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Stochastic aspects of computational neuroscience

Učební texty k semináři

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Chapter 1

Introduction

What is the code used by neurons in conveying information belongs to one of the most frequently asked questions among the contemporary science. Beside an experimental approach to this problem, there have been many attempts to solve this task by using theoretical - biophysical and mathematical - methods (Perkel and Bullock, 1968; Rieke et al., 1997; Theunissen and Miller, 1995). The mathematical methods are often based on stochastic principles, which reflect apparent randomness in behavior of the nervous system. Therefore, the stochastic models of neurons are constructed, analyzed and verified. The aim of this text is to review this effort.

A mathematical model is always an attempt for approximation of some real, usually dynamical, system using one or more equations which represent behavior of the system. To which extent the properties of reality are neglected determines compatibility between the model and the real object. The obvious value of the models is based on their analytical power permitting to test the scientific hypotheses. Variable assumptions about the system are reflected by different versions of the model and can be exploited when verifying and interpreting the experimental results. Less obvious, but not less important, role of the models is based on their indirect contribution to organizing and integration of existing knowledge about the nature. By constructing the models we realize the missing parts of our knowledge and the new experimental questions are proposed.

These facts, so well known in physics and engineering, have been recently taken into account in biology as well. The fast growth of biomathematics and theoretical biology, currently more frequently labeled as computational biology, confirms this trend. These general notes hold in neuroscience even more obviously due to the long tradition of mathematization of this branch of science. The seminal paper (Lapicque, 1907) was published more than hundred years ago and republished a century later in English version (Brunel and van Rossum, 2007). Probably the first great mathematician who got interested in formal description of the brain functions was Norbert Wiener. However, undoubtedly the most significant stimulus for formalization of the neuroscience research was the fact that the neuronal model of Hodgkin and

Huxley, published in 1952 (Hodgkin and Huxley, 1952) was a part of the Nobel prize in Physiology and Medicine by which these scientists were awarded in 1963. This event probably caused an increased interest of the mathematicians, who usually had made their most important achievements in pure mathematics, in this type of applications. Many examples can be found, but in relation to this short text we can point out the names like - S.I. Amari, S.E. Fienberg, G. Kallianpur and B. Mandelbrot (Amari et al., 1977; Fienberg, 1974; Gerstein and Mandelbrot, 1964; Kallianpur and Wolpert, 1985). Despite the choice cannot be representative and can be found biased, these are always applications of mathematics in single neuron description. Due to the transdisciplinarity of this research, the results are scattered in a wide range of journals. Equally broad is the range of the books published on this topic. On one side there are theoretically oriented monographs (for example, Tuckwell, 1988; Gerstner and Kistler, 2002), on the other one, there are many books towards biophysical foundations of the field or on the theory of artificial neural networks.

Enormous progress of computational power enables to perform extensive numerical experiments on the mathematical models, either varying their parameters or using the Monte-Carlo methods. The numerical experiments are incomparably cheaper than those realized in the laboratories and despite that the theoretical conclusions cannot replace experimental evidence, they can substantially extend their conclusions. In this way the economical requirements of the research can be much better controlled. This fact substantially underlines the importance of the applications of mathematics in biological sciences. Simultaneously, we must not accept the superficial point of view that the super-computers can replace analytical methods of mathematics and real experimental data. It would be a fundamental error and the only correct approach is that containing all four components of modern applied mathematics - reality observation, model formulation, its analytical and computerized treatment and finally statistical comparison with the real data. Only this complete sequence can result in generation of new ideas and new experiments to open a new cycle at a higher level.

The topic of the seminar has been from mathematical point of view already shortly mentioned. It is characterized by the term “stochastic process”, either one- or multidimensional, such that its dynamics characterize neuronal behavior in time and in dependency on its inputs. Such a stochastic process is usually in continuous time, but its values change either continuously or with discrete jumps. The basic problem is how close one to the other are these two variants, thus we study the problem of “diffusion approximation”.

The next connecting feature is the "first-passage-time problem". It is a question about the properties of the time interval during which a deterministic threshold is reached by a stochastic process. Thus, instead of a trajectory of a random process we have at disposal this random variable only. Importance of this task follows from the fact that the basic principle of neuronal transmission is transformation of an analog signal, for example of the membrane potential, into a sequence of discrete neuronal pulses, so called action potentials, which appear randomly in time and this phenomenon is modeled as the first-passage time. Then, the basic question is to deduce statistical properties of the first-passage time from the properties of the input signal. There is also an inverse problem to characterize properties of the signal knowing only the first-passage time distribution or its properties. The last common term is "parametric inference" for the considered stochastic models which are observed either continuously or in discrete time instants or, and it the most important, which are observed only via the mentioned first-passage times. The crucial question of all verification procedures for model construction is the identification and estimation of the parameters. Despite that any stochastic model is just an approximation of reality, it is important to underline its probabilistic form and thus the fact that it covers all possible situations and we have to judge the probability distribution of these situations. To determine the parameters as precisely as possible is an unavoidable condition for that purpose, and in addition we need to quantify the precision. The developed models are not only descriptive but their parameters have biological interpretation. For that reason qualitative comparison is important but quantitative values of the parameters play their indisputable role. The model construction permits to use statistical methods for testing the significance of the parameters as well as their mutual differences. We have to remind that the estimation of the statistical parameters can also be seen as identification of the incoming signal (Jolivet et al., 2008; Greenwood and Lansky, 2005).

From a biophysical point of view, the models of a single neuron reflect the electrical properties of its membrane via electric circuit description containing energy storage elements. Such circuit models can be written in terms of differential equations for the membrane voltage. Reducing these models, we can end up with an integrate-and-fire type of the models (Kistler et al., 1997) and they will be discussed here. These models are sometimes criticized for their too drastic simplification of reality, however, after reduction of the Hodgkin-Huxley four dimensional model, Kistler et al. (1997) claim that the integrate-and-fire model with a properly selected threshold predicts 90 percent of the spikes correctly. Of course, this type of simplification implies that

spike duration and its shape are neglected and all neuronal activity is represented by uniform events appearing in time; a point process (Johnson, 1996). Thus, the models aim only to describe the dynamics of interspike intervals and they are based on a one-dimensional representation of the time evolution of the neuronal membrane potential. The trigger zone serves as a reference point and all the other properties of the neuron have to be integrated into it. This one-point representation induces several strong restrictions which will be mentioned later and which cannot be removed unless the spatial properties of neurons are taken into account.

1.1 Deterministic Approach

It is hardly possible to speak about stochastic modeling without mentioning the deterministic approach and in such a way to point out to what is gained (and lost) by using the stochastic approach. The simplest realistic model which has been used for description of stimulus intensity coding is the deterministic leaky-integrator model,

$$\frac{dx(t)}{dt} = -\frac{x(t)}{\tau} + \mu\,(t)\ , x(0) = x_0, \tag{1}$$

where $x(t)$ represents the cell membrane voltage, x_0 is the initial voltage after spike generation, $\mu(t)$ being an input signal, and $\tau > 0$ is a time constant governing the spontaneous decay of the voltage back to a resting level, which for the notational simplicity is set to zero. The initial depolarization is usually, but not always, put to be equal to the resting potential, $x(0) = 0$. The model can be derived from the basic biophysical model of the neuronal membrane which assumes that its depolarization is described by a circuit with a generator, a resistor and a capacitor in parallel. This model is usually called RC circuit, Lapicque model or a deterministic leaky integrator, e.g., (Knight, 1972; Scharstein, 1979, for a review see Tuckwell, 1988), and in this interpretation for τ in (1) holds, $\tau = RC$, where R denotes the resistance and C the capacitance of the circuit. We should keep in mind that $\mu(t)$ appearing in (1) is already a representation of an external signal (light, sound, odorant, or a sequence of incoming action potentials) transformed into an internal generator potential, a quantity having a dimension of voltage by itself. Following the circuit representation, then $\mu(t) = I(t)/C$. It has to be stressed that while the electrical representation is related to a small isopotential patch of neuronal membrane, the variable $x(t)$ in (1) reflects an abstract representation of a complete neuron.

Due to the simplicity of (1), the action potential generation is not an inherent

part of the model like in more complex models and the firing threshold S, such that $S > x_0$, has to be imposed here. The model neuron fires whenever the threshold is reached and then the voltage $x(t)$ is reset to its initial value. This means that in the electrical circuit representation a switch is added to the circuit. The reset following the threshold crossing introduces a strong nonlinearity into the model. For a constant $\mu = \mu(t)$, such that $\mu > S/\tau$, the firing intervals t_S for model (1) are

$$t_S(\mu) = -\tau \, ln \left(\frac{\mu\tau - S}{\mu\tau - x_0} \right) \tag{2}$$

and for $\mu \leq S/\tau$, the model neuron remains silent - never reaching the threshold S. These two regimes are usually called sub and supra-threshold stimulations and play equally important role in the stochastic models. We can see from (2), that the firing frequency as a function of the stimulus intensity increases to infinity with increasing μ and this drawback can be removed by imposing an absolute refractory period t_{ref} on the interspike interval length. Then the relation between the intensity of stimulation and frequency follows from (2),

$$f_S(\mu) = \frac{1}{t_{ref} - \tau \, ln \left(\frac{\mu\tau - S}{\mu\tau - x_0} \right)} \tag{3}$$

assuring the saturation frequency $f_{sat} = t_{ref}^{-1}$. Note a discontinuity of $f_S(\mu)$ derivative at point S/τ, which is removed if the model with noise is considered.

We have seen that the simplest way how to model the absolute refractory period was by adding t_{ref} to each interspike interval. Time dependent thresholds in neural modeling may aim to simulate various aspects of the time varying behavior of the neuron, but they are used mainly to mimic the relative refractory period. These thresholds need to have a high initial value (or infinity) and to decay with time to the constant value S. An example of such a threshold is

$$S(t) = S + S_1 exp(-t/\gamma) \tag{4}$$

where $S_1 > 0$ and γ is a positive constant characterizes how fast the constant threshold is established. Various forms for time-dependent thresholds can be found in (Tuckwell, 1988).

Model (1) has been often used for description of sensory neurons under external periodic stimulation by applying a periodic signal $\mu(t)$. Then the model takes the form,

$$\frac{dx(t)}{dt} = -\frac{x(t)}{\tau} + \mu \, + \mu_0 sin(\omega t + \theta) \; , x(t_k) = x_0 \, , \tag{5}$$

where μ_0 is the amplitude of the variable component, ω and θ are constants characterizing the period and phase of the driving force and t_k is the time instant of the last crossing of the firing threshold. We are interested in a distribution of time points $t_1 < t_2 < \cdots < t_k < \cdots$, such that at each of these instants the threshold is reached for the first time, $x(t_k^-) = S$, the function $x(t)$ is reset to its initial value, $x(t_k^+) = x_0$, and for $t > t_k$ the function $x(t)$ is defined by (5). Interspike intervals can be calculated as $t_{k+1} - t_k$ and they can be histogramed. This makes the difference between (1) and (5) apparent being that for (1) only a constant interspike interval can be produced. The main characteristic of (5) is that it is able to produce a phase locking effect; a special type of input-output synchronization. In other words, the crossings of $x(t)$ through the threshold S may get phase locked with a period of stimulus. Thus, the most intuitive form of the results for (5) is a cycle histogram presenting the spike appearance with respect to the phase of the driving force. Using this method, the interspike intervals are converted mod $2\pi/\omega$ so they fell within the interval of one period of stimulation. In such a way, a synchronization of the spikes with stimulus intensity is reflected. This is still an example of the rate coding, just copying the stimulus variation. Another feature of real neurons successfully modeled by (1) is the effect of self-inhibition. This can be easily achieved by changing $\mu(t)$ in accordance with the previous activity of the model neuron. For other results on deterministic leaky integrate-and-fire model from computational point of view, see (Bugmann, 1991; Tal and Schwartz, 1997).

Chapter 2

Stochastic Models

2.1 General Considerations

Many different experimental results suggest a presence of stochastic variables in neuronal activity. We may assume that there is a random component, generally denoted as noise, contained in the incoming signal. The other source of noise can be the neuron itself where a random component is added to the signal. Unfortunately, there is an unclear distinction between noise contained in the signal and the system noise, again due to the one-point approach. The term noise usually denotes something negative and blurring the signal processing. However, in this case it could be a message by itself or a highly desirable part of the message important for its processing, as we will see later. From a mathematical point of view an introduction of stochasticity into the description of the neuron represents some type of complexity increase. On the other hand, from a point of view of biophysical reality it simplifies the task substantially as all the features considered at a current stage as marginal can be declared as a system noise.

The simplest stochastic model of a neuron, and thus rather unrealistic, would assume that any incoming pulse, or any incoming quanta of external stimulation is reflected by generation of an output spike. If the incoming stimulation has many independent sources, then the output of such a pooling device is described by a Poisson process with intensity which is proportional to the intensity of stimulation. In this case the neuron serves only as a superposing device, however, we will see that there are other mechanisms leading to the Poisson model of a neuron. In any case, the Poisson model is a representation of pure randomness without any memory as the probability of firing is constant and independent of the past at any time instant. The consequence of the model assumptions is linearity of the input-output curve, similar to (3) for large τ, and neglected refractoriness. This linearity of the input-output curve handicaps the Poisson process in being a real neuron model. On the contrary, we may easily consider the input to a neuron as Poissonian. This character appears to be an appropriate imitation mainly for spontaneous activity or for evoked activity due to a constant stimulus of a long duration if

the input to the neuron is composed from activities of many relatively independent sources. Even for a dynamically stimulated system this assumption is well established, though only the constant intensity has to be replaced by a function of time properly mimicking the time evolution of the stimulation and consequently the input becomes a time-nonhomogeneous Poisson process (Johnson, 1996).

A phenomenological way how to introduce stochasticity into the deterministic leaky-integrator model is simply by assuming an additional noise term in (1),

$$\frac{dX(t)}{dt} = -\frac{X(t)}{\tau} + \mu\,(t) + F(t)\ , X(0) = x_0\,, \tag{6}$$

where $F(t)$ represents Gaussian and δ correlated noise with zero mean and strength 2σ (the capital X is used in (6) and further to distinguish formally between deterministic and stochastic models) and we will mention later why the white noise $F(t)$ or a stream of Poissonian pulses are the only suitable ones for this purpose. Model (6) is well known in physical literature as an Ornstein-Uhlenbeck model (Abbott, 1994).

In integrate-and-fire stochastic models, not only in (6), the membrane potential $X(t)$ makes random excursions to the firing threshold S, which is commonly taken to be a deterministic function of time similar to (4), but most often a constant. As soon as the threshold is reached, a firing event occurs and the membrane potential is reset deterministically to its starting point $X(0)$. The interspike intervals are identified with the first passage time of X across S,

$$T_S = inf\big\{t \geq 0, X(t) > S \mid X(0) = x_0 < S\big\}\ . \tag{7}$$

The properties of the random variable T_S are studied and compared with properties of interspike intervals. In general, we investigate the distribution of T_S represented for example by the probability density function $g_S(t \mid x_0)$. When the distribution $g_S(t \mid x_0)$ is too difficult to obtain, the analysis is usually restricted to its moments, $m_n(S \mid x_0)$, primarily the mean

$$m_1(S \mid x_0) = E(T_S \mid x_0) \tag{8}$$

and the variance

$$Var(T_S \mid x_0) = m_2(S \mid x_0)\ -\ m_1^2(S \mid x_0)\,. \tag{9}$$

The reciprocal relationship between the instantaneous frequency on one hand and the interspike interval on the other leads to the plotting of reciprocal value of $m_1(S \mid x_0)$ versus the intensity of stimulation as a stochastic counterpart of relation (3). The terminology is ambiguous here: the

reciprocal to the mean interspike interval, $1/m_1(S \mid x_0)$, can be confused with the mean of the reciprocal value of T_S (mean of instantaneous frequency). If $x_1, x_2, \ldots, x_n$ are n observed interspike intervals, then the first corresponds to $[(x_1 + x_2 + \cdots + x_n)/n]^{-1}$, while the latter is estimated by $(x_1^{-1} + x_2^{-1} + \cdots + x_n^{-1})/n$. For a different view on firing frequency representation see (Kohn, 1989).

Irrespectively of the selected model X in (7), for a constant input the neuronal output is a renewal process (intervals between threshold crossing are independent and identically distributed). This is caused by unidimensionality of the description in conjecture with input constancy. There can be only two kinds of information prevailing the spike generation. First, that which is accumulated in the neuron, but under this scenario it is deleted by the reset after spike generation because only single-variable function X is available for its recording. Second, the information which is contained in an incoming signal, but which is against the assumption of the constant (time unstructured) input, in other words, the input noise can be only the white noise or Poissonian. To obtain non-renewal output from a single-point model can be achieved only by a more or less apparent introduction of the variable (time structured) input or by considering spatial properties of the model neuron (Lansky and Rospars, 1995). Another way how to reach non-renewal output, we can assume that the initial value of the membrane potential is a random variable X_0 taking its values in the state space of X. If the density $w(x_0)$ of X_0 exists, we may write the density of interspike intervals, $g_S(t)$, in the form of a randomized distribution with respect to the parameter x_0, (Lansky, et al., 1992),

$$g_S(t) = \int_r^S g_S(t \mid x_0) w(x_0) dx_0, \tag{10}$$

where r is a lower depolarization boundary. Assuming that X_0 takes value depending on one or several previous interspike intervals, a kind of memory is introduced into interspike interval generation. Biological interpretation in terms of facilitation or hyperpolarization was mentioned in connection with random reset after spike generation (Lansky, et al., 1992; Lansky and Smith, 1989). Probably the most striking effect of the random reset is that the coefficient of variation, is greater than one for the reset concentrated above the resting level which reflects highly erratic (bursting) activity (Lansky, et al., 1992; Lansky and Smith, 1989; Bugmann et al., 1997).

The simplest, biologically acceptable and most common way how to derive model (6) is to start from Stein's model of the membrane potential fluctuation (Stein, 1965). Stein's model is characterized as a one-dimensional stochastic

process, which can be expressed in the form

$$dX(t) = -\frac{X(t)}{\tau} + adP^+(t) + idP^-(t)\,;\; X(0) = x_0\,, \tag{11}$$

where $\tau > 0$ plays the same role as in (1), $i < 0 < a$ are constants; $P^+(t)$, $P^-(t)$ are two independent homogeneous Poisson processes with intensities λ and β, respectively. Following model (11), the values a and i represent the amplitudes of excitatory and inhibitory postsynaptic potentials as they contribute to the membrane potential at the trigger zone. Properties of model (11) are as follows: synaptic activation of a neuron leads to a postsynaptic potential which is characterized by a short rise time. Therefore, the corresponding membrane potential change is modeled by a step discontinuity. This simple assumption can be based on Lapicque model response to a current pulse or on a kinetic model with proper time constants (Desthexe et al., 1994).
The first and second infinitesimal moments of X defined by (11) are

$$M_1(x) = \lim_{\Delta\to 0} \frac{E\big[\Delta X(t)|\, X(t) = x\big]}{\Delta} = -\frac{x}{\tau} + \lambda a + \beta i\ , \tag{12}$$

$$M_2(x) = \lim_{\Delta\to 0} \frac{E\big[(\Delta X(t))^2\,|\, X(t) = x\big]}{\Delta} = \lambda a^2 + \beta i^2\ , \tag{13}$$

where $\Delta X(t) = X(t+\Delta) - X(t)$. In diffusion models, the membrane potential is described by a scalar diffusion process $X(t)$ given by the Itô-type stochastic differential equation

$$dX(t) = \nu(X(t))dt + \sigma(X(t))dW(t)\,;\; X(0) = x_0\ , \tag{14}$$

where ν and σ are real-valued functions (called a drift and an infinitesimal variance) of their arguments satisfying certain regularity conditions and W(t) is a standard Wiener process (Brownian motion). The drift coefficient reflects the local average rate of displacement and local variability is represented by the infinitesimal variance. The first two infinitesimal moments of the process (14) are $M_1(x) = \nu(x)$ and $M_2(x) = \sigma^2(x)$ and let us only remind how (6) can be obtained from (13); detailed description can be found in (Lansky, 1984). In general, a sequence of models X_n given by (13) characterized by a quadruplet $\{\lambda_n, \beta_n, a_n, i_n\}$ is needed such that with $\lambda_n \to +\infty$, $\beta_n \to +\infty$, $a_n \to 0_+$, $i_n \to 0_-$ the quantities (14) and (13) converge to the drift and infinitesimal variance of the Ornstein-Uhlenbeck process (6) whereas the higher infinitesimal moments tend to zero. Comparing (6) and (14), we can see that the stochastic leaky-integrator is a diffusion model and that the

white noise is a formal derivative of the Wiener process with respect to time, or in other words Wiener process is an integral of the white noise.
The description of the process via (14) is apparently an intuitive extension of the deterministic approach. Its advantage is in giving a method for a computer simulation of the process sample trajectories whenever there is a lack of analytical results (Kloeden and Platten, 1992). The simplest discrete time approximation of (14) is a stochastic analogue of the Euler scheme for ordinary differential equations,

$$X_{i+1} = X_i + \nu(X_i)h + \sigma(X_i)\Delta W_i \ ; \ X_0 = x_0, \tag{15}$$

where h denotes the time step of simulation, X_i $(i = 1, 2, ...)$ are the simulated values of the process and ΔW_i are independent and normally distributed random variables, $\Delta W_i \sim N(0, h)$. The increments ΔW_i in (15) can be replaced by $\pm\sqrt{h}$ selecting these values with equal probability $1/2$, which substantially decreases the simulation time (Tuckwell and Lansky, 1997). An alternative way for description of the process (14) is oriented on distributional properties of the model (Abbott, 1994; Ricciardi, 1977). This latter description, while being analytically very powerful is formal and does not contain a self-explanatory part as (14) or (15). As pointed above, the spiking of a model neuron is mathematically represented by the first-passage-time problem (7). In the distributional approach many analytical results have been derived (see the above cited monographs) and numerical techniques had been proposed. On the other hand, with a few exceptions, for the simulation techniques the precision of the first-passage-time problem has not been studied in detail (Lansky and Lanska, 1994).

2.2 Wiener Process

In the previous section stochastic leaky-integrator (diffusion) has been introduced. However, there is still a simpler model available. The simplest diffusion neuronal model is the Wiener process. The increments of a standard Wiener process were mentioned in relation with the definition of a diffusion process (14) and its general version is defined by (14) with the constant infinitesimal moments

$$\nu(x) = \mu > 0 \, , \, \sigma(x) = \sigma > 0 \tag{16}$$

where positivity of the drift is a substantial requirement. The model can be considered as a limiting case of (6) for τ very large and means, in interpretation of (15), that the spontaneous decay of the membrane potential is

negligible within an interspike interval. The density function of T_S for model (16) is

$$g_S(t \mid x_0) = \frac{S - x_0}{\sigma\sqrt{2\pi t^3}}\, exp\left\{-\frac{(S - x_0 - \mu t)^2}{2\sigma^2 t}\right\} \tag{17}$$

which is known as the inverse Gaussian distribution. The mean and variance for the distribution (17) are

$$E(T_S \mid x_0) = \frac{S - x_0}{\mu}\ , \tag{18}$$

$$Var(T_S \mid x_0) = \frac{S - x_0}{\mu}\frac{\sigma^2}{\mu^2}\ . \tag{19}$$

The assumption made in (16) that μ is a positive constant ensures that the mean interspike interval is finite. The square of the coefficient of variation is

$$CV^2 = \frac{\sigma^2}{\mu(S - x_0)} = \frac{\alpha}{\beta}\ , \tag{20}$$

which shows that as $x_0 \to S$, $\mu \to 0$, or $\sigma \to \infty$ (fixing the other parameters), CV is not only greater than one but it increases without limit. The position and width of interspike interval distribution is reflected by its mean and variance. The distribution (15) is positively skewed, $\beta_1 > 0$, and it is also indicated by the position of its mode,

$$t_{mode} = \sqrt{E^2(T_S \mid x_0) + \frac{9\sigma^4}{4\mu^4}} - \frac{3\sigma^2}{2\mu^2} < E(T_S \mid x_0)\ . \tag{21}$$

There have been several reports on preserving the shapes of histograms when the adjacent interspike intervals are summed, e.g., (Gerstein and Mandelbrot, 1964) and this is an interesting property of distribution (15) for $\mu = 0$, however, it induces $E(T_S \mid x_0) = \mu$. There are two main reasons for considering a time-varying threshold in the Wiener process neuronal model. One is, as mentioned before, a direct modeling of relative refractory period. The second reason arises when there is a constant threshold potential assumed, but the membrane potential is described by some more complex diffusion process. By transforming that process into the Wiener process, the constant threshold becomes time dependent. Methods for the solution of the first-passage-time problem for the Wiener process in the presence of a time-varying threshold have been extensively studied.

Several generalizations of the Wiener process as a neuronal model have been made. Nevertheless, as stressed at the beginning of this section, the lack of leakage is a strong objection against the use of the Wiener process for modeling neuronal depolarization. Further, the model does not reflect other

physiological properties of neurons such as the state space is not restricted from below, or the membrane potential changes are not state-dependent. From a formal point of view, the distribution (15) is not a proper one ($Prob(T_S = \infty) > 0$) when $\mu < 0$. If we consider an interpretation via Stein's model, then $\mu < 0$ means prevailing inhibition over excitation; a situation which may arise quite naturally. Finally, using (17) to create input-output curve, we see that it is a linear function of μ independent of the noise and other characteristics of the model, so analogous to the Poisson description of the neuron. Non-restricted state space for hyperpolarization can be removed by imposing a reflecting boundary at some $r < x_0$. The models created by removing the other objections against the Wiener model are discussed in the following sections.

2.3 Ornstein-Uhlenbeck process

The most common diffusion model proposed for nerve membrane behavior is the Ornstein-Uhlenbeck process (6) which is a direct consequence of a general acceptance of model (1). Model (6) can be defined by (14) with infinitesimal moments

$$\nu(x) = -\frac{x}{\tau} + \mu \, , \, \sigma(x) = \sigma > 0 \, . \tag{22}$$

As for the Wiener process, the state space of the Ornstein-Uhlenbeck process is not restricted from below. However, unlike for the Wiener process model here the threshold crossing is a certain event, $Prob(T_S < \infty) = 1$, independent of the value of μ. Further, again unlike the Wiener process, the objection against the fact that the state space is unrestricted from below and consequently that any value for hyperpolarization can be achieved with a positive probability is only formal for the Ornstein-Uhlenbeck model. Here the parameters (σ, τ and μ) control whether this situation may arise with probability which should be considered and in this way these parameters are responsible for the reality of the model. For a fixed time t, $X(t)$ given by (22) is a Gaussian random variable with mean

$$E(X(t)) = x_0 exp(-t/\tau) + \mu\tau(1 - exp(-t/\tau)) \, , \tag{23}$$

which is the solution of the deterministic model (1) for a constant input μ. The variance of X is

$$Var(X(t)) = \frac{\sigma^2\tau}{2}(1 - exp(-t/\tau)) \, , \tag{24}$$

which gives a preliminary indication of the variability of T_S.

Despite enormous efforts an analytical solution for the first-passage-time density has not been found with the exception of the case $S = \mu\tau$ (see e.g., Ricciardi, 1977), which is, as follows from (23), the asymptotic value of $E(X(t))$. The general expression for the Laplace transform of the $g_S(t \mid x_0)$ is available from which the moments of T_S can be computed.

2.4 Models with state-dependent variance

It is a well know fact, also reflected in the Hodgkin-Huxley model, that the change of the membrane depolarization by a synaptic input depends on its actual value. Basically, the depolarization of the membrane caused by an excitatory postsynaptic potential decreases with decreasing distance of the membrane potential from the excitatory reversal potential, V_E. In the same manner, the hyperpolarization caused by inhibitory postsynaptic potential is smaller if the membrane potential is closer to the inhibitory reversal potential, V_I. Stein's model with reversal potentials is given by the stochastic differential equation

$$dX = -\frac{X}{\tau} + a(V_E - X)dP^+ + i(X - V_I)dP^- \,;\, X(0) = x_0 \qquad (25)$$

where the notation follows (15). However, constants $-1 < i < 0 < a < 1$ have a different interpretation now as they reflect the fractional change of the membrane potential in a response to the input pulse. In model (27) the jumps caused by the input are state-dependent in such a way that their magnitudes decrease linearly as X approaches the boundaries V_I or V_E. Hence the process remains confined within these boundaries. This is the main qualitative advantage of model (25) over the Stein's model. Due to the transformation of the resting level to zero, we have $V_I < 0 < S < V$. For the basic model, as well as for its modification with the reversal potentials, the analysis is complicated and thus the diffusion variants have been examined (Hanson and Tuckwell, 1983; Kalianpur and Wolpert, 1985; Lansky and Lanska, 1987; Lanska et al., 1994). While Stein's model has been always substituted by the Ornstein-Uhlenbeck process, there is a whole class of diffusion processes which can be substituted for its versions with reversal potentials. Two of these substitutes have been studied in detail. The first one takes into account both reversal potentials

$$dX = \left(-\frac{X}{\tau} + \mu_1(V_E - X) + \mu_2(X - V_I)\right)dt + \sigma\sqrt{(V_E - X)(X - V_I)}\,dW(t) \qquad (26)$$

while the second one stresses the importance of the inhibitory reversal potential

$$dX = \left(-\frac{X}{\tau} + \mu_1(V_E - X) + \mu_2(X - V_I)\right)dt + \sigma\sqrt{X - V_I}\, dW(t) \quad (27)$$

where notation follows (14) and interpretation of parameters is the same as in (25), $\mu_1 > 0$, $\mu_2 < 0$ are constants. The results for model (27) were established by (Lanska et al., 1994) and there are also given the first two moments of X. Model (29) has been studied more often but mainly in a different context. It is known as the Feller process and a detailed numerical study of the differences between the Ornstein-Uhlenbeck model and (29) was performed by Lansky et al. (1995). Model (27) has also been applied in mathematical finance (Cox et al., 1985). The effect of the inclusion of reversal potentials into the diffusion models is apparent when comparing (26) or (27) with (6). From a qualitative point of view it means that the infinitesimal variance becomes state-dependent variable while the drift preserves its linearity. However, the parameters in the drift term are entirely different. There is constant "leakage term" τ^{-1} in (6) while for the models with reversal potentials the leakage is input dependent ($\tau^{-1} + \mu_1 - \mu_2$). Further, the absolute term of the drift is multiplied by the reversal potentials in the models (26) and (27). We should stress that the diffusion approximations of the model which takes into account the existence of the reversal potentials lead always to the models with multiplicative noise (Lansky and Lanska, 1987). We can note, an additive noise is generated by events outside the transmitted message and the multiplicative noise accompanies the passage of the message either from point to point in the network or is generated inside the processing unit - inside the system.

For models (26) and (27), similarly to the Ornstein-Uhlenbeck model, the Laplace transform of the $g_S(t \mid x_0)$ is available and the moments of T_S can be calculated. Having the mean interspike interval permits us to construct the input-output curves for both these models. The asymptotic exponentiality for low level of excitation defined by $\mu\alpha \ll$S exists for both models as for the Ornstein-Uhlenbeck process.

Hanson and Tuckwell (1983) considered two other diffusion models with reversal potential; the first is given by equation

$$dX = \left(-\frac{X}{\tau} + \mu_1(V_E - X)\right)dt + \sigma(V_E - X)\, dW(t)\,. \quad (28)$$

Model (28) is studied in the cited paper either without any additional boundary or being restricted from below by the reflecting boundary imposed at the

resting potential. The second model proposed and analyzed by these authors had the same drift term $\nu(x)$ as (26) or (27) but was characterized by an infinitesimal variance

$$\sigma(x) = \sqrt{\sigma_1^2(V_E - X)^2 + \sigma_2^2(X - V_I)^2}\,. \tag{29}$$

For both models (28) and (29) the first two moments of X were derived in the absence of the threshold S and the first two moments of the first-passage time through the boundary S were computed.

From the modeling point of view, the variety of forms for the infinitesimal variance and the linear form of the infinitesimal mean are not unexpected. These models are trying to reflect by an "equivalent" noisy ordinary differential equation, the properties at a single location, of a spatially distributed neuron with noisy inputs, i.e., a stochastic partial differential equation. The linear mean term describes the passive electrical circuit properties of the membrane at the trigger zone and the mean effect of the noisy input. The infinitesimal variance, on the other hand, must not only take into account the diversity of spatial configurations for different neurons, but the location and type of synaptic input on that neuron as well. Hence, a variety of forms for this term in the diffusion equation are appropriate.

Chapter 3

Complex Stochastic Models

3.1 Parameters of the models

Following from the structure of the above discussed models, it is clear that they contain parameters of two kinds: the parameters characterizing the neuron by itself, so-called intrinsic parameters, and the parameters characterizing the input (Tuckwell and Richter, 1978). This distinction can be well illustrated on the Ornstein-Uhlenbeck model (6). There are three intrinsic parameters, the firing threshold S,the initial depolarization x_0 and the membrane time constant τ. We may assume that these parameters are not varying in time, or at least not varying within the time for which the model is compared with the data; that these parameters are independent of the activity of the neuron, and finally, that the values of these parameters can be deduced by some direct methods, rather than on the basis of the observation of interspike intervals. In other words, the intrinsic parameters play the role of constants given prior the verification of the model. On the other hand, the input parameters are related to the signal which is coded by the neuron. For model (6) it is $\mu(t)$ and σ, if we assume the signal has a random component as it follows for example from diffusion approximation of Stein's model. One can also assume that $F(t)$ in (6) is an intrinsic noise characterizing the neuron in itself. In this case information about the membrane potential fluctuation would be a source for σ identification. An obvious conclusion follows from this deduction. If $F(t)$ is not an intrinsic noise but a parameter related to the input, then the neuron, by using rate coding serves as a variability encoder. Estimating the input parameters thus has a twofold role; to quantify the input and to prepare the model verification.
Wiener process. There are three parameters in distribution (15), the distance between the initial depolarization x_0 and the threshold S,(the model is space homogenous and only the distance is relevant), μ and σ. We may assume that $S - x_0$ is known, approximately 10-20 [mV] and only μ and σ should be estimated. Using the method of moments, μ can be estimated comparing (18) with the mean interspike interval and σ by using (19) and sample variance of interspike intervals. Of course, another method for the estimation of μ and σ, as for example the maximum-likelihood, are available.

Usually, the density (17) is reparametrized because in reality there are only two independent parameters in (17). Then these two new parameters are estimated either by the method of moments or by the maximum-likelihood method and the fit of the data to the model can be tested. This approach implicitly reveals that the model is not interpretable in biophysical terms as such an attempt would, due to model oversimplification, lead to wrong conclusions. In general, a simple fit of the data to the model may lead to a misleading interpretation of the parameters and thus must be done with utmost care. It is an everlasting question whether the Wiener process can be considered as a neuronal model or if its first-passage-time distribution is only an unspecified kind of statistical distribution suitable for experimental data description like lognormal or gamma distribution. On one hand, using the term "model" should induce a possible biophysical reinterpretation of the estimated parameters. On the other hand, the statistical "model" characterizes the activity and reflects a change following from variation of experimental conditions. Despite the fact that the Wiener model is not realistic and there are objections against its use, in contrast to other model it may serve as a reference point since the analytical results are available. It is especially true when the network properties are studied.

The Wiener model is the only diffusion neuronal model which has been relatively often compared with experimental data. This fit helps to achieve a better insight into the data character and it may prove to be useful especially when data recorded under different conditions are compared. Of course, similar advantages and disadvantages have a comparison with any other type of distributions. Among many successful fittings of the Wiener model to the data we can mention, e.g., (Gerstein and Mandelbrot, 1964; Berger and Pribram, 1992).

Ornstein-Uhlenbeck model. Introduction of the leakage into the model has a striking effect and (6) for constant μ has been in the neuronal modeling context studied very deeply and for more than three decades. However, in all this period there had been only one attempt to fit it to the experimental data (Inoue et al., 1995). Two unknown input parameters μ and σ were estimated in this paper. The estimation method was based on the experimentally observed mean and variance of interspike intervals. A comparison was made between the estimates for the Wiener model and for the Ornstein-Uhlenbeck one. Rather extensive tables are included in the paper permitting anyone who has sufficiently large samples of firing data to perform his own, at least preliminary, estimation of the parameters.

It is apparent from numerical studies on the models that whatever shape of

the first-passage-time density for the Ornstein-Uhlenbeck process is selected, there is an inverse Gaussian distribution whose shape would be similar and hardly distinguishable on the basis of sample sizes usually used in spiking activity recordings (we have to keep in mind, that all this is conditioned by stationarity and lack of stationarity may appear with increasing record length). Therefore, the result of fitting will not be a strikingly better (the fit is already good for the Wiener process) but a possibility to interpret the parameters and check the model plausibility is a great achievement of the Ornstein-Uhlenbeck model application.

Models with variable infinitesimal variance. In addition to the parameters of the Ornstein-Uhlenbeck model, these models have two more intrinsic parameters, V_E and V_I.

Up to now we have summarized the procedure for fitting the data to model when only interspike intervals are available. Despite we have assumed that the intrinsic parameters are a priori known - to estimate the input parameters is a difficult task. An entirely different situation arises when intracellular recording is available. In that case we record the values of the membrane voltage (the process X) in-between the spikes and available information is much higher than in the situation when only intervals are studied. The results can available in this case can be found in (Lansky, 1983; Lansky et al., 2006; Lansky and Ditlevsen, 2008; Bibbona et al., 2008).

3.2 Spatial properties

In the above text, we purposefully left out several extensions of stochastic diffusion models which play a very important role, but which are outside the topic of this review. Nevertheless, to complete the picture and for a better orientation general features of these models have to be mentioned. As stressed several times, all our previous models were single-point models totally neglecting all the neuronal morphology. This is a very strong abstraction and for any detailed model this has to be removed. The simplest way how to overcome this lack is to characterize the neuronal depolarization not in one but two abstract points (Rospars and Lansky, 1995). This approach implies that the model describing the voltage at the trigger zone has a different kind of noise from those employed before. So, instead of Poissonian or white noise we may achieve a colored noise (the Ornstein-Uhlenbeck process) at the input to the trigger zone. Of course, this generalization introduces a correlation structure into the interspike interval generation even without a feedback, so for time-unstructured input. From this simple generalization we

can realize that the correlation patterns of spiking activity can be either of an internal nature (due to the neuronal morphology) or already contained in the incoming signal. Introduction of a larger number of discrete points where the membrane potential is described leads to mathematically very complex problems. Finally, a classical approach, under the deterministic scenario, of how to introduce spatial properties of a neuron is an application of the cable theory (Tuckwell, 1988).

3.3 Time-dependent input

Up to recently the models met in applications of diffusion processes in theoretical neuroscience have been predominantly time homogeneous, which is reflected by the fact that the functions ν and σ appearing in (14) do not depend on t. There are only few examples where the models were mentioned in connection with a periodic input, which is substantially different from numerous studies on the deterministic model (5). Several authors used numerical methods and computer simulations for the Ornstein-Uhlenbeck process with time dependent infinitesimal moments to describe the stimulated activity of a neuron. They assumed a non-homogeneous periodic input for the model in order to produce a multimodal probability density of the first-passage time, some historical notes on time-nonhomogenous models can be found in (Lansky, 1984). Only very recently an interest in stochastic resonance (a cooperative effect that arises out of the coupling between deterministic and random dynamics in a nonlinear system) revived an interest in diffusion with time dependent parameters. The stochastic resonance effect consists of a noise-induced enhancement in the signal-to-noise ratio. The integrate-and-fire models operate in two distinct regimes coinciding with deterministic and Poissonian regimes mentioned previously for the Ornstein-Uhlenbeck model. In the first one the signal (μ term) is large enough so the firing events occur even in the absence of noise. The noise activated regime corresponds to the situation when the drift term alone is not sufficient to cause a firing and it is the noise which activates the firing. The "positive" role of noise in information transfer and processing within the nervous system, and especially in sensory neurons, has been noted for decades. The methods of stochastic resonance extend this view mainly in the situation when the coded signal is periodic (Longtin et al., 1994; Bulsara et al., 1994, Bulsara et al., 1996; Chapeau-Blondeau et al., 1996). However, recently also the non-periodic signal were studied in the framework of the stochastic resonance.

A stochastic counterpart of model (5) can be also derived via diffusion ap-

proximation of (15). This can be done from a biological point of view in two different manners; assuming either an endogenous periodicity or a periodicity of input intensities. The latter is obviously more natural and serving to our purpose of describing a reaction of the system to a periodical signal. The exogenous periodicity was even mentioned in the original Stein's paper (Stein, 1965) as a tool for simulation of multipeaked histograms of interspike intervals. Both these modifications result in the model of the membrane potential,

$$dX(t) = -\left(\frac{X(t)}{\tau} + \mu + \mu_0 cos(\omega t + \theta)\right) dt + \sigma dW(t)\ , x(t_k^+) = x_0\,,$$

where the notation follows from (5) and (14). However, for exogenous periodicity the phase of the signal continues after a spike while in the endogenous case it is always reset which simplifies the calculations (for details see Lansky, 1997).

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