Conduction in excitable cells - the cable equation

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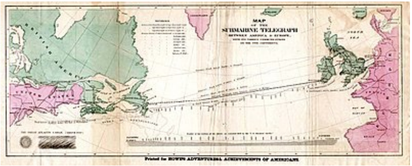
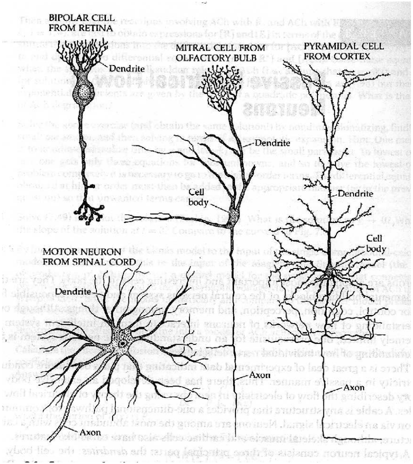
Outline

- Introduction
  - History
  - Brief overview of neurons
- Derivation of the cable equation
- Scaling/dimensionless form
- Example models



The TAT-1 Cable used for the transatlantic cable system on board the HMTS Monarch

Neurons (1)



BIPOLAR CELL
FROM RETINA
Dendrite
MITRAL CELL FROM
OLFACTORY BULB
Dendrite
Cell
body
PYRAMIDAL CELL
FROM CORTEX
Dendrite
Cell
body
MOTOR NEURON
FROM SPINAL CORD
Dendrite
Axon
Axon
Axon

Neurons (2)

The neuron consists of three parts:

- Dendrite-tree, the "input stage" of the neuron, converges on the soma.
- Soma, the cell body, contain the "normal" cellular functions
- Axon, the output of the neuron, may be branched. Synapses at the ends are connected to neighboring dendrites.

The axon has an excitable membrane, gives rise to active conduction. We will first look at conduction in the dentrites, passive conduction.

Why is the cable equation important?

- Fundamental for modeling neurons
- Signal propagation in Purkinje network
- Extends to cardiac conduction in 3D (bidomain, monodomain)

Fundamental quantities and assumptions

The cell typically has a potential gradient along its length. Radial components will be ignored. Notation:

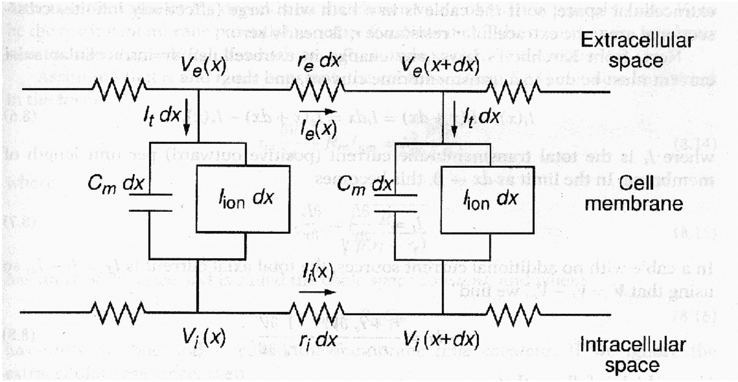
- V_i and V_e are intra- and extracellular potentials
- I_i and I_e are intra- and extracellular (axial) current
- r_i and r_e; intra- and extracellular resistance per unit length

We have

$$r_i = \frac{R_c}{A_i},$$

where R_c is the cytoplasmic resistivity and A_i is the cross sectional area of the cable.

Sketch of a discrete cable



Currents are assumed to be Ohmic

We assume Ohmic resistance:

$$V_i(x + \Delta x) - V_i(x) = -I_i(x) r_i \Delta x$$
$$V_e(x + \Delta x) - V_e(x) = -I_e(x) r_e \Delta x$$

In the limit:

$$I_i = -\frac{1}{r_i}\frac{\partial V_i}{\partial x}$$
$$I_e = -\frac{1}{r_e}\frac{\partial V_e}{\partial x}$$

Conservation of current (1)

Any current leaving the intracellular domain has to enter the extracellular domain, and vice-versa. Total current is conserved between x and $x + \Delta x$:

$$I_i(x) - I_i(x + \Delta x) = -(I_e(x) - I_e(x + \Delta x)) = I_t \Delta x$$

where I_t is transmembrane current, per unit length.

Taking the limit $\Delta x \to 0$ yields

$$I_t = -\frac{\partial I_i}{\partial x} = \frac{\partial I_e}{\partial x}$$

Conservation of current (2)

We now have the membrane current I_t expressed in terms of I_i, I_e.
We want a relation between the I_t and the membrane potential V.

$$\frac{1}{r_e}\frac{\partial^2 V_e}{\partial x^2} = -\frac{1}{r_i}\frac{\partial^2 V_i}{\partial x^2} = -\frac{1}{r_i}(\frac{\partial^2 V}{\partial x^2} + \frac{\partial^2 V_e}{\partial x^2})$$

$$(\frac{1}{r_e} + \frac{1}{r_i})\frac{\partial^2 V_e}{\partial x^2} = -\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2}$$

Conservation of current (3)

cont.

$$\left(\frac{1}{r_e} + \frac{1}{r_i}\right)\frac{\partial^2 V_e}{\partial x^2} = -\frac{1}{r_i}\frac{\partial^2 V}{\partial x^2}$$

$$\frac{\partial^2 V_e}{\partial x^2} = -\frac{\frac{1}{r_i}}{\frac{1}{r_e} + \frac{1}{r_i}}\frac{\partial^2 V}{\partial x^2} = -\frac{r_e}{r_e + r_i}\frac{\partial^2 V}{\partial x^2}$$

so

$$I_t = \frac{\partial I_e}{\partial x} = -\frac{1}{r_e}\frac{\partial^2 V_e}{\partial x^2} = \frac{1}{r_e + r_i}\frac{\partial^2 V}{\partial x^2}$$

Incorporating cell membrane physiology

From the membrane model previously derived we have

$$I_t = p(C_m \frac{\partial V}{\partial t} + I_{ion})$$

where p is the circumference of the cable. The total 1D cable model is then:

$$p(C_m \frac{\partial V}{\partial t} + I_{ion}(V)) = (\frac{1}{r_e + r_i} \frac{\partial^2 V}{\partial x^2})$$

Physical units

So far we have not considered the physical units of the terms. Typical units are

Quantity	Dimension	Typical unit
p	length	cm
C_m	capac./area	$\mu F/cm^2$
V	voltage	mV
I_{ion}	current/area	$\mu A/cm^2$
r_i, r_e	res./length	$10^3\Omega/cm$
x	length	cm
t	time	ms

Exercise

Verify that all the terms in the cable equation have the same physical units:

$$p(C_m \frac{\partial V}{\partial t} + I_{ion}(V)) = (\frac{1}{r_e + r_i} \frac{\partial^2 V}{\partial x^2})$$

Quantity	Dimension	Typical unit
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What is the unit of the terms in the equation?

Scaling the cable equation (1)

We can scale the variables to reduce the number of parameters. Define a membrane resistance:

$$\frac{1}{R_m} = \frac{\Delta I_{ion}}{\Delta V}(V_0)$$

where V_0 is the resting potential. Multiplywith R_m to get

$$C_m R_m \frac{\partial V}{\partial t} + R_m I_{ion} = \frac{R_m}{p(r_i + r_e)} \frac{\partial^2 V}{\partial x^2}$$

Here we have assumed r_i and r_e constant.

Defining $f = -R_m I_{ion}$, $\tau_m = C_m R_m$ (time constant) and $\lambda_m^2 = R_m/(p(r_i + r_e))$ (space constant squared) we can write

$$\tau_m \frac{\partial V}{\partial t} - f = \lambda_m^2 \frac{\partial^2 V}{\partial x^2}$$

Scaling the cable equation (2)

We introduce the dimensionless variables:

$$T = t/\tau_m, X = x/\lambda_m$$

We can then write:

$$\frac{\partial V}{\partial T} = f + \frac{\partial^2 V}{\partial X^2}$$

A solution $\hat{V}(T, X)$ of (17) implies that $V(t, x) = \hat{V}(t/\tau_m, x/\lambda_m)$ will satisfy the unscaled equation.

The scaled equation has units of voltage, but can easily be non-dimensionalized by introducing $V = V_0 + \bar{V}\tilde{V}$, where $\bar{V}$ is a characteristic voltage and $\tilde{V}$ is a dimensionless variable.

The reaction term

The form of f depends on the cell type we want to study. For the axon $I_{ion}(m, n, h, V)$ of the HH-model is a good candidate.

For the dendrite, which is non-excitable, a linear resistance model is good:

$$I_ion = \frac{1}{R_m}(V - V_{eq})$$

or in dimensionless form $f = -V$:

$$\frac{\partial V}{\partial T} = \frac{\partial^2 V}{\partial X^2} - V$$

Boundary- and initial conditions

Need boundary and initial values. Initially at rest:

Initially at rest:

$$V(X,0) = 0$$

Types of boundary conditions:

- Dirichlet: $V(x_b, T) = V_b$, voltage clamp.
- Neumann: $\frac{\partial V}{\partial X} = -r_i \lambda_m I$, current injection.

Justification:

$$\frac{\partial V_i}{\partial x} = -r_i I_i \Rightarrow \frac{\partial V}{\partial x} - \frac{\partial V_e}{\partial x} = -r_i I_i \overset{r_e=0}{\Longrightarrow} \frac{\partial V}{\partial x} = -r_i I_i$$

Passive conduction

The linear cable in dimensionless form

$$\frac{\partial V}{\partial T} = \frac{\partial^2 V}{\partial X^2} - V$$

We consider a semi-infinite (i.e. long) cable with voltage clamped to a constant V_c at $X = 0$. At steady state, we have

$$\frac{\partial^2 V}{\partial X^2} = V$$

with solution

$$V = V_c e^{-X} = V_c e^{-x/\lambda_m}$$

What does this tell you about how a signal decays along the cable? How strong is the signal one space constant from the source? How about ten space constants?

Exercise

Remember the expression for the space constant:

$$\lambda_m = \sqrt{R_m/(p(r_i + r_e))} \approx \sqrt{R_m/(pr_i)} = \sqrt{R_m/(pR_c/A)},$$

Assume a circular cross section with diameter d. Typical values for a mammalian neuron are
$R_m = 7000\Omega\mathrm{cm}^2, R_c = 150\Omega\mathrm{cm}, d = 10.0\mu m$

Calculate the space constant λ_m. How does it compare to the length of a human axon?

The bistable equation (1)

The simplest model of active conduction in neuron is obtained by choosing the reaction term

$$f(V) = AV(1 - V)(V - \alpha),$$

where α is a parameter between 0 and 1, and A is a scaling parameter for the reaction term.

The bistable equation (2)

We have

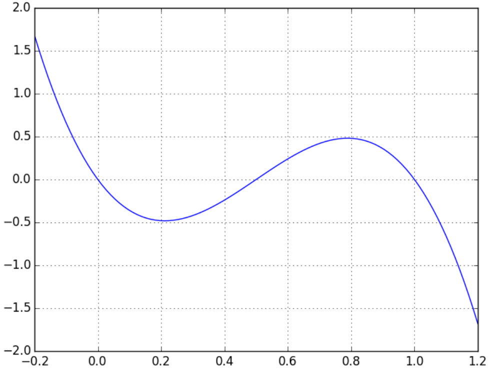
$$\frac{\partial V}{\partial t} = \frac{\partial^2 V}{\partial x^2} + AV(1 - V)(V - \alpha),$$

and if we neglect the diffusion term we get

$$\frac{\partial V}{\partial t} = AV(1 - V)(V - \alpha),$$

The right hand side has three zero's; $V = 0$, $V = 1$, $V = \alpha$. These are equilibrium points for the equation ($\partial V / \partial t = 0$).

The bistable equation (3)



Here $\alpha = 0.5$. What happens if the solution is perturbed away from the three equilibrium points $V = 0$, $V = 1$, $V = \alpha$? (Recall that $\partial V/\partial t = f(V)$)

The bistable equation (4)

- The equation has one unstable and two stable equilibrium points
- Any initial condition $V < \alpha$ will approach $V = 0$
- Any initial condition $V > \alpha$will approach $V = 1$

In 1D (with diffusion), the solution is a traveling front.

The FitzHugh-Nagumo model (1)

- The bistable equation describes a traveling front, but never returns to the resting potential
- To describe a propagating action potential we need to add a *recovery variable*
- The result is the FitzHugh-Nagumo (FHN) model, the simplest model for qualitatively realistic propagation in excitable cells

$$
\begin{aligned}
\frac{\partial V}{\partial t} &= \frac{\partial^2 V}{\partial x^2} + AV(1-V)(V-\alpha) - w, \\
\frac{\partial w}{\partial t} &= \epsilon(V - \gamma w),
\end{aligned}
$$

with $\epsilon, \gamma > 0$ and $w(0, x) = 0$.

The FitzHugh-Nagumo model (2)

Again, we can examine the behavior of the model by neglecting diffusion:

$$\frac{\partial V}{\partial t} = AV(1-V)(V-\alpha) - w,$$
$$\frac{\partial w}{\partial t} = \epsilon(V - \gamma w),$$

- Initially, the model behaves as the bistable equation
- As V increases, $\frac{\partial w}{\partial t} > 0$
- $w > 0$ will "pull" V back towards $V = 0$
- In 1D, the solution is a traveling wave resembling an action
- potential

Summary

- The cable equation describes signal propagation in *leaky* cables
- 1D reaction-diffusion equation, the form of the reaction term depends on the application (properties of the membrane):
  - Linear; passive membrane
  - Cubic; bistable equation (propagating front)
  - FHN; coupled to ODE (propagating AP)
  - Hodgkin-Huxley, cardiac cell models, etc...