Stochastic Modelling of the Neuronal Membrane Potential in response to Synaptic Input

by

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Abstract A synapse is the term used to describe the connection between the axon of the donor cell and the part of the membrane of the target cell onto which the axon impinges . The arrival of an impulse at the site of the synapse causes the release of a chemical neurotransmitter which then diffuses across a narrow gap and binds onto the receptors of the postsynaptic neuron, altering the behaviour of the membrane and allowing the movement of ions between the intracellular and extracellular regions. These neurotransmitters differ in their strength, timing and their ability to excite or inhibit the postsynaptic neuron. Consequently, these inputs have a significant impact on the electrophysiological properties of the neuron. However synaptic properties are difficult to measure at microscopic level, whereas the stationary distribution of the membrane potential, while easy to measure, incorporates the underlying microscopic properties of synapses.

The ion flow across the membrane of the postsynaptic neuron at the synapse is modelled as the product of the membrane conductance and of the potential difference, that is the difference of the membrane potential at the site of the synapse and the reversal potential for the specific ionic species to which the synapse is particularised . Therefore , synaptic behaviour is closely linked to synaptic conductance. Two models of synaptic behaviour are examined, namely the point conductance model proposed by Richardson (2004) and the exponential conductance model proposed by Rudolph and Destexhe (2003,2005). Each article aims to determine the stationary distribution of the membrane potential by solving the underlying equation describing its evolution. The latter work describes the evolution of the membrane potential in terms of the solution of a family of three linked stochastic differential equations (SDEs). In this thesis it is demonstrated that the conclusion of the lengthy analysis of Rudolph and Destexhe (2003, 2005) can be obtained directly from the system of SDEs. Through the use of a spectral procedure based on Hermite Polynomials it is shown that the marginal probability density function of the membrane potential can be estimated to arbitrarily accuracy. The procedure is illustrated for one level of approximation.

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Contents

Chapter 1

Introduction

1.1 Biological background

This thesis investigates the behaviour of the stochastic models proposed by Rudolph and Destexhe (2003) and Richardson (2004) to describe the fluctuations in the membrane potential of a point neuron with a passive membrane in the presence of voltage-regulated synaptic input. The aim of these models is to estimate neuronal parameters from the stationary distribution of the membrane potential in the presence of stochastic input due to the activity of excitatory and inhibitory synapses.

Although a biological neuron consists of a cell body (soma) to which are connected "tree-like" structures called dendrites and an axon by means of which it transmits electrical signal to other neurons, the model neuron considered in this work is regarded as a lumped region with a passive membrane of known specific capacitance c_m (μF/cm^2) and known leakage resistance g_m (mS/cm^2). In addition to morphology, neurons have physiological specializations, one of which is a wide variety of membrane-spanning ionic channels that allow many species of ions to cross the membrane of the cell, most notably chloride ions (Cl^-), sodium ions (Na^+), potassium ions (K^+) and calcium ions (Ca^{+2}). Differences in the intracellular and extracellular concentrations of each ionic species causes a potential difference, called the *membrane potential*, to exist across the membrane. In the absence of synaptic and exogenous current, the intracellular and extracellular concentrations of each ionic species assume values such that the membrane potential is constant at its resting value E_m (mV) and the flux of ions across the cell membrane is such that no net current crosses the membrane. Current in the form of positively charged ions flowing out of the cell depresses the membrane potential below E_m and is said to *hyperpolarize* the membrane.

On the other hand current flowing into the cell (negatively charged ions flowing into the cell) elevates the membrane potential above E_m and is said to *depolarize* the membrane.

When a neuronal membrane is sufficiently depolarized, an *action potential* or *spike* is generated. This can be regarded as an electrical signal which propagates along the axon of that neuron until it reaches the *synapses* of other neurons. At a synapse, the voltage transient of the action potential opens ionic channels through the release of a chemical neurotransmitter which diffuses across a narrow synaptic cleft and activates the receptors on the membrane of the postsynaptic neuron. The resulting current flow across the membrane due to the arrival of an action potential at a synapse is modelled as the product of a membrane conductance and the potential difference $\big(V - E_a\big)$ where V (mV) is the membrane potential of the postsynaptic neuron at the site of the synapse and E_a (mV) is the reversal potential of the ionic species associated with the synapse, that is, it is the potential at which the net flux of that ionic species crossing the membrane is zero. In particular, a synapse with reversal potential below the threshold potential for the generation of an action potential is called an *inhibitory* synapse whereas a synapse with reversal potential above that of the threshold for the generation of action potential is called an *excitatory* synapse.

1.1.1 Model of synaptic conductance

The arrival of action potentials at a synapse is modelled mathematically by a *spike train* in which the times of arrival of each action potential defines the *spikes* or point events in the train. The conventional assumption is that the arrival of spikes at a synapse is independent of the history of the spiking activity at that synapse, and for this reason a spike train is often modelled as a Poisson process. Let $\mathcal{N}$ be a spike train with $N(t, t+u)$ denoting the number of spikes of $\mathcal{N}$ to occur during the time interval $[t, t+u)$. The number of spikes of $\mathcal{N}$, $N(t)$ may be independent or correlated [1]. The arrival of a spike at a synapse at time t contributes to the conductance $g(t)$ of the synapse at that time. The effect is assumed to be additive in the respect that the conductance of the synapse will be the sum of the residual conductances prior to the arrival of the spike and that contributed by the spike.

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[1] For example the probability of two spikes occurring together in a sequence need not be the product of the probabilities that each occurs individually since the presence of one spike may effect the occurrence of the other.

Suppose that a synapse receives spikes at times $t_1, t_2, \cdots$ prior to time t then

$$g(t) = \sum_{k=1}^{\infty} G\big(t - t_k\big)$$

where $G(s)$ describes the residual conductance contributed by a single spike s milliseconds after its arrival at the site of the synapse. Writing $dN(s) = N(t, t + ds)$ then

$$dN(s) = \left[\begin{array}{ll} 1 & \text{Spike in } [t, t+ds) \\ & \\ 0 & \text{No spike in } [t, t+ds) \end{array}\right.$$

and thus

$$g(t) = \int_{-\infty}^{t} G(t-s)\, dN(s)\,.$$

Although G is a deterministic function, $\mathcal{N}$ is a random point process and so $g(t)$ behaves as a random process. One common choice of kernel function is $G(u) = G(0)e^{-u/\tau}$ where τ (msec) is the synaptic time constant. This is a convenient mathematical form[2] but it can also be rationalized by assuming that the neurotransmitter, once released, loses its effectiveness at rate τ^{-1} by which is meant that transmitter which is active at time u becomes inactive in the interval $(u, u + du)$ with probability $du/\tau + o(du)$. The factor $e^{-u/\tau}$ is simply the fraction of neurotransmitter still active u milliseconds after it was released as a result of the voltage transient generated by the arrival of the action potential at the site of the synapse. Consider now a site at which there are n synapses of the same ionic species and let $g_1(t), g_2(t), ..., g_n(t)$ be their respective conductances then

$$\sum_{k=1}^{n} g_k(t) = \sum_{k=1}^{n} \int_{-\infty}^{t} G(t-s)\, dN_k(s) = \int_{-\infty}^{t} G(t-s) \sum_{k=1}^{n} dN_k(s)\,.$$

The fundamental theorem of Calculus applied to the previous equation yields

$$d\Big(\sum_{k=1}^{n} g_k(t)\Big) = dt \int_{-\infty}^{t} \frac{dG(t-s)}{dt} \sum_{k=1}^{n} dN_k(s) + G(0) \sum_{k=1}^{n} dN_k(t)\,,$$

and when particularised to the exponential kernel, the total conductance satisfies

$$d\Big(\sum_{k=1}^{n} g_k(t)\Big) = -\frac{dt}{\tau}\Big(\sum_{k=1}^{n} g_k(t)\Big) + G(0) \sum_{k=1}^{n} dN_k(t)$$

where, as usual, $dN_k(t)$ takes the value one if an action potential arrives at the k-th synapse during the time interval $[t, t + dt)$ and zero otherwise. Typically n is large, and therefore $dN_k(t)$ has finite mean and variance. The central limit theorem may be used

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[2] Another common constitutive equation for the conductance $G(u)$ is the "alpha" function $G(u) = G\,\frac{u}{\tau}\,e^{-u/\tau}$.

to approximate the second term of the previous equation by a Gaussian random variable with mean value $\mu\, dt$ and variance $\sigma^2\, dt$ where

$$\mu = G(0) \sum_{k=1}^{n} \mu_k\,, \qquad \sigma^2 = [G(0)]^2 \sum_{k,j=1}^{n} \frac{\mathrm{Cov}\,(dN_j(t), dN_k(t))}{dt}$$

and μ_k is the rate of the k-th spike train. For example, if the spike trains are mutually independent then $\mathrm{Cov}\,(dN_j(t), dN_k(t)) = \sum_{k=1}^{n} \mu_k\, dt$ and therefore $\sigma^2 = [G(0)]^2 \sum_{k=1}^{n} \mu_k$. The application of the central limit theorem gives

$$\sum_{k=1}^{n} G(0) dN_k(t) \approx \mu\, dt + \sigma\, dW(t)$$

where $dW(t)$ is a Gaussian process with mean value zero, variance dt, and such that $\mathrm{E}\,\big[dW(t)dW(s)\big] = \delta(t-s)$. Let $g(t)$ be the total conductance of all n synapses of this type acting at the site, then

$$g(t) = \sum_{k=1}^{n} g_k(t)$$

and the evolution of $g(t)$ satisfies the equation

$$dg(t) = \Big(\mu - \frac{g(t)}{\tau}\Big)\, dt + \sigma\, dW(t) \tag{1.1}$$

where $dW(t)$ is the differential of the Wiener process. Equation (1.1) is an example of a stochastic differential equation (SDE), and the particular equation satisfied by $g(t)$ in this case is called an Ornstein-Uhlenbeck or OU process.

1.1.2 Wiener process

The Wiener process, named after its inventor Norbert Wiener, is a continuous (but not differentiable) Gaussian process starting with $W(0) = 0$ and such that $W(t)$ has mean value zero and variance t for all $t > 0$. The process is uncorrelated through time so that

$$\mathrm{E}\,\big[W(t)W(s)\big] = \min(t,s)\,, \qquad \mathrm{E}\,\big[dW(t)dW(s)\big] = \delta(s-t)\, dt\, ds\,. \tag{1.2}$$

The Wiener process is intended to be a mathematical description of the irregular motion of pollen grains floating on water as observed by the Scottish botanist Robert Brown in 1827. Using a microscope he reported that minute particles within the vacuoles of the pollen grains executed a jittery motion. By repeating the experiment with particles of dust, Brown observed a similar behaviour from which he deduced that the behaviour could not be attributed to the fact that pollen particles were "alive". Prior to the study of Brown, Jan Ingenhousz had noted in 1765 that carbon dust on alcohol moved in an irregular way, but it was Brown's study of pollen particles that led subsequently to the term "Brownian motion" for this irregular pattern of motion.

Thorvald Thiele in 1880 was the first person to describe the mathematics behind Brownian motion in an article concerning the method of least squares. In 1900 Louis Bachelier in his PhD thesis entitled "The theory of speculation" independently developed a model of Brownian motion for use in a stochastic analysis of stock markets and option markets. However, it was Albert Einstein's independent research of the problem, by the use of a probabilistic model in 1905 that could explain sufficiently the Brownian motion and brought the problem to the attention of mathematical physicists. At that time the atomic nature[3] of matter was still a controversial idea. Einstein and Marian Smoluchowski observed that, if the kinetic theory of fluids was correct, then the molecules of water would move at random. Therefore, a small particle would receive a random number of impacts of random strength and from random directions in any short period of time. This random bombardment by the molecules of the fluid would cause a sufficiently small particle to move in exactly the way described by Brown. Theodor Svedberg made important demonstrations of Brownian motion in colloids and Felix Ehrenhaft, of particles of silver in air. Jean Perrin carried out experiments to test the new mathematical models, and his published results finally put an end to the two thousand year-old dispute about the reality of atoms and molecules.

1.1.3 Ornstein-Uhlenbeck process

Some important properties of the Ornstein-Uhlenbeck process are now developed as a precursor for future analysis. The stochastic differential equation (1.1) is an example of the OU process

$$dx = \alpha(\theta - x)\,dt + \sigma\,dW \tag{1.3}$$

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[3] The atomic dispute had started with Democritus (approx. 490BC to 460BC) and Anaxagoras (born about 500BC, the teacher of Socrates). There were opposing atomic theories distinguished, for example, by the issue of whether or not a drop of water could be divided repeatedly without limit such that each sub-division preserved the properties of the original. The atomic school of Democritus believed that subdivision could not continue indefinitely whereas the doctrine of homoiomereia (homogeneity) followed by Anaxagoras believed that the drop could be divided indefinitely because the size of a body did not reflect the nature of its substance.

in which $x(t) = g(t)$, is the total synaptic conductance at the site, and $\alpha = \tau^{-1}$ and $\theta = \mu\tau$. The solution of equation (1.3) can be obtained by using Ito's lemma by noting that if x satisfies the OU process (1.3) then

$$d\big[\, e^{\alpha t}(x-\theta)\,\big] = \alpha e^{\alpha t}(x-\theta)\,dt + e^{\alpha t}\,dx = \sigma\, e^{\alpha t}\,dW\,.$$

This equation can now be integrated to get the solution

$$x(t) = \theta + e^{-\alpha(t-t_0)}(x(t_0)-\theta) + \sigma\int_{t_0}^{t} e^{-\alpha(t-s)}\,dW(s)\,. \tag{1.4}$$

This solution describes the evolution of the process $x(t)$ in the interval $[t_0, t]$. The solution in the interval $(-\infty, t)$ is derived from expression (1.4) by taking the limit as $t_0 \to -\infty$ to obtain

$$x(t) = \theta + \sigma\int_{-\infty}^{t} e^{-\alpha(t-s)}\,dW(s)\,. \tag{1.5}$$

The correlation structure of $x(t)$ may be computed directly from this expression to get

$$\begin{aligned}
\mathrm{E}\big[(x(t)-\theta)(x(t_0)-\theta)\big] &= \mathrm{E}\Big[\sigma^2\int_{-\infty}^{t}\int_{-\infty}^{t_0} e^{-\alpha(t-s)}e^{-\alpha(t_0-u)}\;dW(s)\,dW(u)\Big]\\
&= \sigma^2\int_{-\infty}^{t}\int_{-\infty}^{t_0} e^{-\alpha(t-s)}e^{-\alpha(t_0-u)}\,\mathrm{E}\big[dW(s)\,dW(u)\big]\\
&= \sigma^2\int_{-\infty}^{t}\int_{-\infty}^{t_0} e^{-\alpha(t-s)}e^{-\alpha(t_0-u)}\delta(s-u)\,ds\,du\\
&= \sigma^2\int_{-\infty}^{\min(t,t_0)} e^{-\alpha(t+t_0-2s)}\,ds = \frac{\sigma^2}{2\alpha}\,e^{-\alpha|t-t_0|}\,.
\end{aligned}$$

Some general properties of the solution of the OU process may now be asserted. First, it follows directly from the solution (1.5) that $\mathrm{E}\,[x(t)] = \theta$, and from the previous calculation that $\mathrm{E}\,[(x(t)-\theta)^2] = \sigma^2/2\alpha$. The solution (1.5) also indicates that $x(t)$ is the weighted sum of an infinite number of Gaussian processes and therefore it follows directly from the properties of the normal distribution that in the absence of conditional information such as the value of $x(t_0)$, the value of $x(t)$ may be regarded as a draw from a Gaussian distribution with mean value θ and variance $\sigma^2/2\alpha$. On the other hand, when $x(t_0)$ is known then the value of $x(t)$ for $t > t_0$ is now drawn from a Gaussian distribution with mean value $(1-e^{-\alpha(t-t_0)})\theta + e^{-\alpha(t-t_0)}x(t_0)$ and variance $\sigma^2\big[1-e^{-2\alpha(t-t_0)}\big]/2\alpha$.

In order to simplify the analysis of the OU process it is convinient to use the substitution $y(t) = x(t) - \theta$. It follows directly from equation (1.3) that the stochastic differential equation satisfied by $y(t)$ would be of the form $dy = -\alpha y\,dt + \sigma\,dW$ with solution

$$y(t) = e^{-\alpha(t-t_0)}\,y(t_0) + \sigma\int_{t_0}^{t} e^{-\alpha(t-s)}\,dW(s)\,. \tag{1.6}$$

and has the further properties that the condition process, $y = y(t_0)$ at $t = t_0$ satisfies

$$\mathrm{E}\,[y(t)] \;=\; e^{-\alpha(t-t_0)}\,y(t_0)\,, \qquad \mathrm{E}\,[y(t)y(t_0)] \;=\; \sigma^2\Big[1-e^{-2\alpha|t-t_0|}\Big]/2\alpha\,.$$

In the case of the unconditional process $t_0 \to -\infty$

$$\mathrm{E}\,[y(t)] = 0\,, \qquad \mathrm{E}\,[y(t)y(t_0)] = \frac{\sigma^2}{2\alpha}\,e^{-\alpha|t-t_0|}\,. \tag{1.7}$$

1.1.4 Integrated Ornstein-Uhlenbeck process

The integrated Ornstein-Uhlenbeck process $w(t)$ is defined by

$$w(t) = \int_0^t x(s)\,ds = \theta t + \int_0^t y(s)\,ds\,. \tag{1.8}$$

It is clear from this definition that the properties of the general integrated OU process can be constructed from those of the simplified integrated OU process

$$z(t) = \int_0^t y(s)\,ds \tag{1.9}$$

in which the integrand has mean value zero. Expression (1.6) for $y(t)$ is now substituted into definition (1.9) to obtain

$$\begin{aligned} z(t)-z(t_0) = \int_{t_0}^t y(s)\,ds \;&=\; \int_{t_0}^t \Big[e^{-\alpha(s-t_0)}y(t_0) + \sigma\int_{t_0}^s e^{-a(s-u)}\,dW(u)\Big]\,ds \\ &=\; \frac{y(t_0)}{\alpha}\Big[1-e^{-\alpha(t-t_0)}\Big] + \sigma\int_{t_0}^t\int_{t_0}^s e^{-\alpha(s-u)}\,dW(u)\,ds \\ &=\; \frac{y(t_0)}{\alpha}\Big[1-e^{-\alpha(t-t_0)}\Big] + \sigma\int_{t_0}^t e^{\alpha u}\,dW(u)\int_u^t e^{-\alpha s}\,ds \\ &=\; \frac{y(t_0)}{\alpha}\Big[1-e^{-\alpha(t-t_0)}\Big] + \frac{\sigma}{\alpha}\int_{t_0}^t (1-e^{-\alpha(t-u)})\,dW(u)\,. \end{aligned}$$

The properties of the integrated OU process conditional on the starting conditions at t_0 may be extracted from this expression to give

$$\mathrm{E}\,\big[z(t)\big] = z(t_0) + \frac{y(t_0)}{\alpha}\Big[1-e^{-\alpha(t-t_0)}\Big]\,. \tag{1.10}$$

The correlation between $z(t)$ and $z(t_0)$ can be obtained from

$$\mathrm{E}\,\big[z(t)z(t_0)\big] = \mathrm{E}\,\big[z^2(t_0)\big] + \mathrm{E}\,\big[z(t_0)y(t_0)\big]\Big[\frac{1-e^{-\alpha(t-t_0)}}{\alpha}\Big] \tag{1.11}$$

by calculating $\mathrm{E}\,\big[z(t_0)y(t_0)\big]$ and $\mathrm{E}\,\big[z^2(t_0)\big]$. These quantities are calculated by the following arguments. It follows directly from the unconditional expectation of $y(t_0)y(s)$ from equation (1.7) that

$$\begin{aligned} \mathrm{E}\big[z(t_0)y(t_0)\big] &= \int_0^{t_0} \mathrm{E}\big[y(s)y(t_0)\big]\,ds = \frac{\sigma^2}{2\alpha^2}\big[1-e^{-\alpha t_0}\big] \\ \mathrm{E}\big[z(t_0)^2\big] &= \int_0^{t_0}\int_0^{t_0} \mathrm{E}\big[y(s)y(u)\big]\,ds\,du = \frac{\sigma^2}{\alpha^3}\Big[\alpha t_0 - 1 + e^{-\alpha t_0}\Big]\,. \end{aligned} \tag{1.12}$$

The values for $\mathrm{E}\big[z(t)z(t_0)\big]$ and $\mathrm{E}\big[z^2(t_0)\big]$ are now substituted into equation (1.11) to get the final result that

$$\mathrm{E}\big[z(t)z(t_0)\big] = \frac{\sigma^2}{2\alpha^3}\Big[2\alpha t_0 + e^{-\alpha t_0} + e^{-\alpha t} - e^{-\alpha(t-t_0)} - 1\Big]\,. \tag{1.13}$$

1.1.5 Neuronal model

When a point neuron with specific membrane capacitance c_{m}, specific membrane conductance g_{m} receives current input of density $J(t)$ (μA/cm^2), then conservation of current demands that the membrane potential $V(t)$ (mV) satisfies

$$c_{\mathrm{m}}\frac{dV}{dt} + g_{\mathrm{m}}(V - E_m) + I(t) = 0 \tag{1.14}$$

where E_m (mV) is the resting membrane potential of the neuron, that is the membrane potential of the neuron in the absence of sources of synaptic current embodied in the term $I(t)$. In the problem to be studied in this work, the contributions to the current $I(t)$ come from inhibitory synapses with total conductance $g_i(t)$ (mS/cm^2) and reversal potential E_i (mV), excitatory synapses with total conductance $g_e(t)$ (mS/cm^2) and reversal potential E_e (mV) and exogenous current $I_{\mathrm{ex}}(t)$ with mean value zero. The role of $I_{\mathrm{ex}}(t)$ is to describe unidentified synaptic input, that is, current received by the neuron but not accounted for by the activity of the excitatory and inhibitory synapses. Thus the total membrane current is

$$I(t) = g_i(t)(V - E_i) + g_e(V - E_e) + I_{\mathrm{ex}}(t) \tag{1.15}$$

and therefore the membrane potential is the solution of the ordinary differential equation

$$c_m\frac{dV}{dt} = -g_m\big(V - E_m\big) - g_e(t)\big(V - E_e\big) - g_i(t)\big(V - E_i\big) - I_{\mathrm{ex}}(t)\,. \tag{1.16}$$

In our analysis the values of $g_i(t)$ and $g_e(t)$ will be assumed to depend solely on the pre-synaptic spike activity received by the inhibitory and excitatory synapses alone. Modifications of synaptic conductance due to postsynaptic spike activity will be ignored in this analysis which will focus on how properties of the excitatory and inhibitory synapses, in combination with their activity, translate into observable properties of the distribution of the membrane potential V. With this background in place, the point-neuron models of Richardson (2004) and Rudolph and Destexhe (2003, 2005) are now discussed.

Chapter 2

Richardson model for the membrane potential

2.1 Introduction

Richardson (2004) investigates how models of synaptic behaviour based on the injection of point current differ from models based on a time-varying synaptic conductance. The comparison focuses on the distribution of membrane potential within a neuron and its firing rate or rate of generation of action potentials. Action potentials in a neuron are generated by an exchange of ions across the neuronal membrane. The initiation of an action potential begins with sodium ions from the extracellular region crossing the membrane causing the membrane potential to rise (depolarisation). At approximately -55mV, the membrane potential rises particularly rapidly towards the sodium equilibrium potential. Simultaneously, potassium ions in the intracellular region begin to flow to the extracellular region, at first restraining the rapidly rising membrane potential but subsequently reversing the rise and restoring the membrane potential to its resting value (≈ -60mV) via an overshoot into a region in which the membrane approaches closely the potassium equilibrium potential (≈ -72mV) before returning to its resting value. This explosion of electrical activity takes place over a short period of time and is called an *action potential.* The conventional view is that levels of synaptic activity which cause the membrane potential to reach approximately -55mV will in a real neuron cause the kinetic properties of the sodium and potassium currents to generate an action potential with very high likelihood. For this reason one popular way to model the generation of an action potential is through the use of a threshold membrane potential. When synaptic activity causes the membrane potential in the model to reach this threshold value, the cell is deemed to have generated an action potential and the model membrane potential is reset instantaneously to its resting value in recognition of the fact that action potentials take place over a short interval of time and that after the event, the membrane potential would relax to its resting state in the absence of continuing synaptic activity.

2.2 Conductance as Delta function

The model adopted by Richardson is a particularisation of equation (1.16) in which exogenous current input is ignored, that is $I_{\rm ex}(t) = 0$, and the excitatory and inhibitory synapses respond instantaneously to the arrival of pre-synaptic spikes. This means that the conductance $g_i(t)$ and $g_e(t)$ behave mathematically as delta functions. Suppose, for example, that pre-synaptic spikes arrive at the excitatory synapses at times $t_k^{(e)}$ then the conductance of the excitatory synapses is

$$g_e(t) = c_m a_e \sum_k \delta(t - t_k^{(e)}) \tag{2.1}$$

where a_e is a non-dimensional constant associated with the biophysical properties of the excitatory synapses. The conductance of the inhibitory synapses is likewise represented by the formula

$$g_i(t) = c_m a_i \sum_k \delta(t - t_k^{(i)}) \tag{2.2}$$

where $t_k^{(i)}$ now refers to the times of occurrence of pre-synaptic spikes at the inhibitory synapses and a_i is a non-dimensional constant associated with the biophysical properties of the inhibitory synapses.

To appreciate how the delta-function like behaviour of synaptic conductance affects the membrane potential of the neuron, suppose that a pre-synaptic spike arrives at a synapse at time $t = T$ and in the process induces the conductance change

$$g(t) = c_m a\, \delta(t - T) \tag{2.3}$$

where $a = a_e$ in the case of an excitatory synapse and $a = a_i$ in the case of an inhibitory synapse. Let $t_0 < T < t_1$ such that t_0 and t_1 are sufficiently close to T to ensure that no other pre-synaptic spikes arrive in the interval (t_0, t_1), then the membrane potential in this interval satisfies the differential equation

$$c_m \frac{dV}{dt} = -g_m\big(V - E_m\big) - c_m a\big(V - E\big)\delta(t - T) \tag{2.4}$$

where E is the reversal potential for the ionic species of the active synapse. In terms of the auxiliary function

$$\phi(t) = \frac{g_m}{c_m} + a\,\delta(t-T)\,,$$

equation (2.4) can be re-expressed in the standard form

$$\frac{d(V-E_m)}{dt} + \phi(t)\big(V-E_m\big) = a\,\big(E-E_m\big)\delta(t-T)$$

with solution

$$V_1 = E_m + (V_0 - E_m)\exp\Big[-\int_{t_0}^{t_1}\phi(s)\,ds\Big] + a\,\big(E-E_m\big)\int_{t_0}^{t_1}\delta(u-T)\,\exp\Big[-\int_{u}^{t_1}\phi(s)\,ds\Big]\,du$$

where $V_0 = V(t_0)$ and $V_1 = V(t_1)$. It follows directly from the definition of $\phi(t)$ that

$$\begin{aligned} a&\int_{t_0}^{t_1}\delta(u-T)\,\exp\Big[-\int_{u}^{t_1}\phi(s)\,ds\Big]\,du \\ &= \int_{t_0}^{t_1}\Big(\phi(u)-\frac{g_m}{c_m}\Big)\,\exp\Big[-\int_{u}^{t_1}\phi(s)\,ds\Big]\,du \\ &= 1-\exp\Big[-\int_{t_0}^{t_1}\phi(s)\,ds\Big] - \frac{g_m}{c_m}\int_{t_0}^{t_1}\exp\Big[-\int_{u}^{t_1}\phi(s)\,ds\Big]\,du \end{aligned}$$

and therefore the final solution of equation (2.4) is

$$V_1 = E + (V_0 - E)\exp\Big[-\int_{t_0}^{t_1}\phi(s)\,ds\Big] - \big(E-E_m\big)\frac{g_m}{c_m}\int_{t_0}^{t_1}\exp\Big[-\int_{u}^{t_1}\phi(s)\,ds\Big]\,du\,.$$

Let $t_0 \to T^{(-)}$ and $t_1 \to T^{(+)}$ then

$$V^{(+)} = E + (V^{(-)} - E)\exp\Big[-\int_{T^{(-)}}^{T^{(+)}}\phi(s)\,ds\Big] = E + (V^{(-)}-E)\,e^{-a}$$

where $V^{(-)} = V(T^{(-)})$ and $V^{(+)} = V(T^{(+)})$. Thus

$$\Delta V = V^{(+)} - V^{(-)} = \big(E - V^{(-)}\big)\big(1-e^{-a}\,\big)\,. \tag{2.5}$$

This result forms the basis of the discretised Richardson model of the spiking neuron. When a pre-synaptic spike arrives at an excitatory synapse the membrane potential is instantaneously changed by

$$\Delta V = \big(E_e - V^{(-)}\big)\big(1-e^{-a_e}\,\big)\,, \tag{2.6}$$

and when the pre-synaptic spike arrives at an inhibitory synapse the change in membrane potential is

$$\Delta V = \big(E_i - V^{(-)}\big)\big(1-e^{-a_i}\,\big)\,. \tag{2.7}$$

Between the arrival of pre-synaptic spikes, the membrane potential decays to its resting value E_m with time constant c_m/g_m. In practice, a_e and a_i take values close to zero and so $1-e^{-a}$ is calculated using the identity $1-e^{-a} = 2e^{-a/2}\sinh a/2$ to avoid errors in numerical cancellation.

2.2.1 Simulation of Richardson's conductance based model

The excitatory and inhibitory conductances are given respectively by equations (2.1) and (2.2). Let $t_k^{(e)}$ and $t_k^{(i)}$ $k = 1, 2, \cdots$ denote respectively the times of occurrence of the Poisson-distributed incoming excitatory and inhibitory pulses arriving at rates R_e and R_i. Since the arrival times of the synapses are Poisson-distributed, it means that spikes are equally likely at any time. Let T denote the random interval between events. Values of T are simulated by noting that the cumulative distribution function (CDF) is uniformly distributed in $[0, 1]$. If $F(t)$ is the CDF of T, then T is constructed by solving

$$F(t) = U \,, \qquad U \sim (0,1)\,.$$

The definition of the CDF is

$$F(t) = \text{Prob}(T \leq t)$$

and therefore

$$F(t+\Delta t) = F(t) + (1 - F(t))\big(\mu \Delta t + o(\Delta t)\big)\,.$$

Straightforward algebra now yields

$$\frac{F(t+\Delta t) - F(t)}{\Delta t} = \Big(1 - F(t)\Big)\left(\mu + \frac{o(\Delta t)}{\Delta t}\right).$$

Now let, $\Delta t \to 0^+$ to obtain

$$\frac{dF}{dt} = \mu(1-F)$$

with solution

$$F(t) = 1 - e^{-\mu t}$$

satisfying the initial condition $F(0) = 0$. Realisations of T are now constructed by solving the equation $F(T) = U$ to get

$$T = -\frac{\log(1-U)}{\mu}\,.$$

But since U is uniform in $(0, 1)$, then so is $1 - U$ and therefore

$$T = -\frac{\log U}{\mu}\,.$$

It is a straightforward calculation to show that

$$\text{E}[T] = \frac{1}{R} = \int_0^\infty t f(t)\, dt = \frac{1}{\mu}\,.$$

This general result is now applied to generate trains of spikes at excitatory and inhibitory synapses. Inter-spike intervals for the simulation of these spikes are generated respectively from the formulae

$$T_e = -\frac{\log U}{R_e}\,, \qquad\qquad T_i = -\frac{\log U}{R_i}\,.$$

Richardson's model can now be simulated to find the firing rate and the distribution of the membrane potential in a firing neuron. The neuronal potential is first initialised at its resting value. As time advances the membrane potential V is updated to take account of the arrival of excitatory and inhibitory spikes, otherwise it decays towards the resting potential of the cell. The activity of the neuron is simulated by stepping through time in small steps and in each interval applying a membrane threshold potential for the generation of spikes. The distribution of the membrane potential itself is constructed by sampling its value at points widely spaced in time.

Richardson claims for the conductance (symbolized IF_g) model that balanced increase in both R_e and R_i (while the equilibrium potential remains constant) leads to an increase in the synaptic noise. This in turn leads to an increase of the total conductance and has the effect of decreasing the effective time constant τ of the membrane, which means less fluctuations (all of which can be justified by equations (2.13)). These two effects are in competition. In Figure 2.1 the standard deviation σ_V of the membrane potential is plotted against the balanced increased drive for different values of fixed E.

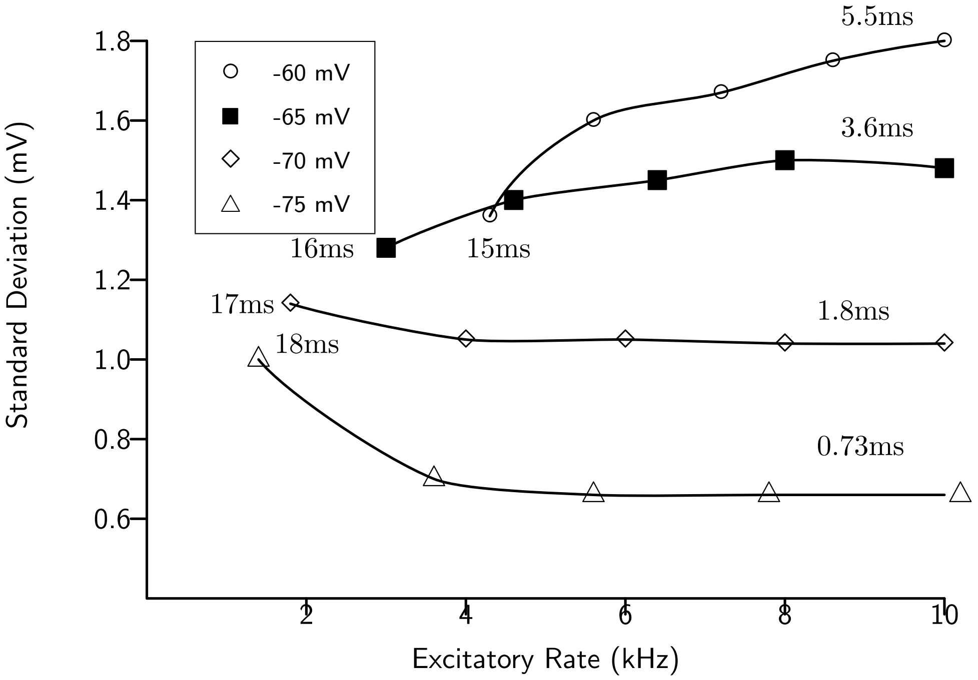

Figure 2.1: The effect of increasing synaptic drive reverses at a mean membrane voltage of -68 mV

As observed from Figure 2.1, at depolarized potentials the fluctuation increase dominates over the conductance increase. The increase of the fluctuations means that it is easy to overcome the threshold value and produce a spike. Richardson also states that it is possible for the conductance (IF_g) model to increase its fluctuations by keeping the values for E and τ constant. This is achievable through increasing $\widetilde{a}_e$ and $\widetilde{a}_i$ and at the same time decreasing the values of R_e and R_i. This action has the same effect as in neurons when the input is correlated. Thus in vivo, if the input is correlated we end up with "bigger" membrane fluctuations. Figure 2.2 gives the membrane voltage distribution before and long after the change in synaptic drive for depolarized potentials.

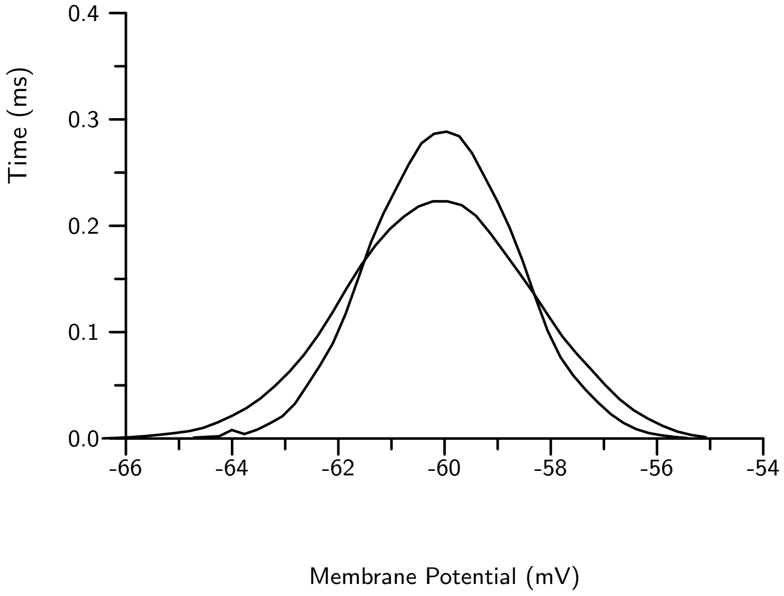

Figure 2.2: The membrane voltage distributions before and long after the change in synaptic drive while $V_{thr} = -56mV$. The curve with the smallest peak is for $R_e = 4.17kHz$, $R_i = 0.0kHz$, $\alpha_e = 0.004$, $\alpha_i = 0.026$. The increase in the synaptic drive to $R_e = 10.0kHz$ and $R_i = 3.59kHz$ leads to an increase in the synaptic fluctuations represented by the curve with the smallest peak.

At hyperpolarized potentials we observe the exact opposite. The conductance increase dominates over the increase in the synaptic fluctuations and we end up with decreased membrane fluctuations. This is what occurs in vivo. Figure 2.3 gives the exact same as Figure 2.2 but for hyperpolarized potentials.

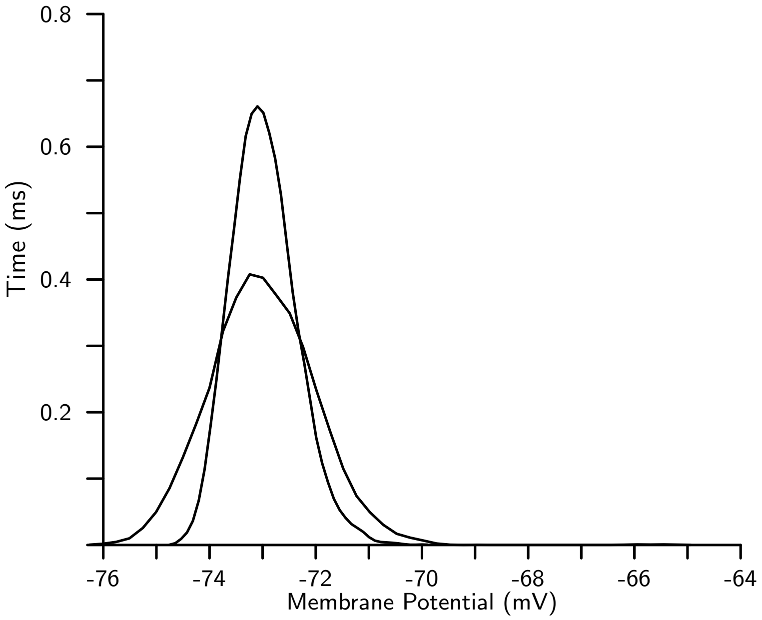

Figure 2.3: The membrane voltage distributions before and long after the change in synaptic drive while $V_{thr} = -69mV$. The curve with the smallest peak is for $R_e = 1.20kHz$, $R_i = 0.0kHz$, $\alpha_e = 0.004$, $\alpha_i = 0.026$. The increase in the synaptic drive to $R_e = 10.0kHz$ and $R_i = 49.42kHz$ leads to decreased membrane fluctuations as is seen by the curve with the greatest peak

2.3 Continuous model

The primary drawback of a delta function model of synaptic conductance is that the resulting membrane potential behaves as a piecewise continuous function of time whereas in reality the membrane potential is necessarily a continuous function of time. To overcome this difficulty, Richardson (2004) replaces the delta function expression for synaptic conductance by a continuous stochastic conductance with the same mean rate. Suppose that the spikes of the presynaptic spike trains are Poisson distributed with rate R where $R = R_e$ in the case of an excitatory synapse and $R = R_i$ for an inhibitory synapse. In the interval $(t, t + \Delta t)$ the expected number of presynaptic spikes to arrive at this class of synapse is $R\Delta t$ with variance $R\Delta t$. For suitably large[1] Δt, the central limit theorem asserts that the number of presynaptic spikes to arrive in this interval is normally distributed with mean value $R\Delta t$ and variance $R\Delta t$, that is, $N(t, t + \Delta t) = R\Delta t + \sqrt{R}\,\Delta W(t)$ where ΔW is the change in the Wiener process over the interval $(t, t + \Delta t)$. Since each presynaptic spike

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[1] The meaning of "large" will depend on the rate R. For the central limit theorem to be effective, it is essential that, on average, at least 6 spikes occur in the interval Δt and preferably more.

contributes conductance $a\,c_m$ then the conductance generated in the interval $(t, t+\Delta t)$ is $a\,c_m(R\Delta t + \sqrt{R}\,\Delta W(t))$ and the resulting synaptic current is

$$a\,c_m\big[R\Delta t + \sqrt{R}\,\Delta W(t)\big](V - E)\,. \tag{2.8}$$

When the amplitudes a_e, a_i are small and the rates R_e, R_i are large, the continuous approximation (2.8) of the synaptic current will give an accurate description of the membrane dynamics, and the continuous version of equation (1.16) is

$$dV = -\frac{g_m}{c_m}\big(V - E_m\big)\,dt - a_e\big[R_e\,dt + \sqrt{R_e}\,dW_e(t)\big]\big(V - E_e\big) - a_i\big[R_i\,dt + \sqrt{R_i}\,dW_i(t)\big]\big(V - E_i\big)\,. \tag{2.9}$$

Thus $V(t)$ now satisfies a stochastic differential equation making $V(t)$ a continuous, but not a differentiable function of time. The presynaptic spike trains to the excitatory and inhibitory synapses are now assumed to be independent processes so that the differentials dW_e and dW_i are independent Gaussian processes. With this assumption in place

$$a_e\sqrt{R_e}\big(V - E_e\big)\,dW_e(t) + a_i\sqrt{R_i}\big(V - E_i\big)\,dW_i(t)$$

is the sum of two independent Gaussian random variables and is therefore a Gaussian process with expected value zero and variance $\sigma^2(V)\,dt$ where

$$\begin{aligned} \sigma(V) &= \sqrt{a_e^2 R_e (V - E_e)^2 + a_i^2 R_i (V - E_i)^2} \\ &= \sqrt{\big(a_e^2 R_e + a_i^2 R_i\big)}\,\sqrt{(V - E_S)^2 + E_D^2} \end{aligned} \tag{2.10}$$

and the potentials E_S (mV) and E_D (mV) are defined by

$$E_S = \frac{a_e^2 R_e E_e + a_i^2 R_i E_i}{a_e^2 R_e + a_i^2 R_i}\,, \qquad E_D = \frac{a_i a_e \sqrt{R_e R_i}\,\big|E_e - E_i\big|}{a_e^2 R_e + a_i^2 R_i}\,. \tag{2.11}$$

The outcome of this calculation is that equation (2.9) simplifies to

$$dV = -\Big[\frac{g_m}{c_m}\big(V - E_m\big) + a_e R_e\big(V - E_e\big) + a_i R_i\big(V - E_i\big)\Big]\,dt + \sigma(V)\,dW(t)\,. \tag{2.12}$$

The constants τ and E with respective values

$$\tau = \frac{1}{g_m/c_m + a_e R_e + a_i R_i}\,, \qquad E = \frac{g_m E_m/c_m + a_e R_e E_e + a_i R_i E_i}{g_m/c_m + a_e R_e + a_i R_i} \tag{2.13}$$

are now introduced into (2.12) to obtain the final stochastic differential equation

$$dV = -\frac{(V - E)\,dt}{\tau} + \sigma(V)\,dW(t) \tag{2.14}$$

where $dW(t)$ is the differential of the Wiener process. As mentioned previously, the overall effect of the stochastic procedure is to replace a membrane potential that is a piecewise continuous function of time by a membrane potential that is a continuous function of time.

2.4 Stationary distribution of membrane potential

It is proved in the Appendix that the transitional probability density function $f(v,t|V_0,t_0)$ of the process described by the stochastic differential equation

$$dv = \mu(v)\,dt + \sigma(v)\,dW\,, \qquad v(t_0) = V_0 \tag{2.15}$$

with drift specification $\mu(v)$ and diffusion $\sigma^2(v)$ satisfies the Fokker-Planck equation

$$\frac{\partial f}{\partial t} = -\frac{\partial J}{\partial v}\,, \qquad J = \mu(v)f - \frac{1}{2}\frac{\partial(\sigma^2(v)f)}{\partial v} \tag{2.16}$$

where J is the flux of probability density. The process (2.15) has a stationary distribution provided it is possible to find a probability density function $f(v)$ for which $J(v)$ is a piecewise constant function. The explicit form for J in Richardson's problem is

$$-\tau J(v) = \frac{1}{\gamma}\frac{\partial}{\partial v}\Big[\Big(\big(v-E_S\big)^2 + E_D^2\Big)f\Big] + \big(V-E\big)f \tag{2.17}$$

where

$$\gamma = \frac{2\big(g_m/c_m + a_eR_e + a_iR_i\big)}{a_e^2R_e + a_i^2R_i}\,. \tag{2.18}$$

The firing rate R of the neuron when the membrane potential has attained its stationary state is the value of the flux of probability at the threshold potential $V_{\rm thr}$. To conserve probability density in this system, the flux of probability crossing the threshold potential $V_{\rm thr}$ is instantaneously restored at the potential $V_{\rm res}$. This criterion applies independently on whether or not the membrane potential has reached its stationary state, but when stationarity has been attained, the flux condition is satisfied immediately by the condition $J = R$ for $v \in (V_{\rm res}, V_{\rm thr})$. Elsewhere $J = 0$, and so the stationary probability density of membrane potential satisfies the ordinary differential equation

$$\frac{1}{\gamma}\frac{d}{dv}\Big[\Big(\big(v-E_S\big)^2 + E_D^2\Big)f\Big] + \big(v-E\big)f = \left[\begin{array}{ll} 0 & v \le V_{\rm res} \\ & \\ -\tau R & V_{\rm res} \le v \le V_{\rm thr} \end{array}\right. \tag{2.19}$$

where the constant value of R is chosen to enclose unit probability density in $(-\infty, V_{\rm thr})$. Richardson takes $V_{\rm thr} = -55$mV and $V_{\rm res} = -65$mV.

To solve equation (2.19) for the stationary density $f(V)$, Richardson changes the independent variable from V to x where

$$v = E + x\,\alpha\,\sqrt{(E-E_S)^2 + E_D^2}\,, \qquad \alpha = \frac{1}{\sqrt{\gamma}}\,. \tag{2.20}$$

It a straightforward exercise to show that $f_X(x)$, the stationary density of X, satisfies the ordinary differential equation

$$\frac{d}{dx}\Big[\big(\alpha^2x^2 - 2\alpha\beta x + 1\big)f_X\Big] + xf_X = -\tau RH(x - x_{\rm res}) \tag{2.21}$$

where $H(x)$ is the Heaviside function and

$$\beta = \frac{(E_S - E)}{\sqrt{(E_S - E)^2 + E_D^2}}\,. \tag{2.22}$$

Integration of equation (2.21) produces

$$f_X(x) = e^{-\int_{x_{\rm res}}^{x}\phi(u)\,du}\Big[C + \int_x^{x_{\rm thr}} \psi(s)e^{\int_{x_{\rm res}}^{s}\phi(u)\,du}\,ds\Big] \tag{2.23}$$

where C is a constant of integration and the functions $\phi(x)$ and $\psi(x)$ are defined by

$$\phi(x) = \frac{(2\alpha^2 + 1)x - 2\alpha\beta}{\alpha^2x^2 - 2\alpha\beta x + 1}\,, \qquad \psi(x) = -\frac{\tau RH(x - x_{\rm res})}{\alpha^2x^2 - 2\alpha\beta x + 1}\,. \tag{2.24}$$

However $f(x_{\rm thr}) = 0$ since the process cannot reside at the threshold potential. Restoration to $x_{\rm res}$ is instantaneous and therefore $C = 0$ in expression (2.23). Thus the simplified form of $f_X(x)$ is

$$f_X(x) = e^{\int_{x_{res}}^{x}}\phi(u)\,du \int_x^{x_{\rm thr}} \psi(s)e^{-\int_s^x \phi(u)\,du}\,ds\,. \tag{2.25}$$

In terms of the function $\Delta(x)$ defined by

$$\Delta(x) = \frac{1+\gamma}{2}\log\Big[(\alpha x - \beta)^2 + (1 - \beta^2)\Big] + \frac{\beta\gamma}{\sqrt{1-\beta^2}}\tan^{-1}\Big(\frac{\alpha x - \beta}{\sqrt{1-\beta^2}}\Big)\,,$$

it is straightforward to show that $\phi(x) = d\Delta(x)/dx$ from which it follows that $f_X(x)$ can be expressed in the more compact form

$$f_X(x) = \tau Re^{-\Delta(x)}\int_x^{x_{\rm thr}} \frac{H(s - x_{\rm res})\,e^{\Delta(s)}\,ds}{(\alpha s - \beta)^2 + (1 - \beta^2)}\,ds$$

which simplifies further to give

$$f_X(x) = \tau Re^{-\Delta(x)}\left[\begin{array}{ll} \displaystyle\int_x^{x_{\rm thr}} \frac{e^{\Delta(s)}\,ds}{(\alpha s - \beta)^2 + (1 - \beta^2)} & x \in (x_{\rm res}, x_{\rm thr}) \\ \displaystyle\int_{x_{\rm res}}^{x_{\rm thr}} \frac{e^{\Delta(s)}\,ds}{(\alpha s - \beta)^2 + (1 - \beta^2)} & x \in (-\infty, x_{\rm res})\,. \end{array}\right. \tag{2.26}$$

The spiking rate R is determined from expression (2.26) by requiring $f_X(x)$ to be a probability density, that is,

$$\frac{1}{\tau R} = \int_{-\infty}^{x_{\rm thr}} e^{-\Delta(x)}\Big(\int_x^{x_{\rm thr}} \frac{H(s - x_{\rm res})e^{\Delta(s)}\,ds}{(\alpha s - \beta)^2 + (1 - \beta^2)}\Big)\,dx\,. \tag{2.27}$$

By this procedure, a closed form expression for the spike rate R is determined in terms of a double integral. The computation of the value of this integral is not straightforward, and so another approach based on the solution of a system of ordinary differential equations is described.

2.4.1 Shooting method to find the spike rate

The spike rate R is now determined by a shooting procedure involving the solution of a pair of ordinary differential equations. The cumulative function $F(v)$ of the probability density function $f(v)$ is defined by the formula

$$F(v) = \int_v^{V_{\text{thr}}} f(x)\, dx$$

and satisfies the conditions

$$F(V_{\text{thr}}) = 0\,, \qquad \frac{dF}{dv} = -f(v)\,, \qquad \lim_{v \to -\infty} F(v) = 1\,.$$

The problem of determining the value of R is now reformulated in terms of the problem of finding the solution of the system of differential equations

$$\begin{aligned} \frac{dF}{dv} &= -f(v)\,, \\ \frac{df}{dv} &= \left[\begin{array}{ll} \dfrac{-\tau\,\gamma\,R - f\,[\gamma\,(v-E) + 2\,(v-E_S)]}{(v-E_S)^2 + E_D^2} & v > V_{\text{res}} \\ \dfrac{-f\,[\gamma\,(v-E) + 2\,(v-E_S)]}{(v-E_S)^2 + E_D^2} & v < V_{\text{res}}\,. \end{array} \right. \end{aligned} \tag{2.28}$$

satisfying the initial conditions $F(V_{\text{thr}}) = f(V_{\text{thr}}) = 0$ and is such that $F(v) \to 1$ as $t \to \infty$. The value of R is obtained by the following iterative procedure.

(a) Guess a value of R and choose a value of v, say V_{low}, that is a sufficientlty low potential as to be effectively negative infinity.

(b) Given a value of R, integrate equations (2.28) from $v = V_{\text{thr}}$ to $v = V_{\text{res}}$.

(c) One of the differential equations is modified by the absence of probability flux, but f and F remain continuous. The final values of the integration in item (b) provide the initial values for the integration of the equations from $v = V_{\text{res}}$ to $v = V_{\text{low}}$.

(d) At $v = V_{\text{low}}$ the value of $F(V_{\text{low}})$ is compared with one and the value of R is adjusted in a shooting procedure to converge $F(V_{\text{low}})$ to one. This the iterative procedure either terminates now and the final value of R is the estimate of the spike rate, or alternatively, a new valuer of R is computed and the calculation returns to step (b) and repeats.

2.5 Richardson's conclusions

The comparison of the response of the conductance based model (IF_g) and the current based model (IF_I) to step current injection, leads to the conclusion that the former captures many of the response properties that are missed by the later, such as reduced membrane fluctuations, a shortened time constant and suppressed response to injected current.

Richardson also investigates the behavior of these models for achieving an increase in the firing rate. For the conductance-based model this is possible through three different ways

1. Increasing the excitatory drive.
2. Increasing the excitatory drive but at the same time decreasing the inhibitory drive.
3. Decreasing the inhibitory drive.

For the current-based model under similar circumstances the firing rate would be expected to grow linearly with E for strong drive. A similar response is seen for case 2 where the conductance remains constant due to balanced input. For case 1 the increased excitatory drive leads to a smaller time constant that means a faster increase in the firing rate. Finally, for case 3, decreasing inhibition leads to an increased time constant that means a decrease in the firing rate.

There is also a comparison of the response of the two models subject to correlated synaptic input. For the current model (IF_I) there is a high frequency response as compared to the same model subject to white-noise drive. The conductance (IF_g) model on the other hand when subject to temporally correlated input exhibits voltage fluctuations with the same statistics as those seen in real-life neurons. The form of the filtered synaptic input is

$$\frac{dg_e}{dt} = \frac{g_{e0} - g_e}{\tau_e} + \sigma_e \sqrt{\frac{2}{\tau_e}}\, \xi_e(t) \tag{2.29}$$

where τ_e is the filtering constant, g_{e0} is the tonic conductance, σ_e the standard deviation and ξ_e is a δ correlated white-noise process. The corresponding equation for the voltage is

$$\tau_0 \frac{dV}{dt} = -(V - E) - u_e(t)\,(E_0 - E_e) - u_i(t)\,(E_0 - E_i) \tag{2.30}$$

where

$$\tau_0 = \frac{C}{g_L + g_{e0} + g_{i0}}, \qquad E_0 = \frac{g_L\, E_L + g_{e0}\, E_e + g_{i0}\, E_i}{g_L + g_{e0} + g_{i0}}. \tag{2.31}$$

The fluctuating part can easily be abstracted from equation (2.29) to be

$$u_e(t) \;=\; \frac{\sigma_e \tau_0}{C}\sqrt{\frac{2}{\tau_e}} \int_{-\infty}^{t} e^{(t-s)/\tau_e}\, \xi_e(s)\, ds\,. \tag{2.32}$$

The expressions for the mean and the variance can be calculated from either the expansion of the full solution

$$V(t) = \frac{1}{C}\int_{-\infty}^{t} e^{\int_s^t i\, dr/\tau(r)} \big[g_L\, E_L + g_e(s)\, E_e + g_i(s)\, E_i\big]\, ds \tag{2.33}$$

where $\tau(r) = C/\big(g_L + g_e(r) + g_i(r)\big)$, or by taking moments of the corresponding Fokker-Planck equation (the method used in the Appendix). Such results agree with the Gaussian or effective time constant approximation.

Generally the comparison between the current (IF_I) model and the conductance (IF_g) model demonstrated that a current-based model with a drive dependent time constant provides a simple and accurate description of biologically relevant models of neuronal response to conductance-based synaptic input.

Chapter 3

Rudolph and Destexhe's model

3.1 Introduction

Rudolph and Destexhe (2003, 2005) characterize the subthreshold behavior of neuronal models in which synaptic noise is represented by either additive (current) or multiplicative (conductance) noise described by the Ornstein-Uhlenbeck (OU) process. They derive the Fokker-Planck equation describing the time evolution of the transitional probability density function for the membrane potential. They obtain an analytic expression for the distribution of membrane potentials at steady state and compare this result with that of the Hodgkin-Huxley model. By comparing these distributions for current-based and conductance-based models of synaptic activity, they suggest that the conductance-based model is adequate to describe the behavior of real neurons. They state that the distribution of the steady-state membrane potential is easily obtained experimentally, and therefore their method provides a possible way to estimate the mean and the variance of synaptic conductances in real neurons.

Rudolph and Destexhe (2005) re-examined their expression for the distribution of the steady-state membrane potential and state that it differs from the numerical solution because only expected values of the differentials of the stochastic variables were taking into account in the solution procedure, and then suggest a procedure which corrects for these deviations. Their analysis leads to an extended analytic solution for the distribution of the membrane potential that is valid for a parameter regime covering several orders of magnitude of physiologically realistic values.

Rudolph and Destexhe (2003, 2005) develop the work of Richardson (2004) by generalising the specification of the synaptic conductance used in equation (1.16) describing the time course of the membrane potential, namely

$$c_m \frac{dV}{dt} = -g_m\big(V - E_m\big) - g_e(t)\big(V - E_e\big) - g_i(t)\big(V - E_i\big) - I_{\rm ex}(t) \tag{3.1}$$

where $g_e(t)$ and $g_i(t)$ describe respectively the time courses of the conductances of the excitatory and inhibitory synapses, E_e and E_i are the respective reversal potentials for the ionic species of these synapses and $I_{\rm ex}(t)$ is exogenous current describing all unidentified synaptic currents.

The arrival times of the action potentials in a train of action potentials are stochastic, and this in turn causes the conductance of each synapse to behave as a random process. Richardson (2004) assumed that each presynaptic spike, on arrival at the synaptic bouton, produced a spike of conductance which in turn induced an instantaneous jump in membrane potential. In the Richardson model, the conductance of a synapse returns instantaneously to zero after the arrival of a presynaptic spike and stays there until the arrival of the next presynaptic spike, and so no history of the spike activity at that synapse is recorded in the time course of its conductance. The procedure of using the central limit theorem to approximate large scale synaptic activity by a Gaussian process simply smooths the membrane potential as a function of time but fails to generate synaptic input which retains some memory for the presynaptic events at the synapse.

In order to incorporate temporal correlation into synaptic conductance, Rudolph and Destexhe (2003) argue that the time courses of the total conductances $g_e(t)$ and $g_i(t)$ of large pools of independently functioning excitatory synapses and inhibitory synapses behave like solutions of the Ornstein-Uhlenbeck (OU) processes

$$\begin{aligned} dg_e(t) &= -\big(g_e(t) - G_e\big)\,\frac{dt}{\tau_e} + \sigma_e\, dW_e(t)\,, \\ dg_i(t) &= -\big(g_i(t) - G_i\big)\,\frac{dt}{\tau_i} + \sigma_i\, dW_i(t)\,, \end{aligned} \tag{3.2}$$

in which the parameters τ_e, τ_i (msec), G_e, G_i, (mS/cm^2), σ_e and σ_i are the respective volatilities of the excitatory and inhibitory synapses. In equations (3.2) τ_e, τ_i (msec) are the respective time constants for the decay of the conductances of excitatory and inhibitory synapses, G_e, G_i, (mS/cm^2) are respectively the average conductance of these synapses and D_e and D_i (mS/sec$^{1/2}$) are their respective noise diffusion coefficients.

Rudolph and Destexhe (2003) similarly propose that the exogenous current $I_{\rm ex}(t)$ in equation (3.1) introduced to describe unidentified background synaptic activity follows the OU process

$$dI(t) = -\big(I(t) - I_0\big)\,\frac{dt}{\tau_{\rm I}} + \sigma_{\rm I}\, dW_{\rm I}(t) \tag{3.3}$$

where I_0 is the mean background synaptic current, $\tau_{\rm I}$ is the time constant for the decay of this current to its mean value I_0, $D_{\rm I}$ is the associated noise diffusion coefficient and $dW_{\rm I}(t)$ is the increment in the Wiener process $W_{\rm I}(t)$. Let

$$\widetilde{g}_e(t) = g_e(t) - G_e\,, \quad \widetilde{g}_i(t) = g_i(t) - G_i\,, \quad \widetilde{I}_{\rm ex}(t) = I_{\rm ex}(t) - I_0 \tag{3.4}$$

then $\widetilde{g}_e(t)$, $\widetilde{g}_i(t)$ and $\widetilde{I}_{\rm ex}(t)$ satisfy the stochastic differential equations

$$\begin{aligned} d\widetilde{g}_e &= -\frac{dt}{\tau_e}\,\widetilde{g}_e + \sigma_e\,dW_e\,, \\ d\widetilde{g}_i &= -\frac{dt}{\tau_i}\,\widetilde{g}_i + \sigma_i\,dW_i\,, \\ d\widetilde{I}_{\rm ex} &= -\frac{dt}{\tau_{\rm I}}\,\widetilde{I}_{\rm ex} + \sigma_{\rm I}\,dW_{\rm I} \end{aligned} \tag{3.5}$$

where $D_e\,\tau_e = 2\sigma_e^2$, $D_i\,\tau_i = 2\sigma_i^2$ and $D_{\rm I}\,\tau_{\rm I} = 2\sigma_{\rm I}^2$. When the conductances g_e and g_i are expressed in terms of the zero-mean processes $\widetilde{g}_e(t)$, $\widetilde{g}_i(t)$ and $\widetilde{I}_{\rm ex}(t)$ introduced in definitions (3.4), equation (3.1) for the membrane potential takes the form

$$\begin{aligned} c_m\frac{dV}{dt} &= -g_m\big(V - E_m\big) - \widetilde{g}_e(t)\big(V(t) - E_e\big) - \widetilde{g}_i(t)\big(V(t) - E_i\big) - \widetilde{I}_{\rm ex}(t) \\ &\qquad -G_e\big(V - E_e\big) - G_i\big(V - E_i\big) - I_0 \end{aligned} \tag{3.6}$$

which simplifies in turn to the Langevin equation

$$\frac{dV}{dt} = f(V) + h_e(V)\,\widetilde{g}_e(t) + h_i(V)\,\widetilde{g}_i(t) + \beta\,\widetilde{I}_{\rm ex}(t) \tag{3.7}$$

where $\beta = 1/c_m$ and the functions $f(V)$, $h_e(V)$ and $h_i(V)$ are defined by the formulae

$$f(V) = \alpha\,\big(E_0 - V\big)\,, \qquad h_e(V) = \beta\,\big(E_e - V\big)\,, \qquad h_i(V) = \beta\,\big(E_i - V\big) \tag{3.8}$$

in which the constant α and potential E_0 are respectively

$$\alpha = \frac{g_m + G_e + G_i}{c_m}\,, \qquad E_0 = \frac{g_m E_m + G_e\,E_e + G_i\,E_i - I_0}{g_m + G_e + G_i}\,. \tag{3.9}$$

Rudolph and Destexhe (2003) assert that equation (3.7) has no simple closed-form solution due to the presence of stochastic terms. They then proceed to use stochastic Calculus to show that equation (3.7) can be interpreted as the Stratonovich stochastic differential equation

$$dV = f(V)\,dt + \sigma(V) \circ dW \tag{3.10}$$

with diffusion

$$\sigma^2(V) = h_e^2(V)\,\sigma_e^2 + h_i^2(V)\,\sigma_i^2 + \beta^2\sigma_{\rm I}^2\,. \tag{3.11}$$

The notation $\sigma \circ dW$ is conventionally used to indicate that a stochastic differential equation is to be interpreted as a Stratonovich equation as opposed to an Ito equation. The difference between these specifications lies in that fact that the Stratonovich representation of a stochastic process is anticipatory whereas the equivalent Ito representation is not anticipatory. In particular, the solution of the Stratonovich equation (3.10) is identical to that of the Ito equation

$$dV = \Big(f(V) + \frac{\sigma(V)}{2}\,\frac{d\sigma(V)}{dV}\Big)\,dt + \sigma(V)\,dW\,. \tag{3.12}$$

It follows directly from the Fokker-Planck equation for this Ito stochastic differential equation that the transitional probability density function $\rho(V,t)$ associated with equation (3.10) satisfies the Fokker-Planck equation

$$\frac{\partial \rho}{\partial t} + \frac{\partial q}{\partial V} = 0 \tag{3.13}$$

where the probability flux q is defined in terms of $f(V)$ and $\sigma(V)$ by

$$q = f(V)\rho - \frac{\sigma(V)}{2}\,\frac{\partial\big(\sigma(V)\,\rho\big)}{\partial V}\,. \tag{3.14}$$

In general the stationary distribution of the membrane potential is obtained by solving the ordinary differential equation $q =$ constant with the constant of integration determined by the requirement that the probability density function encloses unit probability mass. The stationary flux of probability density can be non-zero if the sample space of the membrane potential is finite, for example, when a threshold potential is imposed and the neuron generates an action potential and is then discharged. On the other hand, if the sample space of the membrane potential is unrestricted then the stationary probability flux is necessarily zero. The stationary probability density function for the membrane potential is now determined by integrating equation (3.14) with $q = 0$ to obtain

$$\rho = \frac{A}{\sigma(V)}\,\exp\Big[\int_{-\infty}^{V} \frac{2f(s)\,ds}{\sigma^2(s)}\Big]\,. \tag{3.15}$$

The constant A is obtained by requiring that $\rho(V)$ encloses unit probability mass. The argument proposed by Rudolph and Destexhe (2003) as the basis for assuming equation (3.10) is now described in detail.

3.1.1 Derivation of the SDE satisfied by the membrane potential

Rudolph and Destexhe (2003) begin their analysis of equation (3.7) by introducing the "integrated OU process"

$$w(t) = \int_0^t g(s)\,ds \tag{3.16}$$

where $g(s)$ is the solution of a zero-mean OU process. In terms of the integrated OU processes $w_e(t)$ for $g_e(t)$, $w_i(t)$ for $g_i(t)$ and $w_{\rm I}(t)$ for $g_{\rm I}(t)$, the formal solution of equation (3.7) now becomes

$$V(t)-V(0)=\int_0^t f(V)\,ds+\int_0^t h_e(V)\,dw_e(s)+\int_0^t h_i(V)\,dw_i(s)+\beta\,w_{\rm I}(t)\,. \qquad (3.17)$$

The right hand side of this equation consists of a Riemann integral of the drift term $f(V)$ with the remaining stochastic integrals expressed as Riemann-Stieltjes integrals.

Consider now the computation of the Riemann-Stieltjes integrals

$$S^{(1)}=\int_0^t h_e(V)\,dw_e(s)\,,\qquad S^{(2)}=\int_0^t h_i(V)\,dw_i(s) \qquad (3.18)$$

where V is the solution of equation (3.7) and $w_e(s), w_i(s)$ are integrated OU processes with zero mean. Let $0=t_0<t_1<\cdots<t_n=t$ be a dissection $\mathcal{D}_n$ of $[0,t]$ and let $S_n^{(1)}$ and $S_n^{(2)}$ be the Riemann-Stieltjes partial sums for the integrands of (3.18) over $\mathcal{D}_n$. *i.e.*

$$\begin{aligned}
S_n^{(1)} &= \sum_{k=1}^n h_e(V(\tau_k))\big(w_e(t_k)-w_e(t_{k-1})\big)\\
S_n^{(2)} &= \sum_{k=1}^n h_i(V(\tau_k))\big(w_i(t_k)-w_i(t_{k-1})\big)\,.
\end{aligned}$$

Given an arbitrary differentiable function $h(V)$, the first task is to expand this function by Taylor's theorem about $V=V_{k-1}$ to obtain

$$h(V(\tau_k))=h(V_{k-1})+\big(V(\tau_k)-V(t_{k-1})\big)\frac{dh(V_{k-1})}{dV}+O\big(V(\tau_k)-V(t_{k-1})\big)^2\,.$$

The quantity $V(\tau_k)-V(t_{k-1})$ is now replaced by the differential form of equation (3.17) to get

$$\begin{aligned}
h(V(\tau_k)) &= h(V_{k-1})+\frac{dh(V_{k-1})}{dV}\Big[f(V_{k-1})\big(\tau_k-t_{k-1}\big)+h_e(V(t_{k-1}))\big(w_e(\tau_k)-w_e(t_{k-1})\big)\\
&\qquad +h_i(V(t_{k-1}))\big(w_i(\tau_k)-w_i(t_{k-1})\big)+\beta\,w_{\rm I}(t)\Big]+O(dt)^2
\end{aligned}$$

taking account of the fact that $dV=O(dt)$. This expansion is now used with $h=h_e$ to replace $h_e(V(\tau_k))$ in the expression for $S_n^{(1)}$ and with $h=h_i$ to replace $h_i(V(\tau_k))$ in the expression for $S_n^{(2)}$ to obtain

$$\begin{aligned}
S_n^{(1)} &= \sum_{k=1}^{n} \Big[h_e(V(t_{k-1})) + \frac{dh_e(V(t_{k-1}))}{dV} \Big[f(V(t_{k-1}))\,\big(\tau_k - t_{k-1}\big) \\
&\qquad + h_e(V(t_{k-1}))\,\big(w_e(\tau_k) - w_e(t_{k-1})\big) + h_i(V(t_{k-1}))\,\big(w_i(\tau_k) - w_i(t_{k-1})\big) \\
&\qquad\quad - \beta\, w_{\mathrm{I}}(t) \Big]\Big]\,\big(w_e(t_k) - w_e(t_{k-1})\big) + O(dt^2)\,, \\
S_n^{(2)} &= \sum_{k=1}^{n} \Big[h_i(V(t_{k-1})) + \frac{dh_i(V(t_{k-1}))}{dV} \Big[f(V(t_{k-1}))\,\big(\tau_k - t_{k-1}\big) \\
&\qquad + h_e(V(t_{k-1}))\,\big(w_e(\tau_k) - w_e(t_{k-1})\big) + h_i(V(t_{k-1}))\,\big(w_i(\tau_k) - w_i(t_{k-1})\big) \\
&\qquad\quad - \beta\, w_{\mathrm{I}}(t) \Big]\Big]\,\big(w_i(t_k) - w_i(t_{k-1})\big) + O(dt^2)\,.
\end{aligned}$$

Since these sums involve stochastic terms, the limiting process must be taken in the mean-square sense, that is, the limiting value $S^{(1)}$ of $S_n^{(1)}$ and $S^{(2)}$ of $S_n^{(2)}$ satisfy

$$\lim_{n\to\infty} \mathrm{E}\Big[\,\big(S_n^{(1)} - S^{(1)}\,\big)^2\,\Big] = 0\,, \qquad \lim_{n\to\infty} \mathrm{E}\Big[\,\big(S_n^{(2)} - S^{(2)}\,\big)^2\,\Big] = 0\,.$$

The previous expressions for $S_n^{(1)}$ and $S_n^{(2)}$ may be further simplified by taking account of the fact that w_e and w_i are uncorrelated processes, and by ignoring contributions to $S_n^{(1)}$ and $S_n^{(2)}$ that are $o(dt)$. When these considerations are taken into account, the expressions for $S_n^{(1)}$ and $S_n^{(2)}$ further simplify to give

$$\begin{aligned}
S_n^{(1)} &= \sum_{k=1}^{n} h_e(V(t_{k-1}))\,\big(w_e(t_k) - w_e(t_{k-1})\big) + o(dt) \\
&\qquad + \frac{1}{2}\sum_{k=1}^{n} \frac{dh_e^2(V(t_{k-1}))}{dV}\,\big(w_e(\tau_k) - w_e(t_{k-1})\big)\,\big(w_e(t_k) - w_e(t_{k-1})\big)\,, \\
S_n^{(2)} &= \sum_{k=1}^{n} h_i(V(t_{k-1}))\,\big(w_i(t_k) - w_i(t_{k-1})\big) + o(dt) \\
&\qquad + \frac{1}{2}\sum_{k=1}^{n} \frac{dh_i^2(V(t_{k-1}))}{dV}\,\big(w_i(\tau_k) - w_i(t_{k-1})\big)\,\big(w_i(t_k) - w_i(t_{k-1})\big)\,.
\end{aligned} \tag{3.19}$$

Further progress with equations (3.19) requires the computation of

$$\mathrm{E}\,\big[\,\big(w(\tau_k) - w(t_{k-1})\big)\,\big(w(t_k) - w(t_{k-1})\big)\,\big] = \int_{t_{k-1}}^{\tau_k}\int_{t_{k-1}}^{t_k} \mathrm{E}\,[g(u)g(s)]\,du\,ds$$

where $w(t)$ is the integrated OU process defined from $g(t)$. It follows from the correlation properties of the zero-mean OU process that

$$\begin{aligned}
&\frac{\sigma^2}{2}\int_{t_{k-1}}^{\tau_k}\Big(\int_{t_{k-1}}^{t_k} e^{-\alpha|u-s|}\,du\Big)\,ds \\
&\quad = \frac{\sigma^2}{2}\int_{t_{k-1}}^{\tau_k}\Big(\int_{\tau_k}^{t_k} e^{-\alpha(u-s)}\,du\Big)\,ds + \frac{\sigma^2}{2}\int_{t_{k-1}}^{\tau_k}\Big(\int_{t_{k-1}}^{\tau_k} e^{-\alpha|u-s|}\,du\Big)\,ds \\
&\quad = \frac{\sigma^2}{2\alpha^2}\Big[2\alpha(\tau_k - t_{k-1}) + e^{-\alpha(t_k - t_{k-1})} + e^{-\alpha(\tau_k - t_{k-1})} - e^{-\alpha(t_k - \tau_k)} - 1\Big]\,.
\end{aligned}$$

To make further progress, Rudolph and Destexhe (2003) suggest that the contributions from the terms with $w = w_e$ and $w = w_i$ should be approximated by $2a_e(t_{k-1})(\tau_k - t_{k-1})$ and $2a_i(t_{k-1})(\tau_k - t_{k-1})$ respectively where

$$\begin{aligned} 2a_e(t) &= \sigma_e^2\tau_e\big(1 - e^{-t/\tau_e}\big) + \frac{\tilde{w}_e^2(t)}{2\tau_e} - \sigma_e^2\, t\,, \\ 2a_i(t) &= \sigma_i^2\tau_i\big(1 - e^{-t/\tau_i}\big) + \frac{\tilde{w}_i^2(t)}{2\tau_i} - \sigma_i^2\, t\,. \end{aligned} \tag{3.20}$$

They state that this is equivalent to treating the integrals (3.18) as Ito integrals rather than Riemann-Stieltjes integrals. With this interpretation, equations (3.19) become

$$\begin{aligned} S_n^{(1)} &= \sum_{k=1}^{n} h_e(V(t_{k-1}))\,\big(w_e(t_k) - w_e(t_{k-1})\big) + o(dt) \\ &\qquad + \sum_{k=1}^{n} a_e(t_{k-1})\,\frac{dh_e^2(V(t_{k-1}))}{dV}\,\big(\tau_k - t_{k-1}\big)\,, \\ S_n^{(2)} &= \sum_{k=1}^{n} h_i(V(t_{k-1}))\,\big(w_i(t_k) - w_i(t_{k-1})\big) + o(dt) \\ &\qquad + \sum_{k=1}^{n} a_i(t_{k-1})\,\frac{dh_i^2(V(t_{k-1}))}{dV}\,\big(\tau_k - t_{k-1}\big)\,. \end{aligned} \tag{3.21}$$

When these result are applied to equation (3.7), the conclusion is that

$$\begin{aligned} dV &= \Big[f(V) + a_e(t)h_e(V)\frac{dh_e(V)}{dV} + a_i(t)h_i(V)\frac{dh_i(V)}{dV}\Big]\,dt \\ &\qquad + h_e(V)dw_e(t) + h_i(V)\,dw_i(t) + \beta\,dw_{\mathrm{I}}(t)\,. \end{aligned} \tag{3.22}$$

This expression for dV is now used to expand any given arbitrary function $F(V)$ to obtain

$$\begin{aligned} dF &= \frac{dF}{dV}\,dV + \frac{1}{2}\,\frac{d^2F}{dV^2}(dV)^2 + o(dV^3) \\ &= \frac{dF}{dV}\Big[f(V)dt + h_e(V)\,dw_e + h_i(V)\,dw_i + \beta\,dw_I + \frac{\alpha_e}{2}\,\frac{dh_e^2(V)}{dV}\,dt + \frac{a_i}{2}\,\frac{dh_i^2(V)}{dV}\,dt\Big] \\ &\qquad + \frac{1}{2}\,\frac{d^2F}{dV^2}\,\Big[h_e^2(V)\,dw_e^2 + h_i^2(V)\,dw_i^2 + 2h_e(V)\,h_i(V)\,dw_e\,dw_i\Big]\,. \end{aligned}$$

Taking into account the fact that

$$dw_e^2 = 2\alpha_e\,dt + o(dt)\,,\quad dw_i^2 = 2\alpha_i\,dt + o(dt)\,,\quad dw_I^2 \;=\; 2\alpha_I\,dt + o(dt)\,,\quad dw_e\,dw_i = o(dt)\,.$$

The previous equations may be written in the form

$$\begin{aligned} dF &= \Big[\frac{dF}{dV}\Big(f + \alpha_e h_e\frac{dh_e}{dV} + \alpha_i h_i\,\frac{dh_i}{dV}\Big) + \frac{d^2F}{dV^2}\Big(h_e^2\,\alpha_e + h_i^2\,\alpha_i + \beta^2\alpha_I\Big)\Big]\,dt \\ &\qquad + \frac{dF}{dV}\Big(h_e\,dw_e + h_i\,dw_i + \beta\,dw_I\Big)\,. \end{aligned} \tag{3.23}$$

The Fokker-Planck equation satisfied by the transitional density $\rho(V,t)$ is obtained from the identity

$$\int F(V)\,\frac{\partial\rho(V,t)}{\partial t}\,dV = \frac{d\,\mathrm{E}\,[F(V)]}{dt} = \mathrm{E}\Big[\frac{dF}{dt}\Big] = \int \mathrm{E}\Big[\frac{dF(V)}{dt}\Big]\,\rho(V,t)\,dV \tag{3.24}$$

where $F(V)$ is an arbitrary function of V satisfying suitably differentiability conditions. It follows directly from equation (3.23) that

$$\mathrm{E}\Big[\frac{dF}{dt}\Big] = \frac{dF}{dV}\Big(f + \alpha_e h_e \frac{dh_e}{dV} + \alpha_i h_i \frac{dh_i}{dV}\Big) + \frac{d^2F}{dV^2}\Big(h_e^2\,\alpha_e + h_i^2\,\alpha_i + \beta^2\alpha_I\Big)\,.$$

This result is now used in equation (3.24) to obtain

$$\begin{aligned}&\int \mathrm{E}\Big[\frac{dF(V)}{dt}\Big]\,\rho(V,t)\,dV\\ &\qquad = \int \Big[\frac{dF}{dV}\Big(f(V) + \alpha_e\,h_e\frac{dh_e}{dV} + \alpha_i\,h_i\frac{dh_i}{dV}\Big) + \frac{d^2F}{dV^2}\Big(h_e^2\,\alpha_e + h_i^2\,\alpha_i + \beta^2\,\alpha_I\Big)\Big]\rho\,dV\,.\end{aligned}$$

Integration by parts, applied to the second term of the right hand side of the previous equation, yields

$$\begin{aligned}&\int \mathrm{E}\Big[\frac{dF(V)}{dt}\Big]\,\rho(V,t)\,dV\\ &\qquad = \int \frac{dF}{dV}\Big(f(V) + \alpha_e\,h_e\frac{dh_e}{dV} + \alpha_i\,h_i\frac{dh_i}{dV}\Big)\rho\,dV + \Big[\frac{dF}{dV}\Big(h_e^2\,\alpha_e + h_i^2\,\alpha_i + \beta^2\,\alpha_I\Big)\rho\Big]\\ &\qquad\qquad - \int \frac{dF}{dV}\,\frac{\partial}{\partial V}\Big(\big(h_e^2\,\alpha_e + h_i^2\,\alpha_i + \beta^2\,\alpha_{\mathrm{I}}\big)\rho\Big)\,dV\,.\end{aligned}$$

The boundary term vanishes on the right hand side of the previous equation and the integrals can be combined to give

$$\begin{aligned}&\int \mathrm{E}\Big[\frac{dF(V)}{dt}\Big]\,\rho(V,t)\,dV\\ &\qquad = \int \frac{dF}{dV}\,\Big[\Big(f(V) - \alpha_e\,h_e\frac{dh_e}{dV} - \alpha_i\,h_i\frac{dh_i}{dV}\Big)\rho - \Big(h_e^2\,\alpha_e + h_i^2\,\alpha_i + \beta^2\,\alpha_{\mathrm{I}}\Big)\frac{\partial\rho}{\partial V}\,\Big]\,dV\,.\end{aligned}$$

A further integration by parts applied to the integral on the right hand side of the previous equation gives

$$\begin{aligned}&\int \mathrm{E}\Big[\frac{dF(V)}{dt}\Big]\,\rho(V,t)\,dV\\ &\qquad = \int F(V)\,\frac{\partial}{\partial V}\Big[\Big(h_e^2\,\alpha_e + h_i^2\,\alpha_i + \beta^2\,\alpha_{\mathrm{I}}\Big)\frac{\partial\rho}{\partial V} - \Big(f(V) - \alpha_e\,h_e\frac{dh_e}{dV} - \alpha_i\,h_i\frac{dh_i}{dV}\Big)\rho\,\Big]\,dV\end{aligned}$$

where, as previously, the boundary contribution vanishes on the right hand side of the previous equation. It now follows from equation (3.24) that for all suitably differentiable arbitrary functions $F(V)$,

$$\begin{aligned}&\int F(V)\,\frac{\partial\rho(V,t)}{\partial t}\,dV\\ &\qquad = \int F(V)\,\frac{\partial}{\partial V}\Big[\Big(h_e^2\,\alpha_e + h_i^2\,\alpha_i + \beta^2\,\alpha_{\mathrm{I}}\Big)\frac{\partial\rho}{\partial V} - \Big(f(V) - \alpha_e\,h_e\frac{dh_e}{dV} - \alpha_i\,h_i\frac{dh_i}{dV}\Big)\rho\,\Big]\,dV\end{aligned}$$

which in turn leads to the identity

$$\frac{\partial\rho(V,t)}{\partial t}=\frac{\partial}{\partial V}\Big[\Big(h_e^2\,\alpha_e+h_i^2\,\alpha_i+\beta^2\,\alpha_{\rm I}\Big)\frac{\partial\rho}{\partial V}-\Big(f(V)-\alpha_e\,h_e\frac{dh_e}{dV}-\alpha_i\,h_i\frac{dh_i}{dV}\Big)\rho\Big]\,. \quad (3.25)$$

This is the Fokker-Planck equation describing the behaviour of the transitional density of the membrane potential from an initial state at $t=0$. The right hand side of this equation may be re-organised into the more familiar form

$$\frac{\partial\rho}{\partial t}=\frac{\partial}{\partial V}\Big(\alpha_e h_e\frac{\partial(\rho\,h_e)}{\partial V}+\alpha_i h_i\frac{\partial(\rho\,h_i)}{\partial V}-\rho\,f(V)+\beta^2\,\alpha_I\,\frac{\partial\rho}{\partial V}\Big)\,. \quad (3.26)$$

3.2 Distribution of steady-state membrane potentials

The Fokker-Planck equation (3.26) describes the evolution of the transitional probability density of the membrane potential from its initial distribution at time $t=0$ for the stochastic process determined by equation (3.1). The equation satisfied by the probability density function of the membrane potential in its state-state, say $\rho(V)=\lim_{t\to\infty}\rho(V,t)$, is constructed from equation (3.26) by setting $\partial\rho/\partial t=0$ and letting $t\to\infty$ in the expressions for $\alpha_e(t)$ and $\alpha_i(t)$. Since

$$\lim_{t\to\infty}\alpha_e(t)=\frac{\tau_e\sigma_e^2}{2}\,,\qquad \lim_{t\to\infty}\alpha_i(t)=\frac{\tau_i\sigma_i^2}{2}\,,\qquad \lim_{t\to\infty}\alpha_{\rm I}(t)=\frac{\tau_{\rm I}\sigma_{\rm I}^2}{2}$$

it follows directly from equation (3.26) that probability density function of the the steady-state membrane potential satisfies the ordinary differential equation

$$\frac{h_e\tau_e\sigma_e^2}{2}\frac{\partial(\rho\,h_e)}{\partial V}+\frac{h_i\tau_i\sigma_i^2}{2}\frac{\partial(\rho\,h_i)}{\partial V}-\rho\,f(V)+\beta^2\,\frac{\tau_{\rm I}\sigma_{\rm I}^2}{2}\,\frac{\partial\rho}{\partial V}=0\,.$$

This equation may be rearranged into the standard form

$$\frac{1}{2}\frac{d\rho}{dV}\Big(\tau_e h_e^2\sigma_e^2++\tau_i h_i^2\sigma_i^2+\tau_{\rm I}\beta^2\sigma_{\rm I}^2\Big)+\rho\Big(\frac{h_e\tau_e\sigma_e^2}{2}\frac{\partial h_e}{\partial V}+\frac{h_i\tau_i\sigma_i^2}{2}\frac{\partial h_i}{\partial V}-f(V)\Big)=0\,. \quad (3.27)$$

Since $h_e(V)$ and $h_i(V)$ are linear functions of V, equation (3.27) can be solved analytically to obtain the probability density function

$$\rho(V)=N\exp\Big[\frac{2b_2a_0-a_1b_1}{b_2\sqrt{4b_2b_0-b_1^2}}\,\tan^{-1}\Big(\frac{2b_2V-b_1}{\sqrt{4b_2b_0-b_1^2}}\Big)+\frac{a_1}{2b_2}\log(b_2V^2+b_1\,V+b_0)\Big] \quad (3.28)$$

for the distribution of the steady-state membrane potential. In this equation

$$\begin{aligned} a_0 &= \frac{2(g_m E_m + G_e E_e + G_i E_i - I_0)}{c_m} - \frac{b_1}{2} \\ a_1 &= -\frac{2(g_m + G_e + G_i)}{c_m} - b_2 \\ b_0 &= \frac{1}{c_m^2}\Big(\sigma_e^2\,\tau_e\,E_e^2 + \sigma_i^2\,\tau_i\,E_i^2 + \sigma_I^2\,\tau_I\Big) \\ b_1 &= -\frac{2(\sigma_e^2\,\tau_e\,E_e + \sigma_i^2\,\tau_i\,E_i)}{c_m^2} \\ b_2 &= \frac{(\sigma_e^2\,\tau_e + \sigma_i^2\,\tau_i)}{c_m^2}\,. \end{aligned} \tag{3.29}$$

and N is a normalization factor, the value of which is determined by requiring that

$$\int_{-\infty}^{\infty} \rho(V)\,dV = 1\,.$$

3.2.1 Current based synaptic input

The steady-state distribution of membrane potential when synaptic activity is modelled by stochastic current input is the special case of equation (3.27) in which $G_e = G_i = \sigma_e = \sigma_i = 0$. In this case the stationary density of the membrane potential satisfies the differential equation

$$\frac{\tau_{\rm I}\beta^2\sigma_{\rm I}^2}{2}\frac{d\rho}{dV} - \rho\,f(V) = 0 \tag{3.30}$$

with solution

$$\rho_{\rm cur}(V) = \frac{1}{\sqrt{2\pi\,\sigma_V^2}}\ \exp\Big[-\frac{(V-E_0)^2}{2\sigma_V^2}\Big]$$

where

$$E_0 = E_m - \frac{I_0}{g_m}\,, \qquad \sigma_V^2 = \frac{\sigma_I^2\,\tau_I}{2g_m\,c_m}\,.$$

3.2.2 Conductance based synaptic input

The steady-state distribution of membrane potential when synaptic activity is modelled by stochastic excitatory and inhibitory conductance base input is the special case of equation (3.27) in which $I_0 = \sigma_{\rm I} = 0$. In this case, expression (3.28) takes the simplified form

$$\begin{aligned} \rho_{cond}(V) &= N\exp\Big[A_1\log\Big(\frac{\sigma_e^2\,\tau_e}{c_m^2}(V-E_e)^2 + \frac{\sigma_i^2\,\tau_i}{c_m^2}(V-E_i)^2\Big) \\ &\quad + A_2\tan^{-1}\Big(\frac{\sigma_e^2\,\tau_e(V-E_e) + \sigma_i^2\,\tau_i(V-E_i)}{(E_e-E_i)\sqrt{\sigma_e^2\,\tau_e\,\sigma_i^2\,\tau_i}}\Big)\Big] \end{aligned}$$

where

$$A_1 = -\frac{2c_m(G_e + G_i) + 2c_m g_m + \sigma_e^2\tau_e + \sigma_i^2\tau_i}{\sigma_e^2\tau_e + \sigma_i^2\tau_i}$$

and

$$A_2 = \frac{2c_m(g_m(\sigma_e^2\tau_e(E_m - E_e) + \sigma_i^2\tau_i(E_m - E_i)) + (G_e\sigma_i^2\tau_i - G_i\sigma_e^2\tau_e)(E_e - E_i))}{(E_e - E_i)(\sigma_e^2\tau_e + \sigma_i^2\tau_i)\sqrt{\tau_e\tau_i\sigma_e^2\sigma_i^2}}.$$

An important feature of this solution is that the time constants for the excitatory and inhibitory synapses, namely τ_e and τ_i respectively, enter the solution for the probability density function of the steady-state membrane potential only via the combinations $\sigma_e^2\tau_e$ and $\sigma_i^2\tau_i$.

3.3 Conclusions

Rudolph and Destexhe (2003) simulate the distribution of membrane potential for a passive membrane driven by a current-based input modelled by an OU process and excitatory and inhibitory conductance-based input with conductances modelled as independent OU processes. As posed, this model does not have a straightforward analytical solution. However, by approximating the excitatory and inhibitory synaptic currents as independent random processes, the effect of these currents can be combined to give an approximation of the original model for which an analytical expression for the distribution of the membrane potential is available. Rudolph and Destexhe (2003) compare this analytical expression for the probability density function of the membrane potential with that obtained by simulation of the original model and with the probability density function of membrane potentials occurring in cortical networks in vivo.

Their conclusion is that the description of synaptic noise in terms of the Ornstein-Unhlebeck stochastic process, along with the analytic solution of the corresponding stochastic membrane equation (3.1), provides a good description of the subthreshold activity of neuronal membranes. Deviations between the simulated distribution and that derived analytically by approximating the original model were small in general, but largest for the current-based description of synaptic input. They attributed this behaviour to statistical errors.

In Rudolph and Destexhe (2005) they suggest a straightforward way to correct for the deviation between the simulated density of the membrane potential and that derived from the model obtained by approximation. The correction leads to an extended analytic solution for the membrane potential valid for a parameter region covering several orders of magnitude around physiologically realistic values.

3.4 Extended Analytic Solution

The full conductance-based system used by Rudolph and Destexhe (2005) is

$$\frac{dV}{dt} = -\frac{1}{\tau_m}\big(V(t) - E_0\big) - \frac{1}{c_m}\widetilde{g}_e(t)\big(V(t) - E_e\big) - \frac{1}{c_m}\widetilde{g}_i(t)\big(V(t) - E_i\big)\,, \tag{3.31}$$

where the conductances $\widetilde{g}_e\,, \widetilde{g}_i$ are given by equations (3.5) and the average membrane potential E_0 by equation (3.9). The Fokker-Planck equation of this system is obtained using the same method as the one used in Rudolph and Destexhe (2003) and from the steady-state they obtain the membrane potential

$$\begin{aligned}\rho(V) &= N \exp\Big[A_1 \log\Big(\frac{\sigma_e^2\,\tau_e'}{c_m^2}(V-E_e)^2 + \frac{\sigma_i^2\,\tau_i'}{c_m^2}(V-E_i)^2\Big) \\ &\qquad + A_2\,\tan^{-1}\Big(\frac{\sigma_e^2\,\tau_e'(V-E_e) + \sigma_i^2\,\tau_i'\,(V-E_i)}{(E_e-E_i)\,\sqrt{\tau_e'\tau_i'\sigma_e^2\sigma_i^2}}\Big)\Big]\end{aligned} \tag{3.32}$$

where

$$A_1 = -\frac{2c_m(G_e+G_i) + 2c_m g_m + \sigma_e^2\tau_e' + \sigma_i^2\tau_i'}{\sigma_e^2\tau_e' + \sigma_i^2\tau_i'}$$

and

$$A_2 = \frac{2c_m(g_m(\sigma_e^2\tau_e'(E_m-E_e) + \sigma_i^2\tau_i'(E_m-E_i)) + (G_e\sigma_i^2\tau_i' - G_i\sigma_e^2\tau_e')(E_e-E_i))}{(E_e-E_i)(\sigma_e^2\tau_e' + \sigma_i^2\tau_i')\sqrt{\tau_i'\tau_e'\sigma_e^2\sigma_i^2}}\,.$$

This form of $\rho(V)$ differs from the one presented in Rudolph and Destexhe (2003) by the use of "effective" noise time constants, which in general are such that $\tau_e' \neq \tau_e$ and $\tau_i' \neq \tau_i$.

The simplified version of equation (3.1) used by Rudolph and Destexhe (2005) for the membrane potential distribution of conductance-based omits stochastic current input.

$$\frac{dV}{dt} = -\frac{1}{\tau_m}\big(V(t) - E_0\big) - \frac{1}{c_m}\widetilde{g}_e(t)\big(E_0 - E_e\big) - \frac{1}{c_m}\widetilde{g}_i(t)\big(E_0 - E_i\big) \tag{3.33}$$

where the conductances $\widetilde{g}_e\,, \widetilde{g}_i$ are given by equations (3.5) and the average membrane potential E_0 by equation (3.9).

This simplified system is chosen since it can be solved explicitly. The correction required to adjust the solution of equation (3.1) is found using the rules of stochastic Calculus. Rudolph and Destexhe (2005) proceed as follows

1. Solve the simplified equation (3.33) by direct integration. This procedure gives

$$\sigma_V^2 = \Big(\frac{\sigma_e \tau_m}{c_m}\Big)^2 \frac{\tau_e}{\tau_e + \tau_m}(E_0 - E_e)^2 + \Big(\frac{\sigma_i \tau_m}{c_m}\Big)^2 \frac{\tau_i}{\tau_i + \tau_m}(E_0 - E_i)^2 \tag{3.34}$$

   for the variance of the membrane potential.

2. Treat the simplified system (3.33) within the framework of stochastic calculus (as was done in Rudolph and Destexhe (2003)) to get the Fokker-Planck equation

$$\begin{aligned} \frac{\partial \rho(V,t)}{\partial t} &= -\frac{1}{\tau_m}\rho(V,t) - \frac{V - E_0}{\tau_m}\frac{\partial \rho(V,t)}{\partial t} \\ &\quad -\Big(\frac{(E_0 - E_e)^2}{c_m^2}\alpha_e(t) + \frac{(E_0 - E_i)^2}{c_m^2}\alpha_i(t)\Big)\frac{\partial^2 \rho(V,t)}{\partial t^2} \end{aligned} \tag{3.35}$$

   which, as $t \to \infty$, yields an equation that can be solved explicitly for $\rho(V)$ to produce the solution

$$\rho(V) = \exp^{-\frac{(V-E_0)^2}{2\sigma_V^2}} \Big[C_1 \exp\Big(\frac{E_0^2}{2\sigma_V^2}\Big) + C_2 \sigma_V \sqrt{\frac{\pi}{2}}\, \mathrm{Erfi}\Big(\frac{V - E_0}{\sigma_V \sqrt{2}}\Big)\Big] . \tag{3.36}$$

3. The variance is also found to be

$$\sigma_V^2 = \frac{\tau_m}{2}\frac{\sigma_e \tau_e'}{c_m^2}(E_0 - E_e)^2 + \frac{\tau_m}{2}\frac{\sigma_i \tau_i'}{c_m^2}(E_0 - E_i)^2 . \tag{3.37}$$

4. After applying boundary conditions and normalization a simplified expression for the expression (3.36) is obtained in the form

$$\rho(V) = \frac{1}{\sigma_V \sqrt{2\pi}} \exp\Big(- \frac{(V - E_0)^2}{2\sigma_V^2}\Big) . \tag{3.38}$$

5. The distribution of the membrane potential based on the full model given by expression (3.32) and the distribution (3.38) based on the simplified model are claimed to be equal. They now compare the variance of the distribution of $\rho(V)$ obtained by "two qualitatively" different methods for the simplified model. The expression for σ_V^2 in equation (3.34) obtained by direct integration is compared with the expression for σ_V^2 given by equation (3.37) deduced via the methods of stochastic Calculus. This comparison yields the desired link between the time constants, namely

$$\tau_e' = \frac{2\tau_e \tau_m}{\tau_e + \tau_m} , \qquad \tau_i' = \frac{2\tau_i \tau_m}{\tau_i + \tau_m} . \tag{3.39}$$

7. Further, Rudolph and Destexhe (2005) claim that equations (3.39) when substituted into equation (3.34) should provide the required correction to the simplified model (3.33) obtained by a solution procedure based on stochastic Calculus.

3.5 Rudolph's and Destexhe's simulation

The validity of the extended analytic solution was tested by incorporating the effective time constants $\tau'_{\{e,i\}}$ into the analytic solution of the full model given by equation (3.28) and was compared against the numerical solution of the original model for extreme parameter regimes. This regime consisted of very small and very large time constants τ_m as well as noise time constants $\tau'_{\{e,i\}}$. These time constants had little or no effect in parameter regimes that the agreement was already good enough (see figure 3.1), but they incredibly improved the agreement for very small time constants as seen in figures 3.2,3.3. In all cases the parameter values are : $G_L = 0.0452, C_m = 1mF/cm^2, E_L = -80mV, G_E = 12nS, G_I = 57nS, \tau_e = 2.728ms, \tau_i = 10.49ms, E_e = 0mV, E_i = -75mV$.

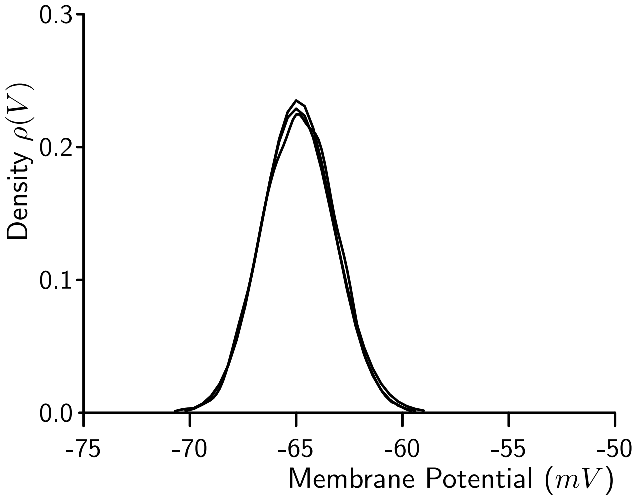

Figure 3.1: Comparison of the membrane potential distribution obtained numerically,using the analytic expression and the extended analytic expression. The membrane time constant τ_m is set to be 3.63. Also in this case $\sigma_e = 3nS$, $\sigma_i = 6.6nS$ and the area is 30.000 μm^2.As it is seen by the graph the curves are almost identical

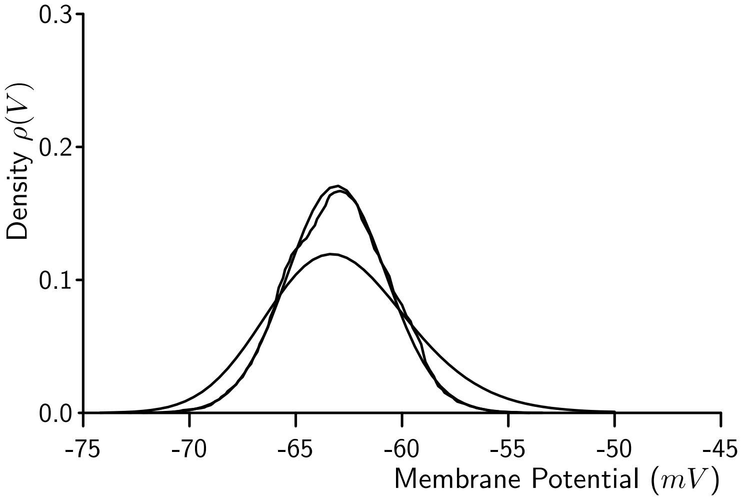

Figure 3.2: The membrane time constant is set to be 1.36ms, the area 10.000 μm^2 and $\sigma_e = 3nS$,$\sigma_i = 6.6nS$. The greatest peak is for the extended analytic solution, the one bellow it is for the numerical solution and the smallest peak is for the analytic solution.

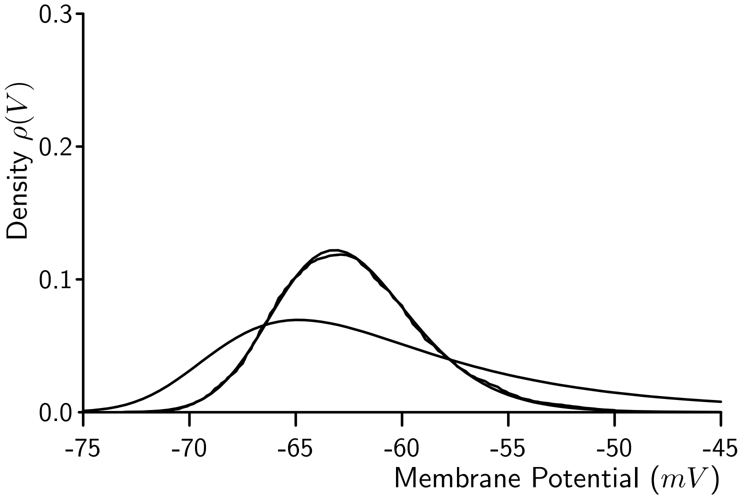

Figure 3.3: The membrane time constant is set to be 1.03ms, the area 7.500 μm^2 and $\sigma_e = 3nS$,$\sigma_i = 15nS$. The curve with the greatest peak is obtained by the extended analytic expression, the one below it is obtained by the numerical solution and the curve with the smallest peak is for the analytic solution.

Chapter 4

Direct approach

4.1 Introduction

It has already been shown that the full conductance-based differential equation satisfied by the membrane potential $V(t)$ is

$$c_m \frac{dV}{dt} + g_m(V - E_m\big) + g_e(t)\big(V - E_e\big) + g_i(t)\big(V - E_i\big) = 0\,. \tag{4.1}$$

In this equation the conductances $g_e(t)$ and $g_i(t)$ satisfy the stochastic differential equations

$$\begin{aligned} dg_e &= -\frac{\big(g_e - G_e\big)\,dt}{\tau_e} + \sqrt{\frac{2\sigma_e^2}{\tau_e}}\,dW_e\,, \\ dg_i &= -\frac{\big(g_i - G_i\big)\,dt}{\tau_i}\,g_i + \sqrt{\frac{2\sigma_i^2}{\tau_i}}\,dW_i\,. \end{aligned} \tag{4.2}$$

In these equations τ_e and τ_i are time constants describing the rates at which the total excitatory conductance g_e and the total inhibitory conductance g_i are restored to their respective equilibrium values G_e and G_i. The parameters σ_e and σ_i (dimensionally conductances) are respectively the standard deviations of the stationary distributions of g_e and g_i respectively. When expressed in terms of the voltage

$$E_0 = \frac{g_m E_m + G_e E_e + G_i E_i}{g_m + G_e + G_i} \tag{4.3}$$

and the time constant

$$\tau = \frac{1}{g_m + G_e + G_i}\,, \tag{4.4}$$

equation (4.1) for the membrane potential takes the form

$$\frac{dV}{dt} + \frac{V - E_0}{\tau} + \frac{g_e(t) - G_e}{c_m}\big(V - E_e\big) + \frac{g_i(t) - G_i}{c_m}\big(V - E_i\big) = 0\,. \tag{4.5}$$

Non-dimensional conductances x and y and now introduced by the definitions

$$x(t) = \frac{\big(g_e - G_e\big)}{\sigma_e}\,, \qquad\qquad y(t) = \frac{\big(g_i - G_i\big)}{\sigma_i}\,. \tag{4.6}$$

In terms of these variables equations (4.2) and (4.5) simplify to give

$$\begin{aligned}
\frac{dv}{dt} &= -\frac{v}{\tau} - \frac{x\sigma_e}{c_m}\big(v-\alpha\big) - \frac{y\sigma_i}{c_m}\big(v-\beta\big)\,, \\
dx &= -\frac{x\,dt}{\tau_e} + \sqrt{\frac{2}{\tau_e}}\,dW_e\,, \\
dy &= -\frac{y\,dt}{\tau_i}\,g_i + \sqrt{\frac{2}{\tau_i}}\,dW_i\,.
\end{aligned} \tag{4.7}$$

where $v = V - E_0$, the departure of the membrane potential from E_0, and the constants α and β denote respectively the potential differences $(E_e - E_0)$ and $(E_i - E_0)$.

It has been shown in the appendix how Ito's lemma can be used to show that equations (4.7_2) and (4.7_3) have exact solutions

$$x(t) = \sqrt{\frac{2}{\tau_e}}\int_{-\infty}^{t} e^{-(t-s)/\tau_e}\,dW_e(s)\;, \qquad y(t) = \sqrt{\frac{2}{\tau_i}}\int_{-\infty}^{t} e^{-(t-s)/\tau_i}\,dW_i(s)\;. \tag{4.8}$$

It is also shown in the appendix that these exact solutions lead to the autocorrelation properties

$$\mathrm{E}\left[x(t)x(t+u)\right] = e^{-u/\tau_e}\;, \qquad \mathrm{E}\left[y(t)y(t+u)\right] = e^{-u/\tau_i}\;. \qquad\qquad u \geq 0\,. \tag{4.9}$$

With these results in place, we now focus attention on equation (4.7_1) for the membrane potential.

4.1.1 Motivation

In order to motivate the strategy to be adopted in the subsequent analysis of equation (4.7_1), it is useful to re-express this equation in the conventional form

$$\frac{dv}{dt} + v\Big(\frac{1}{\tau} + \frac{x\sigma_e}{c_m} + \frac{y\sigma_i}{c_m}\Big) = \frac{x\sigma_e\alpha}{c_m} + \frac{y\sigma_i\beta}{c_m}\,. \tag{4.10}$$

Since x and y are continuous random functions, then $v(t)$ is a continuously differentiable random function. The expectation of equation (4.10) taken over trials, bearing in mind that $\mathrm{E}\left[x(t)\right] = \mathrm{E}\left[y(t)\right] = 0$, leads to the observation that

$$\frac{d\mathrm{E}\left[v(t)\right]}{dt} + \frac{\mathrm{E}\left[v(t)\right]}{\tau} + \frac{\sigma_e}{c_m}\mathrm{E}\left[v(t)x(t)\right] + \frac{\sigma_i}{c_m}\mathrm{E}\left[v(t)y(t)\right] = 0\,. \tag{4.11}$$

Since x and y are independent random processes, each with mean value zero and each driving v, it is anticipated that the correlations between v and x and between v and y are weak, not withstanding the fact that the factors σ_e/c_m and σ_i/c_m are themselves small. Of course, these are issues to be checked when the analysis is complete, but the overall thrust of this argument is that, to a first approximation, $\mathrm{E}\,[v(t)]$ is driven towards zero with time constant τ. Put another way, E_0 may be regarded as an good first estimate of the equilibrium potential of the cell.

With this interpretation of the meaning of E_0, the value of α is now a good first estimate of the potential difference between the reversal potential of the excitatory synapses and the equilibrium potential of the cell. Similarly, β is a good first estimate of the potential difference between the reversal potential of the inhibitory synapses and the equilibrium potential of the cell. In particular, we anticipate that the fluctuation in the membrane potential are in the first instance driven by the right hand side of equation (4.10), which is independent of v. The discrepancies $x(t)v(t)$ and $y(t)v(t)$ in the excitatory and inhibitory currents introduced by this assumption are of secondary importance and serve to fine-tune the solution for the membrane potential at time t.

This argument suggests that equation (4.10) may be solved by calculating the successive iterates of the equation

$$\frac{dv_{n+1}}{dt} + \frac{v_{n+1}}{\tau} = \frac{\big(x\sigma_e\alpha + y\sigma_i\beta\big)}{c_m} - \frac{v_n}{c_m}\big(x\sigma_e + y\sigma_i\big)\,, \qquad v_0(t) = 0\,. \tag{4.12}$$

If these iterates converge, then they will converge to the solution of equation (4.10). This argument indicates that the first non-trivial estimate of $v(t)$ is $v_1(t)$, the solution of equation

$$\frac{dv_1}{dt} + \frac{v_1}{\tau} = \frac{\big(x\sigma_e\alpha + y\sigma_i\beta\big)}{c_m}\,. \tag{4.13}$$

4.1.2 Linear model

Another approach to the problem of determining the marginal distribution of membrane potential stems from the observation that equation (4.10) is linear in v and may therefore be solved analytically for v using the integrating factor

$$\phi(t) = e^{t/\tau}\,\exp\Big(\frac{1}{c_m}\int_{-\infty}^{t}\big(\sigma_e x(s) + \sigma_i y(s)\big)\,ds\Big)\,. \tag{4.14}$$

Note that since $x(s)$ and $y(s)$ are continuous random functions, then the integral appearing in the definition of $\phi(t)$ is understood in the sense of a Riemann integral, and of course, $\phi(t)$ itself behaves as a continuously differentiable random function. Equation (4.10) is now multiplied by $\phi(t)$ and then integrated from t to negative infinity to obtain

$$\phi(t)\,v(t)=\frac{1}{c_m}\int_{-\infty}^{t}\phi(u)\,\Big[\alpha\sigma_e x(u)+\beta\sigma_i y(u)\Big]\,du\,. \tag{4.15}$$

The integrating factor is now replace by its definition to obtain the exact analytical solution

$$v(t)=\frac{1}{c_m}\int_{-\infty}^{t}e^{-(t-u)/\tau}\Big(\alpha\sigma_e x(u)+\beta\sigma_i y(u)\Big)\,\exp\Big(-\int_{u}^{t}\frac{\sigma_e x(s)+\sigma_i y(s)}{c_m}\,ds\Big)\,du\,. \tag{4.16}$$

Of course, the distributional properties of $v(t)$ are not apparent from this closed form solution. One way to get useful information from expression (4.16) is to replace

$$\exp\Big(-\int_{u}^{t}\frac{\sigma_e x(s)+\sigma_i y(s)}{c_m}\,ds\Big)$$

by its absolutely convergent power series expansion

$$\sum_{k=0}^{\infty}\frac{(-1)^k}{k!\,c_m^k}\Big(\int_{u}^{t}\big(\sigma_e x(s)+\sigma_i y(s)\,\big)\,ds\Big)^k\,.$$

By this manipulation $v(t)$ is expressed as the absolutely convergent series

$$\begin{aligned} v(t) &= \alpha\sigma_e\sum_{k=0}^{\infty}\frac{(-1)^k}{k!\,c_m^{k+1}}\int_{-\infty}^{t}e^{-(t-u)/\tau}\,x(u)\,\Big(\int_{u}^{t}\big(\sigma_e x(s)+\sigma_i y(s)\,\big)\,ds\Big)^k\,du \\ &\quad+\beta\sigma_i\sum_{k=0}^{\infty}\frac{(-1)^k}{k!\,c_m^{k+1}}\int_{-\infty}^{t}e^{-(t-u)/\tau}\,y(u)\,\Big(\int_{u}^{t}\big(\sigma_e x(s)+\sigma_i y(s)\,\big)\,ds\Big)^k\,du\,. \end{aligned} \tag{4.17}$$

This expression for $v(t)$ can now be used to generate a sequence of approximations to the solution of equation (4.1). The first and second order approximations are now examined.

4.1.3 First order approximation

The first order approximation to $v(t)$ is obtained by ignoring the second and higher order terms in expression (4.17) to get

$$v_1(t)=\frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t}e^{-(t-u)/\tau}\,x(u)\,du+\frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t}e^{-(t-u)/\tau}\,y(u)\,du\,. \tag{4.18}$$

This solution is identical to that obtained as the first iterate of equation (4.12). First, since $\mathrm{E}\,[x(u)]=\mathrm{E}\,[y(u)]=0$ then clearly $\mathrm{E}\,[v_1(t)]=0$.

Correlation of membrane potential with synaptic processes

The autocorrelation properties of $v_1(t)$ with respect to the processes $x(t)$ and $y(t)$ are computed from the formulae

$$\begin{aligned}
\mathrm{E}\,[v_1(t+u)x(t)] &= \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t+u} e^{-(t+u-z)/\tau}\,\mathrm{E}\,[x(z)x(t)]\,dz \\
&\quad+\frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t+u} e^{-(t+u-z)/\tau}\,\mathrm{E}\,[y(z)x(t)]\,dz \\
\mathrm{E}\,[v_1(t+u)y(t)] &= \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t+u} e^{-(t+u-z)/\tau}\,\mathrm{E}\,[x(z)y(t)]\,dz \\
&\quad+\frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t+u} e^{-(t+u-z)/\tau}\,\mathrm{E}\,[y(z)y(t)]\,dz\,.
\end{aligned}$$

in which it is understood that $u > 0$. Since $x(t)$ and $y(t)$ are independent random variables, then $\mathrm{E}\,[y(z)x(t)] = 0$ and $\mathrm{E}\,[x(z)y(t)] = 0$. The correlations between $v_1(t+u)$ and the processes $x(t)$ and $y(t)$ therefore simplify to obtain

$$\begin{aligned}
\mathrm{E}\,[v_1(t+u)x(t)] &= \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t+u} e^{-(t+u-z)/\tau}\,\mathrm{E}\,[x(z)x(t)]\,dz \\
&= \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t+u} e^{-(t+u-z)/\tau}\,e^{-|t-z|/\tau_e}\,dz \\
\mathrm{E}\,[v_1(t+u)y(t)] &= \frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t+u} e^{-(t+u-z)/\tau}\,\mathrm{E}\,[y(z)y(t)]\,dz \\
&= \frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t+u} e^{-(t+u-z)/\tau}\,e^{-|t-z|/\tau_i}\,dz\,.
\end{aligned} \tag{4.19}$$

Let $w = t - z$ in the computation of the integral defining the value of $\mathrm{E}\,[v_1(t+u)x(t)]$ then

$$\begin{aligned}
\mathrm{E}\,[v_1(t+u)x(t)] &= \frac{\alpha\sigma_e}{c_m}\int_{-u}^{\infty} e^{-(w+u)/\tau}\,e^{-|w|/\tau_e}\,dw \\
&= \frac{\alpha\sigma_e}{c_m}\,\frac{\tau\tau_e}{(\tau+\tau_e)(\tau-\tau_e)}\Big[2\tau e^{-u/\tau}-(\tau+\tau_e)e^{-u/\tau_e}\Big]\,.
\end{aligned}$$

Taking account of the fact that $x(t)$ and $y(t)$ are independent processes, the correlations $\mathrm{E}\,[v_1(t)x(t+u)]$ and $\mathrm{E}\,[v_1(t)y(t+u)]$ in which $u > 0$ leads to the calculation

$$\begin{aligned}
\mathrm{E}\,[v_1(t)x(t+u)] &= \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t} e^{-(t-z)/\tau}\,\mathrm{E}\,[x(z)x(t+u)]\,dz \\
\mathrm{E}\,[v_1(t)y(t+u)] &= \frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t} e^{-(t-z)/\tau}\,\mathrm{E}\,[y(z)y(t+u)]\,dz\,.
\end{aligned}$$

The correlation structure of $x(t)$ now gives

$$\begin{aligned}
\mathrm{E}\,[v_1(t)x(t+u)] &= \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t} e^{-(t-z)/\tau}\,e^{-|t+u-z|/\tau_e}\,dz \\
&= \frac{\alpha\sigma_e}{c_m}\,e^{-u/\tau_e}\int_{0}^{\infty} e^{-w/\tau}\,e^{-w/\tau_e}\,dw \\
&= \frac{\alpha\sigma_e}{c_m}\,\frac{\tau\tau_e}{\tau+\tau_e}\,e^{-u/\tau_e}\,.
\end{aligned}$$

A similar calculation applies to the computation of $\mathrm{E}\left[v_1(t+u)y(t)\right]=0$. To summarize,

$$\begin{aligned}
\mathrm{E}\left[v_1(t+u)x(t)\right] &= \frac{\alpha\sigma_e}{c_m}\,\frac{\tau\tau_e}{(\tau+\tau_e)(\tau-\tau_e)}\Big[2\tau e^{-u/\tau}-(\tau+\tau_e)e^{-u/\tau_e}\Big]\,,\\
\mathrm{E}\left[v_1(t+u)y(t)\right] &= \frac{\beta\sigma_i}{c_m}\,\frac{\tau\tau_i}{(\tau+\tau_i)(\tau-\tau_i)}\Big[2\tau e^{-u/\tau}-(\tau+\tau_i)e^{-u/\tau_i}\Big]\,.
\end{aligned} \tag{4.20}$$

In the particular case in which $u=0$, the correlations $\mathrm{E}\left[v_1(t)x(t)\right]$ and $\mathrm{E}\left[v_1(t)y(t)\right]$ have values

$$\mathrm{E}\left[v_1(t)x(t)\right]=\frac{\alpha\sigma_e}{c_m}\,\frac{\tau\tau_e}{(\tau+\tau_e)}\,,\qquad \mathrm{E}\left[v_1(t)y(t)\right]=\frac{\beta\sigma_i}{c_m}\,\frac{\tau\tau_i}{(\tau+\tau_i)}\,. \tag{4.21}$$

Recall that part of the motivation for this approach lay in the argument that the correlations between $v(t)$ and the processes $x(t)$ and $y(t)$ is weak. It is clear from this argument that these correlations are respectively $O(\sigma_e)$ and $O(\sigma_i)$, and in combination with the multipliers σ_e and σ_i already present in equation (4.11), indicate that deviations in the expected value of the membrane potential from E_0 are $O(\sigma_e^2+\sigma_i^2)$, that is, in practice very small indeed.

Autocorrelation of membrane potential

The autocorrelation function of the membrane potential is defined by

$$\begin{aligned}
\mathrm{E}\left[v_1(t)v_1(t+u)\right] &= \int_{-\infty}^{t+u}\int_{-\infty}^{t} e^{-(t+u-z)/\tau}\,e^{-(t-w)/\tau}\\
&\qquad \mathrm{E}\Big[\Big(\frac{\alpha\sigma_e}{c_m}\,x(z)+\frac{\beta\sigma_i}{c_m}\,y(z)\Big)\Big(\frac{\alpha\sigma_e}{c_m}\,x(w)+\frac{\beta\sigma_i}{c_m}\,y(w)\Big)\Big]\,dz\,dw\,.
\end{aligned} \tag{4.22}$$

After taking account of the fact that the processes $x(t)$ and $y(t)$ are independent, the expression for the autocorrelation function of $v_1(t)$ simplifies to

$$\begin{aligned}
\mathrm{E}\left[v_1(t)v_1(t+u)\right] &= \frac{\alpha^2\sigma_e^2}{c_m^2}\int_{-\infty}^{t+u}\int_{-\infty}^{t} e^{-(t+u-z)/\tau}\,e^{-(t-w)/\tau}\mathrm{E}\left[x(z)x(w)\right]dz\,dw\\
&\quad+\frac{\beta^2\sigma_i^2}{c_m^2}\int_{-\infty}^{t+u}\int_{-\infty}^{t} e^{-(t+u-z)/\tau}\,e^{-(t-w)/\tau}\mathrm{E}\left[y(z)y(w)\right]dz\,dw\,.
\end{aligned} \tag{4.23}$$

Each integral on the right hand side of equation (4.23) is calculate in a similar way, and so we focus our effort on the computation of the first of these integrals by first noting that $\mathrm{E}\left[x(z)x(w)\right]=e^{-|z-w|/\tau_e}$. The value of the second integral is obtained from that of the first integral by replacing each occurrence of τ_e by τ_i. For convenience, define

$$\begin{aligned}
I_x &= \int_{-\infty}^{t+u}\int_{-\infty}^{t} e^{-(t+u-z)/\tau}\,e^{-(t-w)/\tau}\mathrm{E}\left[x(z)x(w)\right]dz\,dw\\
&= \int_{-\infty}^{t+u}\int_{-\infty}^{t} e^{-(t+u-z)/\tau}\,e^{-(t-w)/\tau}e^{-|z-w|/\tau_e}\,dz\,dw\,.
\end{aligned}$$

The change of variables $p = t + u - z$ and $q = t - w$ is now used to simplify I_x to get

$$\begin{aligned}
I_x &= \int_0^\infty e^{-q/\tau}\Big(\int_0^\infty e^{-p/\tau}e^{-|q+u-p|/\tau_e}\,dp\Big)\,dq \\
&= \int_0^\infty e^{-q/\tau}\Big[\int_0^{q+u} e^{-p/\tau}e^{-(q+u-p)/\tau_e}\,dp\Big]\,dq \\
&\quad + \int_0^\infty e^{-q/\tau}\Big[\int_{q+u}^\infty e^{-p/\tau}e^{-(p-q-u))|/\tau_e}\,dp\Big]\,dq \\
&= \frac{\tau\tau_e}{\tau-\tau_e}\int_0^\infty e^{-q/\tau}\Big(e^{-(q+u)/\tau} - e^{-(q+u)/\tau_e}\Big)\,dq + \frac{\tau\tau_e}{\tau+\tau_e}\int_0^\infty e^{-q/\tau}e^{-(q+u)/\tau}\,dq \\
&= \frac{\tau\tau_e}{\tau-\tau_e}\Big(\frac{\tau}{2}e^{-u/\tau} - \frac{\tau_e\tau}{\tau+\tau_e}\,e^{-u/\tau_e}\Big) + \frac{\tau\tau_e}{\tau+\tau_e}\,\frac{\tau}{2}\,e^{-u/\tau} \\
&= \frac{\tau^2\tau_e}{\tau^2-\tau_e^2}\Big(\tau e^{-u/\tau} - \tau_e\,e^{-u/\tau_e}\Big)\,.
\end{aligned}$$

Similarly,

$$\begin{aligned}
I_y &= \int_{-\infty}^{t+u}\int_{-\infty}^{t} e^{-(t+u-z)/\tau}\,e^{-(t-w)/\tau}\mathrm{E}\,[y(z)y(w)]\,dz\,dw \\
&= \frac{\tau^2\tau_i}{\tau^2-\tau_i^2}\Big(\tau e^{-u/\tau} - \tau_i\,e^{-u/\tau_i}\Big)\,.
\end{aligned}$$

Consequently, expression (4.23) for the autocorrelation function of $v_1(t)$ becomes

$$\begin{aligned}
\mathrm{E}\,[v_1(t)v_1(t+u)] &= \frac{\alpha^2\sigma_e^2}{c_m^2}\,I_x + \frac{\beta^2\sigma_i^2}{c_m^2}\,I_y \\
&= \frac{\alpha^2\sigma_e^2}{c_m^2}\,\frac{\tau^2\tau_e}{\tau^2-\tau_e^2}\Big(\tau e^{-u/\tau} - \tau_e\,e^{-u/\tau_e}\Big) \qquad (4.24) \\
&\quad + \frac{\beta^2\sigma_i^2}{c_m^2}\,\frac{\tau^2\tau_i}{\tau^2-\tau_i^2}\Big(\tau e^{-u/\tau} - \tau_i\,e^{-u/\tau_i}\Big)\,.
\end{aligned}$$

The variance of $v_1(t)$ is the value of the autocorrelation function of v_1 when $u = 0$. It follows directly from expression (4.24) that

$$\mathrm{Var}\,[v_1(t)] = \frac{\alpha^2\sigma_e^2}{c_m^2}\,\frac{\tau^2\tau_e}{\tau+\tau_e} + \frac{\beta^2\sigma_i^2}{c_m^2}\,\frac{\tau^2\tau_i}{\tau+\tau_i}\,. \qquad (4.25)$$

Stationary membrane potential

Recall that the first estimate for the membrane potential is

$$v_1(t) = \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t} e^{-(t-u)/\tau}\,x(u)\,du + \frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t} e^{-(t-u)/\tau}\,y(u)\,du\,. \qquad (4.26)$$

in which $x(t)$ and $y(t)$ denote the respective time courses of the non-dimensional conductances of the excitatory and inhibitory synapses. Since $x(t)$ and $y(t)$ are stationary Gaussian processes with zero mean and unit variance, then the integrals appearing in expression (4.26) are independent Gaussian random variables. Thus the stationary distribution of $v_1(t)$ is a Gaussian process with mean value zero and variance

$$\sigma_V^2 = \frac{\alpha^2\sigma_e^2}{c_m^2}\,\frac{\tau^2\tau_e}{\tau+\tau_e} + \frac{\beta^2\sigma_i^2}{c_m^2}\,\frac{\tau^2\tau_i}{\tau+\tau_i}\,.$$

The first approximation of the probability density function of the stationary membrane potential is therefore

$$\rho(V) = \frac{1}{\sigma_V\sqrt{2\pi}}\,\exp\Big(-\frac{(V-E_0)^2}{2\sigma_V^2}\Big)\,. \tag{4.27}$$

4.1.4 Second order approximation

The second order approximation of the membrane potential is derived from the exact solution (4.17) by retaining the first two terms of the power series expansion of the exponential function to get

$$\begin{aligned} v_2(t) \;=\;& \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t} e^{-(t-u)/\tau}\,x(u)\Big(1-\frac{1}{c_m}\int_u^t \big[\sigma_e x(s)+\sigma_i y(s)\big]\,ds\Big)\,du \\ &+\frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t} e^{-(t-u)/\tau}\,y(u)\Big(1-\frac{1}{c_m}\int_u^t \big[\sigma_e x(s)+\sigma_i y(s)\big]\,ds\Big)\,du\,. \end{aligned} \tag{4.28}$$

On taking account of the fact that $x(t)$ and $y(t)$ are independent processes, the mean value of $v_2(t)$ becomes

$$\begin{aligned} \mathrm{E}\,[v_2(t)] \;=\;& -\frac{\alpha\sigma_e^2}{c_m^2}\int_{-\infty}^{t} e^{-(t-u)/\tau}\Big(\int_u^t \mathrm{E}\,[x(u)x(s)]\,ds\Big)\,du \\ &-\frac{\beta\sigma_i^2}{c_m^2}\int_{-\infty}^{t} e^{-(t-u)/\tau}\Big(\int_u^t \mathrm{E}\,[y(u)y(s)]\,ds\Big)\,du \\ =\;& -\frac{\alpha\sigma_e^2}{c_m^2}\int_{-\infty}^{t} e^{-(t-u)/\tau}\Big(\int_u^t e^{-(s-u)/\tau_e}\,ds\Big)\,du \\ &-\frac{\beta\sigma_i^2}{c_m^2}\int_{-\infty}^{t} e^{-(t-u)/\tau}\Big(\int_u^t e^{-(s-u)/\tau_i}\,ds\Big)\,du \\ =\;& -\frac{\alpha\sigma_e^2}{c_m^2}\,\tau_e\int_{-\infty}^{t} e^{-(t-u)/\tau}\Big(1-e^{-(t-u)/\tau_e}\Big)\,du \\ &-\frac{\beta\sigma_i^2}{c_m^2}\,\tau_i\int_{-\infty}^{t} e^{-(t-u)/\tau}\Big(1-e^{-(t-u)/\tau_i}\Big)\,du\,. \end{aligned}$$

The change of variable $w=t-u$ finally leads to the result that

$$\begin{aligned} \mathrm{E}\,[v_2(t)] \;=\;& -\frac{\alpha\tau_e\sigma_e^2}{c_m^2}\int_0^\infty e^{-w/\tau}\Big(1-e^{-w/\tau_e}\Big)\,dw-\frac{\beta\tau_i\sigma_i^2}{c_m^2}\int_0^\infty e^{-w/\tau}\Big(1-e^{-w/\tau_i}\Big)\,dw \\ =\;& -\Big(\frac{\alpha\tau_e\sigma_e^2}{c_m^2}\,\frac{\tau^2}{\tau+\tau_e}+\frac{\beta\tau_i\sigma_i^2}{c_m^2}\,\frac{\tau^2\tau_i}{\tau+\tau_i}\Big)\,. \end{aligned} \tag{4.29}$$

Thus the mean value of the membrane potential differs from E_0 by $O(\sigma_e^2+\sigma_i^2)$. To calculate the new variance of the membrane potential we first consider

$$
\begin{aligned}
v_2(t) - \mathrm{E}\,[v_2(t)] \;=\; & \frac{\alpha\sigma_e}{c_m}\int_{-\infty}^{t} e^{-(t-u)/\tau}\, x(u)\Big(1-\frac{1}{c_m}\int_u^t \sigma_i y(s)\big]\, ds\Big)\, du \\
& -\frac{\alpha\sigma_e^2}{c_m^2}\int_{-\infty}^{t} e^{-(t-u)/\tau}\Big(\int_u^t \big[x(u)x(s)-e^{-(s-u)/\tau_e}\big]\, ds\Big)\, du \\
& +\frac{\beta\sigma_i}{c_m}\int_{-\infty}^{t} e^{-(t-u)/\tau}\, y(u)\Big(1-\frac{1}{c_m}\int_u^t \sigma_e x(s)\, ds\Big)\, du \\
& -\frac{\beta\sigma_i^2}{c_m^2}\int_{-\infty}^{t} e^{-(t-u)/\tau}\Big(\int_u^t \big[y(u)y(s)-e^{-(s-u)/\tau_i}\big]\, ds\Big)\, du\,.
\end{aligned}
\tag{4.30}
$$

The variance of $v_2(t)$ is now given by taking the expected value of the square of the previous expression. The fact that $x(t)$ and $y(t)$ are uncorrelated processes will eliminate a number of terms from this calculation, but nevertheless the final expression for the variance of $v_2(t)$ will be complicated. However, it is clear that, in overview, the result of this calculation will be that

$$
\mathrm{Var}\,[v_2(t)] = \frac{\alpha^2\sigma_e^2}{c_m^2}\,\frac{\tau^2\tau_e}{\tau+\tau_e} + \frac{\beta^2\sigma_i^2}{c_m^2}\,\frac{\tau^2\tau_i}{\tau+\tau_i} + O(\sigma_e^2+\sigma_i^2)^2\,. \tag{4.31}
$$

4.2 Hermite polynomial solution

The previous section has argued that the stationary distribution of the membrane potential is approximately Gaussian with mean value E_0 and variance

$$
\sigma_v^2 = \frac{\alpha^2\sigma_e^2}{c_m^2}\,\frac{\tau^2\tau_e}{\tau+\tau_e} + \frac{\beta^2\sigma_i^2}{c_m^2}\,\frac{\tau^2\tau_i}{\tau+\tau_i}\,.
$$

This observation suggests that it will be beneficial to re-express the equation for the membrane potential in terms of the non-dimensional potential $v = (V - E_0)/\sigma_v$. When this is done, the non-dimensional potential satisfies the equation

$$
\frac{dv}{dt} = -\frac{v}{\tau} - x\frac{\sigma_e}{c_m}\Big(v-\frac{\alpha}{\sigma_v}\Big) - y\frac{\sigma_i}{c_m}\Big(v-\frac{\beta}{\sigma_v}\Big) = -\xi(v) - xh_e(v) - yh_i(v)
$$

where

$$
\xi(v) = \frac{v}{\tau}\,, \qquad h_e(v) = \frac{\sigma_e}{c_m}\Big(v-\frac{\alpha}{\sigma_v}\Big)\,, \qquad h_i = \frac{\sigma_i}{c_m}\Big(v-\frac{\beta}{\sigma_v}\Big)\,. \tag{4.32}
$$

In particular, this rescaling procedure means that the non-dimensional membrane potential has stationary distribution which is standard Normal.

The starting point for our analysis is the observation that the non-dimensional membrane potential v and non-dimensional conductances $x(t)$ and $y(t)$ satisfy

$$\begin{aligned}
\frac{dv}{dt} &= -\xi(v) - xh_e(v) - yh_i(v)\,, \\
dx &= -\frac{x\,dt}{\tau_e} + \sqrt{\frac{2}{\tau_e}}\,dW_e\,, \\
dy &= -\frac{y\,dt}{\tau_i}\,g_i + \sqrt{\frac{2}{\tau_i}}\,dW_i\,.
\end{aligned}$$

Let $\mathbf{y}$ denote the time evolving three-dimensional random process with components (v, x, y) then $\mathbf{y} = (v, x, y)$ satisfies the stochastic differential equations

$$\begin{bmatrix} dv \\ dx \\ dy \end{bmatrix} = -\begin{bmatrix} \xi(v) + x\,h_e(v) + y\,h_i(v) \\ \dfrac{x}{\tau_e} \\ \dfrac{y}{\tau_i} \end{bmatrix} dt + \begin{bmatrix} 0 & 0 & 0 \\ 0 & \sqrt{\dfrac{2}{\tau_e}} & 0 \\ 0 & 0 & \sqrt{\dfrac{2}{\tau_i}} \end{bmatrix} \begin{bmatrix} dW_v \\ dW_e \\ dW_i \end{bmatrix}. \tag{4.33}$$

It can be shown that the transitional density $f(v, x, y, t)$ satisfied by the process $\mathbf{y}$ is the solution of the Fokker-Planck equation satisfied

$$\begin{aligned}
\frac{\partial f}{\partial t} &= \frac{1}{\tau_e}\frac{\partial}{\partial x}\Big(\frac{\partial f}{\partial x} + xf\Big) + \frac{1}{\tau_i}\frac{\partial}{\partial y}\Big(\frac{\partial f}{\partial y} + yf\Big) \\
&\quad + \frac{\partial}{\partial v}\Big[f\big(\xi(v) + x\,h_e(v) + y\,h_i(v)\big)\Big]\,.
\end{aligned} \tag{4.34}$$

The subsequent analysis of equation (4.34) is based on an expansion of $f(v, x, y, t)$ as a spectral series in modified Hermite polynomials. Before considering the details of this analysis, we begin by providing a brief description of the analytical and algebraic properties of modified Hermite polynomials.

Modified Hermite polynomials

The modified Hermite polynomial of degree k, here denoted conveniently by $H_k(z)$ but not to be confused with the conventional Hermite polynomial, is defined by the Rodrigues's formula

$$H_k(z) = \frac{1}{\phi(z)}\frac{d^k\phi(z)}{dz^k} \qquad k \geq 0\,, \tag{4.35}$$

where $\phi(z)$ be the probability density function of the standardised normal distribution. An equivalent definition is given by the generating formula

$$\sum_{k=0}^{\infty} \frac{H_k(z)}{k!}\,s^k = e^{-s^2/2-sz} \tag{4.36}$$

which is obtained by interpreting the derivative in equation (4.35) as a constituent of the coefficient of s^k in the Taylor series expansion of $e^{-s^2/2-sz}$ about $s = 0$. From formula (4.35) it follows directly that modified Hermite polynomials satisfy the identity

$$\int_{-\infty}^{\infty} \phi(z)H_j(z)H_k(z)\,dz = \int_{-\infty}^{\infty} \frac{d^k\phi(z)}{dz^k}\,H_j(z)\,dz = (-1)^j \int_{-\infty}^{\infty} \phi(z)\,\frac{d^kH_j(z)}{dz^k}\,dz\,, \quad (4.37)$$

which is constructed by applying integration by parts k times to the middle integral and differentiating the modified Hermite polynomial on each occasion. When $j < k$, the integral on the right-hand side of equation (4.37) has value zero since $H_j(z)$ is a polynomial of degree j. Similarly, symmetry demands that the value of this integral is also zero when $j > k$. Thus result modified Hermite polynomials satisfy the orthogonality property

$$\int_{-\infty}^{\infty} \phi(z)H_j(z)H_k(z)\,dz = \left[\begin{array}{ll} 0 & j \neq k \\ k! & j = k \end{array}\right. \qquad (4.38)$$

where the value when $j = k$ is obtained by noting that $d^kH_k(z)/dz^k = k!$ and that $\phi(z)$ is a PDF. The defining properties (4.35) and (4.36) can be used to establish the respective results

$$\frac{dH_k(z)}{dz} = -kH_{k-1}(z)\,, \qquad H_{k+1}(z) + zH_k(z) + kH_{k-1}(z) = 0\,. \qquad (4.39)$$

By combining results (4.39), the modified Hermite polynomial may be shown to satisfy the second order differential equation by multiplying the first of equations (4.39) by $\phi(z)$ and differentiating the result to obtain

$$\frac{d^2H_k(z)}{dz^2} - z\frac{dH_k(z)}{dz} + kH_k(z) = 0\,.$$

4.2.1 Analysis of the Fokker-Planck equation

For convenience, let $a_{j,k}(v,t)$ be the function defined by

$$a_{p,q,r}(t) = \iiint_{\mathbb{R}^3} f(v,x,y,t)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy\,. \qquad (4.40)$$

We shall see in due course that $a_{i,j,k}(t)$ are the coefficients of the spectral expansion of the transitional PDF $f(v,x,y,t)$ in terms of modified Hermite polynomials. In the interim we use the Fokker-Planck equation (4.34) to establish their properties. These are constructed from the Fokker-Planck equation by first multiplying this equation by $H_i(v)H_j(x)H_k(y)$

and then integrating the resulting equation over $\mathbb{R}^3$ to obtain.

$$\begin{aligned}\frac{\partial a_{p,q,r}(t)}{\partial t} &= \frac{1}{\tau_e}\iiint_{\mathbb{R}^3}\frac{\partial}{\partial x}\Big(\frac{\partial f}{\partial x}+xf\Big)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy\\ &+\frac{1}{\tau_i}\iiint_{\mathbb{R}^3}\frac{\partial}{\partial y}\Big(\frac{\partial f}{\partial y}+yf\Big)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy\\ &+\iiint_{\mathbb{R}^3}\frac{\partial}{\partial v}\Big[f\Big(\xi(v)\;+x\,h_e(v)+y\,h_i(v)\Big)\Big]H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy\,.\end{aligned}\tag{4.41}$$

Now consider separately each integral on the right hand side of this equation recognising in the process that the behaviour of $f(v,x,y,t)$ for large values of x and y allows all boundary terms to be discarded.

First integral

One integration by parts gives

$$\begin{aligned}&\iiint_{\mathbb{R}^3}\frac{\partial}{\partial x}\Big(\frac{\partial f}{\partial x}+xf\Big)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy\\ &\qquad=-\iiint_{\mathbb{R}^3}\Big(\frac{\partial f}{\partial x}+xf\Big)H_p(v)\frac{dH_q(x)}{dx}H_r(y)\,dv\,dx\,dy\end{aligned}$$

and another integration by parts yields the final result

$$\begin{aligned}&\iiint_{\mathbb{R}^3}\frac{\partial}{\partial x}\Big(\frac{\partial f}{\partial x}+xf\Big)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy\\ &=\iiint_{\mathbb{R}^3}\Big(\frac{d^2H_q(x)}{dx^2}-x\frac{dH_q(x)}{dx}\Big)f\,H_p(v)H_r(y)\,dv\,dx\,dy\\ &=-q\iiint_{\mathbb{R}^3}f(v,x,y,t)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy=-q\,a_{p,q,r}(t)\,.\end{aligned}\tag{4.42}$$

Second integral

Integration by parts applied in this instance to the variable y likewise gives the final result

$$\iiint_{\mathbb{R}^3}\frac{\partial}{\partial y}\Big(\frac{\partial f}{\partial y}+yf\Big)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy=-r\,a_{p,q,r}(t)\,.\tag{4.43}$$

Third integral

In this instance integration is first applied to the variable v to get

$$\begin{aligned}&\iiint_{\mathbb{R}^3}\frac{\partial}{\partial v}\Big[f\Big(\xi(v)+xh_e(v)+yh_i(v)\Big)\Big]H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy\\ &\quad=-\iiint_{\mathbb{R}^3}f\big(\xi(v)+xh_e(v)+yh_i(v)\big)\frac{dH_p(v)}{dv}H_q(x)H_r(y)\,dv\,dx\,dy\\ &\quad=-p\iiint_{\mathbb{R}^3}\big(\xi(v)+xh_e(v)+yh_i(v)\big)f\,H_{p-1}(v)H_q(x)H_r(y)\,dv\,dx\,dy\,.\end{aligned}\tag{4.44}$$

No further integration is used in the analysis of equation (4.44). Instead, the recurrence properties of modified Hermite polynomials expressed in the form

$$\begin{aligned} vH_{p-1}(v) &= -H_p(v) - (p-1)H_{p-2}(v)\,, \\ xH_q(x) &= -H_{q+1}(x) - qH_{q-1}(x)\,, \\ yH_r(y) &= -H_{r+1}(y) - rH_{r-1}(y)\,, \end{aligned} \tag{4.45}$$

allow the right hand side of equation (4.44) to be expressed in terms of the coefficients $a_{p,q,r}(t)$ by the following argument.

First integral The first integral on the right hand side of (4.44) expands to give

$$\begin{aligned} &\iiint_{\mathbb{R}^3} f\,\xi(v)H_{p-1}(v)H_q(x)H_r(y)\,dv\,dx\,dy \\ &= \frac{1}{\tau}\iiint_{\mathbb{R}^3} f\,vH_{p-1}(v)H_q(x)H_r(y)\,dv\,dx\,dy \\ &= -\,\frac{a_{p,q.r} + (p-1)a_{p-2,q,r}}{\tau}\,. \end{aligned} \tag{4.46}$$

Second integral The second integral on the right hand side of (4.44) expands to give

$$\begin{aligned} &\iiint_{\mathbb{R}^3} f\,xh_e(v)H_{p-1}(v)H_q(x)H_r(y)\,dv\,dx\,dy \\ &= -\iiint_{\mathbb{R}^3} f\,h_e(v)H_{p-1}(v)\big(H_{q+1}(x) + qH_{q-1}(x)\big)H_r(y)\,dv\,dx\,dy \\ &= -\,\frac{\sigma_e}{c_m}\iiint_{\mathbb{R}^3} f\,\Big(v - \frac{\alpha}{\sigma_v}\Big)H_{p-1}(v)\big(H_{q+1}(x) + qH_{q-1}(x)\big)H_r(y)\,dv\,dx\,dy \\ &= -\,\frac{\sigma_e}{c_m}\iiint_{\mathbb{R}^3} f\,\big(H_p(v) + (p-1)H_{p-2}(v)\big)\big(H_{q+1}(x) + qH_{q-1}(x)\big)H_r(y)\,dv\,dx\,dy \\ &\qquad + \frac{\sigma_e}{c_m}\frac{\alpha}{\sigma_v}\iiint_{\mathbb{R}^3} f\,H_{p-1}(v)\big(H_{q+1}(x) + qH_{q-1}(x)\big)H_r(y)\,dv\,dx\,dy \\ &= -\,\frac{\sigma_e}{c_m}\Big(a_{p,q+1,r} + (p-1)a_{p-2,q+1,r} + qa_{p,q-1,r} + q(p-1)a_{p-2,q-1,r}\Big) \\ &\qquad + \frac{\sigma_e}{c_m}\frac{\alpha}{\sigma_v}\Big(a_{p-1,q+1,r} + qa_{p-1,q-1,r}\Big)\,. \end{aligned} \tag{4.47}$$

Third integral A similar analysis to that described for equation (4.47) applies to the third integral on the right hand side of (4.44). The result of the corresponding calculation is that

$$\begin{aligned}
&\iiint_{\mathbb{R}^3} f\, y h_i(v) H_{p-1}(v) H_q(x) H_r(y)\, dv\, dx\, dy \\
&= -\frac{\sigma_i}{c_m}\Big(a_{p,q,r+1} + (p-1)a_{p-2,q,r+1} + r a_{p,q,r-1} + r(p-1)a_{p-2,q,r-1}\Big) \qquad (4.48)\\
&\qquad + \frac{\sigma_i}{c_m}\frac{\beta}{\sigma_v}\Big(a_{p-1,q,r+1} + r a_{p-1,q,r-1}\Big)\,.
\end{aligned}$$

4.2.2 The spectral representation

Results (4.42), (4.43), (4.46), (4.47) and (4.48) are now incorporated into equation (4.41) to show that the coefficients $a_{p,q,r}(t)$ satisfy the ordinary differential equations

$$\begin{aligned}
\frac{da_{p,q,r}(t)}{dt} &= -\Big(\frac{q}{\tau_e} + \frac{r}{\tau_i} - \frac{p}{\tau}\Big) a_{p,q,r} + \frac{p(p-1)}{\tau}\, a_{p-2,q,r} \\
\frac{da_{p,q,r}(t)}{dt} &= -p\frac{\sigma_e}{c_m}\Big(a_{p,q+1,r} + (p-1)a_{p-2,q+1,r} + q a_{p,q-1,r} + q(p-1)a_{p-2,q-1,r}\Big) \\
\frac{da_{p,q,r}(t)}{dt} &= -p\frac{\sigma_e}{c_m}\frac{\alpha}{\sigma_v}\Big(a_{p-1,q+1,r} + q a_{p-1,q-1,r}\Big) \qquad (4.49)\\
\frac{da_{p,q,r}(t)}{dt} &= -p\frac{\sigma_i}{c_m}\Big(a_{p,q,r+1} + (p-1)a_{p-2,q,r+1} + r a_{p,q,r-1} + r(p-1)a_{p-2,q,r-1}\Big) \\
\frac{da_{p,q,r}(t)}{dt} &= -p\frac{\sigma_i}{c_m}\frac{\beta}{\sigma_v}\Big(a_{p-1,q,r+1} + r a_{p-1,q,r-1}\Big)
\end{aligned}$$

where it is understood that $a_{p,q,r} = 0$ if at least one of p, q or r is a negative integer.

To appreciate why $a_{p,q,r}(t)$ are related to the coefficients of the spectral representation of the solution of the Fokker Planck equation in terms of modified Hermite polynomials, note that the transitional PDF can be represented by the triple spectral series

$$f(v,x,y,t) = \phi(v)\phi(x)\phi(y)\sum_{k=0}^{\infty}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}\frac{f_{k,n,m}(t)}{k!\,n!\,m!}\,H_k(v)H_n(x)H_m(y)\,. \qquad (4.50)$$

The requirements that $f(v,x,y,t)$ is a probability density function is seen to satisfy the constraint

$$\iiint_{\mathbf{R}^3} f(v,x,y,t)\, dx\, dy\, dv = 1\,.$$

When expression $f(v,x,y,t)$ is replaced by (4.50) in this equation, the coefficients $f_{k,n,m}(t)$ are required to satisfy

$$\begin{aligned}
&\iiint_{\mathbf{R}^3} f(v,x,y,t)\, dv\, dx\, dy \\
&= \sum_{k=0}^{\infty}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}\iiint_{\mathbf{R}^3}\frac{f_{k,n,m}(t)}{k!\,n!\,m!}\phi(v)\phi(x)\phi(y)H_k(v)H_n(x)H_m(y)\, dv\, dx\, dy \\
&= \sum_{k=0}^{\infty}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty}\frac{f_{k,n,m}(t)}{k!\,n!\,m!}\,\delta(k,0)\,\delta(n,0)\,\delta(m,0) = f_{0,0,0}(t) = 1\,.
\end{aligned}$$

The fact that $f(v,x,y,t) \geq 0$ for all values of v, x and y cannot be imposed, but rather is a consequence of the properties of the behaviour of the coefficients $a_{p,q,r}(t)$. However, it is anticipated that because $\phi(v)\phi(x)\phi(y)$ is a good estimate of $f(v,x,y,t)$, then the values of all coefficients other than $f_{0,0,0}$ will be small. Finally, to obtain the relationship between $a_{p,q,r}(t)$ and the coefficients of equation (4.50), this spectral representation is first multiplied by $H_p(v)H_q(x)H_r(y)$ and the resulting equation integrated over $\mathbf{R}^3$ to obtain

$$\begin{aligned} a_{p,q,r}(t) &= \iiint_{\mathbb{R}^3} f(v,x,y,t)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy \\ &= \sum_{k=0}^{\infty}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} \frac{f_{k,n,m}(t)}{k!\,n!\,m!} \iiint_{\mathbb{R}^3} \phi(v)\phi(x)\phi(y)H_k(v)H_n(x)H_m(y)H_p(v)H_q(x)H_r(y)\,dv\,dx\,dy \\ &= \sum_{k=0}^{\infty}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} \frac{f_{k,n,m}(t)}{k!\,n!\,m!} \Big[\int_{\mathbb{R}} \phi(v)H_k(v)H_p(v)\,dv\Big]\cdots\Big[\int_{\mathbb{R}} \phi(y)H_m(y)H_r(y)\,dy\Big] \\ &= \sum_{n=0}^{\infty}\sum_{m=0}^{\infty} \frac{f_{k,n,m}(t)}{k!\,n!\,m!} \Big[k!\,\delta(k,p)\Big]\Big[n!\,\delta(n,q)\Big]\Big[m!\,\delta(m,r)\Big] = f_{p.q,r}(t)\,. \end{aligned} \tag{4.51}$$

4.2.3 The stationary density

The objective of the analysis is to compute the stationary marginal density of the membrane potential, that is, the marginal density of the membrane potential when $t \to \infty$. First, the marginal density of the membrane potential at any time t is by definition.The specification of the stationary density of (x,y,v) becomes

$$f_{\mathrm{M}}(v,t) = \iint_{\mathbb{R}^2} \phi(v)\phi(x)\phi(y) \sum_{k=0}^{\infty}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} \frac{f_{k,n,m}(t)}{k!\,n!\,m!}\,H_k(v)H_n(x)H_m(y)\,dx\,dy\,.$$

This double integral can be expressed as a repeated integral to obtain

$$f_{\mathrm{M}}(v,t) \quad = \quad \phi(v)\sum_{k=0}^{\infty}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} \frac{f_{k,n,m}(t)}{k!\,n!\,m!} H_k(v)\Big[\int_{\mathbb{R}} \phi(x)\,H_n(x)\,dx\Big]\Big[\int_{\mathbb{R}} \phi(y)\,H_m(y)\,dy\Big]\,,$$

and this in turn simplifies to give the final formula

$$\begin{aligned} f_{\mathrm{M}}(v,t) &= \phi(v)\sum_{k=0}^{\infty}\sum_{n=0}^{\infty}\sum_{m=0}^{\infty} \frac{f_{k,n,m}(t)}{k!\,n!\,m!} H_k(v)\,\delta(n,0)\,\delta(m,0) \\ &= \phi(v)\sum_{k=0}^{\infty} \frac{f_{k,0,0}(t)}{k!} H_k(v)\,. \end{aligned} \tag{4.52}$$

Therefore, the computation of the marginal density of the membrane potential requires the calculation of the coefficients $f_{k,0,0}$, although of course, to achieve this objective will require the solution of the system of ordinary differential equations (4.51).

Since we anticipate that coefficients corresponding to higher order modified Hermite polynomials will be smaller, it is appropriate to truncate equations (4.49) at order N by asserting that all coefficients with any index exceeding N are zero. By this approximation, equations (4.49) are reduced to a system of $(N+1)^3-1$ ordinary differential equations for the coefficients $a_{p,q,r}$ where $0 \geq p,q,r \leq N$, with the proviso at $a_{0,0,0}=1$ - the differential equation satisfied by $a_{0,0,0}$ is $da_{0,0,0}/dt=0$. In general initial values for $a_{p,q,r}$ would come from the initial probability density of $\mathbf{y}=(x,y,v)$. However, if the intention is to compute the stationary marginal density of the membrane potential, then the initial conditions are unimportant and what is of concern is the limiting values of these coefficients as $t \to \infty$. These values are the solution of the system of linear equations

$$\begin{aligned}
&-\Big(\frac{q}{\tau_e}+\frac{r}{\tau_i}-\frac{p}{\tau}\Big)a_{p,q,r}+\frac{p(p-1)}{\tau}a_{p-2,q,r}-p\frac{\sigma_e}{c_m}\frac{\alpha}{\sigma_v}\Big(a_{p-1,q+1,r}+qa_{p-1,q-1,r}\Big)\\
&\quad -p\frac{\sigma_e}{c_m}\Big(a_{p,q+1,r}+(p-1)a_{p-2,q+1,r}+qa_{p,q-1,r}+q(p-1)a_{p-2,q-1,r}\Big)\\
&\qquad -p\frac{\sigma_i}{c_m}\Big(a_{p,q,r+1}+(p-1)a_{p-2,q,r+1}+ra_{p,q,r-1}+r(p-1)a_{p-2,q,r-1}\Big)\\
&\qquad\quad -p\frac{\sigma_i}{c_m}\frac{\beta}{\sigma_v}\Big(a_{p-1,q,r+1}+ra_{p-1,q,r-1}\Big)=0
\end{aligned} \tag{4.53}$$

where $a_{0,0,0}=1$ and it is understood that $a_{p,q,r}=0$ if at least one of p, q or r is a negative integer. It is useful to consider separately the case $p=0$, $p=1$ and $p=2$.

Case $p=0$ When $p=0$, equation (4.53) gives

$$\Big(\frac{q}{\tau_e}+\frac{r}{\tau_i}\Big)a_{0,q,r}=0$$

from which it follows that

$$a_{0,q,r}=\left[\begin{array}{ll} 0 & q\geq 0\,,\quad r\geq 0\,,\quad q+r>0\,,\\ 1 & p=r=0\,. \end{array}\right. \tag{4.54}$$

Case $p=1$ When $p=1$, equation (4.53) gives

$$\begin{aligned}
&-\Big(\frac{q}{\tau_e}+\frac{r}{\tau_i}-\frac{1}{\tau}\Big)a_{1,q,r}-\frac{\sigma_e}{c_m}\frac{\alpha}{\sigma_v}qa_{0,q-1,r}-\frac{\sigma_i}{c_m}\frac{\beta}{\sigma_v}r\,a_{0,q,r-1}\\
&\quad -\frac{\sigma_e}{c_m}\Big(a_{1,q+1,r}+qa_{1,q-1,r}\Big)-\frac{\sigma_i}{c_m}\Big(a_{1,q,r+1}+ra_{1,q,r-1}\Big)=0\,.
\end{aligned} \tag{4.55}$$

Case $p=2$ When $p=2$, equation (4.53) gives

$$\begin{aligned}
&-\Big(\frac{q}{\tau_e}+\frac{r}{\tau_i}-\frac{2}{\tau}\Big)\,a_{2,q,r}+\frac{2}{\tau}\,a_{0,q,r}-\frac{2\sigma_e}{c_m}\frac{\alpha}{\sigma_v}\Big(a_{1,q+1,r}+qa_{1,q-1,r}\Big)\\
&\quad-\frac{2\sigma_e}{c_m}\Big(a_{2,q+1,r}+qa_{2,q-1,r}+qa_{0,q-1,r}\Big)-\frac{2\sigma_i}{c_m}\Big(a_{2,q,r+1}+ra_{2,q,r-1}+ra_{0,q,r-1}\Big)\\
&\qquad-\frac{2\sigma_i}{c_m}\frac{\beta}{\sigma_v}\Big(a_{1,q,r+1}+ra_{1,q,r-1}\Big)=0
\end{aligned}\tag{4.56}$$

4.2.4 Special case $N=1$

In this special case there are in principle $2^3-1=7$ coefficients to be determined although, of course, $a_{0,0,1}=a_{0,1,0}=a_{0,1,1}=0$. The coefficients to be determined are therefore $a_{1,0,0}$, $a_{1,0,1}$, $a_{1,1,0}$ and $a_{1,1,1}$. It follow from the previous analysis that these coefficients satisfy the linear equations

$$\begin{array}{ll}
\left.\begin{array}{l} q=0\\ r=0\end{array}\right] & -\dfrac{1}{\tau}\,a_{1,0,0}+\dfrac{\sigma_e}{c_m}\,a_{1,1,0}+\dfrac{\sigma_i}{c_m}\,a_{1,0,1}=0\\[2ex]
\left.\begin{array}{l} q=0\\ r=1\end{array}\right] & \Big(\dfrac{1}{\tau_i}-\dfrac{1}{\tau}\Big)\,a_{1,0,1}+\dfrac{\sigma_i}{c_m}\dfrac{\beta}{\sigma_v}\,a_{0,0,0}+\dfrac{\sigma_e}{c_m}\,a_{1,1,1}+\dfrac{\sigma_i}{c_m}\,a_{1,0,0}=0\\[2ex]
\left.\begin{array}{l} q=1\\ r=0\end{array}\right] & \Big(\dfrac{1}{\tau_e}-\dfrac{1}{\tau}\Big)\,a_{1,1,0}+\dfrac{\sigma_e}{c_m}\dfrac{\alpha}{\sigma_v}\,a_{0,0,0}+\dfrac{\sigma_e}{c_m}\,a_{1,0,0}+\dfrac{\sigma_i}{c_m}\,a_{1,1,1}=0\\[2ex]
\left.\begin{array}{l} q=1\\ r=1\end{array}\right] & \Big(\dfrac{1}{\tau_e}+\dfrac{1}{\tau_i}-\dfrac{1}{\tau}\Big)\,a_{1,1,1}+\dfrac{\sigma_e}{c_m}\,a_{1,0,1}+\dfrac{\sigma_i}{c_m}\,a_{1,1,0}=0
\end{array}\tag{4.57}$$

When expressed in matrix notation, the coefficients $a_{1,0,0}$, $a_{1,0,1}$, $a_{1,1,0}$ and $a_{1,1,1}$ satisfy the linear equations

$$\begin{bmatrix}
\dfrac{1}{\tau} & -\dfrac{\sigma_i}{c_m} & -\dfrac{\sigma_e}{c_m} & 0\\[2ex]
\dfrac{\sigma_i}{c_m} & \Big(\dfrac{1}{\tau_i}-\dfrac{1}{\tau}\Big) & 0 & \dfrac{\sigma_e}{c_m}\\[2ex]
\dfrac{\sigma_e}{c_m} & 0 & \Big(\dfrac{1}{\tau_e}-\dfrac{1}{\tau}\Big) & \dfrac{\sigma_i}{c_m}\\[2ex]
0 & \dfrac{\sigma_e}{c_m} & \dfrac{\sigma_i}{c_m} & \Big(\dfrac{1}{\tau_e}+\dfrac{1}{\tau_i}-\dfrac{1}{\tau}\Big)
\end{bmatrix}
\begin{bmatrix} a_{1,0,0}\\[2ex] a_{1,0,1}\\[2ex] a_{1,1,0}\\[2ex] a_{1,1,1}\end{bmatrix}
=\begin{bmatrix} 0\\[2ex] -\dfrac{\sigma_i}{c_m}\dfrac{\beta}{\sigma_v}\\[2ex] -\dfrac{\sigma_e}{c_m}\dfrac{\alpha}{\sigma_v}\\[2ex] 0\end{bmatrix}.\tag{4.58}$$

In this case the approximate expression for the marginal density of v is therefore

$$f_{\mathrm{M}}(v)=\phi(v)\Big(1+f_{1,0,0}H_1(v)\Big)=\phi(v)\big(1+a_{1,0,0}H_1(v)\big)$$

where $a_{1,0,0}$ is obtained by solving equations (4.58). The expected value of v based on this density is

$$\mathrm{E}\left[v\right]=\int_{\mathbb{R}}v\phi(v)\big(1+a_{1,0,0}H_1(v)\big)\,dv=-a_{1,0,0}$$

taking account of the fact that $H_1(v) = -v$, and its variance is $1 - a_{1,0,0}^2$. More accurate expressions for the mean value and variance of v can be obtained by incorporating further terms into the marginal density of v. For example, the approximation

$$f_{\mathrm{M}}(v) = \phi(v)\Big(1 + f_{1,0,0}H_1(v) + \frac{f_{2,0,0}}{2}\,H_2(v)\Big)$$

will require the solution of a system of 18 linear equations. In general, a marginal density involving contributions from $H_0(v)$ to $H_{\mathrm{N}}(v)$ will require the solution of a system of $N(N+1)^2$ linear equations. This is because the $(N+1)^2$ coefficients $a_{0,q,r}$ are all known, since they either take the value 1 in the case of $a_{0,0,0}$ or zero otherwise.

4.2.5 Conclusions

In this last Chapter we demonstrated that the first term in the expansion of the full solution is a Gaussian process and a good approximation of the density. This was then followed by the next term approximation that concludes to the same result as the variances of the noise conductances are small and so their contribution in the calculation of the mean value and the variance is unimportant. Then we described the transformation process in order to proceed to a solution that would require the use of Hermite Polynomials. For that reason we re-scaled the membrane equation and made it a non-dimensional equation that has stationary distribution that is Normal. We constructed a system of ordinary differential equations that consisted of coefficients that needed to be calculated in order to obtain the marginal density.

Using this solution procedure the initial conditions are of no importance and the only concern is the value of the coefficients, to be calculated through the system of ODE'S, as $t \to \infty$. This way we avoid deviations between the numerical and analytical solution as the one's seen in Rudolph and Destexhe (2003) due to the use of stochastic calculus.

Chapter 5

Conclusions

In chapter 1 we gave a short description of all the mathematical and biological background needed in order to understand the function of a neuron during the synapse phase and how it could be expressed in mathematical terms. Then we started our examination of a number of different conductance models. Chapter 2 investigated the models of synaptic conductance used by Richardson (2004). His first model treated synaptic conductance as a delta function so that the history of synaptic activity manifested itself entirely through the membrane potential and not via any residual conductance. In this model the membrane potential jumps discontinuously on the arrival of a presynaptic spike at a synapse, but unlike an exogenous current-based model of a synapse, the size of this discontinuity is not fixed but rather depends of the membrane potential immediately preceding the arrival of the spike. Between spikes the membrane potential decays exponentially towards its resting value. This model was then simulated in order to find the firing rate and the stationary distribution of the membrane potential. Richardson (2004) then introduced his second model in which the membrane potential was regarded as a continuous stochastic process evolving in accordance with a stochastic differential equation. The motivation for this model was based on the idea that although the membrane potential behaves discontinuously as spikes arrive, the size of the discontinuity is so small and the rate at which spikes arrive is so large that in practice the membrane potential evolves as a continuous process, but one which is not differentiable. Richardson (2004) came to the conclusion that conductance based models subject to temporally correlated input experience the same voltage fluctuations as those seen in real neurons. Also he considered current based models of conductance, namely models in which the effect of the arrival of a spike was to cause a fixed amount of charge to across the membrane, and concluded that a current based model with a drive dependent time constant provided a simple and biologically relevant model of neuronal response.

Chapter 3 considers the synaptic conductance model of Rudolph and Destexhe (2003,2005). The conductances satisfied stochastic differential equations of Ornstein-Unhlebeck type. We examined their method for the derivation of the expression for the distribution of the steady state membrane potential. The expression in Rudolph and Destexhe (2003) did not match that given in Rudolph and Destexhe (2005) since it was seen that the former differed significantly from the numerical simulation and led to the correction proposed in Rudolph and Destexhe (2005). Rudolph and Destexhe (2003,2005) made the same comparison as Richardson (2004) between current and conductance based models and concluded that the latter is adequate to describe the high-conductance states similar to those occurring in real life.

Chapter 4 provided a simple explanation for the final conclusion of the Rudolph and Destexhe (2003,2005) papers and extended their result. The difficulty stems from the fact that synaptic conductance decays exponentially after the arrival of a spike, and this in turn causes the synaptic conductance to be an autocorrelated random process. Rudolph and Destexhe (2003) did not take account of this autocorrelation and consequently they obtained marginal distributions of membrane potential that were too diffuse. Rudolph and Destexhe (2005) corrected this shortcoming after an extensive and technical analysis. Chapter 4, however, provides a simple explanation for the final conclusion of the Rudolph and Destexhe (2003,2005) papers. It uses a central limit property of random variables to argue that the stationary distribution of the membrane potential is approximately Gaussian but with a value for variance incorporating the persistence in conductance that results from the arrival of a presynaptic spike. In an alternative procedure the underlying Fokker Planck equation satisfied by the probability density function of the membrane potential and the synaptic conductances was formulated. It was then shown how the stationary distribution of this equation can be approximated to arbitrary accuracy by a spectral series based on modified Hermite polynomials. The technique was illustrated by computing the second order approximation to the marginal distribution of the membrane potential.

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Appendix A

Properties of the OU process

Suppose that

$$dg = -agdt + \sigma\, dW$$

where a and σ are non negative constants. In order to obtain an expression for $g(t)$ we multiply the above equation by e^{at} and so

$$e^{at}dg(t) + ag(t)e^{at} = \sigma\, dW e^{at}$$

and that now becomes

$$\frac{d}{dt}\Big[e^{at}g(t)\Big] = \sigma\, e^{at}dW\,.$$

If we integrate from t_0 to t

$$e^{at}g(t) - e^{at_0}g(t_0) = \sigma \int_{t_0}^{t} e^{as}\, dW_s$$

it is now easy to see that the expression for $g(t)$ is the following

$$g(t) = g(t_0)e^{-a(t-t_0)} + \sigma \int_{t_0}^{t} e^{-a(t-s)}\, dW_s \tag{A.1}$$

Correlation between $g(t)$ and $g(t_0)$:

Using the expression given by A.1 we get

$$\begin{aligned}
E\Big[g(t)g(t_0)\Big] &= E\Big[\sigma^2 \int_{-\infty}^{t} e^{-a(t-s)}\, dW_s \int_{-\infty}^{t_0} e^{-a(t_0-u)}\, dW_u\Big] \\
&= \sigma^2 E\Big[\int_{-\infty}^{t}\int_{-\infty}^{t_0} e^{-a(t-s)}e^{-a(t_0-u)}\, dW_s\, dW_u\Big] \\
&= \sigma^2 \int_{-\infty}^{t}\int_{-\infty}^{t_0} e^{-a(t-s)}e^{-a(t_0-u)}\, E\Big[dW_s\, dW_u\Big] \\
&= \sigma^2 \int_{-\infty}^{t}\int_{-\infty}^{t_0} e^{-a(t-s)}e^{-a(t_0-u)}\delta(s-u)\, dsdu\,.
\end{aligned}$$

If $t_0 > t$ then

$$\sigma^2 \int_{-\infty}^{t} e^{-a(t+t_0-2s)}\,ds = \sigma^2 \Big[\frac{e^{-a(t+t_0-2s)}}{2a}\Big]_{-\infty}^{t} = \frac{\sigma^2}{2a} e^{-a(t_0-t)}\,.$$

If $t_0 < t$ then

$$\sigma^2 \int_{-\infty}^{t_0} e^{-a(t+t_0-2u)}\,du = \sigma^2 \Big[\frac{e^{-a(t+t_0-2u)}}{2a}\Big]_{-\infty}^{t_0} = \frac{\sigma^2}{2a} e^{-a(t-t_0)}\,.$$

In general

$$E\Big[g(t)g(t_0)\Big] = \frac{\sigma^2}{2a}\, e^{-a|t-t_0|}$$

but because $t > t_0$ we will always use

$$E\Big[g(t)g(t_0)\Big] = \frac{\sigma^2}{2a}\, e^{-a(t-t_0)}\,.$$

Properties of $W(t) = \int_0^t g(s)\,ds$:

Using the integral definition of $w(t)$ it can also be said that

$$w(t) - w(t_0) = \int_{t_0}^{t} g(s)\,ds$$

so now it is possible to obtain an expression for $w(t)$.

$$\begin{aligned}
w(t) &= w(t_0) + \int_{t_0}^{t} \Big[g(t_0)e^{-a(s-t_0)} + \int_{t_0}^{s} e^{-a(s-u)}\,dW_u\Big]\,ds \\
&= w(t_0) - \frac{g(t_0)}{a}\Big[e^{-a(s-t_0)}\Big]_{t_0}^{t} + \sigma \int_{t_0}^{t}\int_{t_0}^{s} e^{-a(s-u)}\,dW_u ds \\
&= w(t_0) - \frac{g(t_0)}{a}\Big[e^{-a(t-t_0)} - 1\Big] + \sigma \int_{t_0}^{t} e^a u\,dW_u \int_{u}^{t} e^{-as}\,ds \\
&= w(t_0) - \frac{g(t_0)}{a}\Big[e^{-a(t-t_0)} - 1\Big] - \frac{\sigma}{a}\int_{t_0}^{t} (e^{-a(t-u)} - 1)\,dW_u
\end{aligned}$$

The correlation structure of $W(t)$:

Since we have obtained an expression for $W(t)$ it easy to see that

$$E\Big[w(t)w(t_0)\Big] = E\Big[w(t_0)^2\Big] - \frac{\Big[e^{-a(t-t_0)} - 1\Big]}{a} E\Big[w(t_0)g(t_0)\Big] - 0 \qquad \text{(A.2)}$$

because as we know $E(dW_u) = 0$. So

$$\begin{aligned}
E\Big[g(t_0)w(t_0)\Big] &= E\Big[\int_0^{t_0} g(s)\,dsg(t_0)\Big] \\
&= \int_0^{t_0} E\Big[g(s)g(t_0)\Big]\,ds \\
&= \int_0^{t_0} \frac{\sigma^2}{2a} e^{-a|s-t_0|}\,ds = \frac{\sigma^2}{2a^2}\Big[1 - e^{-at_0}\Big]\,.
\end{aligned}$$

Also

$$\begin{aligned}
E\Big[w(t_0)^2\Big] &= E\Big[\int_0^{t_0} g(s)\,ds \int_0^{t_0} g(u)\,du\Big] \\
&= \int_0^{t_0}\int_0^{t_0} E\Big[g(s)g(u)\Big]\,ds\,du \\
&= \int_0^{t_0}\int_0^{t_0} \frac{\sigma^2}{2a}e^{-a|s-u|}\,ds\,du \\
&= \int_0^{t_0} \frac{\sigma^2}{2a}2\Big(\int_0^{s} e^{-a(s-u)}\,du\Big)\,ds \\
&= \frac{\sigma^2}{a^2}\int_0^{t_0}\Big(1-e^{-as}\Big)\,ds = \frac{\sigma^2}{a^3}\Big[at_0+e^{-at_0}-1\Big].
\end{aligned}$$

Finally we return to equation A.2 and by substitution we derive an expression for the correlation between $w(t)$ and $w(t_0)$

$$\begin{aligned}
E\Big[w(t)w(t_0)\Big] &= \frac{\sigma^2}{a^3}\Big[at_0+e^{-at_0}-1\Big] - \frac{\sigma^2}{2a^3}\big[e^{-a(t-t_0)}-1\big]\big[1-e^{-at_0}\big] \\
&= \frac{\sigma^2}{2a^3}\Big[2at_0+e^{-at_0}+e^{-at}-1-e^{-a(t-t_0)}\Big].
\end{aligned}$$

Appendix B

Listing of computer programs

All differential equations were integrated using the freely available numerical integrator DLSODA.

B.1 Program Flux

```
      PROGRAM FLUX
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
      PARAMETER( AE=0.002D0, AI=0.013D0, RE=15.0D0, RI=9.23D0,
      *          EE=0.0D0, EI=-75.0D0, CM=1.0D0, GL=0.05D0,
      *          EL=-80.0D0, VTHR=-55.0D0, VRES=-65.0D0)
      PARAMETER( N=2, EPS=5.0D-7)
      DOUBLE PRECISION JUMP
      LOGICAL START, REPEAT
      COMMON / PARMS / E, ED, ES, GAMA, RVAL, TAU

C   STEP 1 - Initialise parameters
      ES = (AE*AE*RE*EE+AI*AI*RI*EI)/(AE*AE*RE+AI*AI*RI)
      ED = AI*AE*SQRT(RE*RI)*ABS(EE-EI)/(AE*AE*RE+AI*AI*RI)
      E = (GL*EL/CM+AE*RE*EE+AI*RI*EI)/(GL/CM+AE*RE+AI*RI)
      TAU = 1.0D0/(GL/CM+AE*RE+AI*RI)
      GAMA = 2.0D0*(GL/CM+AE*RE+AI*RI)/(AE*AE*RE*EE+AI*AI*RI*EI)

C   STEP 2 - INITIALISE ESTIMATES
      JUMP = 0.5D0
      EOLD = -4.0
      ENEW = EOLD+JUMP
      START = .TRUE.
      REPEAT = .TRUE.

C   STEP 3 - ITERATE BY BISECTION ALGORITHM
      VOLD = TARGET(EOLD)-1.D0
```

```
      DO WHILE ( REPEAT )
        IF ( START ) THEN
          VNEW = TARGET(ENEW)-1.D0
          IF ( VOLD*VNEW .GE. 0.D0 ) THEN
            VOLD = VNEW
            EOLD = ENEW
            ENEW = ENEW+JUMP
            WRITE(*,*) EOLD, VOLD
            WRITE(*,*) ENEW, VNEW
            READ(*,*)
          ELSE
            START = .FALSE.
          ENDIF
        ELSE
          EMID = 0.5D0*(EOLD+ENEW)
          VMID = TARGET(EMID)-1.0D0
          IF ( VOLD*VMID .GE. 0.D0 ) THEN
            EOLD = EMID
          ELSE
            ENEW = EMID
          ENDIF
          REPEAT = (ABS(EOLD-ENEW) .GT. EPS)
        ENDIF
      ENDDO

C   STEP 4 - OUTPUT ANSWER
      WRITE(*,*) "FLUX = ", 0.5D0*(EOLD+ENEW)
      STOP
      END


C ******************************************************************
C Specifies the system of ODEs
C
C   VARIABLES:-
C       Y(1) = F
C       Y(2) = RHO
C
C   DERIVATIVES:-
C       DY(1) = -Y(2)
C       DY(2) = -(TAU*GAMA*RVAL+Y(2)*(X-E)+2*Y(2)*(X-ES))/((X-ES)**2+ED**2)
C ******************************************************************
      SUBROUTINE FCN(N,X,Y,DY)
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
      DIMENSION Y(N), DY(N)
      COMMON / PARMS / E, ED, ES, GAMA, RVAL, TAU
```

```
      DY(1) = -Y(2)
      FAC = 1.0D0/((X-ES)**2+ED**2)
      DY(2) = -FAC*(TAU*GAMA*RVAL+Y(2)*(3.0D0*X-E-2.0D0*ES))
      RETURN
      END


C ******************************************************************
C   Specifies the Jacobian of system of ODEs
C
C   VARIABLES:-
C       Y(1) = F
C       Y(2) = RHO
C
C   DERIVATIVES:-
C       DY(1) = -Y(2)
C       DY(2) = -(TAU*GAMA*RVAL+Y(2)*(X-E)+2*Y(2)*(X-ES))/((X-ES)**2+ED**2)
C ******************************************************************
      SUBROUTINE JAC(N, X, Y, ML, MU, PD, NROWPD)
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
      DOUBLE PRECISION T, Y(*), PD(NROWPD,*)
      COMMON / PARMS / E, ED, ES, GAMA, RVAL, TAU

      FAC = 1.0D0/((X-ES)**2+ED**2)
      PD(1,1) = 0.D0;
      PD(1,2) = -1.0D0
      PD(2,1) = 0.0D0
      PD(2,2) = -FAC*(3.0D0*X-E-2.0D0*ES)
      RETURN
      END


      FUNCTION TARGET(EVAL)
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
      PARAMETER( N=2, LRW=22+N*MAX(16,N+9), LIW=20+N )
      PARAMETER( AE=0.002D0, AI=0.013D0, RE=15.0D0, RI=9.23D0,
     *           EE=0.0D0, EI=-75.0D0, CM=1.0D0, GL=0.05D0,
     *           EL=-80.0D0, VTHR=-55.0D0, VRES=-65.0D0)
      DIMENSION Y(N), WORK(LRW), IWORK(LIW)
      EXTERNAL FCN
      COMMON / PARMS / E, ED, ES, GAMA, RVAL, TAU

      RVAL = EVAL
      XIN = VTHR
      Y(1) = 0.0D0
      Y(2) = 0.0D0
      XOUT = VRES
```

```
      ITOL = 1
      RTOL = 5.0D-11
      ATOL = 5.0D-11
      ITASK = 1
      IFLAG = 1
      IOPT = 0
      JT = 1
      CALL DLSODA(FCN, N, Y, XIN, OUT, ITOL, RTOL, ATOL, ITASK,
     1            IFLAG, IOPT, RWORK, LRW, IWORK, LIW, JAC, JT)

C   MEANING OF ERROR OUTPUT FLAGS
C
C IFLAG = 2  if DLSODA was successful, negative otherwise.
C        -1 means excess work done on this call (perhaps wrong JT).
C        -2 means excess accuracy requested (tolerances too small).
C        -3 means illegal input detected (see printed message).
C        -4 means repeated error test failures (check all inputs).
C        -5 means repeated convergence failures (perhaps bad Jacobian
C           supplied or wrong choice of JT or tolerances).
C        -6 means error weight became zero during problem. (Solution
C           component i vanished, and ATOL or ATOL(i) = 0.)
C        -7 means work space insufficient to finish (see messages).

      IF ( IFLAG .NE. 2 ) THEN
         WRITE(*,*) "IRREGULAR EXIT FROM ODE", IFLAG
         STOP
      ENDIF
      TARGET = Y(1)
      RETURN
      END
```

B.2 Conductance treated as a delta function

```
      PROGRAM RICHARDSON
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
      PARAMETER( AE=0.004D0, AI=0.026D0, RE=1.20D0, RI=0.00D0,
     *           EE=0.0D0, EI=-75.0D0, CM=1.0D0, GL=0.05D0,
     *           EL=-80.0D0, VTHR=-68.0D0, VRES=-65.0D0,
     *           TAUL=20.0D0, MAXT=10000 )
      DIMENSION  V(10*MAXT+1)
      LOGICAL  REPEAT
      DATA     IX, IY, IZ / 5, 9, 48 /

C   STEP 1 - INITIALISE PARAMETERS
      VOLT = VRES
      TIME = 0.0D0
      TMAX = 1.0D3*DBLE(MAXT)
```

```
      ALPHAL = 1.0D0/TAUL
      FACI = 2.0D0*EXP(-0.5D0*AI)*SINH(0.5D0*AI)
      FACE = 2.0D0*EXP(-0.5D0*AE)*SINH(0.5D0*AE)
      CONE = -1.0D0/RE
      CONI = -1.0D0/RI
      NEXT = 1
      TNEXT = 100.0D0*DBLE(NEXT)

C   STEP 2 - INITIALISE FIRING TIMES
      CALL URAND( RAN, IX, IY, IZ)
      TE = CONE*LOG(RAN)
      CALL URAND( RAN, IX, IY, IZ)
      TI = CONI*LOG(RAN)

C   STEP 3 - RUN MAIN LOOP
      REPEAT = .TRUE.
      NSPK = 0
      OPEN(UNIT=2,
     1     FILE="RICH_INT1.DAT",
     1     ACTION="WRITE")
      DO WHILE ( REPEAT )

C   STEP 3A - ASK IF WE NEED TO SAMPLE BEFORE ANOTHER FIRING
        DT = TNEXT-TIME
        IF ( DT .LT. MIN(TI,TE) ) THEN
           V(NEXT) = EL+(VOLT-EL)*EXP(-ALPHAL*DT)
           NEXT = NEXT+1
           TNEXT = 100.0D0*DBLE(NEXT)
        ENDIF
        IF( TE .GT. TI) THEN
           VOLT = EL+(VOLT-EL)*EXP(-ALPHAL*TI)
           VOLT = VOLT+(EI-VOLT)*FACI
           TE = TE-TI
           TIME = TIME+TI
           CALL URAND( RAN, IX, IY, IZ)
           TI = CONI*LOG(RAN)
        ELSE
           TIME = TIME+TE
           VOLT = EL+(VOLT-EL)*EXP(-ALPHAL*TE)
           VOLT = VOLT+(EE-VOLT)*FACE
           IF ( VOLT .GE. VTHR ) THEN
              IF ( NSPK .EQ. 0 ) THEN
                 TOLD = TIME
              ELSE
                 WRITE(2,*) TIME-TOLD
                 TOLD = TIME
              ENDIF
```

```
              NSPK = NSPK+1
              VOLT = VRES
           ENDIF
           TI = TI-TE
           CALL URAND( RAN, IX, IY, IZ)
           TE = CONE*LOG(RAN)
        ENDIF
        REPEAT = ( TIME .LT. TMAX )
      ENDDO
      CLOSE(2)
      WRITE(*,*) "NUMBER OF SPIKES FIRED ", NSPK

C   STEP 4 - OUTPUT POTENTIALS
      OPEN(UNIT=1,
     1     FILE="RICH1.DAT",
     1     ACTION="WRITE")
      DO K=1, NEXT-1
         WRITE(1,*) V(K)
      ENDDO
      CLOSE(1)
      STOP
      END
```

B.3 Conductance treated as a stochastic processes

```
      PROGRAM RD
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
      PARAMETER( AE=0.004D0, AI=0.026D0, RE=10.0D0, RI=49.42D0,
     *           EE=0.0D0, EI=-75.0D0, CM=1.0D0, GL=0.05D0,
     *           EL=-80.0D0, VTHR=-62.0D0, VRES=-65.0D0, TAUE=10.0D0,
     *           TAUI=0.1D0, TAUL=20.0D0, MAXT=1000, NT=1000 )
      LOGICAL  REPEAT
      DATA     IX, IY, IZ / 5, 9, 48 /

C   STEP 1 - INITIALISE PARAMETERS
      NSTEP = NT*1000*MAXT
      CONE = -1.0D0/RE
      CONI = -1.0D0/RI

C   STEP 2 - SET INITIAL CONDUCTANCES
      GENEW = 0.0D0
      GINEW = 0.0D0

C   STEP 3 - INITIALISE FIRING TIMES
      DT = 1.0D0/DBLE(NT)
      DE = EXP(-DT/TAUE)
      DI = EXP(-DT/TAUI)
```

```
      CALL URAND( RAN, IX, IY, IZ)
      TE = CONE*LOG(RAN)
      NE = NINT(TE/DT)
      CALL URAND( RAN, IX, IY, IZ)
      TI = CONI*LOG(RAN)
      NI = NINT(TI/DT)
C   STEP 4 - RUN MAIN LOOP
      OPEN(UNIT=1,
     1     FILE="RICH2.DAT",
     1     ACTION="WRITE")
      OPEN(UNIT=2,
     1     FILE="RICH_INT2.DAT",
     1     ACTION="WRITE")
      VNEW = EL
      NSPK = 0
      DO K=1,MAXT
         DO NSTEP=1,1000*NT

C   STEP 4A - TREAT EXCITATORY SYNAPSES
            GEOLD = GENEW
            GENEW = GENEW*DE
            IF ( NE.LE.0 ) THEN
               GENEW = GENEW+CM*AE/TAUE
               CALL URAND( RAN, IX, IY, IZ)
               TE = CONE*LOG(RAN)
               NE = NINT(TE/DT)
            ELSE
               NE = NE-1
            ENDIF

C   STEP 4B - TREAT INHIBITORY SYNAPSES
            GIOLD = GINEW
            GINEW = GINEW*DI
            IF ( NI.LE.0 ) THEN
               GINEW = GINEW+CM*AI/TAUI
               CALL URAND( RAN, IX, IY, IZ)
               TI = CONI*LOG(RAN)
               NI = NINT(TI/DT)
            ELSE
               NI = NI-1
            ENDIF

C   STEP 4C - COMPUTE NEW MEMBRANE POTENTIAL
            TIME = DT*DBLE(K)
            TMP1 = 0.5D0*(2.0D0*CM-DT*(GL+GEOLD+GIOLD))
            TMP2 = 0.5D0*(2.0D0*CM+DT*(GL+GENEW+GINEW))
            TMP3 = 2.0D0*GL*EL+(GEOLD+GENEW)*EE+(GIOLD+GINEW)*EI
```

```
            TMP3 = TMP3*0.5D0*DT
            VOLD = VNEW
            VNEW = (TMP1*VOLD+TMP3)/TMP2
            IF ( VNEW .GT. VTHR ) THEN
               IF ( NSPK .EQ. 0 ) THEN
                  TOLD = TIME
               ELSE
                  WRITE(2,*) TIME-TOLD
               TOLD = TIME
               ENDIF
              VNEW = VRES
               NSPK = NSPK+1
            ENDIF

C   STEP 5 - OUTPUT POTENTIALS
            IF ( MOD(NSTEP,100*NT) .EQ. 0 ) THEN
               WRITE(1,*) 0.5D0*(VOLD+VNEW)
            ENDIF
         ENDDO
      ENDDO
      WRITE(*,*) "NUMBER OF SPIKES", NSPK
      CLOSE(1)
      CLOSE(2)
      STOP
      END
```

B.4 Simulation of Rudolph-Destexhe(2003) Model for the distribution of the membrane potential

```
C ****************************************************************
C  Program to simulate distribution of membrane potential based
C  on OU model of excitatory and inhibitory synaptic activity
C  for the extended analytic solution
C
C    dv  = -(v-E0)*dt/tm+(ge-GE)*(V-EE)*dt+(gi-GI)*(V-EI)*dt
C    dge = -(ge-GE)*dt/te+sqrt{2.0*se*se/te)*dWe
C    dgi = -(gi-GE)*dt/ti+sqrt{2.0*si*si/ti)*dWi
C****************************************************************
      PROGRAM SIMRD
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
      PARAMETER( EL=-80.0D0, GM=0.0452D0, CM=1.0D0, AREA=0.000100D0,
     *           EE=0.0D0, TE0=2.728D0, GE0=0.000012D0, SE0=0.000003D0,
     *           EI=-75.0D0, TI0=10.49D0, GI0=0.000057D0,
     *           SI0=0.0000066D0, NT=100, MT=1000, NDEN=1000 )
      DIMENSION V(0:NDEN), PDF(0:NDEN)
      COMMON / PARMS / IX, IY, IZ
```

```
C   STEP 1 - SET SEEDS OF RANDOM NUMBER GENERATOR
      IX = 10
      IY = 20
      IZ = 30

C   STEP 2 - SET MODEL PARAMETERS
      GE = GE0/AREA
      GI = GI0/AREA
      SE = SE0/(CM*AREA)
      SI = SI0/(CM*AREA)
      TM = 1.36D0
      E0 = (GM*EL+GE*EE+GI*EI)/(GM+GE+GI)

C    STEP 3 - INITIALISE SIMULATION
      DT = 1.0D0/DBLE(NT)
      FAC = 1.0D0/TM
      DFE = EXP(-DT/TE0)
      DFI = EXP(-DT/TI0)
      SE = SE*SQRT(2.D0*DFE*SINH(DT/TE0))
      SI = SI*SQRT(2.D0*DFI*SINH(DT/TI0))
      NSTEP = MT*1000*NT
      GENEW = 0.0D0
      GINEW = 0.0D0
      VNEW = 0.0D0

C    STEP 4 - BURN IN PHASE OF SIMULATION
      DO K = 0,1000*NT
        GEOLD = GENEW
        GENEW = DFE*GEOLD+GAUSS(0.D0,SE)
        GIOLD = GINEW
        GINEW = DFI*GIOLD+GAUSS(0.D0,SI)
        RHS = 1.D0+0.5D0*DT*(GEOLD+GIOLD-FAC)
        LHS = 1.D0-0.5D0*DT*(GENEW+GINEW-FAC)
        TMP = 0.5D0*DT*((E0-EE)*(GEOLD+GENEW)+(E0-EI)*(GIOLD+GINEW))
        VOLD = VNEW
        VNEW = (TMP+VOLD*RHS)/LHS
      ENDDO

C    STEP 5 - THE MAIN SIMULATION
      M = 100*NT
      OPEN( UNIT=1, FILE="VOLT.DAT", ACTION="WRITE")
      DO K=0, NSTEP
        GEOLD = GENEW
        GENEW = DFE*GEOLD+GAUSS(0.D0,SE)
        GIOLD = GINEW
        GINEW = DFI*GIOLD+GAUSS(0.D0,SI)
```

```
          RHS = 1.D0+0.5D0*DT*(GEOLD+GIOLD-FAC)
          LHS = 1.D0-0.5D0*DT*(GENEW+GINEW-FAC)
          TMP = 0.5D0*DT*((E0-EE)*(GEOLD+GENEW)+(E0-EI)*(GIOLD+GINEW))
          VOLD = VNEW
          VNEW = (TMP+VOLD*RHS)/LHS
          IF ( K .EQ. M*(K/M) ) WRITE(1,*) VNEW+E0
        ENDDO
        CLOSE(1)

C     STEP 6 - BUILD THEORETICAL DENSITY
        SE = SE0/(CM*AREA)
        SI = SI0/(CM*AREA)
        COP1 = SE**2*TE0+SI**2*TI0
        A1 = -0.5D0-(GE+GI+GM)/COP1
        COP2 = GE*SI**2*TI0-GI*SE**2*TE0
        COP3 = SE*SI*SQRT(TE0*TI0)
        COP4 = SE**2*TE0*(EL-EE)
        COP5 = SI**2*TI0*(EL-EI)
        COP6 = COP2*(EE-EI)
        A2 = (2.D0*(GM*(COP4+COP5)+COP6))/((EE-EI)*COP3*COP1)
        VMIN = -85.D0
        VMAX = -45.D0
        DV = (VMAX-VMIN)/DBLE(NDEN)
        DO K=0,NDEN
          V(K) = VMIN+DV*DBLE(K)
          TOP1 = SE**2*TE0*(V(K)-EE)
          TOP2 = SI**2*TI0*(V(K)-EI)
          TMP = (TOP1*(V(K)-EE)+TOP2*(V(K)-EI))
          RHO = TMP**A1
          TMP = (TOP1+TOP2)/(COP3*(EE-EI))
          PDF(K) = RHO*EXP(A2*ATAN(TMP))
        ENDDO

C     STEP 7 - NORMALISE DENSITY USING SIMPSONS RULE
        SUM = 0.0D0
        DO K=0,(NDEN-1)/2
          KK = 2*K
          SUM = SUM+2.0D0*PDF(KK)+4.0D0*PDF(KK+1)
        ENDDO
        SUM = SUM-PDF(0)+PDF(NDEN)
        SUM = SUM*DV/3.0D0
        OPEN( UNIT=1, FILE="DENA.DAT", ACTION="WRITE")
        DO K=0,NDEN
          IF ( 10*(K/10) .EQ. K ) WRITE(1,*) V(K), PDF(K)/SUM
        ENDDO
        CLOSE(1)
        END
```

B.5 Simulation of Rudolph-Destexhe(2005) Model for the distribution of the membrane potential

```
C ****************************************************************
C  Program to simulate distribution of membrane potential based
C  on OU model of excitatory and inhibitory synaptic activity
C
C    dv = -(v-E0)*dt/tm +(ge-GE)*(V-EE)*dt+(gi-GI)*(V-EI)*dt
C   dge = -(ge-GE)*dt/te+sqrt{2.0*se*se/te)*dWe
C   dgi = -(gi-GE)*dt/ti+sqrt{2.0*si*si/ti)*dWi
C ****************************************************************
      PROGRAM SIMRD
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
      PARAMETER( EL=-80.0D0, GM=0.0452D0, CM=1.0D0, AREA=0.000100D0,
     *           EE=0.0D0, TE0=2.728D0, GE0=0.000012D0, SE0=0.000003D0,
     *           EI=-75.0D0, TI0=10.49D0, GI0=0.000057D0,
     *           SI0=0.0000066D0, NT=100, MT=1000, NDEN=1000 )
      DIMENSION V(0:NDEN), PDF(0:NDEN)
      COMMON / PARMS / IX, IY, IZ

C   STEP 1 - SET SEEDS OF RANDOM NUMBER GENERATOR
      IX = 10
      IY = 20
      IZ = 30

C   STEP 2 - SET MODEL PARAMETERS
      GE = GE0/AREA
      GI = GI0/AREA
      SE = SE0/(CM*AREA)
      SI = SI0/(CM*AREA)
      TM = 1.36D0
      E0 = (GM*EL+GE*EE+GI*EI)/(GM+GE+GI)

C    STEP 3 - INITIALISE SIMULATION
      DT = 1.0D0/DBLE(NT)
      FAC = 1.0D0/TM
      DFE = EXP(-DT/TE0)
      DFI = EXP(-DT/TI0)
      SE = SE*SQRT(2.D0*DFE*SINH(DT/TE0))
      SI = SI*SQRT(2.D0*DFI*SINH(DT/TI0))
      NSTEP = MT*1000*NT
      GENEW = 0.0D0
      GINEW = 0.0D0
      VNEW = 0.0D0

C    STEP 4 - BURN IN PHASE OF SIMULATION
      DO K = 0,1000*NT
```

```
        GEOLD = GENEW
        GENEW = DFE*GEOLD+GAUSS(0.D0,SE)
        GIOLD = GINEW
        GINEW = DFI*GIOLD+GAUSS(0.D0,SI)
        RHS = 1.D0+0.5D0*DT*(GEOLD+GIOLD-FAC)
        LHS = 1.D0-0.5D0*DT*(GENEW+GINEW-FAC)
        TMP = 0.5D0*DT*((E0-EE)*(GEOLD+GENEW)+(E0-EI)*(GIOLD+GINEW))
        VOLD = VNEW
        VNEW = (TMP+VOLD*RHS)/LHS
      ENDDO

C    STEP 5 - THE MAIN SIMULATION
      M = 100*NT
      OPEN( UNIT=1, FILE="VOLT.DAT", ACTION="WRITE")
      DO K=0, NSTEP
        GEOLD = GENEW
        GENEW = DFE*GEOLD+GAUSS(0.D0,SE)
        GIOLD = GINEW
        GINEW = DFI*GIOLD+GAUSS(0.D0,SI)
        RHS = 1.D0+0.5D0*DT*(GEOLD+GIOLD-FAC)
        LHS = 1.D0-0.5D0*DT*(GENEW+GINEW-FAC)
        TMP = 0.5D0*DT*((E0-EE)*(GEOLD+GENEW)+(E0-EI)*(GIOLD+GINEW))
        VOLD = VNEW
        VNEW = (TMP+VOLD*RHS)/LHS
        IF ( K .EQ. M*(K/M) ) WRITE(1,*) VNEW+E0
      ENDDO
      CLOSE(1)

C    STEP 6 - BUILD THEORETICAL DENSITY
      TE = (2.0D0*TE0*TM)/(TE0+TM)
      TI = (2.0D0*TI0*TM)/(TI0+TM)
      SE = SE0/(CM*AREA)
      SI = SI0/(CM*AREA)
      COP1 = SE**2*TE+SI**2*TI
      A1 = -0.5D0-(GE+GI+GM)/COP1
      COP2 = GE*SI**2*TI-GI*SE**2*TE
      COP3 = SE*SI*SQRT(TE*TI)
      COP4 = SE**2*TE*(EL-EE)
      COP5 = SI**2*TI*(EL-EI)
      COP6 = COP2*(EE-EI)
      A2 = (2.D0*(GM*(COP4+COP5)+COP6))/((EE-EI)*COP3*COP1)
      VMIN = -85.D0
      VMAX = -45.D0
      DV = (VMAX-VMIN)/DBLE(NDEN)
      DO K=0,NDEN
        V(K) = VMIN+DV*DBLE(K)
        TOP1 = SE**2*TE*(V(K)-EE)
```

```
        TOP2 = SI**2*TI*(V(K)-EI)
        TMP = (TOP1*(V(K)-EE)+TOP2*(V(K)-EI))
        RHO = TMP**A1
        TMP = (TOP1+TOP2)/(COP3*(EE-EI))
        PDF(K) = RHO*EXP(A2*ATAN(TMP))
      ENDDO

C    STEP 7 - NORMALISE DENSITY USING SIMPSONS RULE
      SUM = 0.0D0
      DO K=0,(NDEN-1)/2
        KK = 2*K
        SUM = SUM+2.0D0*PDF(KK)+4.0D0*PDF(KK+1)
      ENDDO
      SUM = SUM-PDF(0)+PDF(NDEN)
      SUM = SUM*DV/3.0D0
      OPEN( UNIT=1, FILE="DEN.DAT", ACTION="WRITE")
      DO K=0,NDEN
        IF ( 10*(K/10) .EQ. K ) WRITE(1,*) V(K), PDF(K)/SUM
      ENDDO
      CLOSE(1)
      END
```

B.6 Kernel Density

```
C ******************************************************************
C   PROGRAM TO SIMULATE THE DISTRIBUTION OF THE MEMBRANE
C   POTENTIAL FOR THE MODEL OF RUDOLPH AND DESTEXHE (2005).
C   NEURAL COMPUTATION 17, 2301-2315 IN WHICH THE INHIBITORY
C   AND EXCITATORY SYNAPSES FOLLOW OU PROCESSES.
C
C      PARAMETER( AE=0.004D0, AI=0.026D0, RE=10.0D0, RI=49.42D0,
C     *           EE=0.0D0, EI=-75.0D0, CM=1.0D0, GL=0.05D0,
C     *           EL=-80.0D0, VTHR=-62.0D0, VRES=-65.0D0, TAUE=10.0D0,
C     *           TAUI=0.1D0, TAUL=20.0D0, MAXT=1000, NT=1000 )
C ******************************************************************
      PROGRAM MAIN
      IMPLICIT DOUBLE PRECISION (A-H,O-Z)
      PARAMETER(  EL=-80.0D0, GE=12.1D-6, GI=57.3D-6, SE=3.0D-6,
     +            SI=6.60D-6, TE=2.728D0, TI=10.49D0, AM=100.0D-6,
     +            EE=0.0D0,   EI=-75.0D0, CM=1.0D0,   GL=45.2D-3,
     +            VL=-80.0D0, VU=-50.0D0 )
      PARAMETER( N=201, NT=100, M=2200, LAG=500 )
      DOUBLE PRECISION MU, MPNEW, MPOLD, MP
      DIMENSION V(N), PDF(N), MP(M)
      LOGICAL  REPEAT
      COMMON / PARMS / IX, IY, IZ
```

```
C   SET SEEDS OF RANDOM NUMBER GENERATOR
      IX = 10
      IY = 20
      IZ = 30

C   RESCALE MODEL PARAMETERS BY CELL SURFACE AREA
      PI = 4.0D0*ATAN(1.0D0)
      DT = 1.0/DBLE(NT)
      NS = NT*LAG
      TEXCIT = GE/(CM*AM)
      TINHIB = GI/(CM*AM)

C   SET SIMULATION PARAMETERS FOR MEMBRANE
      TMEMBR = GL/CM
      FACM = 0.735D0
      FACNEW = 0.5D0*DT*FACM
      E0 = (TMEMBR*EL+TEXCIT*EE+TINHIB*EI)/(TMEMBR+TEXCIT+TINHIB)

C   SET SIMULATION PARAMETERS FOR EXCITATORY SYNAPSES
      FACE = DT/TE
      SIGX = SE/(AM*CM)
      SIGX = SIGX*SQRT(2.0D0*EXP(-FACE)*SINH(FACE))
      FACE = EXP(-FACE)

C   SET SIMULATION PARAMETERS FOR INHIBITORY SYNAPSES
      FACI = DT/TI
      SIGY = SI/(AM*CM)
      SIGY = SIGY*SQRT(2.0D0*EXP(-FACI)*SINH(FACI))
      FACI = EXP(-FACI)

C   INITIALISE MODEL
      GENEW = 0.0D0
      GINEW = 0.0D0
      MPNEW = E0

C   BURN IN PERIOD
      DO J=1,10
         DO K=1,NS
            GEOLD = GENEW
            RAN = GAUSS( 0.0D0, SIGX)
            GENEW = FACE*GEOLD+RAN

            GIOLD = GINEW
            RAN = GAUSS( 0.0D0, SIGY)
            GINEW = FACI*GIOLD+RAN

            FACOLD = FACNEW
```

```
            FACNEW = 0.5D0*DT*(FACM+GENEW+GINEW)

            MPOLD = MPNEW
            VIN = DT*(E0*FACM+0.5D0*EE*(GENEW+GEOLD)
     +                       +0.5D0*EI*(GIOLD+GINEW))

            MPNEW = (MPOLD*(1.0D0-FACOLD)+VIN)/(1.0D0+FACNEW)
         ENDDO
      ENDDO

C   COMPUTE MEMBRANE POTENTIAL
      MP(1) = MPNEW
      DO J=2,M
         DO K=1,NS
            GEOLD = GENEW
            RAN = GAUSS( 0.0D0, SIGX)
            GENEW = FACE*GEOLD+RAN

            GIOLD = GINEW
            RAN = GAUSS( 0.0D0, SIGY)
            GINEW = FACI*GIOLD+RAN

            FACOLD = FACNEW
            FACNEW = 0.5D0*DT*(FACM+GENEW+GINEW)

            MPOLD = MPNEW
            VIN = DT*(E0*FACM+0.5D0*EE*(GENEW+GEOLD)
     +                       +0.5D0*EI*(GIOLD+GINEW))

            MPNEW = (MPOLD*(1.0D0-FACOLD)+VIN)/(1.0D0+FACNEW)
         ENDDO
         MP(J) = MPNEW
         IF ( MOD(J,100) .EQ. 0 ) WRITE(*,*) 'DONE J = ', J
      ENDDO

C   ESTIMATE MEAN AND VARIANCE OF DISTRIBUTION OF MEMBRANE POTENTIAL
      MU = 0.0D0
      SD = 0.0D0
      DO K=1,M
         MU = MU+MP(K)
         SD = SD+MP(K)*MP(K)
      ENDDO
      MU = MU/DBLE(M)
      SD = SD/DBLE(M)
      SD = SQRT(SD-MU*MU)
      H = 0.9D0*SD/(DBLE(M)**0.2D0)
      SD = H*H
```

```
C   CONSTRUCT KERNEL DENSITY
      DV = (VU-VL)/DBLE(N-1)
      DO K=1,N
         V(K) = VL+DV*DBLE(K-1)
      ENDDO
      DO J=1,N
         PDF(J) = 0.0D0
         DO K=1,M
            TMP = 0.5D0*(V(J)-MP(K))*(V(J)-MP(K))/SD
            IF ( TMP .LT. 20.0D0 ) THEN
               PDF(J) = PDF(J)+EXP(-TMP)
            ENDIF
         ENDDO
         PDF(J) = PDF(J)/SQRT(2.0D0*SD*PI)
         PDF(J) = PDF(J)/DBLE(M)
      ENDDO

C   OUTPUT DENSITY
      OPEN(UNIT=1,
     +     FILE="RDSIM.DAT",
     +     ACTION="WRITE")
      DO K=1,N
         WRITE(1,*) V(K), PDF(K)
      ENDDO
      CLOSE(1)
      STOP
      END
```

B.6.1 Utility programs appearing several different files

```
C *****************************************************
C  Function returns a uniform random deviate in [0,1]
C *****************************************************
      SUBROUTINE URAND( RAN, IX, IY, IZ)
      IMPLICIT DOUBLE PRECISION(A-H,O-Z)
      PARAMETER( ONE=1.0D0 )
C
      IX = MOD(171*IX,30269)
      IY = MOD(172*IY,30307)
      IZ = MOD(170*IZ,30323)
      RAN = DBLE(IX)/30269.0D0+DBLE(IY)/30307.0D0+DBLE(IZ)/30323.0D0
      RAN = MOD(RAN,ONE)
      RETURN
      END


C *****************************************************
```

```
C  Function returns Gaussian deviate N[MU,SD]
C *****************************************************
      FUNCTION GAUSS( MU, SD)
      DOUBLE PRECISION GAUSS, MU, SD, G1, G2, V1, V2, URAND, W
      LOGICAL START, REPEAT
      COMMON / PARMS / IX, IY, IZ
      DATA START / .TRUE. /
      SAVE START, G1, G2

      IF ( START ) THEN
        REPEAT = .TRUE.
        DO WHILE ( REPEAT )
            V1 = 2.0D0*URAND(IX, IY, IZ)-1.0D0
            V2 = 2.0D0*URAND(IX, IY, IZ)-1.0D0
            W = V1*V1+V2*V2
            REPEAT = ( (W .EQ. 0.0D0) .OR. (W .GE. 1.0D0) )
        ENDDO
        W = LOG(W)/W
        W = SQRT(-W-W)
        G1 = V1*W
        G2 = V2*W
        START = .FALSE.
        GAUSS = MU+SD*G1
      ELSE
        START = .TRUE.
        GAUSS = MU+SD*G2
      ENDIF
      END
```