

## STOCHASTIC EQUATIONS FOR NERVE MEMBRANE POTENTIAL

HENRY C. TUCKWELL

*Department of Mathematics, Monash University, Clayton, Victoria 3168, Australia*

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### Abstract

Stochastic versions of the Hodgkin-Huxley, Fitzhugh-Nagumo and Frankenhaeuser-Huxley equations are formulated. In the case of space clamping the corresponding vector Markov processes are obtained with special reference to the multidimensional diffusions. In all cases the backward and forward Kolmogorov equations are explicitly obtained.

### 1. Introduction

Since the 1940s, when observations were first made on the stochastic nature of the sequences of discharges from nerve cells (Brink *et al.*, 1946), many models have appeared to account for this behaviour. Most of these models have involved one-dimensional random processes which represent the level of excitation in the neuron. For example  $\{X(t), t \geq 0\}$  might be a stationary Gaussian process mimicking the depolarization in the cell. When  $X$  hits a deterministic threshold function the cell emits an action potential. The threshold was re-set following a spike. This was the structure of the models of Hagiwara (1954), Geisler and Goldberg (1966) and Calvin and Stevens (1968).

In another class of models  $\{X(t), t \geq 0\}$  was usually a Markov process in continuous time which on first reaching threshold caused an action potential to be emitted. Subsequently, usually following a refractory period, the depolarization  $X$  was reset and a renewal process was generated representing a spike train. This was the structure of the models of Gerstein and Mandelbrot (1964) and Stein (1965) which gave rise to the respective diffusion processes — Wiener process and Ornstein-Uhlenbeck process.

More recently, in view of the success of the Rall model of the neuron, with its inclusion of the spatially extended dendritic trees, attention has been turned to stochastic cable model nerve cells involving both one-parameter (Tuckwell *et al.*, 1984) and two-parameter (Tuckwell and Walsh, 1983) white noise input currents. Such models have been energetically studied as they involve infinite-dimensional processes of much interest to probabilists (Kallianpur and Wolpert, 1984).

As mentioned above, even in the one-dimensional models there is an arbitrary choice of threshold mechanism. The situation is even more perplexing in the stochastic cable models — there is an endless variety of threshold conditions that one might impose. If  $\{V(x,t), 0 < x < L, t > 0\}$  is the depolarization on the cable, then

$$T_1 = \inf\{t: \sup_{0 \leq x \leq L} V(x,t) \geq \theta\}$$

and

$$T_2 = \inf\{t: V(x,t) \geq \theta, x_1 \leq x \leq x_2\}$$

are two candidates for the interspike interval.

The reason for the arbitrary nature of the threshold condition is of course that the system (usually a differential equation) has no natural threshold properties. The situation may be compared with the Hodgkin-Huxley equations. In that system a local excitation, if strong enough, will grow into an action potential. This will then propagate according to the trajectories of the system in a 4-dimensional phase space.

There are three systems of equations often employed in the deterministic modelling of nerve cell activity. These are the Hodgkin-Huxley (1952) equations, the Fitzhugh-Nagumo (Nagumo *et al.*, 1962) equations and the Frankenhaeuser-Huxley (1964) equations. These three systems are all nonlinear and are of dimensions 4, 2 and 5 respectively. In this paper we will formulate stochastic versions of these three systems of reaction-diffusion equations. In addition, the vector-valued Markov processes obtained for them in the space-clamped case will be studied and equations obtained which must be satisfied by their transition probability functions.

## 2. Stochastic Hodgkin-Huxley equations

When the input current density  $I(x,t)$  is a random process in space-time, the depolarization  $V(x,t)$ , the potassium activation  $n(x,t)$ , the sodium activation  $m(x,t)$  and the sodium inactivation  $h(x,t)$  are all random processes in space-time also. So long as the noisy input current is additive we have, realizing that often derivatives are merely formal because the processes involved may be almost surely nowhere differentiable,

$$(2.1) \quad C_m \frac{\partial V}{\partial t} = \frac{\alpha}{2\rho_i} \frac{\partial^2 V}{\partial x^2} + \bar{g}_K n^4 (V_K - V) + \bar{g}_{Na} m^3 h (V_{Na} - V) + g_l (V_l - V) + I(x,t), \quad a < x < b,$$

$$(2.2) \quad \frac{\partial n}{\partial t} = \alpha n(V) (1 - n) - \beta_n(V) n,$$

$$(2.3) \quad \frac{\partial m}{\partial t} = \alpha_m(V) (1 - m) - \beta_m(V) m,$$

$$(2.4) \quad \frac{\partial h}{\partial t} = \alpha_h(V) (1 - h) - \beta_h(V) h,$$

where  $C_m$  = membrane capacitance per unit area,  $a$  = nerve fiber radius,  $\rho_i$  is the intracellular resistivity,  $\bar{g}_K$  = constant maximal available potassium conductance per unit area,  $V_K$  = potassium equilibrium potential relative to resting potential,  $\bar{g}_{Na}$ ,  $V_{Na}$  are the corresponding quantities for sodium,  $g_l$  is the leakage conductance per unit area,  $V_l$  the equilibrium potential for the leakage current, the coefficients ( $\alpha$ 's and  $\beta$ 's) in the  $n$ ,  $m$  and  $h$  equations being in the standard case

$$(2.5) \quad \alpha_n(V) = \frac{10 - V}{100(e^{(10-V)/10} - 1)}$$

$$(2.6) \quad \beta_n(V) = \frac{1}{8} e^{-V/80}$$

$$(2.7) \quad \alpha_m(V) = \frac{25 - V}{10(e^{(25-V)/10} - 1)}$$

$$(2.8) \quad \beta_m(V) = 4e^{-V/18}$$

$$(2.9) \quad \alpha_h(V) = \frac{7}{100} e^{-V/20}$$

$$(2.10) \quad \beta_h(V) = \frac{1}{e^{(30-V)/10} + 1}.$$

Choices of interest for the input current density are:

(i) *Gaussian white noise at a point*  $x_0 \in [a, b]$ ,

$$(2.11) \quad I(x,t) = \delta(x - x_0) \left( \mu + \sigma \frac{dW}{dt} \right),$$

where  $\{W(t), t \geq 0\}$  is a standard Wiener process and  $\mu$  and  $\sigma$  are constants;

(ii) *Uniform two-parameter Gaussian white noise*

$$(2.12) \quad I(x,t) = \mu + \sigma \frac{\partial^2 W}{\partial x \partial t}, \quad a < x < b,$$

where  $\{W(x,t), x \in [a, b], t \geq 0\}$  is a two-parameter standard Wiener process;

(iii) *Poisson excitation and Poisson inhibition at single space points,*

$$(2.13) \quad I(x,t) = \delta(x - x_E) a_E \frac{dN_E}{dt} - \delta(x - x_I) a_I \frac{dN_I}{dt},$$

where  $\{N_E(t), t \geq 0\}$  and  $\{N_I(t), t \geq 0\}$  are independent standard Poisson processes with intensities  $\lambda_E$  and  $\lambda_I$ ,  $a_E$  and  $a_I$  are non-negative constants,  $x_E \in [a, b]$ ,  $x_I \in [a, b]$ :

(iv) *Uniform two-parameter Poisson white noise*

$$(2.14) \quad I(x,t) = a_E \frac{\partial^2 N_E(x,t)}{\partial x \partial t} - a_I \frac{\partial^2 N_I(x,t)}{\partial x \partial t}, \quad a < x < b,$$

where  $\{N_E(x,t), x \in [a,b], t \geq 0\}$  and  $\{N_I(x,t), x \in [a,b], t \geq 0\}$  are independent standard two-parameter Poisson processes,  $a_E$  and  $a_I$  being non-negative constants. More general kinds of random input current can be devised but we will not consider them here.

It is clear that with any of these random applied currents, the determination of the probabilities and moments associated with the variables  $V, n, m, h$  is difficult. Simulation is one method of attack (see e.g., Stein, 1967; Skaugen, 1978) but is extremely limited when it comes to presenting results. Notice that even finding the expectation of  $V(x,t)$  is a difficult task.

Of course (2.1)–(2.4) in conjunction with one of the random input current densities (2.11)–(2.14) is physiologically a vastly superior alternative to the one-dimensional process models in which one has to make an arbitrary choice of threshold condition. It is not unreasonable to expect that the stochastic version of (2.1)–(2.4) will have not travelling wave solutions for  $V, n, m,$  and  $h$  but rather their probabilities and moments will be travelling waves. That is, we will be looking for solitary waves of probability and threshold conditions will not have to be artificially invented. It is hoped to address these matters in a subsequent paper, but now we turn to an extremely interesting related development.

## 2.1 Space-clamped system

Neurophysiologists often try to eliminate diffusive effects by employing what they call a “space-clamp”. The word clamp for them means to hold constant so space-clamp means to hold constant in space. If a quantity is constant in space then its space derivatives are zero. Thus if we space-clamp a patch of nerve membrane  $V(x,t)$  can be replaced by  $V(t)$  and  $\partial V/\partial x$  becomes zero.

In order to obtain a more conventional notation let us put  $X$  for  $n, Y$  for  $m$  and  $Z$  for  $h$ . We are now dealing with the vector  $(V(t), X(t), Y(t), Z(t))$  of random processes with  $t \geq 0$ . Let us make the substitutions

$$c_1 = \bar{g}_K / C_m$$

$$c_2 = \bar{g}_{Na} / C_m$$

$$c_3 = g_l / C_m$$

and rewrite  $V_K, V_{Na}$  and  $V_l$  as  $v_K, v_{Na}$  and  $v_l$  respectively.

Putting

$$\frac{I}{C_m} = \mu + \sigma \frac{dW_1}{dt}$$

so that the voltage equation is driven by additive Gaussian white noise, the system of equations can be written in standard form as

$$(2.1.1) \quad d \begin{bmatrix} V \\ X \\ Y \\ Z \end{bmatrix} = \begin{bmatrix} c_1(v_K - V)X^4 + c_2(v_{Na} - V)Y^3Z + c_3(v_l - V) + \mu \\ \alpha_n(V)(1-X) - \beta_n(V)X \\ \alpha_m(V)(1-Y) - \beta_m(V)Y \\ \alpha_h(V)(1-Z) - \beta_h(V)Z \end{bmatrix} dt + \begin{bmatrix} \sigma & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} d \begin{bmatrix} W_1 \\ W_2 \\ W_3 \\ W_4 \end{bmatrix}$$

where  $W_1 - W_4$  are independent standard Wiener processes.

Equation (2.1.1) is in standard form for a multidimensional diffusion process. In fact,  $(V, X, Y, Z)$  is a 4-dimensional temporally homogeneous Markov process.

Let us suppose that the transition probability function for (2.1.1) is defined as

$$(2.1.2) \quad P(v, x, y, z, t; \bar{v}, \bar{x}, \bar{y}, \bar{z}, t) = \\ = Pr\{V(t) \leq v, X(t) \leq x, Y(t) \leq y, Z(t) \leq z \mid V(i) = \bar{v}, X(i) = \bar{x}, Y(i) = \bar{y}, Z(i) = \bar{z}\}$$

with corresponding transition density  $p((v, x, y, z, t; \bar{v}, \bar{x}, \bar{y}, \bar{z}, t))$ . Then we have the following results.

The transition probability density function  $p$  for the space-clamped stochastic Hodgkin-Huxley equations (2.1.1) satisfies the backward Kolmogorov equation

$$(2.1.3) \quad -\frac{\partial p}{\partial t} = \frac{1}{2}\sigma^2 \frac{\partial^2 p}{\partial v^2} + \{c_1(v_K - \bar{v})\bar{x}^4 + c_2(v_{Na} - \bar{v})\bar{y}^3\bar{z} + c_3(v_l - \bar{v}) + \mu\} \frac{\partial p}{\partial v} \\ + \{\alpha_n(\bar{v})(1 - \bar{x}) - \beta_n(\bar{v})\bar{x}\} \frac{\partial p}{\partial \bar{x}} + \{\alpha_m(\bar{v})(1 - \bar{y}) - \beta_m(\bar{v})\bar{y}\} \frac{\partial p}{\partial \bar{y}} \\ + \{\alpha_h(\bar{v})(1 - \bar{z}) - \beta_h(\bar{v})\bar{z}\} \frac{\partial p}{\partial \bar{z}},$$

and the forward Kolmogorov equation

$$(2.1.4) \quad \frac{\partial p}{\partial t} = \frac{1}{2}\sigma^2 \frac{\partial^2 p}{\partial v^2} - \frac{\partial}{\partial v} (p\{c_1(v_K - v)x^4 + c_2(v_{Na} - v)y^3z + c_3(v_l - v) + \mu\}) \\ - \frac{\partial}{\partial x} (p\{\alpha_n(v)(1-x) - \beta_n(v)x\}) - \frac{\partial}{\partial y} (p\{\alpha_m(v)(1-y) - \beta_m(v)y\}) \\ - \frac{\partial}{\partial z} (p\{\alpha_h(v)(1-z) - \beta_h(v)z\}).$$

*Proof*

Just apply corollaries 1 and 2 of Theorem 6 of Gihman and Skorohod, p. 297 (1972) to the system (2.1.1) which has been put in the standard form for a multidimensional diffusion process. ■

We may also easily obtain the Kolmogorov equations when the input current is Poisson white noise, either simple or compound.

*If the Gaussian white noise current in (2.1.1) is replaced with a compound Poisson white noise*

$$(2.1.5) \quad \frac{I}{C_m} = \frac{d}{dt} \int_{\mathbf{R}} uv(t, du),$$

where  $v(\dots)$  is a Poisson random measure with

$$(2.1.6) \quad E(v(t, du)) = t\Pi(du),$$

then the term  $\frac{1}{2}\sigma^2\partial^2p/\partial\bar{v}^2$  in the backward equation (2.1.3) is replaced by

$$(2.1.7) \quad \int_{\mathbf{R}} p(v, x, y, z, t; \bar{v} + u, \bar{x}, \bar{y}, \bar{z}, t) \Pi(du) - \Lambda p$$

where

$$(2.1.8) \quad \Lambda = \int_{\mathbf{R}} \Pi(du).$$

*In particular, if there are jumps up of magnitude  $a_E$  with intensity  $\lambda_E$  and jumps down of magnitude  $a_I$  with intensity  $\lambda_I$ , the term  $\frac{1}{2}\sigma^2\partial^2p/\partial\bar{v}^2$  is replaced by*

$$(2.1.9) \quad \lambda_E p(v, x, y, z, t; \bar{v} + a_E, \bar{x}, \bar{y}, \bar{z}, t) + \lambda_I p(v, x, y, z, t; \bar{v} - a_I, \bar{x}, \bar{y}, \bar{z}, t) - (\lambda_E + \lambda_I)p.$$

*Similarly, the term  $\frac{1}{2}\sigma^2\partial^2p/\partial v^2$  in the forward equation (2.1.4) is replaced by*

$$(2.1.10) \quad \int_{\mathbf{R}} p(v - u, x, y, z, t; \bar{v}, \bar{x}, \bar{y}, \bar{z}, t) \Pi(du) - \Lambda p,$$

*in the compound Poisson white noise case, and in particular by*

$$(2.1.11) \quad \lambda_E p(v - a_E, x, y, z, t; \bar{v}, \bar{x}, \bar{y}, \bar{z}, t) + \lambda_I p(v + a_I, x, y, z, t; \bar{v}, \bar{x}, \bar{y}, \bar{z}, t) - \Lambda p,$$

*when the jumps are  $+a_E$  and  $-a_I$  with intensities  $\lambda_E$  and  $\lambda_I$ .*

*Proof*

Just apply the corollaries quoted above to the case of a multidimensional discontinuous Markov process. ■

A few remarks are in order. Firstly, an experiment corresponding to the system of equations (2.1.1) has been performed by Guttman *et al.* (1974) who applied white noise current to a space clamped squid axon. Hence a comparison of theory and

experiment is feasible. White noise has also been used as a stimulus for nerve cells with more complicated geometries (see, for example, Bryant and Segundo, 1976; Moore and Christensen, 1985). Secondly, whereas the system of stochastic equations (2.1.1) is nonlinear, the Kolmogorov equations (2.1.3) and (2.1.4) are linear and therefore amenable to numerical solution by known methods. Freidlin (1985) has analyzed certain reaction-diffusion systems (deterministic) by studying a Markov process with a similar infinitesimal operator. Furthermore, there is no need to define a threshold function for (2.1.1) and study first passage times to it. One expects that solutions of the Kolmogorov equations will have probability mass concentrated, in the small  $\sigma$  case, near the deterministic action potential trajectories. For certain values of  $\mu$  one might find that the Kolmogorov equations have periodic solutions, corresponding to trains of action potentials.

### 3. Stochastic Fitzhugh-Nagumo equations

Because the Hodgkin-Huxley equations are difficult to analyze, a simpler system with only two components has been employed. This system can be written

$$(3.1) \quad \begin{aligned} \frac{\partial V}{\partial t} &= \frac{\partial^2 V}{\partial x^2} + f(V) - W \\ \frac{\partial W}{\partial t} &= b(V - \gamma W) \end{aligned}$$

where  $V = V(x, t)$ ,  $W = W(x, t)$  and  $f$  is given by the cubic

$$(3.2) \quad f(V) = V(1 - V)(V - a)$$

Here  $a$  is a constant satisfying  $0 < a < 1$  so that  $f$  has zeros at 0,  $a$  and 1. A term  $I(x, t)$  representing an applied current may be inserted on the right of (3.1). Roughly speaking, the variables  $V$  and  $m$  of the Hodgkin-Huxley system are mimicked by the single variable  $V$  in the Fitzhugh-Nagumo equations (3.1); and the variables  $n$  and  $h$  are mimicked by the single variable  $W$ , which may be called a recovery variable. The system (3.1), with the appropriate initial and/or stimulus conditions, supports travelling solitary wave solutions which are supposed to represent action potentials.

Putting

$$(3.3) \quad \begin{aligned} \frac{\partial V}{\partial t} &= \frac{\partial^2 V}{\partial x^2} + f(V) - W + I(x, t) \\ \frac{\partial W}{\partial t} &= b(V - \gamma W), \end{aligned}$$

where  $I$  is given by any of (2.1.2)–(2.1.4) gives stochastic Fitzhugh-Nagumo equations.

### 3.1 Space-clamped system

Let us first consider the space-clamped version of (3.3) driven by Gaussian white noise:

$$(3.1.1) \quad \begin{aligned} dX &= (f(X) - Y + \mu)dt + \sigma dW, \\ dY &= b(X - \gamma Y)dt, \end{aligned}$$

where  $\{W(t), t \geq 0\}$  is a standard Wiener process and  $\mu$  and  $\sigma$  are constants. Defining the transition probability function

$$(3.1.2) \quad \begin{aligned} P(x, y, t; \bar{x}, \bar{y}, t) \\ = \Pr\{X(t) \leq x, Y(t) \leq y \mid X(i) = \bar{x}, Y(i) = \bar{y}\}, \end{aligned}$$

with corresponding density  $p(x, y, t; \bar{x}, \bar{y}, t)$ , we have the following results.

The transition probability density function for the space-clamped Fitzhugh-Nagumo equations (3.1.1) satisfies the backward Kolmogorov equation

$$(3.1.3) \quad -\frac{\partial p}{\partial t} = \frac{1}{2}\sigma^2 \frac{\partial^2 p}{\partial x^2} + (f(\bar{x}) - \bar{y} + \mu) \frac{\partial p}{\partial \bar{x}} + b(\bar{x} - \gamma \bar{y}) \frac{\partial p}{\partial \bar{y}},$$

and the forward Kolmogorov equation

$$(3.1.4) \quad \frac{\partial p}{\partial t} = \frac{1}{2}\sigma^2 \frac{\partial^2 p}{\partial x^2} - \frac{\partial}{\partial x} \{p\{f(x) - y + \mu\}\} - \frac{\partial}{\partial y} \{p\{b(x - \gamma y)\}\}.$$

*Proof.* As in Section 2. ■

In addition we have for Poisson inputs,

The transition density  $p(x, y, t; \bar{x}, \bar{y}, t)$  for the stochastic space-clamped Fitzhugh-Nagumo system

$$(3.1.5) \quad \begin{aligned} dX &= (f(X) - Y)dt + \int_{\mathbf{R}} uv(dt, du) \\ dY &= b(X - \gamma Y)dt \end{aligned}$$

satisfies the backward Kolmogorov equation

$$(3.1.6) \quad \begin{aligned} -\frac{\partial p}{\partial t} &= \int_{\mathbf{R}} p(x, y, t; \bar{x} + u, \bar{y}, t) \Pi(du) - \Lambda p \\ &+ (f(\bar{x}) - \bar{y}) \frac{\partial p}{\partial \bar{x}} + b(\bar{x} - \gamma \bar{y}) \frac{\partial p}{\partial \bar{y}}, \end{aligned}$$

where  $\Lambda$  is given by (2.1.8). In particular if

$$(3.1.7) \quad \int_{\mathbf{R}} uv(dt, du) = a_E dN_E - a_I dN_I,$$

then

$$(3.1.8) \quad \begin{aligned} -\frac{\partial p}{\partial t} &= \lambda_E p + (x, y, t; \bar{x} + a_E, \bar{y}, t) + \lambda_I p(x, y, t; \bar{x} - a_I, \bar{y}, t) \\ &- (\lambda_E + \lambda_I) p + (f(\bar{x}) - \bar{y}) \frac{\partial p}{\partial \bar{x}} + b(\bar{x} - \gamma \bar{y}) \frac{\partial p}{\partial \bar{y}}. \end{aligned}$$

Furthermore, the forward Kolmogorov equations corresponding to (3.1.6) and (3.1.8) are

$$(3.1.9) \quad \begin{aligned} \frac{\partial p}{\partial t} &= \int_{\mathbf{R}} p(x - u, y, t; \bar{x}, \bar{y}, t) \Pi(du) - \Lambda p \\ &- \frac{\partial}{\partial x} \{p\{f(x) - y\}\} - \frac{\partial}{\partial y} \{p\{b(x - \gamma y)\}\}, \end{aligned}$$

and

$$(3.1.10) \quad \begin{aligned} \frac{\partial p}{\partial t} &= \lambda_E p(x - a_E, y, t; \bar{x}, \bar{y}, t) + \lambda_I p(x + a_I, y, t; \bar{x}, \bar{y}, t) \\ &- (\lambda_E + \lambda_I) p - \frac{\partial}{\partial x} \{p\{f(x) - y\}\} - \frac{\partial}{\partial y} \{p\{b(x - \gamma y)\}\}, \end{aligned}$$

respectively.

*Proof.* As in the previous sections. ■

Note that if any of these stochastic nonlinear systems has both Poisson and Gaussian white noise, then the corresponding terms in the Kolmogorov equations just add, so long as the separate noise sources are independent. For example, if the space-clamped Fitzhugh-Nagumo system is driven by Gaussian and compound Poisson white noises, so we have

$$(3.1.11) \quad \begin{aligned} dx &= (f(X) - Y + \mu)dt + \sigma dW + \int_{\mathbf{R}} uv(dt, du) \\ dY &= b(X - \gamma Y)dt, \end{aligned}$$

then the transition density satisfies the forward Kolmogorov equation

$$(3.1.12) \quad \begin{aligned} \frac{\partial p}{\partial t} &= \frac{1}{2}\sigma^2 \frac{\partial^2 p}{\partial x^2} - \frac{\partial}{\partial x} \{p\{f(x) - y + \mu\}\} - \frac{\partial}{\partial y} \{p\{b(x - \gamma y)\}\} \\ &+ \int_{\mathbf{R}} p(x - u, y, t; \bar{x}, \bar{y}, t) \Pi(du) - \Lambda p. \end{aligned}$$

#### 4 Stochastic Frankenhaeuser-Huxley equations

For certain nodal membranes different expressions from those of Hodgkin and Huxley have been found to apply (Frankenhaeuser and Huxley, 1964). It is found that a non-diffusive, five-component system is required and the ionic currents are better described by constant field expressions. Then if the actual membrane potential is  $V_m(t)$ , we have

$$(4.1) \quad C \frac{dV_m}{dt} = \frac{(C_K^i e^{\gamma V_m} - C_K^o)}{e^{\gamma V_m} - 1} \gamma F P_K V_m + \frac{(C_{Na}^i e^{\gamma V_m} - C_{Na}^o)}{(e^{\gamma V_m} - 1)} \gamma F P_{Na} V_m \\ + g_l (V_i - V_m + V_R) + \frac{(C_{Na}^i e^{\gamma V_m} - C_{Na}^o) \gamma F P_p V_m}{(e^{\gamma V_m} - 1)} + I_A$$

where  $C_K^i, C_{Na}^i, C_K^o, C_{Na}^o$  are the internal and external concentrations of potassium and sodium ions,  $\gamma = F/RT$ ,  $F$  = Faraday's constant,  $R$  = gas constant,  $T$  = absolute temperature,  $P_K, P_{Na}$  and  $P_p$  are potassium permeability, the sodium permeability and a nonspecific permeability,  $V_i, g_l$  refer to leakage, as before,  $V_R$  = resting membrane potential,  $C$  is the capacitance and  $I_A$  is the applied current. The permeabilities are given by

$$(4.2) \quad P_{Na} = \bar{P}_{Na} m^2 h,$$

$$(4.3) \quad P_K = \bar{P}_K n^2 k \approx P_K' n^2$$

$$(4.4) \quad P_p = \bar{P}_p p^2,$$

where  $m, h$  are sodium activation and inactivation,  $n, k$  are potassium activation and inactivation,  $p$  is a nonspecific activation variable. The variations in  $n$  are slow enough that  $k$  is regarded as a constant and hence  $P_K n^2$  is set equal to the constant  $P_K'$ . The quantities  $\bar{P}_{Na}, \bar{P}_K$  and  $\bar{P}_p$  are all constant permeabilities. The variables  $m, h, n$  and  $p$  satisfy the equations

$$(4.5) \quad \frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$

$$(4.6) \quad \frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$

$$(4.7) \quad \frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$$(4.8) \quad \frac{dp}{dt} = \alpha_p(V)(1-p) - \beta_p(V)p$$

where  $V$  is the depolarization and the functions  $\alpha_m, \alpha_h, \alpha_n, \alpha_p, \beta_m, \beta_h, \beta_n$  and  $\beta_p$  are given in Tuckwell (1987).

We consider this system with Gaussian white noise current

$$(4.9) \quad \frac{I_A}{C} = \mu + \sigma \frac{dW}{dt}$$

where  $\{W(t), t \geq 0\}$  is a standard Wiener process. We use the symbols  $V, W, X, Y, Z$  to represent  $V_m, n, m, h$  and  $p$  respectively. We define

$$(4.10) \quad \gamma' = \frac{\gamma F}{C},$$

and re-label  $V, V_R$  with lower case letters  $v, v_R$ . Now set

$$(4.11) \quad P(v, w, x, y, z, t; \bar{v}, \bar{w}, \bar{x}, \bar{y}, \bar{z}, \bar{t}) = \\ Pr\{V(t) \leq v, W(t) \leq w, X(t) \leq x, Y(t) \leq y, Z(t) \leq z \mid V(\bar{t}) = \bar{v}, W(\bar{t}) = \bar{w}, \\ X(\bar{t}) = \bar{x}, Y(\bar{t}) = \bar{y}, Z(\bar{t}) = \bar{z}\},$$

with corresponding transition density  $p(v, w, x, y, z, t; \bar{v}, \bar{w}, \bar{x}, \bar{y}, \bar{z}, \bar{t})$ . Note that usually the only version of the Frankenhaeuser-Huxley equations is the space clamped one. We now have,

The transition probability density function  $p$  for the Frankenhaeuser-Huxley equations with Gaussian white noise input current satisfies the backward Kolmogorov equation

$$(4.12) \quad -\frac{\partial p}{\partial \bar{t}} = \frac{1}{2} \sigma^2 \frac{\partial^2 p}{\partial \bar{v}^2} + \left\{ \frac{\gamma' \bar{v}}{e^{\gamma' \bar{v}} - 1} [(C_K^i e^{\gamma' \bar{v}} - C_K^o) P_K' \bar{w}^2 + \right. \\ \left. + (C_{Na}^i e^{\gamma' \bar{v}} - C_{Na}^o) (\bar{P}_{Na} \bar{x}^2 \bar{y} + \bar{P}_p \bar{z}^2)] + \frac{g_l}{C} (v_i - \bar{v} + v_R) + \mu \right\} \frac{\partial p}{\partial \bar{v}} \\ + \{ \alpha_n(\bar{v})(1 - \bar{w}) - \beta_n(\bar{v})\bar{w} \} \frac{\partial p}{\partial \bar{w}} + \{ \alpha_m(\bar{v})(1 - \bar{x}) - \beta_m(\bar{v})\bar{x} \} \frac{\partial p}{\partial \bar{x}} \\ + \{ \alpha_h(\bar{v})(1 - \bar{y}) - \beta_h(\bar{v})\bar{y} \} \frac{\partial p}{\partial \bar{y}} + \{ \alpha_p(\bar{v})(1 - \bar{z}) - \beta_p(\bar{v})\bar{z} \} \frac{\partial p}{\partial \bar{z}},$$

and the forward Kolmogorov equation

$$(4.13) \quad \frac{\partial p}{\partial t} = \frac{1}{2} \sigma^2 \frac{\partial^2 p}{\partial v^2} - \frac{\partial}{\partial v} \left\{ p \left[ \frac{\gamma' v}{e^{\gamma' v} - 1} [(C_K^i e^{\gamma' v} - C_K^o) P_K' w^2 + \right. \right. \\ \left. \left. + (C_{Na}^i e^{\gamma' v} - C_{Na}^o) (\bar{P}_{Na} x^2 y + \bar{P}_p z^2)] + \frac{g_l}{C} (v_i - v + v_R) + \mu \right] \right\} \\ - \frac{\partial}{\partial w} \{ p \{ \alpha_n(v)(1-w) - \beta_n(v)w \} \} - \frac{\partial}{\partial x} \{ p \{ \alpha_m(v)(1-x) - \beta_m(v)x \} \} \\ - \frac{\partial}{\partial y} \{ p \{ \alpha_h(v)(1-y) - \beta_h(v)y \} \} - \frac{\partial}{\partial z} \{ p \{ \alpha_p(v)(1-z) - \beta_p(v)z \} \}.$$

*Proof.* As in the previous sections. ■

Finally, we remark that if the Gaussian white noise  $\mu + \sigma dw/dt$  is replaced by the compound Poisson white noise, then the second derivative terms in (4.12) and (4.13) are replaced by

$$(4.14) \quad \int_{\mathbb{R}} p(v, w, x, y, z, t; \bar{v} + u, \bar{w}, \bar{x}, \bar{y}, \bar{z}, t) \Pi(du) - \Lambda p$$

and

$$(4.15) \quad \int_{\mathbb{R}} p(v - u, w, x, y, z, t; \bar{v}, \bar{w}, \bar{x}, \bar{y}, \bar{z}, t) \Pi(du) - \Lambda p.$$

The analysis and solutions of these various Kolmogorov equations will be reported in a forthcoming publication.

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