MATHEMATICAL MODELS OF EXCITABILITY IN BIOLOGICAL MEMBRANES, CELLS AND NETWORKS

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Contents

Summary

Cellular excitability is at the very heart of life. It is a consequence of the difference in ionic composition which all organisms, uni- or multi-cellular, maintain between their intracellular medium and the environment. The passive electro-diffusion accompanying this concentration difference, along with active ionic pumps, evokes an electric-potential gradient of tens of millivolts between the inside and outside of the cell, and hence a huge field within the tiny cell membrane. Excitable cells like neurons exploit this membrane electric field to convey signals from their environment and to communicate with other cells.

They possess membrane proteins that alter their conformation either under the influence of changes in the membrane electric field itself or when they are exposed to external stimuli of chemical, mechanical or photonic nature. Some of these proteins are ionic channels whose changing conductance in turn modifies the membrane potential, a process transforming the membrane into a complex dynamical system operating on a submillisecond time-scale.

This paper first summarizes the physical principles underlying the passive and active membrane properties, culminating in the model of the propagating action potential. It then examines simplifying mathematical models of excitability, their origin, physical basis and dynamic behavior, illustrated with phase-plane portraits and bifurcation diagrams, and leading to the widely accepted classification of neurons into integrators and resonators. The paper then considers the excitability and dynamics of simple networks of neurons, with an emphasis on mass phenomena like synchronous oscillations. After a few notes on stochastic models, the paper concludes with potential targets for future research.

1. Introduction

The history of bioelectricity developed concurrently with that of electromagnetism. Witness to this is the debate at the end of the 18th century between Galvani and Volta as to whether the muscle contractions observed by Galvani during frog dissection found their origin in electricity within the tissue itself or in the contact between dissimilar metals. The latter view, maintained by Volta, led to the discovery of the voltaic pile, whereas Galvani's view developed to the current theory of cell excitability. At one important characteristic, however, all comparison falls short: electric currents in excitable tissue are carried by ions, mostly sodium (Na^+), potassium (K^+), chlorine (Cl^-) and calcium (Ca^{++}), instead of electrons, and they travel at speeds of meters per second rather than the velocity of light. Forces due to magnetic induction, although detectable, can largely be ignored.

The origin of bioelectricity is closely related to the requirement of all life to generate and maintain an intracellular environment that is quite different from that of the outside world. Electric- potential gradients develop across all membranes that separate compartments of dissimilar ionic composition: hence not only across the cell membrane proper or plasmalemma (which separates the cytoplasm from the extracellular space), but also across the membrane of intracellular organelles such as mitochondria or the tonoplast vacuole of algae. Other organisms, like the uni-cellular malaria parasite, are able to maintain a constant cytoplasmic composition in quite different environments, for instance when they invade the liver cell or red blood cell to become intracellular parasites. They do so by actively pumping ions and nutrients, and through complex gene mechanisms that alter the membrane properties of their host cells.

In animals, the transmembrane electric potentials can largely be explained by electro-diffusion: differences in the speed of migration of different ions across the membrane cause a separation of charges (ions) of opposite polarity. The order of magnitude of the transmembrane potential is from several tens of millivolts to 100 mV, but some animals like the torpedo fish are able to discharge potentials of several hundreds of volts by taking advantage of a pile-like organization of their electric cells.

Electrical excitability arises when cells actively change their transmembrane potential in order to signal changes in the environment or to communicate with other cells. They typically do so by changing the membrane permeability for one particular ion species in a very selective manner, by opening or closing transmembrane ionic channels, a process that can occur on a submillisecond time-scale. The process by which external stimuli modulate the electric potentials in sense organs is called transduction. The stimulus opens or closes membrane channels for particular ionic species either by mechanical forces (hearing, touch), by a photochemical reaction chain (vision), or by the direct binding of chemical compounds to membrane receptors (taste, smell). The communication of changes in the membrane potential from one cell to another can occur electrotonically at electrical synapses, which are poorly selective ionic channels of varying resistance connecting the interiors of adjacent cells, but in vertebrates mostly chemically: neurochemical transmitter molecules locally released by the presynaptic cell bind to receptors on the postsynaptic cell that are either ionic channels or are coupled to them. At the effector side, changes in the membrane potential can trigger

intrinsic signaling pathways, evoke the release of neurotransmitters or secretory substances, induce mechanical forces through excitation-contraction coupling as in muscles, or generate electric fields in the environment (as by electric fish).

By far the most important property of excitable membranes, however, is their ability to change their permeability for ions under the influence of their own electric field. This characteristic makes them genuine dynamical systems, responding not only to stimulation, but able to generate their own intrinsic activity, as exemplified most strikingly by pacemaker cells in the heart and by neurons in the respiratory brain centers.

The mathematical modeling of excitability has a long history. Some of the models have an empirical origin, aiming to reproduce experimental data, but many were inspired by contemporary theories of electric circuits, nonlinear systems or population dynamics. The first sections of this chapter review the macroscopic physical processes underlying excitability, culminating in the Hodgkin-Huxley model of the action potential. Later sections review the physical roots of qualitative, reduced models and summarize more recent insights in the dynamics of excitable networks. Although most of the examples and illustrations were taken from neuroscience, the underlying principles generalize to other excitable tissues like heart and muscle.

2. The Passive Properties of Biological Membranes

This section introduces the electric phenomena underlying the sub-threshold responses to stimuli too weak to recruit full-blown excitation, and provides an indispensable basis for the understanding of genuine (active) excitability, which is the subject of Section 3. The passive phenomena include electro-diffusion (the Nernst-Planck equation), the establishment of the ionic equilibrium potential and the resting membrane potential, and the leaky integration and passive spread of electric potentials (the cable equation).

Because these phenomena involve distinct compartments (intra- versus extracellular) or propagate along one-dimensional cable structures (axons and dendrites), the underlying physical laws are here formulated in only a single spatial dimension x and the time t.

2.1. Diffusion of Ions due to a Concentration Gradient

The flux of ions in an inhomogeneous solution is described by Fick's second low, stating that the concentration at a certain point x will rise or fall if the concentration in the immediate neighborhood (shrinking in the limit to zero) is higher or lower than, respectively, the concentration at that point. Mathematically this corresponds to the second-order derivative with respect to position being positive (convex) or negative (concave)

$$\frac{\partial c(x,t)}{\partial t} = D\frac{\partial^2 c(x,t)}{\partial x^2}. \qquad (1)$$

Here $c(x,t)$ is the space- and time-dependent concentration, and D is the diffusion coefficient for the particular ion in that particular solvent. As diffusion is a process of thermal agitation, D is given by

$$D = \frac{k_B T}{\beta}, \tag{2}$$

where T is the absolute temperature in degrees Kelvin, k_B is a scaling factor (called Boltzmann's constant) that allows kinetic energy to be measured as temperature, and β is a friction factor depending on the size and shape of the solute molecules and solvent.

The second-order derivative in (1) can be understood as the difference between the influx and outflux at position *x*, each being described by Fick's first law:

$$J(x,t) = -D\frac{dc(x,t)}{dx}. \tag{3}$$

The flux J quantifies the number of ions in moles passing through a plane surface of unit area during a unit time interval.

As different ions, having different diffusion coefficients, move with different velocities, a concentration gradient of a solute in a solvent will generate a separation of charges (a local minute violation of electro-neutrality) causing an electric-potential gradient, which is the origin of diffusive potentials and of potentials at the junction of dissimilar solutions (liquid-junction potentials).

2.2. Drift of Ions due to an Electric Field (Potential Gradient)

In a solution, ions move at a constant velocity when under the influence of an electric force, rather than being accelerated as they would in a frictionless medium.

Hence a force F ,

$$F(x) = z\, q_e \frac{d\varphi}{dx}, \tag{4}$$

generated by a field (a gradient of the electric potential φ) and acting on an ion of total charge zq_e (the valence times the unitary proton charge), causes the ion to drift with velocity

$$v_D = \mu F \tag{5}$$

where the mobility μ is related to the diffusion coefficient D as

$$\mu = \frac{D}{k_B T} = \frac{1}{\beta}. \tag{6}$$

The ion flux is proportional to the number of ions available, $c(x)$, and to the drift speed, giving

$$J(x) = c(x)\, v_{\mathrm{D}}\,. \tag{7}$$

2.3. The Nernst-Planck Electro-Diffusion Equation

The Nernst-Planck equation expresses the fact that under the influence of simultaneous electrical and chemical gradients, the respective fluxes can be summed:

$$J = J_{\mathrm{D}} + J_{\mathrm{F}} = -D\frac{dc(x)}{dx} - \mu\, z q_{\mathrm{e}}\, c(x)\frac{d\varphi(x)}{dx}\,. \tag{8}$$

Alternative formulations, using exclusively D or μ to characterize the ion's friction forces, are

$$\begin{aligned} J &= -\mu\left(k_{\mathrm{B}}T\frac{dc(x)}{dx} + z q_{\mathrm{e}} c(x)\frac{d\varphi(x)}{dx}\right) \\ J &= -D\left(\frac{dc(x)}{dx} + \frac{q_{\mathrm{e}}\, z}{k_{\mathrm{B}}T}c(x)\frac{d\varphi(x)}{dx}\right) \end{aligned} \tag{9}$$

Obviously, a single equation does not suffice to describe the evolution over space and time of two physical quantities c and φ. The drift of the ions described by (8) will change their spatial distribution in the solution and hence the electric field they generate. The missing equation is Poisson's law, stating that the gradient of the electric field at any position is proportional to the charge density $\rho(x)$ at that point

$$\nabla^2\varphi(x) = -\frac{\rho(x)}{\varepsilon}\,. \tag{10}$$

The simultaneous system of Nernst-Planck and Poisson equations suffices to calculate the evolution over time and space of the ionic concentrations from given initial and boundary conditions, but is difficult to solve. Nevertheless the Nernst-Planck equation can be used when simplifying assumptions are made, such as electro-diffusive equilibrium, or near constancy of the concentration profile or of the electric field.

2.4. Solutions to the Electro-Diffusion Equation

In this subsection, three solutions to the Nernst-Planck equation are developed. The solutions, and the underlying assumptions, were derived at an age long before the concept of ion channels had been established, but they still form the mathematical basis for the description of excitable cells.

2.4.1. The Nernst Potential

The simplifying assumption here is electro-diffusive equilibrium, or zero flux, for a single ion. Solving the electro-diffusion equation for a particular ion species, say K^+, at zero flux yields its so-called Nernst potential V_K.

$$
\begin{aligned}
J &= -D\left(\frac{dc_K(x)}{dx} + \frac{q_e z_K}{k_B T} c_K(x) \frac{d\varphi(x)}{dx}\right) = 0 \\
\frac{1}{c_K(x)} \frac{dc_K(x)}{dx} &= -\frac{q_e z_K}{k_B T} \frac{d\varphi(x)}{dx} \\
\left[\ln(c_K(x))\right]_{in}^{out} &= -\frac{q_e z_K}{k_B T} \left[\varphi(x)\right]_{in}^{out} \\
V_K &= \frac{k_B T}{q_e z_K} \ln \frac{[K^+]_{out}}{[K^+]_{in}}
\end{aligned}
\qquad (11)
$$

The Nernst potential is the electric potential that must be applied to oppose diffusion due to the concentration gradient. If the ion is free to diffuse, diffusion will continue until it is opposed by an electric potential that generates a flux of equal magnitude in the opposite direction. This electric field can be a consequence of the ion movement itself. For instance, potassium ions, being inside the cell at a concentration far exceeding their extracellular concentration, will diffuse across the cell membrane until the diffused ions have established a potential across the membrane (which acts as a capacitor) that is equal to the Nernst potential.

Table 1 lists typical intra- and extracellular concentrations of the major ions involved in excitability, and the Nernst potentials corresponding to their ratios.

Ion species	Extracellular concentration (mM)	Intracellular concentration (mM)	Ratio	Equilibrium potential (mV)
Na^+	145	12	12	+67
K^+	4	155	0.026	-98
Ca^{2+}	1.5	0.0001	15 000	+129
Cl^-	123	4.2	29	-90
nonpermeant anions	~0	~46	generate potential through Donnan effect	

Sources: Values for permeant ions taken from Hille B. (2001). *Ion Channels of Excitable Membranes*. Sunderland, MA: Sinauer. Values for nonpermeant charges taken from Kurbel S. (2008) Are extracellular osmolality and sodium concentration determined by Donnan effects of intracellular protein charges and of pumped sodium? Journal of Theoretical Biology 252, 769-772.

Table 1. Concentration gradient of the major ions involved in excitability.

It is important to understand that only a small amount of charge is needed to generate an electric field of sufficient strength to oppose a biological concentration gradient. The order of magnitude of the potentials involved in excitability is given by the factor

kT / q_e in the formula for the Nernst potential, and measures 25 mV at 37 °C. These potentials are generated by charges located within a tiny shell, only a few Ångströms wide (1 Å equals 10^{-10} m), surrounding the membrane. (Further away from the cell membrane, ions of opposite polarity completely neutralize the charges by Debye shielding.)

From this value of 25 mV and the electric capacity of the cell membrane (typically 1μF cm^{-2}), the number of elementary charges needed to generate physiological potentials has been calculated to measure only one electron or proton charge per square area of side 250 Å. Hence the number of ions needed to halt net diffusion, and to determine the Nernst potential, is several orders of magnitude less than what would be needed to significantly affect their concentrations. This holds for all ionic currents, except that carried by calcium. Calcium ions are strongly buffered by intracellular proteins and accumulated in endoplasmatic stores, and the cytoplasmic concentration of free Ca^{2+} ions is extremely low (see Table 1). During excitation, influx of Ca^{2+} (through the external cell membrane or from intracellular deposits) can sharply raise its local concentration, and this signal is a major messenger between the extracellular event exciting the cell, and the chain of intracellular events potentially leading to contraction, secretion, etc.

The minute charges involved ensure that, apart from a tiny shell, electro-neutrality is maintained in both the intra- and extracellular environments (implying that the number of negative charges equals the number of charges of positive polarity). As concentration gradients between the intra- and extracellular environments form the basis of changes in the membrane potential, and hence of all excitability, it is appropriate to ask how these differences in ionic concentration are generated and maintained.

Two mechanisms seem to be involved: the passive Donnan equilibrium and active ion pumps. The phenomenon of a Donnan equilibrium is based on the excess number inside the cell of macromolecules having a negative surface charge (proteins, nucleic acids). These molecules, owing to their size, cannot permeate the cell membrane. However, the requirement of electro-neutrality ensures that an equivalent number of diffusible, positive charges stay within the cell. Hence the effect is to impede the outward diffusion of K^+ and the inward diffusion of Cl^-.

If the Donnan equilibrium were the only mechanism underlying concentration gradients, then all ionic species should be distributed such that their concentrations yielded identical Nernst potentials, equal in magnitude to the actual membrane potential. In many excitable cells the resting potential is about -70 mV (inside negative), which indeed is close to the Nernst potentials for K^+ and Cl^- but differs profoundly from the Nernst potential corresponding to the concentration ratio for Na^+ ions (+50 mV, see Table 1). Hence whereas the Donnan equilibrium may explain the abundance of K^+ inside the cell and that of Cl^- outside, it cannot explain the sparseness of Na^+ within the cell. The latter requires an energy-consuming mechanism, pumping Na^+ outward against the electro-chemical gradient. These ion pumps may be electro-neutral (for instance exchanging one Na^+ for one K^+ ion), or electro-genic (for instance 3 Na^+ against 2 K^+). Electro-genic pumps add an extra flux to (8), and hence can generate a membrane potential greater than that generated by electro-diffusion alone.

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Biographical Sketch

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