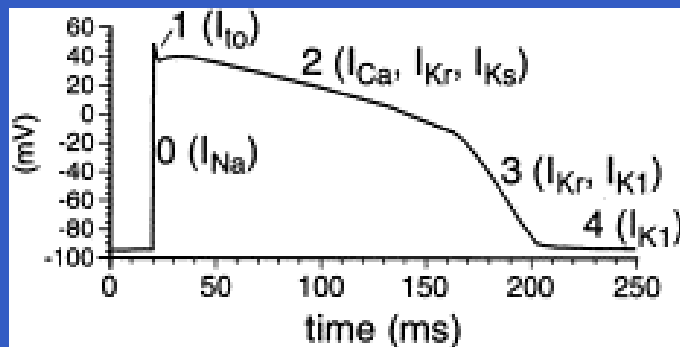
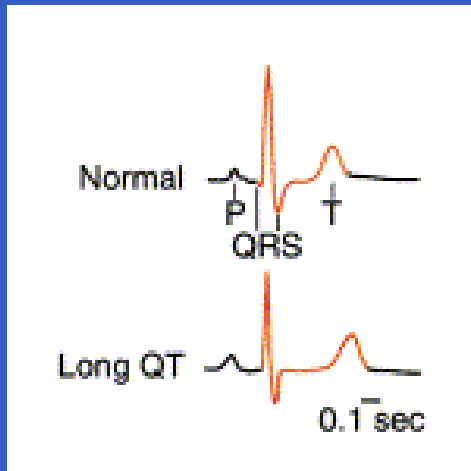


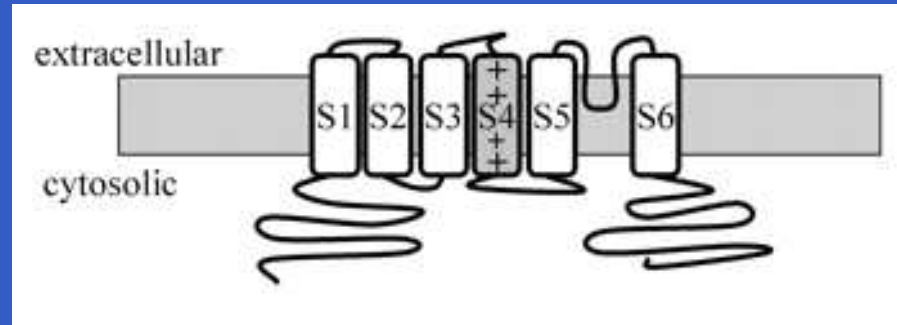
Kinetic Model of Cadmium Binding on HERG Potassium Channels

LQT & Mutation of HERG Channels



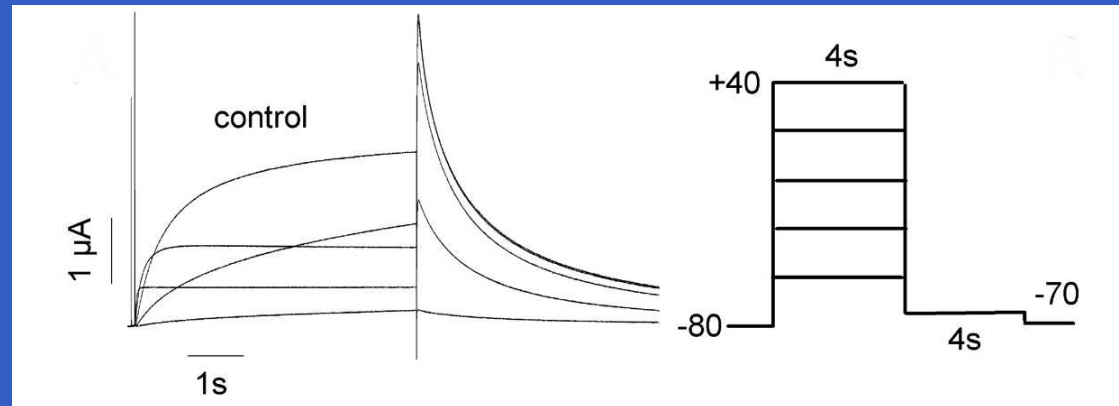
- Long QT (LQT) syndrome is a disorder of ventricular repolarization
- May cause sudden cardiac death
- LQT2 are caused by abnormalities in the HERG gene

Structure of HERG Channels

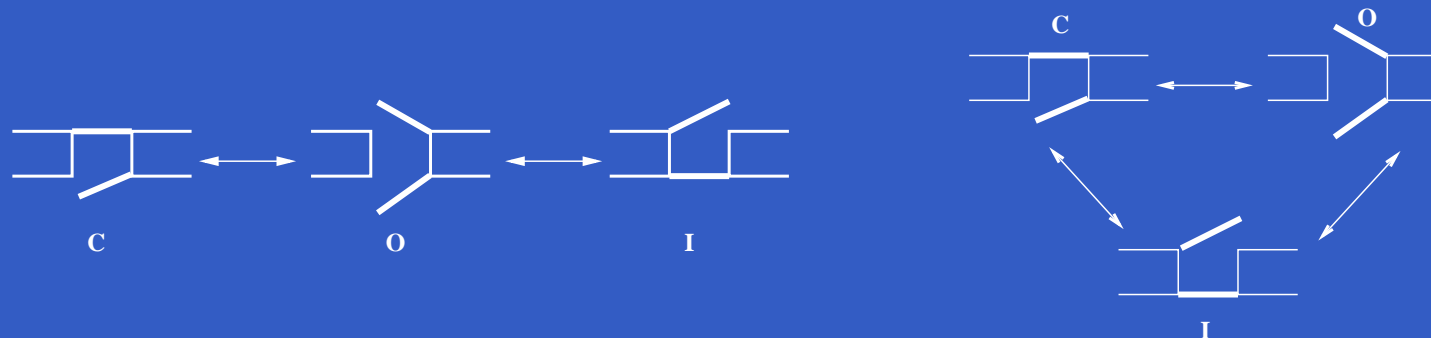


- HERG is a voltage-gated potassium channel
- Tetrameric channel
- Each subunit consists of 6 membrane spanning domains (S1-S6)
- S4 acts as a voltage sensor

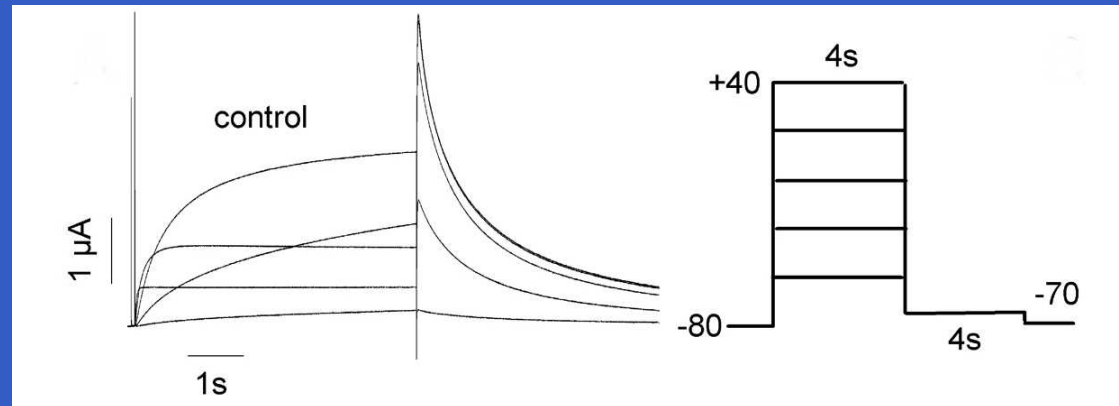
HERG Current



- Inactivation occurs much faster than activation

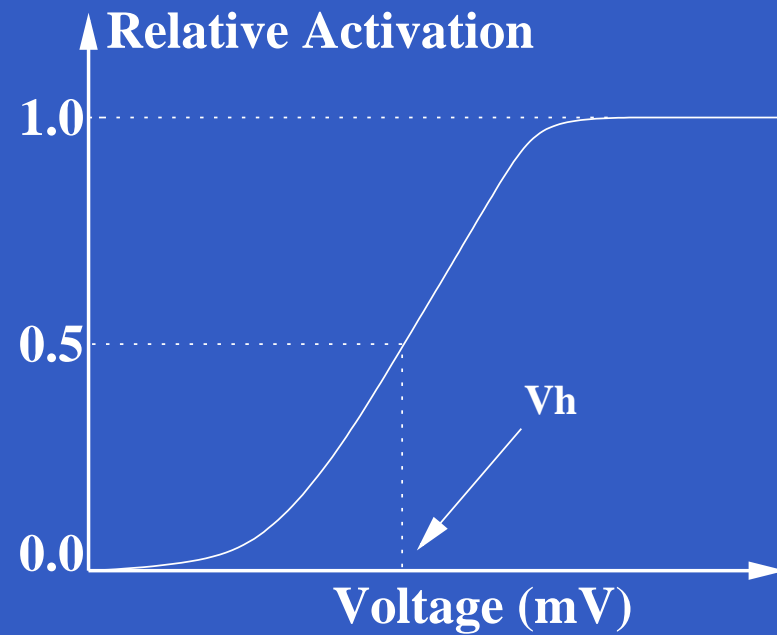
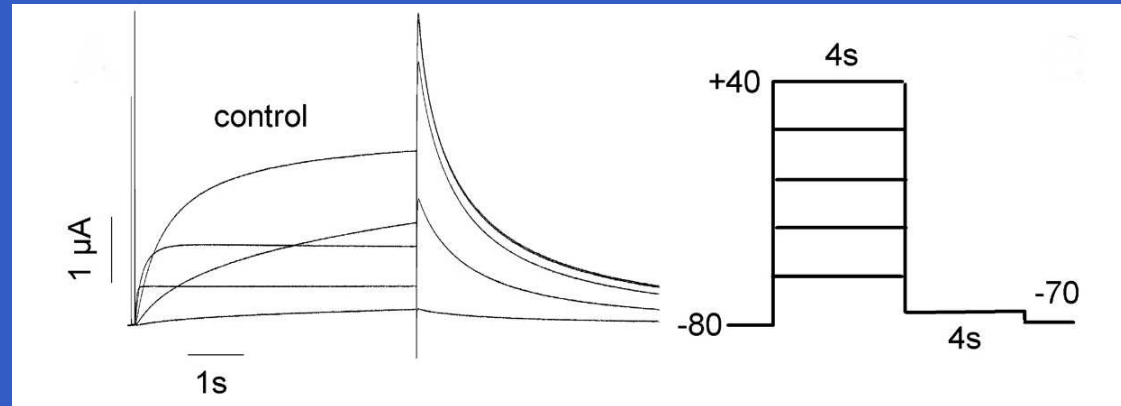


HERG Current

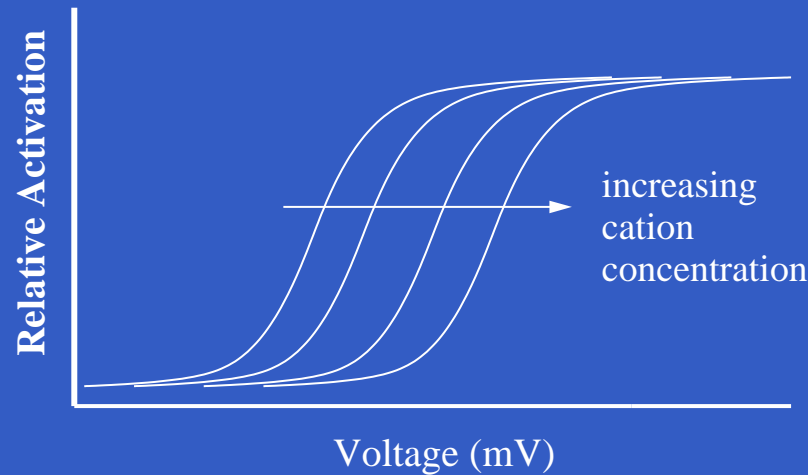


- Inactivation occurs much faster than activation
- Tail-current represents deactivation: to go from inactivation, channel activates transiently before deactivating
- Amount of activation is reflected by peak tail-current

HERG Current

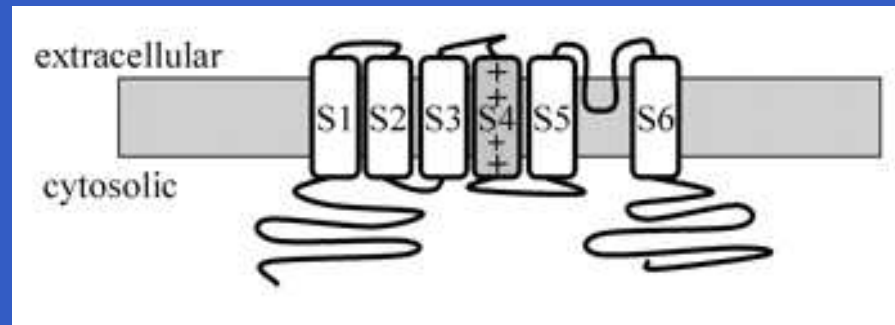


Effects of Cd^{2+} on HERG Current



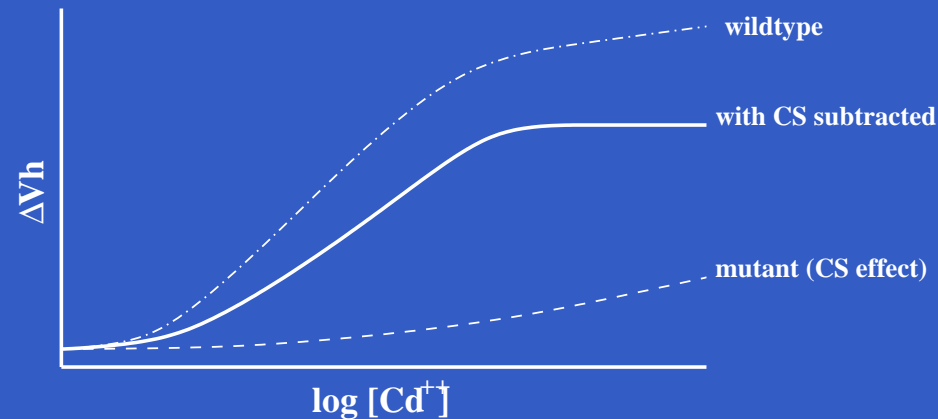
- Increasing extracellular concentration of Cd^{2+} shifts ΔV_h of activation towards a more positive voltage.
- Stabilizing action : threshold for activation and membrane resistance are raised.

Cd^{2+} Binding Hypothesis



- Three positively-charged amino-acid residues in the S4/S5 subunits form a binding site for Cd^{2+} within the channel
- Tetrameric channel hence four such binding sites per channel.

Experimental Measurements of Shifts



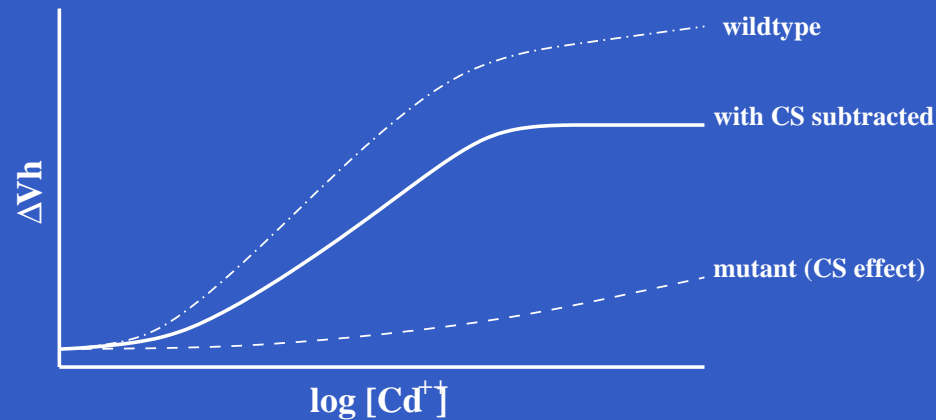
- Charge-screening (CS) effect: local electric field near the membrane will bias the voltage-sensor within the channel
- "Saturating" behavior is observed upon subtraction of presumed CD effect

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Experimental Measurements of Shifts

However ...

Experimental Measurements of Shifts



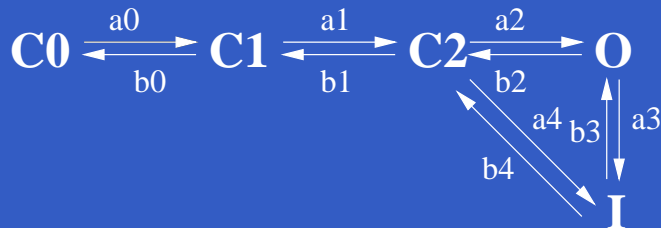
- CANNOT conclude cooperativity in Cd^{2+} binding
- Measured quantity, ΔVh , is not a direct measurement of binding

List of Questions

- Are there cooperativity in Cd^{2+} binding among the four sites?
- How does sequence of binding affect the activation shift?
- What happens when binding occur independently?

...

Model of HERG Channel



Forward and Backward rates:

$$a_j = \alpha_j \cdot \exp\left(z_j^a \cdot \frac{V_m \cdot F}{R \cdot T}\right)$$

$$b_j = \beta_j \cdot \exp\left(z_j^b \cdot \frac{V_m \cdot F}{R \cdot T}\right)$$

- System of ODE's are written using law of mass actions.

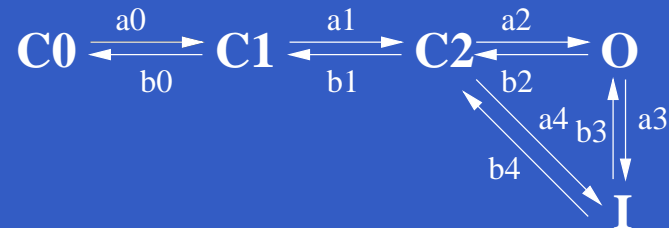
$$\frac{dC_1}{dt} = a_0 C_0 - b_0 C_1 - a_1 C_1 + b_1 C_2$$

- Current I_{HERG} are then computed using

$$I_{HERG} = N \cdot G_{max} \cdot O \cdot (V_m - E_{rev})$$

- Fitting to experimental data are performed to obtain rate-constants.

Accounting for Ca^{2+} Binding



- S_{ijkl} represents channel states. That is,
 $S = C_0, C_1, C_2, O, \text{ or } I$
- i, j, k, l represents binding states
 $i, j, k, l = 0$ if unoccupied OR $i, j, k, l = 1$ if occupied

We thus have 25 possible channel/bound states with *LOTS* of parameters to be fitted to data.

What more can be done?

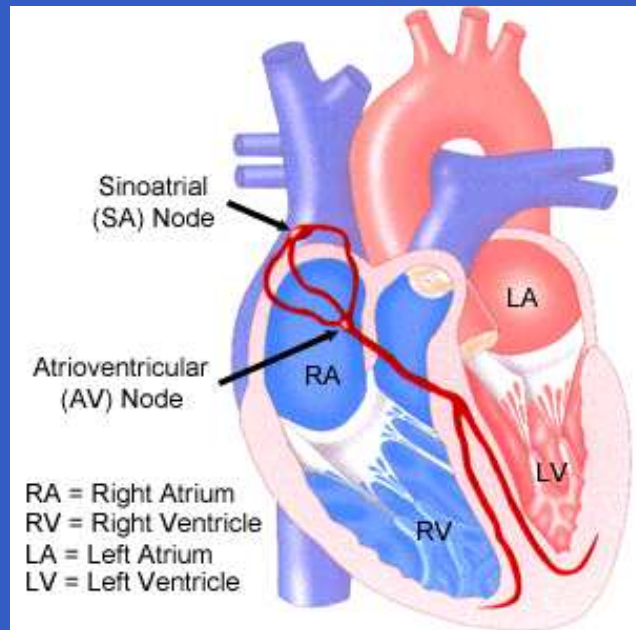
- Simplify, simplify, simplify!
- In particular, seek a good way to built-in a measure of cooperativity so as to reduce the number of fitting-parameters.
- Try to answer questions before

Acknowledgements

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- Michael Sanguinetti, Jim Keener
- David Fernandez, Azad Ghanta
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Conduction Pathway



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