1 Hodgkin-Huxley Theory of Nerve Membranes: The FitzHugh-Nagumo model

Alan Hodgkin and Andrew Huxley developed the first quantitative model of the propagation of an electrical signal (the action potential) along a squid giant axon, but their ideas have since been extended and applied to a wide variety of excitable cells. FitzHugh showed how the essentials of the excitable process could be distilled into a simpler model analytically tractable.

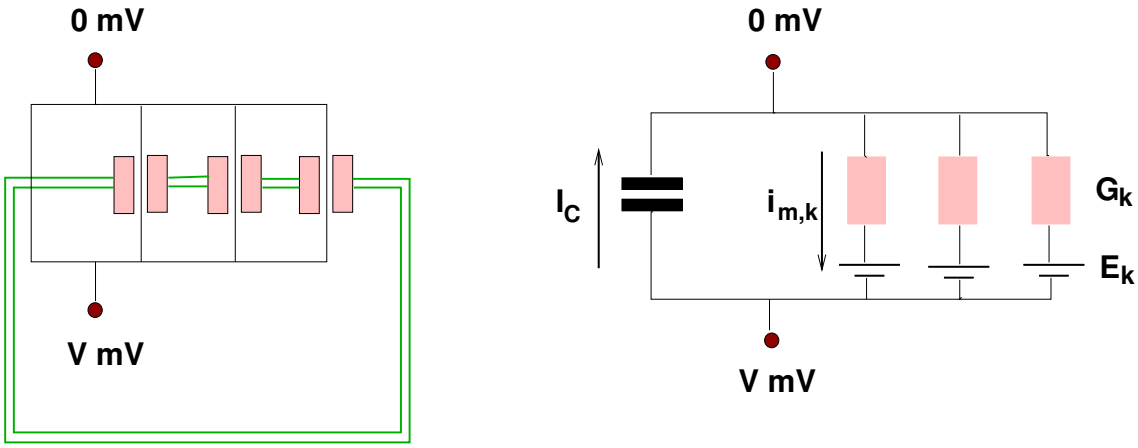

Figure 1: Equivalent circuit for the space-clamp dynamics of the membrane voltage in Hodgkin-Huxley like models.

A. The Hodgkin-Huxley (HH) model.

We consider the spatially homogeneous or space clamped dynamics of the membrane of the axon. Experimentally this can be obtained by having a wire down the middle of the axon maintained at a fixed potential difference to the outside. In this conditions, the total current is the sum of the current due to the individual ions which pass through the membrane (I_k) and the contribution from the time variation in the transmembrane potential, that is the membrane capacitance contribution ($I_C = C_m \frac{dV}{dt}$):

$$I(t) = I_C + \sum_k i_{m,k} \tag{1}$$

Using the Kirchoff's current law, the net current in a node of an electrical circuit must be zero, then we have $I(t) = 0$. The ionic currents are modeled using the Ohm's law: $i_{m,k} = G_k(V - E_k)$ (figure 1), where G_k is the ionic conductance for the ion k through the membrane. E_k is the Nernst equilibrium potential for the ion k. Thus, we obtain the membrane voltage equation:

$$C_m \frac{dV}{dt} = -\sum_k G_k(V - V_k) \tag{2}$$

Based in experimental observation Hodgkin and Huxley took:

$$\begin{aligned}\sum_k i_{m,k} &= I_{Na} + I_K + I_L \\ &= \bar{G}_{Na} m^3 h (V - E_{Na}) + \bar{G}_K n^4 (V - E_K) + \bar{G}_L (V - E_L).\end{aligned} \tag{3}$$

that is, a sodium current (I_{Na}), a potassium current (I_K) and *leakage* current (I_L). The last one is the contribution from all other ions which may contribute to the total current. The $m,\ n,\ h$ are variables, bounded by 0 and 1, which follow the differential equation:

$$\begin{aligned}&\frac{dx}{dt} = \alpha_x(V)(1-x) - \beta_x(V)x; \quad \frac{dx}{dt} = \frac{x_\infty(V) - x}{\tau_x(V)} \\ &x_\infty(v) = \tfrac{\alpha(V)}{\alpha(V)+\beta(V)}, \quad \tau_x = \tfrac{1}{\alpha(V)+\beta(V)}\end{aligned} \tag{4}$$

with $x = m,\ n,\ h$. The variables m and h drive, respectively, the activation and inactivation of the sodium current, whereas n is responsible for the activation of the potassium current. The functions $\alpha_x(V)$ and $\beta_x(V)$ are transition rates between open or close states of the different gates involved in each ionic channel (figure 2). For any fixed voltage step, they are determined by fitting to experimental data. In eq. (4), x_∞ and τ_x are steady state variable and time constant, respectively. If an external current $I_e(t)$ is applied the governing

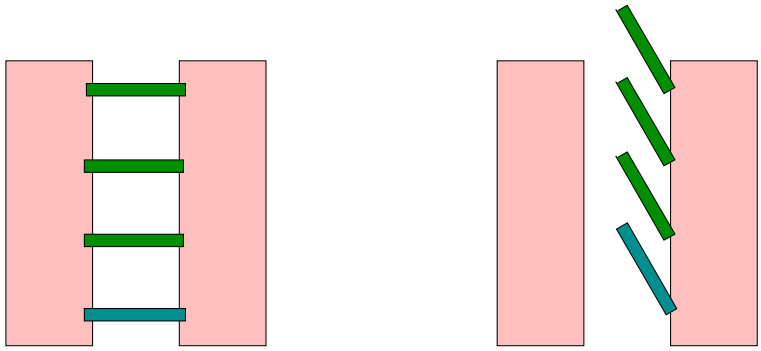

Figure 2: Channel model of the Na^+.

equation becomes:

$$C_m \frac{dV}{dt} = -[\bar{G}_{Na} m^3 h (V - E_{Na}) + \bar{G}_K n^4 (V - E_K) + \bar{G}_L (V - E_L)] + I_e \tag{5}$$

If $I_e = 0$ it can be proved that the rest state is linearly stable but it is excitable[1] if the perturbation from the steady state is sufficiently large. For $I_e \neq 0$ there is a range where repetitive firing occurs. Both types of phenomena have been observed experimentally in the giant axon of the squid.

[1] A mechanism is excitable if a stimulus of sufficient size can initiate a large excursion in the phase plane.

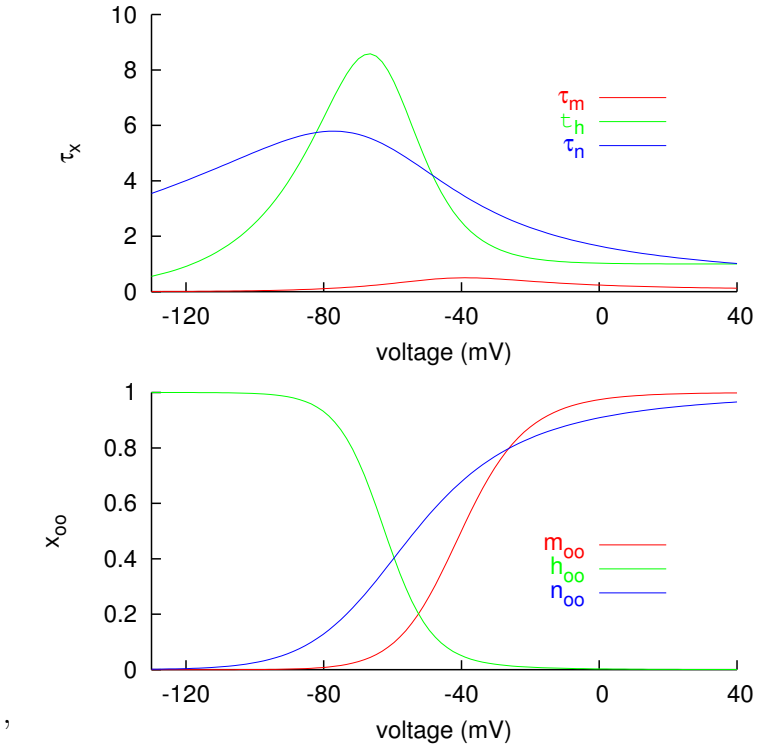

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Figure 3: Dependence with V of the time constants and steady states of gating variables for the Hodgkin-Huxley model.

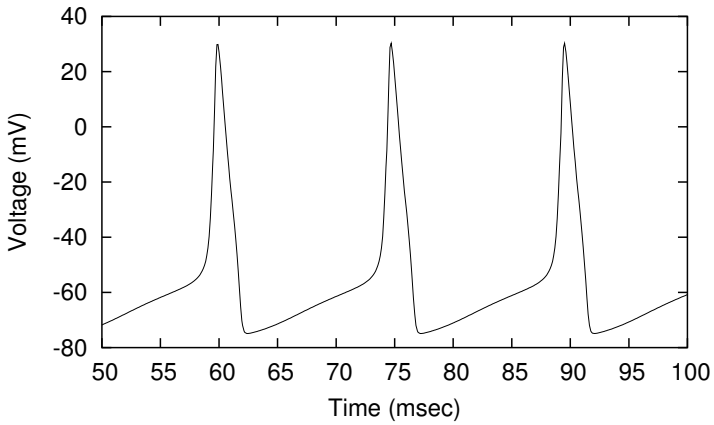

Figure 4: Tonic spiking activity generated in the Hodgkin-Huxley model for $I_e = 10\mu A/cm^2$.

B. The FitzHugh-Nagumo Model. A simplified model of spiking is justified by the observation that both $V(t)$ as well as $m(t)$ evolve on similar time scale during an action potential, while $h(t)$ and $n(t)$ change on much slower time scales. Given the similarity between V and m it make sense to lump them in to a single "activation" variable V. The same observation can be made for n and $1-h$. Again we can combine both into a single variable W, characterizing the degree

of "refractoriness" of the system. The behavior of such a two-dimensional system is qualitatively similar to the four-dimensional Hodgkin-Huxley model.

FitzHugh (1961) and, independently, Nagumo et al. (1962) derived the following two equations to qualitatively describe the events occurring in an excitable neuron

$$\begin{aligned} \frac{dV}{dt} &= V - \frac{V^3}{3} - W + I \\ \frac{dW}{dt} &= \phi(V - a - bW) \end{aligned} \tag{6}$$

The parameters a, b, and ϕ are dimensionless and positive. The amplitude of ϕ, corresponding to the inverse of a time constant, determines how fast W changes relative to V. Because the nonlinear nature of these differential equations we can not derive closed-form solutions. However, we can deduce qualitative topological properties in the phase space spanned by V and W, just looking the phase portrait. In cases like eqs. (6) where derivatives on the right-hand side do not depend explicitly on time, different trajectories can never cross. [2]

In order to understand how the system evolves in time we will plot the *null-clines* in the (V, W) plane. [3] The nullcline associated to the fast variable is the cubic function $W = V - V^3/3 + I$. If the system is located on the V nullcline its imminent future trajectory must be vertical, pointing upward ($\dot{W} > 0$) or downward ($\dot{W} < 0$). Furthermore, for all points in the plane above this line, we have $\dot{V} < 0$ while the converse is true for all points below this line. The nullcline associated to the slow variable, $\dot{W} = 0$ is specified by the linear equation $W = (V + a)/b$ (see figure 5).

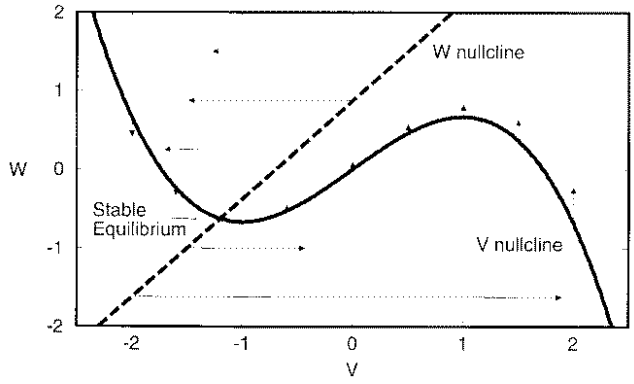

Figure 5: Phase portrait of the FitzHugh-Nagumo model.

[2] If two trajectories intersect, there would be two different solution starting from the same point that is in contradiction with the existence and uniqueness theorem associated with a set of coupled differential equations.

[3] An isocline is a curve in the phase plane along which one of the derivatives is constant. In particular the null isocline, or nullcline, is the curve along which one of the derivatives is zero.

The equilibrium points are those points (V^*, W^*) at which both derivatives in (6) are zero. We can check the stability of the equilibria by linearizing around the fixed points and computing the eigenvalues

$$\frac{d}{dt}\begin{pmatrix} x \\ y \end{pmatrix} \approx \begin{pmatrix} (1 - V^{*2}) & -1 \\ \phi & -b\phi \end{pmatrix}\begin{pmatrix} x \\ y \end{pmatrix} \tag{7}$$

where $x = V - V^*$ and $y = W - W^*$. The eigenvalues can be computed easily obtaining

$$\lambda_{1,2} = \frac{-(V^{*2} - 1 + b\phi) \pm \sqrt{(V^{*2} - 1 - b\phi)^2 - 4\phi}}{2} \tag{8}$$

For $I = 0$ and $a = 0.7,\ b = 0.8$ and $\phi = 0.08$ the two eigenvalues are complex conjugate $(-0.5 \pm 0.42i)$. Then the fixed point is asymptotically stable (stable spiral) and the system will oscillate before reach it.

How will the FN model respond if an instantaneous current pulse $I(t) = Q\delta(t)$ (with $Q > 0$) is applied. Then the initial value of V will jump by Q thereby moving the system in phase space a certain horizontal distance away from the equilibrium point (figure 6).

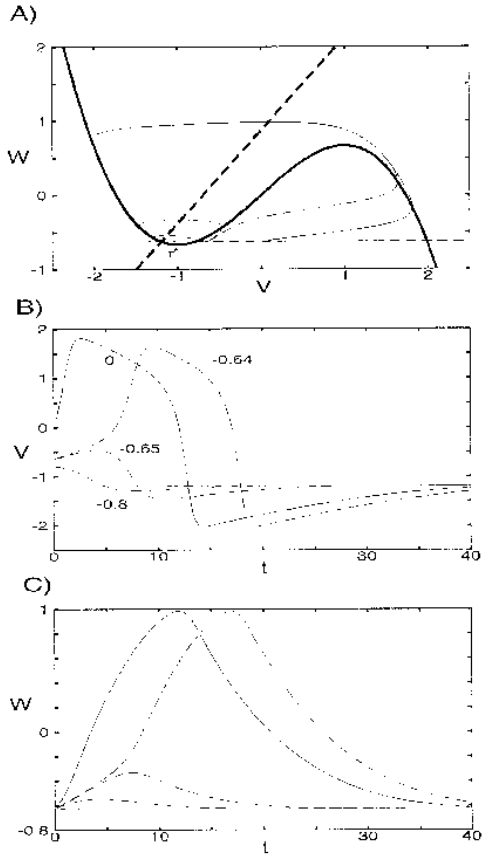

Figure 6: Response of the FitzHugh-Nagumo model to current pulses.

If the current input is small, the system will almost immediately return to the rest following a tight trajectory around the equilibrium point.

If the amplitude of the current pulse is made larger, that is V is moved instantaneously past -0.64, the system evolution of the system sharply veers away from the V nullcline and undergoes a large phase trajectory excursion before returning to the fixed point.

If we stimulate the quiescent system with a sustained current step of amplitude I at $t = 0$. Then for positive current step, in the new phase portrait the V nullcline is shifted upward (figure 7). This changes the position of the equilibrium point. The

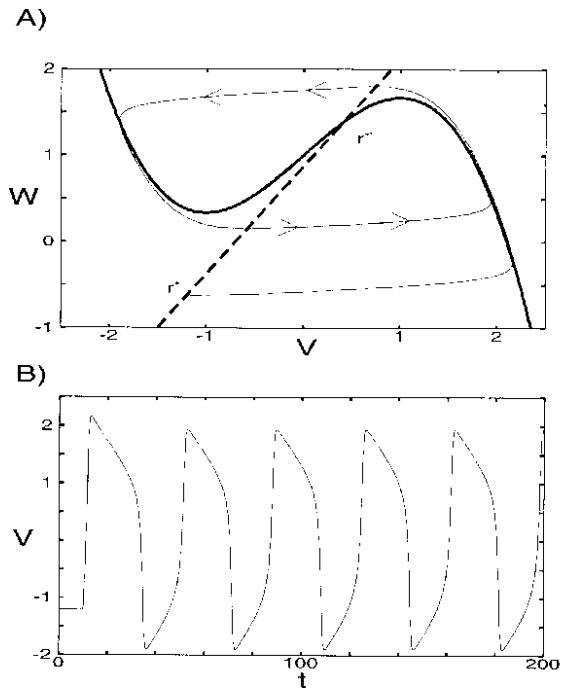

Figure 7: Response of the FitzHugh-Nagumo model to current steps.

solution is stable as long as the real part of the two eigenvalues is negative. Once the real part becomes zero and then positive, even infinitesimal small perturbations will become amplified and diverge away from the equilibrium. The real part changes sign at the two locations where

$$V_{\pm}^{*} = \pm\sqrt{1 - b\phi}. \tag{9}$$

Thus, the equilibrium is stable whenever the W nullcline meets the cubic nullcline along its right-and leftmost branches. Here the slope is negative and $|V^{*}| \geq 1$. However, along the central part of the V nullcline, $|V^{*}| < \sqrt{1 - b\phi}$ and the eigenvalue will acquire a positive real part and the point is unstable. Due to the cubic nonlinearity the system does not diverge and follow a stable limit cycle in the phase plane (which correspond to an action potential).

2 Calcium dynamics

Calcium ions have a crucial role in regulating the day-to-day life of the neurons. The dynamics of the free intracellular calcium is controlled by a number of physical and chemical processes, foremost among them *diffusion* and *binding* to a host of different proteins, which serve as calcium *buffers* and as calcium sensors or triggers. Whereas buffers simple bind Ca^{2+} above some critical concentration, releasing it back into the cytoplasm when $[Ca^{2+}]$ has been reduced below this level, certain proteins – such as calmodulin– change their conformation when they bind to calcium, thereby activating or modulating enzymes, ionic channels, or other proteins. Moreover, the $[Ca^{2+}]$ inside the cell, for instance, determines the activation of $I_{K(Ca)}$ currents, it is relevant for synaptic plasticity (facilitation). It is crucial that we have some understanding of the role that diffusion and chemical kinetics play in governing of the behavior of cytosolic calcium.

2.1 Diffusion equation

The mathematical theory of diffusion in a isotropic milieu is based on the simplest phenomenological expression possible (also called Fick's first law) that the rate of transfer (or flux) $S(x,t)$ of a diffusing substance across a surface of unit area is given by:

$$S(x,t) = -D\frac{\partial C(x,t)}{\partial x}. \tag{10}$$

The minus is because diffusion occurs against a concentration increase. D is the constant of proportionality and it has dimensions of $\mu m^2/msec$. Suppose we have

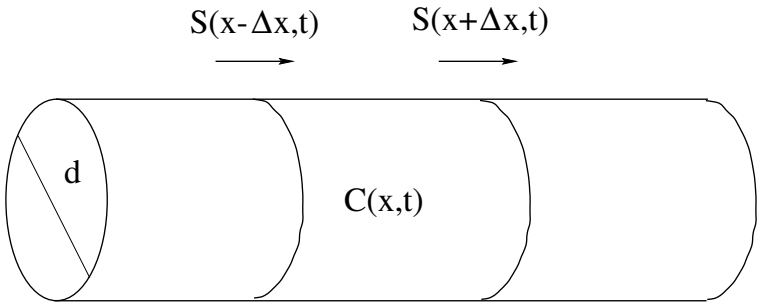

Figure 8: Dendrite compartment

a cylindrical compartment (see figure 8) where the concentration only varies along the x dimension (we assume that the radial diffusion is short compared to the longitudinal diffusion). If the concentration inside of the compartment centered at x and with boundaries $x \pm \Delta x$, varies by $\partial C/\partial t$ the change in the number of ions is given by:

$$\frac{\Delta x \pi d^2}{2}\frac{\partial C(x,t)}{\partial t} \tag{11}$$

This change should be identically to the net rate of transfer across one boundary minus the rate of transfer across the other.

$$\frac{\pi d^2}{4}(S(x-\Delta x,t)-S(x+\Delta x,t)) \tag{12}$$

Setting these two expressions equal and taken the limit $\Delta x \to 0$ we obtain the diffusion equation (here we have used the Fick's law):

$$\frac{\partial C(x,t)}{\partial t} = D\frac{\partial^2 C(x,t)}{\partial x^2} \tag{13}$$

- Steady-state solution for and Infinite cable. Suppose we clamp the concentration at the origin ($C(x=0,t)=C_0$ for all times) then

$$\frac{d^2 C(x)}{dx^2} = 0 \tag{14}$$

  and its solution for and infinite cable is $C(x)=C_0$ for all values of x. After enough time has passed, the concentration in the entire cable rises to the concentration at the origin.

- Time-dependent solution for an infinite cable. Suppose that an amount S_0 of calcium is injected instantaneously into the cylinder at $x=0$. Then the evolution of C is given by

$$C_\delta(x,t) = \frac{S_0}{\sqrt{2\pi}}\frac{1}{(2Dt)^{1/2}}e^{-\frac{x^2}{4Dt}} \tag{15}$$

  The associated concentration profile is represented on figure 9. The variance of the Gaussian increases linearly with time $\sigma^2 = 2Dt$.

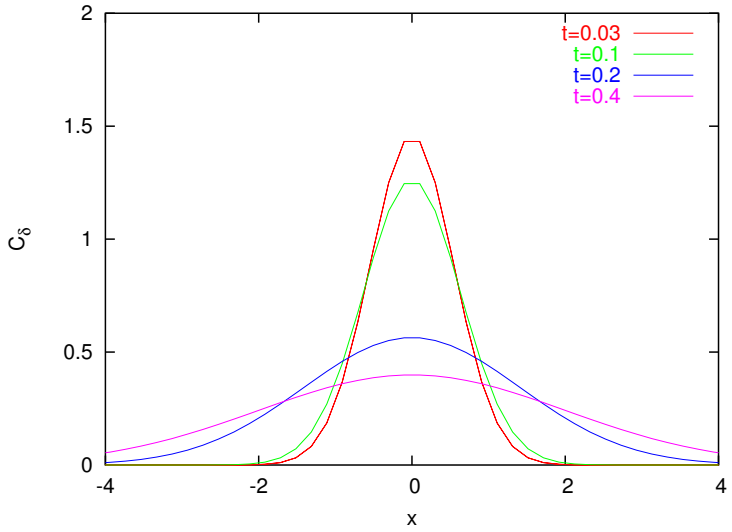

Figure 9: Impulse Response of the diffusion equation in an infinite cable.

2.2 Electrodiffusion and the Nernst-Planck Equation

This equation arises when one include the movement of ions caused by concentration differences as well as by drift along an electric field. Even if a dendrite is initially at equilibrium with respect to the spatial distribution of sodium, potassium, calcium and chloride ions (which are the most important for fast signaling) the influx and efflux of these ions disturb this equilibrium, creating concentration gradients that propel the ions down this gradient. This is specilly important in dendrites and spines for calcium ions. Then, it can be derive the electrodiffusion equation combining the Ohm's law, and Fick's law as follow

$$I_{i,k}(x,t) = -z_k F D_k \frac{\partial C_k(x,t)}{\partial x} - \frac{z_k^2 F^2 D_k C_k(x,t)}{RT} \frac{\partial V_m(x,t)}{\partial x} \tag{16}$$

where $I_{i,k}(x,t)$ is the axial current for a particular ion k. Ions drift down the potential gradient while simultaneously spreading due to diffusion.

On the other hand, in the perpendicular direction to the membrane (radial direction) we have at equilibrium that

$$\frac{dV_m}{dr} + \frac{RT}{z_k F} \frac{1}{C_k(r)} \frac{dC_k(r)}{dr} = 0 \tag{17}$$

that is the net current across the membrane must be zero at equilibrium.

Due to reason of conservation, the change in concentration for a particular ion in an infinitesimal cylindrical segment of length dx and diameter d must be compensate by the sum of current across the membrane per unit length (weighted by the surface-to-volume ratio) and the difference between the ingoing and outgoing axial currents, that is:

$$\frac{4}{d} i_{m,k}(x,t) + \frac{\partial I_{i,k}(x,t)}{\partial x} + z_k F \frac{\partial C_k(x,t)}{\partial t} = 0 \tag{18}$$

that using the electrodiffusion equation becomes

$$\frac{\partial C_k(x,t)}{\partial t} = -\frac{4}{z_k F d} i_{m,k}(x,t) + D_k \frac{\partial^2 C_k(x,t)}{\partial x^2} + \frac{z_k F D_k}{RT} \frac{\partial}{\partial x} \left(C_k(x,t) \frac{\partial V_m(x,t)}{\partial x} \right) \tag{19}$$

2.3 Buffering of Calcium

Experiments in living cell shows that the effective diffusion constant for calcium ions is 1/10 of that observed in aqueous solution. This is in contrast to the behavior of the potassium ions under similar circumstances. This showed that once calcium enters the intracellular cytoplasm it is not free to diffuse. Indeed, 95% of the entering calcium is quickly bound by a host of systems (protein buffers to cellular organelles, such as mithocondria and endoplasmic reticulum). A large number of Calcium binding proteins as calmodulin are present in neurons. As the concentration of calcium in the cytoplasm drops, the calcium ions are progressively released from the buffer and are free to wander about.

Suppose that calcium ion binds to a buffer with forward binding rate f and backward rate b

$$B + Ca^{2+} \leftrightarrows B \cdot Ca \tag{20}$$

In terms of associated kinetic equations, we have:

$$\begin{aligned} \frac{d[Ca^{2+}]}{dt} &= b[B \cdot Ca] - f[B][Ca^{2+}] \\ \frac{d[B]}{dt} &= b[B \cdot Ca] - f[B][Ca^{2+}] \\ T_B &= [B \cdot Ca] + [B] \end{aligned} \tag{21}$$

where T_B is the total amount of buffer. The steady state distribution of the buffer-calcium complex is given by

$$[B \cdot Ca] = \frac{T_B[Ca^{2+}]}{K_d + [Ca^{2+}]} \tag{22}$$

where $K_d = b/f$ is the dissociation constant of the buffer.

2.4 Ionic pumps

The crucial component of the system controlling the homeostasis of ions in cells are specialized molecules that act as *ionic pumps.* They maintain the ionic gradients across the membrane that enable, for example, neurons to signal and propagate action potentials. In addition to buffers and other mechanism they provide exquisite regulation of the intracellular free calcium. One simple way to model the dynamics of these pumps is via saturable first-order Michaelis-Menten kinetics

$$\frac{\partial[Ca^{2+}]_{pump}}{\partial t} = \frac{4P_m}{d} \frac{[Ca^{2+}]}{1 + [Ca^{2+}]/K_{d-pump}} \tag{23}$$

2.5 Reaction-diffusion equation for calcium dynamics

Our starting point is the distribution of calcium ions in a cylinder following the influx of calcium current $I_{Ca}(x,t)$ across the membrane. The inflowing calcium ions diffuse to neighboring locations, bind to various buffers, and can be pumped back out of the cable. The buffer itself can also diffuse with a diffusion coefficient D_B. Then we have

$$\begin{aligned}
&\frac{\partial[Ca^{2+}](x,t)}{\partial t} = D\frac{\partial^2[Ca^{2+}](x,t)}{\partial x^2} - f[Ca^{2+}](x,t)[B](x,t) + b[B\cdot Ca](x,t) \\
&\qquad\qquad - \frac{\partial[Ca^{2+}](x,t)_{pump}}{\partial t} - \frac{2I_{Ca}(x,t)}{Fd} \\
&\frac{\partial[B\cdot Ca](x,t)}{\partial t} = D_B\frac{\partial^2[B\cdot Ca](x,t)}{\partial x^2} + f[Ca^{2+}](x,t)[B](x,t) - b[B\cdot Ca](x,t) \\
&T_B = [B\cdot Ca] + [B]
\end{aligned} \tag{24}$$