Cardiac cells

Excitable like neurons, display great variability

- SA node cells: Pace maker cells, controls the heart rate, self depolarizing
- AV node cells: Transmit signal from atria to ventricles with a delay
- Purkinje cells: Very high conductivity, propagate signal from AV out to the ventricles.
- Myocardial cells: Muscle cells (can contract)

These cells have different action potentials.

The HH-model was based on neuron. Other models necessary for cardiac cells.

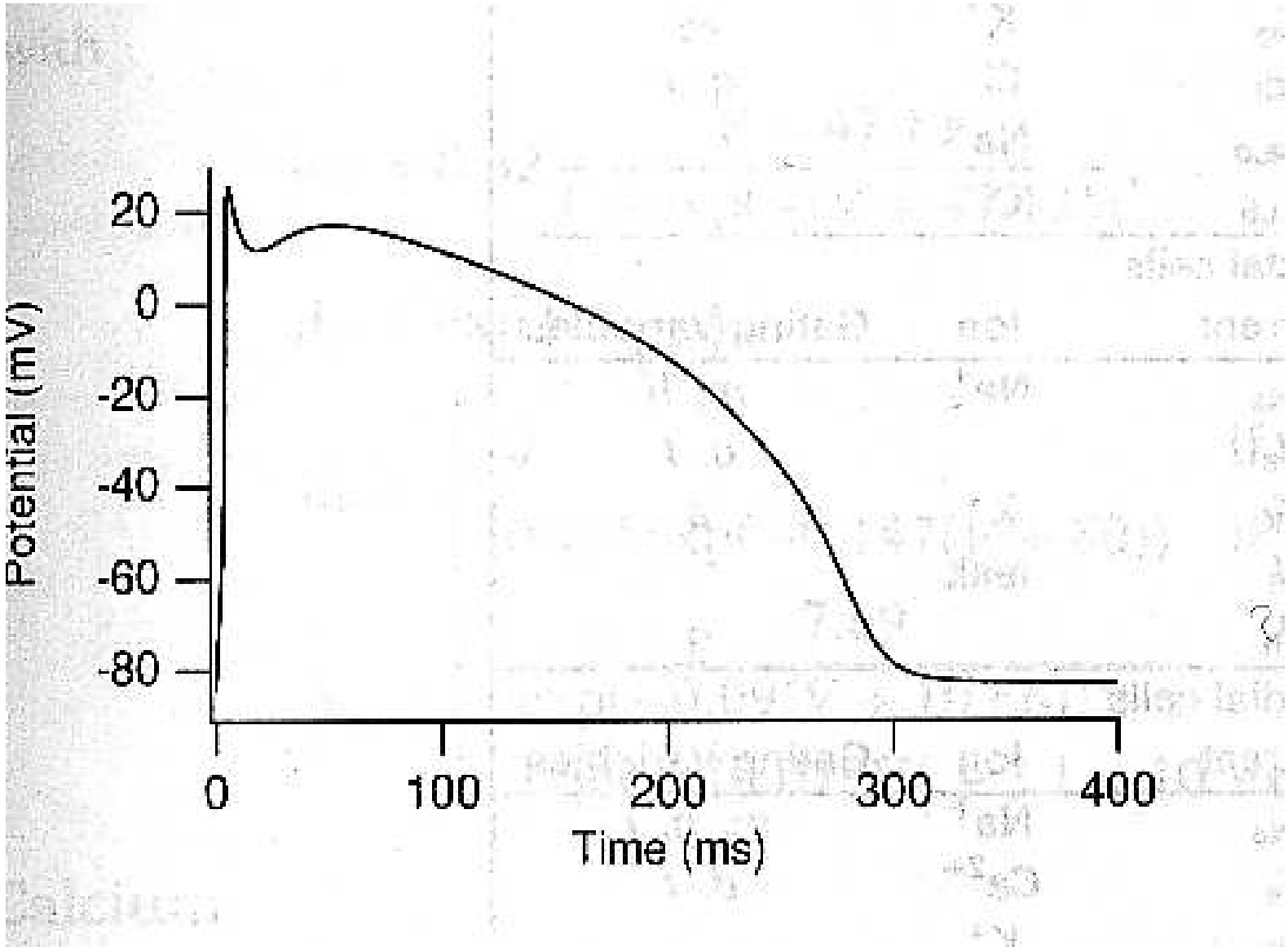
The Beeler-Reuter model

A model for ventricular cells, includes three currents, six gates and one ionic concentration.

$$-C_m \frac{dV}{dt} = I_{\mathsf{Na}}(V, m, h, j) + I_{\mathsf{K}}(V, x) + I_{\mathsf{S}}(V, f, g, [Ca]_i)$$

Here m, h, j, x, f, g are gating variables and [Ca]$_i$ is the intra cellular Calcium concentration
The action potential is much longer then for HH. Early repolarization (notch).

Action potential produced by the Beeler-Reuter



Currents of the Beeler-Reuter model

Sodium current:

Third gating variable included to model the slow recovery (long refractory period). The model also include an ungated “leakage” current:

$$I_{\text{Na}} = (4m^3hj + 0.003)(V - 50)$$

Potassium:

One singled gated (with x) and one ungated component:

$$I_{\text{K}} = f(v) + xg(v)$$

Calcium:

To gates, d activates, f inactivates:

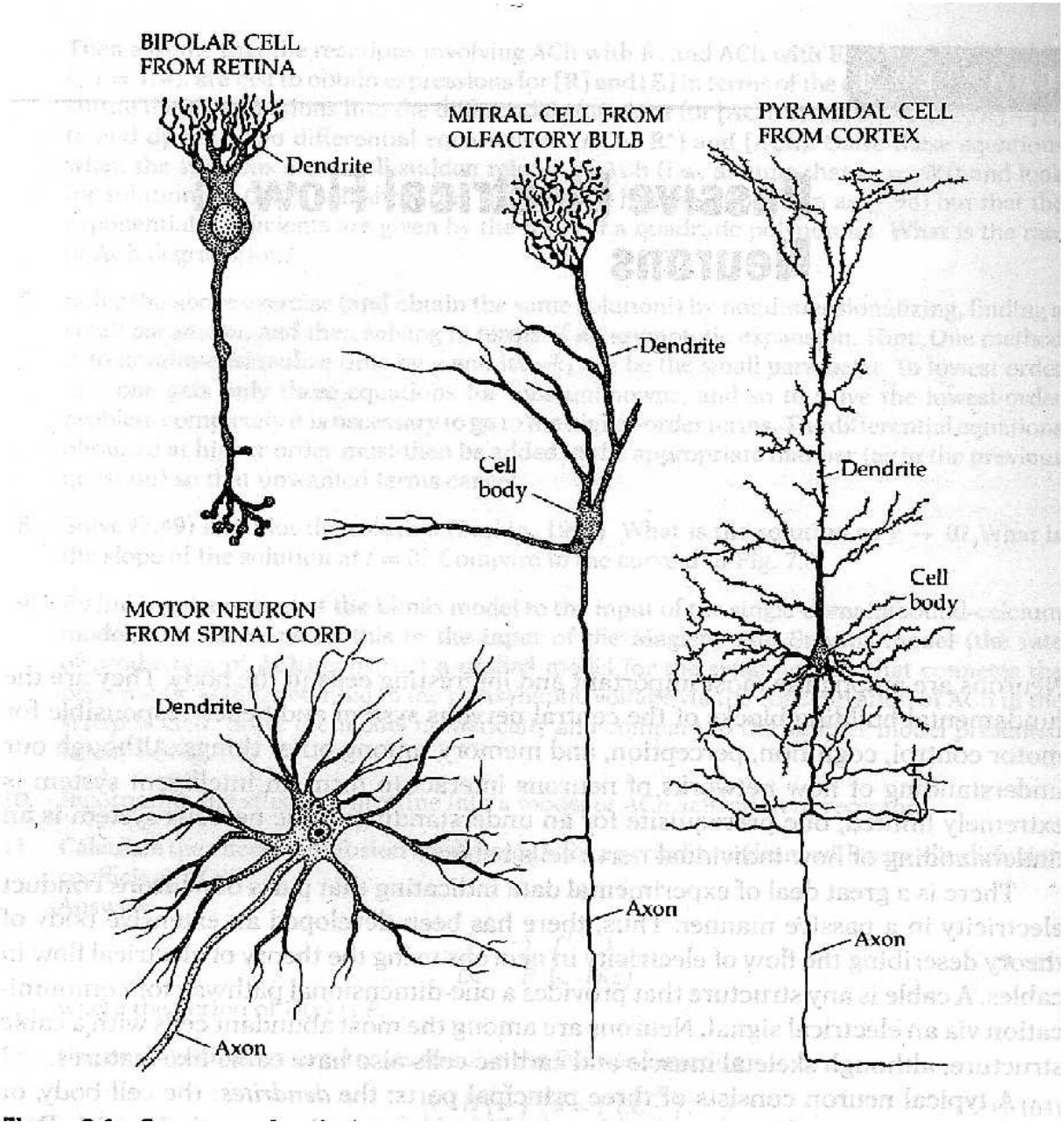
$$I_{\mathsf{S}} = 0.09 f g (V - V_{\mathsf{Ca}})$$

In addition the $[Ca]_i$ is updated:

$$\frac{dc}{dt} = 0.07(1 - c) - I_{\mathsf{S}}$$

where $c = 10^7 [\mathsf{Ca}]_i$

Neurons


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

Electric flow in neurons

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. Will first look at conduction in the dentrites, passive conduction.

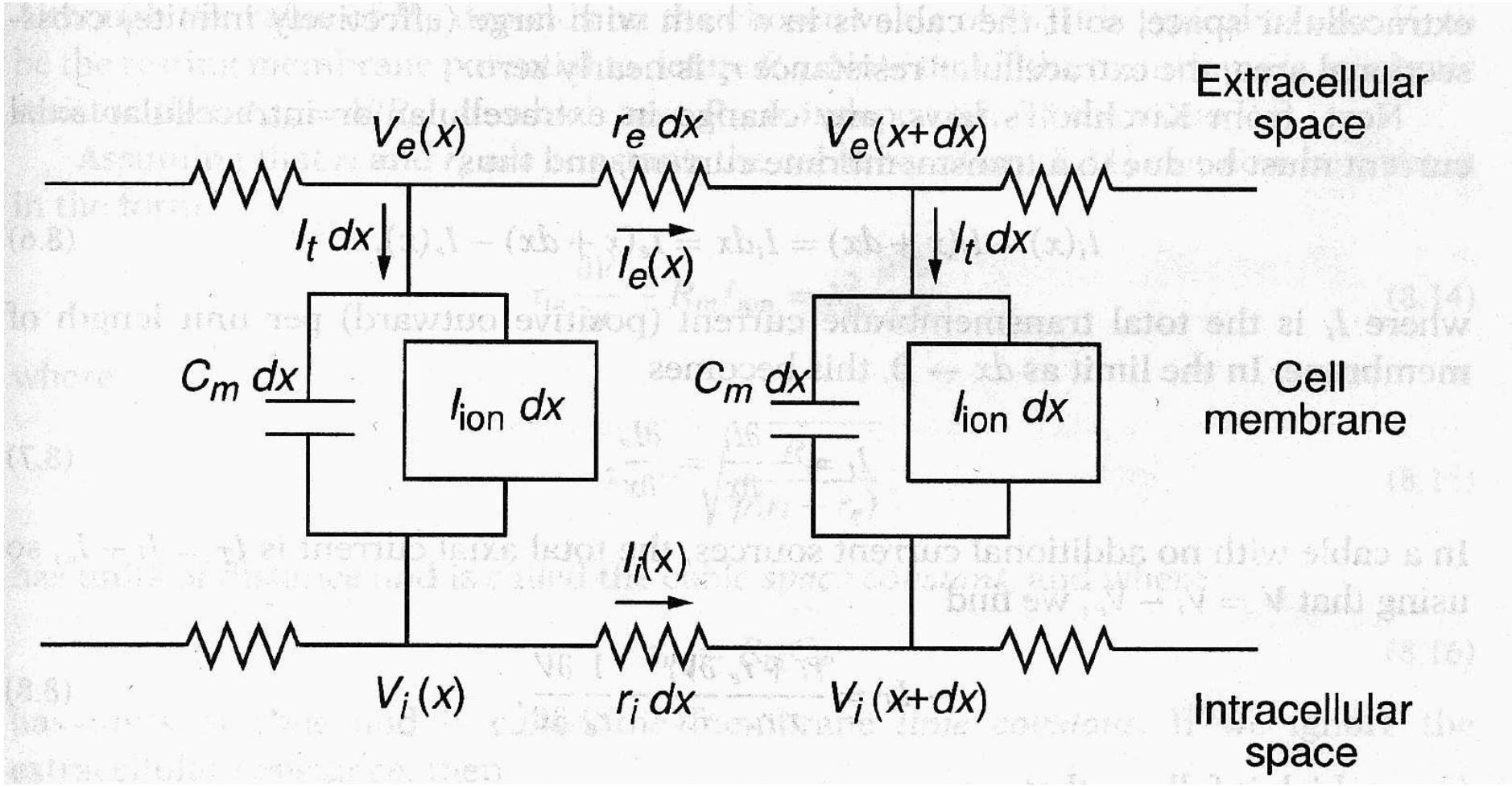
The cable equation

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

Notation:

V_i and V_e are intra- and extra cellular potential
I_i and I_e are intra- and extra cellular (axial) current
r_i and r_e are intra- and extra cellular resistance per unit length

Discrete cable



Ohmic resistance assumed:

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

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

In the limit:

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

Conservation of current yields:

$$I_i(x) - I_i(x + \Delta x) = -(I_e(x) - I_e(x + \Delta x)) = I_t \Delta x \qquad (1)$$

where I_t is transmembrane current, per unit length. In the limit (1) yields:

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

We would like to express I_t in terms of V.

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

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

cont.

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

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

so

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

From the membrane model previously derived we have

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

where p is the circumference of the cable. The total expression will be in Ampere/meter.

The total 1D cable model is then:

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

Dimensionless form

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

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

where V_0 is the resting potential. Multiplication with R_m

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

Here we have assumed r_i and r_e constant.

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

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

Introduces the dimensionless variables:

$$T = t/\tau_m \text{ and } \quad X = x/\lambda_m$$

We can then write:

$$\frac{\partial V}{\partial T} = f + \frac{\partial^2 V}{\partial X^2} \tag{3}$$

A solution $\hat{V}(T, X)$ of (3) will imply that $V(t, x) = \hat{V}(t/\tau_m, x/\lambda_m)$ will satisfy (2).

The reaction term

The form of f depends on the cell type we want to study.

For the axon $I_{\text{ion}}(m, n, h, V)$ of the HH-model is a good candidate.

For the dendrite, which is non-excitable, a linear resistance model is good. Shift V so $V = 0$ is the resting potential:

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

Need boundary and initial values. Initially at rest:

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

Boundary conditions

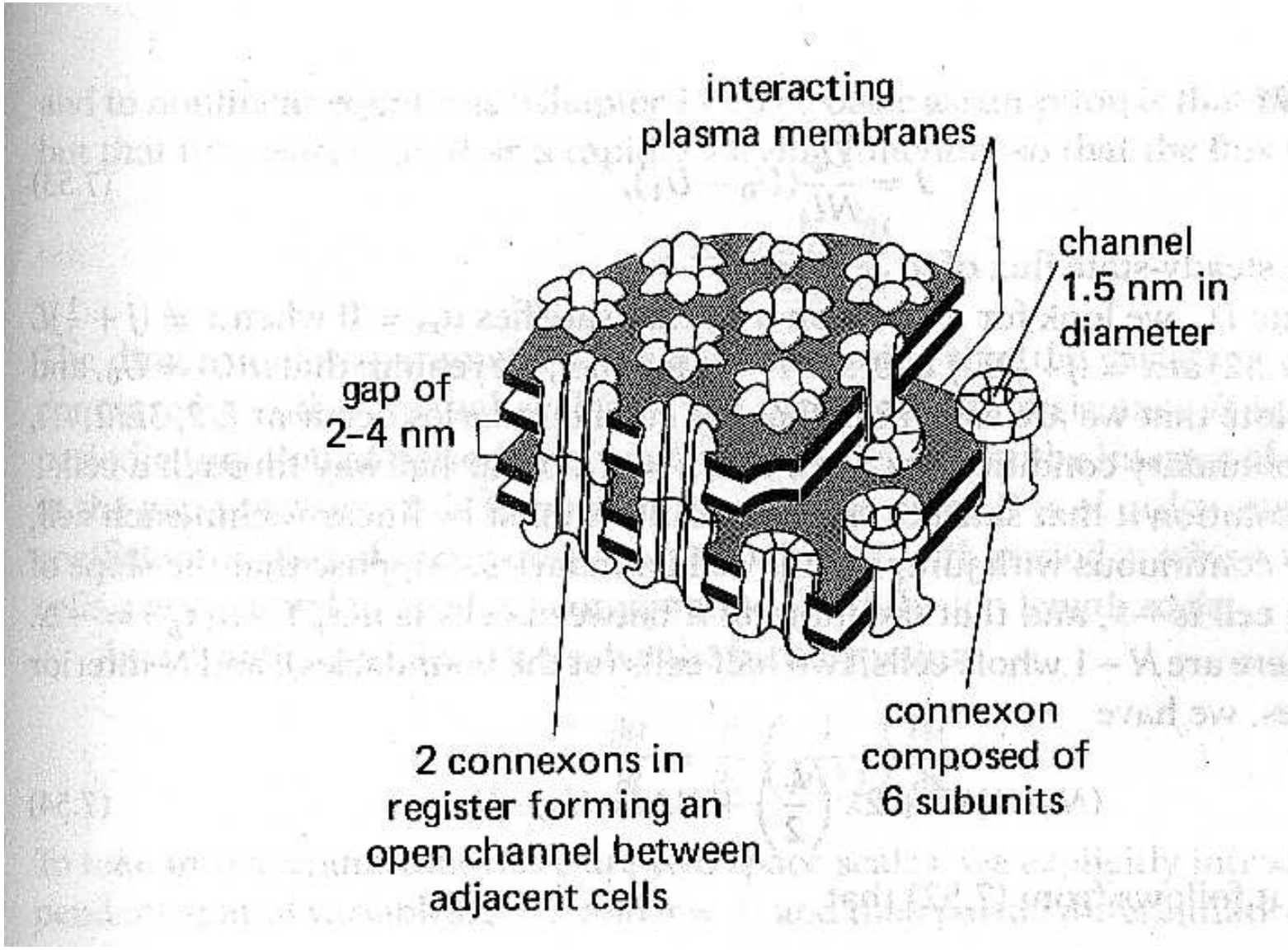
Types of boundary conditions:

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

Justification:

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

Gap junctions



Gap junctions

Gap junctions are located between cell and ions may pass through them.

The junctions have a high resistance to flow compared to the intra cellular environment.

Consider a 1D line of cell and assume that Fick's law holds in the interior:

$$J = -D\frac{dc}{dx}$$

Between cells we must have continuity of flow:

$$-D\frac{dc(x_b^-)}{dx} = -D\frac{dc(x_b^+)}{dx}$$

Here x_b^- and x_b^+ indicates that the function is evaluated in the limit from left and right, respectively.
Furthermore we assume this flow to be proportional to the fall:

$$J = F[c(x_b^-) - c(x_b^+)]$$

where F is a permeability constant.

Would like relate F and D into an average, large scale, effective diffusion coefficient. Consider N cells of length L:

$$J = -D_e \frac{\Delta c}{\Delta x} = -D_e \frac{c_1 - c_0}{NL}$$

Steady flux with fixed gradient.

At steady state J is constant, so from $J = -D(dc/dx)$ we have that c is linear in the interior. The solution c will be piecewise linear with jump at the cell boundaries.

Continuity of flow over the gaps gives $dc/dx = -\lambda$ for all interfaces. For the same reason the steps must all be equal, $c(x_b^-) - c(x_b^+) = \Delta$.

The size on Δ and λ must fit the drop $(c_0 - c_1)$:

N intervals of length L: $NL\lambda$
N jumps of size Δ: $N\Delta$

So in total we must have:

$$NL\lambda + N\Delta = c_0 - c_1$$

From the definition of F we have $D\lambda = F\Delta$. In steady state the flux is the same on every scale:

$$\begin{aligned} J = D\lambda &= \tfrac{D_e}{NL}(c_0 - c_1) = \tfrac{D_e}{NL}(NL\lambda + N\Delta) \\ &= \tfrac{D_e}{NL}(NL\lambda + N\tfrac{D\lambda}{F}) = D_e\lambda(1 + \tfrac{D}{FL}) \end{aligned}$$

So

$$D = D_e(1 + \frac{D}{FL}) \Rightarrow \frac{1}{D_e} = \frac{1}{D} + \frac{1}{FL}$$

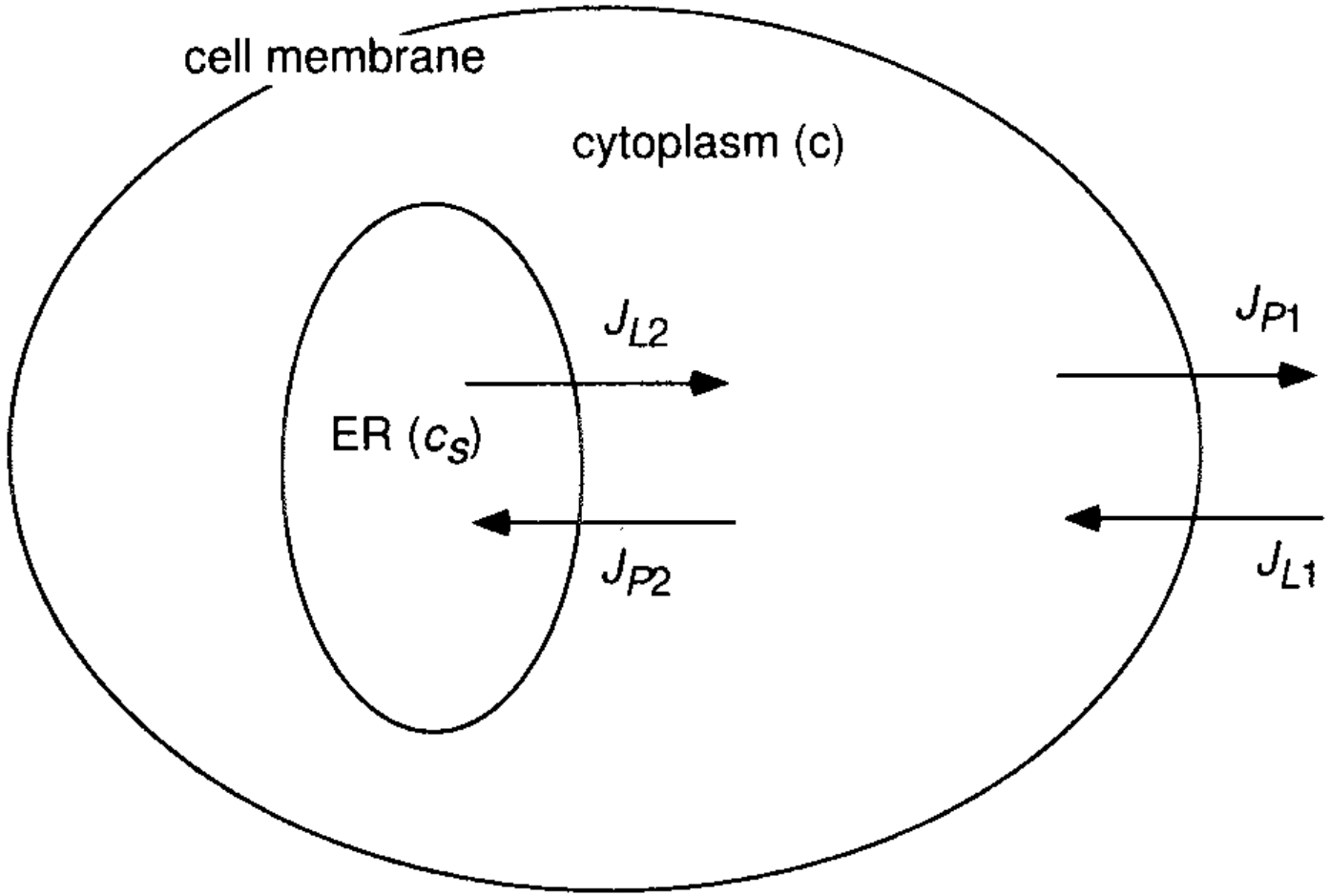
Calcium dynamics

- Calcium is an important ion in the biochemistry of cells
- Is used a signal carrier, i.e. causes contraction of muscle cells
- Is toxic at high levels
- The concentration is regulated through buffers and intra cellular compartments

Ryanodine Receptors

- Sits at the surface of intra cellular calcium stores
  - Endoplasmic Reticulum (ER)
  - Sarcoplasmic Reticulum (SR)
- Sensitive to calcium. Both activation and inactivation.
- Upon stimulation calcium is released from the stores.
- To different pathways
  - Triggering from action potential through extra cellular calcium inflow.
  - Calcium oscillations observed in some neurons at fixed membrane potentials.

Compartments and fluxes in the model



Model equations

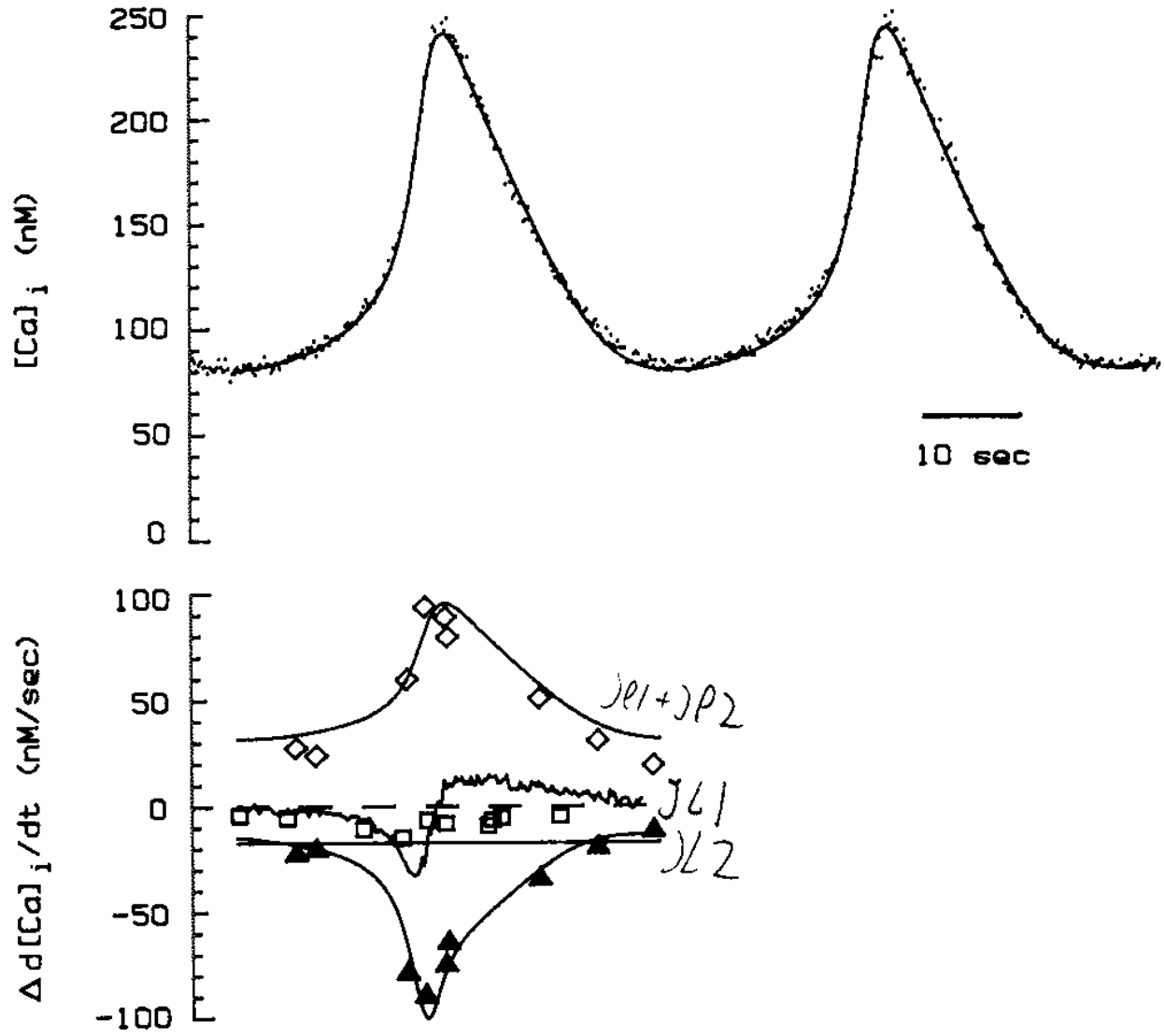
$$
\begin{aligned}
\frac{d[c]}{dt} &= J_{\mathsf{L1}} - J_{\mathsf{P1}} + J_{\mathsf{L2}} - J_{\mathsf{P2}} \\
\frac{d[c_s]}{dt} &= -J_{\mathsf{L2}} + J_{\mathsf{P2}} \\
J_{\mathsf{L1}} &= k_1(c_e - c), \quad \mathsf{Ca}^{2+} \text{ entry} \\
J_{\mathsf{P1}} &= k_2 c, \quad \mathsf{Ca}^{2+} \text{ extrusion} \\
J_{\mathsf{L2}} &= k_3(c_s - c), \quad \mathsf{Ca}^{2+} \text{ release} \\
J_{\mathsf{P2}} &= k_4 c, \quad \mathsf{Ca}^{2+} \text{ uptake}
\end{aligned}
$$

The calcium sensitivity

Release modelled with Hill type dynamics:

$$J_{\mathsf{L2}} = k_3(c_s - c) = (\kappa_1 + \frac{\kappa_2 c^n}{K_d^n + c^n})(c_s - c)$$

Experiments and simulations



- Good agreement between experiments and simulations
- Inactivation through calcium not included, but does not seem to be an important aspect

A more refined model

- Inclusion of both activation and inactivation sites at the RyR

$$\begin{array}{ccc} S_{00} & \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} & S_{10} \\ {\scriptstyle k_{-2}}\downarrow\uparrow{\scriptstyle k_2} & & {\scriptstyle k_{-2}}\downarrow\uparrow{\scriptstyle k_2} \\ S_{01} & \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} & S_{11} \end{array}$$

- Better models for the pumps

$$J_{\mathrm{P}} = V\mathrm{max}\frac{c^2}{K^2 + c^2}$$

Model equations

$$
\begin{aligned}
\frac{dx_1}{dt} &= k_{-1}x_2 + k_{-2}x_4 - (k_1 + k_2)x_1 c \\
\frac{dx_2}{dt} &= -k_{-1}x_2 + k_{-2}x_3 + (k_1 x_1 - k_2 x_2)c \\
\frac{dx_2}{dt} &= (k_2 x_2 + k_1 x_4)c - (k_{-2} + k_{-1})x_3 \\
\frac{dc}{dt} &= v_c(J_{\mathsf{L2}} - J_{\mathsf{P2}}) + J_{\mathsf{L1}} - J_{\mathsf{P1}} \\
\frac{dc_s}{dt} &= -J_{\mathsf{L2}} + J_{\mathsf{P2}} \\
J_{\mathsf{L1}} &= g_2(c_e - c) \\
J_{\mathsf{L2}} &= (k_f x_2 + g_1)(c_s - c) \\
J_{\mathsf{P1}} &= \frac{q_1 c^2}{q_2^2 + c^2} \\
J_{\mathsf{P2}} &= \frac{p_1 c^2}{p_2^2 + c^2}
\end{aligned}
$$