Markov models for ionic channels

From “Computational biology in the study of cardiac ion channels and cell electrophysiology,”
Y. Rudy and J. R. Silva, Quarterly Reviews in Biophysics, 2006.

- # Questions:

- What are the limitations of HH-type models for ion channels? How can Markov models better represent ion channels?

- HH and Markov channel models are equivalent under what condition? Illustrate with an example.

- What is the current density function for a Markov-modeled channel X?

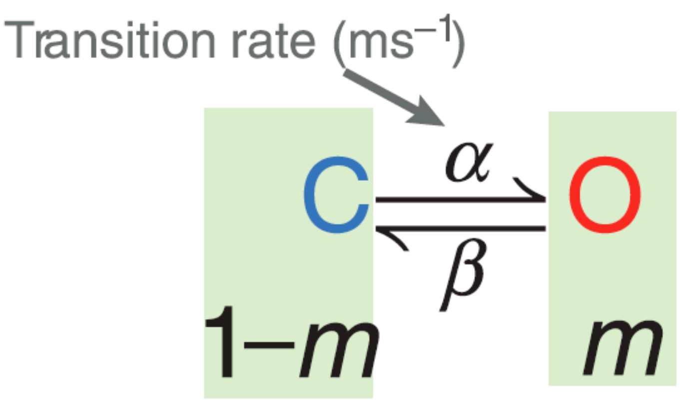
- Sketch the Markov models for the wild-type Na^+ channel and the mutant Na^+ channel responsible for LQT3 syndrome, outlining the main differences between them.

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^2h is not valid
- Models with explicit representation of single ion-channel states are needed

Markov models

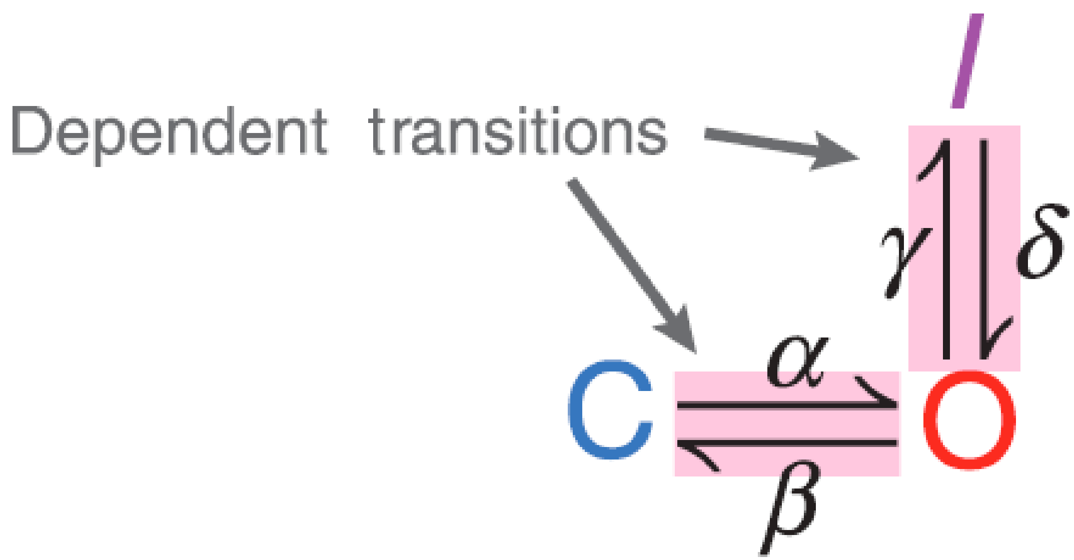
- Model the states of single ion channels
- When channel gates are assumed to be independent, Markov and Hodgkin-Huxley models are equivalent



m: probability in O

$1-m$: probability in C

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



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

$$\frac{\mathrm{dC}}{\mathrm{d}t} = \alpha \cdot \mathrm{C} - \beta \cdot \mathrm{O},$$

$$\frac{\mathrm{dO}}{\mathrm{d}t} = \alpha \cdot \mathrm{C} + \delta \cdot I - (\beta + \gamma) \cdot \mathrm{O},$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \gamma \cdot \mathrm{O} - \delta \cdot I,$$

- alpha, beta, gamma and delta are transition rates

- Most channels have 4 subunits, so more than one transition is need to describe activation

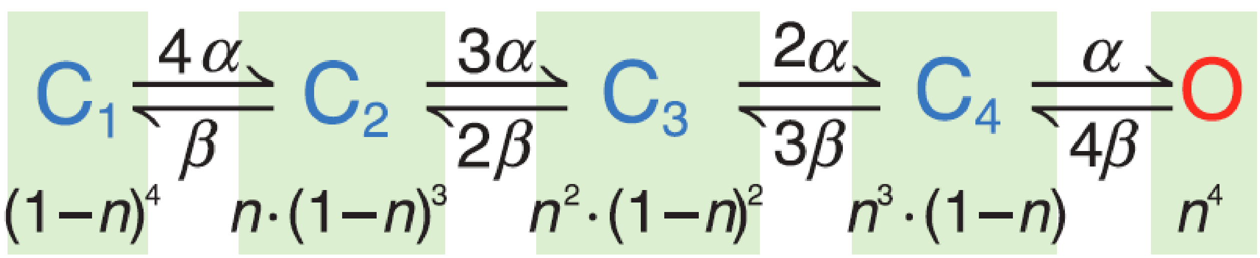
$$C_1 \underset{\beta}{\overset{4\alpha}{\rightleftharpoons}} C_2 \underset{2\beta}{\overset{3\alpha}{\rightleftharpoons}} C_3 \underset{3\beta}{\overset{2\alpha}{\rightleftharpoons}} C_4 \underset{4\beta}{\overset{\alpha}{\rightleftharpoons}} O$$

- 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

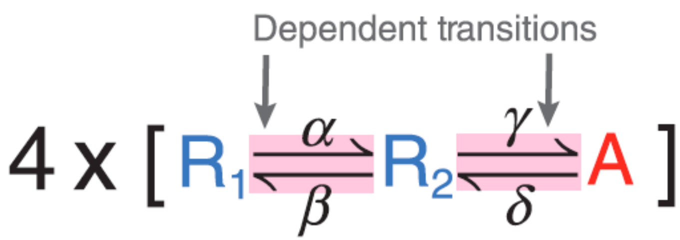
- The 4 subunits are identical and activate independently

- 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 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:

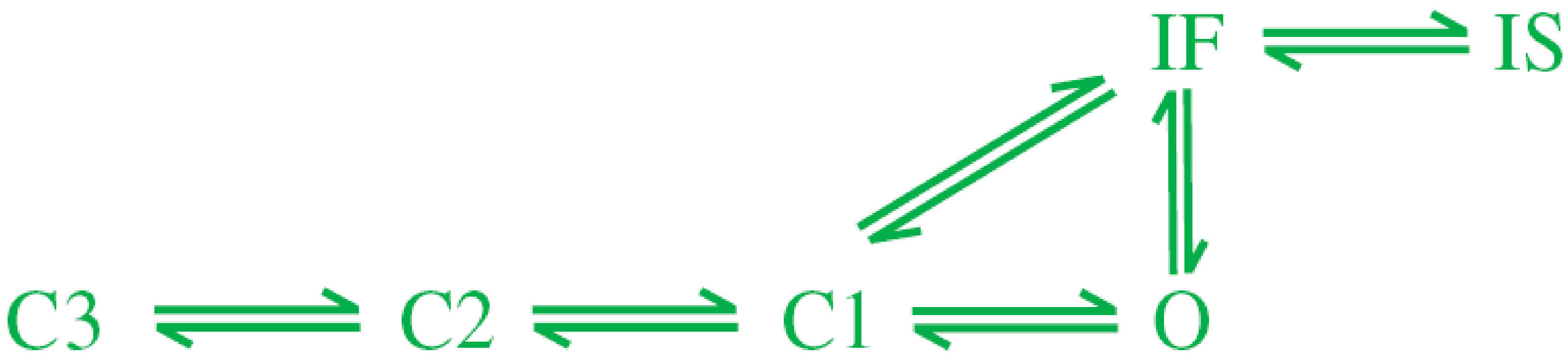
$$I_X = \overline{g_{sc,x}} \cdot n \cdot O \cdot (V_m - E_X)$$

- $\overline{g_{sc,x}}$ 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

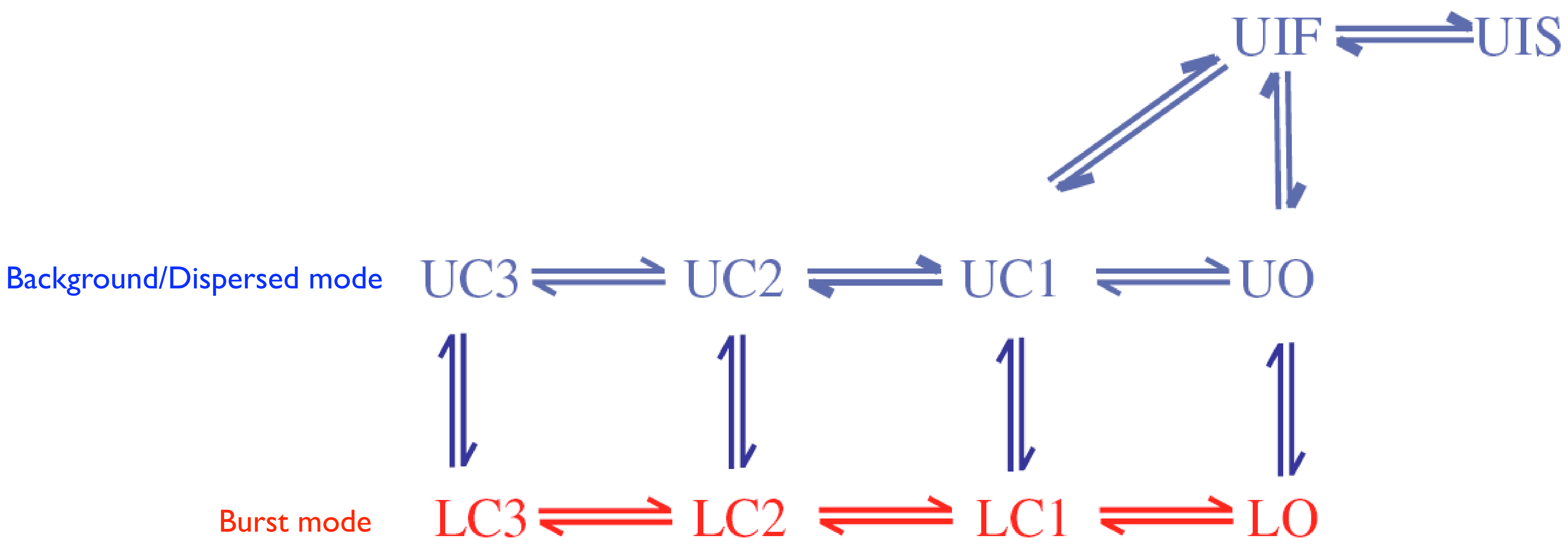
- Markov models are used to model ion channel mutations
- For example, Clancy and Rudy (1999) developed a Markov model for the Na^+ channel mutation responsible for long QT syndrome (LQT3)

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 (or dispersed) mode and burst mode

- The background mode of 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