

STOCHASTIC PROCESSES IN THE NEUROSCIENCES

JAMES A. KOZIOL

*Department of Basic and Clinical Research
Scripps Clinic and Research Foundation
10666 North Torrey Pines Road, La Jolla, California 92037*

(Received August 6, 1986)

A conference on stochastic processes in the neurosciences was held June 23-27, 1986, at North Carolina State University, Raleigh, NC. The conference was sponsored by the Conference Board of Mathematical Sciences and the National Science Foundation, and organized by Professor Charles Smith of the Department of Statistics of the host institution. The principal lecturer was Dr. Henry C. Tuckwell of Monash University, who presented ten one-hour lectures during the course of the conference. The following are titles and synopses of Dr. Tuckwell's lectures.

1. Introduction; Historical Overview

Tuckwell opened lecture 1 with a historical review of the interplay between mathematics and neurobiology. Probability theory, the theory of random processes, and the theory of stochastic ordinary and partial differential equations are fundamental tools in neurobiology, which in turn has required new mathematical tools to meet developing needs. For example, the pioneering efforts of Wiener, Hodgkin and Huxley, and Gerstein and Mandelbrot have led to exciting new developments in both theory and application. Tuckwell gave a thumbnail sketch of basic neuroanatomy, with emphasis on the anatomy and physiology (electrical activity) of single neurons. He summarized the major deterministic theories of Goldman, Hodgkin, and Katz, and of Lapicque, and then developed the cable theory for spatial and temporal variation of membrane potential in certain axons. Of note here was the summarization of recent work by Walsh and Tuckwell, in which the weighted sum of depolarizations across a dendritic tree is reduced to the solution of one cable equation (versus the more conventional consideration of separate cable equations over different branches). Implications of their work are immediate: the potential on the trunk can easily be found; and, under certain conditions one cable equation is sufficient to characterize potential for the equivalent cylinder. Tuckwell concluded lecture 1 with a sketch of the historical evolution of interest in stochastic phenomena of the central nervous system: such phenomena as electroencephalographs, evoked potentials, fluctuations in excitability of nerves, variability in interspike intervals, miniature end plate potentials, 1/f noise, and channel noise have provided challenging areas of research for both mathe-

maticians and neurobiologists through the years. How investigators have responded to these challenges would be the topics of later lectures.

2. Early Models; Poisson Processes and Random Walks

Lecture 2, focusing on stochastic models for neural firing, opened with some historical notes. Interestingly, the McCulloch-Pitts model for neural firing preceded actual intracellular recording from motoneurons by several years. Hagiwara subsequently introduced the notion of a threshold function which had to be reached for the cell to fire, and Junge and Moore added a refractory period to their model. Tuckwell viewed these early models as a starting point for the theory of neuronal integration; in particular, he gave a mathematically simple yet elegant treatment of a single neuron with Poisson excitation and linear decay. He then developed the random walk model of Gerstein and Mandelbrot, both heuristically and with considerable mathematical detail. He commented that the random walk model and its diffusion approximation contribute prominently to the interplay between probability and neurobiology.

3. Discontinuous Markov Processes with Exponential Decay

In lecture 3, Tuckwell introduced Stein's model for neural potential in response to synaptic input: briefly, this model is a Lapicque model neuron receiving random impulsive currents which represent synaptic excitation and inhibition, with the added factor of exponential decay inserted between the jumps. Though this model accurately reflects many of the realities of nerve cell physiology, mathematical calculations with it are rather daunting. Tuckwell embedded Stein's model within a continuous time Markov process formulation, and derived the forward and backward Kolmogorov equations for the associated transition function. He then generalized further to the class of temporarily homogeneous Markov processes described by Ito's stochastic differential equation so as to utilize the first passage time theory available, as from Gihman and Skorohod. Application to Stein's model proceeds directly; in particular, moments of the firing time for Stein's model have been found by several investigators. Tuckwell concluded the lecture by introducing a modification of Stein's model to include reversal potentials, but deferred investigation of this generalization until a later lecture.

4. One Dimensional Diffusions

The discontinuous models described in these early lectures oftentimes present difficult computational problems which are obviated with diffusion approximations. Tuckwell thus turned to one dimensional diffusion approximations in lecture 4, with particular emphasis on reducing problems of interest to solving differential equations for which a voluminous literature on analytical and numerical methods exists. Tuckwell demonstrated how the Gerstein-Mandelbrot random walk model is naturally generalized via a stochastic differential to a standard diffusion approxima-

tion, which can be taken to be the usual Wiener process with drift. Analogously, Stein's discontinuous Markov process model can be related via a stochastic differential equation to the Ornstein-Uhlenbeck process. Of interest, then, is the issue of how close are the properties (e.g., transition densities, first passage time distributions) of the original and approximating processes. Of equal relevance, of course, is the issue of which processes are consistent with experiments. In this regard, the Gerstein-Mandelbrot and Stein models can fare poorly, whereas the Ornstein-Uhlenbeck process has been found to represent nerve membrane potential quite accurately. Because of its relevance, then, Tuckwell summarized many standard and not so standard results pertaining to first passage time theory for the OUP, including his joint work with Cope and with Wan in this area. Tuckwell concluded the lecture with an extension of the standard diffusion approximation to incorporate the physiologically meaningful reversal potentials, and summarized his seminal work with Hanson on this topic.

5. Stochastic Partial Differential Equations

In lecture 5, Tuckwell gave a more detailed account of the application of stochastic differential equations to various models of membrane potential. He began by recounting his joint work with Wan in which they had attempted to elucidate how a neuron responds to a white noise current injected at some location on its dendritic tree. (The idea of using white noise was to simulate randomly arriving post-synaptic potentials in the manner of a diffusion approximation.) Their investigation of the cable equation under this scenario is both definitive and elegant. The corresponding cable equation with two parameter white noise has been extensively studied by Walsh; Tuckwell and Walsh have calculated some quantities of interest for this model. Tuckwell concluded the lecture by outlining various non-linear stochastic equation models for nerve membrane potential. Stochastic versions of the deterministic Hodgkin-Huxley equations, Fitzhugh-Nagumo equations, Frankenhauser-Huxley equations, and cable model nerve cells involving both one and two parameter white noise input currents are all topics of active research interest.

6. The Analysis of Stochastic Neuronal Activity

Starting from the one dimensional stochastic models described in lectures 2-4, Tuckwell noted that neuronal spike trains typically consist of sequences of interspike intervals which may be considered to be independent identically distributed random variates. The counting process of the number of spikes in any fixed interval then forms a renewal process. Tuckwell briefly summarized standard statistical techniques for estimation and hypothesis testing, with emphasis on characterization and interpretation of ISI distributions. Of particular interest was a classification scheme for ISI distributions based on empirical density estimates. Brief mention was made of tests for temporal structure (i.e., stationarity independence, renewal process, Poisson process). Tuckwell concluded with a simple model for the processes underlying post-stimulus time histograms obtained from stimulus-response studies on single neurons, and encouraged further work in this area.

7. Channel Noise

This lecture was concerned with conductance fluctuations induced by the opening and closing of ionic channels. Tuckwell first described the background biophysics of channels. He briefly reviewed some of the mathematics of continuous time Markov chains, which he immediately applied to a two-state (open, or conducting, and closed, or non-conducting) channel. Single channel recordings can thereby be rigorously analyzed statistically. Several two-state channels as, for example, from a patch of membrane with channels dispersed over it, can be analyzed in an analogous manner. Tuckwell lastly summarized the technically involved extension by Colquhoun and Hawkes of the two-state Markov chain model to incorporate many states, which may appropriately be applied to n -state channels.

8. Wiener Kernel Expansions

The motivation behind this lecture is "system identification". Consider, for example, the enormous complexity of functional neuronal networks. One approach to studying such networks might be the integration of complex anatomical wiring diagrams with detailed electrophysiological and neurochemical properties of perhaps thousands of cells. An alternative approach, attributed to Wiener, is to characterize the network by feeding in a white noise stimulus and deducing some functions called kernels which appear in an expansion of the output in terms of the input. The mathematical basis of the expansion is due to Wiener, Cameron and Martin, and Ito. Tuckwell's purpose in this lecture was to provide an introduction to their work. To this end, he first summarized some mathematical prerequisites on Hilbert spaces of random variables, Fourier series, and stochastic integrals. He then described Cameron and Martin's expansion of an L_2 functional of a Wiener process (in terms of products of Hermite polynomials of stochastic integrals of the usual orthonormal functions with respect to a Wiener process). An equivalent expansion in terms of multiple Wiener integrals is available from Ito. Rearrangement of the terms of this latter expansion yields the expansion Wiener obtained. Tuckwell concluded his lucid exposition by describing applications of Wiener kernel expansions to experimental studies of the visual system.

9. Further Results and Further Problems

Tuckwell began this lecture with a description of a clever mathematical technique for obtaining first passage times of certain one-dimensional neuron models to time dependent thresholds by utilizing first exit time theory for vector-valued Markov processes. He illustrated the technique by summarizing details of joint research with Wan on the Ornstein-Uhlenbeck process with exponential barrier. He then turned to Stein's model, and discussed three aspects of the model that he had investigated in previous research: (i) the coefficient of variation — exact results versus simulation studies, (ii) factors influencing motoneuron firing rates — in particular, recurrent inhibition via the Renshaw circuit; (iii) effects of reversal potentials.

10. The Stochastic Activity of Neuronal Populations

In this concluding lecture, Tuckwell turned from individual cells to populations of cells for mathematical motivation. He first introduced evoked potentials, then compared the Wiener filter and Brillinger's method for estimating the evoked response. He similarly described biomedical aspects of the EEG, then summarized relevant time series techniques for EEG analysis. He ended with some speculative remarks on stochastic models for neuronal populations.

In addition to Dr. Tuckwell's presentations there were three invited lectures: (i) stochastic differential equation models for spatially distributed neurons, by Professor G. Kallianpur; (ii) a stochastic model of neuronal response, by Professor J. Walsh; and (iii) modeling of sodium channel conductance and estimation of parameters, by Professor G. Yang. Also, contributed papers were delivered by most of the 30 invited participants in the conference, a group that was equally divided among experimentalists, applied mathematicians, and probabilists. Dr. Tuckwell's lectures will be published in the CBMS series by SIAM.