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Analysis of Parallel Spike Trains

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Foreword

Close to fifty years ago, when two generations of neuroscientists contributing to this book had not yet been born and I was still happy in high school, George Gerstein, Donald Perkel, and colleagues, in a series of papers, laid the foundations for what was to become the quantitative analysis of the dynamics of neuronal spiking activity and the interactions within and across neuronal networks. In the context of the present textbook, it is instructive to reread some of these papers.

The full abstract of the 1960 *Science* paper (Gerstein 1960) reads:

> *The use of a high-speed digital computer for investigation of neural firing patterns is described. The high sensitivity of the method permits detection of stimulus-response relations buried in a background of spontaneous activity.*

The abstract of the 1964 *Science* paper (Gerstein and Clark 1964) continues:

> *A tungsten microelectrode with several small holes burnt in the vinyl insulation enables the action potentials from several adjacent neurons to be observed simultaneously. A digital computer is used to separate the contributions of each neuron by examining and classifying the waveforms of the action potentials. These methods allow studies to be made of interactions between neurons that lie close together.*

Such studies were indeed made, albeit that their numbers increased only very slowly initially, mostly due to rather formidable problems with the experimental technology involved. With regard to the analysis of data resulting from such experiments, the abstracts of the two companion papers in *Biophysical Journal* 1967 (Perkel et al. 1967a, 1967b) are strikingly explicit and, even in 2010, scaringly timely. In fact, taken together, they read as an ambitious programme manifesto, aimed at establishing a novel, theory-driven data analysis paradigm for network physiology, which, as we now know, it indeed did.

First, on the spiking activity of single neurons:

> *In a growing class of neurophysiological experiments, the train of impulses* ("*spikes*") *produced by a nerve cell is subjected to statistical treatment involving the time intervals between spikes. The statistical techniques available for the analysis of single spike trains are described and related to the underlying mathematical theory, that of stochastic point processes, i.e., of stochastic processes whose realizations may be described as series of point events occurring in time, separated by random intervals. For single stationary spike trains,*

> *several orders of complexity of statistical treatment are described; the major distinction is that between statistical measures that depend in an essential way on the serial order of interspike intervals and those that are order-independent. The interrelations among the several types of calculations are shown, and an attempt is made to ameliorate the current nomenclatural confusion in this field. Applications, interpretations, and potential difficulties of the statistical techniques are discussed, with special reference to types of spike trains encountered experimentally. Next, the related types of analysis are described for experiments which involve repeated presentations of a brief, isolated stimulus. Finally, the effects of nonstationarity, e.g. long-term changes in firing rate, on the various statistical measures are discussed. Several commonly observed patterns of spike activity are shown to be differentially sensitive to such changes.*

Then, on the activity of pairs of neurons and their interactions:

> *The statistical analysis of two simultaneously observed trains of neuronal spikes is described, using as a conceptual framework the theory of stochastic point processes. The first statistical question that arises is whether the observed trains are independent; statistical techniques for testing independence are developed around the notion that, under the null hypothesis, the times of spike occurrence in one train represent random instants in time with respect to the other. If the null hypothesis is rejected—if dependence is attributed to the trains—the problem then becomes that of characterizing the nature and source of the observed dependencies. Statistical signs of various classes of dependencies, including direct interaction and shared input, are discussed and illustrated through computer simulations of interacting neurons. The effects of nonstationarities on the statistical measures for simultaneous spike trains are also discussed. For two-train comparisons of irregularly discharging nerve cells, moderate nonstationarities are shown to have little effect on the detection of interactions. Combining repetitive stimulation and simultaneous recording of spike trains from two* (*or more*) *neurons yields additional clues as to possible modes of interaction among the monitored neurons; the theory presented is illustrated by an application to experimentally obtained data from auditory neurons.*

Rereading these abstracts leaves us wondering, what the present book is all about and why, in the year 2010, we would still need it. Indeed, these early studies in the 1960s already formulated the fundamental questions that are still very much with us: How can neuronal interactions be segregated from ongoing background activity? How can the concepts of activity dynamics and correlations be refined and reconciled? And, most of all: What is their role in brain function? It is, therefore, a reassuring thought to have the same George Gerstein contributing a chapter on these issues in this new textbook.

In the 1980s, Computational Neuroscience established itself as a new research field in the neurosciences (Sejnowski et al. 1988; Schwartz 1990; Rumelhart et al. 1986). As Valentino Braitenberg so aptly put it (Braitenberg 1992): “We are convinced that ultimately a satisfactory explanation of thought and behavior will be given in a language akin to that of physics, i.e. in mathematical terms.” Indeed, the theory of neuronal networks explaining basic features of single neurons and simple networks made rapid progress, and many theoreticians were attracted to the field. Thus, over the next decade, many papers, dedicated conferences (e.g., Palm and Aertsen 1987; Aertsen and Braitenberg 1992; Aertsen 1993; Aertsen and Braitenberg 1996), and monographs (e.g., Abeles 1982; Amit 1992; Braitenberg 1984; Palm 1982) explored the foundations of a future theory of brain function. Soon, text books suitable for advanced courses, followed (e.g., Abeles

1991; Dayan and Abbot 2001; Gerstner and Kistler 2002; Hertz et al. 1991; Koch 1998).

Compared to this rapid progress in the development of computational models and theory, progress in the analysis of experimental spike train recordings soon lagged behind. The nonstationarity and irregularity of spiking activity recorded from the brain in action, its considerable variability across repetitions of a task, and the complex interplay of multiple time scales, all taken together constituted very severe problems—and continue to do so—for the adequate handling of the experimental data. As a result, an unambiguous interpretation of the various quantitative measures and the search for meaningful structure in the recorded data all too often remained illusive. I recall that one night, many years ago, I awoke in front of the TV screen after the program had ended. After studying the nonprogram on the screen for a while, I concluded that it was evidently packed with highly interesting spatiotemporal patterns—in any case, I saw them occurring and recurring virtually anywhere, almost at will. Needless to say, though, that it proved a bit hard to establish their statistical and functional significance. Thus, despite some early groundbreaking overviews on advanced data analysis methods for specific areas (e.g., Eggermont 1990; Rieke et al. 1997), it should take another 20 years before this first comprehensive textbook on the state of the art in the analysis of parallel spike train recordings could be produced.

Important techniques are now available for routine usage in the laboratory, and their limits are in most cases well understood. Thus, it is timely to bring this knowledge to the classroom now. Consequently, the present book luckily avoids the repetition of lengthy conceptual discussions from earlier times and, instead, hurries to present the material in a format suitable for the practitioner and the student. The scope of the contributions ranges from the mathematical framework underlying the various methods to practical questions like the generation of random numbers. Closing the cycle, one chapter in the book returns to the earlier cited question on *The use of a high-speed digital computer for investigation of neural firing patterns.* It explains how, with the help of modern computer clusters and high-level parallel programming, we can now compute statistical tests capturing biological constraints to a precision inaccessible by analytical approaches of the past.

However, this book in no way presents an end point to the quest. The authors can only hint at the challenges posed by the advent of massively parallel recording technology. Many such systems are already installed worldwide. Yet, presently they are still mostly used to increase the speed of data collection, rather than utilizing the qualitatively new opportunity to assess the higher-order structure of neuronal assemblies in action. I am confident that in the years to come, the authors will continue in their endeavor and will surprise us with many fascinating new insights into the functioning of the brain. A rewarding prospect, indeed, since the alternative of studying a TV screen outside broadcasting time has meanwhile ceased to be an option.

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