BE6003/Physiol 6003

Cellular Electrophysiology and Biophysics

Modeling of Ion Channels II

CVRTI

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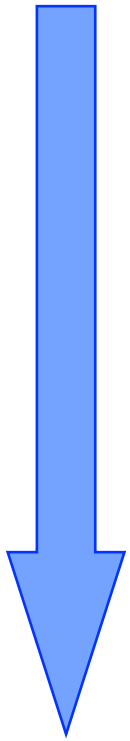
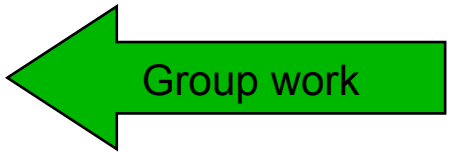
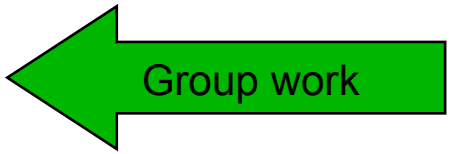
Overview



- Modeling of Mutations
- Modeling of Drug Effects
- Model Parameterization
- Solution Methods
- Software Tools
- Molecular Modeling
  - Background
  - Homology
  - Drug Binding





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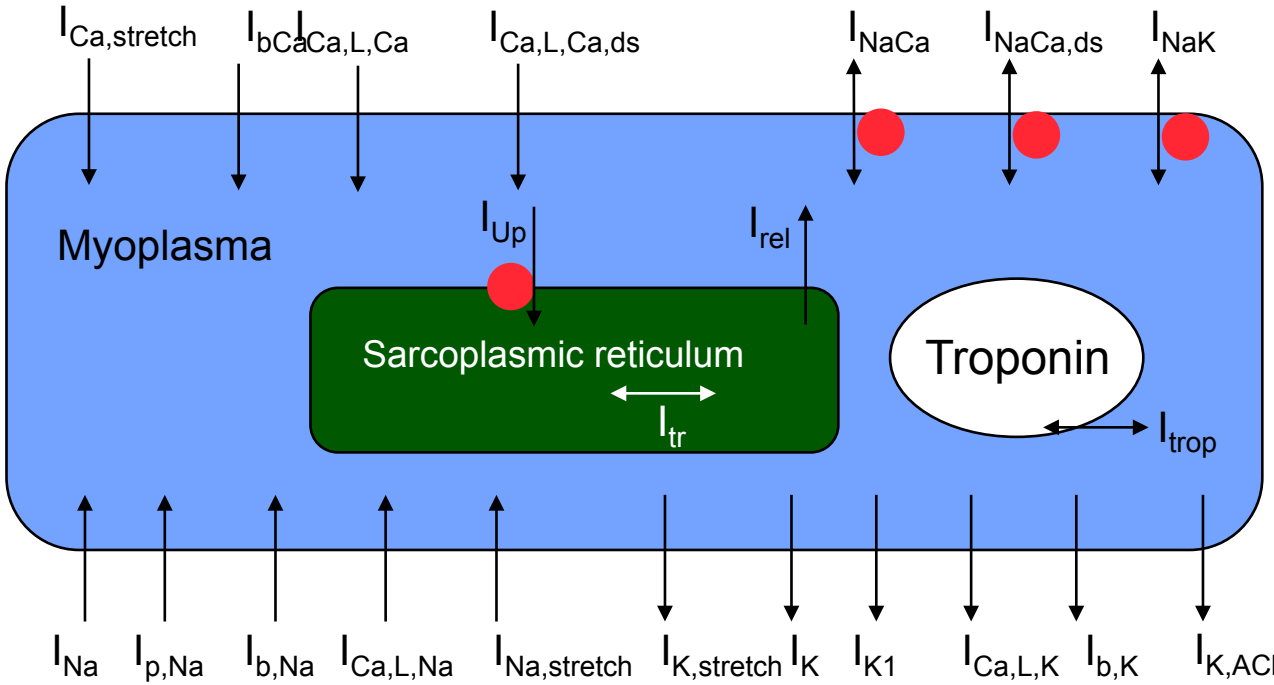
Applications of Ion Channel Models in System Biology

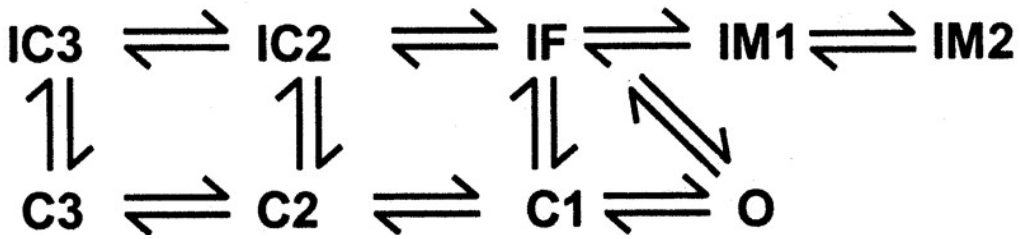


Noble et al, 1998: Mathematical description of ionic currents and concentrations, transmembrane voltage, and conductivities of guinea-pig ventricular myocytes

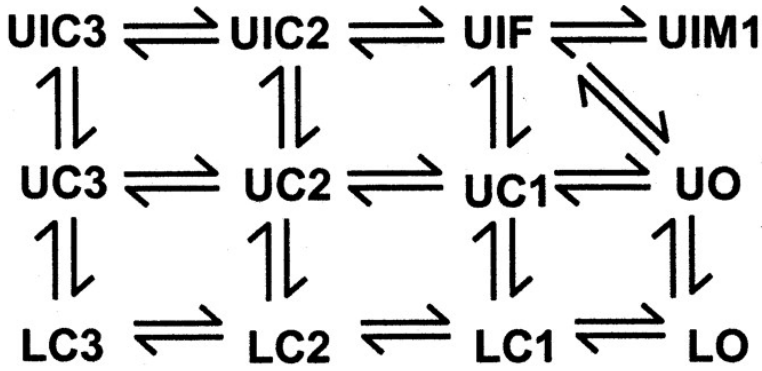
- Approach: Ion channel models are integrated into cell models
- Many recent cell models are based on Markov ion channel models
- Application: Studies of complex electrophysiological interactions in cells
  - Mutations: Wild type models are modified with/extended to models of mutations
  - Drug effects: “Normal” models are modified with/extended to “drug” models

Markov Models for WT and 1795insD Cardiac Na Channels

Wild-type Na channel



1795insD Na channel: Insertion of amino acid aspartic acid at location 1795

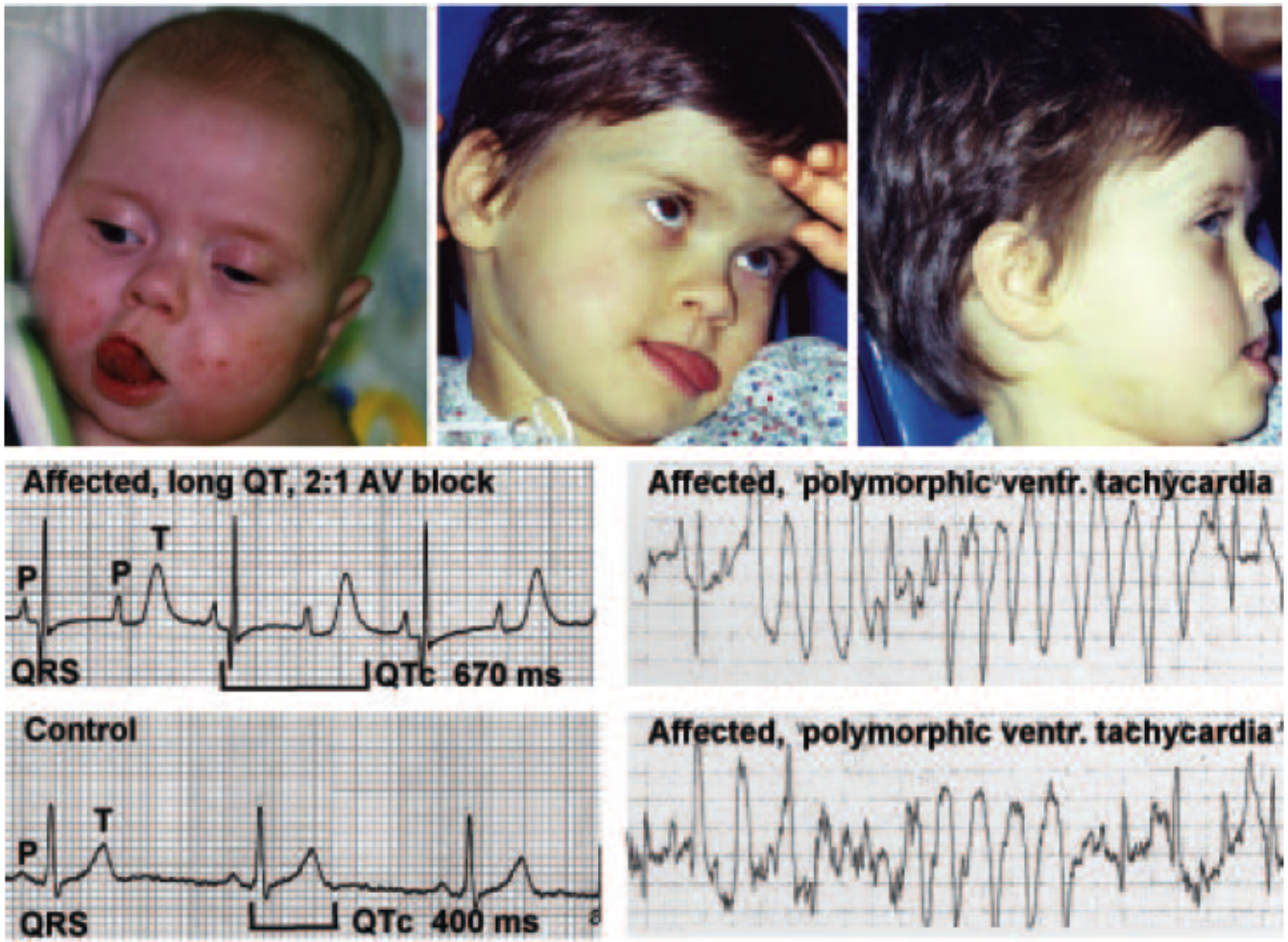


Background mode (normal)

Burst mode (pathological)

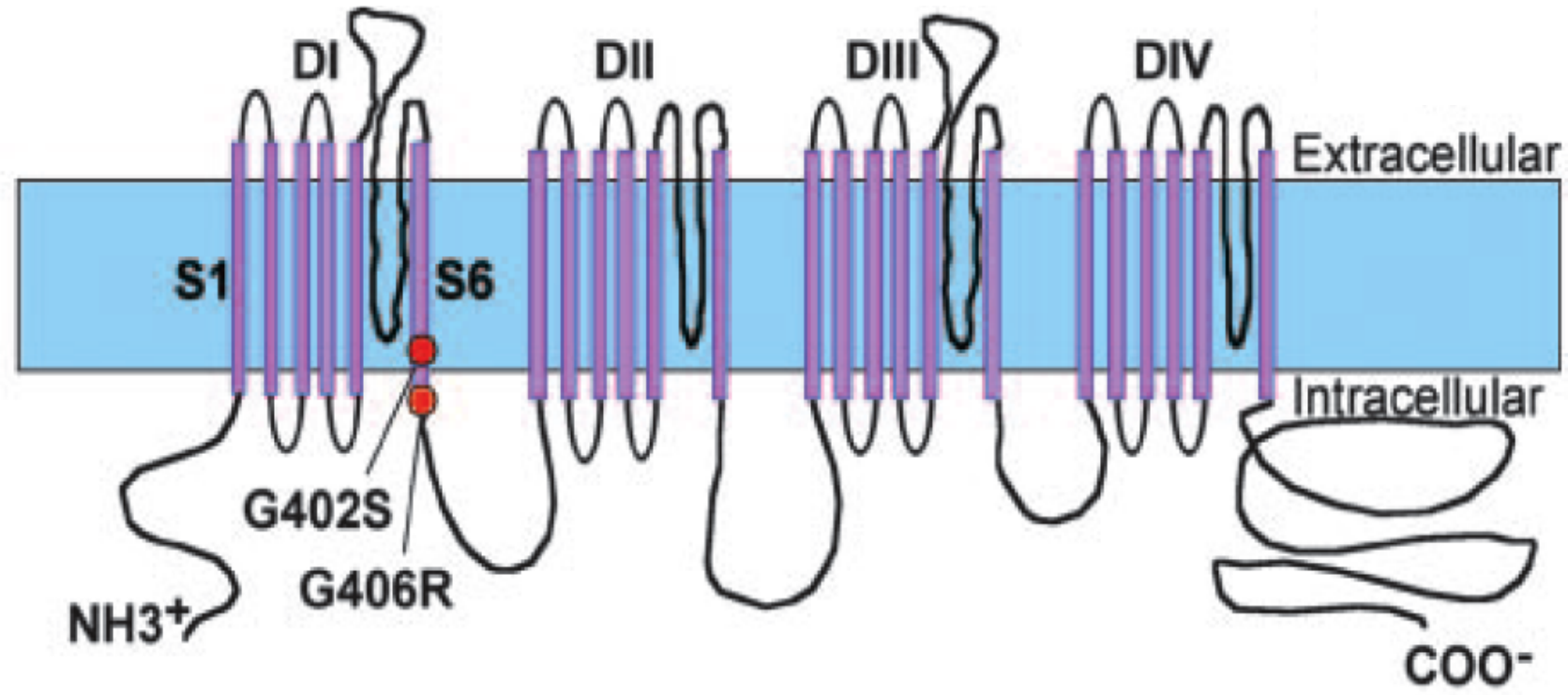
(Clancy and Rudy. Circulation 2002;105:1208-1213)

Genetic Disease: Timothy Syndrome



(Splawski et al, Proc Natl Acad Sci USA, 2005)

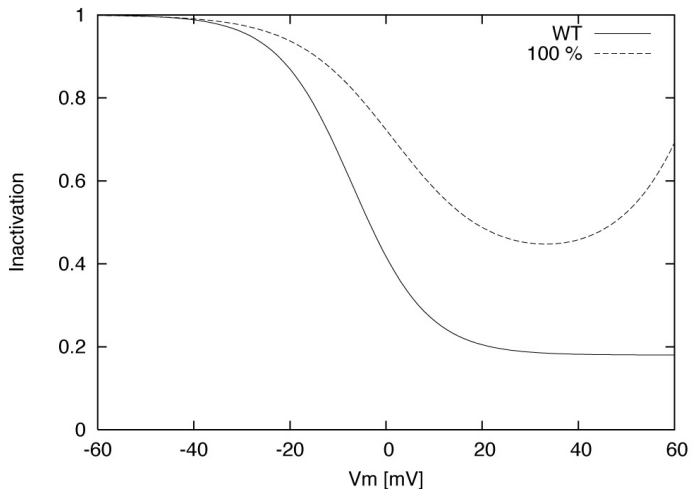
Topology of Ion Channel Protein $Ca_V1.2$



"De novo" mutations

- G402S: Glycine → Serine
- G406R: Glycine → Arginine

Modeling of Timothy Syndrome



Channel Modeling

Steady state inactivation
is reduced in mutated channels
versus wild type (WT)

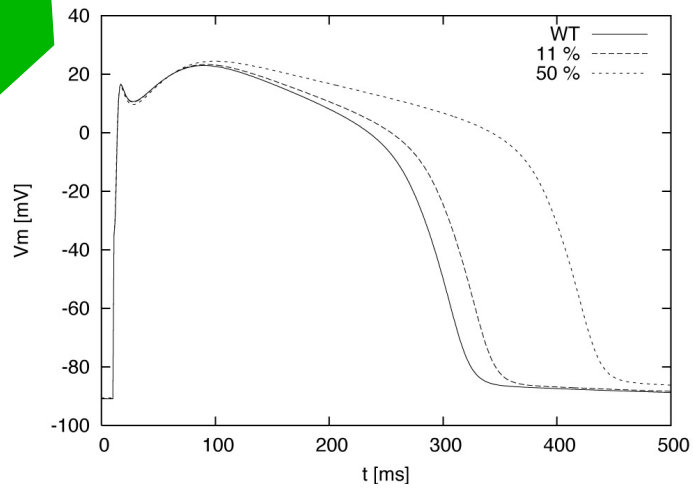
Model of mutated channels
created with numerical optimization

Integration in Myocyte Model

Prediction of course of transmembrane voltage in myocyte

Changes dependent on % of channels with mutation

Significant increase of action potential duration (and intracellular calcium concentrations)



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Genetic Disease: Mutation of KCNQ1

Slow Inward Rectifying Potassium Current I_{Ks} { KCNQ1, KCNE1

KCNQ1

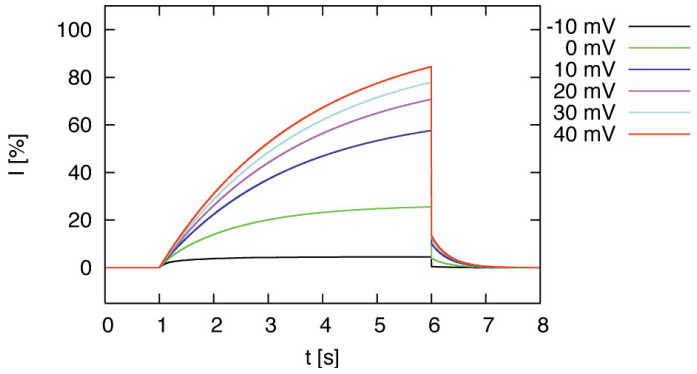
Mutations

- **S140G**
  Serine → Glycine
  found in family with hereditary atrial fibrillation
  (Chen et al., Science, 2003)
- **V141M**
  Valine → Methionine
  found in new born child with atrial fibrillation and short QT syndrome “de novo”
  (Kong et al., Cardiovasc Res, 2005)

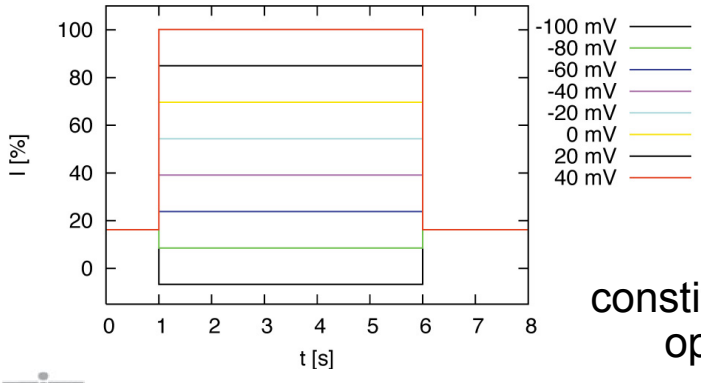
* Location of Mutation S4: Voltage sensing subunit

Model-Based Prediction of Ion Current

WT KCNQ1 + KCNE1

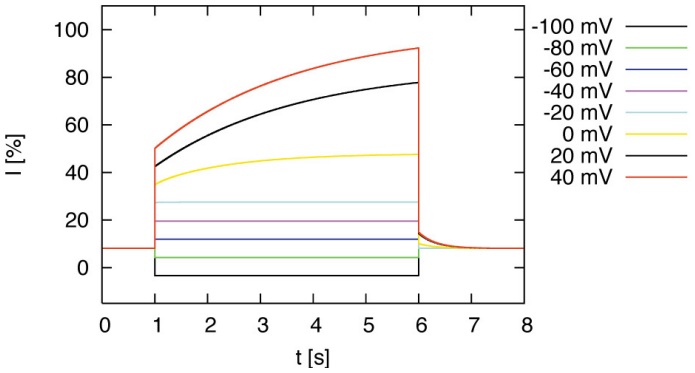


KCNQ1 (S140G or V141M) + KCNE1



constitutively open

50 % WT / 50 % mutation



gain of function!

(Kong et al., Cardiovasc Res, 2005)

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Group Work

Predict the effect of mutation S140G or V141M on action potential duration in myocytes!

Modeling of Drug Effects

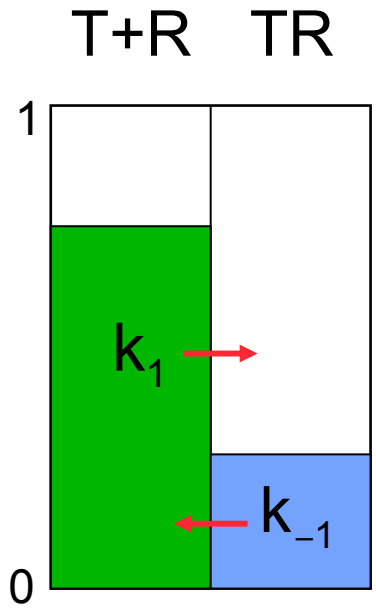
$$T + R \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} TR$$

T : Toxin

R : Receptor

k_1 : forward rate constant [$s^{-1}\ M^{-1}$]

k_{-1} : backward rate constant [s^{-1}]



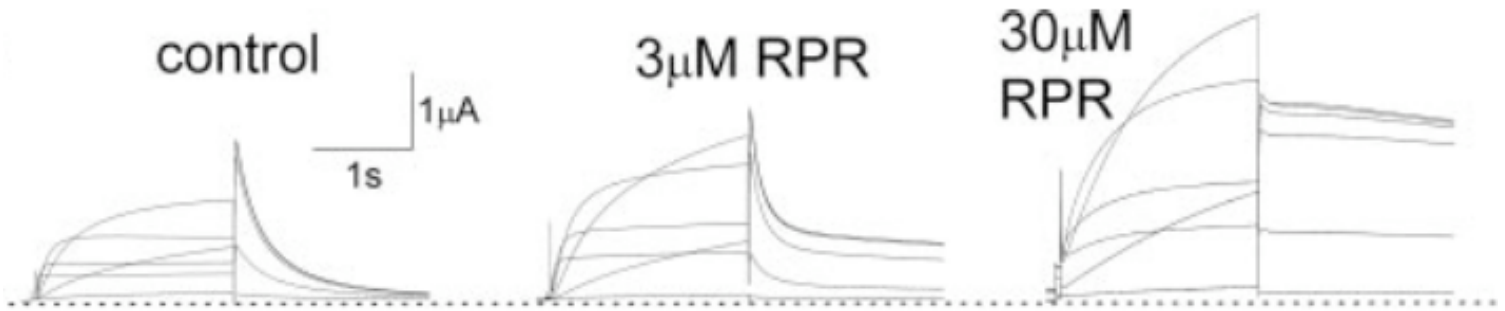
1:1 binding

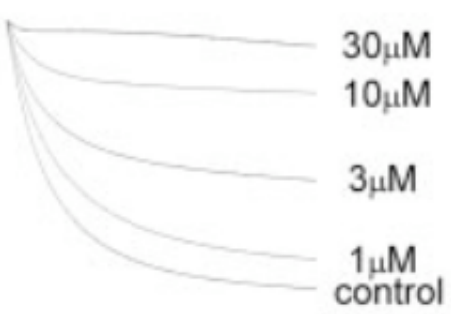
Dissociation constant [M] : $K_d = \frac{k_{-1}}{k_1} = \frac{[T][R]}{[TR]}$

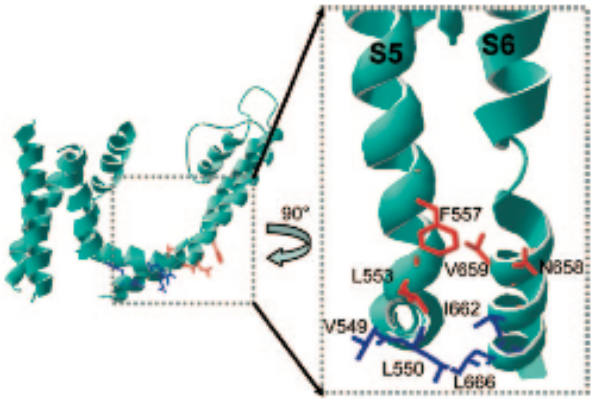
Fractional occupancy : $y = \frac{[TR]}{[TR]+[R]} = \frac{1}{1+K_d/[T]}$

Markovian Modeling of Drug Effects: Example

- RPR: Activator of hErg1 channel current
- Whole cell voltage clamp data measured in oocytes







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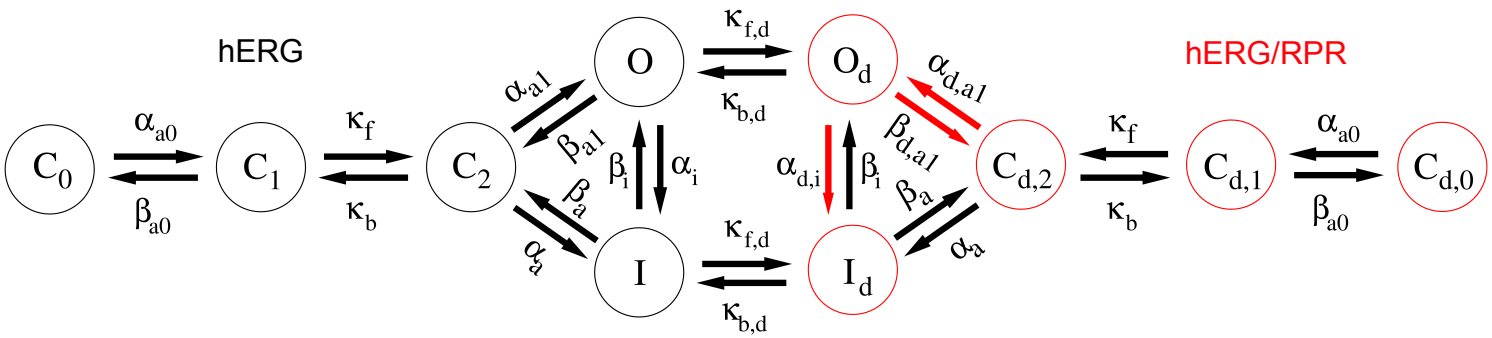
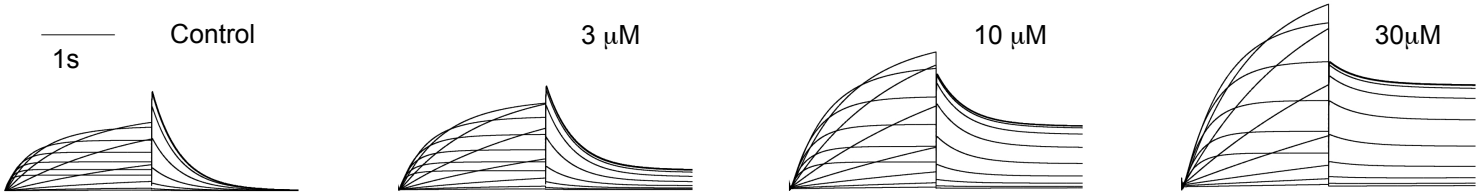
Markovian Modeling of Drug Effects: Example

Model includes two compartments connected by transitions between the open state O and inactivated state I:





(Perry et al. Proc Natl Acad Sci U S A, 2007)

Model Parameterization by Optimization Approaches

Commonly, model parameterization does not directly apply measurement data, but is based on numerical optimization procedures to minimize an error function.

Error function can be defined as the difference between features extracted from experimental and simulated data:

$$E = \sqrt{\sum_{i=1\ldots n} \left(\frac{\left\| f_{m,i} - f_{e,i} \right\|_2}{\left\| f_{e,i} \right\|_2} \right)^2}$$

f_e : Experimental data

f_m : Model data

$\left\| \ldots \right\|_2$: Euclidean norm

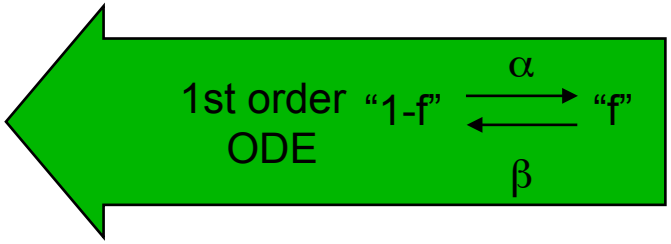
Numerical approaches:

- Steep descent
- Conjugate gradient
- Levenberg–Marquardt
- Stochastic approaches, e.g. particle swarm
- ...

Hodgkin-Huxley Channel Model: 1st Order ODE

$$I_{ion} = G_{ion,max} f\left(V_m - E_{ion}\right)$$

$$\frac{df}{dt} = \alpha_f\left(1 - f\right) - \beta_f f$$



$\alpha_f \equiv \alpha_f\left(V_m\right)$: Rate coefficient

$\beta_f \equiv \beta_f\left(V_m\right)$: Rate coefficient

f : Gating variable

$G_{ion,max}$: Maximal conductivity for ion

E_{ion} : Nernst voltage

V_m : Transmembrane voltage

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Analytical Solution of 1st Order ODE

$$\frac{df}{dt} = \alpha_f\left(1 - f\right) - \beta_f f \quad \longleftrightarrow \quad \frac{df}{dt} = \frac{f_\infty - f}{\tau_f}$$

Time constant : $$\tau_f = \frac{1}{\alpha_f + \beta_f}$$

Steady – state value : $$f_\infty = \frac{\alpha_f}{\alpha_f + \beta_f}$$

Response to step : $$f\left(t\right) = f_\infty - \left(f_\infty - f_0\right)e^{-\frac{t}{\tau_f}}$$

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Markov Models: System of 1st Order ODEs

$$\frac{d}{dt}P = QP$$

N-dimensional system of 1st order ODEs

with the N states $P = \begin{pmatrix} p_1 \\ \vdots \\ p_N \end{pmatrix}$

and the matrix $Q = \begin{pmatrix} q_{11} & \cdots & q_{1N} \\ \vdots & \ddots & \vdots \\ q_{N1} & \cdots & q_{NN} \end{pmatrix}$

CVRTI

Analytical Solution of Markov Model

$$P(t) = P(0)e^{Qt}$$

$$e^{Qt} = 1 + Qt + \frac{(Qt)^2}{2!} + \frac{(Qt)^3}{3!} + \ldots$$

$$P(t) = P_\infty + P(0)\sum_{i=2}^{k} A_i \, e^{-\frac{t}{\tau_i}}$$

(Colquhoun and Hawkes, chap. 20, Single-Channel Recording, eds. Sakmann and Neher)

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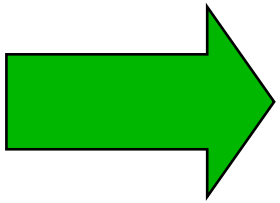
Numerical Solution of Systems of ODEs

- "Numerical integration"
- Necessary for solving ODEs, which do not have analytical solutions
- ODEs of n-th order can be reduced to set of 1st order ODEs

$$\frac{\partial^2 u}{\partial t^2} + q(t)\frac{\partial u}{\partial t} = r(x)$$

2nd order ODE



$$\frac{\partial u}{\partial t} = z(x)$$

$$\frac{\partial z}{\partial t} = r(x) - q(t)z(x)$$

System of 1st order ODEs

Convergence of Numerical Method

$$\lim_{h \to 0} \max_{n=0,1,\ldots,[d/h]} \left\| u_{n,h} - u(t_n) \right\| = 0$$

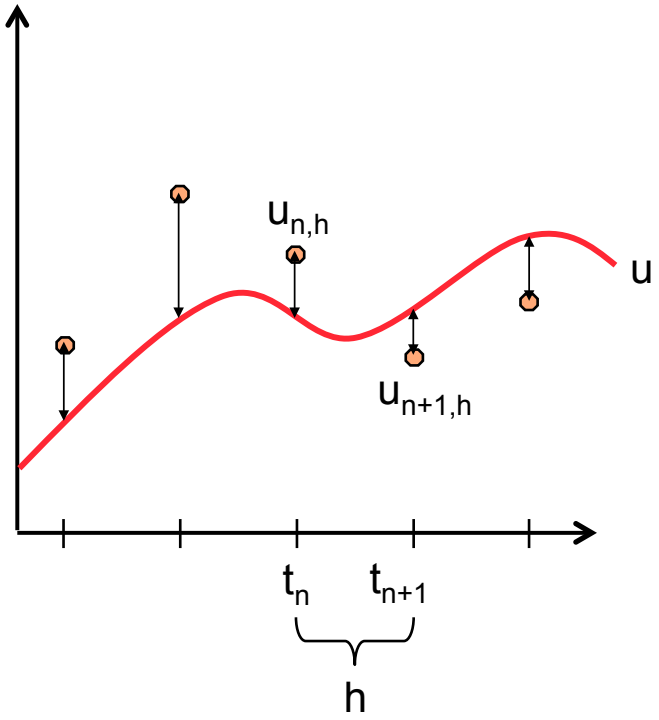
h : step size

$u_{n,h}$: n - th solution with step size h

u : exact solution function

d : duration of integration

t_n : time associated with time step n



Numerical Solution of ODEs

Procedure

Discretization: $\frac{\partial u}{\partial t} \Rightarrow \frac{\Delta u}{\Delta t}$

Choose appropriate step length Δt: Distance between t_n and t_{n+1}
Criteria: numerical error and computational demand

Numerical Methods

- **Euler Method**
- **Runge-Kutta Method 2. Order**
- **Runge-Kutta Method 4. Order**
- Richardson-Extrapolation, Bulirsch-Stoer Method
- Predictor-Corrector Methods
- …

Euler Method

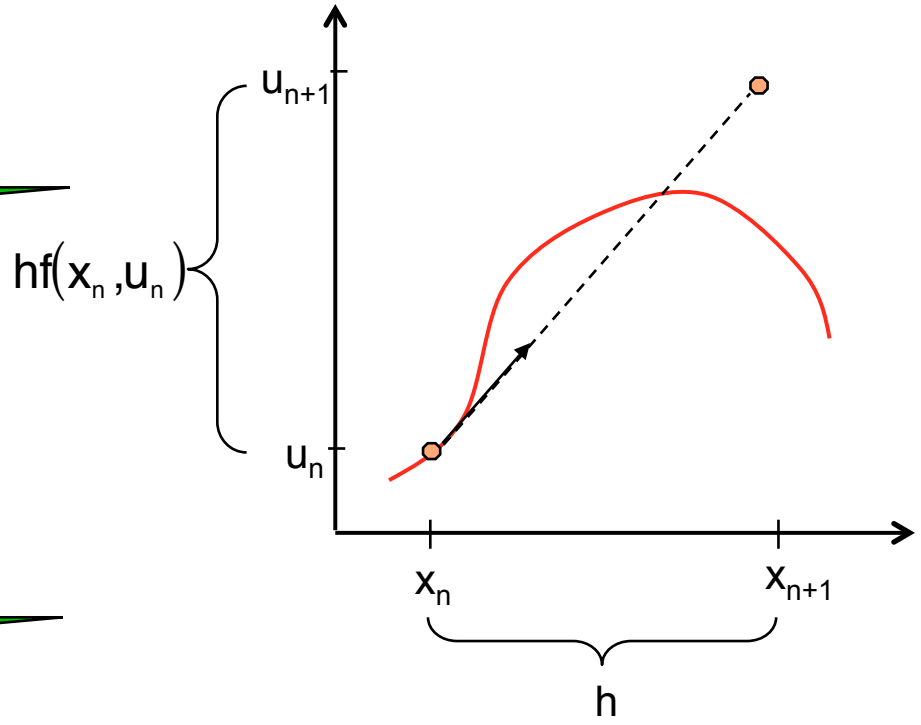
$$\frac{\partial u}{\partial x} = f(x,u)$$

Finite Difference Approximation

$$\frac{u_{n+1} - u_n}{x_{n+1} - x_n} = f(x_n,u_n)$$

Rewriting

$$u_{n+1} = u_n + h\, f(x_n,u_n)$$



Euler Method: Example 2-State Markov Model

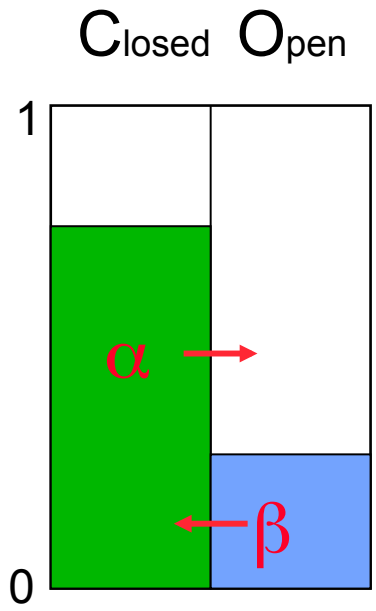
$$\frac{dO}{dt} = -\alpha O + \beta C \qquad \frac{dC}{dt} = -\beta C + \alpha O$$

Finite Difference Approximation

$$\frac{O_{n+1} - O_n}{t_{n+1} - t_n} = -\alpha O_n + \beta C_n \qquad C_n = 1 - O_n$$

Rewrite

$$O_{n+1} = O_n + h\left(-\alpha O_n + \beta\left(1 - O_n\right)\right) \qquad C_{n+1} = 1 - O_{n+1}$$



Runge-Kutta Method 2nd Order

$$\frac{\partial u}{\partial x} = f(x,u)$$

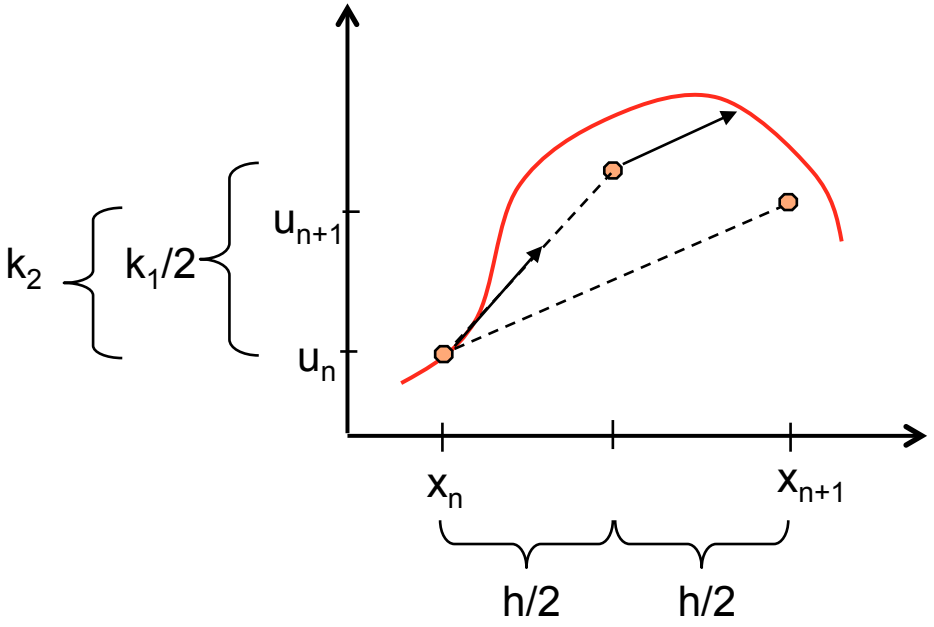
Discretization

$$k_1 = h f(x,u_n)$$

$$k_2 = h f\left(x_n + \frac{1}{2}h, u_n + \frac{1}{2}k_1\right)$$

Step

$$u_{n+1} = u_n + k_2$$



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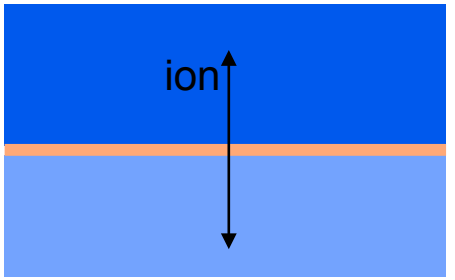
Runge-Kutta Method 2nd Order: Example

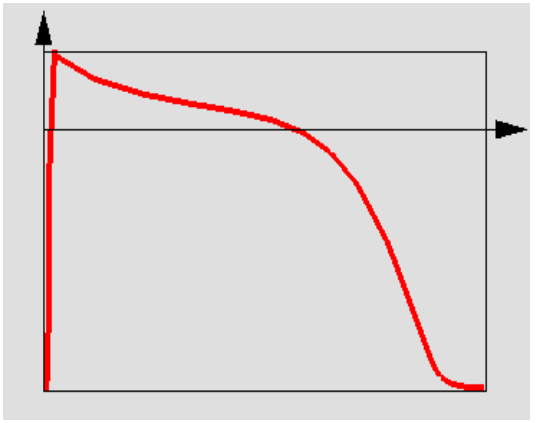
$$\frac{dV_m}{dt} = I_{stim}(t) - \frac{1}{C_m} I_{ion}(t, V_m)$$



Discretization

$$k_1 = \Delta t \left(I_{stim}(t_n) - \frac{1}{C_m} I_{ion}(t_n, V_n) \right)$$

$$k_2 = \Delta t \left(I_{stim}(t_n + \frac{h}{2}) - \frac{1}{C_m} I_{ion}(t_n + \frac{h}{2}, V_n + \frac{k_1}{2}) \right)$$



Step

$$V_{n+1} = V_n + k_2$$

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Runge-Kutta Method 4th Order

$$\frac{\partial u}{\partial x} = f(x,u)$$

Discretization

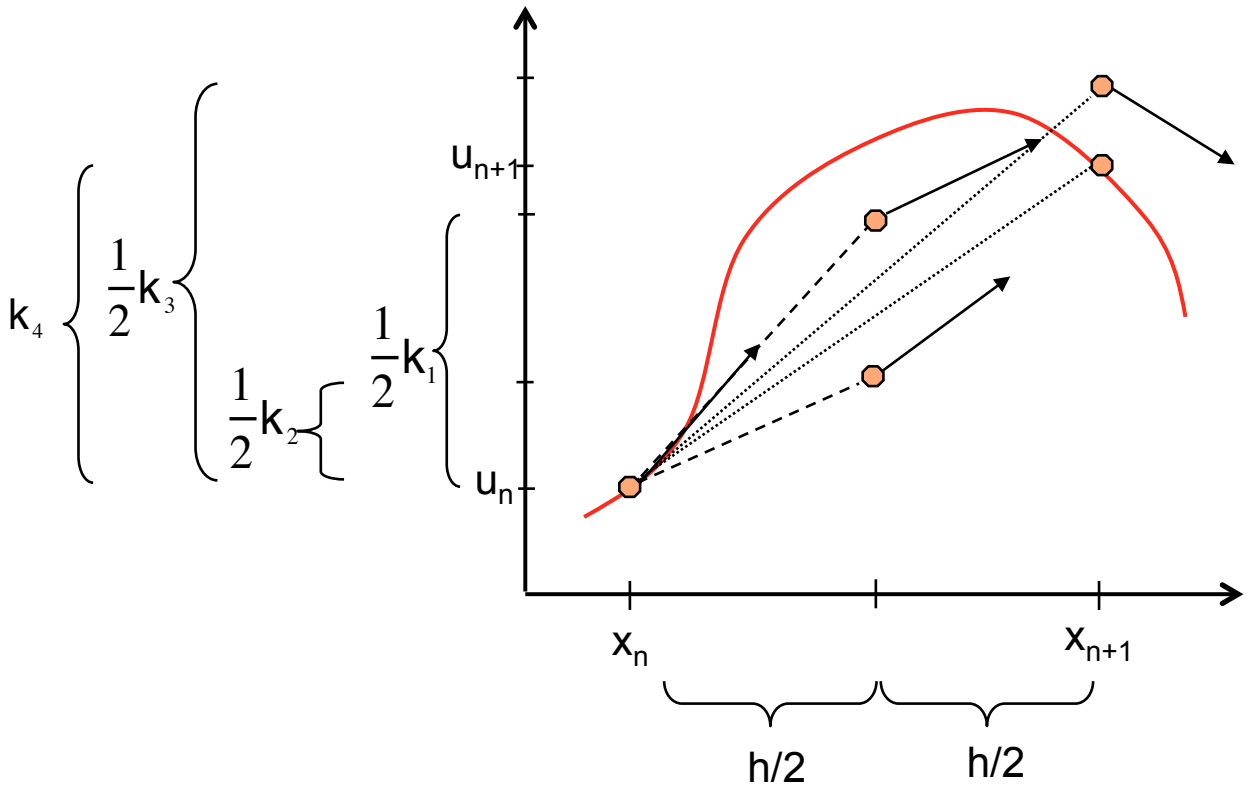
$$k_1 = h\,f(x,u_n) \qquad k_2 = h f\left(x_n + \frac{1}{2}h, u_n + \frac{1}{2}k_1\right)$$

$$k_3 = h f\left(x_n + \frac{1}{2}h, u_n + \frac{1}{2}k_2\right) \qquad k_4 = h\,f(x_n + h, u_n + k_3)$$

Step

$$u_{n+1} = u_n + \frac{k_1}{6} + \frac{k_2}{3} + \frac{k_3}{3} + \frac{k_4}{6}$$

Runge-Kutta Method 4th Order: Example



Group Work

Solve manually applying some steps of the Euler method:

$$\frac{dO}{dt} = \alpha\,(1 - O) - \beta\,O$$

with $\alpha = 10/\mathrm{s}$, $\beta = 1/\mathrm{s}$ and $O(0) = 0.5$

Choose an appropriate time step *h*! Motivate your choice.

Software Tools and Languages

OpenCell
- open source tool based on Mozilla
- model editing, simulation and visualization

JSim
- Java-based
- model building, simulation and analysis
- imports CellIML and SBML

Genesis
- C/X11
- model building, simulation and analysis

CellML
- open standard based on XML markup language
- model storage, exchange and integration

System Biology Markup Language (SBML)
- open standard based on XML markup language
- model storage, exchange and integration

Ion channel models are significant subset of models handled!

CellML/MathML: Sodium Channel Definition

Component: sodium_current

E_Na=RT/Fln(Na_o/Na_i)

i_Na=g_Nam3hj(V−E_Na)

Component: sodium_current_m_gate

m_infinity=1/(1+e(V+45)/−6.5)

tau_m=0.00136/(0.32(V+47.13)/(1−e−0.1(V+47.13))+0.08e−V/11)

dmd time =(m_infinity−m)/tau_m

Component: sodium_current_h_gate

h_infinity=1/(1+e(V+76.1)/6.07)

tau_h={0.0004537(1+e−(V+10.66)/11.1)

if V≥−400.00349/(0.135e−(V+80)/6.8+3.56e0.079V+310000e0.35V) if

dhd time =(h_infinity−h)/tau_h

Component: sodium_current_j_gate

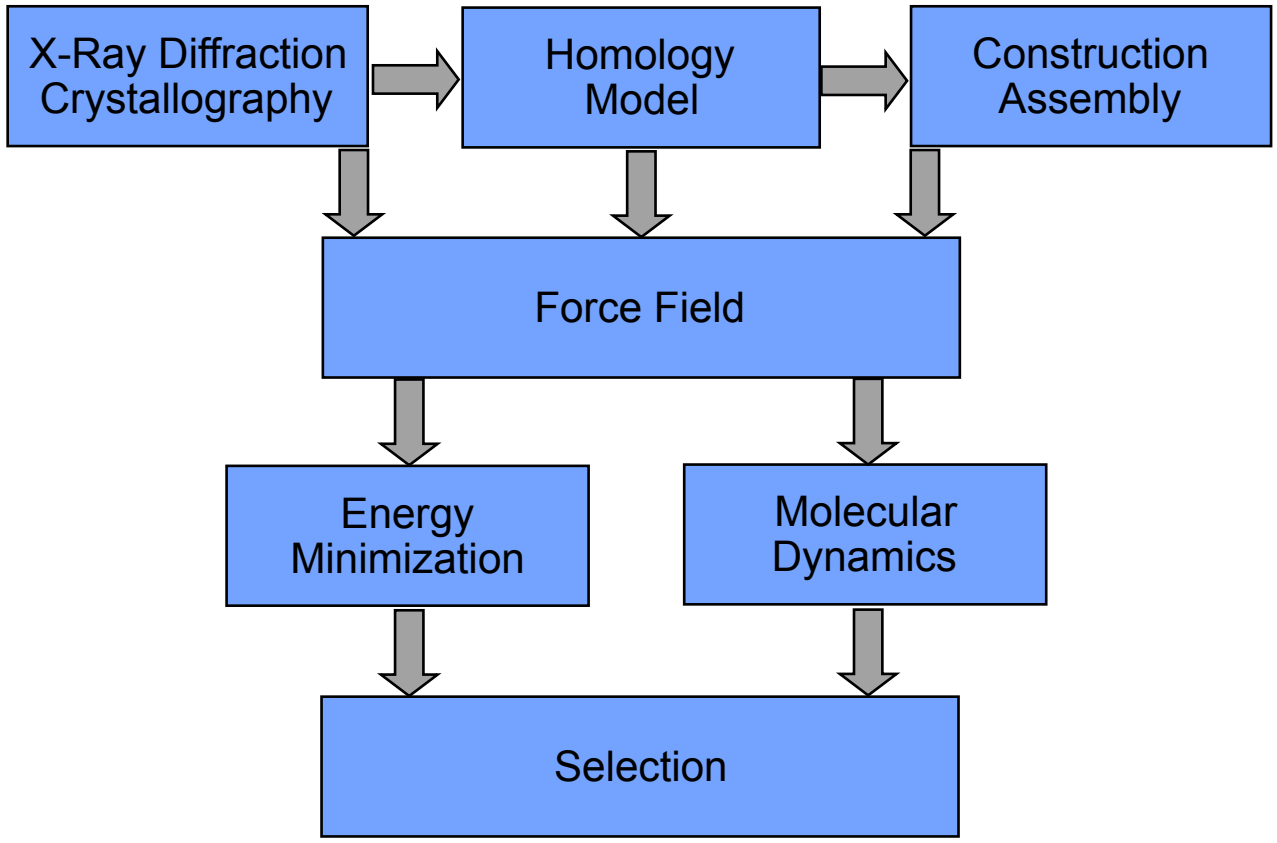
j_infinity=1/(1+e(V+76.1)/6.07)

tau_j={0.01163(1+e−0.1(V+32))/e−0.0000002535V

ifV≥−400.00349/((V+37.78)/(1+e0.311(V+79.23))(−127140e0.2444V−0.00003474e−0.04391V)+0.1212e−0.01052V/(1+e−0.1378(V+40.14))) if

djd time =(j_infinity−j)/tau_j

Molecular Modeling: Concepts



Molecular Mechanics Energy

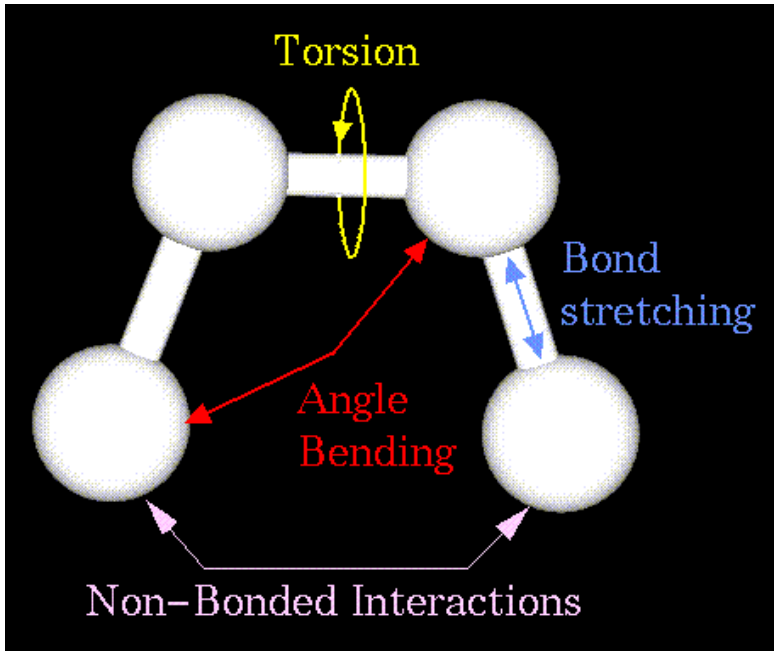
Approximation
Atoms ~ Spheres
Bonds ~ Springs

Energy defined as sum of bonded and non-bonded energies:

$$E = E_{stretch} + E_{bend} + E_{torsion} + E_{electrostatic} + E_{vanderWaals}$$

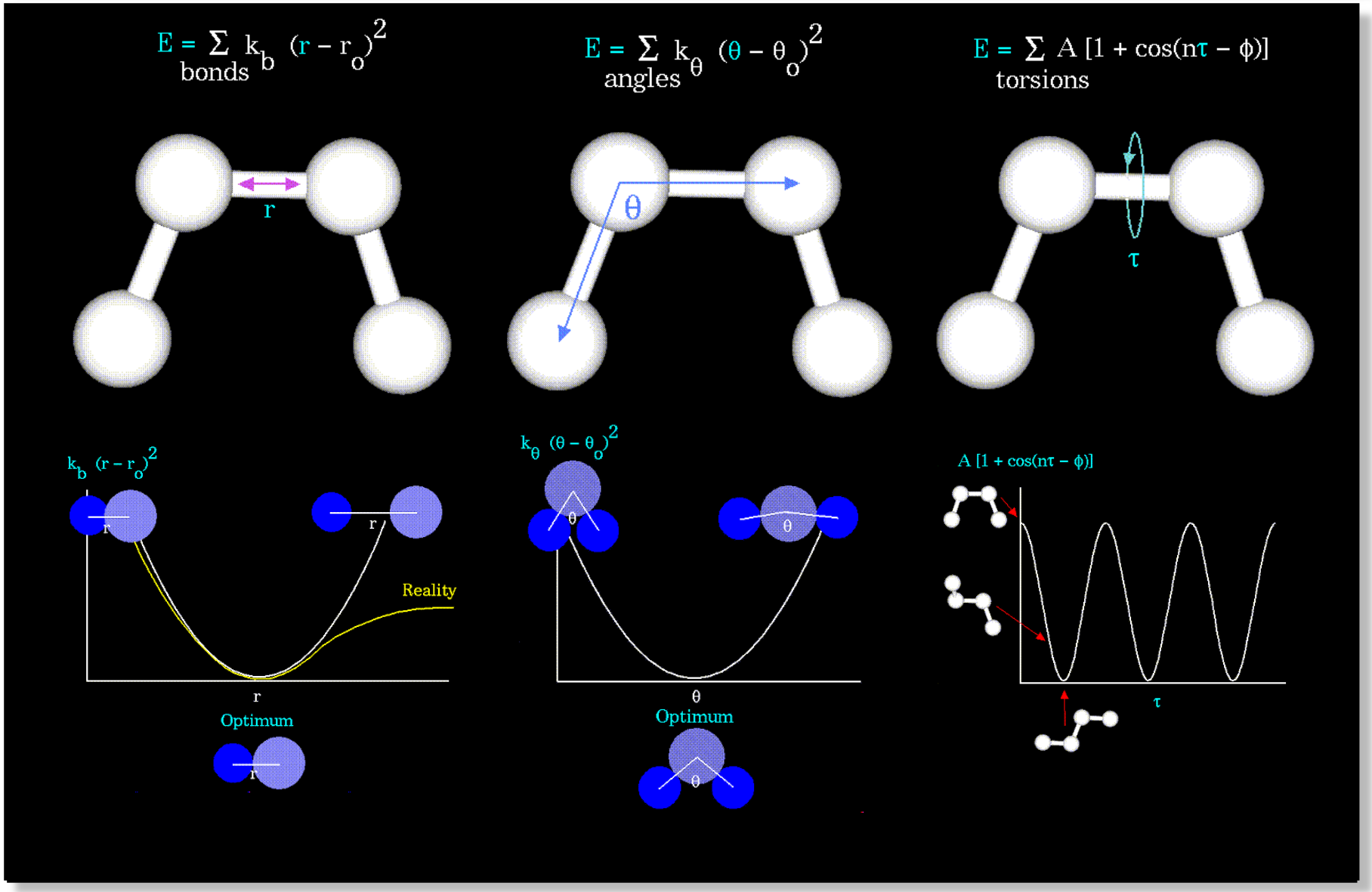
Force field defined by parameterized energy functions.

Various force fields have been defined for different applications.



(http://cmm.cit.nih.gov/modeling/guide_documents/molecular_mechanics_document.html)

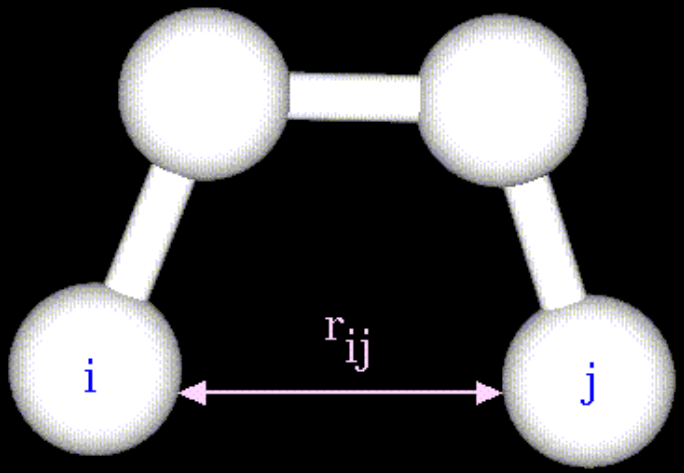
Stretch, Bend and Torsion Energies



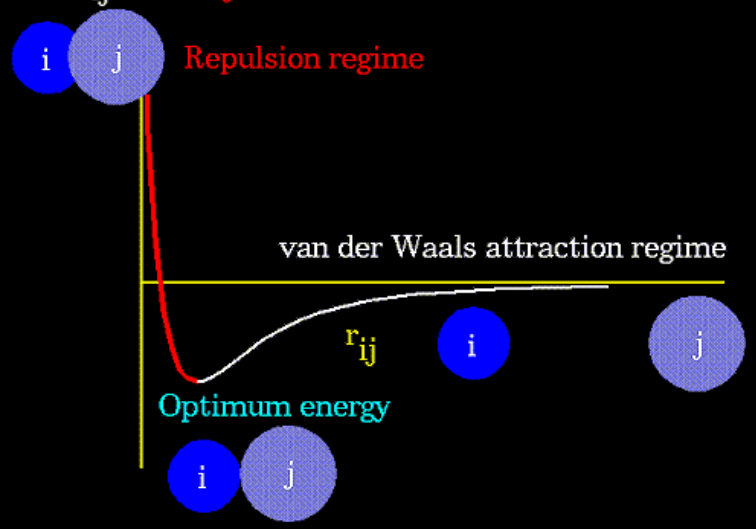
Non-Bonded Energy

$$E = \sum_i \sum_j \frac{-A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}} + \sum_i \sum_j \frac{q_i q_j}{r_{ij}}$$

van der Waals term Electrostatic term



$$- \frac{A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}}$$



Homology Modeling

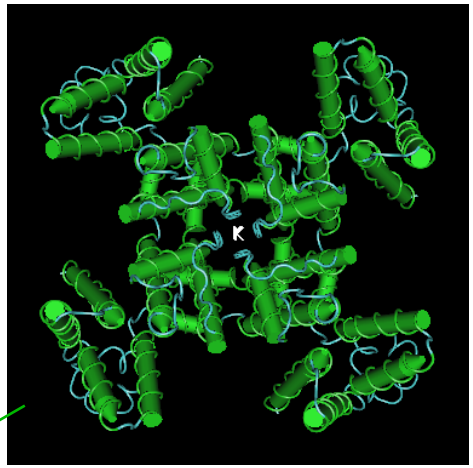
Motivation: Structure of many proteins is unknown!

Approach: Annotation of template protein structure with target amino acid sequence

Quality of annotated structural model is dependent on quality of
- template protein structure
- sequence alignment

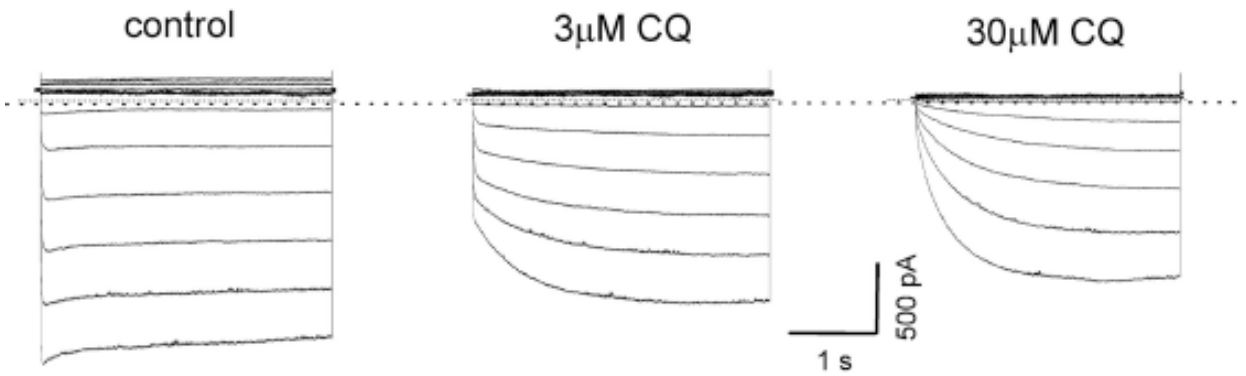
Templates for ion channel models
- KcsA, K^+ channel, Streptomyces lividans (bacterium)
- MthK, Ca^{2+} gated K^+ channel, Methanobacterium autotrophicum
- Voltage gated K^+ channel, Escherichia coli (bacterium)
- MscS, voltage modulated and mechanosensitive channel, Escherichia coli (bacterium)
- MscL, mechanosensitive channel, Mycobacterium tuberculosis
- KirBac1.1, inward rectifier K^+ channel, Burkholderia pseudomallei
- Kir2.1, inward rectifier K^+ channel, Mus musculus (mouse)
- Kir3.1, G-protein sensitive inward rectifier K^+ channel, Mus musculus (mouse)
- Kv1.2, voltage gated K^+ channel, Shaker family, rattus norvegicus

...



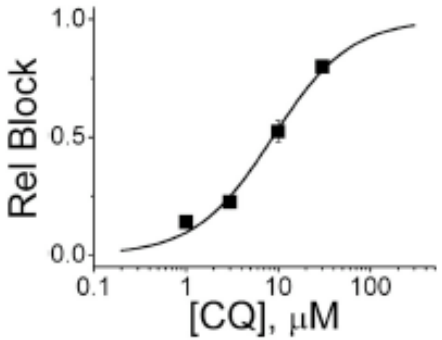
(http://www.ncbi.nlm.nih.gov/sites/entrez?db=structure)

Modeling of Drug Binding: Measurements

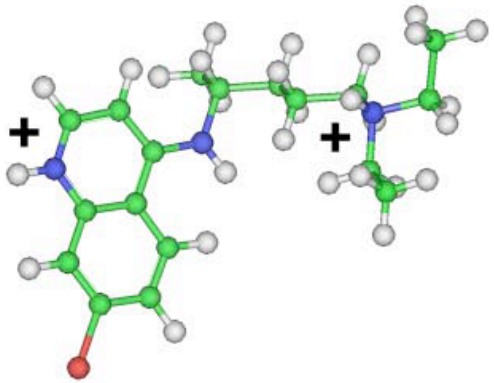


Chloroquine blocks

Kir2.1 currents!

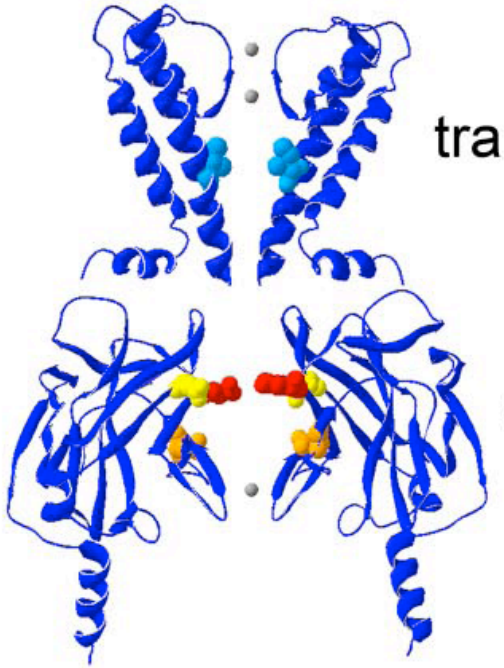


Modeling of Drug Binding: Structure



Chloroquine

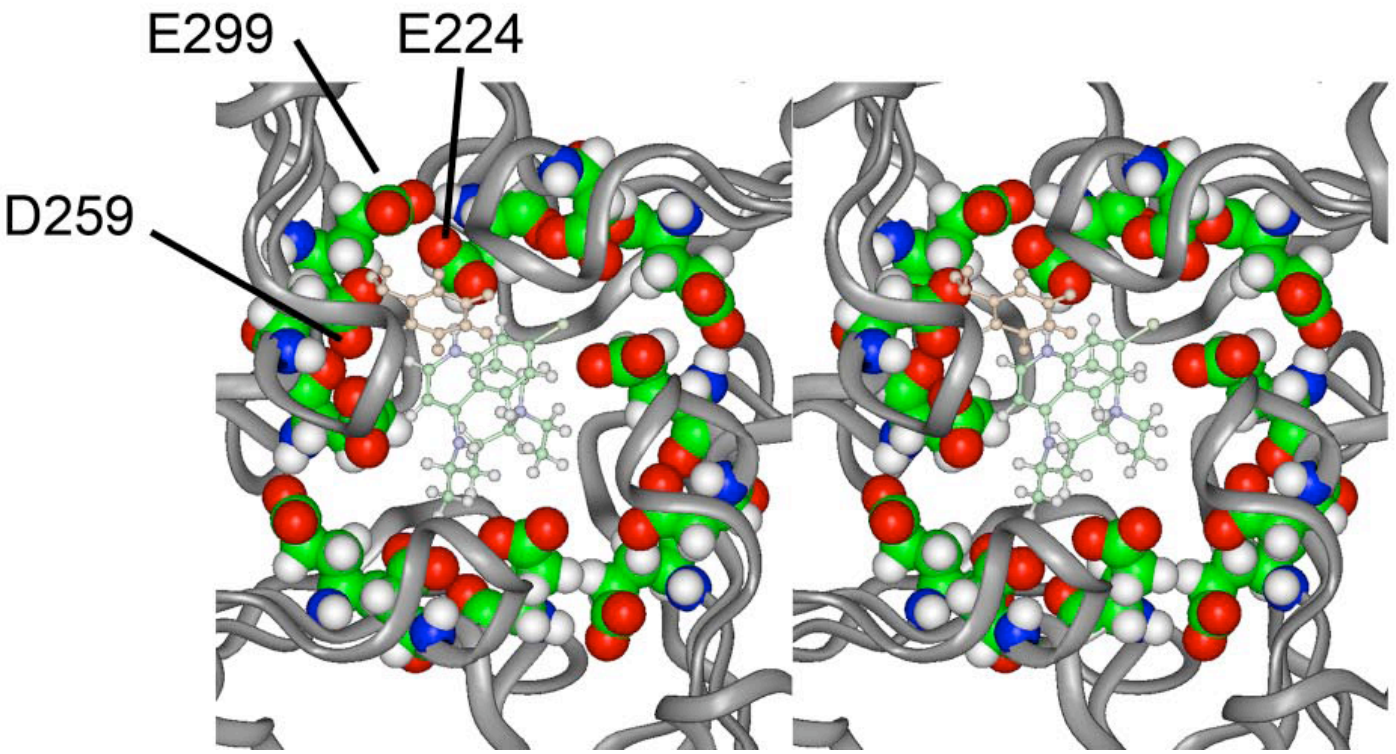
(malaria prophylaxis and treatment)



Structural model of Kir2.1

(Rodríguez-Menchaca et al. Proc Natl Acad Sci U S A, 2008)

Modeling of Drug Binding: Docking



Modeling suggests that chloroquine blocks Kir2.1 channels by plugging the cytoplasmic pore region

Group Work

Suggest modeling approaches which are intermediate the Markovian and molecular modeling. What types of equations are these based on?

Summary

- Modeling of Mutations
- Modeling of Drug Effects
- Model Parameterization
- Solution Methods
- Software Tools
- Molecular Modeling
  - Background
  - Homology
  - Drug Binding