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Some unsolved problems relating to noise in biological systems

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Abstract. A faithful description of many biological processes requires us to take into account noise and fluctuations. Simplified stochastic models may help to shed light on the role of fluctuations in biological systems. Two kinds of theoretical problems for such simplified models are discussed in this paper. Firstly, I review approaches for calculating analytically the statistics of stochastic non-linear models of spontaneous neural activity. In particular, I discuss (i) interspike interval correlations in non-renewal neurons and (ii) the effect of synaptic short-term plasticity on neural signal transfer. Secondly, I discuss the more conceptual problem of how more detailed models are related to simplified models. I consider, as an example of an open problem of this kind, the relation between detailed models of coupled molecular motors and models of active Brownian motion.

Keywords: molecular motors (theory), signal transduction (theory), self-propelled particles

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Contents

1. Introduction

Understanding the cellular basis for many features of biological systems requires a modeling of the probabilistic nature of intercellular and intracellular processes; noise and fluctuations have to be taken into account. Two examples of such noise-affected biological phenomena that will be discussed here are (i) the spontaneous activity and signal transmission of neurons and (ii) intracellular transport by molecular motors. Biological questions of interest are how the respective systems cope with fluctuations inevitably present in these mesoscopic systems, to what extent noise limits their performance and—counter-intuitively—how they may use the noise to enhance their performance, i.e. to reliably transmit signals or transport cargo.

To answer questions like these, many researchers nowadays use stochastic approaches to model biophysical problems and employ non-linear dynamical systems driven by noise. What we need for a deeper understanding of the biophysics is a thorough comprehension of how these non-linear models behave when driven by non-equilibrium stochastic forces. Indispensable in this respect are analytical approaches and solvable toy models that form our picture of dynamic and stochastic mechanisms. They are helpful 'caricatures' that may also provide simple formulae and estimates which can serve as rules of thumb for more complicated models and—last but not least—for the real biological system that we are interested in. So a first important kind of problem is that of developing analytical approaches that permit the calculation of the statistics of interest in simplified stochastic models of biophysical phenomena. In this paper, I will sketch two such problems, namely (i) that of calculating an important correlation statistics for spontaneous neural spiking and (ii) that of estimating the effect of short-term synaptic plasticity on neural signal transfer.

A second kind of problem is often encountered in and is typical for biological modeling: complex systems like a neuron or a molecular motor can be described on different

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J. Stat. Mech. (2009) P01008

theoretical levels of increasing biophysical realism. For a deeper understanding of what is essential for the biophysics of a phenomenon, it is important that more complicated models can be mapped onto the simpler ones in a controlled way where one knows what is neglected in each single step.

In theoretical neuroscience, systematic simplification schemes have already been discussed for a while. For instance, as regards the dynamics of single neurons, a well-studied problem is how to get from a more realistic model like a Hodgkin–Huxley type neuron model to efficient (and analytically tractable) integrate-and-fire type neurons [1, 2]. In contrast, for non-equilibrium transport and motility phenomena such schemes are rare: there are different levels of modeling, for instance, comparably simple ones like random walk models [3] and active Brownian particles [4], and more detailed descriptions that model the biophysical origin of a self-propelled motion, for instance, for whole cells like sperm [5] or for motor proteins that run inside cells [6]. The connection between those levels of modeling is less clear and may be worthy of study. In particular, for molecular motors, we face a problem that resembles that of Brownian motion in statistical mechanics: for a mesoscopic particle embedded in a liquid or gas a reduction to a simple Langevin description can be achieved by eliminating the heat bath of surrounding molecules. Similarly, an effective non-linear Langevin equation reproduces the nature and statistics of the motion of coupled molecular motors displayed in experiments (see, e.g., [7]) as well as in detailed models [6]; however, so far we are not able to map detailed motor models quantitatively to such a simple description. This is in my opinion an important unsolved problem that I will also discuss in some detail.

2. Stochastic neural activity

As a first example, let me consider the activity of neural systems which encode information in stereotypical pulses—discharges of the voltage across the nerve membrane (cf figure 1). At their junctions (synapses) the arrival of a spike leads to the release of a neurotransmitter which drives the postsynaptic cell towards its firing threshold (excitatory synapse) or away from it (inhibitory synapse) [8]. Neurons are subject to synaptic input from many other cells that drive them effectively in a stochastic manner. As a consequence, the firing of a cortical cell looks highly random: the standard deviation of the time intervals between adjacent spikes is roughly as large as the mean interval itself, i.e. the so-called coefficient of variation of the interspike interval (ISI) is about one [8]. Also, upon sensory stimulation the cell response is reproducible only to a certain extent—there is trial-to-trial variability for the same stimulus. We understand the transmission of information through a single isolated neuron: models like the integrate-and-fire (IF) neuron (see [9] for a review) have been used to mimic the spike statistics and the subthreshold behavior of real cells *in vitro* surprisingly well [10]. Such models are described by just one equation for the subthreshold voltage $v(t)$ across the cell membrane

$$\tau_m \dot{v} = g(v) + \mu + \sqrt{2D}\xi(t) \tag{1}$$

complemented with a fire-and-reset rule: whenever the voltage reaches a threshold a spike is fired and the voltage v is reset to a value v_{reset}; fluctuations are taken into account in this simple model via an additive white Gaussian noise with correlation function $\langle \xi(t)\xi(t')\rangle = \delta(t-t')$. The function $g(v)$ can be a constant (perfect IF model), a linear

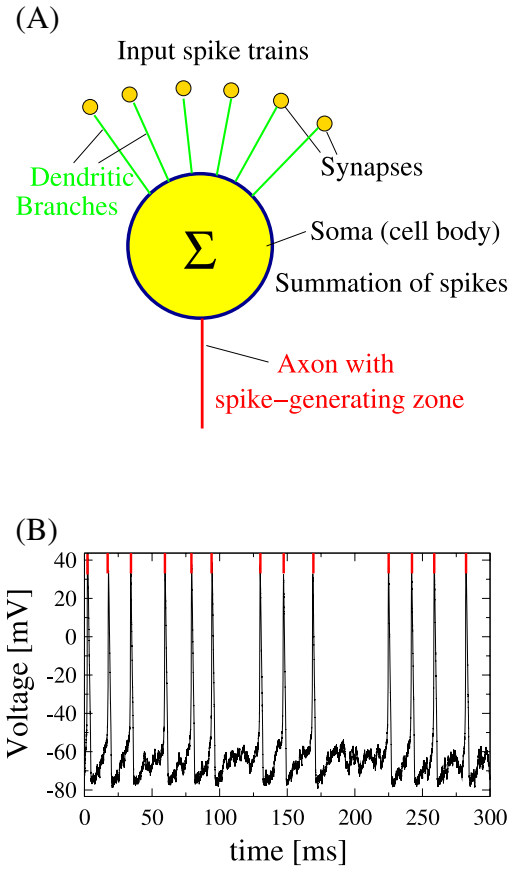

Figure 1. Neural anatomy and neural dynamics (strongly simplified). (A) Scheme of a neuron that receives many (10^2–10^4) spike train inputs from other neurons via synapses on the dendritic branches. If the input is sufficiently strong, an action potential or spike is generated in the axon. (B) Voltage trace of a stochastic model neuron (Hodgkin–Huxley model) showing randomly occurring action potentials due to the noisy synaptic input. Information is entirely encoded in the spike train (red bars).

function (leaky IF model) or even strongly non-linear (as, for instance, in the exponential IF model); its choice depends on the desired simplicity or realism of the model and on the statistics that one wants to calculate analytically. IF models can reproduce a number of noise-induced effects that are also observed in experiments: (i) noise under certain conditions can induce an almost periodic firing [11], an effect known as coherence resonance [12, 13]; (ii) noise may have a beneficial effect for the transmission of weak signals [14]–[16] which is referred to in general as stochastic resonance [17]–[19] and [13]. In networks of IF models (i) noise can cause fast oscillations beyond the frequency of the single cell [20]; (ii) spatial correlation of the driving noise in combination with recurrent feedback can result in slow oscillations [21]–[23].

For IF models, we can determine the statistics of spontaneous and driven activity as quantified, for instance, by the spike train power spectrum and the susceptibility upon periodic stimulation, respectively; in special cases such as for the leaky integrate-and-fire

J. Stat. Mech. (2009) P01008

neuron we can calculate them analytically [16, 11]. For more non-linear functions there exist efficient numerical algorithms for computing these functions [15, 24]. IF models can also be used in theories for spectral measures in neural networks [20, 25, 23]. However, there are several instances where the simple IF model is not sufficient for describing neuron behavior *in vivo*.

2.1. Open problem: non-renewal spiking due to slower timescales

There are processes acting on a slower timescale (e.g. adaptation) which effectively change the parameters of the neuron. Also larger timescales in the driving noise/signals (as for instance caused by synaptic filtering) contribute to changes of the spike train statistics. These slower processes of either intrinsic or extrinsic origin have first of all a pronounced effect on the spontaneous activity of the neuron: the intervals between spikes may become correlated. Typically, all neuron models considered above generate if driven only by uncorrelated (i.e. white) noise a sequence of uncorrelated intervals; hence, correlations in the interspike interval sequence are something qualitatively new that relies on slower processes. One can observe all kinds of interspike interval correlations in real neurons: intervals can be correlated in an oscillatory fashion versus lag [26]; they can show strong negative correlations at short lags [27] or positive correlations over many lags [28].

For the IF models we know of two simple mechanisms for generating positive and negative correlations. Driving an IF model with exponentially correlated noise will lead to a likewise exponentially correlated ISI sequence:

$$\tau_m \dot{v} = g(v) + \mu + \eta(t) \tag{2}$$

$$\tau \dot{\eta} = -\eta + \sqrt{2D}\xi(t). \tag{3}$$

Here we have replaced the white noise $\xi(t)$ by a colored noise, the Ornstein–Uhlenbeck process, which exhibits exponential correlations. For this example it becomes evident what the mathematical problem is: the ISI sequence is generated by repeated first passage from reset to threshold point driven by a colored noise. Hence, the calculation of the ISI correlation coefficient (measured in experiments) boils down to calculating the correlations in a sequence of first-passage times. This has been done in the above model for the perfect IF model ($g(v) \equiv 0$) in [29], for the leaky IF model ($g(v) = -v$) in [30], and also outside the neurobiological context [31]. In these cases, which are now well understood, input correlations shape output correlations in a predictable fashion.

A more complicated form, namely, a feedback mechanism, is required to make the ISIs generated by an IF model strongly negatively correlated. It has been shown that a slow inhibitory current or a dynamic threshold implement a cumulative refractoriness which causes negative correlations in adjacent ISIs. The prototype model for this kind of model is the following modified IF neuron:

$$\tau_m \dot{v} = g(v) - a + \mu + \sqrt{2D}\xi(t) \tag{4}$$

$$\tau \dot{a} = -a + \varepsilon \sum \delta(t - t_i). \tag{5}$$

Here we have returned to a white noise driving and added an inhibitory current a which is driven by the output spikes (the sum is over the spike times t_i) which are generated by the

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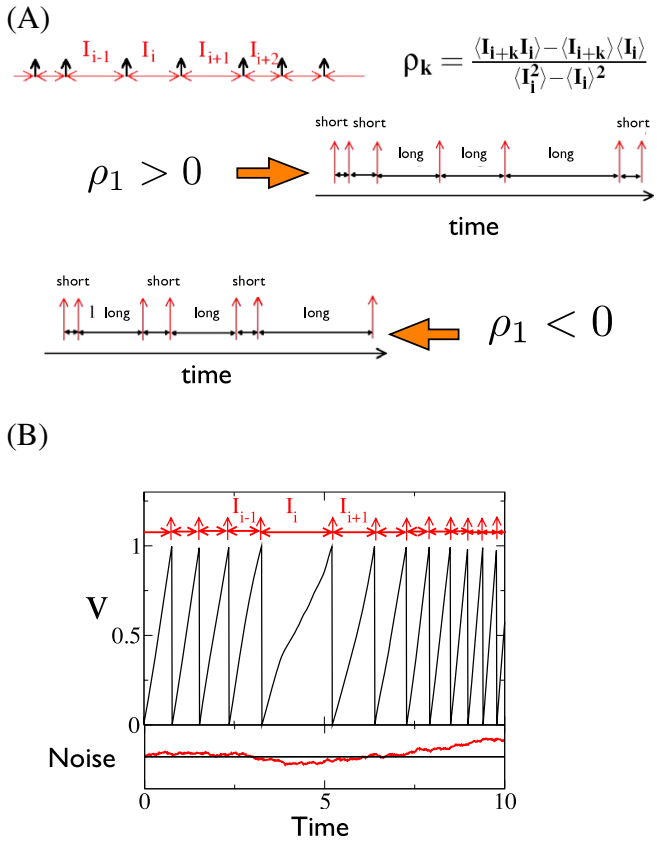

Figure 2. Correlations in the interspike interval (ISI) sequence. (A) An ISI sequence as indicated upper left can be analyzed in terms of the serial correlation coefficient (formula on the right). Below, two simple examples are given that yield positive or negative correlations at lag 1. (B) An Ornstein–Uhlenbeck process (lower trace in red) drives a perfect IF model which generates a spike train (upper trace in red) with intervals that are positively correlated, i.e. here $\rho_1 > 0$ as can also be calculated analytically. The unsolved problem here is that of finding analytical solutions for ρ_k for IF models with negative feedback (cf (4)) in which strong negative ISI correlations are observed.

first-passage problem for the voltage $v(t)$. For this system it is much harder to calculate the correlations between the ISIs. Weak correlations can be estimated as follows. In between spikes the variable a decays exponentially: $a(t) = [a_{i-1}+\varepsilon/\tau]\,\mathrm{e}^{-(t-t_{i-1})/\tau}$ where t_{i-1} denotes the last spiking time and $a_{i-1} = a(t_{i-1})$, taken right before the spike occurrence. The ISI $I_i = t_i - t_{i-1}$ will be affected by this inhibitory current and in particular by the value a_{i-1} and will itself also determine the next value $a_i = [a_{i-1} + \varepsilon/\tau]\,\mathrm{e}^{-I_i/\tau}$. If one knows how an exponentially decaying pulse affects the first-passage-time statistics, one can determine how subsequent intervals are correlated given a certain initial value a_i. Furthermore, assuming a weak inhibitory current, one can also determine self-consistently the steady-state statistics of a_i which is required to calculate the stationary correlations among intervals. The effect of an exponentially decaying input or equivalently of an exponentially decaying threshold has been tackled in [29, 32] in a perturbation calculation. At this point

we may recall that even the statistics of the first-passage time with no time dependent parameters (except for the white noise) presents a difficult problem which is, of course, even more complicated when time dependent driving forces are present. Although the approach outlined above can indeed describe weak negative interval correlations, it fails to reproduce correlation coefficients close to $-1/2$, as were observed in sensory cells of weakly electric fish. What is missing is a theory which calculates (i) the effect of a strong inhibitory current or a strong threshold decay on the ISI statistics, (ii) the steady-state distribution $P(a_i)$ of the current values right before firing. The formulation of the problem in terms of a two-dimensional Fokker–Planck equation may be helpful in this context. However, the boundary conditions in this case are rather difficult.

Why are we so interested in calculating the serial correlation coefficients of the interspike interval sequence? Besides the general reasons given above there is one more aspect making these correlations interesting: their potential biological function. It has been shown in numerical [33, 34] and analytical [35, 36] studies as well as in experiments [37] that negative correlations in the spontaneous activity of a sensory cell increase the information transfer as regards a time dependent stimulus, measured, for instance, by means of the mutual information rate. This underlines that the analytical calculation of these correlations in simplified biophysical neuron models with adaptation is worth more effort.

2.2. Open problem: how short-term plasticity does or does not shape neural signal transfer

Another important aspect of the neural dynamics that is not yet fully understood is the effect of short-term synaptic plasticity on the signal transmission through a single cell. The transmission of information between neurons takes place at synapses—for most cells these are chemical synapses that work by the release of neurotransmitter in the presynaptic cell which causes the opening of ion channels and thereby a small current in the postsynaptic cell [8]. The strength of this connection can change in time, a phenomenon referred to as synaptic plasticity and believed to form the basis for memory and learning. For the latter, the plastic changes occur on timescales of hours and days. There are, however, also changes observed at a much smaller timescale of about 100 ms that are not directly linked to memory and learning. These changes are called short-term plasticity (STP) and their biological functions are still debated [38]. What is observed in experiment is that the postsynaptic amplitude (efficacy) of a presynaptic spike depends on how many spikes have preceded it in a certain time window. A short burst of spikes can increase the efficacy of the last spike (facilitation) or decrease it (depression)—these effects have different physiological origins and can be present at the same synapse. Phenomenological models for the postsynaptic amplitude have been proposed (see [38] and references therein) that describe the latter as a product of facilitation and depression variables. Their dynamics is mathematically similar to that of the spike-driven inhibitory current in the previous subsection except that the spikes are now of presynaptic origin. As a consequence, the postsynaptic amplitude becomes a non-linear functional of the presynaptic spike train with consequences for neural variability and neural signal transmission that are largely still to be explored.

What the synapse with STP does to a presynaptic spike train is the following (see figure 3): without changing the spiking times, each spike is modulated in its amplitude by

J. Stat. Mech. (2009) P01008

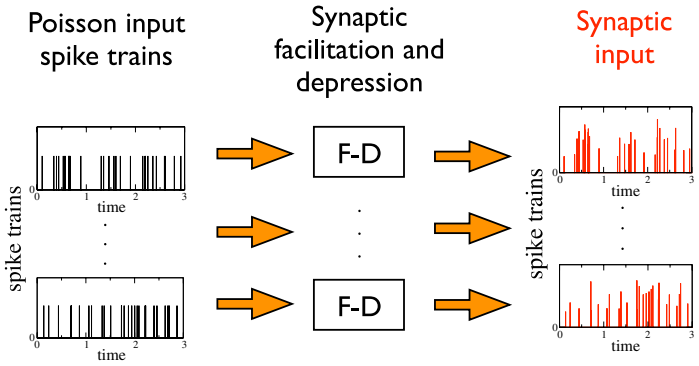

Figure 3. Short-term plasticity of a synapse. Poissonian spike trains pass through a number of independent synapses; while the spike instants remain unchanged, the amplitude of each postsynaptic spike becomes a non-linear functional of the spike train 'seen' so far by the synapse. The unsolved problem is that of how signals that are encoded in the incoming spike trains (for instance, by means of a time dependent modulation of the spike rate) are affected by this history dependent amplitude modulation.

a value that is a complicated non-linear functional of the spike train seen so far. Although one can estimate the steady-state statistics of these amplitudes and of the spike train if it has simple Poisson statistics [39], it is so far not possible to calculate response and coherence functions for time dependent stimuli because we do not know how to treat this kind of statistics analytically. However, synaptic short-term plasticity is ubiquitous and thus the potential importance of understanding its effect on the neural signal transfer cannot be overestimated.

3. Intracellular transport by coupled molecular motors

Transport and force generation in eukaryotic cells are realized by means of molecular motors that run along filaments. Typical examples are kinesin on microtubuli pulling cargo along and myosin on actin used, for instance, in our muscles as force generators. The filaments are made up of monomers and show a characteristic asymmetry and periodicity (about 10 nm). Upon consumption of ATP, a single motor walks only in one direction in a stochastic step-like manner (see, for instance, [40]). This behavior can be understood by means of ratchet models where an effective bias is introduced by stochastic switchings between different free-energy landscapes, corresponding to the interaction of a molecular motor and filament for different conformational states of the motor (related to the binding and release of ATP). For simplified models one can analytically calculate the mean velocity and the diffusion coefficient of the motion.

However, in various situations the motors do not move on their own but team up. They are, for instance, coupled by a (much larger) cargo to which several motors attach or they are connected by the sarcomere as in the case of muscle myosin. In these situations novel collective effects have been predicated theoretically and observed in experiments. Theoretically, models of infinitely many coupled motors (the system in the thermodynamic limit) have been intensively studied by mean-field methods: spontaneous

J. Stat. Mech. (2009) P01008

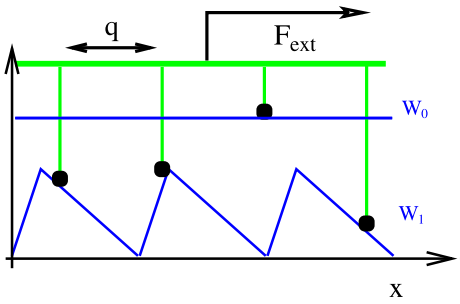

Figure 4. Sketch of the model of rigidly coupled molecular motors [6]. Motors are subject to a periodic piecewise-linear ratchet potential if they are in state 1. They switch to a potential-free state W_0 with a likewise spatially periodic rate $r_1(x)$ that has its maxima in the potential minima (not shown). As a result of the coupling, the backbone (green) will move to the right or left and will switch directions from time to time randomly. The unsolved problem here is that of eliminating the motor degrees of freedom and mapping the backbone's dynamics to a non-linear Brownian motion.

symmetry breaking (i.e. a finite mean velocity for a completely symmetric system) as well as oscillations (for groups of motors that are harmonically bound to a certain position) have been demonstrated [41]. More recently, finite size effects have also been discussed [6]: a finite group of motors shows bidirectionality of motion, i.e. stochastic switchings between two metastable (finite) velocities, which is also found in experimental data.

3.1. Open problem: reducing many-variable models of coupled molecular motors to a non-linear Langevin equation

An interesting simplification for a specific model has been proposed in [6]: the collective dynamics of a finite group of molecular motors corresponds to a Brownian motion with non-linear friction. More specifically, we consider the model developed in [6] for N molecular motors (see figure 4):

$$\lambda\dot{x} = F_{\mathrm{ext}} - \frac{1}{N}\sum W'(x + \mathrm{i}q)\sigma_i(t) + \sqrt{\frac{2k_{\mathrm{B}}T\lambda}{N}}\eta(t). \tag{6}$$

All motors are attached to a backbone whose collective coordinate is denoted by $x(t)$. The backbone is subject to an external bias F_{ext}, to the summed forces on the single motors by the filament, and to thermal fluctuations $\eta(t)$ assumed to be Gaussian and delta correlated in time. The interaction between filament and motor is represented by the periodic and asymmetric potential $W(x)$. A motor at position $x + \mathrm{i}q$ contributes the force exerted by the periodic and asymmetric potential $W(x)$ provided the respective motor is switched on ($\sigma_i = 1$). The switching of the dichotomous motor state $\sigma_i \in \{0, 1\}$ is governed by state dependent switching rates r_0 (going from the free-diffusion state into the 'potential' state) and $r_1(x)$ (for the inverse transition). In the limit of many motors ($N \gg 1$) we look for a mapping to the following effective dynamics:

$$\dot{x} = v + \sqrt{\frac{2k_{\mathrm{B}}T}{N\lambda}}\xi(t), \qquad \dot{v} = f(v) + g(v)\xi(t) \tag{7}$$

J. Stat. Mech. (2009) P01008

where $f(v)$ and $g(v)$ are (generally non-linear) functions of the velocity. These functions are unknown and have to be determined by the model reduction; $\xi(t)$ is white Gaussian noise and independent of the thermal fluctuations (it rather represents the 'motor noise', i.e. the switchings in $\sigma_i(t)$ which originate in the switchings of the conformational state). Essential for the bidirectionality of motion is that the function $f(v)$ has two stable zeros at finite velocities and that the multiplicative function does not prevent these two velocities from being metastable. Models like (7) have been studied (mostly with additive noise, i.e. constant $g(v) \equiv \sqrt{2Q}$) under the label of active Brownian motion [42]–[46]; in the context of the above motor model (6) an equation with a cubic $f(v)$ and a constant noise intensity has been used in [6] in order to capture the bidirectionality of the motor system.

Mean values of the velocity and even the diffusion coefficient in the symmetric case [46] can be calculated exactly for one-dimensional versions of (7). The active particles show interesting noise-induced effects like a minimum of the diffusion coefficient versus strength of the fluctuations [46]. Conceptually, the mapping from the N-state model of molecular motors to the non-linear Brownian motion is similar to the mapping of the $N+1$-particle dynamics of a mesoscopic (Brownian) particle and its surrounding heat bath to the simple (linear) Langevin equation.

A very simple case may help to illustrate what is meant by this mapping. Assume that the periodic potential force is replaced by a constant force F and that the switching rates do not depend on the position x and are equal; we also set $F_{\mathrm{ext}} = 0$. Then v becomes essentially the superposition of N independent dichotomous variables

$$v = -\frac{F}{N\lambda}\sum_{i=1}^{N}\sigma_i(t). \tag{8}$$

This sum has the same correlation function as the single dichotomous process (namely, an exponential correlation function) which can be seen as follows:

$$\begin{aligned} K_v(\tau) &= \langle v(t)v(t+\tau)\rangle - \langle v(t)\rangle\langle v(t+\tau)\rangle \\ &= \frac{F^2}{N^2\lambda^2}\sum_{n,l}\langle\sigma_n(t)\sigma_l(t+\tau)\rangle - \langle\sigma_n(t)\rangle\langle\sigma_l(t+\tau)\rangle \\ &= \frac{F^2}{N^2\lambda^2}\sum_{n}[\langle\sigma_n(t)\sigma_n(t+\tau)\rangle - \langle\sigma_n(t)\rangle\langle\sigma_n(t+\tau)\rangle] \\ &\quad + \frac{F^2}{N^2\lambda^2}\sum_{n\neq l}[\langle\sigma_n(t)\sigma_l(t+\tau)\rangle - \langle\sigma_n(t)\rangle\langle\sigma_l(t+\tau)\rangle]. \end{aligned}$$

The terms in the last line vanish since by assumption the processes $\sigma_n(t)$ are mutually independent. Hence, we find

$$K_v(\tau) = \frac{F^2}{N^2\lambda^2}K_\sigma(\tau). \tag{9}$$

The sum v also approaches Gaussian statistics by virtue of the central limit theorem. According to Doob's theorem, the only stationary continuous stochastic process with Gaussian density $N(\langle v\rangle, \langle\Delta v^2\rangle)$ and exponential autocorrelation function $\langle v(t)v(t+\tau)\rangle = \langle\Delta v^2\rangle\,\mathrm{e}^{-r\tau}$ is the Ornstein–Uhlenbeck process which obeys (7) where $f(v)$ is linear in v and $g(v)$ is just a constant. A similar consideration is still possible if the bias is replaced by

the periodic potential and the switching rates are still independent of the position because the motors will be uniformly distributed over space and in a position independent manner on the two states. However, if we make the switching rates dependent on space, we invoke a feedback of the motion on the switching events and consequently the picture changes qualitatively. This is where the non-linear nature of $f(v)$ and $g(v)$ originates and novel analytical approaches are required to find the connection between the different levels of modeling in terms of these functions.

4. Summary

I have discussed some open problems for stochastic phenomena in different biological systems. I discussed, as specific examples, the interspike interval correlation statistics in simple integrate-and-fire neurons and the role of short-term plasticity; here I focused on the problem of calculating the spike train statistics in the different situations. The second problem was of a more conceptual nature: bridging different theories of a biophysical phenomenon (e.g. the dynamics of coupled molecular motors) by mapping one theory onto the other. The two kinds of approaches are complementary and may find applications for other biophysical problems. It is hoped that we will see some progress on the problems discussed here in the near future.

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