Structure and dynamics of proteins

Tamás Hegedűs

tamas.hegedus@hegelab.org

Dept. of Biophysics and Radiation Biology

Importance of protein dynamics

The atomic level basis of a disease…
The shape of a drug binding site…

There is no single structure
but a conformational ensemble at 37°C

Importance of computational modelling

Atomic level information on motions

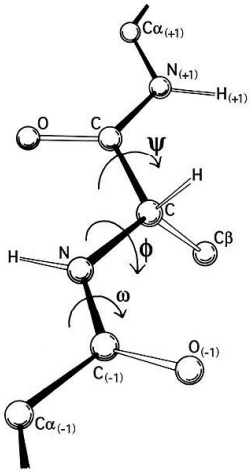
Experiments usually do not provide atomic level information on events.

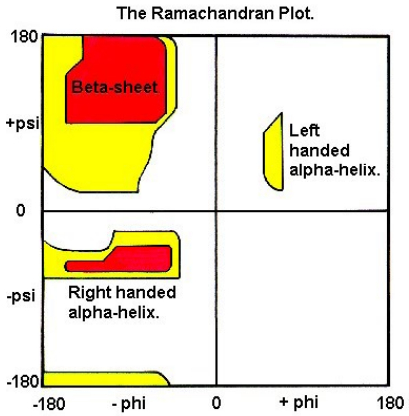
Exceptions e.g. NMR

Topics

- Introduction to protein structure and dynamics
- Characterization of protein structure
  - Prediction of secondary structure
  - Intrinsically disordered proteins
  - Tertiary structure

Secondary structure





wikipedia

Prediction of secondary structure

Using only available structures 60 %

Combining with sequence aligments 70-80 %

Implementations:
- neural networks,
- support vector machines,
- hidden Markov models, etc.

Scoring each positions
GOR4, HNN, Prof, JPred/JNet

Intrinsically Disordered Proteins

25 % of proteins are predicted disordered

Increased disorder with increased complexity
50 % of human proteins contains a disordered region with 30 a.a. or longer

Not fully random.

Structure flexibility.

No compact globular folding and residual structure

The paradigm
protein function needs a well-defined 3D structure
has changed.

Intrinsically Disordered Proteins

Benefits	Specificity and adaptation	
	Reversible transition between ordered/disordered states	
	Large binding surface	
	Fast binding	
Roles	Entropic chain:	inactivation of K+ channels
	Effectors:	peptide inhibitors
	Scavengers:	casein
	Assembly:	calmodesmon, F-actin
	Presentation:	phosphorylation and cleavage sites

Intrinsically Disordered Proteins

DisProt database: http://www.disprot.org

K. Dunker – Indiana University

Péter Tompa, Lajos Kalmár, Zsuzsa Dosztányi – Institute of Enzymology

Disorder prediction

Learning algorithms
Based on disordered sequences in the PDB database

Disopred2

Predicting interaction energies

IUPred.enzim.hu

IUPred

For an existing 3D structure:

$$E_{calculated} = \sum_{i,j} M_{ij} C_{ij}$$

There is only protein sequence:

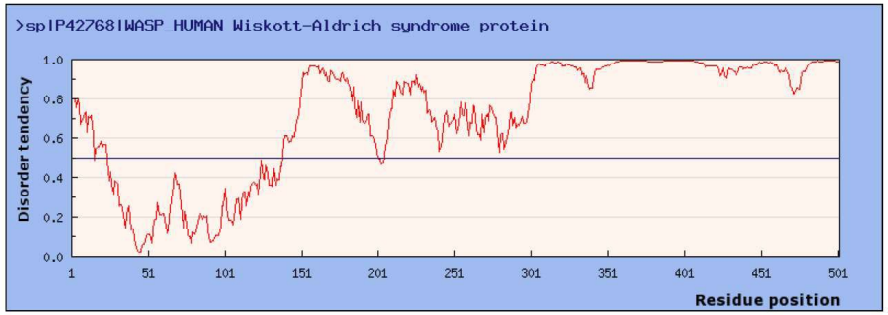
$$E_{estimated} = L \sum_{i,j} P_{ij} f_i f_j$$

Disorder level of an a.a.:

$$E_j^k = \sum_{i=1}^{20} P_{ij} f_i^k (w_0)$$

B. Mészáros, PhD dissertation

An output from IUPred



3D structure prediction

***Ab initio* folding**

- **CASP** (Critical Assessment of Techniques for Protein Structure Prediction)
- **constraints from experiments**

Homology modelling

- **conserved sequence == conserved structure**
- **> 30% similarity**
- **most important: the sequence alinement**

Homology modelling

- Searching a template
- Sequence alignment
- Modelling
- Energy minimization

BLOSUM (BLOcks of Amino Acid SUbstitution Matrix) matrix is a substitution matrix

	Ala	Arg	Asn	Asp	Cys	Gln	Glu	Gly	His	Ile	Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val
Ala	4																			
Arg	-1	5																		
Asn	-2	0	6																	
Asp	-2	-2	1	6																
Cys	0	-3	-3	-3	9															
Gln	-1	1	0	0	-3	5														
Glu	-1	0	0	2	-4	2	5													
Gly	0	-2	0	-1	-3	-2	-2	6												
His	-2	0	1	-1	-3	0	0	-2	8											
Ile	-1	-3	-3	-3	-1	-3	-3	-4	-3	4										
Leu	-1	-2	-3	-4	-1	-2	-3	-4	-3	2	4									
Lys	-1	2	0	-1	-3	1	1	-2	-1	-3	-2	5								
Met	-1	-1	-2	-3	-1	0	-2	-3	-2	1	2	-1	5							
Phe	-2	-3	-3	-3	-2	-3	-3	-3	-1	0	0	-3	0	6						
Pro	-1	-2	-2	-1	-3	-1	-1	-2	-2	-3	-3	-1	-2	-4	7					
Ser	1	-1	1	0	-1	0	0	0	-1	-2	-2	0	-1	-2	-1	4				
Thr	0	-1	0	-1	-1	-1	-1	-2	-2	-1	-1	-1	-1	-2	-1	1	5			
Trp	-3	-3	-4	-4	-2	-2	-3	-2	-2	-3	-2	-3	-1	1	-4	-3	-2	11		
Tyr	-2	-2	-2	-3	-2	-1	-2	-3	2	-1	-1	-2	-1	3	-3	-2	-2	2	7	
Val	0	-3	-3	-3	-1	-2	-2	-3	-3	3	1	-2	1	-1	-2	-2	0	-3	-1	4

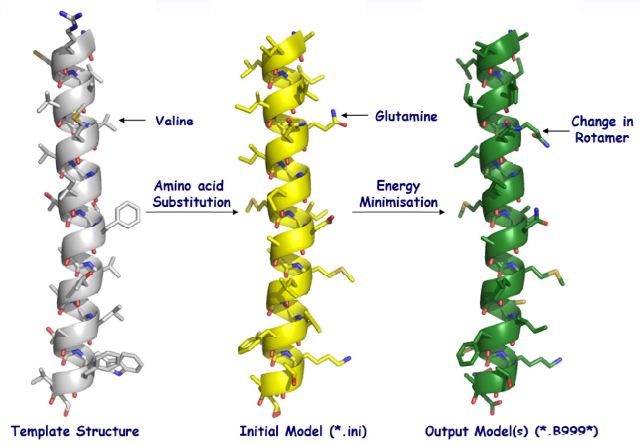
Basic Local Alignment Search Tool (BLAST)

Alignement – pl. ClustalW

```
CLUSTAL W (1.83) multiple sequence alignment

2HYD        ----------MIKRYLQFVK-----PYKYRIFATIIVGIIKFGIPMLIP
3B5X        ---------WQTFKRLWTYIR-----LYKAGLVVSTIALVINAAADTYMI
CFTR_HUMAN  MQRSPLEKASVVSKLFFSWTRPILRKGYRQRLELSDIYQIPSVDSADNLS
                          *    : :      *:  :  : *  : .      :
```

Homology modelling

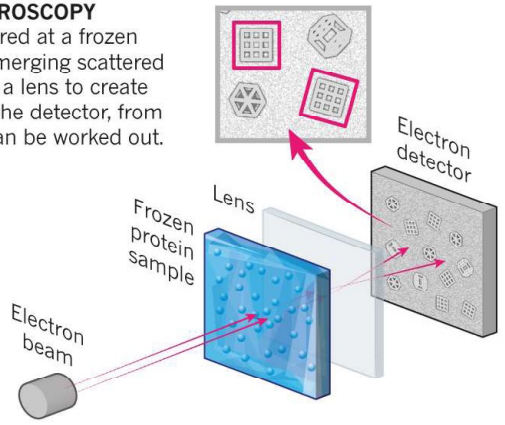


source: SBCB, Oxford, UK

Structure determination – „single particle"

Cryo-electron microscopy

CRYO-ELECTRON MICROSCOPY
A beam of electron is fired at a frozen protein solution. The emerging scattered electrons pass through a lens to create a magnified image on the detector, from which their structure can be worked out.

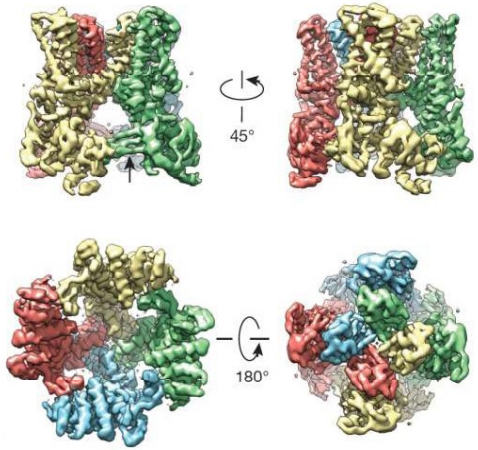


© nature

Ewen Callaway, Nature | News Feature
The revolution will not be crystallized: a new method sweeps through structural biology, 09 September 2015

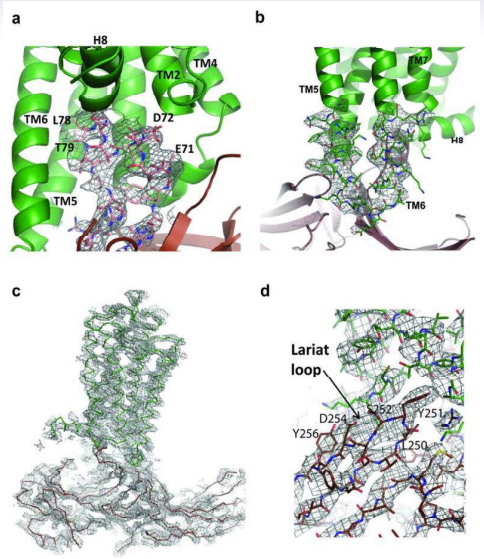
Structure determination – „single particle"

The TRPV1 channel detects the burn of chilli peppers, and this 3.4-Å structure is considered super-hot in the structural-biology world.



Structure determination – „single particle”

Free Electron Laser (FEL)

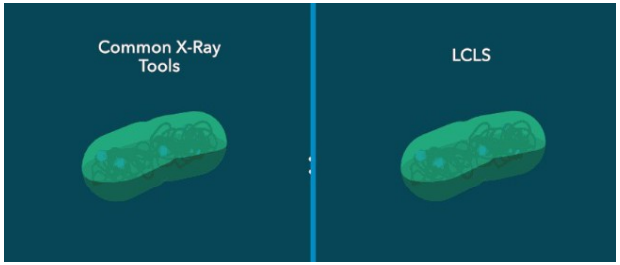


Nature. 2015 Jul 30;523(7562):561-7.

Crystal structure of rhodopsin bound to arrestin by femtosecond X-ray laser.

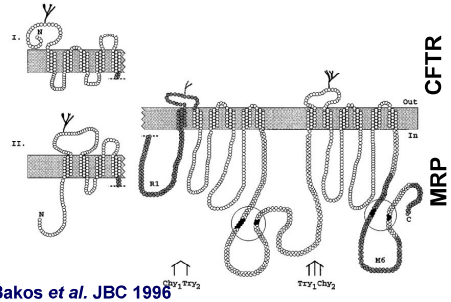
Structure determination – complete cell

Free Electron Laser (FEL)



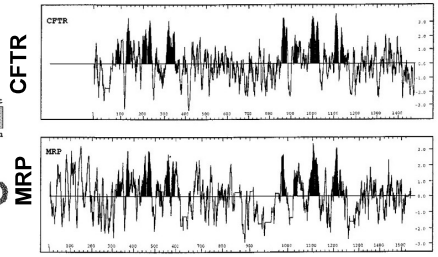
Membránfehérjék topológiája

MRP



Bakos *et al.* JBC 1996

Hidrofóbicitási görbék:



CFTR topológiája kísérletekből ismert

Chang et al. J Biol Chem. 1994 Jul 15;269(28):18572-5

Kísérletes topológia meghatározási módszerek:

- *tag* – felismerés
- Cys hozzáférhetőség

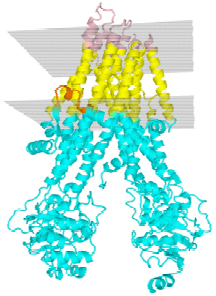
Prediction of membrane topology and TM helices

E.g. CCTOP.enzim.hu

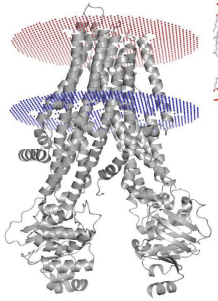
- **Based on sequence**
- **a.a. distribution in TMH and soluble regions**
- **Incorporation of experimental knowledge**
- **Integration of several predictors**

Prediction of TM helices based on structure

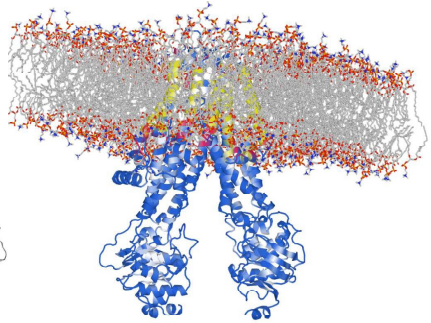
TMDET
PDBTM



PPM
OPM

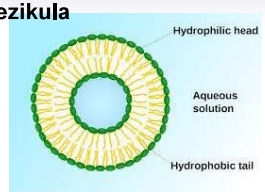


MemProtMD

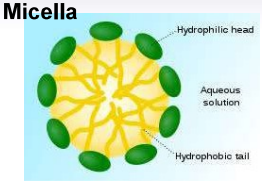


Membrane mimetics

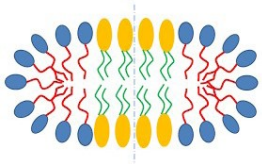
Vezikula



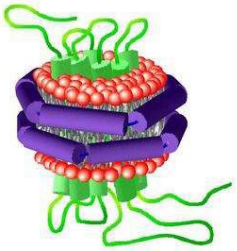
Micella



Bicella



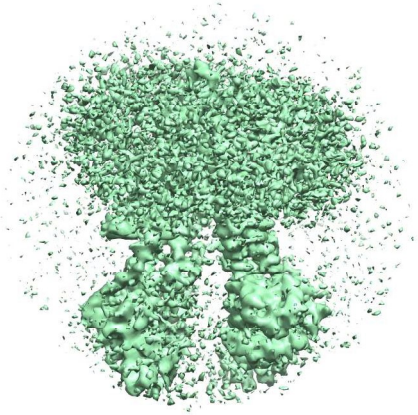
Nanodisc



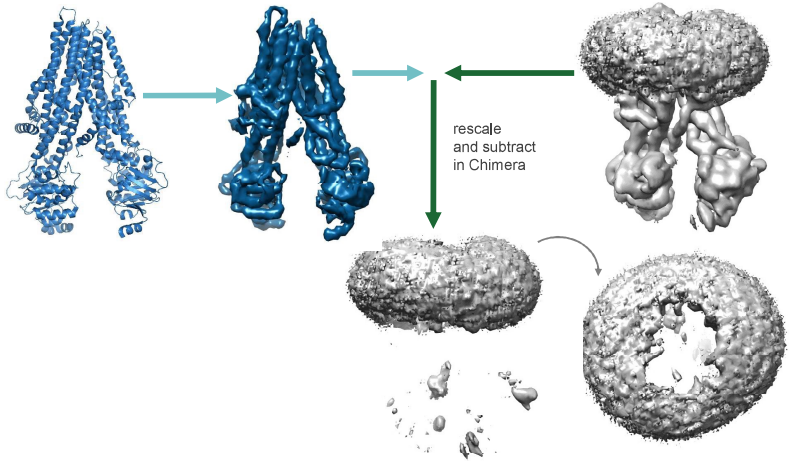
Amphipol

Membrane embedment data is in the electron density maps

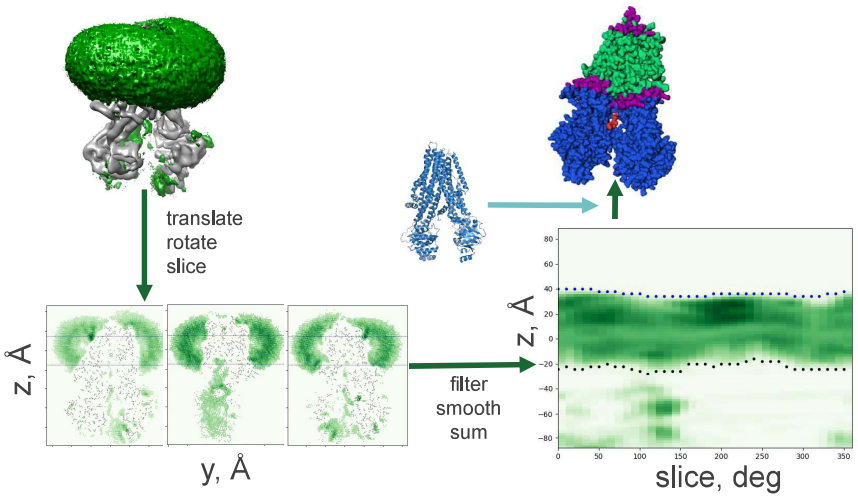
CFTR (PDBID: 5UAK) EMD



A membrane blob can be extracted from the electron density map



The MemBlob can be converted to membrane boundaries



http://memblob.hegelab.org

TOPICS

- **Protein structure**
- **Protein dynamics**
- **Protein folding**

Protein-protein interactions

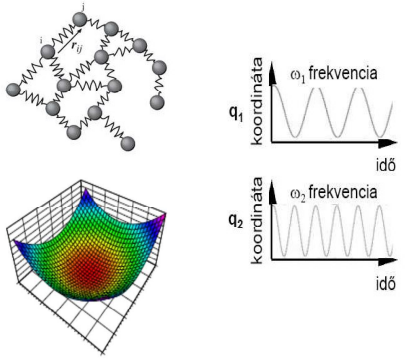
Docking of proteins – challenging (surface shape, dynamics)

PISA - Protein Interfaces, Surfaces and Assemblies
Molecular Dinamics

Methods for studying protein dynamics

Normal mode analysis

- harmonic potential
- analytic equation of motions
- normal modes



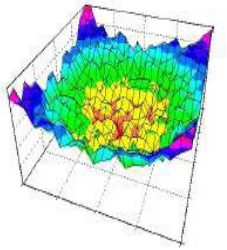
- Gaussian network model (GNM)
  mean squared displacements
  cross-correlations between fluctuations
- Anisotropic network model (ANM)
  Directionality by projection of motions to a mode space of N dimensions

Tools: http://prody.csb.pitt.edu

Methods for studying protein dynamics

Molecular dynamics

- realistic potential surface
- numerical integration of Newton's equations
- a system of interacting particles
- forces between the particles and their potential energies are calculated by using interatomic potentials (molecular mechanics force fields)
- output: trajectory



The force field

$$E_{prot} = W_{rot}E_{rot} + W_{atr}E_{atr} + W_{rep}E_{rep} + W_{solv}E_{solv} + W_{pair}E_{pair} + W_{mbenv}E_{mbenv} + W_{hbond}E_{hbond} - E_{ref}$$

$$E_{solv} = -\sum_{i}^{natom}\sum_{j>i}^{natom}\left\{\frac{2\Delta G_i^{free}}{\Lambda\pi\sqrt{\pi}\lambda_i r_{ij}^2}\exp\left(-d_{ij}^2\right)V_j + \frac{2\Delta G_j^{free}}{\Lambda\pi\sqrt{\pi}\lambda_j r_{ij}^2}\exp\left(-d_{ji}^2\right)V_i\right\}$$ Lazaridis (2003)

Lazaridis (1999)

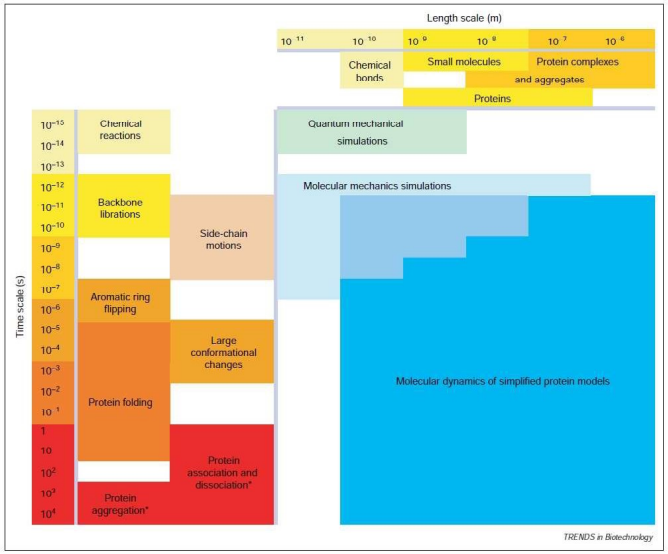
TABLE I. Solvation Parameters[†]

Atom types[a]	Volume	$\Delta G_i^{ref\,b}$	$\Delta G_i^{free\,c}$	$\Delta H_i^{ref\,b}$	$\Delta Cp_i^{ref\,d}$
C	14.7	0.000	0.00	0.000	0.00
CR	8.3	−0.890	−1.40	2.220	6.90
CH1E	23.7	−0.187	−0.25	0.876	0.00
CH2E	22.4	0.372	0.52	−0.610	18.60
CH3E	30.0	1.089	1.50	−1.779	35.60
CR1E	18.4	0.057	0.08	−0.973	6.90
NH1	4.4	−5.950	−8.90	−9.059	−8.80
NR	4.4	−3.820	−4.00	−4.654	−8.80
NH2	11.2	−5.450	−7.80	−9.028	−7.00
NH3	11.2	−20.000	−20.00	−25.000	−18.00
NC2	11.2	−10.000	−10.00	−12.000	−7.00
N	0.0	−1.000	−1.55	−1.250	8.80
OH1	10.8	−5.920	−6.70	−9.264	−11.20
O	10.8	−5.330	−5.85	−5.787	−8.80
OC	10.8	−10.000	−10.00	−12.000	−9.40
S	14.7	−3.240	−4.10	−4.475	−39.90
SH1E	21.4	−2.050	−2.70	−4.475	−39.90

The limitations of MD

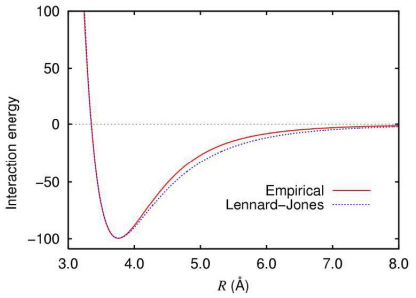
- time (computation time versus real time)
- calculation of the potential is the bottle-neck
- fs long integration steps
- „periodic boundary condition"
- solvent (explicit/implicit)

The time scale of various molecular events

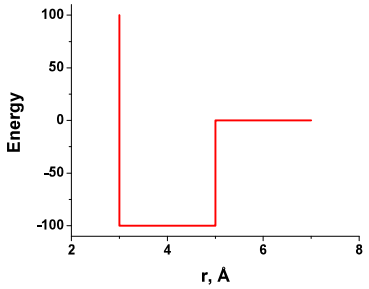


F. Ding and N.V. Dokholyan, TRENDS in Biotechnology, **23:**450 (2005)

Discrete Molecular Dynamics (DMD)



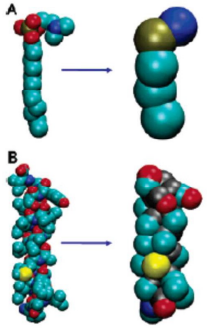
wikipedia

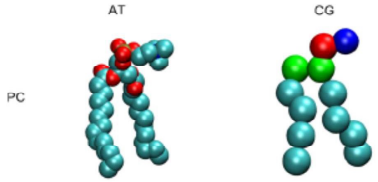


Ding, F., Dokholyan, N. V. PLoS Comput Biol 2:e85

$$\mathcal{V}(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] = \varepsilon\left[\left(\frac{R_{min}}{r}\right)^{12} - 2\left(\frac{R_{min}}{r}\right)^{6}\right]$$

Simplified coarse-grained models

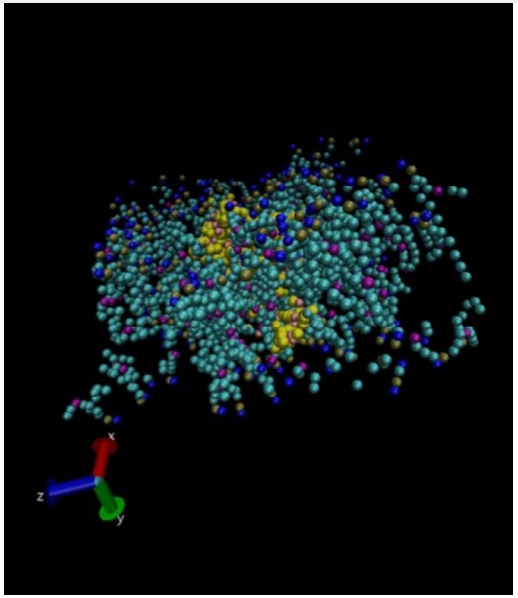




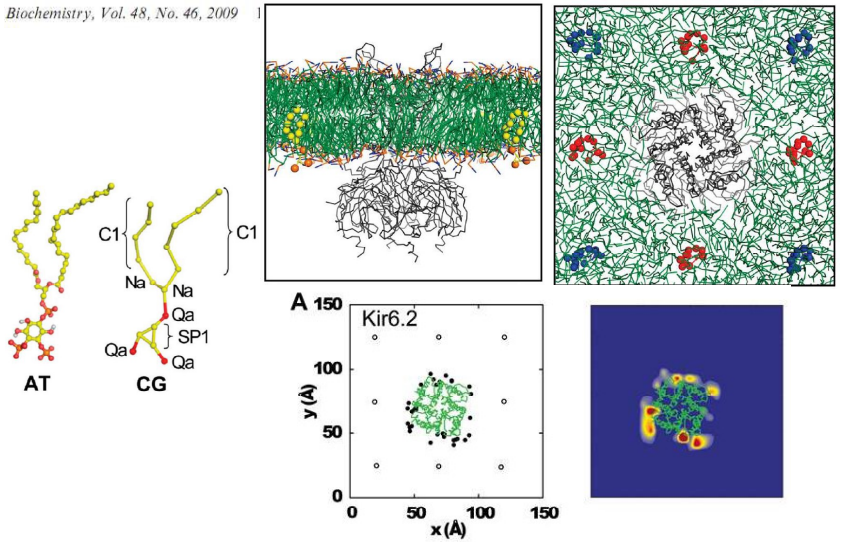
AT: atomistic, all-atom
CG: coarse grained

e.g. 2 bead or 4+ bead models for proteins
e.g. MARTINI CG force field

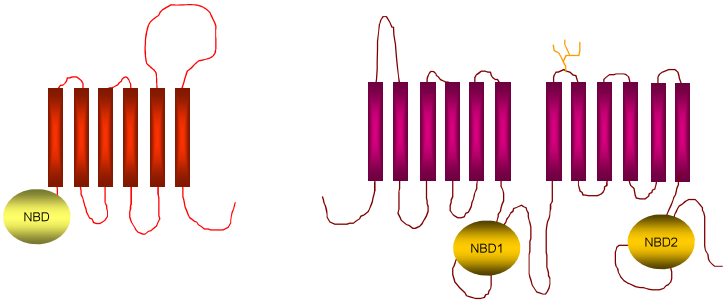
Membrane bilayer formation



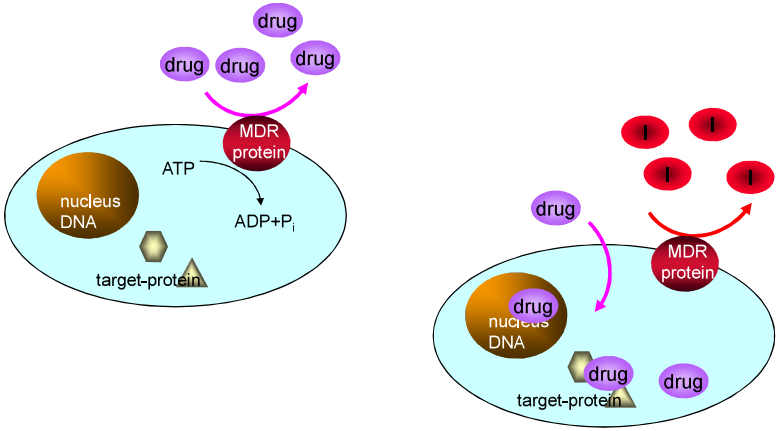
Binding of PIP2 to a Kir channel



ATP Binding Cassette (ABC) proteins

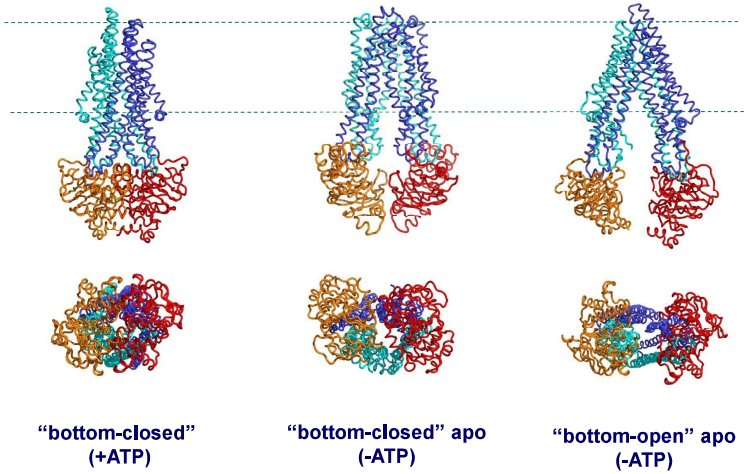


Multidrug resistance

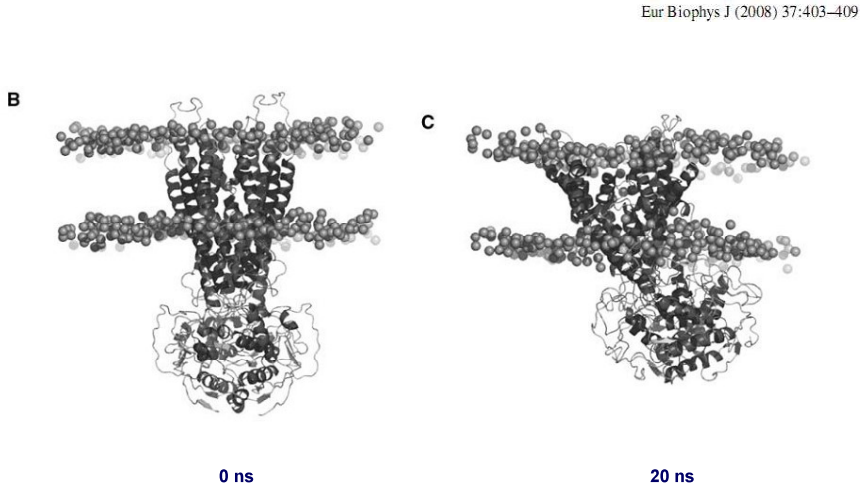


I: inhibitor

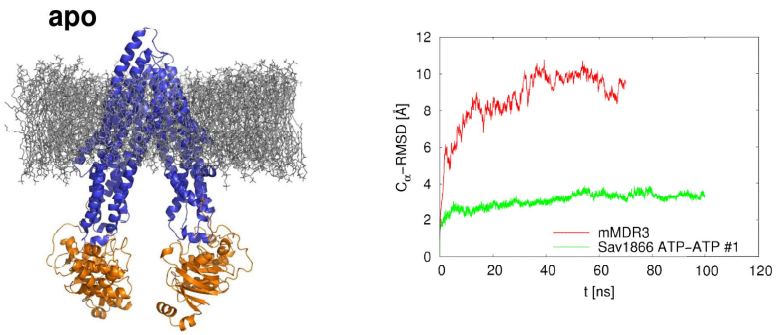
Conformation of ABC proteins



Stability of simulations

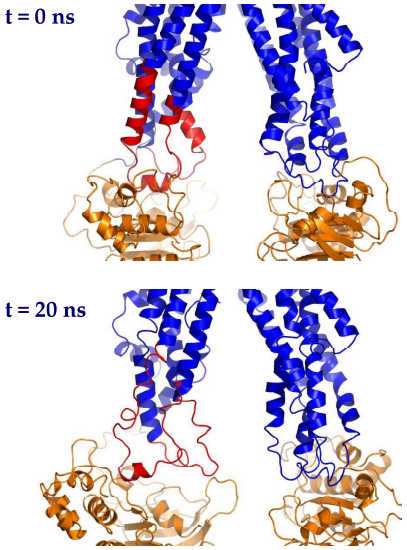


The bottom-open apo conformation is unstable



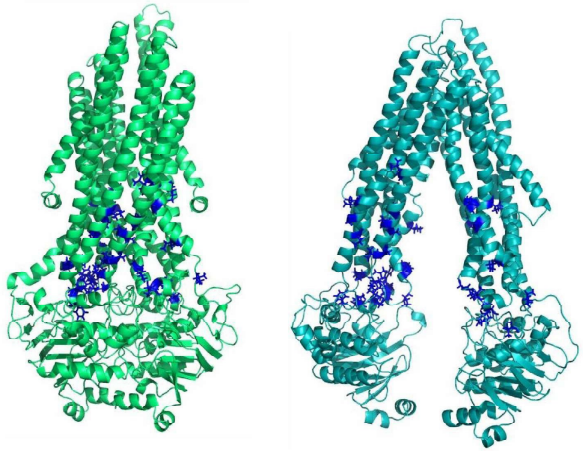
Gyimesi *et al*. BBA 2012

The bottom-open apo conformation is unstable



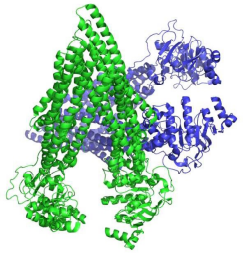
system	helical content
Sav1866 ATP/ATP #1	90.04%
hMDR1 holo	91.84%
hMDR1 apo	64.30%
mMDR3	63.13%

Hydrophobic amino acids are surface exposed

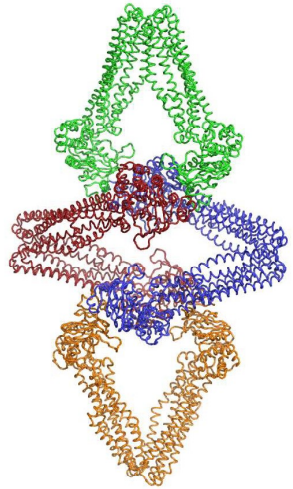


The content of the unit cell

mMDR3, PDBID:3G5U



MsbA, PDBID:3B5W

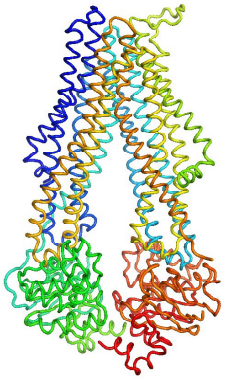


Simulating special and slow events

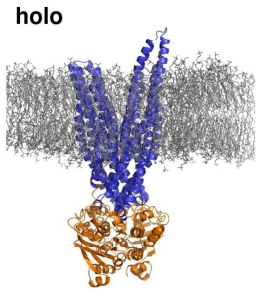
- How does ATP hydrolysis affect the protein dynamics?
  e.g. steered MD
- What is the transition pathway between the bottom-open and bottom-closed conformation?

  e.g. targeted MD, Metadynamics

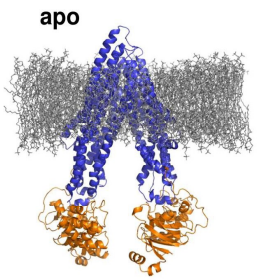
Targeted MD



Describing the transition using MD+ED



hMDR1 homology model
(3x100 ns)



hMDR1 homology model

MD trajectories

⇩

Essential Dynamics

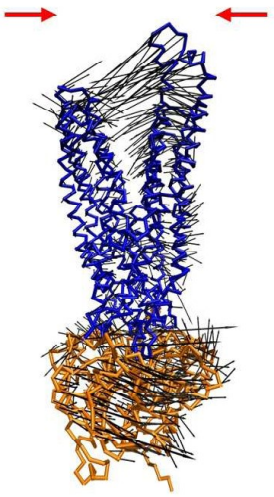
⇩

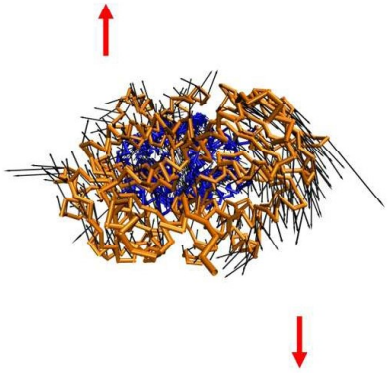
Selection of modes

⇩

Collective motions

Describing the transition using MD+ED



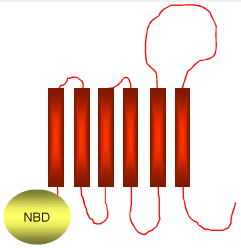


Calculating the correlation of motions

- Pearson correlation
- MI (mutual information)
- DiCC (distance correlation coefficient)

The complex example of ABCG2

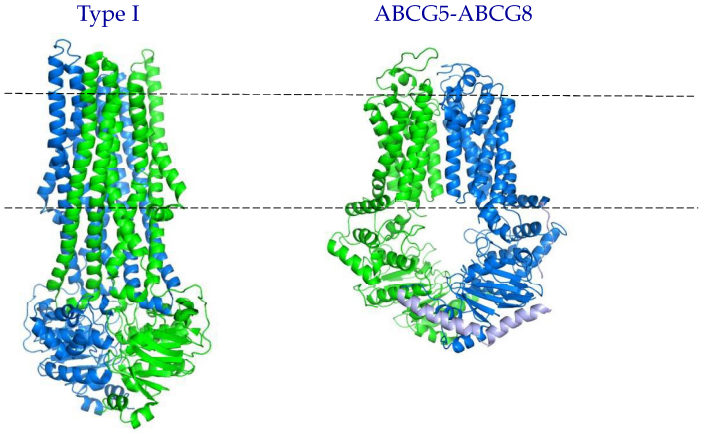
- Homology modelling of the structure (2016)
- Investigating the effect of mutations using MD
- Effect of cholesterol on function
- Identification of drug binding sites
- Describing the transport process by MD and METAD



Importance of ABCG2

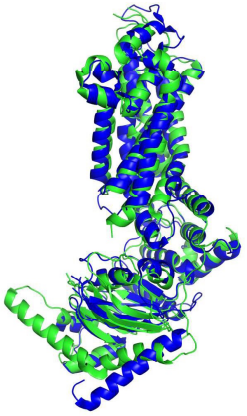
- Expressed in stem cells, tissue barriers, cancer cells
- Multidrug transporter of xenobiotics and endobiotics
  - antitumor agents
  - uric acid
- The Q141K variant exhibit decreased function and expression

The type II ABC exporter fold



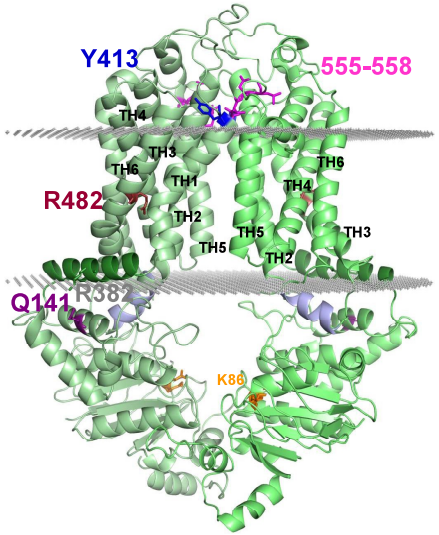
Homology modelling of ABCG2 based on ABCG5/G8

- Approx. 25% identity and 45% similarity
- Generation of a sequence alignment was ~trivial
- 100 models were built using Modeller
- The model with the best DOPE score was selected and used



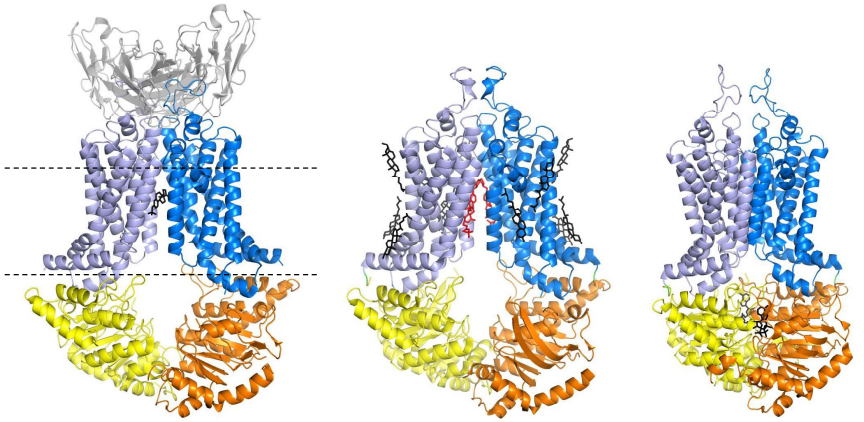
ABCG5-ABCG8
PDBID:5DO7

The ABCG2 model

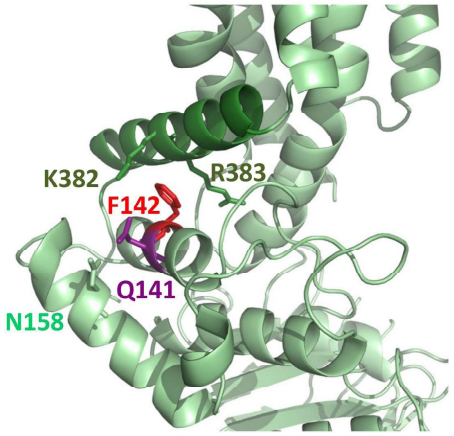


ABCG2 structures

K. Locher, ETH, Zurich



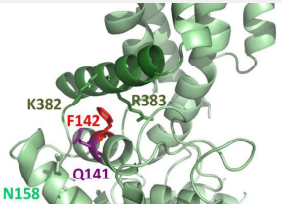
The Q141 position

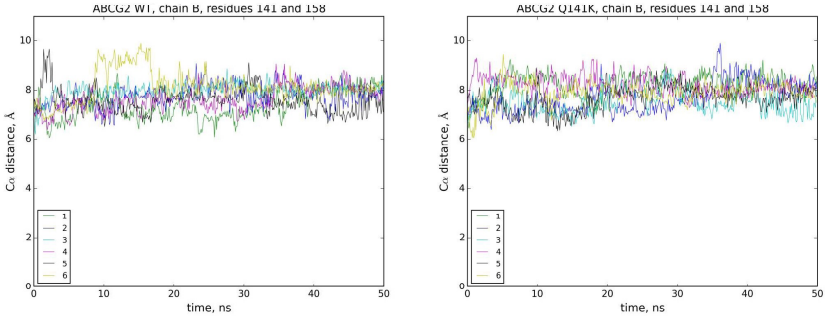


MD simulations

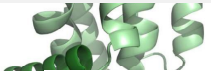
- The protein was embedded in POPC bilayer
- Optimizing the orientation of water, lipids, amino acid side chains:
  - energy minimization
  - equilibration
  - minimal backbone motions (position constrains)
- Production run
  - no constraints
  - 50 ns x 6 = 300 ns
- Comparing WT és mutants (e.g. Q141K, R482G)

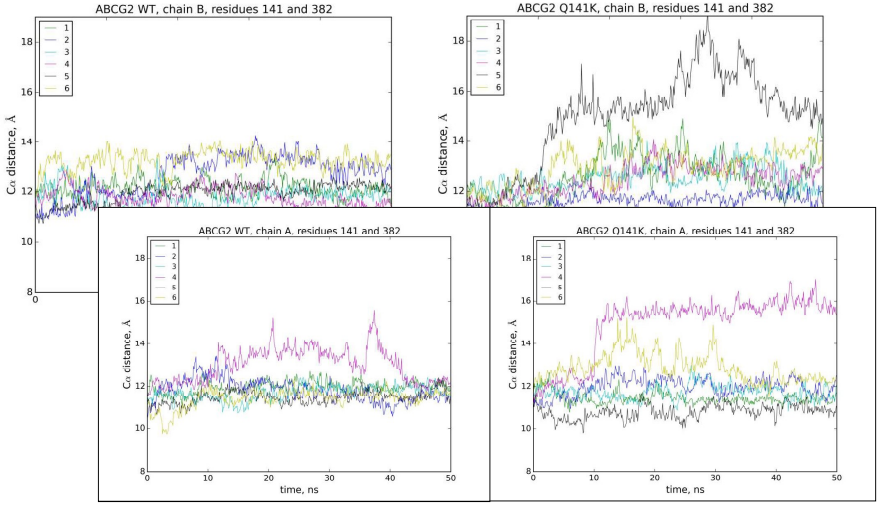
The effect of Q141K on protein dynamics



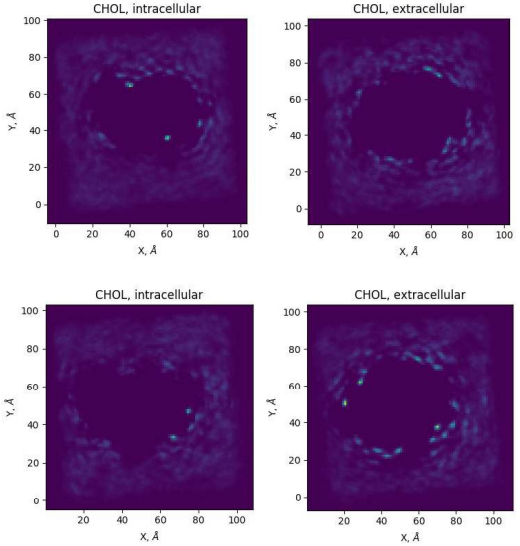


The effect of Q141K on protein dynamics





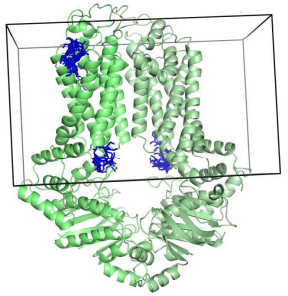
The effect of cholesterol on ABCG2



Identification of drug binding sites

in silico **docking, AutoDock Vina**

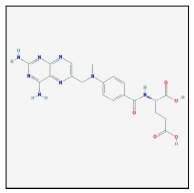
- Flexible ligand, non-flexible protein
- Several conformations from simulations
- Search space defined by a box



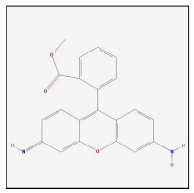
Identification of drug binding sites
in silico docking, AutoDock Vina

- Flexible ligand, non-flexible protein
- Several conformations from simulations
- Search space defined by a box
- Everything gets docked; docking substrates and non-substrates

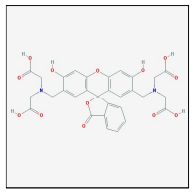
methotrexate



rhodamine123



calcein

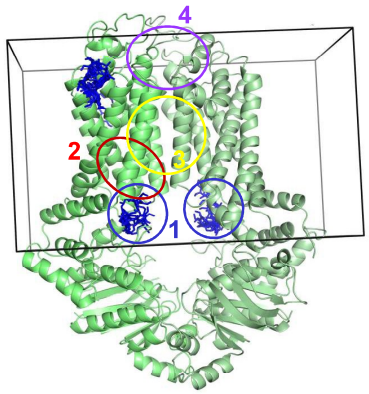


Identification of drug binding sites
in silico docking, AutoDock Vina

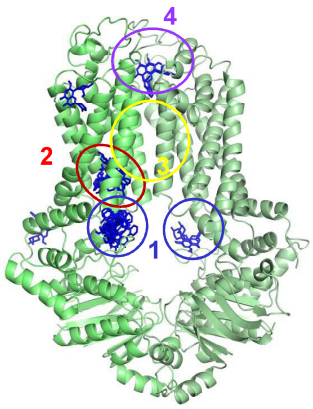
- Flexible ligand, non-flexible protein
- Several conformations from simulations
- Search space defined by a box
- Everything gets docked; docking substrates and non-substrates
- (6 ABCG2 conformations) * (3 parallel dockings) * (20 poses) * (25 substrates + 14 non-substrates)
- Clustering poses

Identification of drug binding sites
in silico docking, AutoDock Vina

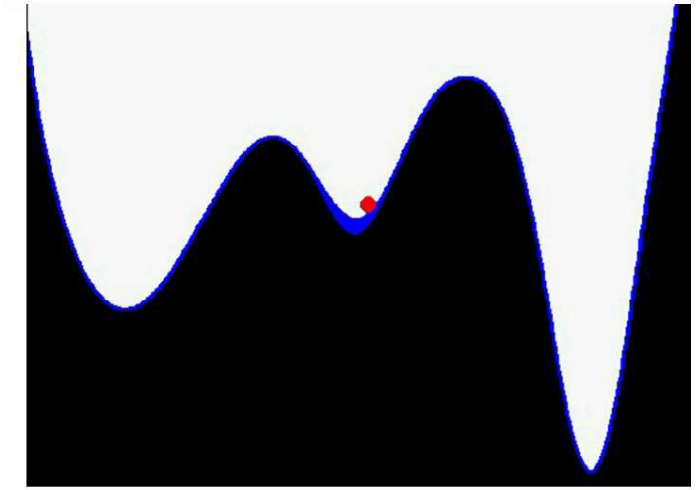
verapamil



flavopiridol

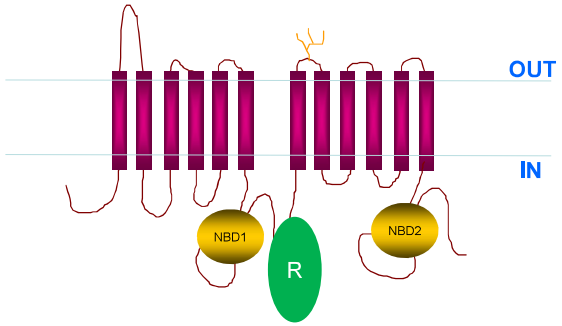


Exploring substrate transport by biased MD simulations

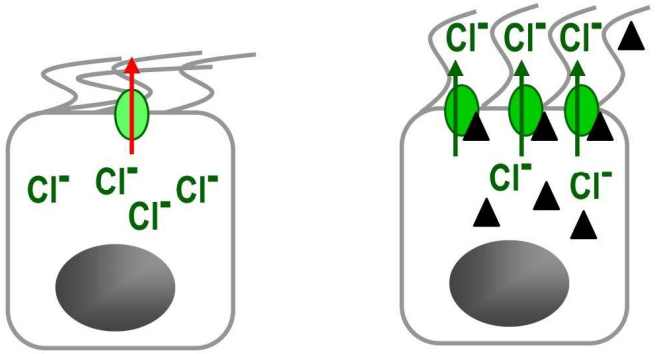


ABCC7/CFTR

Cystic Fibrosis Transmembrane Conductance Regulator

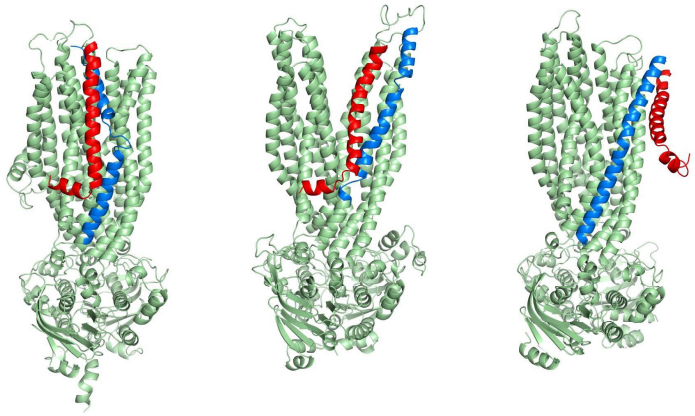


Cisztás fibrózis (CF)



Full-length CFTR structures

Cryo-EM revolution



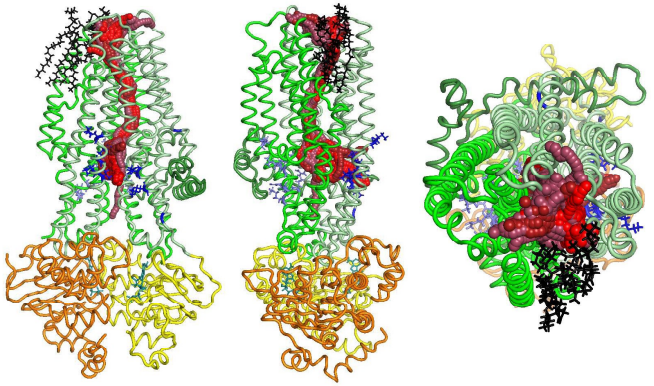
Zhang et al. (2017) Cell 170: 483-491.e8
PDBID:5W81

Bob Ford
University of Manchaster, UK

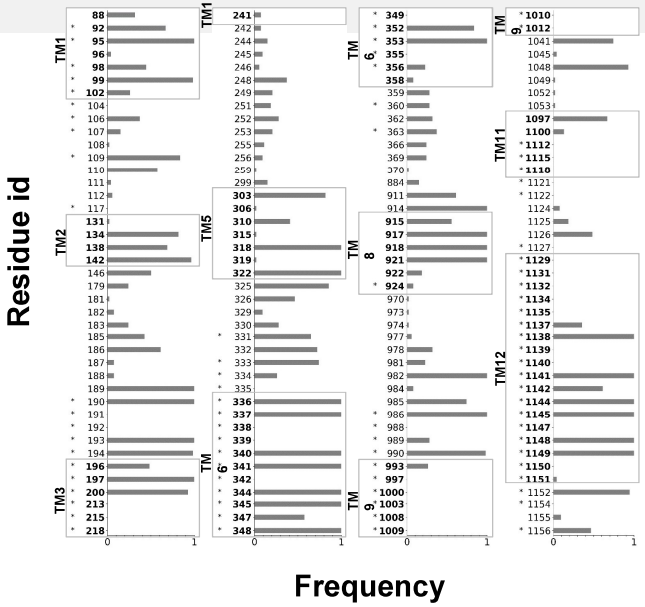
J. Fay, Jack Riordan
UNC, Chapel Hill, USA

Identification of the chloride permeation pathway

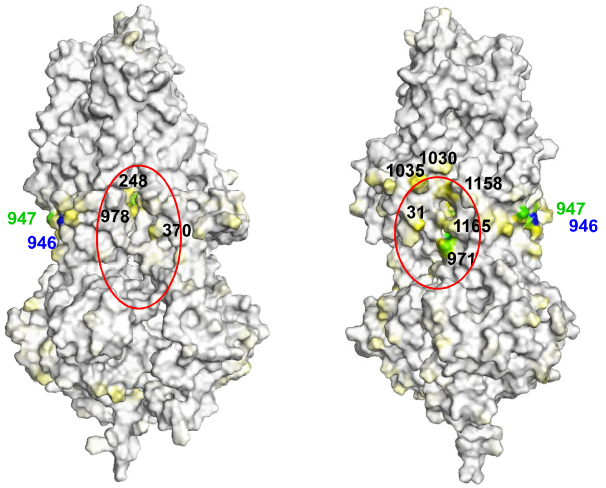
Farkas *et al.* Cell Mol Life Sci. 2019 Jul 20. doi: 10.1007/s00018-019-03211-4



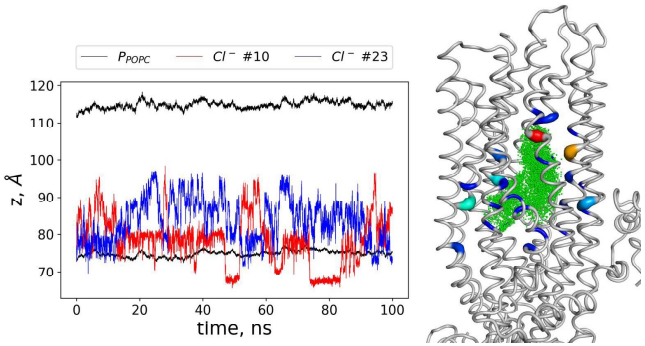
Simulations versus experiments



Chloride entry

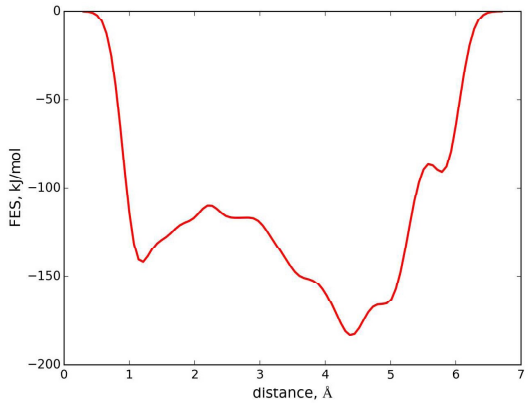


Ion movements in the channel

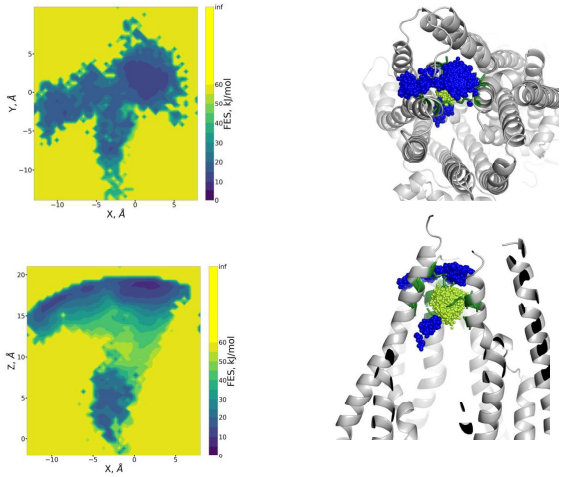


Calculating the free energy of the permeation

FES – Free Energy Surface

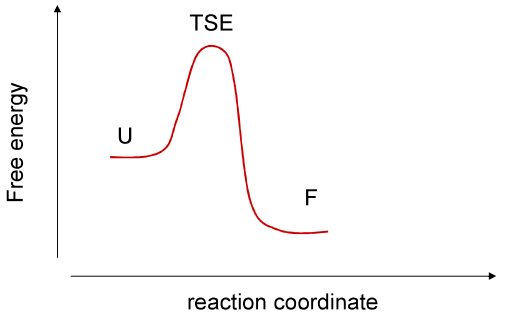


Characterizing the permeation by metadynamics



Protein folding

Two-state model



nucleation

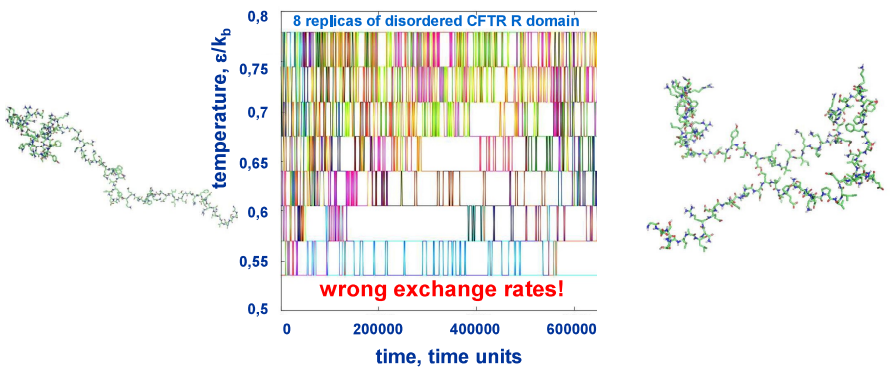
Levinthal's paradox

Simulation techniques for protein folding

All atom force-field

Umbrella sampling

replica exchange

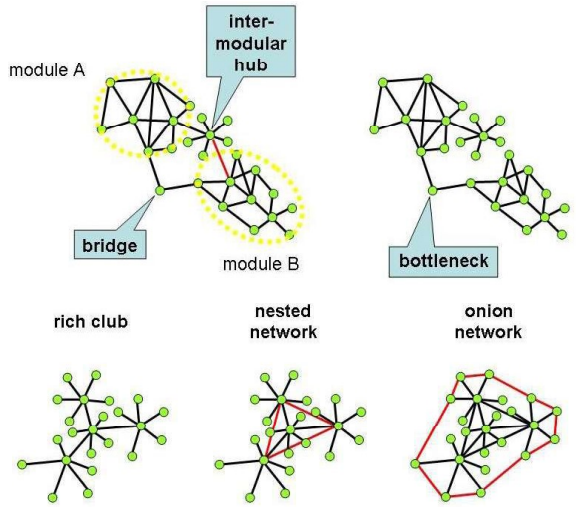


Systems biology

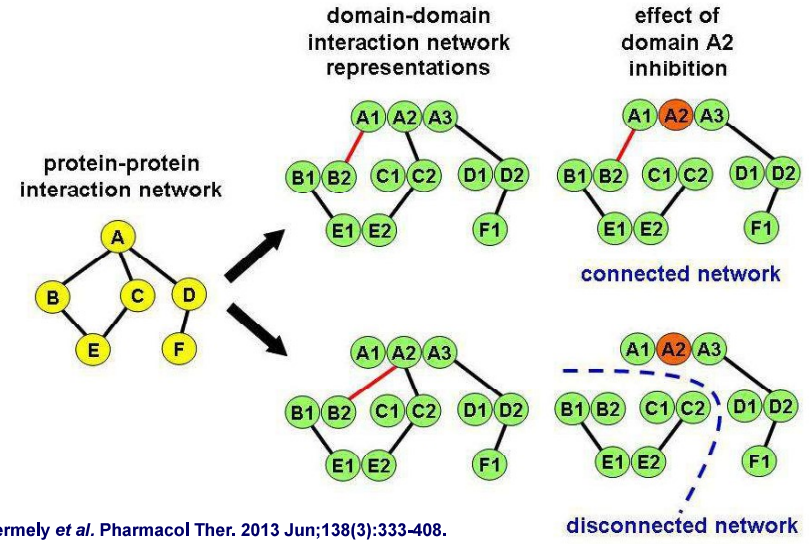
- **Protein-protein interactions**
- **Interactions of genes, proteins, and drugs**
- **Graph theory methods – amino acid movements**

Csermely P. *et al.* 2012, http://arxiv.org/abs/1210.0330

Graph/network structure

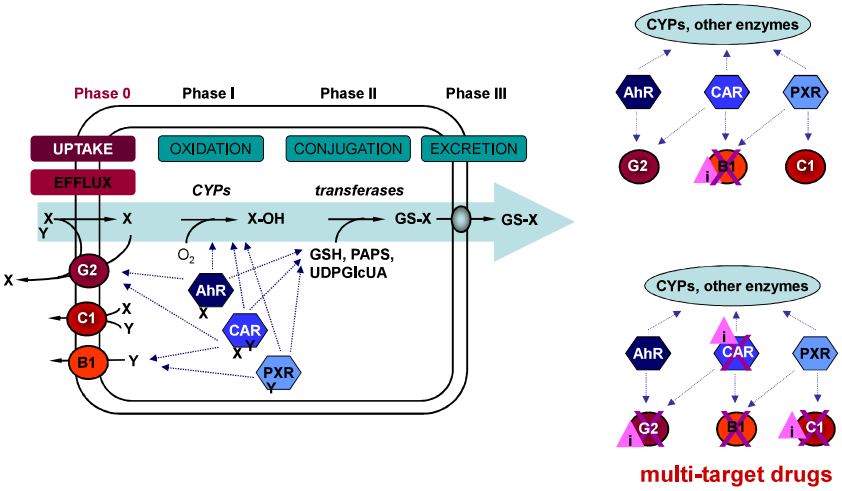


Protein-protein interaction networks

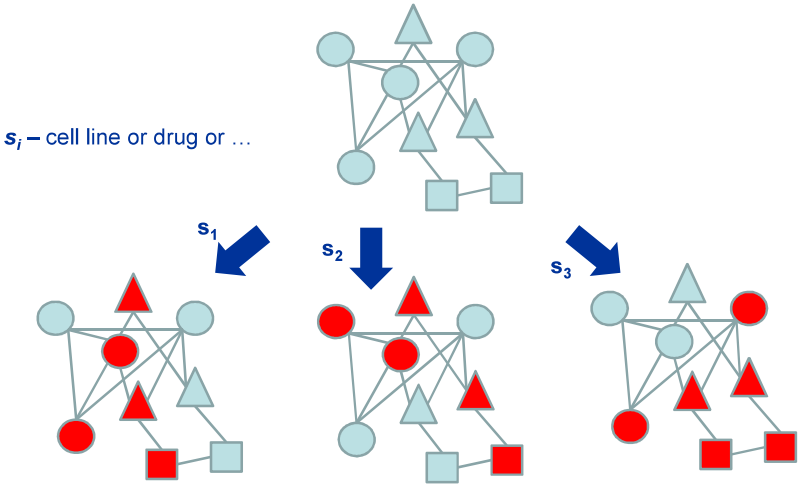


Csermely *et al.* Pharmacol Ther. 2013 Jun;138(3):333-408.

The chemoimmune (ChI) system



The chomoimmune system



Pipeline of analysis

- Human samples treated with drugs
- NCBI Gene Expression Omnibus (GEO) database
- Preprocessed (by GEO) data & quality check

	our interest	example(s)
DataSet (GDS)[1]	180 (1 335 human)	Anti-cancer agent sapphyrin PCI-2050 effect on lung cancer cell line: dose response (GDS2499)
Experiment[2]	883 (2786 cont.+treat.)	treatment: 1) Actinomycin-D 5 ug/ml 2-3) Sapphyrin PCI-2050 1.25 ug/ml, 2.5 ug/ml
Tissue/cell	132	lung cancer cell line, MCF-7, HUVEC, primary fetal astrocytes, tumor biopsies ...
Drug or xenobiotic	222	actinomycin D, sapphyrin PCI-2050, thapsigargin, tunicamycin, doxorubicin ...
Microarray platform (GPL)	26	Affymetrix - Human Genome U133 Plus 2.0 Array (GPL570)

[1]Collection of coherent experiments (by GEO)
[2]One celltype, one agent, one timecourse, one dose

Pipeline of analysis

- Calculate the expression changes
  - Discretization

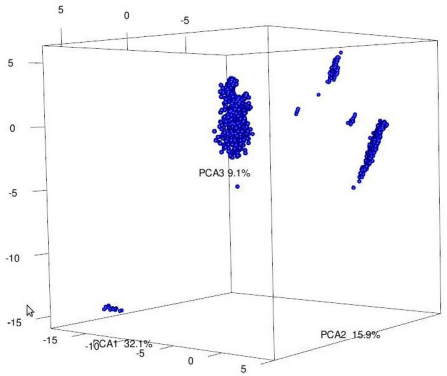
	Expression change (fold)	Discret value
upregulated	>2x	1
downregulated	<0,5x	-1
no change	-	0
no probe on chip	-	2

  - Vectors

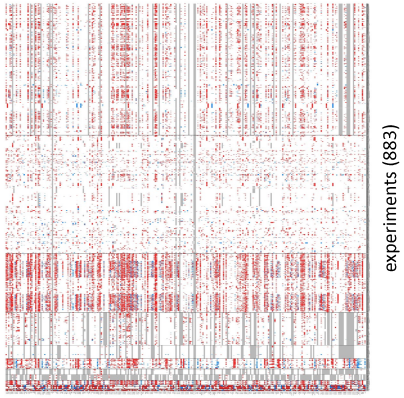
experiment	ABCA1	ABCA8	ABCB1	ABCB11	ABCB4	ABCB5	ABCC1	ABCC2	ABCC3	ABCC4	ABCC5	ABCC6	ABCD2	ABCG2	ABHD10	ABL1	ADH1A	ADH1B	ADH1C	ADH4	ADH6	AHR	AHRR	AKAP13	AKR1A1	AKR1C1	AKR1C2	ALDH16A1	(...)
GDS1249_1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	1	0	0	0	0	0	1	0	0	0	0	(...)
GDS1249_2	1	1	1	0	0	0	0	0	0	1	0	1	0	0	-1	0	0	1	0	0	1	0	0	1	0	1	0	0	(...)
GDS1249_3	1	1	0	0	0	1	1	0	1	1	1	1	0	0	0	0	0	1	0	1	1	0	0	1	0	1	1	0	(...)
(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)	(...)

Whole dataset

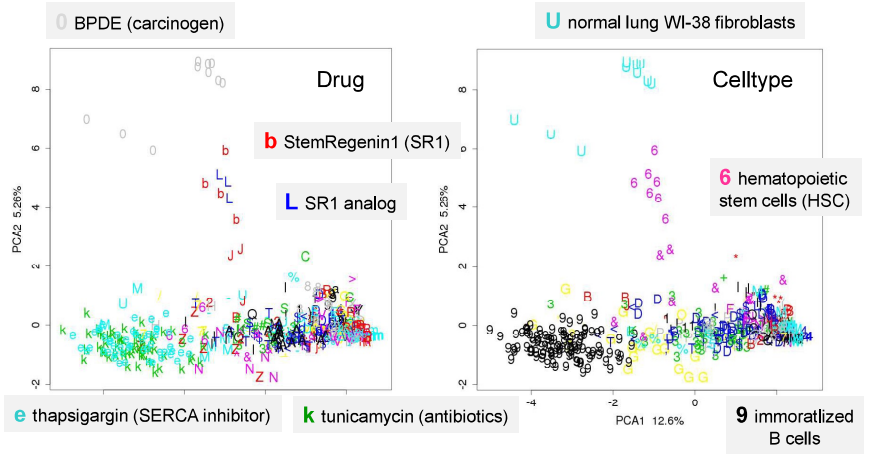
PCA analysis (the first 3 component)



Heatmap (result of clustering)



PCA analysis



REVIEW

COMPUTATIONAL BIOLOGY

Avoiding common pitfalls when clustering biological data

Tom Ronan, Zhijie Qi, Kristen M. Naegle*

www.SCIENCESIGNALING.org 14 June 2016 Vol 9 Issue 432 re6

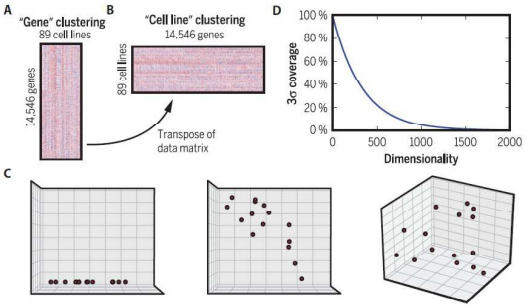
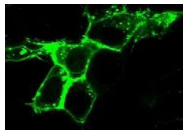


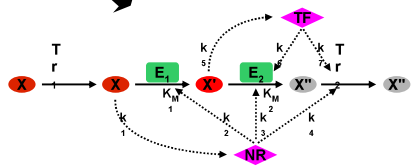
Fig. 1. Determining the dimensionality of a clustering problem. (A and B) Representation of the mRNA clustering problem consisting of >14,000 mRNAs measured across 89 cell lines. Data are from Lu *et al.* (6). When the mRNAs are clustered, the mRNAs are the objects and each cell line represents a feature, resulting in an 89-dimensional problem (A). When attempting to classify normal and tumor cell lines using gene expression, the cells lines are the objects and each mRNA is a feature, resulting in a clustering problem with thousands of dimensions (B). (C) Effect of dimensionality on sparsity. (D) Effect of dimensionality on coverage of the data based on SD from the mean.

A kinetic model of the ChI system

kísérletes kutatások

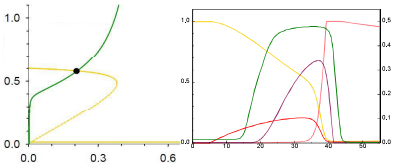


fiziológia



hálózati diagram

fázissík analízis



numerikus szimulációk

$$\frac{dX'}{dt} = k_1 X - \frac{k_2 E_2 X'}{K_{M2} + X'}$$

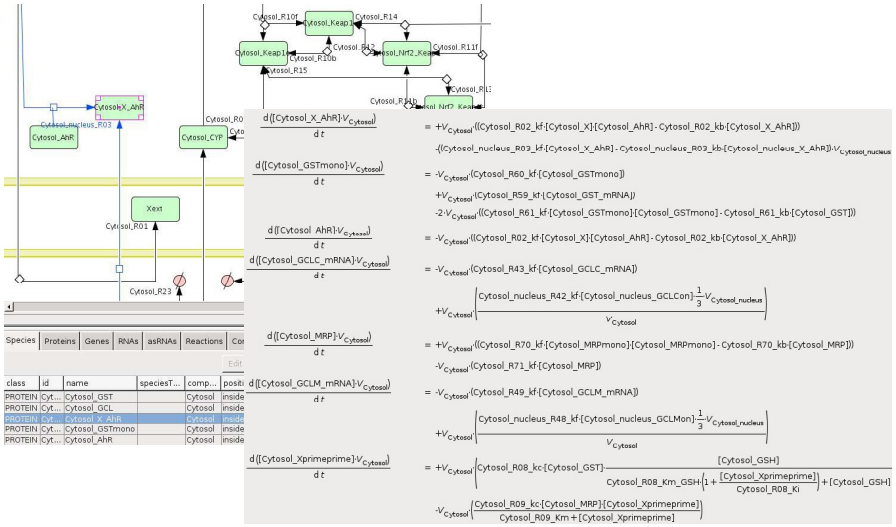
$$\frac{dX''}{dt} = \dots$$

$$\frac{dNR}{dt} = \dots$$

$$\frac{dTF}{dt} = \dots$$

matematikai modell

A kinetic model of the ChI system



$$\frac{d([\text{Cytosol\_X\_AhR}]\cdot V_{\text{Cytosol}})}{dt} = +V_{\text{Cytosol}}\cdot((\text{Cytosol\_R02\_kf}\cdot[\text{Cytosol\_X}]\cdot[\text{Cytosol\_AhR}] - \text{Cytosol\_R02\_kb}\cdot[\text{Cytosol\_X\_AhR}])) - (\text{Cytosol\_nucleus\_R03\_kf}\cdot[\text{Cytosol\_X\_AhR}] - \text{Cytosol\_nucleus\_R03\_kb}\cdot[\text{Cytosol\_nucleus\_X\_AhR}])\cdot V_{\text{Cytosol\_nucleus}}$$

$$\frac{d([\text{Cytosol\_GSTmono}]\cdot V_{\text{Cytosol}})}{dt} = -V_{\text{Cytosol}}\cdot(\text{Cytosol\_R60\_kf}\cdot[\text{Cytosol\_GSTmono}]) + V_{\text{Cytosol}}\cdot(\text{Cytosol\_R59\_kt}\cdot[\text{Cytosol\_GST\_mRNA}]) - 2\cdot V_{\text{Cytosol}}\cdot((\text{Cytosol\_R61\_kf}\cdot[\text{Cytosol\_GSTmono}]\cdot[\text{Cytosol\_GSTmono}] - \text{Cytosol\_R61\_kb}\cdot[\text{Cytosol\_GST}]))$$

$$\frac{d([\text{Cytosol\_AhR}]\cdot V_{\text{Cytosol}})}{dt} = -V_{\text{Cytosol}}\cdot((\text{Cytosol\_R02\_kf}\cdot[\text{Cytosol\_X}]\cdot[\text{Cytosol\_AhR}] - \text{Cytosol\_R02\_kb}\cdot[\text{Cytosol\_X\_AhR}]))$$

$$\frac{d([\text{Cytosol\_GCLC\_mRNA}]\cdot V_{\text{Cytosol}})}{dt} = -V_{\text{Cytosol}}\cdot(\text{Cytosol\_R43\_kf}\cdot[\text{Cytosol\_GCLC\_mRNA}]) + V_{\text{Cytosol}}\left(\frac{\text{Cytosol\_nucleus\_R42\_kf}\cdot[\text{Cytosol\_nucleus\_GCLCon}]\cdot\frac{1}{3}\cdot V_{\text{Cytosol\_nucleus}}}{V_{\text{Cytosol}}}\right)$$

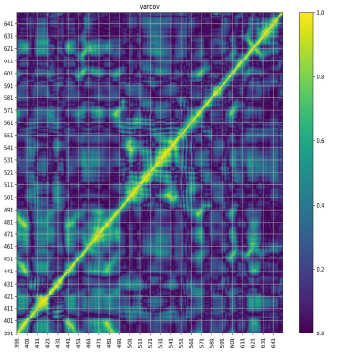
$$\frac{d([\text{Cytosol\_MRP}]\cdot V_{\text{Cytosol}})}{dt} = +V_{\text{Cytosol}}\cdot((\text{Cytosol\_R70\_kf}\cdot[\text{Cytosol\_MRPmono}]\cdot[\text{Cytosol\_MRPmono}] - \text{Cytosol\_R70\_kb}\cdot[\text{Cytosol\_MRP}])) - V_{\text{Cytosol}}\cdot(\text{Cytosol\_R71\_kf}\cdot[\text{Cytosol\_MRP}])$$

$$\frac{d([\text{Cytosol\_GCLM\_mRNA}]\cdot V_{\text{Cytosol}})}{dt} = -V_{\text{Cytosol}}\cdot(\text{Cytosol\_R49\_kf}\cdot[\text{Cytosol\_GCLM\_mRNA}]) + V_{\text{Cytosol}}\left(\frac{\text{Cytosol\_nucleus\_R48\_kf}\cdot[\text{Cytosol\_nucleus\_GCLMon}]\cdot\frac{1}{3}\cdot V_{\text{Cytosol\_nucleus}}}{V_{\text{Cytosol}}}\right)$$

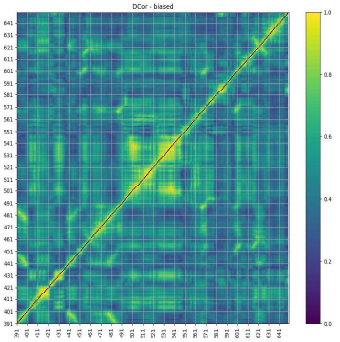
$$\frac{d([\text{Cytosol\_Xprimeprime}]\cdot V_{\text{Cytosol}})}{dt} = +V_{\text{Cytosol}}\left(\text{Cytosol\_R08\_kc}\cdot[\text{Cytosol\_GST}]\cdot\frac{[\text{Cytosol\_GSH}]}{\text{Cytosol\_R08\_Km\_GSH}\cdot\left(1+\frac{[\text{Cytosol\_Xprimeprime}]}{\text{Cytosol\_R08\_Ki}}\right)+[\text{Cytosol\_GSH}]}\right) - V_{\text{Cytosol}}\left(\frac{\text{Cytosol\_R09\_kc}\cdot[\text{Cytosol\_MRP}]\cdot[\text{Cytosol\_Xprimeprime}]}{\text{Cytosol\_R09\_Km}+[\text{Cytosol\_Xprimeprime}]}\right)$$

Correlation in amino acid motions

Pearson



DiCC
Gábor Székely



Notes on information technology

Data
: do not trust!
RDBMS, ORM

Logic
: learn at least one tool (Python?) thoroughly!

Visualization
: browser, javascript, jQuery, templating

Thanks for your attention!

hegedus.tamas@hegelab.org