Excitable cells

In a sense all the specialized cells of a complex organism like the human body are excitable since they all perform specific actions on receipt of external signals. Here, however, we confine attention to cells that perform their functions by undergoing a macroscopic transition in response to an external stimulus. Mostly the transitions are reversible, although in some cells they occur but once. Examples of repetitively excitable cells are muscle-, nerve- and sensory transducer cells.

In this chapter we study cellular excitation and its consequences. Many of the details of cellular excitation are as yet unknown, despite decades of patient research. Therefore the emphasis will be on aspects for which simple physics lends insight.

Some references that might prove useful are:


1. Electrophysiology

The heart undergoes cyclic electrical activity while performing its pumping function. We infer this by measuring the electric and magnetic fields of the beating heart. The measurement of cardiac electric fields at the body surface is called electrocardiography. This measurement technique has, in the 99 years since its invention (in 1903) by Willem Einthoven, become a crucial diagnostic tool for both congenital and disease-induced heart abnormalities.

The beating heart gives rise to an electric field that can be detected for some distance. Because the fluids within the body are electrically conductive, the heart cannot produce its electric field by de-

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1. Generally the signals are chemical, e.g. hormones.
2. For example the muscle cell’s contraction in response to a chemical signal from a motor neuron.
3. An example of one-time excitations is the ovarian follicle, which ruptures, expelling the ovum and corpus luteum from the ovary.
veloping a net electric charge. In fact the heart remains electrically neutral but exhibits an overall time-varying electric multipole moment. Although all multipoles are present in an asymmetric charge distribution like the heart, the dipole moment dominates because it has the longest range.

The pioneers of electrocardiography therefore modeled the beating heart as an electric dipole \( \mathbf{D}(t) \) that varies cyclically with time, both in magnitude and direction. This model was called “vector cardiography”. Since we now know a lot more about hearts than these pioneers, we shall construct a simplified, but realistic, physical model of a heart that produces an appropriately time-varying dipole moment.

To begin with we shall suppose the heart is spherical and that its surface can be represented as a layer of electric dipoles, as shown below. We then calculate the electric field from arbitrary distributions of surface dipoles, so that we can relate the electric potentials measured by electrodes attached to a patient’s skin to the time variations of the charge distribution at the surface of the heart. Of course the heart changes shape and size as the coronary muscles contract and relax, but we assume this affects distant electric fields only in a minor way.

Excitable cells (such as heart muscle) actively pump sodium ions from their interiors. This produces a net polarization of charge at the surface with more negative charges inside the cell than outside. (These individual cell polarizations cancel out everywhere but at the heart’s exterior surface or pericardium.) Thus the heart begins its cycle in a state of polarization. The muscular contraction begins at the sino-atrial (SA) node, and is accompanied by a wave of depolarization that flows through the atrial muscle tissue. Once the atria are depolarized the atrio-ventricular (AV) node is stimulated and Purkinje cells cause the depolarization of the ventricles from the bottom up. (See below.)

4. ...like the cow in the Preface.
5. More properly, the contraction is initiated by the depolarization of the cell membranes which initiates a flow of calcium ions that actually triggers the contraction of muscle.
Our model of what happens during the heartbeat will thus be that the upper hemisphere (representing the atria) depolarizes from the North Pole downwards. Once the atria are depolarized, the southern hemisphere (the ventricles) depolarizes from the South Pole upward. The depolarized tissues become recharged for their next beat by a slow, diffusive process that nonuniformly repolarizes the exterior of the sphere.

The electrostatic potential arising from an isolated electric dipole $\mathbf{D}$ at the origin is

$$V(r) = \frac{\mathbf{r} \cdot \mathbf{D}}{r^3}.$$  

This is easily seen by calculating the potential from a point charge $+Q$ located at

$$\mathbf{r}_1 = (0, 0, a/2)$$

and one of charge $-Q$ located at

$$\mathbf{r}_2 = (0, 0, -a/2),$$

as shown below.

$$V(r) = \frac{2Qa}{r^3} + O\left(a^2\right)$$

so if $a$ is much smaller than $r$ we keep only the leading term. The dipole moment is the vector whose magnitude is $Qa$ and points in the direction from the negative to the positive charge.

The potential resulting from a distribution of electric dipoles $d\mathbf{D}(\mathbf{r'})$ is

$$V(\mathbf{r}) = \int d^3r' \frac{\mathbf{r} - \mathbf{r'}}{r'^3} \cdot \mathbf{D}(\mathbf{r'}).$$

Obviously, from Gauss's Law the potential outside a neutral sphere of uniform surface dipoles vanishes identically. So we may say the initial potential (when the heart has a uniform surface dipole distribution) is zero or close to it, at any exterior point of observation.

Our next task is to calculate the potentials resulting from fractions of the sphere, as seen by an exterior observer. To keep things simple we observe from a point directly below the sphere. The surface charge $s$ multiplied by the surface thickness $s$ (that is, the dipole moment per unit area) is related to the potential across a capacitor. By Gauss's Law, the electric field inside a parallel plate capacitor of surface charge $\sigma$ is

$$E = 4\pi\sigma,$$

so the potential across the capacitor is

$$V = Es;$$

in other words the dipole moment per unit area is the membrane potential when the polarization is maximum, i.e. just before the muscles contract.

Hence the potential from the heart is

$$V = \frac{V_0}{2} \int_{\theta_1}^{\theta_2} \sin\theta \left(\frac{r \cos\theta - R}{r^2 + R^2 - 2rR\cos\theta}\right)^{3/2}$$

where $V_0$ is the maximum potential across a capacitor of surface charge $\sigma.$
where $V_0$ is the membrane potential. The angles $\theta_1$ and $\theta_2$ are functions of time, in our model given by

$$
\theta_2 = \begin{cases} 
\omega t, & 0 \leq t < \frac{\pi}{2\omega} \\
0, & t \geq \frac{\pi}{2\omega}
\end{cases}
$$

and

$$
\theta_1 = \begin{cases} 
\pi, & t < \frac{\pi}{2\omega} \\
\frac{3\pi}{2} - \omega t, & t \geq \frac{\pi}{2\omega}
\end{cases}
$$

The symmetry makes it possible to perform the integral in closed form, giving

$$
V = \frac{V_0}{2} \left( \frac{r + R \cos \theta_1}{\left( r^2 + R^2 + 2rR \cos \theta_1 \right)^{1/2}} - \frac{r + R \cos \theta_2}{\left( r^2 + R^2 + 2rR \cos \theta_2 \right)^{1/2}} \right).
$$

The predicted potential, as a function of time, is shown below:

With a resting membrane potential of 60–100 mV, and taking $R = 5$ cm, $r = 15$ cm, the predicted magnitude of the spike is about 1.5–2.5 mV. This is typically what is measured in electrocardiograms.

2. **Neurons**

The neurons are cells specialized to transmit signals rapidly over long distances. A simple experiment yields a lower bound on the speed of neural transmission: one person drops a dollar bill (held vertically just above a second person’s hand) and the second person tries to catch it between his thumb and forefinger. If the bill is dropped without warning, the second person is likely to just miss catching it. Since the time for an object to fall 6 inches starting from rest is 0.17 seconds, we deduce that the nerve impulse to the fingers had to travel from the brain—a distance of about 1 m—in a time no greater than 0.17 sec. That is, the speed of nerve impulses is at least 6 m/sec. We can do better than this, since in order to decide to move our fingers we must see the dollar bill falling. Moreover, we know from the way a motion picture fools the eye that we can process visual information no faster than 10 frames per second (the film speed at which we see a flickering rather than a continuously moving image). Thus if we subtract 0.1 seconds to allow for visual processing, we estimate that the nerve impulse must travel $\geq 14$ m/sec.

In fact, Helmholtz measured the speed of the impulse in a frog’s sciatic nerve in 1850, finding a value of 27 m/sec.

A typical neuron consists of a cell body, with fibers called dendrites that bring signals to the cell, and a long fiber called the axon that carries the output signal. The neuron illustrated on the following page is a motor neuron— that is, it controls muscle fibers.

The axon may be modeled as an electrical circuit (a kind of transmission line) as also shown on the following page. If we think of the axon as a long tube surrounded by cell membrane material and filled with electrically conductive stuff, there will be electrical resistance along its length, as well as from the outside in. The membrane, being an insulator between two conductive regions acts somewhat as a capacitor. The longitudinal resis-
tance is modeled by the resistors $r$, whereas the inward resistance is modeled by the resistors $R$. The membrane capacitance is modeled by the capacitors $C$. If we consider a voltage measured at a node between two longitudinal resistors, it obeys the differential/difference equation

$$\frac{dV_n}{dt} = \lambda \left(V_{n+1} - 2V_n + V_{n-1}\right) - V_n \Lambda$$

where

$$\lambda = \frac{1}{rC}$$

and

$$\Lambda = \frac{1}{RC}$$

are time constants of the system.

Now it is possible to show that under certain conditions on the numbers $|V_n|$ the second difference

$$\Delta(\Delta V_{n-1}) = V_{n+1} - 2V_n + V_{n-1}$$

is a negative operator$^6$. Thus we expect that the time derivative of $V$ will be negative and an initial non-zero value will fall to zero. That is, the network as shown is dissipative. However, if there is another element in the circuit in parallel with the resistor $R$, that can act like a battery—that is, if it depends on the voltage across it in a certain non-linear manner—then the voltage can grow with time.

In fact, if we take the limit of the preceding equation as the spacing between lumped elements becomes small, the equation turns into a partial differential equation of the form

$$\frac{\partial V}{\partial t} = D \frac{\partial^2 V}{\partial x^2} - V \Lambda(V)$$

6. ...in the sense that an appropriately defined inner product $(\psi, \Delta^2 \psi)$ is always negative.
which is a nonlinear diffusion equation. Such equations are known to possess solutions in the form of travelling pulses, such as shown below.

3. Sensory cells
Closely related to neurons are the specialized cells that transform external stimuli into nerve impulses. These include the taste buds and olfactory cells, that respond to particular chemical stimuli; the rod and cone cells of the retina, that respond to light; the cells of the basilar membrane of the cochlea (inner ear), that respond to sound vibration; and various pressure and thermal transducers in our skin, that provide our tactile sensations. They differ in their trigger mechanisms, but they generate action potentials by the same mechanism as the axon—namely depolarization of an initial separated ionic charge.

4. Membrane potentials
We can estimate the electrostatic potential across an excitable cell’s membrane as follows: we recall that the thermodynamic force per unit volume, opposing a concentration gradient of some solute is

\[ K = -k_B T \frac{\partial n}{\partial x}; \]

if the solute is an ion such as Na\(^+\), if there were an electric field \( E_x \) opposing the thermodynamic force (and thereby creating the concentration gradient) we would have, in equilibrium,

\[ e n E_x = -k_B T \frac{\partial n}{\partial x}. \]

Since we may relate an electric field to a voltage gradient,

\[ E_x = -\frac{\partial V}{\partial x} \]

we require a voltage difference

\[ \Delta V = V_2 - V_1 = \frac{k_B T}{e} \ln \left( \frac{n_2}{n_1} \right) \]

to create a difference in concentration,

\[ \Delta n = n_2 - n_1, \]

across—say—a semipermeable membrane. Thus we may associate with such a concentration difference (in the absence of an external electric field) the (thermodynamic) potential energy difference

\[ \Delta \varphi = -k_B T \ln \left( \frac{n_2}{n_1} \right). \]

Assuming an ion pumping mechanism, that maintains a concentration difference across a permeable cell membrane, we expect to find voltage differences. Suppose the concentration difference is a factor \( 20 = e^3 \); then at room temperature, \( T = 300 \, ^\circ K \), the potential across the cell membrane is about \( 3/40 \, V = 75 \, mV \). This is indeed in the range of actually measured potentials.

We may ask how much power is required to maintain an ionic concentration gradient across a membrane. An electric current density

\[ \mathbf{j} = -eD \nabla n \]

moving against a voltage difference \( \Delta V \) requires power

\[ P = eA \Delta V \frac{D |\nabla n|}{\gamma \delta x} = \frac{A (kT)^2}{\gamma \delta x} \left( n_2 - n_1 \right) \ln \left( \frac{n_2}{n_1} \right). \]
where $\delta x$ is the thickness of the membrane and $A$ its surface area. Now, for (valence 1) ions of (number) density $n$ the charge density is $\rho = en$ and the (electric) current is then

$$J_x = \rho \langle v_x \rangle = \rho \frac{e^n}{\gamma} = \frac{e^2 n}{\gamma} E_x = \sigma E_x$$

from which we can express the mobility (that is, the viscous drag coefficient) $\gamma$ in terms of the electrical conductivity $\sigma$:

$$\gamma = \frac{e^2 n}{\sigma} .$$

The pumping power is thus

$$P = A \frac{(kT)^2 \sigma}{e^2 n \delta x} \Delta n \ln \left( \frac{n_2}{n_1} \right).$$

Consider a cell of radius 10$\mu$ and membrane thickness 50 nm, whose electrical conductivity is that of seawater,

$$\sigma = 3 \text{ mho/m} ,$$

and taking the factor

$$\frac{1}{n} \Delta n \ln \left( \frac{n_2}{n_1} \right) = \frac{(20 - 1)}{(20 + 1)/2} \ln 20 = 5.4$$

we find the ohmic power dissipation to be

$$P = 2.7 \times 10^{-4} \text{ Watts} .$$

This is enormous—enough to boil the cell in less than 0.01 second! What could be wrong? The only factor where there is some play is the electrical conductivity. Manifestly, to bring the power dissipation down to something a cell can handle we must assume the conductivity is some $10^{-7}$ smaller than that of seawater. In fact, a typical average current during a single nerve pulse is about 1.6 pA. The pulses last about 1 ms, so the power is about 64 pW, or about 16 times the average basal metabolism of a mammalian cell.

### 5. Energetics of muscle tissue

Muscle tissue consists of basic contractile units called sarcomeres, as shown below. The sarcomeres are attached end to end, with the demarcations marked by Z-plates. The contractile unit is something like a linear motor or ratcheting jack, that can move only one way. It contains interleaved fibers: actin fibers attached to the Z-plates, and myosin fibers between them.

Each myosin fiber has about 100 cross-bridges, that represent the active elements. During contraction these links move along the actin fibers, dragging the Z-plates closer together and thereby shortening the sarcomere. The maximum longitudinal contraction is about 20%.

A cross-bridge, or myosin "head", is a tiny ratcheting motor that adheres to successive sites on the actin fiber. (It is thought that these sites are actually turns of the helix.) This is shown schematically below. Note that the head is actually a double structure.

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**Schematic Drawing of a Sarcomere**

(basic contractile unit of muscle)

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**Physics of the Human Body**

Chapter 9  
Excitable cells
Shown at the right is an electron micrograph of a myosin head. If one uses one’s imagination liberally one can see the helical structure of the actin fiber (around the green line), as well as the two projections (below the cyan lines).

The adhesive force of a myosin head is about $5.3 \times 10^{-12}$ Nt. To see what this means in energetic terms, imagine that the force is exerted over a distance of $40 \text{ Å}$; the energy is then about

$$\Delta E = F \cdot x = 2 \times 10^{-20} \text{ J},$$

or 0.1 eV. Since typical chemical bonds in stable molecules have much larger energies (of order 1 eV or greater), we see the biochemical machinery that has evolved to enable motility employs forces weak enough that parts can attach and detach repeatedly without damaging the molecules themselves. It is basically the same principle as “sticky notes”: the mucilage forms weak bonds between surfaces, that can be formed and pulled apart without tearing the paper.

On the other hand, the energies associated with the attachment of the ratcheting machinery must be substantially larger than $k_B T$, or else the ratchets would be so buffeted by random thermal motions that they could not function to provide unidirectional motion.

Changes in electron density, or of dielectric constant (at the business ends of the molecules) promote the attachment and detachment of the myosin heads. It is believed the double structure alternates attachments in order to “walk” along the axin helix.

Presumably, successive attachments are fueled by ATP molecules, as with other endoergic processes at the cellular level.

The trigger for muscle contraction and relaxation is the transport of calcium into and out of the cell. The precise mechanism is not known at the time of this writing.