-H., Ann, J.-H., & Lee, J. (2011). Relationship between heart rate variability and the severity of psychotic symptoms in schizophrenia. *Acta Neuropsychiatrica, 23,* 161-166.

Kim, D.-J., Jeong, J., Chaue, J.-H., Park, S., Kim, S. Y., Go, H. J., ... Choi, B. (2000). An estimation of the first positive Lyapunov exponent of the EEG in patients with schizophrenia. *Psychiatry Research: Neuroimaging Section, 98,* 177-189.

Kim, J.-H., Yi, S. H., Yoo, C. S., Yang, S. A., Yoon, S, C., Lee, K. Y., ..., Kim, Y. S. (2004). Heart rate dynamics and their relationship to psychotic symptom severity in clozapine-treated schizophrenic patients. *Progress in Neuropsychopharmacology & Biological Psychiatry, 28,* 371-378.

Kim, J.-H., Ann, J.-H., Lee, J., Kim, M.-H., & Han, A.-Y. (2013). Altered heart rate dynamics associated with antipsychotic-induced subjective restlessness in patients with schizophrenia. *Neuropsychiatric Disease and Treatment, 9,* 989-994.

Kim, J.-H., Yi, S. H., Lee, J., & Kim, Y. S. (2013). Effects of clozapine on heart rate dynamics and their relationship with therapeutic response in treatment-resistant schizophrenia. *Journal of Clinical Psychopharmacology, 33*(1), 69-73.

Kirkpatrick, B., Buchanan, R. W., McKenny, P. D., Alphs, L. D., & Carpenter, W. T. (1989). The schedule for the deficit syndrome: an instrument for research in schizophrenia. *Psychiatry Research, 30,* 119-123.

Kirkpatrick, B., & Galderisi, S. (2008). Deficit schizophrenia: An update. *World Psychiatry, 7*(3), 143-147.

Kirsch, P., Besthorn, C., Klein, S., Rindfleisch, J., & Olbrich, R. (2000). The dimensional complexiy of the EEG during cognitive tasks reflects the impaired information processing in schizophrenic patients. *International Journal of Psychophysiology, 36,* 237-246.

Klieger, R. E. (1995). Heart rate variability and mortality and sudden death post infarction. *Journal of Cardiovascular Electrophysiology, 6,* 365-367.

Koukkou, M., Lehmann, D., Federspiel, A., & Merlo, M. C. G. (1995). EEG reactivity and EEG activity in in never-treated acute schizophrenia, measured with spectral parameters and dimensional complexity. *Journal of Neural Transmission, 99,* 89-102.

Koukkou, M., Lehmann, D., Wackermann, J., Dvorak, I., & Henggeler, B. (1993). Dimensional complexity of EEG brain mechanisms in untreated schizophrenia. *Biological Psychiatry, 33,* 397-407.

Kreindler, D. M., & Lumsden, C. J. (2007). The effects of irregular sampling and missing data on largest Lyapunov exponents. *Nonlinear Dynamics, Psychology, and Life Sciences, 11*(4), 401-412.

Kreindler, D., & Munshi, A. (2015). Entropy and periodicity analysis to investigate mood variability in bipolar disorder. *Bipolar Disorders, 17 (Suppl. 1),* 80-80.

Krystal, A, D., & Greenside, H. S. (2008). Low-dimensional chaos in bipolar disorder? *Archives of General Psychiatry, 55,* 275-275.

Kugiumtzis, D. (2000). Surrogate data test for nonlinearity including nonmonotone transforms. *Physical Review E, 62*(1), 25-28.

Lanata, A., Valenza, G., Nardelli, M., Gentili, C., & Scilingo, E. P. (2015). Complexity index from a personalized wearable monitoring system for assessing remission in mental health. *IEEE Journal of Biomedical and Health Informatics, 19*(1), 132-139.

Lawal, H. B., & Upton, G. J. G. (1984). On the use of χ^2 as a test of independence in contingency tables with small cell expectations. *Australian Journal of Statistics, 26*(1), 75-85.

Lee, S.-H., Choo, J.-S., Im, W.-Y., & Chae, J.-H. (2008). Nonlinear analysis of electroencephalogram in schizophrenia patients with persistent auditory hallucinations. *Psychiatry Investigations, 5,* 115-120.

Lee, J.-S., Kim, B., Hong, Y., & Joo, Y. H. (2012). Heart rate variability in the subsyndromal depressive phase of bipolar disorder. *Psychiatry and Clinical Neurosciences, 66,* 361-366.

Lee, Y.-J., Zhu, Y.-S., Xu, Y.-H., Shen, M.-F., Tong, S., & Thakor, N. V. (2001a). The nonlinear dynamical analysis of the EEG in schizophrenia with temporal and spatial embedding dimension. *Journal of Medical Engineering & Technology, 25*(2), 79-83.

Lee, Y.-J., Zhu, Y.-S., Xu, Y.-H., Shen, M.-F., Zhang, H.-X., & Thakor, N. V. (2001b). Detection of non-linearity in the EEG of schizophrenic patients. *Clinical Neurophysiology, 112,* 1288-1294.

Lempel, A., & Ziv, J. (1976). On the complexity of finite sequences. *IEEE Transactions on Information Theory, IT-22*(1), 75-81.

Levy, B. (2014). Illness severity, trait anxiety, cognitive impairment and heart rate variability in bipolar disorder. *Psychiatry Research, 220,* 890-895.

Levy, M. N. (1990). Autonomic interactions in cardiac control. *Annals of the New York Academy of Science, 601,* 209-221.

Li, Y., Tong, S., Liu, D., Gai, Y., Wang, X., Wang, J., ... Zhu, Y. (2008). Abnormal EEG complexity in patients with schizophrenia and depression. *Clinical Neurophysiology, 119,* 1232-1241.

Lorenz, E. N. (1963). Deterministic nonperiodic flow. *Journal of the Atmospheric Sciences, 20,* 130–141.

Lutzenberger, W., Stevens, A., & Bartels, M. (1995). Do schizophrenics not differentiate between perception and imagination? An EEG study using dimensional analysis. *Neuroscience Letters, 199,* 119-122.

Mandelbrot, B. B. (1977). *Fractals: Form, chance, and dimension.* San Francisco, CA: W. H. Freeman and Co.

Mandelbrot, B. B. (1982). *The fractal geometry of nature.* San Francisco, CA: W. H. Freeman and Co.

Melançon, G., Joanette, Y., & Bélair, J. (2000). Chaos, brain, and cognition: Toward a nonlinear order? *Brain and Cognition, 42,* 33-36.

Migliorini, M., Mendez, M. O., & Bianchi, A. M. (2012). Study of heart rate variability in bipolar disorder: Linear and non-linear parameters during sleep. *Frontiers in Neuroengineering, 4,* 1-7.

Montaquila, J., Trachik, B. J., & Bedwell, J. S. (2015). Heart rate variability and vagal tone in schizophrenia: A review. *Journal of Psychiatric Research, 69,* 57-66.

Moon, E., Lee, S.-H., Kim, D.-H., & Hwang, B. (2013). Comparative study of heart rate variability in patients with schizophrenia, bipolar disorder, post-traumatic stress disorder, or major depressive disorder. *Clinical Psychopharmacology and Neuroscience, 11*(3), 137-143.

Moore, P. J., Little, M. A., McHarry, P. E., Goodwin, G. M., & Geddes, J. R. (2014). Mood dynamics in bipolar disorder. *International Journal of Bipolar Disorders, 2*(11), 1-9.

Mujica-Parodi, L. R., Yeragani, V., & Malaspina, D. (2005). Nonlinear complexity and spectral analyses of heart rate variability in medicated and unmedicated patients with schizophrenia. *Neuropsychobiology, 51,* 10-15.

Murray, R. M., Sham, P., Van Oss, J., Zanelli, J., Cannon, M., & McDonald, C. (2004). A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophrenia Research, 71,* 405-416.

Nardelli, M., Valenza, G., Gentili, C., Lanata, A., & Scilingo, E. P. (2014). Temporal trends of neuro-autonomic complexity during severe episodes of bipolar disorder. *36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society,* 2948-2951.

Ortiz, A., Bradler, K., Garnham, J., Slaney, C., & Alda, M. (2015). Nonlinear dynamics of mood regulation in bipolar disorder. *Bipolar Disorders, 17,* 139-149.

Osborne, A. R., & Provenzale, A. (1989). Finite correlation dimension for stochastic systems with power-law spectra. *Physica D, 35,* 357-381.

Packard, N. H., Crutchfield, J. P., Farmer, J. D., & Shaw, R. S. (1980). Geometry from a time series. *Physical Review Letters, 64,* 712-716.

Palus, M. (1996). Nonlinearity in normal human EEG: Cycles, temporal asymmetry, nonstationarity and randomness, not chaos. *Biological Cybernetics, 75,* 389-396.

Paulus, M. P., & Braff, D. L. (2003). Chaos and schizophrenia: does the method fit the madness? *Biological Psychiatry, 53*(1), 3-11.

Pezard, L., Lachaux, J.-P., Thomasson, N., & Martinerie, J. (1999). Why bother to spatially embed EEG? Comments on Pritchard et al. *Psychophysiology, 36,* 527-531.

Pincus, S. M. (1991). Approximate entropy as a measure of system complexity. *Proceedings of the National Academy of Sciences USA, 88,* 2297-2301.

Pincus, S. M. (1995). Approximate entropy (ApEn) as a complexity measure. *Chaos, 5,* 110-117.

Pincus, S. M. (2006). Approximate entropy as a measure of irregularity for psychiatric serial metrics. *Bipolar Disorders, 8,* 430-4480.

Pritchard, W. S. (1999). On the validity of spatial embedding: A reply to Pezard et al. *Psychophysiology, 36,* 532-535.

Pritchard, W. S., Duke, D. W., & Krieble, K. K. (1995). Dimensional analysis of resting human EEG: Surrogate data testing indicates nonlinearity but not chaos. *Psychophysiology, 32,* 486-491.

Pritchard, W. S., Krieble, K. K., & Duke, D. W. (1996). On the validity of estimating EEG correlation dimension from a spatial embedding. *Psychophysiology, 33,* 362-368.

Raghavendra, B. S., Dutt, D. N., Halahalli, H. N., & John, J. P. (2009). Complexity analysis of EEG in patients using fractal dimension. *Physiological Measurement, 30,* 795-808.

Ribiero, J. G., & Lourenço, C. (2016). Dynamics of resilient and non-resilient mood. *Nonlinear Dynamics, Psychology, and Life Sciences, 20*(1), 23-48.

Richman, J. S., & Moorman, J. R. (2000). Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology, Heart and Circulatory Physiology, 278,* H2039-H2049.

Richman, J. S., Lake, D. E., & Moorman, J. R. (2004). Sample entropy. *Methods in Enzymology, 384*, 172-184.

Röschke, J., Fell, J., & Beckmann, P. (1995). Nonlinear analysis of sleep EEG data in schizophrenia: Calculation of the principal Lyapunov exponent. *Psychiatry Research, 56,* 257-269.

Röschke, J., Mann, K., & Fell, J. (1994). Nonlinear EEG dynamics during sleep in depression and schizophrenia. *International Journal of Neuroscience, 75,* 271-284.

Rosenstein, M. T., Collins, J. J., & De Luca, C. J. (1993). A practical method for calculating largest Lyapunov exponents from small data sets. *Physica D, 65,* 117-137.

Sabeti, M., Katebi, S., & Boostani, R. (2009). Entropy and complexity measures for EEG signal classification of schizophrenic and control participants. *Artificial Intelligence in Medicine, 47,* 263-274.

Saito, N., Kuginuki, T., Yagyu, T., Kinoshita, T., Koenig, T., Pascual-Marqui, R. D., ... Lehmann, D. (1998). Global, regional, and local measures of complexity of multichannel electroencephalography in acute, neuroleptic-naive, first-break schizophrenics. *Biological Psychiatry, 43,* 794-802.

Sauer, T., Yorke. J., & Casdagli, M. (1991). Embedology. *Journal of Statistical Physics, 65,* 579- 616.

Schmid, G. B. (1991). Chaos theory and schizophrenia: Elementary aspects. *Psychopathology, 24,* 185-198.

Schulz, S., Bär, K.-J., & Voss, A. (2008). The influence of treatment on linear and non-linear parameters of autonomic regulation in patients with acute schizophrenia. In J. Vander Sloten, P. Verdonck, M. Nyssen, and J. Hauesein (Eds.), *IFMBE Proceedings 22* (pp. 208-211), Berlin: Springer-Verlag.

Schulz, S., Bär, K.-J., & Voss, A. (2009). The influence of medical treatment on non-linear complexity measures of autonomic regulation of heart rate variability in patients with acute schizophrenia. In D. Dossel and W. C. Schlegel (Eds.), *IFMBE Proceedings 25/IV* (pp. 273-276), Berlin: Springer-Verlag.

Schulz, S., Bär, K.-J., & Voss, A. (2015). Analysis of heart rate, respiration, and cardiorespiratory coupling in patients with schizophrenia. *Entropy, 17,* 483-501.

Sigeti, D. E. (1995a). Exponential decay of power law spectra at high frequency and positive Lyapunov exponents. *Physica D, 82,* 136-153.

Sigeti, D. E. (1995b). Survival of determinsitic dynamics in the presence of noise and exponential decay of power spectra at high frequency. *Physical Review E, 52*(3), 2443-2457.

Silke, B., Campbell, C., & King, D.J. (2002). The potential cardiotoxicity of antipsychotic drugs as assessed by heart rate variability. *Journal of Psychopharmacology, 16*(4), 355-360.

Strauss, S.M. J. M., Bleaumink, G. S., Dieleman, J. P., van der Lei, J., Jong, G. W., Kingma, J. H., . . . , Stricker, B. H. (2004). Antipsychotics and the risk of sudden cardiac death. *Archives of Internal Medicine, 164*(2), 1293-1297.

Taghavi, M., Boostani, R., Sabeti, M., & Taghavi, S. M. A. (2011). Usefulness of approximate entropy in the diagnosis of schizophrenia. *Iran Journal of Psychiatry Behavioral Science, 5*(2), 62-70.

Takahashi, T. (2013). Complexity of spontaneous brain activity in mental disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 45,* 258-266.

Takahashi, T., Cho, R. Y., Mizuno, T., Kikuchi, M., Murata, T., Takahashi, K., & Wada, Y. (2010). Antipsychotics reverse abnormal EEG complexity in drug-naive schizophrenia: A multiscale entropy analysis. *NeuroImage, 51,* 173-182.

Takens, F. (1981). *Detecting strange attractors in turbulence.* Lecture Notes in Mathematics, 898, New York, NY: Springer.

Theiler, J. (1986). Spurious dimension from correlation algorithms applied to limited time-series data. *Physical Review A, 34,* 2427-2432.

Theiler, J. (1990). Estimating fractal dimension. *Journal of Optical Society of America A, 7*(6), 1055-1073.

Theiler, J. (1991). Some comments on the correlation dimension of $1/f^{\alpha}$ noise. *Physics Letters A, 155,* 480-493.

Theiler, J., & Rapp, P. E. (1996). Re-examination of the evidence for low-dimensional, nonlinear structure in the human electroencephalogram. *Electroencephalography and Clinical Neurophysiology, 98,* 213-222.

Theiler, J., Eubank, S., Longtin, A., Galdrikian, B., & Farmer, J. D. (1992). Testing for nonlinearity in time series: the method of surrogate data. *Physica D, 58,* 77-94.

Thilakvathi, B., Shenbaga, D. S., Bhanu, K., & Malaippan, M. (2017). EEG signal complexity analysis for schizophrenia during rest and mental activity. *Biomedical Research, 28*(1), 1-9.

Thomasson, N., & Pezard, L. (1999). Dynamical systems and depression: A framework for theoretical perspectives. *Acta Biotheoretica, 47,* 209-218.

Thomasson, N., Pezard, L., Boyer, P., Renault, B., & Martinerie, J. (2002). Nonlinear EEG changes in a 48-hour cyclic manic-depressive patient. *Nonlinear Dynamics, Psychology, and Life Sciences, 6*(3), 259-267.

Todder, D., Bersudsky, Y., & Cohen, H. (2005). Nonlinear analysis of RR interval in euthymic bipolar disorder. *Autonomic Neuroscience: Basic and Clinical, 117,* 127-131.

Valenza, G., Nardelli, M., Bertschy, G., Lanata, A., & Scilingo, E. P. (2014). Mood states modulate complexity in heartbeat dynamics: A multiscale entropy analysis. *EPL, 107,* 18003, 1-6.

Voggt, A., Berger, M., Obermeier, M., Löw, A., Seemueller, F., Reidel, M., ... Severus, E. (2015). Heart rate variability and Omega-3 Index in euthymic patients with bipolar disorder. *European Psychiatry, 30,* 228-232.

Voss, A., Kurths, J., Kleiner, H. J., Witt, A., Wessel, N., Saparin, P., ..., Dietz, R. (1996). The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death. *Cardiovascular Research, 31,* 419-433.

Voss, A., Baier, V., Schulz, S., & Bär, K. J. (2006). Linear and nonlinear methods for analyses of cardiovascular variability in bipolar disorders. *Bipolar Disorders, 8,* 441-452.

Wolf, A., Swift, J. B., Swinney, H. L., & Vastano, J. A. (1985). Determining Lyapunov exponents from a time series. *Physica D, 16,* 285-317.

Woyshville, M. J., Lackamp, J. M., Eisengart, J. A., & Gilliland, J. A. M. (1999). On the meaning and measurement of affective instability: clues from chaos theory. *Biological Psychiatry, 45,* 261-269.

Yang, A. C., & Tsai, S.-J. (2013). Is mental illness complex? From behavior to brain. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 45,* 253-257.

Yeragani, V. K., Pohl, R., Mallavarapu, M., & Balon, R. (2003). Approximate entropy of symptoms of mood: an effective technique to quantify regularity of mood. *Bipolar Disorders, 5,* 279-286.

Yu, Y., Zhao, Y., Si, Y., Ren, Q., Ren, W., Jing, C.,& Zhang, H. (2016). Estimation of the cool executive function using frontal electroencephalogram signals in first-episode schizophrenia patients. *Biomedical Engineering Online, 15:13.* doi: 10.1186/s12938-016-028-y

Zhao, Q., Hu, B., Liu, L., Ratcliffe, M., Peng, H., Zhai, J., ... Qi, Y. (2012). An EEG based nonlinearity analysis method for schizophrenia diagnosis. *Proceedings of the LASTED International Conference in Biomedical Engineering,* doi:10.2316/P.2012.764-137.

Chapter 4

Concluding Remarks

In this thesis we have focused study on certain observed and potential numerical earmarks of schizophrenia, chiefly in response to cognitive stimuli, but also in response to the behaviour of the ANS. Numerical quantities have a theoretical advantage over behavioural ones in that in principle they may be more objectively measured. However, as we observed in Chapter 3, the inconsistency of outcomes in nonlinear indices in the EEG of schizophrenia patients means there is no simple correspondence between complexity of EEG signals and diagnostic health. Rather, a more involved relationship, such as the L-F proposal, must be entertained which takes into account factors of age, antipsychotic medication, patient symptomatology, and laboratory procedures. To this we may also add the condition, or cognitive stimulus, under which the EEG is taken. We noted in the discussion at the end of Chapter 3 that D_2 was seen to be higher in certain conditions in which encoding load could be considered high. The L-F proposal, with all the above components factored in, has never really been properly investigated in any depth. One might propose a study involving a very large number of participants over a wide range of ages, different medication dosages (including unmedicated), and different symptomatology (in particular deficit syndrome (DS) vs.

nondeficit syndrome (NDS)) and develop a multiple regression model using all these variables. (There would of course be limits on the design as medication dosages, as well as medication presence or absence, would be controlled by the needs of the patient.) The EEG procedure could then be carried out over a range of cognitive stimuli (including those with low and high encoding requirements) and a suite of nonlinear indices could then be evaluated for each participant. In this manner the influence due to different factors might become clearer. The relationship between nonlinear indices and HRV in schizophrenia patients, however, is much more direct; schizophrenia patients seem to exhibit reduced complexity in HRV with a concomitant greater tendency toward adverse cardiac events.

In Chapter 2 we reviewed experimental studies that suggest that prolonged encoding times in response to cognitive stimuli are a numerical earmark of persons with schizophrenia, and noted that this prolonged encoding results in a variety of consequences. The main work of Chapter 2 was then to develop a flexible class of models (the general serial mixture model introduced in Sec 2.2) that could be applied to describe encoding times (and other cognitive processing latencies) and which enabled us to explore and illustrate potential physical and neurophysiological mechanisms behind encoding in various experimental paradigms. These models featured an emphasis on two quantities: the number K of subprocesses being encoded and the speed Θ at which they were encoded. In Sec 2.3 we focussed on a subclass of these models where changes in encoding times were explained solely by changes in K while holding the distribution of Θ constant. These simplified models, which seem sufficient to explain encoding changes in many cases of schizophrenia, were seen to

yield a variety of MIC-VIC signatures which can be used for comparisons between models in terms of fitting them to factorial data. A distinction in these models was made between the case where K varies only over participants and the case where K varies over trials rather than, or in addition to, varying over participants. A numerical test for distinguishing these two cases was developed. Further work in developing the asymptotic behaviour of this numerical test and the sample sizes necessary to effectively implement it is warranted. In Sec 2.5 we focussed on the reverse case where Θ was allowed to vary while holding the distribution of K constant. There has been less experimental evidence linking these models to changes in encoding times in the case of schizophrenia, but it is possible that these models may be useful in some experimental paradigms as well as in the case of cognitive processing latencies other than encoding times. Cases where both K and Θ are allowed to vary simultaneously are a topic for future study, as are cases where the distributions of K and Θ are not independent but linked. It is hoped that continuing investigations into the general serial mixture model will yield a mathematical toolbox of techniques for examining processing latencies in cognitive neuroscience.

Appendix A

Discrete Probability Distributions

1. **Poisson distribution:** K has discrete probability mass function on $k = 0, 1, 2, \ldots$ given by
$$P(K = k) = \frac{m^k e^{-m}}{k!}$$
where $m > 0$ and $E(K) = \mathrm{Var}(K) = m$. **Abbreviation:** $K \overset{\mathcal{D}}{\sim} \mathrm{Pois}(m)$

2. **truncated Poisson distribution:** K has discrete probability mass function on $k = 1, 2, 3, \ldots$ given by
$$P(K = k) = \frac{m^k e^{-m}}{(1-e^{-m})\, k!}$$
where $m > 0$, $E(K) = \frac{m}{1-e^{-m}}$ and $\mathrm{Var}(K) = \frac{m}{1-e^{-m}} - \left(\frac{m}{1-e^{-m}}\right)^2 e^{-m}$

3. **translated Poisson distribution:** Let n be a fixed positive integer. K has a translated Poisson distribution with translation factor n if $K = X + n$ where $X \overset{\mathcal{D}}{\sim} \mathrm{Pois}(m)$. Thus $E(K) = m + n$ and $\mathrm{Var}(K) = m$.

4. **binomial distribution:** K has discrete probability mass function on $k = 0, 1, \ldots, n$ given by
$$P(K = k) = \binom{n}{k} p^k (1-p)^{n-k}$$
where $0 < p < 1$, $E(K) = np$, and $\mathrm{Var}(K) = np(1-p)$. **Abbreviation:** $K \overset{\mathcal{D}}{\sim} \mathrm{binom}(n, p)$

5. **geometric distribution:** K has discrete probability mass function on $k = 1, 2, 3, \ldots$ given by
$$P(K = k) = (1-p)^{k-1} p$$
where $0 < p < 1$, $E(K) = \frac{1}{p}$ and $\mathrm{Var}(K) = \frac{1-p}{p^2}$. (Note the geometric is a special case of the negative binomial (see below) where $r = 1$.) **Abbreviation:** $K \overset{\mathcal{D}}{\sim} \mathrm{geom}(p)$.

6. **negative binomial distribution:** Let r be a fixed positive integer. K has discrete probability mass function on $k = r, r+1, r+2, r+3, \ldots$ given by
$$P(K = k) = \binom{k-1}{r-1} (1-p)^{k-r} p^r$$
where $0 < p < 1$, $E(K) = \frac{r}{p}$ and $\mathrm{Var}(K) = \frac{r(1-p)}{p^2}$. (The case $r = 1$ yields the geometric distribution as noted above.) **Abbreviation:** $K \overset{\mathcal{D}}{\sim} \mathrm{negbinom}(r, p)$.

Appendix B

Continuous Positive Infinite-Tailed Probability Distributions

1. **exponential distribution:** Let $v > 0$ (called the rate parameter; sometimes an alternate parameterization is used where $b = 1/v$ is called the scale parameter). **Abbreviation:** $\ell \overset{\mathcal{D}}{\sim}$ expo(v).Then ℓ has probability density function (pdf) given by

$$\phi(\ell) = ve^{-v\ell} \quad \text{for } \ell > 0$$

and mean and variance given by

$$E(\ell) = \frac{1}{v} \quad \text{and} \quad \text{Var}(\ell) = \frac{1}{v^2}.$$

Note the exponential is a special case of the gamma distribution (see below) where the shape parameter $a = 1$. Thus an alternative abbreviation for the exponential is $\ell \overset{\mathcal{D}}{\sim} \text{Gam}(1, v)$.

2. **gamma distribution:** Let $a > 0$ (shape parameter) and $v > 0$ (rate parameter; the alternate parameterization $b = 1/v$ is sometimes used where b is called the scale parameter). **Abbreviation:** $\ell \overset{\mathcal{D}}{\sim} \text{Gam}(a, v)$. Then ℓ has probability density function (pdf)

$$\phi(\ell) = \frac{\ell^{a-1}v^a}{\Gamma(a)}e^{-v\ell} \quad \text{for } \ell > 0$$

with mean and variance

$$E(\ell) = \frac{a}{v} \quad \text{and} \quad \text{Var}(\ell) = \frac{a}{v^2}$$

Some related moments of interest (for $a > 2$) are:

$$E(1/\ell) = \frac{v}{a-1}\,,\ E(1/\ell^2) = \frac{v^2}{(a-1)(a-2)}\,,\ \text{Var}(1/\ell) = \frac{v^2}{(a-1)^2(a-2)}$$

Also note that the special case of the gamma where $a = k$, a positive integer, is called the Erlang distribution and can be expressed as $\ell \overset{\mathcal{D}}{\sim} \text{Gam}(k, v)$.

3. **inverse Gaussian distribution:** Let $\mu > 0$ (the mean) and $\lambda > 0$ (the shape parameter). **Abbreviation:** $\ell \overset{\mathcal{D}}{\sim}$ IG(μ, λ). Then ℓ has probability density function (pdf)

$$\phi(\ell) = \sqrt{\frac{\lambda}{2\pi\ell^3}}\, e^{-\frac{\lambda(\ell-\mu)^2}{2\mu^2\ell}} \quad \text{for } \ell > 0$$

and the mean and variance are

$$E(\ell) = \mu \quad \text{and} \quad \text{Var}(\ell) = \frac{\mu^3}{\lambda}$$

Some related moments of interest are:

$$E(1/\ell) = \frac{1}{\mu} + \frac{1}{\lambda} \quad \text{and} \quad \text{Var}(1/\ell) = \frac{1}{\mu\lambda} + \frac{2}{\lambda^2}$$

4. **Weibull distribution:** Let $a > 0$ be the shape parameter and $b > 0$ be the scale parameter. **Abbreviation:** $\ell \overset{\mathcal{D}}{\sim} \text{Wei}(a, b)$. Then the pdf is

$$f(\ell) = \frac{a}{b}\left(\frac{\ell}{b}\right)^{a-1} e^{-\left(\frac{\ell}{b}\right)^a} \quad \text{for } \ell > 0$$

and the mean and variance are

$$E(\ell) = b\Gamma(1 + 1/a) \quad \text{and} \quad \text{Var}(\ell) = b^2\left\{\Gamma(1 + 2/a) - (\Gamma(1 + 1/a))^2\right\}$$

The expo(v) distribution is a special case of the Weibull where $a = 1$ and $b = 1/v$.

5. **lognormal distribution:** Here $-\infty < \mu < \infty$ and $\sigma^2 > 0$ are real numbers denoting, respectively, the mean and variance of the associated normal distribution $X \overset{\mathcal{D}}{\sim} N(\mu, \sigma^2)$. Here $\ell = e^X$. **Abbreviation:** $\ell \overset{\mathcal{D}}{\sim} \text{LN}(\mu, \sigma^2)$. The pdf is

$$f(\ell) = \frac{1}{\ell\sqrt{2\pi\sigma^2}}\, e^{-\frac{(\log \ell - \mu)^2}{2\sigma^2}} \quad \text{for } \ell > 0$$

and the mean and variance are

$$E(\ell) = e^{\mu + \frac{\sigma^2}{2}} \quad \text{and} \quad \text{Var}(\ell) = e^{2\mu+\sigma^2}(e^{\sigma^2} - 1)$$

Appendix C

Proof of Corollary 5.1

The conceptual idea behind this corollary is that, conditioning on a specific participant i, the mean of the sequence of observed encoding trials $t_{i1}, \ldots, t_{iN}$ should converge as $N \to \infty$ to the theoretical mean $E(T_i) = E(K_i)E(\mu(\Theta_i))$ of that participant by the strong law of large numbers for i.i.d. sequences. Then, since we can (unconditionally) view the mean $E(T_i)$ of each participant as an i.i.d. observation from a distribution with mixture mean $E^i_*[E(T_i)] = E(T)_*$, the mean $(\sum_{i=1}^{M} E(T_i))/M$ over the participants in the cell then converges as $M \to \infty$ to $E(T)_*$ provided $E(T)_* < \infty$. (A similar conceptual argument can be made for variances.)

The second part of the above argument, concerning the convergence to $E(T)_*$ of $(\sum_{i=1}^{M} E(T_i))/M$, is correct as it stands. However, the first part of the argument requires more nuance. A sequence $T_1, T_2, \ldots$ of encoding times from a random participant is an *exchangeable* sequence (Chow & Teicher, 1988) in that any permutation of a finite number $n \geq 1$ of elements $T_{i_1}, \ldots, T_{i_n}$ has the same distribution as every other permutation of that number of elements, but the sequence is not i.i.d. since the variables are linked through their (unknown) common distributions of K and Θ. However, conditional on the distributions of K and Θ, the sequence does become i.i.d. (Up until now, we have been using the phrase "conditional on participant i" but this has been a convenient mislabelling; all that is needed to render the sequence i.i.d. is to condition on the distributions of K and Θ, and many participants may share the same distributions for these quantities.) An equivalent way to phrase "conditional on

the distributions of K and Θ" is to state "conditional on the σ-algebra $\mathcal{G} = \sigma(K, \Theta)$ of events generated by K and Θ". Combining Theorem 2, p. 224, of Chow and Teicher (1988) with the first theorem of Kuritsyn (1987), we obtain the following convergence theorem:

Theorem C: If the exchangeable sequence $T_1, T_2, \ldots$ from a random participant with mixed marginal distribution T satisfies $E[|T|] < \infty$, then

$$\lim_{N\to\infty} \frac{1}{N} \sum_{j=1}^{N} T_j(\omega) = E(T \,|\, \mathcal{G})(\omega) \quad \text{with probability 1.}$$

Consider first the case of the means. Since encoding times are nonnegative, we may express the mixed marginal mean $E[|T|] = E[T] = E(T)_* = E^i_*[E(K_i)]E^i_*[E(\mu(\Theta_i)]$ where at the last step we revert to our previous notation and employ (2.2.10) in order to make the link clear. Therefore the premise of Theorem C is verified by checking that, for the distributions chosen for K and Θ, the mixed marginal mean $E(T)_* = E^i_*[E(K_i)]E^i_*[E(\mu(\Theta_i)]$ is finite. (This is so for all examples we have considered in Sec 2.4.) Then across a sequence of encoding times on any participant we obtain

$$\lim_{N\to\infty} \frac{1}{N} \sum_{j=1}^{N} T_j(\omega) = E(T \,|\, \mathcal{G})(\omega) \quad \text{with probability 1}$$

where $E(T \,|\, \mathcal{G})(\omega) = E(T \,|\, \sigma(K, \Theta))(\omega) = E(K_i)(\omega)E(\mu(\Theta_i))(\omega) = E(T_i)(\omega)$ for all participants i which share the same distributions for K and Θ. This proves the part of Corollary 5.1 dealing with the convergence to $E(T)_*$. For the case of the variance $E(\mathrm{Var}(T))_*$ we can argue that the mean over participants $(\sum_{i=1}^{M} \mathrm{Var}(T_i))/M$ converges as $M \to \infty$ to $E(\mathrm{Var}(T))_*$ provided $E(\mathrm{Var}(T))_* < \infty$ so we only need to

establish that, with probability 1,

$$s_N^2(\omega) = \frac{1}{N-1}\sum_{j=1}^{N}(T_j(\omega) - \bar{T}_N(\omega))^2 = \frac{1}{N-1}\left(\sum_{j=1}^{N} T_j^2(\omega) - N\bar{T}_N^2(\omega)\right)$$

converges to $\mathrm{Var}(T \,|\, \sigma(K,\Theta))(\omega) = \mathrm{Var}(T_i)(\omega)$ for all participants i which share the same distributions for K and Θ. Since $\mathrm{Var}(T \,|\, \sigma(K,\Theta))(\omega) = E(T^2 \,|\, \sigma(K,\Theta)) - (E(T \,|\, \sigma(K,\Theta)))^2$, this will follow from Theorem C if we can show, for the given choices of distributions on K and Θ, we have $E[T^2] = E(T^2)_* < \infty$, as then both terms in the right hand expression for s_N^2 will converge appropriately. Now $E[T^2] = E_*^i[T_i^2]$ which will be finite iff $E_*^i[\mathrm{Var}(T_i)] = E(\mathrm{Var}(T))_*$ is finite, which can be checked by applying (2.2.11).

In summary, a sufficient condition for the convergence of r_* to the theoretical ratio (2.4.7) is that $0 < E(T)_* < \infty$ and $E(\mathrm{Var}(T))_* < \infty$, which proves Corollary 5.1. (The restriction $E(T)_* > 0$ is made so that the theoretical ratio is not undefined.)

References for Appendix C

Chow, Y. S., & Teicher, H. (1988). *Probability theory: Independence, interchangeability, martingales, 2nd Ed.* New York: Springer-Verlag.

Kuritsyn, Y. G. (1987). On monotonicity in the law of large numbers for exchangeable random variables. *Theory of Probability and its Applications, 29*(1), 150-153.

Appendix D

Copyright Permission

In reference to the article: Cutler, C. D., & Neufeld, R. W. J. (2019). Nonlinear indices with applications to schizophrenia and bipolar disorder. *Nonlinear Dynamics, Psychology, and Life Sciences, 23,* 17-56.

I can attest that you have permission to use information from this publication as part of your thesis.
Sincerely,
David Pincus, Ph.D., Permissions Editor
Nonlinear Dynamics Psychology and Life Sciences
Journal web-site: http://www.societyforchaostheory.org/ndpls/
Fair use policy: http://www.societyforchaostheory.org/ndpls/permissions/files/ AcceptableUseV4tc.pdf

C U R R I C U L U M V I T A E

Colleen Diane Cutler

Degrees

2015 M.Sc.	Clinical Psychology	Western University
2013 B.A. (Hons)	Psychology	University of Guelph
1985 Ph.D.	Mathematics	Carleton University
1980 M.Sc.	Math & Stats	Carleton University
1979 B.Sc. (Dble Hons)	Math & Stats	University of Manitoba

Employment

Sep 2018/Apr 2019	GTA Psych 2810: Statistics	Western University
Sep 2017/Apr 2018	GTA Psych 3316: Trauma	Western University
Sep 2016/Apr 2017	GTA Psych 2810: Statistics	Western University
Sep 2015/Apr 2016	GTA Psych 2810: Statistics	Western University
Sep 2014/Apr 2015	GTA Psych 2810: Statistics	Western University
Sep 2013/Apr 2014	GTA Psych 2800: Research	Western University
Jul 1999/Aug 2009	Professor of Statistics	University of Waterloo
Jul 1991/Jun 1999	Assoc. Professor of Statistics	University of Waterloo
Jul 1986/Jun 1991	Asst. Professor of Statistics	University of Waterloo
Sep 1983/Jun1986	Asst. Professor of Statistics	University of Manitoba

Awards

- **Ontario Graduate Scholarship**[1]: Sep 2013 - Aug 2014 ($15,000)
- **2001 CRM–SSC Prize** for outstanding contributions to statistical science. This award is given at most annually by the Centre de Recherche Mathematique (CRM) and the Statistical Society of Canada (SSC) for research done by a Canadian within 15 years of their Ph.D. ($5,000)

Psychology Publications

Published Articles

Cutler, C. D., & Neufeld, R. W. J. (2017). Addressing very short stimulus encoding times in modeling schizophrenia cognitive deficit. *Journal of Mathematical Psychology, 79,* 53–63.

Cutler, C. D., & Neufeld, R. W. J. (2019). Nonlinear indices with applications to schizophrenia and bipolar disorder. *Nonlinear Dynamics, Psychology, and Life Sciences, 23,* 17–56.

Neufeld, R. W. J., & Cutler, C. D. (2019). Potential contributions of clinical mathematical psychology to robust modeling in cognitive science. *Computational Brain & Behavior, 2,* 251–254. https://doi.org/10.1007/s42113-019-00044z

Conference Papers

Neufeld, R. W. J., & Cutler, C. D. (2019). Potential contributions of clinical mathematical psychology to robust modeling in cognitive science. *Society for Mathematical Psychology, Montreal, Canada, July 22, 2019.*

Neufeld, R. W. J., Taylor, R., Cutler, C. D., Théberge, J., Densmore, M., & Williamson, P. (2017). Analytical modelling as a linchpin between levels of neuroimaging: The case of Stroop task performance in schizophrenia. *Society for Mathematical Psychology Annual Meeting, Warwick, UK, July 22–25, 2017.*

Neufeld, R. W. J., Taylor, R., Cutler, C. D., Théberge, J., Densmore, M., & Williamson, P. (2017). Analytical modelling as a linchpin between levels of neuroimaging: Stroop task performance in schizophrenia as a case in point. *Annual Summer Interdisciplinary Conference in Cognitive Science, Interlaken, Switzerland, July 15–20, 2017.*

[1] ineligible for other external scholarships due to 4 NSERC scholarships held in previous graduate program

C. D. Cutler, & R. W. J. Neufeld (2015). Addressing Very Short Stimulus Encoding Times in Modeling Schizophrenia Cognitive Deficit. *Society for Mathematical Psychology Annual Meeting, Irvine, CA, July 17–21, 2015.*

Selected Mathematics Publications

C.D. Cutler (2009). Building the bridge backwards: some comments on early interdisciplinary efforts between statisticians and physical scientists. (Invited paper) In *Exploration of a nonlinear world: An appreciation of Howell Tong's contributions to statistics,* (K. S. Chan, Ed.) (pp. 231–235), Singapore: World Scientific.

C.D. Cutler (2009). Repeat sampling of extreme observations: regression to the mean revisited. *Extremes.* **12,** 297–325.

Cutler, C.D. (2000). Embedding theorems, scaling structures, and determinism in time series. In L.G. Gorostiza and G. Ivanoff (eds.) *Stochastic models: Proceedings of the International Conference on Stochastic Models.* Canadian Mathematical Society Conference Proceedings, American Mathematical Society, RI, **26**, 85–103.

Cutler, C.D. (2000). Computing pointwise fractal dimension by conditioning in multivariate distributions and time series. *Bernoulli,* **6**, 381–399.

Cutler, C.D. (1998). Some thoughts on chaos and communication between statisticians and physical scientists. 1 page. Invited paper to the IASE/C(PS)^2 panel on Research and Teaching of Probability and Statistics in the Physical Sciences, *51st Session of the International Statistical Institute* (**ISI**) at Istanbul, Turkey, August 1997. In Book 3 of Proceedings, pp. 219–220.

Cutler, C.D. (1997). A general approach to predictive and fractal scaling dimensions in discrete-index time series. In *Nonlinear Dynamics and Time Series: Building a Bridge Between the Natural and Statistical Sciences,* (eds. C.D. Cutler and D.T. Kaplan), Fields Institute Communications **11**, American Mathematical Society, Providence RI, pp. 29–48.

Cutler, C.D. (1995). Discussion of "A personal overview of non-linear time series analysis from a chaos perspective" by H. Tong. *Scandinavian Journal of Statistics* **22** 423–424.

Cutler, C.D. (1995). The density theorem and Hausdorff inequality for packing measure in general metric spaces. *Illinois Journal of Mathematics.* **39** 676–694.

Cutler, C.D. (1995). Strong and weak duality principles for fractal dimension in Euclidean space. *Mathematical Proceedings of the Cambridge Philosophical Society* **118** 393–410.

Cutler, C.D. (1994). A theory of correlation dimension for stationary time series. *Philosophical Transactions of the Royal Society, Series A* **348** 343–355.

Cutler, C.D. (1992). Comment on "Chaos, fractals, and statistics" by S. Chatterjee and M. R. Yilmaz, and "Statistics, probability, and chaos" by L.M. Berliner. *Statistical Science* **7** 91–94.

Cutler, C.D. (1991). Some results on the behavior and estimation of the fractal dimensions of distributions on attractors. *Journal of Statistical Physics* **62** 651–708.

Cutler, C.D. (1990). Connecting ergodicity and dimension in dynamical systems. *Ergodic Theory and Dynamical Systems* **10** 451–462.

Cutler, C.D. (1990). A dynamical system with integer information dimension and fractal correlation exponent. *Communications in Mathematical Physics* **129** 621–629.

Cutler, C.D. and Dawson, D.A. (1990). Nearest neighbor analysis of a family of fractal distributions. *Annals of Probability* **18** 256–271.

Cutler, C.D. and Dawson, D.A. (1989). Estimation of dimension for spatially-distributed data and related limit theorems. *Journal of Multivariate Analysis* **28** 115–148.

Cutler, C.D. (1988). A note on equivalent interval covering systems for Hausdorff dimension on $\mathbb{R}$. *International Journal of Mathematics and Mathematical Sciences* **11** 643–650.

Cutler, C.D. (1986). The Hausdorff dimension distribution of finite measures in Euclidean space. *Canadian Journal of Mathematics* **38** 1459–1484.