Review

Biological Psychiatry: CNNI

Clinical Applications of Stochastic Dynamic Models of the Brain, Part I: A Primer

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ABSTRACT

Biological phenomena arise through interactions between an organism's intrinsic dynamics and stochastic forces—random fluctuations due to external inputs, thermal energy, or other exogenous influences. Dynamic processes in the brain derive from neurophysiology and anatomical connectivity; stochastic effects arise through sensory fluctuations, brainstem discharges, and random microscopic states such as thermal noise. The dynamic evolution of systems composed of both dynamic and random effects can be studied with stochastic dynamic models (SDMs). This article, Part I of a two-part series, offers a primer of SDMs and their application to large-scale neural systems in health and disease. The companion article, Part II, reviews the application of SDMs to brain disorders. SDMs generate a distribution of dynamic states, which (we argue) represent ideal candidates for modeling how the brain represents states of the world. When augmented with variational methods for model inversion, SDMs represent a powerful means of inferring neuronal dynamics from functional neuroimaging data in health and disease. Together with deeper theoretical considerations, this work suggests that SDMs will play a unique and influential role in computational psychiatry, unifying empirical observations with models of perception and behavior.

Keywords: Epilepsy, Computational neuroscience, Computational psychiatry, Mathematical modeling, Melancholia, Stochastic

http://dx.doi.org/10.1016/j.bpsc.2017.01.010

Biological organisms balance a tendency toward internal order and control against the need to preempt and adapt to changing environments (1). Their functioning reflects a dynamic interplay of nonlinearity and feedback with stochastic fluctuations: this exchange of order and entropy yields complexity in its various guises (2). In the brain, innate dynamics arise from neurophysiological processes such as ion channels and dendritic filtering while feedback occurs through short- and long-range axonal connections (3); stochastic inputs arise through sensory fluctuations, brainstem discharges, and thermal energy (random fluctuations at the microscopic level, such as Brownian motion of ions). There is a well-established field devoted to modeling this interplay of dynamic processes and stochastic effects through a melding of calculus and statistical physics. The field is anchored by dynamic equations that govern the temporal (and possibly spatial) behavior of the system's state variables. These equations are derived from the biophysical properties of the system of interest and studied using analysis and simulation. Because the actual state variables (such as firing rates) cannot be directly observed in noninvasive human studies, measurement functions that map neuronal states onto observables (such as scalp electroencephalography or the blood oxygen level–dependent [BOLD] signal) are required to enable empirical predictions. Experimental data then allow models to be tested, compared, refined, or refuted.

In this review, we introduce the equations that arise at the intersection of calculus and statistical physics, namely stochastic differential equations (SDEs). These lie at the heart of stochastic dynamic models (SDMs) of the brain, for which we offer micro- and mesoscopic examples. We also showcase the potential of stochastic differential models to unify observations of functional neuroimaging data with models of behavior. This forms the background for Part II (4), in which we review existing applications of SDEs to clinical disorders in neurology and psychiatry and consider future perspectives.

STOCHASTIC DYNAMIC MODELS OF THE BRAIN: A BRIEF PRIMER

Stochastic Differential Equations: Fundamentals

We first introduce the modeling of neural systems with SDEs. Key to this approach is the notion of a system's state—the core dynamical variables that describe the system at any instant in time, such as firing rates, membrane potentials, and channel conductances. Models describe how states evolve in time—the dynamics. Given the current state and the dynamical rules of a particular model, it is possible to project (integrate) the state dynamics forward in time (i.e., solve the equations). Suppose we model a neuronal system with N state variables. We can represent these variables as a vector, $\mathrm{x} = [x_1, x_2, \ldots, x_N]$, where, for example, x_1 is the cell membrane potential, x_2 is the firing rate, and x_3 is the conductance of a particular class of membrane channels. Then, in the absence of any random fluctuations, the dynamic evolution of the state

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variables obeys a set of ordinary differential equations:

$$\begin{aligned}\frac{dx_1}{dt} &= F_1(x_1(t), x_2(t), \ldots, x_N(t)),\\ \frac{dx_2}{dt} &= F_2(x_1(t), x_2(t), \ldots, x_N(t)),\\ &\vdots\\ \frac{dx_N}{dt} &= F_N(x_1(t),\ x_2(t), \ldots,\ x_N(t)),\end{aligned} \tag{1}$$

where $\frac{d}{dt}$ is the usual differential operator (with respect to time) and the F_j are functions (possibly nonlinear) that embody the properties and interactions of the system. These equations can also be represented in a simpler vector form:

$$\frac{dx_i}{dt} = F_i(\mathbf{x}(t)) \tag{2}$$

An example of simple neural dynamics is given by the Morris-Lecar model (5), a two-dimensional simplification of the Hodgkin-Huxley equations for the excitable membrane potential of a neuron. The membrane potential V is determined by the net current through all transmembrane ion channels (Na^+, K^+, Ca^{2+}, and leaky currents). The change in membrane potential at the cell soma is given by the sum of all ion channel currents plus any current I entering from the dendritic tree. In the full (four-dimensional) Hodgkin-Huxley model, the voltages and temporal behavior of all the major ion channels are modeled explicitly. A reduction to the two-dimensional Morris-Lecar model is achieved by exploiting the fact that calcium and sodium channels respond more quickly to changes in membrane voltage than do slower potassium channels. This means that the calcium and sodium channels follow their voltage-dependent conductances instantaneously, while the potassium channels relax to that value on a slower time scale—allowing us to focus on the slower dynamics, which enslave faster dynamics. That is, because the fast variables reach equilibrium quickly after a perturbation, it is convenient to treat them as always being at equilibrium, such that the only remaining dynamics are in the slow variables—hence, slow variables can be said to enslave fast ones (6). This is a common device in modeling dynamical systems known as an adiabatic approximation, which rests on the separation of time scales. Although widely used, it is of less value in systems where fast, microscopic fluctuations may drive slower, coarser subsystems (e.g., in turbulent fluid dynamics).

The dynamical states for the Morris-Lecar model are {V, n}, the membrane potential V, and the proportion of open potassium ion channels n, which is proportional to the membrane conductance. The dynamic equations for the Morris-Lecar model are presented in the Supplement. An example time series is given in Figure 1A, showing the characteristic rapid spiking waveform of a suprathreshold cell. Figure 1B shows the corresponding limit cycle attractor in the phase space spanned by the dynamical variables {V, n}. The attractor is color coded to show the direction of the (clockwise) flow around the smooth limit cycle attractor.

The equations thus far capture the essence of a neuron that is kept spiking by a constant dendritic current. However, as discussed above, neural dynamics inevitably occur in the presence of noisy fluctuations. In the Morris-Lecar model, such fluctuations reflect stochastic effects at ion channels, thermal energy, the uneven distribution of channels in the membrane, and irregularities in dendritic currents—sources of so-called neural noise (7). Stochastic effects can be introduced by the addition of a random term to the state equation:

$$\frac{dx_i}{dt} = F_i(\mathbf{x}) + \mu_i\eta_i, \tag{3}$$

where η_i represents independent zero-mean, unit-variance Gaussian noise added incrementally at each time point (also called a Wiener process) and μ_i is a coefficient that scales the noise appropriately to each of the variables. Note that while it is apparently simple to add noise in this way (yielding the Langevin equation), neither classic calculus nor standard numerical integration schemes deal with the incorporation of incremental rough discontinuities in this way. An alternative way of writing equation 3 is through the use of more formal SDEs; for the interested reader, we provide the corresponding SDEs in the Supplement, together with a more formal treatment of stochastic fluctuations.[1]

Figure 1C and D shows example dynamics from the Morris-Lecar system with an additive stochastic term. Both the time series (Figure 1C) and the attractor (Figure 1D) show the impact of the irregular roughness of the additive noise term. The roughness is more apparent during the refractory phase of the firing cycle, but only because the underlying flow is slower during these periods, allowing more time for the noise to accrue. The impact of the noise is a relatively modest degradation in the regularity of the periodicity and amplitude of the spikes.

This is a simple example of an SDM with independent dynamic and noise terms. The noise acts to perturb the system as it traverses the limit cycle attractor. However, in many complex systems, noise does not enter as a simple state-independent (additive) term. An example is the well-known coupling between trade volume and volatility in financial markets: as the amount of trade increases, so do fluctuations in market value (9). Therefore, in many applications, the noise mixes with the states as it enters the system, yielding

$$\frac{dx_i}{dt} = F_i(\mathbf{x}) + G_i(\mathbf{x})\eta_i, \tag{4}$$

where G is a function that captures the state-dependence of the stochastic influence. Equation 4 is a generalized Langevin equation. If G is linear in $\mathbf{x}$ and each state mixes with only its own noise term, we have

$$\frac{dx_i}{dt} = F_i(\mathbf{x}) + \mu_i x_i\eta_i. \tag{5}$$

That is, the influence of the noise term is not constant, but rather scales in proportion to the states $\mathbf{x}$. Fluctuations at voltage-dependent ion channels are by definition state dependent. An example of Morris-Lecar dynamics with state dependent noise is shown in Figure 1E and F. The standout feature of these panels is the increase in fluctuations in the subthreshold regime ($<$ –50 mV) compared with the preceding panels, and the contrasting smoother flow in the fast, suprathreshold phase ($>$ –20 mV). This noisier subthreshold phase substantially increases the irregularity of interspike intervals.

[1]All of the equations in this review, together with an integration scheme for SDEs (8), can be downloaded in MATLAB form from http://sng.org.au/Downloads. Python code for integrating SDEs is also available.