Markov models for ionic channels

Limitations of Hodgkin-Huxley channel models

Hodgkin-Huxley (HH) gating parameters do not represent specific kinetic states of ion channels and cannot describe various aspects of channel behavior.

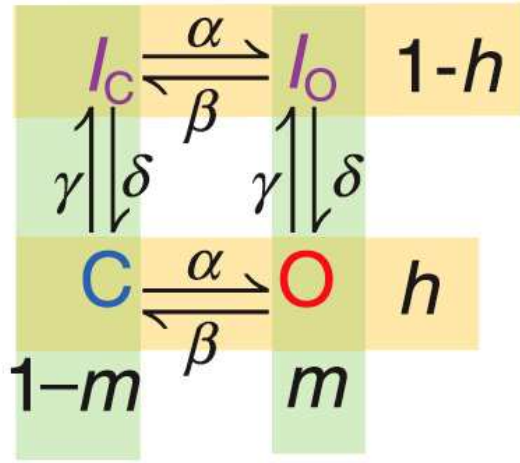
For example, inactivation of the Na^+ channel has a greater probability of occurring when the channel is open; i.e., inactivation depends on activation and the assumption of independent gating that gives the HH conductance m^3h is not valid.

Models with explicit representation of single ion-channel states are needed.

Markov models

Model the states of single ion channels

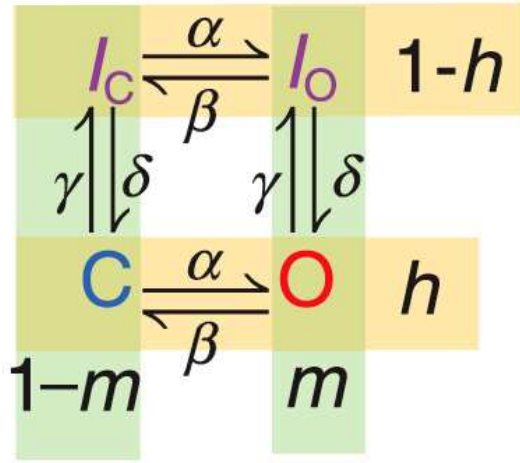
Example:



Hypothetical 4-state model (closed, open, two inactivated); α, β, γ, and δ are transition rates

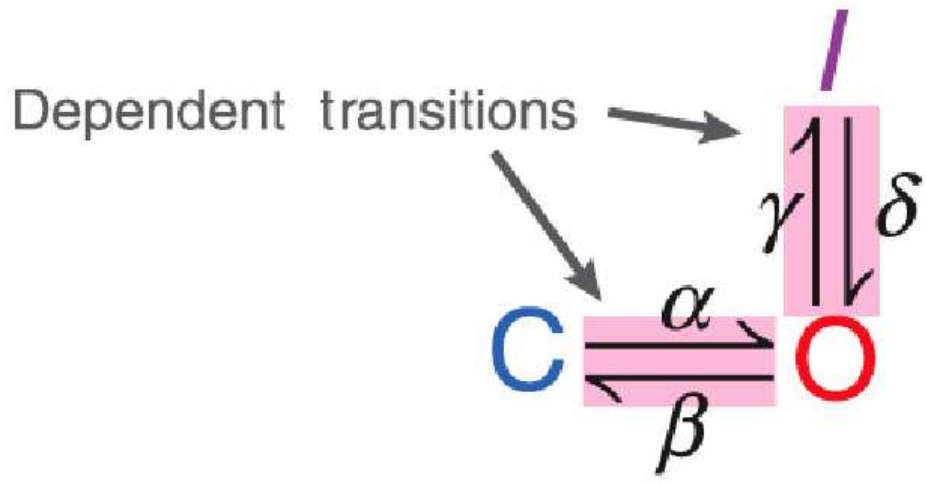
Model equations:

$$
\begin{aligned}
\frac{dC}{dt} &= \beta \cdot O + \delta \cdot I_C - (\alpha + \gamma) \cdot C, \\
\frac{dO}{dt} &= \alpha \cdot C + \delta \cdot I_O - (\beta + \gamma) \cdot O, \\
\frac{dI_C}{dt} &= \beta \cdot I_O + \gamma \cdot C - (\alpha + \delta) \cdot I_C, \\
\frac{I_O}{dt} &= \alpha \cdot I_C + \gamma \cdot O - (\beta + \delta) \cdot I_O,
\end{aligned}
$$



When channel gates are assumed to be independent, Markov and Hodgkin-Huxley models are equivalent; activation gate m and inactivation gate h.

However, experiments have shown that activation and inactivation processes are typically dependent.



In this hypothetical channel, inactivation can only occur from the open state, i.e. state to state transitions are dependent

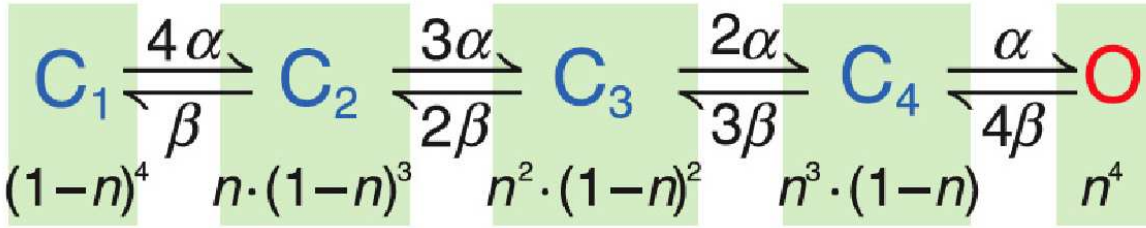
Each state must be described individually by a differential equation

$$\begin{aligned}
\frac{dC}{dt} &= \alpha \cdot C - \beta \cdot O, \\
\frac{dO}{dt} &= \alpha \cdot C + \delta \cdot I - (\beta + \gamma) \cdot O, \\
\frac{dI}{dt} &= \gamma \cdot O - \delta \cdot I.
\end{aligned}$$

Here, α, β, γ, and δ are transition rates.

Hodgkin-Huxley formalism, in terms of gating parameters, can not be applied here; independent gating is not valid.

Most channels have 4 subunits, so more than one transition is needed to describe activation.

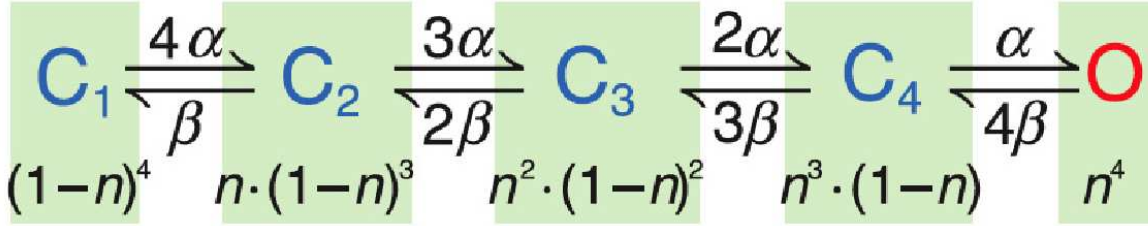


C_1-C_4 are closed states; O is the open state.

C_1 is a closed state where all subunits are inactivated; C_2 is a closed state where one subunit is activated and 3 are inactivated; open (O) is where all 4 subunits are activated.

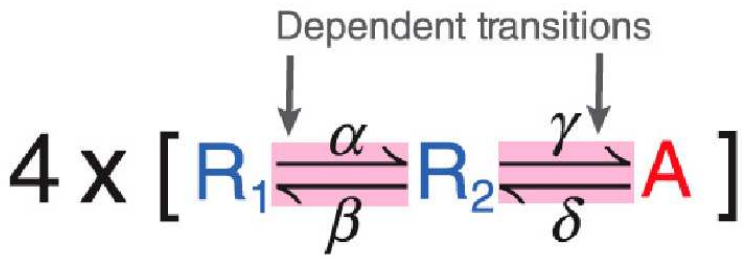
The 4 subunits are identical and activate independently.

They can be represented by identical gates (n) to give a Hodgkin-Huxley type model with open probability n^4



Channel activation itself may also contain dependent transitions.

For example, Shaker K^+ channel activation:



4 subunits each going through two conformational transitions (R_1 and R_2) before reaching the activated state A

Transitions are dependent; no analogous Hodgkin-Huxley type model

Markov current equation

Markov models compute the occupancy of the channel in its various kinetic states as a function of voltage and time.

The channel conducts ions when it occupies its open state.

Macroscopic current density through an ensemble of open channels is given by:

$$I_X = \overline{g_{sc,x}} \cdot n \cdot O \cdot (V_m - E_X). \quad (1)$$

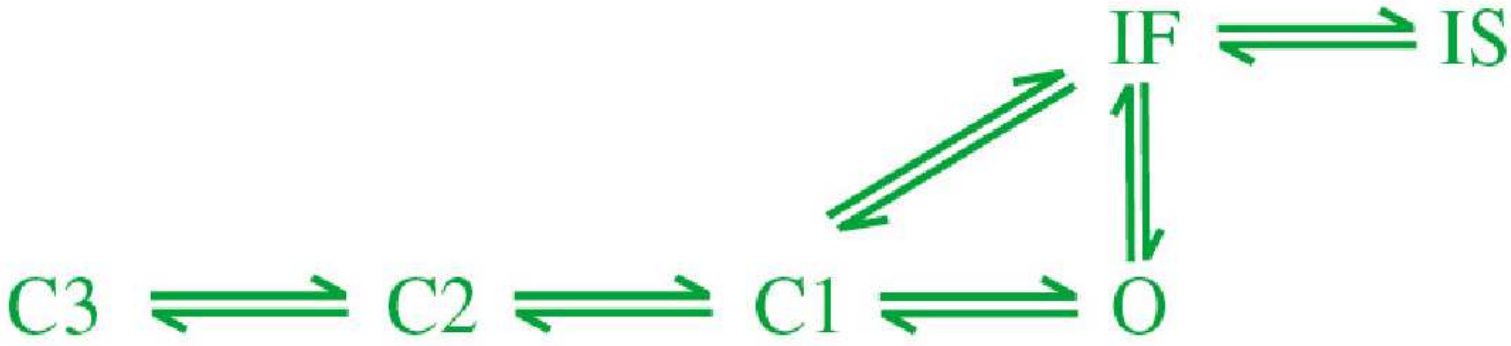
Here, $\overline{g_{sc,x}}$ is the single channel conductance, n is the number of channels per unit membrane area, O is the probability that a channel is open, and $(V_m - E_X)$ is the driving force.

Modeling ion-channel mutations

Markov models are used to model ion channel mutations.

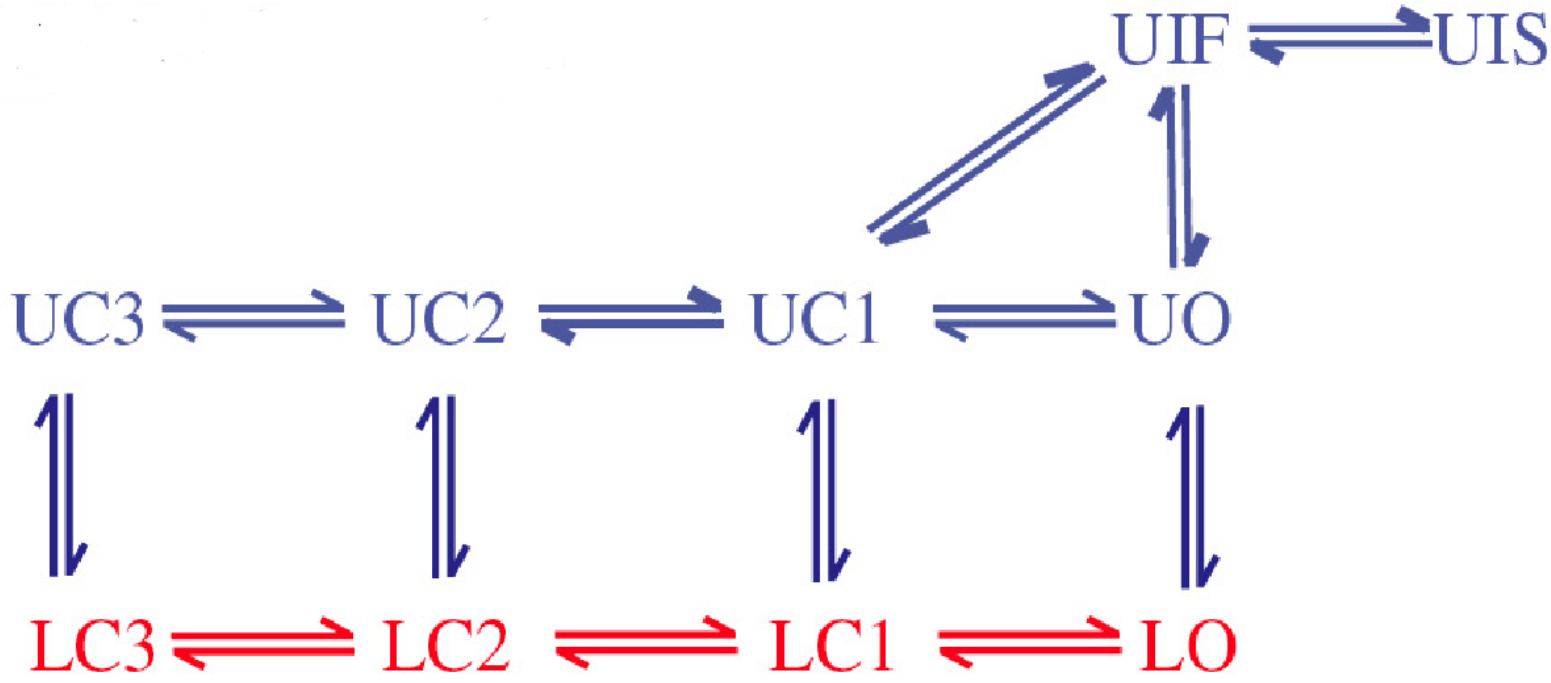
For example, Clancy and Rudy (1999) developed a Markov model for the Na^+ channel mutation responsible for long QT syndrome (LQT3).

Markov model for wild-type Na^+ channel



- 3 closed states (C1,C2,C3)
- 1 open (conducting) state (O)
- Fast and slow inactivation states (IF,IS)

Markov model for Na^+ channel mutation



2 gating modes: background mode (blue) and burst mode (red)

The background mode of the mutant Na^+ channel is similar to the wild-type model but has faster activation and recovery from inactivation.

The burst mode does not include an inactivation state, simulating the transient failure of mutant Na^+ channels to inactivate.

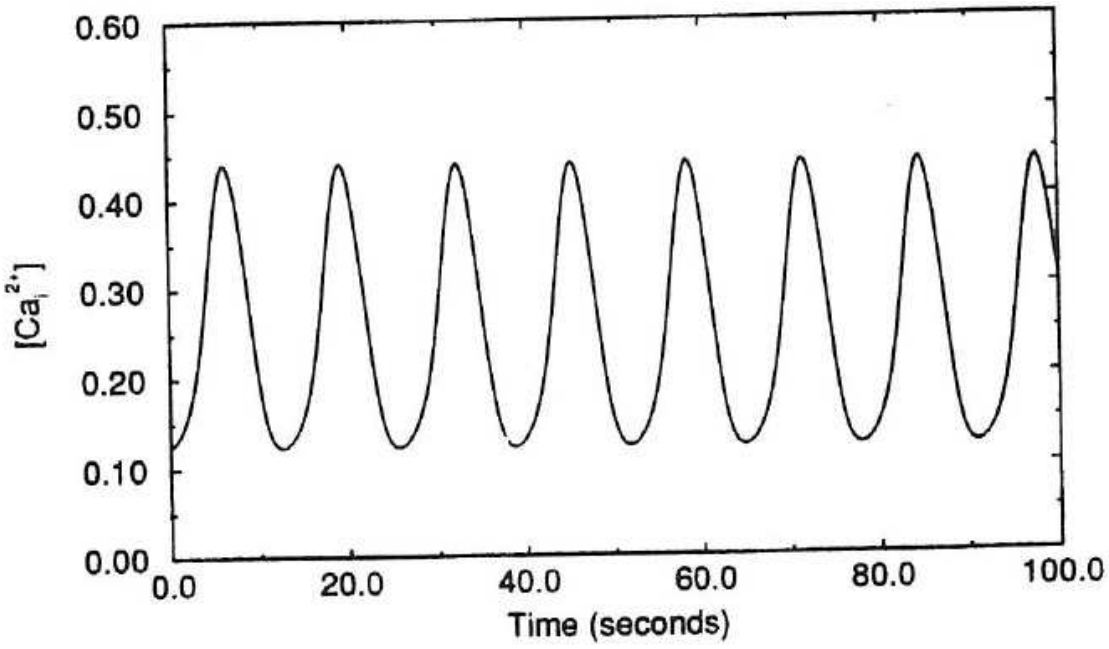
Calcium dynamics

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

Typical periodic orbit in Ca^{2+}

Cells exhibit oscillations in intracellular [Ca^{2+}] in response to, for example, hormones and neurotransmitters.



Calcium release

Calcium released from internal stores is mediated by 2 types of channels (receptors)

- Inositol (1,4,5)-triphosphate (IP_3) receptors
- Ryanodine receptors

IP_3 receptors

- Situated on the endoplasmic reticulum (ER) membrane
- Sensitive to the second messenger IP_3
- Binding of an extracellular agonist (hormone, neurotransmitter) to a receptor on the surface membrane causes cleavage of phosphotidylinositol (4,5)-bisphosphate (PIP_2) into diacylglycerol (DAG) and IP_3
- IP_3 diffuses through the cell, binds to IP_3 receptors and Ca^{2+} is released from the ER

The two-pool model

- One of the earliest models for IP_3-dependent Ca^{2+} release
- Assumes the existence of 2 distint Ca^{2+} stores: one sensitive to IP_3 and one sensitive to Ca^{2+}
- IP_3 binds to IP_3-sensitive stores releasing Ca^{2+}, which triggers further Ca^{2+} release from Ca^{2+}-sensitive stores (possibly via ryanodine receptors)

The two-pool model schematic

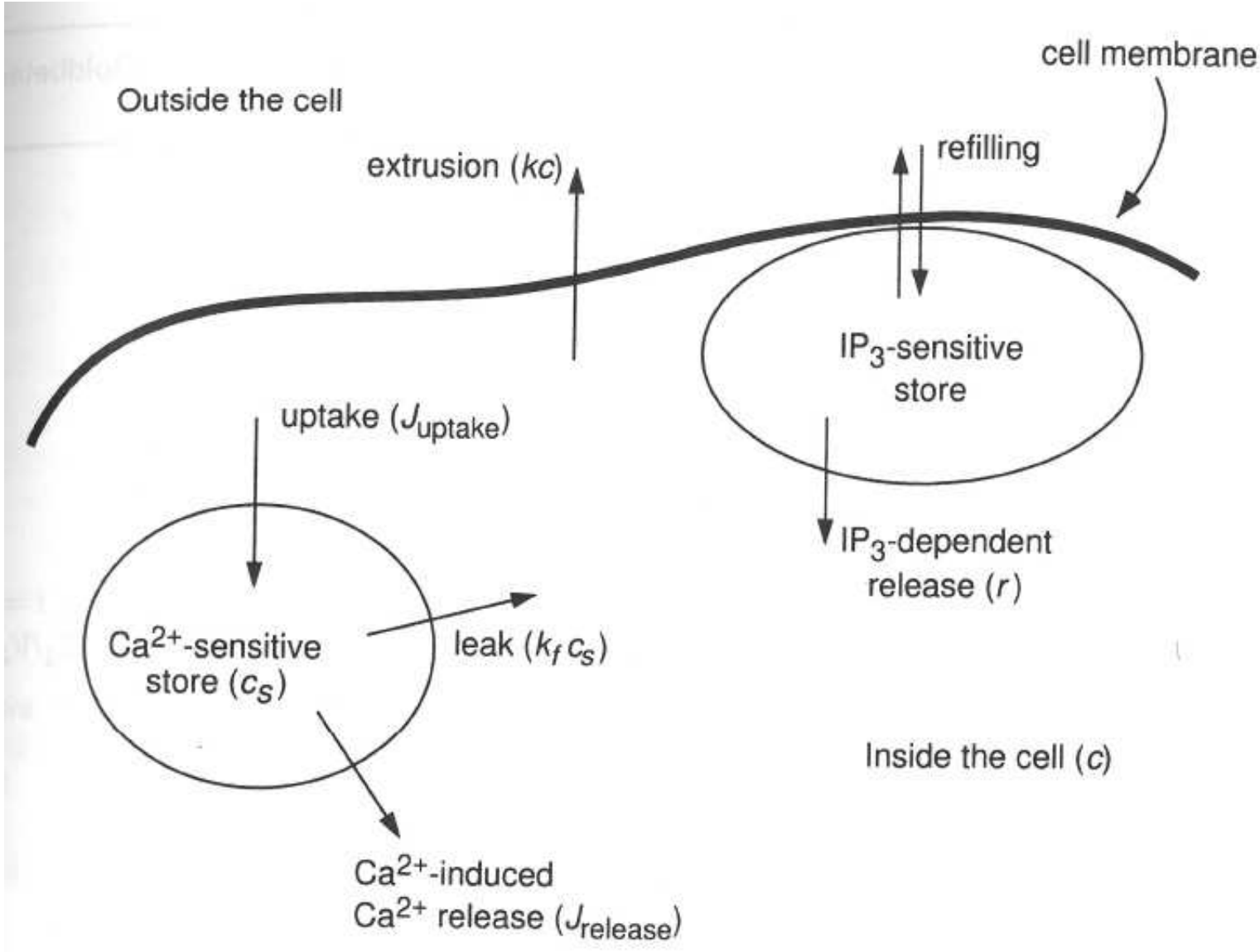


Figure 5.3 Schematic diagram of the two-pool model of Ca^{2+} oscillations.

The two-pool model equations

$$
\begin{aligned}
\frac{dc}{d\tau} &= r - kc - \tilde{f}(c, c_s) \\
\frac{dc_s}{d\tau} &= \tilde{f}(c, c_s) \\
\tilde{f}(c, c_s) &= J_{uptake} - J_{release} - k_f c_s \\
J_{uptake} &= \frac{V_1 c^n}{K_1^n + c^n} \\
J_{release} &= \left(\frac{V_2 c_s^m}{K_2^m + c_s^m} \right) \left(\frac{c^p}{K_3^p + c^p} \right)
\end{aligned}
$$

Detailed IP_3 receptor model

- The role of Ca^{2+} is more complicated than is assumed in the two-pool model
- Ca^{2+} both activates and inactivates the IP_3 receptor
- So instead, the IP_3 receptor is modeled as consisting of 3 equivalent and independent subunits, all of which must be in a conducting state for the receptor to allow Ca^{2+} flux
- Each subunit has an IP_3 binding site, an activating Ca^2 binding site, and an inactivating Ca^{2+} binding site; each of these can be either occupied or unoccupied, thus each subunit can be in one of eight states

Detailed IP_3 receptor model diagram

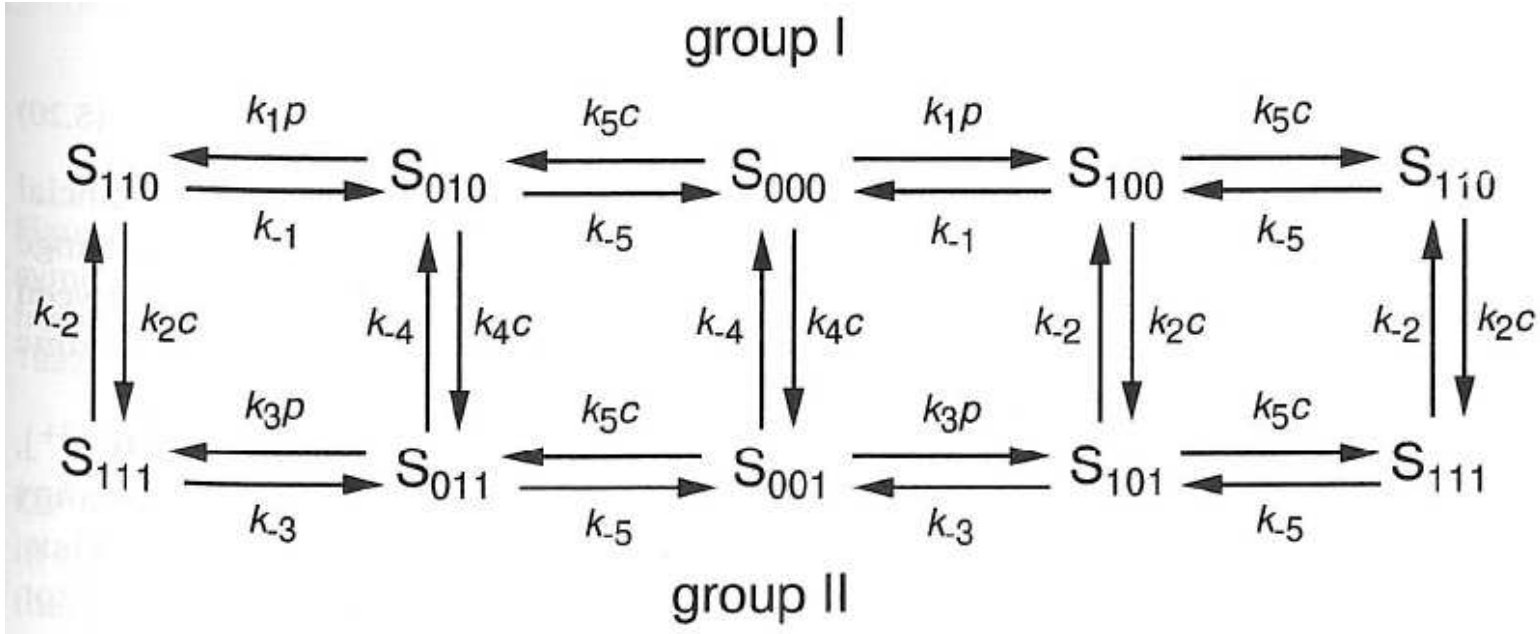


Figure 5.6 The binding diagram for the IP_3 receptor model. Here, c denotes $[Ca^{2+}]$, and p denotes $[IP_3]$.

Detailed IP_3 receptor model equations

$$
\begin{aligned}
\frac{dx_{000}}{dt} &= -x_{000}(k_5c + k_1p + k_4c) + k_{-5}x_{010} + k_{-1}x_{100} + k_{-4}x_{001} \\
\frac{dx_{100}}{dt} &= -x_{100}(k_5c + k_{-1} + k_2c) + k_{-5}x_{110} + k_1px_{000} + k_{-2}x_{101} \\
\frac{dx_{010}}{dt} &= -x_{010}(k_{-5} + k_1p + k_4c) + k_5cx_{000} + k_{-1}x_{110} + k_{-4}x_{011} \\
\frac{dx_{001}}{dt} &= -x_{001}(k_{-4} + k_5c + k_3p) + k_{-5}x_{011} + k_4cx_{000} + k_{-3}x_{101} \\
\frac{dx_{011}}{dt} &= -x_{011}(k_{-4} + k_3p + k_{-5}) + k_{-3}x_{111} + k_4cx_{010} + k_5cx_{001} \\
\frac{dx_{101}}{dt} &= -x_{101}(k_{-2} + k_{-3} + k_5c) + k_3px_{001} + k_2cx_{100} + k_{-5}x_{111} \\
\frac{dx_{110}}{dt} &= -x_{110}(k_{-1} + k_2c + k_{-5}) + k_{-2}x_{111} + k_5cx_{100} + k_1px_{010}
\end{aligned}
$$

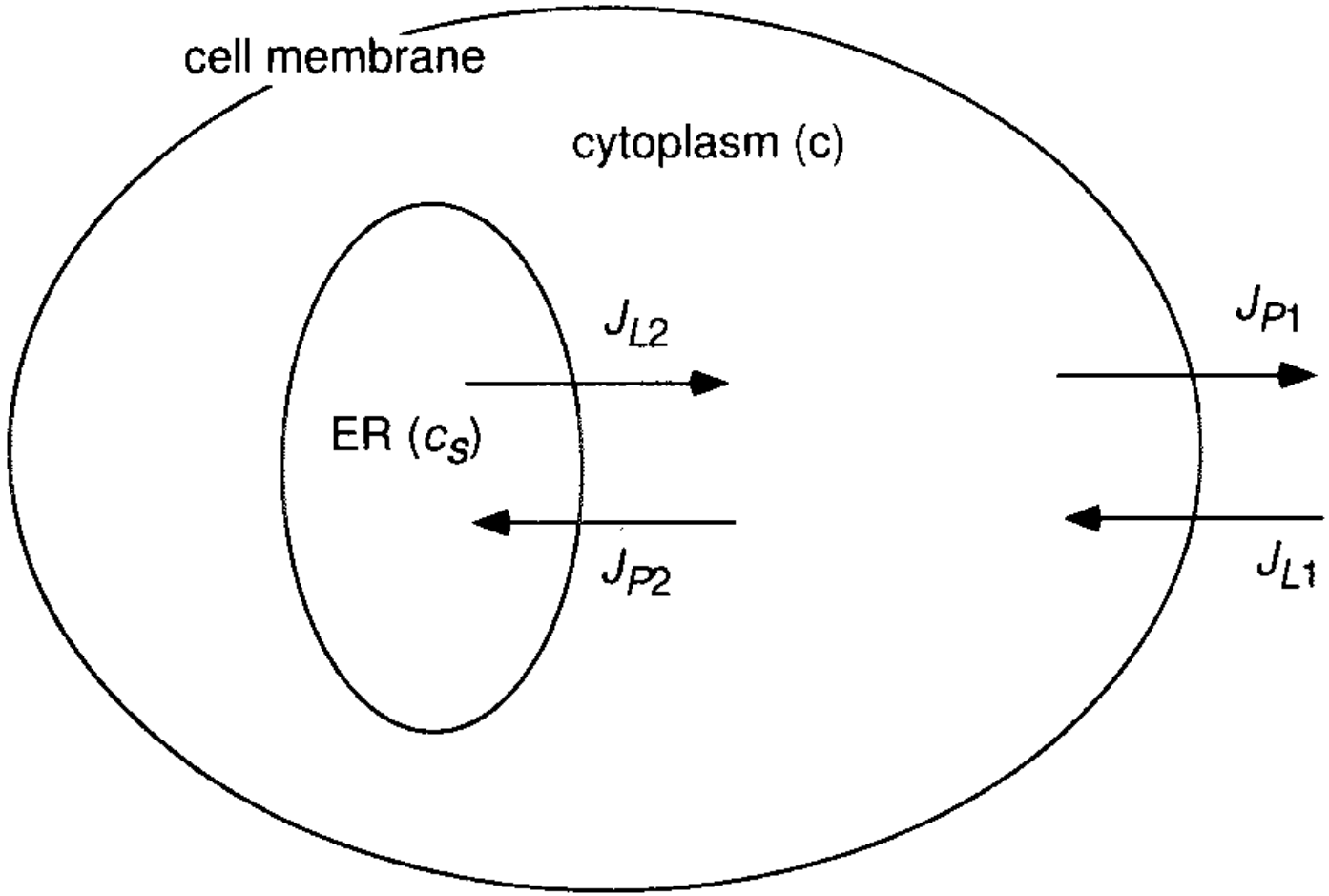
Detailed IP_3 receptor model equations (cont.)

$$\frac{dc}{dt} = \overbrace{(r_1 x_{110}^3 + r_2)(c_s - c)}^{receptor\,flux} - \overbrace{\frac{r_3 c^2}{c^2 + k_p^2}}^{pumping}$$

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

$$\frac{d[c]}{dt} = J_{\mathsf{L1}} - J_{\mathsf{P1}} + J_{\mathsf{L2}} - J_{\mathsf{P2}}$$

$$\frac{d[c_s]}{dt} = -J_{\mathsf{L2}} + J_{\mathsf{P2}}$$

$$J_{\mathsf{L1}} = k_1(c_e - c), \quad \mathsf{Ca}^{2+} \text{ entry}$$

$$J_{\mathsf{P1}} = k_2 c, \quad \mathsf{Ca}^{2+} \text{ extrusion}$$

$$J_{\mathsf{L2}} = k_3(c_s - c), \quad \mathsf{Ca}^{2+} \text{ release}$$

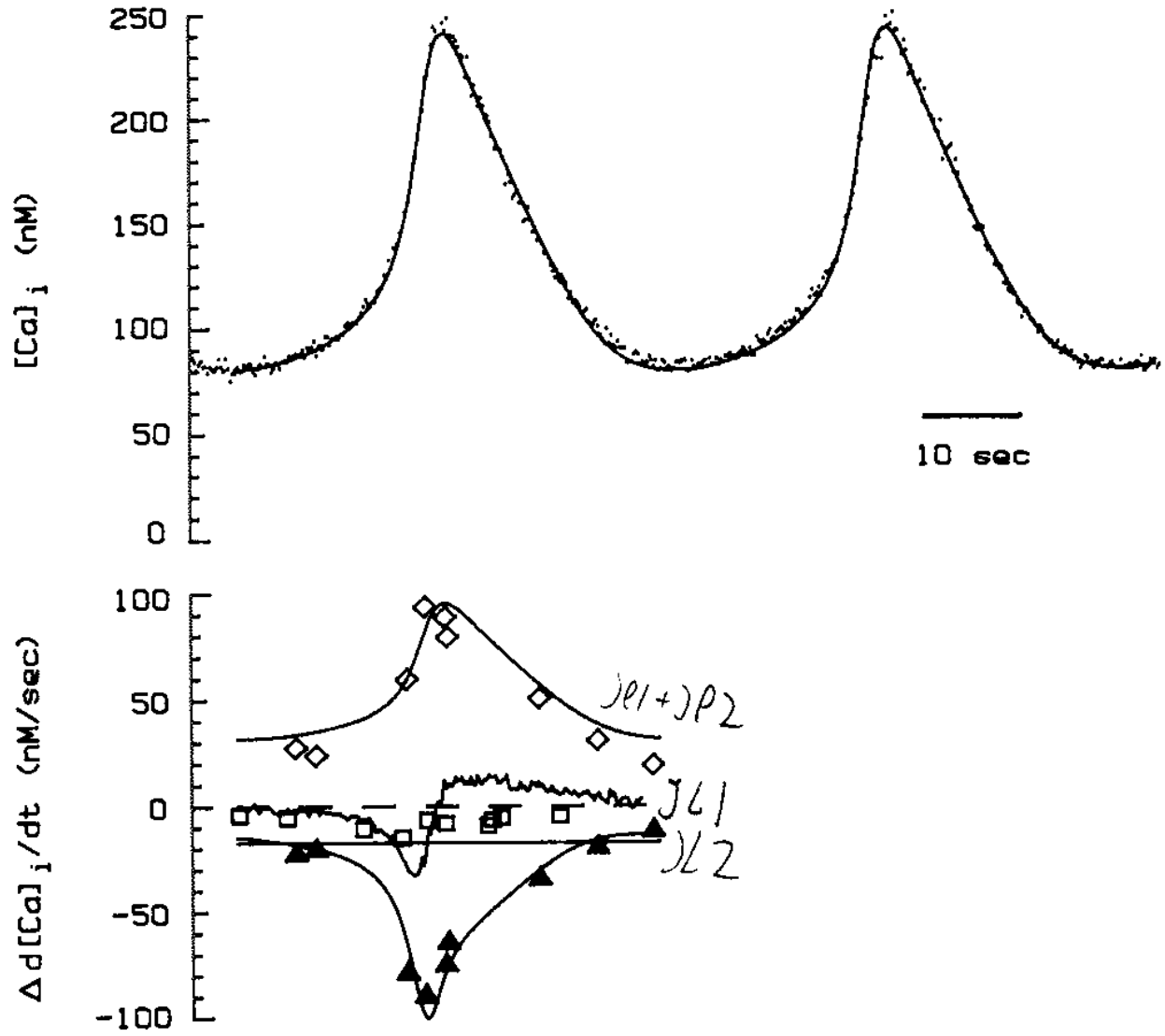
$$J_{\mathsf{P2}} = k_4 c, \quad \mathsf{Ca}^{2+} \text{ uptake}$$

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
- Four states of the RyR
  - S_{00} No Ca ions attached, closed
  - S_{10} Ca attached to activating site, open
  - S_{01} Ca attached to inactivating site, closed
  - S_{11} Ca attached both sites, closed
- Define the fractions x_i:
  - $x_1 = S_{00}/S_T$
  - $x_2 = S_{10}/S_T$
  - $x_3 = S_{11}/S_T$
  - $x_4 = S_{01}/S_T = 1 - x_1 - x_2 - x_3$

The state transitions

- The state transitions

$$\begin{array}{ccc} \mathsf{S}_{00} & \underset{k_{-1}}{\overset{ck_1}{\rightleftarrows}} & \mathsf{S}_{10} \\ k_{-2} \uparrow\downarrow ck_2 & & k_{-2} \uparrow\downarrow ck_2 \\ \mathsf{S}_{01} & \underset{k_{-1}}{\overset{ck_1}{\rightleftarrows}} & \mathsf{S}_{11} \end{array}$$

- Better models for the pumps

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

Model equations

$$
\begin{aligned}
\frac{dx_1}{dt} &= k_{-1}x_2 + k_{-2}x_4 - (k_1 + k_2)x_1 c \\
\frac{dx_2}{dt} &= -k_{-1}x_2 + k_{-2}x_3 + (k_1 x_1 - k_2 x_2)c \\
\frac{dx_3}{dt} &= (k_2 x_2 + k_1 x_4)c - (k_{-2} + k_{-1})x_3 \\
\frac{dc}{dt} &= v_c(J_{\mathsf{L2}} - J_{\mathsf{P2}}) + J_{\mathsf{L1}} - J_{\mathsf{P1}} \\
\frac{dc_s}{dt} &= -J_{\mathsf{L2}} + J_{\mathsf{P2}} \\
J_{\mathsf{L1}} &= g_2(c_e - c) \\
J_{\mathsf{L2}} &= (k_f x_2 + g_1)(c_s - c) \\
J_{\mathsf{P1}} &= \frac{q_1 c^2}{q_2^2 + c^2} \\
J_{\mathsf{P2}} &= \frac{p_1 c^2}{p_2^2 + c^2}
\end{aligned}
$$