Stochastic dynamical systems in neuroscience

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The success of Statistical Physics is largely due to the huge separation between microscopic and macroscopic scales, which enables us to apply limit theorems from probability theory, such as the law of large numbers and the central limit theorem. The difficulty of biological systems, such as those arising in neuroscience, is that instead of only two scales, they involve a whole hierarchy of them:

- The dynamics of the brain as a whole can be modeled in the continuum limit by *neural field equations*, which are partial differential or integro-differential equations for the synaptic electric potential [1].
- Localised populations of excitatory and inhibitory neurons are described by coupled integro-differential or delay equations, as in the *Wilson–Cowan model* for decision making [2].
- The dynamics of the action potential along the axons of individual neurons is described by partial or ordinary differential equations such as the *Hodgkin–Huxley equations* [3].
- The number of open and closed ion channels, which regulate action potentials across the neuron's membrane, can be described by a Markovian jump process [4]. Similarly, the interactions between genes, proteins and enzymes within cells involve complicated networks that can be modeled by large systems of coupled maps or differential equations [5].

Even though the scale separation is not as radical as in Statistical Physics, the different levels of the hierarchy are often still separated by one or two orders of magnitude.

Randomness arises in these models from simplifying the dynamics of higher or lower levels in the hierarchy, using reduction procedures such as stochastic averaging or continuum approximations (see Richard Sowers' and Martin Riedler's contributions to these Reports). For instance, models for action potential generation involve two variables: the voltage x across the membrane, and the vector y of proportions of open ion channels of different types. External noise, arising from fluctuations in synaptic currents coming from other neurons, originates in the next higher level of the hierarchy. Internal noise, stemming from the random dynamics of ion channels, comes from the level below. In the simplest case, one is thus led to a system of stochastic differential equations (SDEs) of the form

$$
\begin{aligned}
\mathrm{d}x_t &= \frac{1}{\varepsilon} f(x_t, y_t)\, \mathrm{d}t + \frac{\sigma_1}{\sqrt{\varepsilon}}\, \mathrm{d}W_t^{(1)}\;, \\
\mathrm{d}y_t &= g(x_t, y_t)\, \mathrm{d}t + \sigma_2\, \mathrm{d}W_t^{(2)}\;,
\end{aligned}
\tag{1}
$$

where ε describes the time scale separation, and $W_t^{(1)}$ and $W_t^{(2)}$ are independent Wiener processes, respectively modelling external and internal noise.

Choosing the appropriate model for noise is a difficult problem, influenced by parameters such as the existence of space and time correlations, and the discrete or

continuous nature of the dynamics. The simplest model for noise is Gaussian white noise as used in (1), but depending on the situation it may be more appropriate to use correlated noise such as Ornstein–Uhlenbeck processes, more general Lévy processes including jumps, or discrete-time noise such as Poisson or more general renewal processes.

Another important difference between Statistical Physics and biological problems is that while in the former, the emphasis lies on asymptotic behaviour, such as existence of stationary states and convergence to them, in biology transients play a fundamental rôle. There are several reasons for this: time-dependent forcing may prevent the existence of equilibrium states; the system may spend very long time spans in metastable states; non-equilibrium phenomena such as excitability and stochastic resonance often are of central importance to the system's behaviour.

As a paradigm illustrating transient behaviour, consider the SDE

$$(2) \qquad \mathrm{d}x_t = f(x_t)\,\mathrm{d}t + \sigma\,\mathrm{d}W_t\;, \qquad x_t \in \mathbb{R}^n$$

for a dissipative vector field f. For small noise intensity σ, solutions of (2) tend to spend long time spans in localised regions of space, separated by quick transitions between these regions. The *stochastic exit problem* consists in quantifying this behaviour: Given a domain $D \subset \mathbb{R}^n$, determine the distribution of the *first-exit time* $\tau = \inf\{t > 0\colon x_t \notin D\}$, and the law of the *first-exit location* $x_\tau \in \partial D$, known as the *harmonic measure*. If τ is likely to be large, the dynamics in D is called *metastable*, and can be described by a *quasistationary distribution* (QSD). The transitions between metastable domains can typically be reduced to a Markovian jump process, thereby providing an effective scale separation of the dynamics. A number of different techniques are available in order to achieve this program:

- The *theory of large deviations* for sample paths of the SDE (2) has been developed by Freidlin and Wentzell [6]. The probability of sample paths tracking a given deterministic path $\{\varphi_t\}$ behaves like $\mathrm{e}^{-I(\varphi)/2\sigma^2}$, for an explicitly known *rate function* I. This allows in particular to determine, by solving a variational problem, a constant V (the *quasipotential*) such that the expected first-exit time behaves like e^{V/σ^2} in the limit $\sigma \to 0$. Furthermore, this approach provides a way to characterise metastable regions and the transitions between them in this limit.
- A number of *analytic techniques* provide more detailed information on the exit problem. In particular, the expected first-exit time and location are linked, via Dynkin's formula, to the solutions of Dirichlet–Poisson boundary value problems involving the diffusion's infinitesimal generator [7]. These equations can be explicitly solved only in dimension 1 and in certain linear cases, but are accessible to WKB perturbation theory in more general cases.
- For fast–slow SDEs of the form (1), methods from *stochastic analysis* and *singular perturbation theory* provide a sharp control of the behaviour of sample paths in metastable regions and near bifurcation points [8] (see Barbara Gentz's contribution to these Reports).

- The theory of *random dynamical systems* [9] provides information on the asymptotic behaviour of the system, when it is meaningful to describe the system's reaction to the same random forcing, for different initial conditions. This is the case, e.g., for the phenomenon of *reliability* (see Kevin Lin's contribution to these Reports).

As an illustration, consider the FitzHugh–Nagumo equations, given by (1) with

$$ f(x,y) = x - x^3 + y , \qquad \text{and} \qquad g(x,y) = a - x . \tag{3} $$

The deterministic equations admit a stationary point at $P = (a, a^3 - a)$, which is stable if $\delta = (3a^2 - 1)/2$ is positive. However, if δ is small, the system is *excitable*, meaning that small random perturbations may cause large excursions in phase space, corresponding to the neuron emitting a spike. For applications it is important to determine the interspike interval statistics. The invariant measure of the system is of little use here, as it only gives the probability of the neuron being in the spiking or quiescent state at any given time.

Let D be a neighbourhood of P, and let F be a curve joining P to the boundary ∂D, parametrised by a variable $r \in [0, 1]$. The successive intersections of (x_t, y_t) with F up to its first exit from D define a substochastic Markov chain $(R_0, R_1, \ldots, R_{N-1})$ with kernel $K(r, A) = \mathbb{P}\{R_1 \in A | R_0 = r\}$.

Theorem 1 ([10]). *Assume $\sigma_1, \sigma_2 > 0$. Then K admits a QSD π_0, solution to $\pi_0 K = \lambda_0 \pi_0$, where the* principal eigenvalue λ_0 *is strictly less than 1. The survival time N of the Markov chain is almost surely finite and asymptotically geometric in the sense that*

$$ \lim_{n \to \infty} \mathbb{P}\{N = n + 1 | N > n\} = 1 - \lambda_0 . \tag{4} $$

The random variable N determines the length of the quiescent phase between spikes, and (4) shows that this length follows an approximately exponential law. More quantitative information is provided by the following result:

Theorem 2 ([10]). *For δ and ε small enough, and $\sigma_1^2 + \sigma_2^2 \leqslant (\varepsilon^{1/4}\delta)^2 / \log(\varepsilon/\sqrt{\delta})$, there exists $\kappa > 0$ such that*

$$ 1 - \lambda_0 \leqslant \exp\left\{ -\kappa \frac{(\varepsilon^{1/4}\delta)^2}{\sigma_1^2 + \sigma_2^2} \right\} . \tag{5} $$

Furthermore, the expectation of N satisfies

$$ \mathbb{E}(N) \geqslant C(\mu_0) \exp\left\{ \kappa \frac{(\varepsilon^{1/4}\delta)^2}{\sigma_1^2 + \sigma_2^2} \right\} , \tag{6} $$

where $C(\mu_0)$ depends on the initial distribution μ_0 on F.

This result describes the weak-noise regime, and confirms the result of an approximate computation in [11]. An open problem which is currently under investigation is to obtain similar results in other parameter regimes, as well as for other models such as the Morris–Lecar equations.

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