7.5 Hodgkin–Huxley Theory of Nerve Membranes: FitzHugh–Nagumo Model

Neural communication is clearly a very important field. We make no attempt here to give other than a basic introduction to it and discuss one of the key mathematical models which has been studied extensively. Rinzel (1981) gives a short review of models in neurobiology; see also Keener and Sneyd (1998).

Electric signalling or firing by individual nerve cells or neurons is particularly common. The seminal and now classical work by Hodgkin and Huxley (1952) on this aspect of nerve membranes was on the nerve axon of the giant squid. (They were awarded a Nobel prize for their work.) Basically the axon is a long cylindrical tube which extends from each neuron and electrical signals propagate along its outer membrane, about 50 to 70 Ångströms thick. The electrical pulses arise because the membrane is preferentially permeable to various chemical ions with the permeabilities affected by the currents and potentials present. The key elements in the system are potassium (K^+) ions and sodium (Na^+) ions. In the rest state there is a transmembrane potential difference of about -70 millivolts (mV) due to the higher concentration of K^+ ions within the axon as compared with the surrounding medium. The deviation in the potential across the membrane, measured from the rest state, is a primary observable in experiments. The membrane permeability properties change when subjected to a stimulating electrical current I: they also depend on the potential. Such a current can be generated, for example, by a local depolarisation relative to the rest state.

In this section we are concerned with the *space-clamped* dynamics of the system; that is, we consider the spatially homogeneous dynamics of the membrane. With a real axon the space-clamped state can be obtained experimentally by having a wire down the middle of the axon maintained at a fixed potential difference to the outside. Later, in Chapter 1, Volume II, we shall discuss the important spatial propagation of action potential impulses along the nerve axon; we shall refer back to the model we discuss here. We derive here the Hodgkin–Huxley (1952) model and the reduced analytically tractable FitzHugh–Nagumo mathematical model (FitzHugh 1961, Nagumo et al. 1962) which captures the key phenomena. The analysis of the various mathematical models has indicated phenomena which have motivated considerable experimental work. The theory of neuron firing and propagation of nerve action potentials is one of the major successes of real mathematical biology.

Basic Mathematical Model

Let us take the positive direction for the membrane current, denoted by I, to be outwards from the axon. The current $I(t)$ is made up of the current due to the individual ions which pass through the membrane and the contribution from the time variation in the transmembrane potential, that is, the membrane capacitance contribution. Thus we have

$$I(t) = C\frac{dv}{dt} + I_i, \tag{7.35}$$

where C is the capacitance and I_i is the current contribution from the ion movement across the membrane. Based on experimental observation Hodgkin and Huxley (1952) took

$$\begin{aligned} I_i &= I_{Na} + I_K + I_L, \\ &= g_{Na} m^3 h(V - V_{Na}) + g_K n^4 (V - V_K) + g_L (V - V_L), \end{aligned} \tag{7.36}$$

where V is the potential and I_{Na}, I_K and I_L are respectively the sodium, potassium and 'leakage' currents; I_L is the contribution from all the other ions which contribute to the current. The g's are constant conductances with, for example, $g_{Na} m^3 h$ the sodium conductance, and V_{Na}, V_K and V_L are constant equilibrium potentials. The m, n and h are variables, bounded by 0 and 1, which are determined by the differential equations

$$\begin{aligned} \frac{dm}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V)m, \\ \frac{dn}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V)n, \\ \frac{dh}{dt} &= \alpha_h(V)(1 - h) - \beta_h(V)h, \end{aligned} \tag{7.37}$$

where the α and β are given functions of V (again empirically determined by fitting the results to the data); see, for example, Keener and Sneyd (1998). α_n and α_m are qualitatively like $(1 + \tanh V)/2$ while $\alpha_h(V)$ is qualitatively like $(1 - \tanh V)/2$, which is a 'turn-off' switch if V is moderately large. Hodgkin and Huxley (1952) fitted the data with exponential forms.

If an applied current $I_a(t)$ is imposed the governing equation using (7.35) becomes

$$C\frac{dV}{dt} = -g_{Na} m^3 h(V - V_{Na}) - g_K n^4 (V - V_K) - g_L (V - V_L) + I_a. \tag{7.38}$$

The system (7.38) with (7.37) constitute the 4-variable model which was solved numerically by Hodgkin and Huxley (1952).

If $I_a = 0$, the rest state of the model (7.37) and (7.38) is linearly stable but is excitable in the sense discussed in Chapter 6. That is, if the perturbation from the steady state is sufficiently large there is a large excursion of the variables in their phase space before returning to the steady state. If $I_a \neq 0$ there is a range of values where regular repetitive firing occurs; that is, the mechanism displays limit cycle characteristics. Both types of phenomena have been observed experimentally. Because of the complexity of the equation system various simpler mathematical models, which capture the key features of the full system, have been proposed, the best known and particularly useful one of which is the FitzHugh–Nagumo model (FitzHugh 1961, Nagumo et al. 1962), which we now derive.

The timescales for m, n and h in (7.37) are not all of the same order. The timescale for m is much faster than the others, so it is reasonable to assume it is sufficiently fast that it relaxes immediately to its value determined by setting $dm/dt = 0$ in (7.37). If we also set $h = h_0$, a constant, the system still retains many of the features experi-

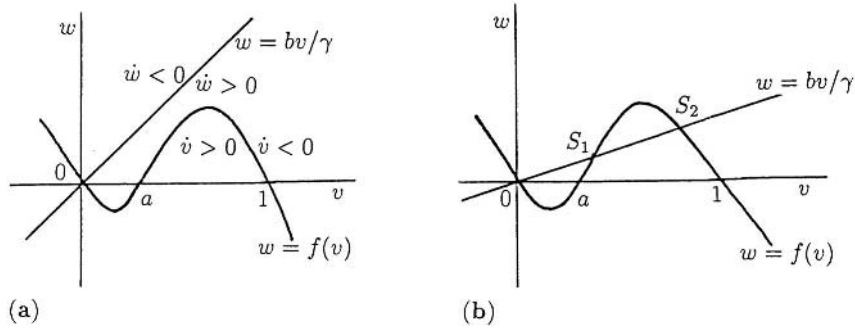

Figure 7.11. Phase plane for the model system (7.39) with $I_a = 0$. As the parameters vary there can be (**a**) one stable, but excitable state or, (**b**) three possible steady states, one unstable, namely, S_1, and two stable, but excitable, namely, (0, 0) and S_2.

mentally observed. The resulting 2-variable model in V and n can then be qualitatively approximated by the dimensionless system

$$\begin{aligned} &\frac{dv}{dt} = f(v) - w + I_a, \quad \frac{dw}{dt} = bv - \gamma w, \\ &f(v) = v(a - v)(v - 1), \end{aligned} \tag{7.39}$$

where $0 < a < 1$ and b and γ are positive constants. Here v is like the membrane potential V, and w plays the role of all three variables m, n and h in (7.37).

With $I_a = 0$, or just a constant, the system (7.39) is simply a 2-variable phase plane system, the null clines for which are illustrated in Figure 7.11. Note how the

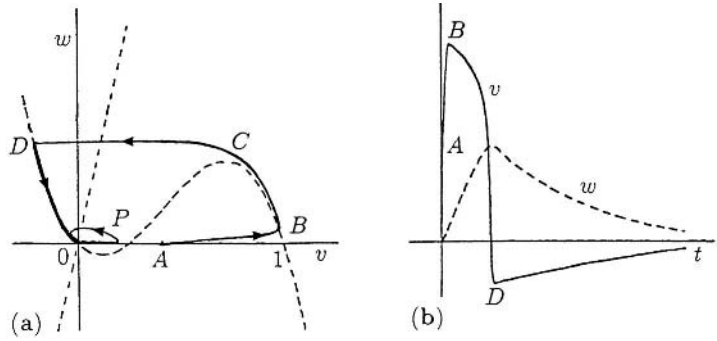

Figure 7.12. (**a**) The phase portrait for (7.39) with $I_a = 0$, $a = 0.25$, $b = \gamma = 2 \times 10^{-3}$ which exhibits the threshold behaviour. With a perturbation from the steady state $v = w = 0$ to a point, P say, where $w = 0$, $v < a$, the trajectory simply returns to the origin with v and w remaining small. A perturbation to A initiates a large excursion along $ABCD$ and then back to (0, 0), effectively along the null cline since b and γ are small. (**b**) The time variation of v and w corresponding to the excitable trajectory $ABCD0$ in (**a**). (Redrawn from Rinzel 1981)

phase portrait varies with different values of the parameters a, b and γ. There can, for example, be 1 or 3 steady states as shown in Figures 7.11(a) and (b) respectively. The situation corresponds to that illustrated in Figure 7.5, except that here it is possible for v to be negative—it is an electric potential. The excitability characteristic, a key feature in the Hodgkin–Huxley system, is now quite evident. That is, a perturbation, for example, from 0 to a point on the v-axis with $v > a$, undergoes a large phase trajectory excursion before returning to 0. Figure 7.12 shows a specific example.

Periodic Neuron Firing

With $I_a = 0$ the possible phase portraits, as illustrated in Figure 7.11, show there can be no periodic solutions (see Section 7.3). Suppose now that there is an applied current I_a. The corresponding null clines for (7.39) are illustrated in Figures 7.13(a) to (c) for several $I_a > 0$. The effect on the null clines is simply to move the v null cline, with $I_a = 0$, up the w-axis. With parameter values such that the null clines are as in Figure 7.13(a) we can see that by varying only I_a there is a window of applied currents (I_1, I_2) where the steady state can be unstable and limit cycle oscillations possible, that is, a null cline situation like that in Figure 7.13(b). The algebra to determine the various parameter ranges for a, b, γ and I_a for each of these various possibilities to hold is straightforward. It is just an exercise in elementary analytical geometry, and is left as an exercise (Exercise 7). With the situation exhibited in Figure 7.13(d) limit cycle solutions are not possible. On the other hand this form can exhibit switch properties.

The FitzHugh–Nagumo model (7.39) is a *model* of the Hodgkin–Huxley *model*. So, a further simplification of the mechanism (7.39) is not unreasonable if it simplifies the analysis or makes the various solution possibilities simpler to see. Of course such a simplification must retain the major elements of the original, so care must be exercised.

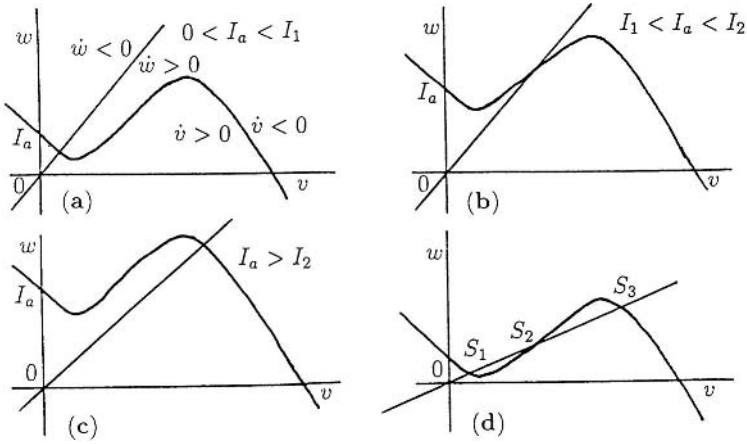

Figure 7.13. Null clines for the FitzHugh–Nagumo model (7.39) with different applied currents I_a. Cases (**a**), where $I_a < I_1$, and (**c**), where $I_a > I_2$, have linearly stable, but excitable, steady states, while in (**b**), where $I_1 < I_a < I_2$, the steady state can be unstable and limit cycle periodic solutions are possible. With the configuration (**d**), the steady states S_1, S_3 are stable with S_2 unstable. Here a perturbation from either S_1 or S_3 can effect a switch to the other.

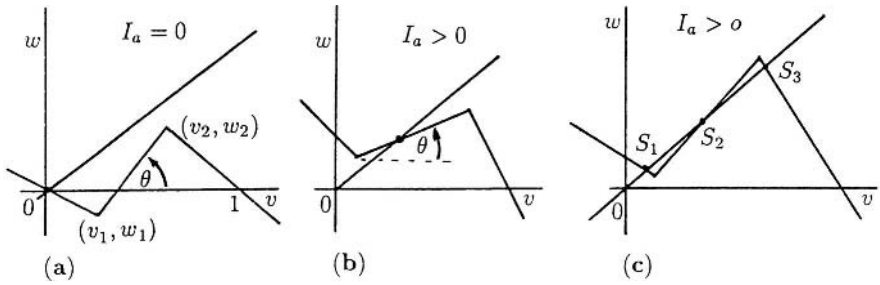

Figure 7.14. (**a**) Phase plane null clines for a piecewise linear approximation to the v null cline in the FitzHugh–Nagumo model (7.30) with $I_a = 0$, where (v_1, w_1) and (v_2, w_2) are given by (7.40). (**b**) The geometric conditions for possible periodic solutions, which require $I_a > 0$, are shown in terms of the angle $\theta = \tan^{-1}[(w_2 - w_1)/(v_2 - v_1)]$. (**c**) Geometric conditions for multiple roots and threshold switch possibilities from one steady state S_1 to S_3 and vice versa.

From Figure 7.11 we can reasonably approximate the v null cline by a piecewise linear approximation as in Figure 7.14, which in Figure 7.14(a) has zeros at $v = 0, a, 1$. The positions of the minimum and maximum, (v_1, w_1) and (v_2, w_2) are obtained from (7.39) as

$$\begin{aligned} v_2, v_1 &= \frac{1}{3}\left[a + 1 \pm \left\{(a+1)^2 - 3a\right\}^{1/2}\right], \\ w_i &= -v_i(a - v_i)(1 - v_i) + I_a, \quad i = 1, 2. \end{aligned} \tag{7.40}$$

The line from (v_1, w_1) to (v_2, w_2) passes through $v = a$ if $a = 1/2$. The acute angle θ the null cline makes with the v-axis in Figure 7.14 is given by

$$\theta = \tan^{-1}\left[\frac{w_2 - w_1}{v_2 - v_1}\right]. \tag{7.41}$$

We can now write down very simply a necessary condition for limit cycle oscillations for the piecewise model, that is, conditions for the null clines to be as in Figure 7.14(b). The gradient of the v null cline at the steady state must be less than the gradient, b/γ, of the w null cline; that is,

$$\tan\theta = \frac{w_2 - w_1}{v_2 - v_1} < \frac{b}{\gamma}. \tag{7.42}$$

Sufficient conditions for a limit cycle solution to exist are obtained by applying the results of Section 7.3 and demonstrating that a confined set exists. Analytical expressions for the limits on the applied current I_a for limit cycles can also be found (Exercise 7).

A major property of this model for the space-clamped axon membrane is that it can generate regular beating of a limit cycle nature when the applied current I_a is in an appropriate range $I_1 < I_a < I_2$. The bifurcation to a limit cycle solution when I_a increases past I_1 is essentially a Hopf bifurcation and so the period of the limit cycle is given by an application of the Hopf bifurcation theorem. This model with periodic

beating solutions will be referred to again in Chapter 9 when we consider the effect of perturbations on the oscillations. All of the solution behaviour found with the model (7.39) have also been found in the full Hodgkin–Huxley model, numerically of course. The various solution properties have also been demonstrated experimentally.

Some neuron cells fire with periodic bursts of oscillatory activity like that illustrated in Figures 7.7(b) and (d). We would expect such behaviour if we considered coupled neuronal cells which independently undergo continuous firing. By modifying the above model to incorporate other ions, such as a calcium (Ca^{++}) current, periodic bursting is obtained; see Plant (1978, 1981). There are now several neural phenomena where periodic bursts of firing are observed experimentally. With the knowledge we now have of the qualitative nature of the terms and solution behaviour in the above models and some of their possible modifications, we can now build these into other models to reflect various observations which indicate similar phenomena. The field of neural signalling, both temporal and spatial, is a fascinating and important one which will be an area of active research for many years.

7.6 Modelling the Control of Testosterone Secretion and Chemical Castration

The hormone testosterone, although present in very small quantities in the blood, is an extremely important hormone; any regular imbalance can cause dramatic changes. In man, the blood levels of testosterone can fluctuate periodically with periods of the order of two to three hours. In this section we discuss the physiology of testosterone production and construct and analyse a model, rather different from those we have so far discussed in this chapter, to try and explain the periodic levels of testosterone observed. Although the phenomenon is interesting in its own right, another reason for discussing it is to demonstrate the procedure used to analyse this type of model. Perhaps most important, however, is to try and understand the mechanism of production with a view to aiding current research in controlling testosterone production in its use in (chemical) male contraception and prostate cancer control.

Before describing the important physiological elements in the process of testosterone production, there are some interesting effects and ideas associated with this important hormone. Men have a testosterone level of between 10 to 35 nanomoles per litre of blood, with women having between 0.7 to 2.7 nanomoles per litre. Reduced levels of testosterone, or rather the level of a sex hormone binding globulin (SHBG) directly related to free testosterone, are often accompanied by personality changes—the individual tends to become less forceful and commanding. On the other hand increased levels of testosterone induce the converse. Although the actual differences in testosterone levels are minute, the effects can be major.

In men the high level of testosterone primarily comes from the testes, which produces about 90%, with the rest from other parts of the endocrine system, which is why women also produce it. The drug Goserelin, for example, which was introduced to treat cancer of the prostate, can achieve chemical castration within a few weeks after the start of treatment. The patient's testosterone level is reduced to what would be achieved by removal of the testes. The body does not seem to adjust to the drug and so effective

castration continues only as long as the treatment is maintained. How the drug works in blocking the production of testosterone is pointed out below when we discuss the physiological production process. Enthusiasm for sex, or sex drive, depends on many factors and not only the level of testosterone, which certainly plays a very significant role. If we consider the problem of an excessive sex drive, it is not uncommon for men sentenced for rape to ask to be treated with drugs to induce castration. There are now several drugs which effect castration: the already mentioned Goserelin, such as Lupron and Depo-provera which is more long lasting. The use of drugs to suppress the production of testosterone has been used in Europe for more than 10 years. In fact it is often a condition of release for convicted sex offenders. In Europe Depo-provera has reduced the recidivism rate of child molesters to 2% whereas in the U.S., where drugs are not generally used it is of the order of 50%. The role of testosterone-reducing drugs, or generally chemical castration, is a controversial area of treatment for sex offenders.

The full physiological process is not yet fully understood although there is general agreement on certain key elements. The following shows how a first model had to be modified to incorporate key physiological facts and points the way to more recent and complex models. We first derive a model for testosterone (T) production in the male suggested by Smith (1980); it is based on accepted basic experimental facts. We then discuss a modification which results in a delay model which incorporates more realistic physiology associated with the spatial separation of the various control regions. A more complicated delay model which is consistent with a wider range of experiments was proposed by Cartwright and Husain (1986): it incorporates more of the physiological process. We discuss it very briefly below.

Let us now consider the basic physiology. The secretion of testosterone from the gonads is stimulated by a pituitary hormone called the luteinising hormone (LH). The secretion of LH from the pituitary gland is stimulated by the luteinising hormone releasing hormone (LHRH). This LHRH is normally secreted by the hypothalmus (part of the third ventricle in the brain) and carried to the pituitary gland by the blood. Testosterone is believed to have a feedback effect on the secretion of LH and LHRH. Based on these, Smith (1980) proposed a simple negative feedback compartment model, such as we discussed in Section 7.2, involving the three hormones T, LH and LHRH and represented schematically in Figure 7.15.

Denote the concentrations of the LHRH, LH and T respectively by $R(t)$, $L(t)$ and $T(t)$. At the simplest modelling level we consider each of the hormones to be cleared from the bloodstream according to first-order kinetics with LH and T produced by their precursors according to first-order kinetics. There is a nonlinear negative feedback by $T(t)$ on $R(t)$. The governing system reflecting this scheme is essentially the model feedback system (7.3), which here is written as

$$\begin{aligned} \frac{dR}{dt} &= f(T) - b_1 R, \\ \frac{dL}{dt} &= g_1 R - b_2 L, \\ \frac{dT}{dt} &= g_2 L - b_3 T, \end{aligned} \tag{7.43}$$