Using Supercomputers for Computer Modeling of Biomolecules & Drug Design

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SLURM USER GROUP MEETING 2016

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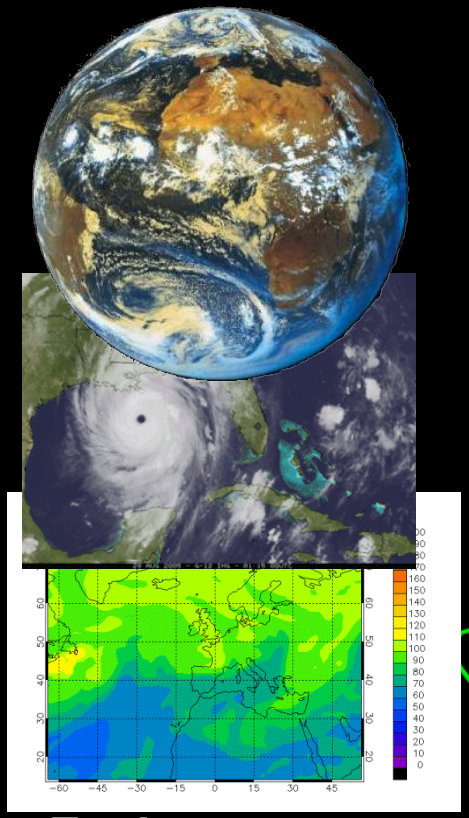
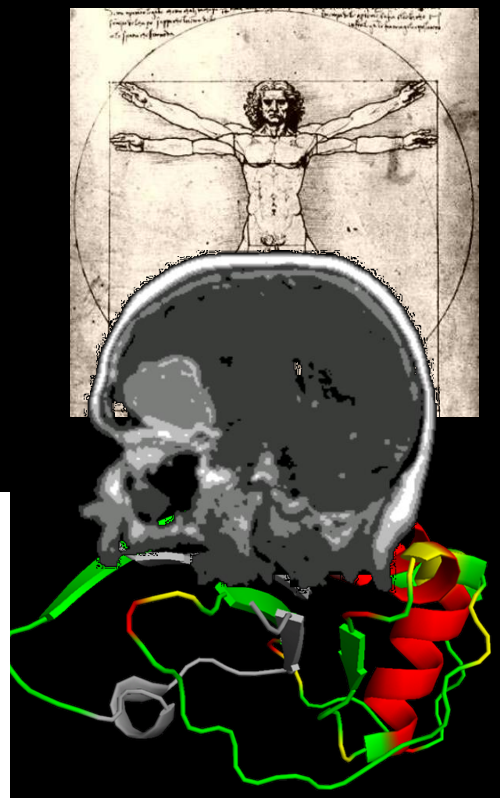
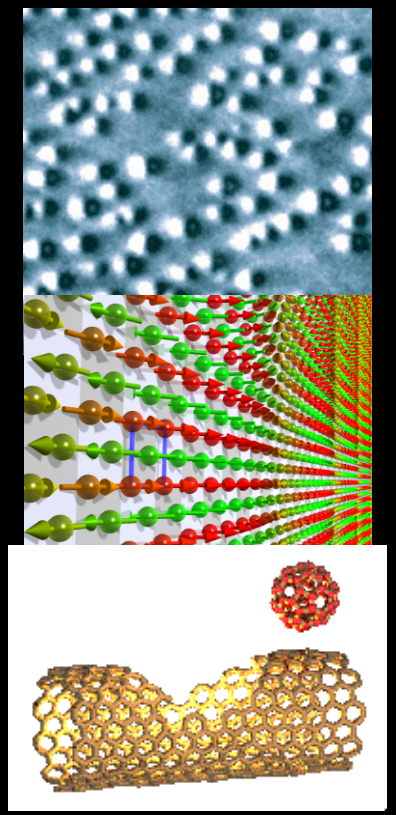
Supercomputing Drives Science through Simulation



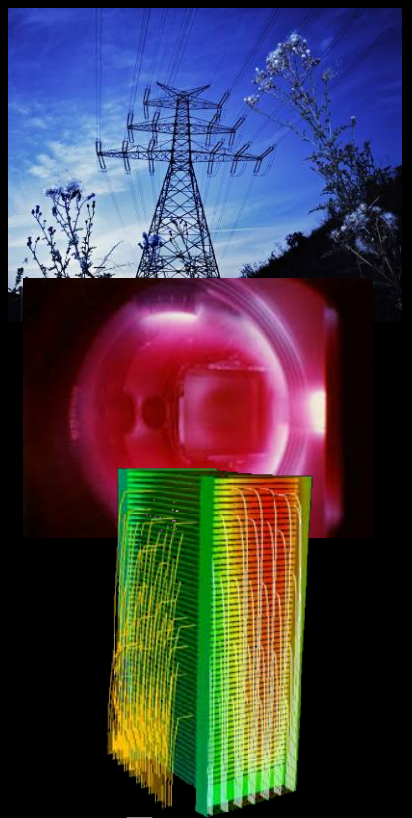
Environment
Weather/ Climatology
Pollution / Ozone Hole



Finding Cures
Medicine
Biology

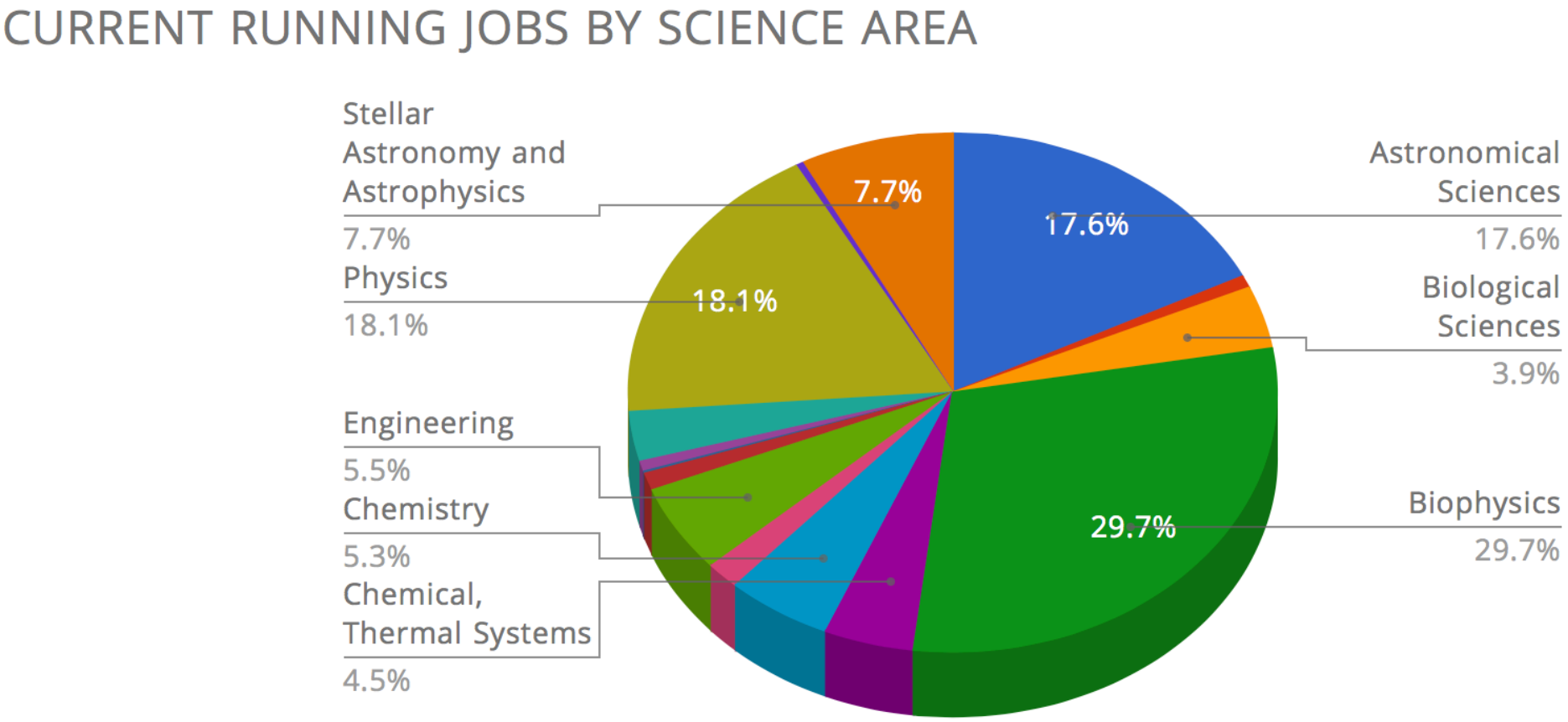


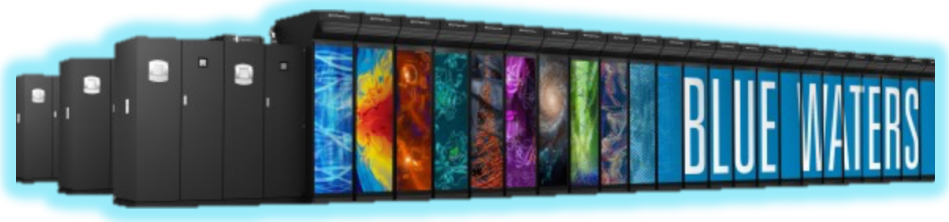
Materials/ Inf. Tech
Spintronics
Nano-science



Energy
Plasma Physics
Fuel Cells

Distribution of HPC based on Science Area





Source: https://bluewaters.ncsa.illinois.edu

Computing is transforming biomedical research

Exascale

Compute Power

time

HP 735
12 CPUs

1993

protein
10k atoms
100s ps

SGI Origin
128 CPUs

1997

ion channel
100k atoms
1 ns

LeMieux
3k CPUs

2002

ATPase
500k atoms
10s ns

Ranger
60k CPUs

2007

ribosome
2 mil atoms
100s ns

LCF
Mira 786k cores
Titan 280k cores
+ GPUs

2015

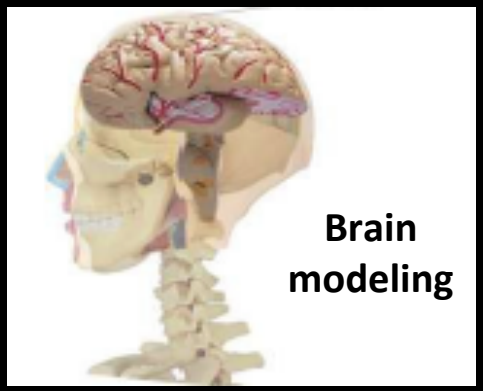
Enveloped virus
200 mil+ atoms
1-100 μs

Performance (in FLOPS):

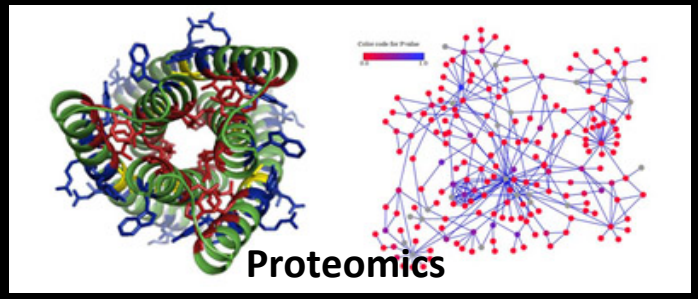
Megaflop	10^6
Gigaflop	10^9
Teraflop	10^{12}
Petaflop	10^{15}

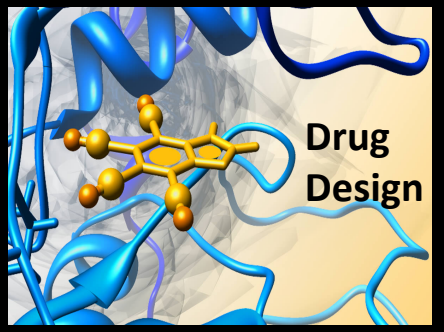
Source: adapted from Prof. Rommie Amaro

Key areas of biomedical research where HPC is key

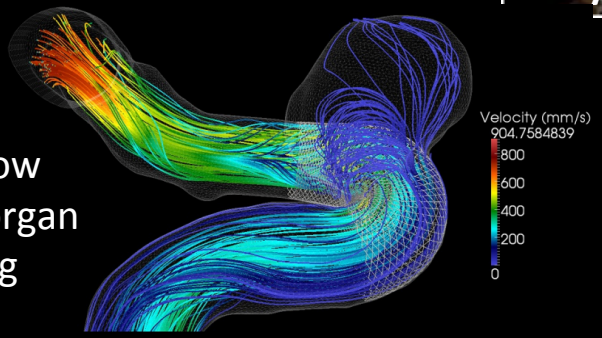


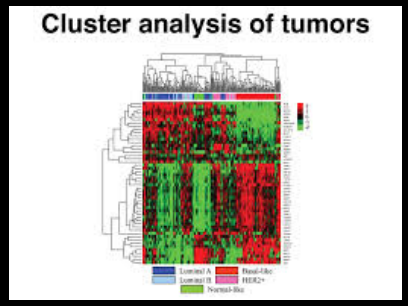
Protein Biophysics



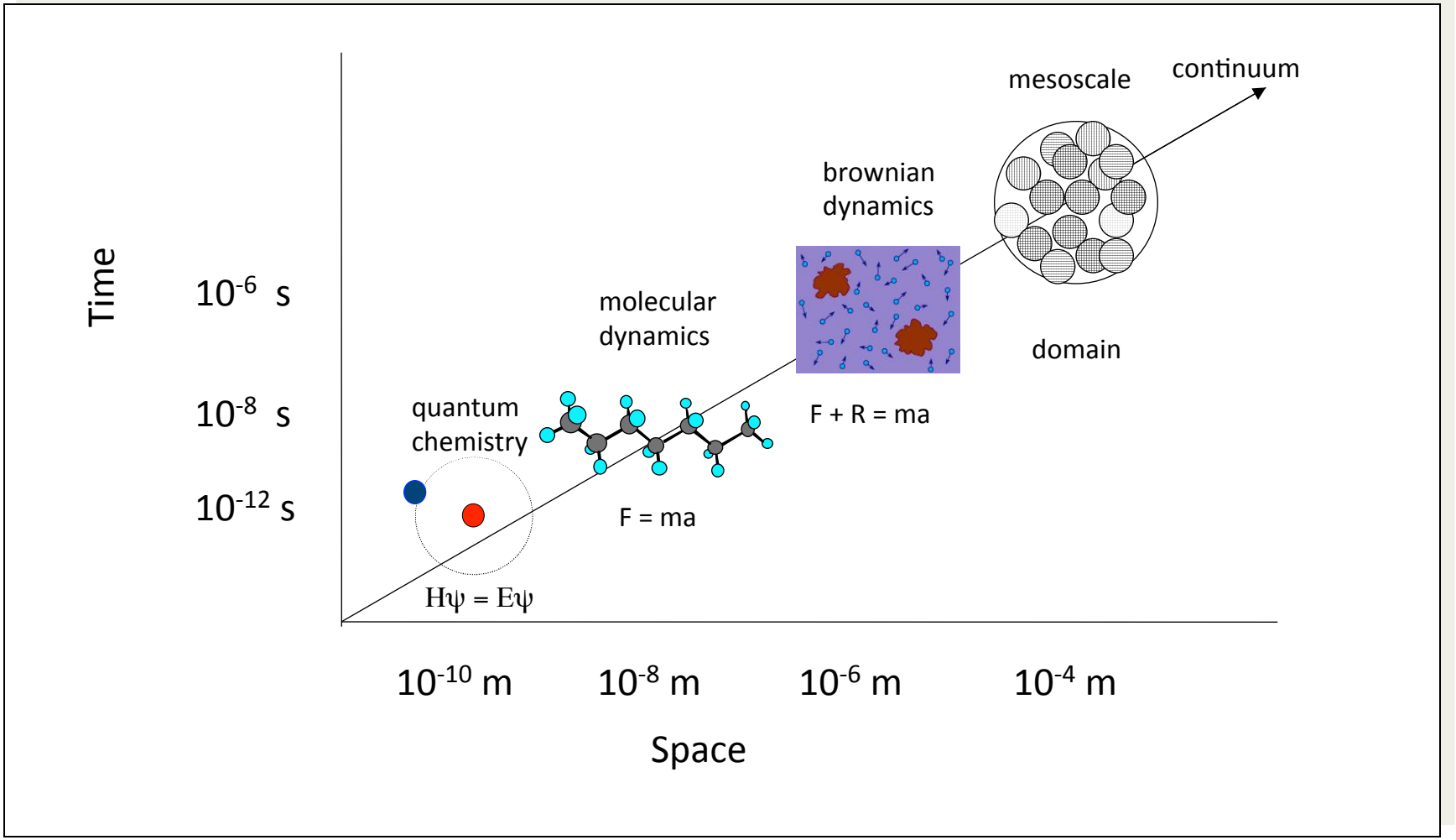


Blood flow
Whole organ
modeling





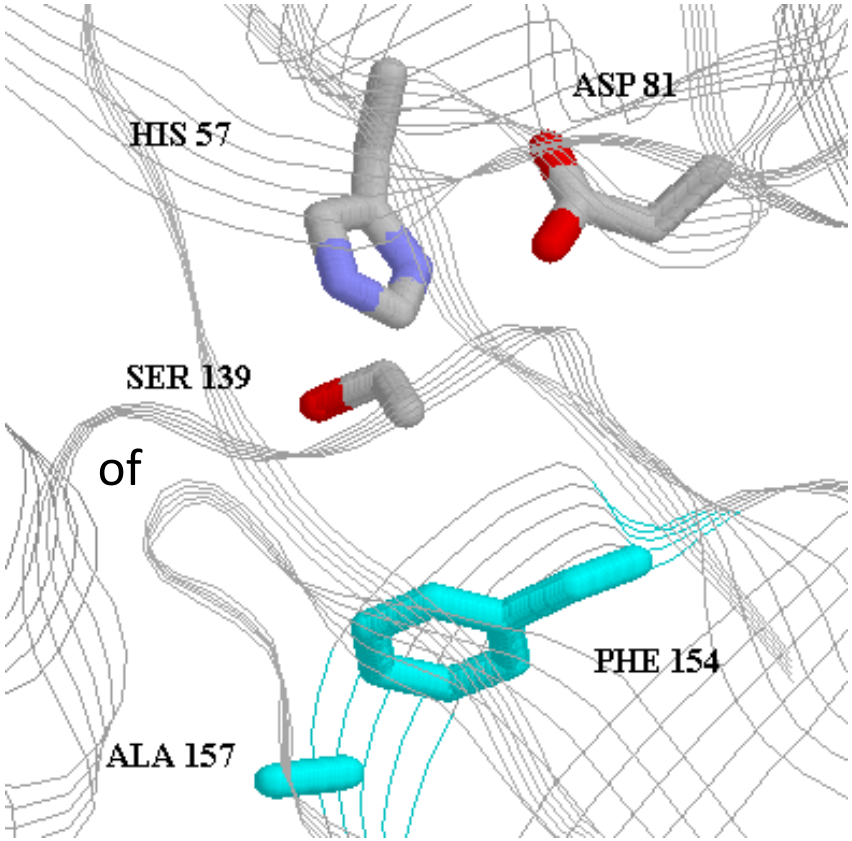
Molecular Simulations across scales



Molecular Modeling

dynamics

Structure --------> function

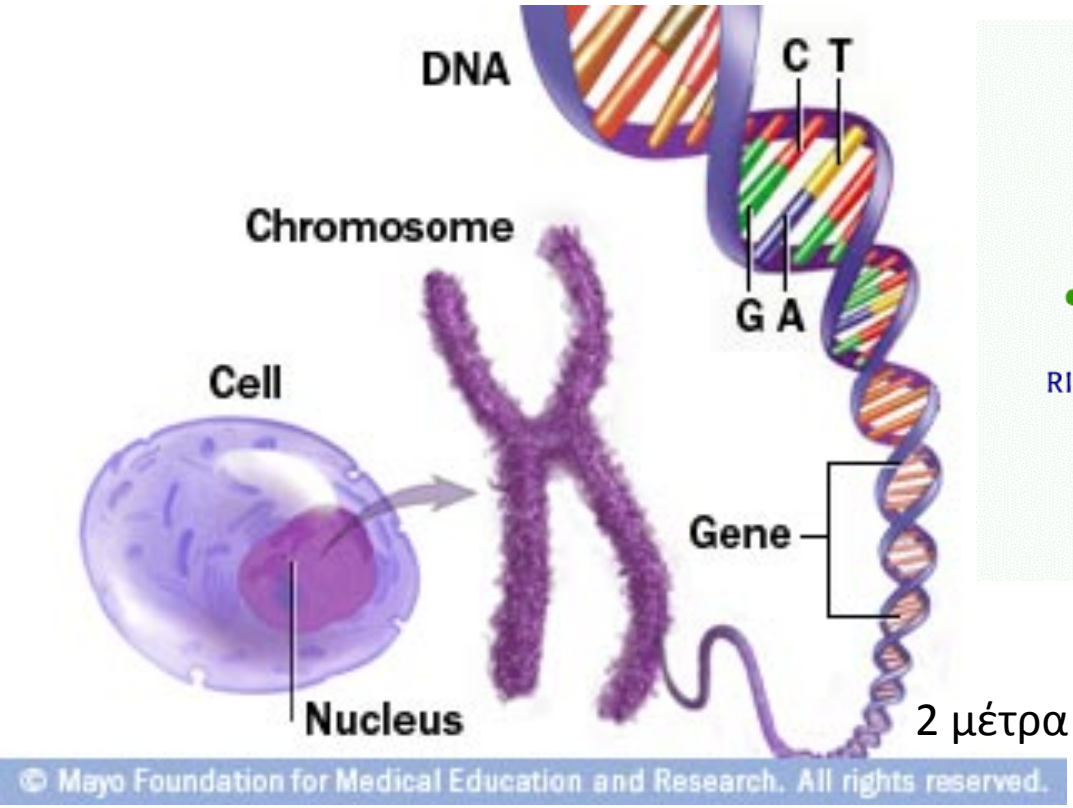


Molecular Dynamics

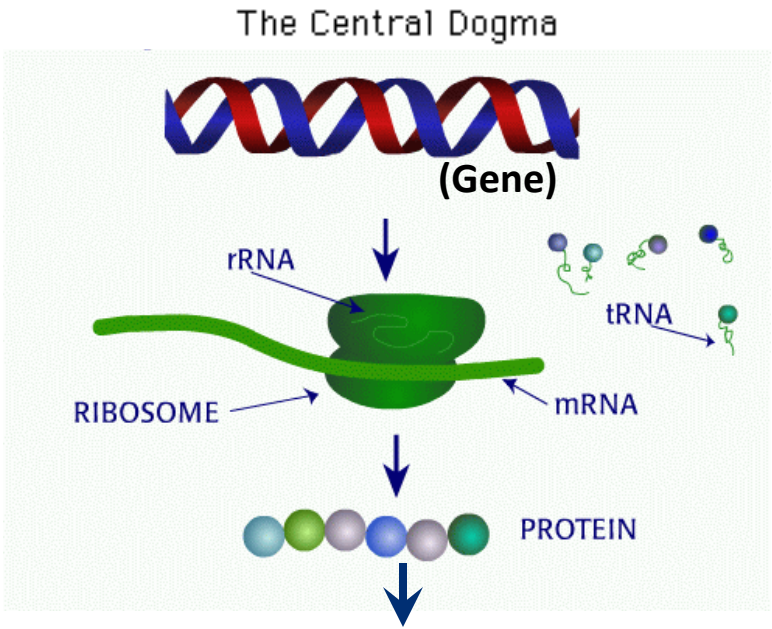
of

- molecular/atomic level picture structure and dynamics
- property prediction
- ion transport
- solvent effects
- protein stability / conform. changes, …

From DNA, to genes and proteins



2 μέτρα!

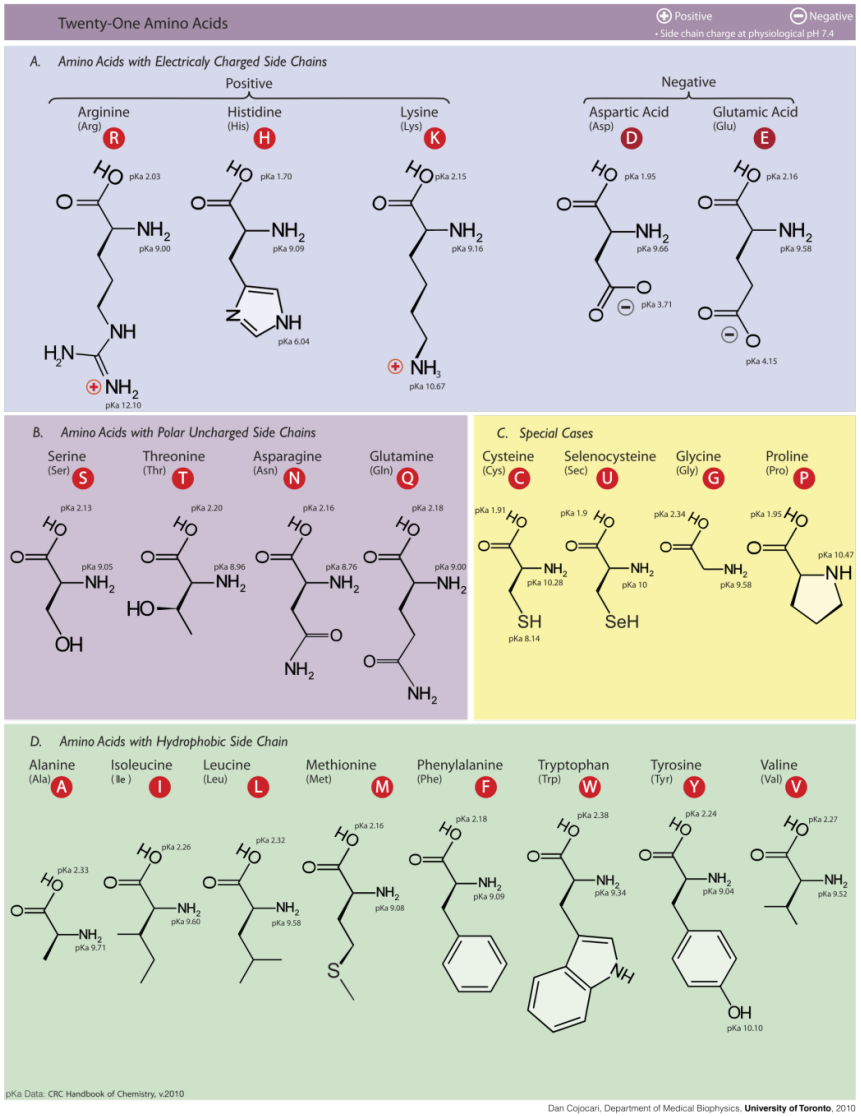


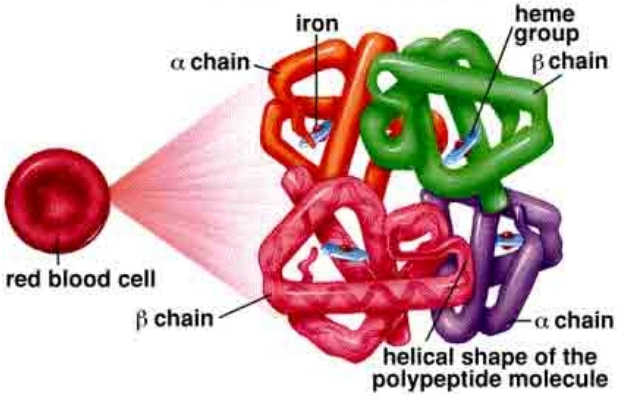
X - Rays = Protein Pictures

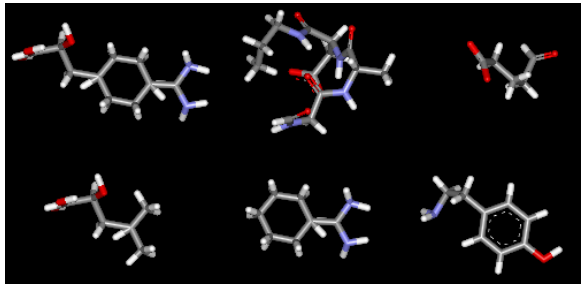
20.000 genes in the nuclei of our cells
→ PROTEINS

- **Proteins are the means of expression of genes to functional molecules**
- **Proteins perform essential functions in the cell**

Protein Modeling, Protein-Drug Modeling







Drugs associate with proteins through Intermolecular Interactions!

Hydrogen Bonds

Electrostatic Interactions

van der Waals Forces

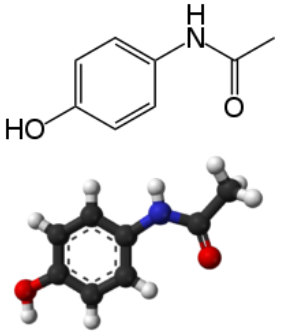
π – π Interactions

Drugs

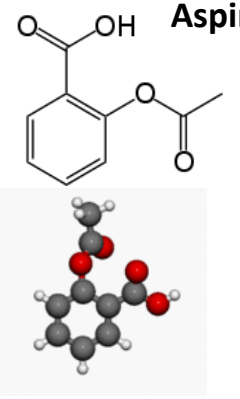
Normally they are small organic molecules

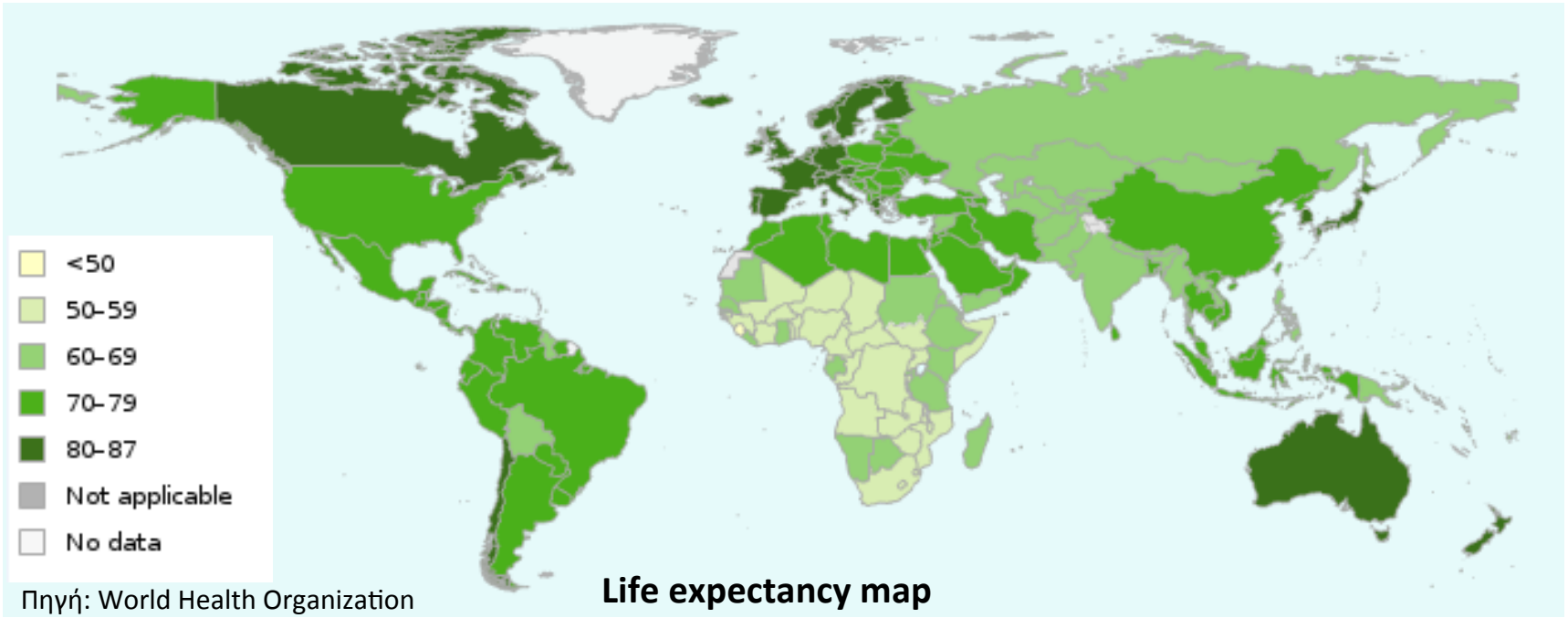
- **Therapy**
- **Relief**
- **Prevention**
- **Quality of life improvement**
- **Life expectancy prolongation**

Paracetamol (Depon)



Aspirin

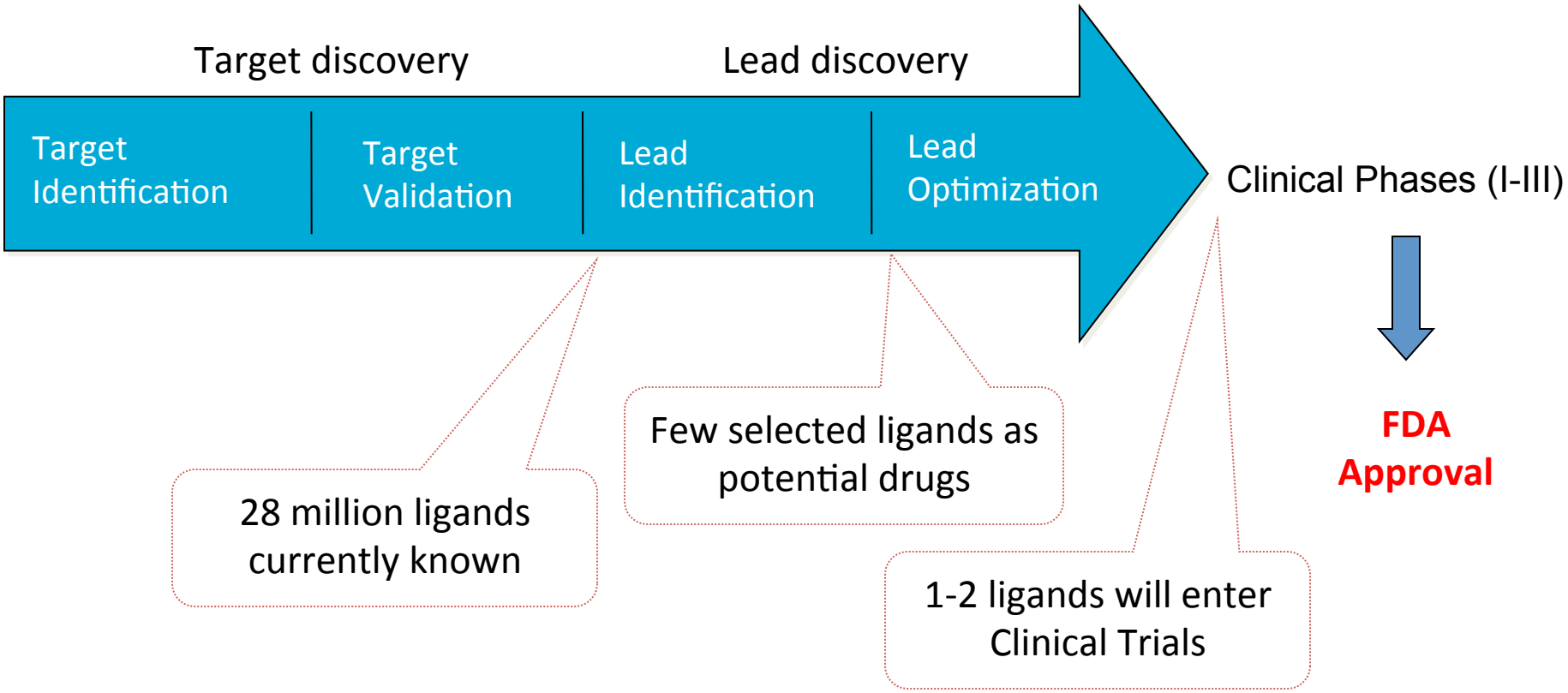




Πηγή: World Health Organization

Life expectancy map

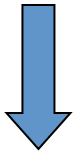
Phases of Pharmaceutical Development



Duration: 12 – 15 years, Cost: ~ 1 billion US $

Traditional Drug Discovery

- Random screening of hundreds of thousands of molecules with High Throughput Screening (HTS) for combating the pathogen
- Random discoveries (i.e. penicillin, viagra)
- Trying out existing drugs and modifications
- Estimated number of small molecules that can act as drugs **10^{66}**
- Estimated number of atoms in the world **10^{50}**

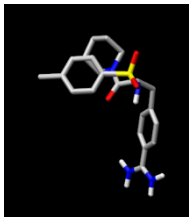


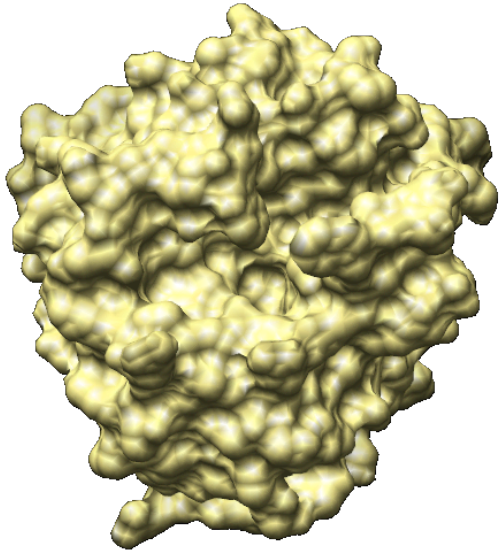
Structure-based approaches + Targeted Therapy

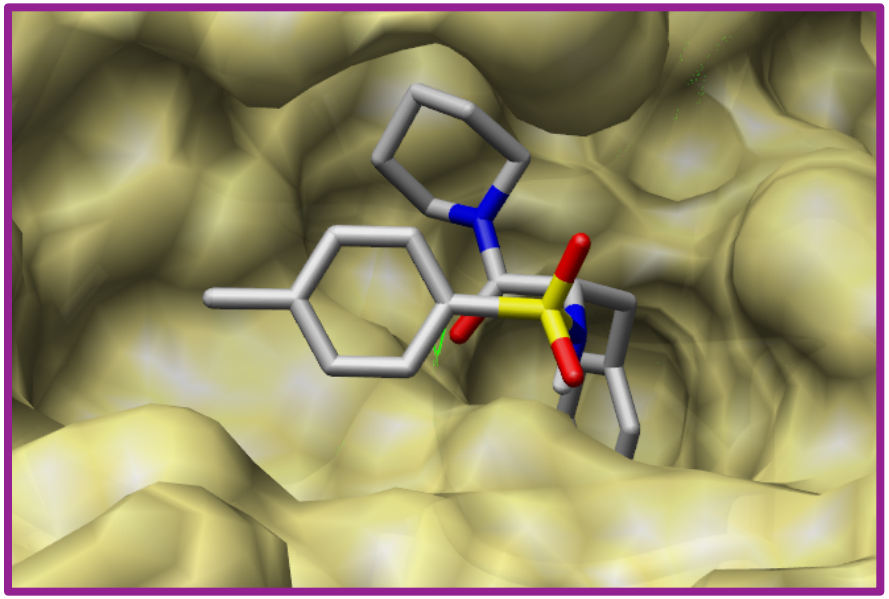
Rational Drug Discovery

- **Identify important genes for a diseases**
- **Targeting/inactivating genes (proteins) of the pathogen with small molecules = drugs**

TARGETED THERAPY!

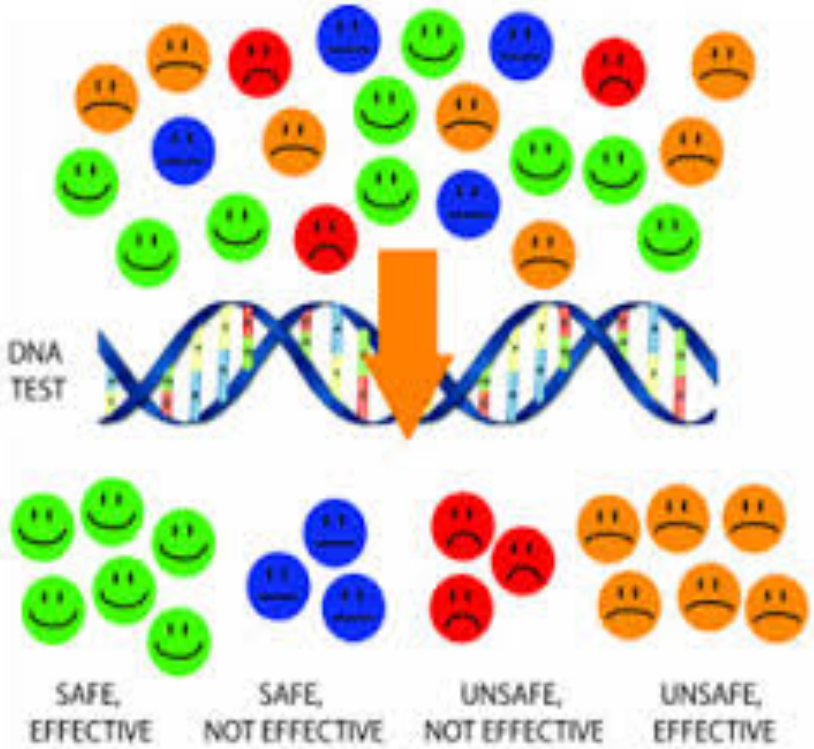






Curr Opin Drug Discov Devel. 2002 May; 5(3): 355–360

The era of Personalized Medicine



Lung Cancer

↓

genotyping

↓

4% of patients with
non-small cell lung carcinoma
Rearrangement in **ALK protein**

↓

carcinogenesis

↓

Drug design for this specific
subset of patients

↓

Crizotinib for ALK+
lung cancer patients

Personalized Medicine: new drug generation

Table 1 | **Selected oncology agents in Phase III biomarker-driven clinical trials**

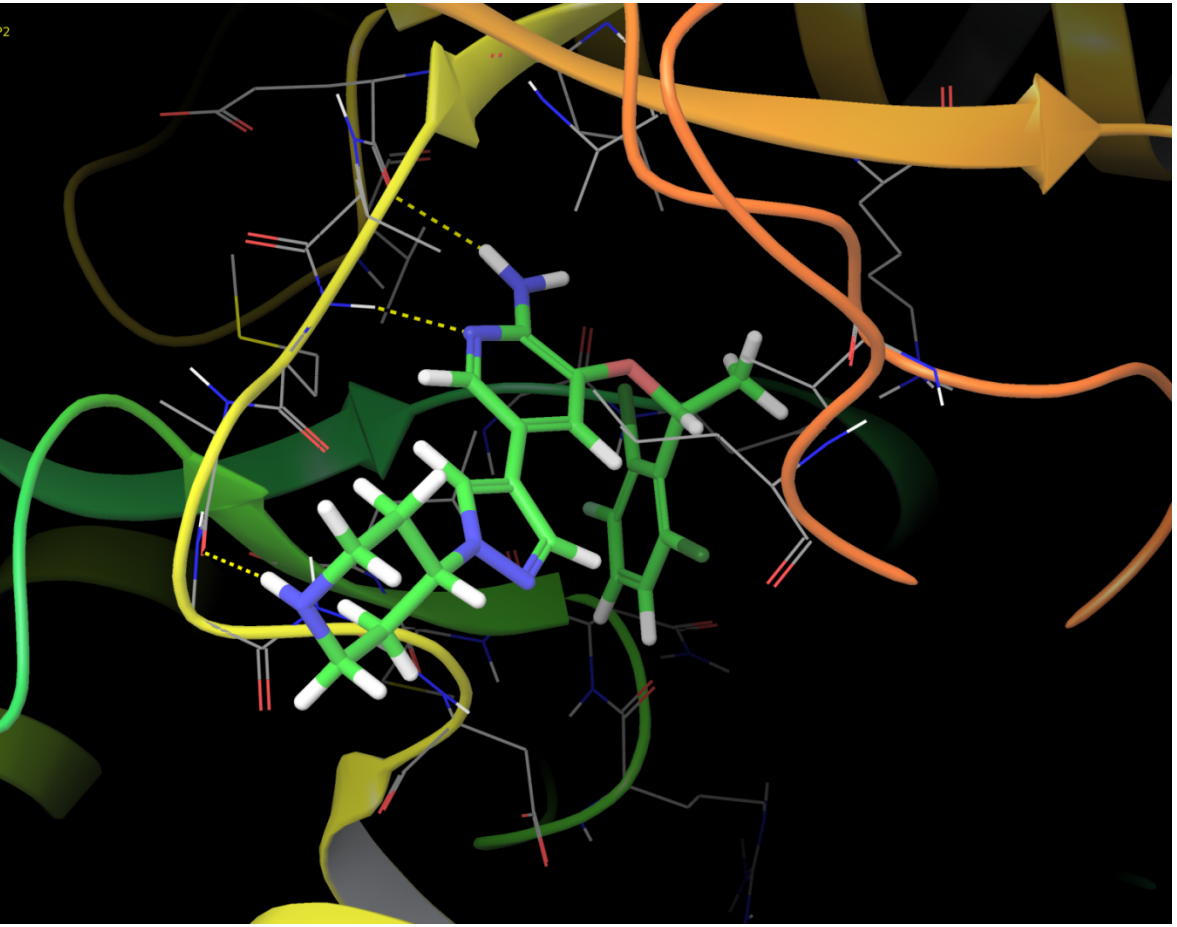
Drug	Company	Indication	Biomarker
Precedented biomarkers			
Iniparib	Sanofi/BiPar Sciences	Breast cancer	Triple-negative
Pertuzumab	Roche/Chugai	Breast cancer	HER2
Neratinib	Pfizer	Breast cancer	HER2
Bosutinib	Pfizer	CML	Philadelphia
Nimotuzumab	YM BioSciences	Breast cancer	HER2
Afatinib	Boehringer Ingelheim	NSCLC	EGFR
Dacomitinib	Pfizer	NSCLC	EGFR and KRAS
Novel biomarkers			
Midostaurin	Novartis	AML	FLT3
Cilengitide	Merck Serono	Glioblastoma	Methylated *MGMT*
Trabedersen	Antisense Pharma	Glioma	TGFβ2
GSK2118436	GlaxoSmithKline	Melanoma	BRAF
GSK1120212	GlaxoSmithKline	Melanoma	BRAF

AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; EGFR, epidermal growth factor receptor; FLT3, FMS-like tyrosine kinase 3; MGMT, 6-*O*-methylguanine-DNA methyltransferase; NSCLC, non-small-cell lung cancer; TGFβ2, transforming growth factor-β2.

Chiang and Million, Nature 2011

Crizotinib (Xalkori, Pfizer)

Structure of the anaplastic lymphoma kinase (ALK)
Complexed with the drug crizotinib – (PDB ID: 2XP2)



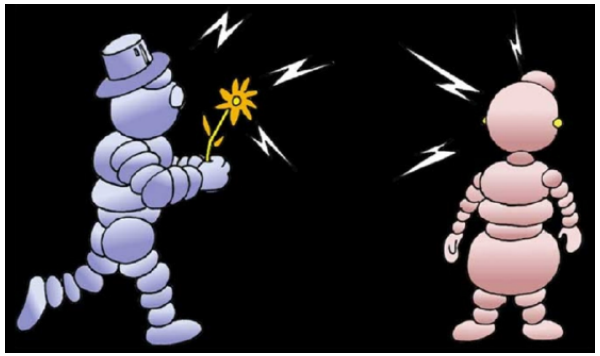
Protein-Ligand interactions:

Intermolecular Interactions (Enthalpy)

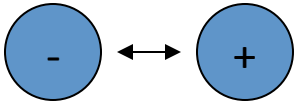
Hydrogen Bonds
Electrostatic Interactions
van der Waals Forces
π – π Interactions

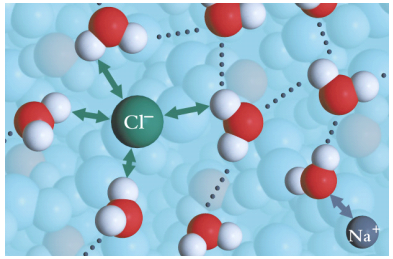
Entropy

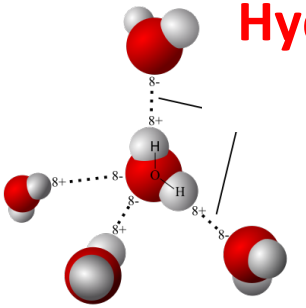
Intermolecular Interactions



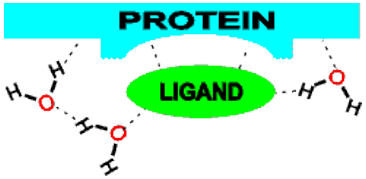
Electrostatic Interactions

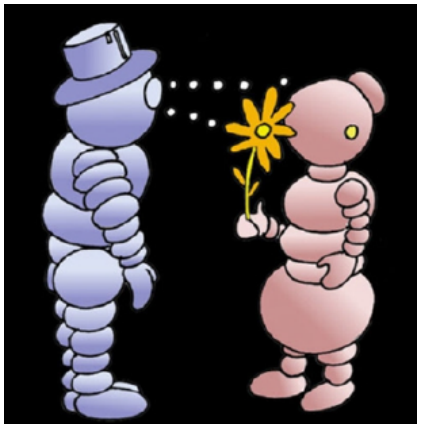




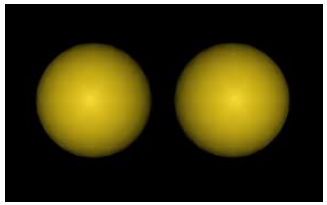


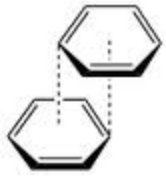
Hydrogen Bonds

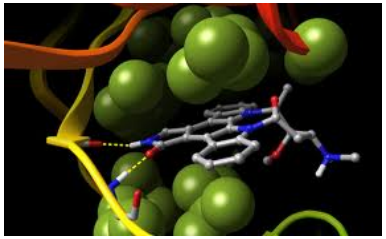




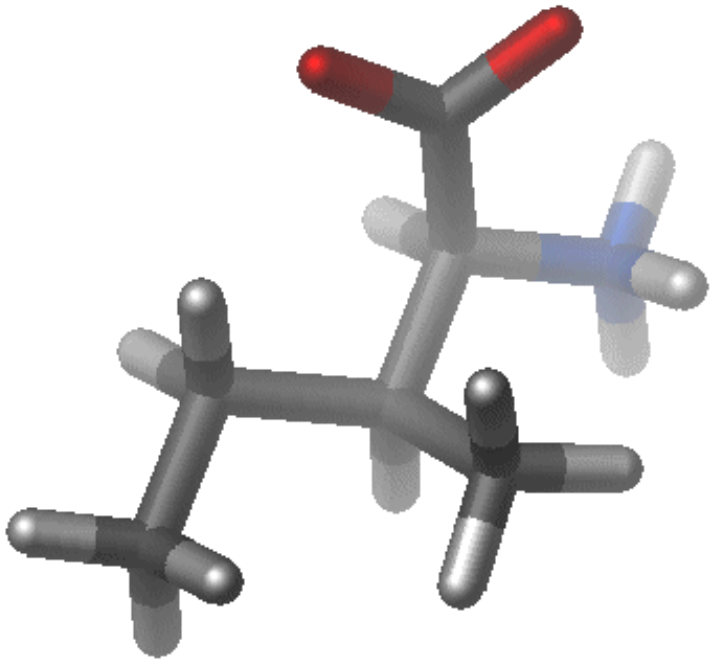
van der Waals Forces
π – π, cation - π interactions







Molecular Simulations?



Nobel Prize in Chemistry 2013

Nobel Prizes and Laureates
Chemistry Prizes ▼ 2013

▼ About the Nobel Prize in Chemistry 2013
Summary
Prize Announcement
Press Release
Advanced Information
Popular Information
Greetings

▶ Martin Karplus
▶ Michael Levitt
▶ Arieh Warshel

All Nobel Prizes in Chemistry
All Nobel Prizes in 2013

The Nobel Prize in Chemistry 2013
Martin Karplus, Michael Levitt, Arieh Warshel

The Nobel Prize in Chemistry 2013


© Nobel Media AB
Martin Karplus


Photo: Keilana via Wikimedia Commons
Michael Levitt


Photo: Wikimedia Commons
Arieh Warshel

The Nobel Prize in Chemistry 2013 was awarded jointly to Martin Karplus, Michael Levitt and Arieh Warshel *"for the development of multiscale models for complex chemical systems"*.

MD Simulations study structure + dynamics

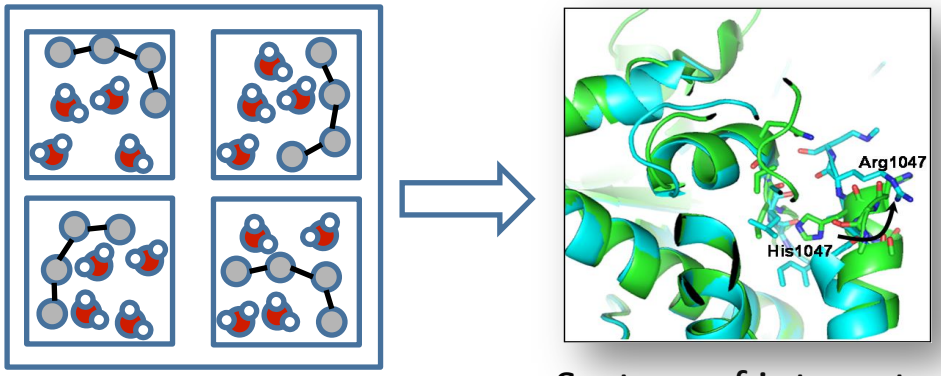
Is there a fast and efficient way to study the structure and dynamics of biomolecules in atomic-level detail?

Molecular Dynamics simulations

Step 1. Model the potential energy and use coordinates from experimental structures and assign initial velocities (Etotal = Epotential + Ekinetic)

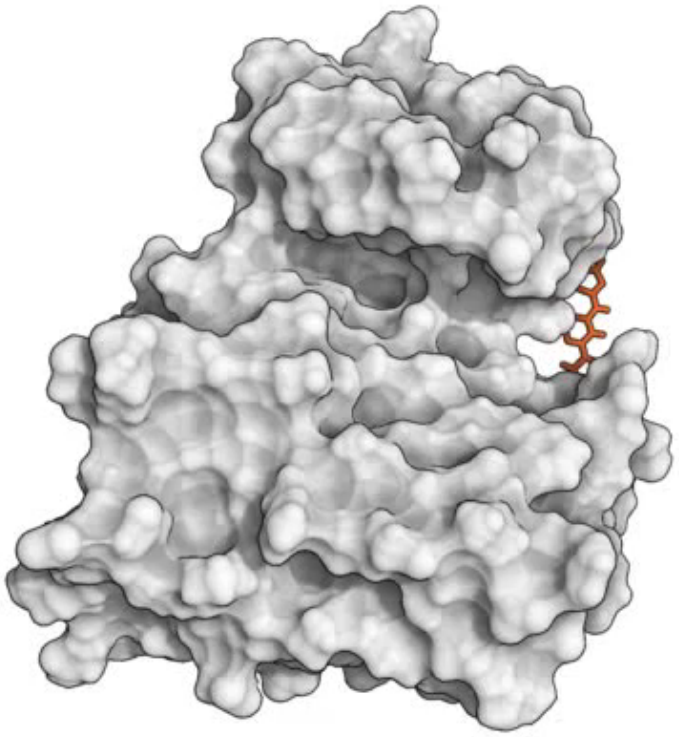
Step 2. Integrate Newton's second law and get the new velocities (**v**) of the system and the new coordinates (**r**) of the atoms

Step 3. Macroscopic properties can be expressed through **v** and **r** *via statistical mechanics*

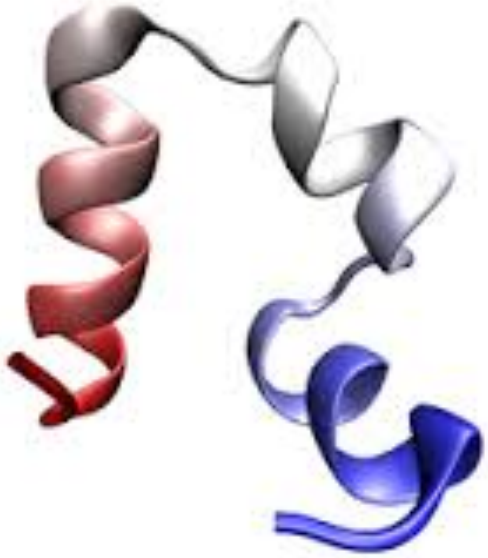


System of interest

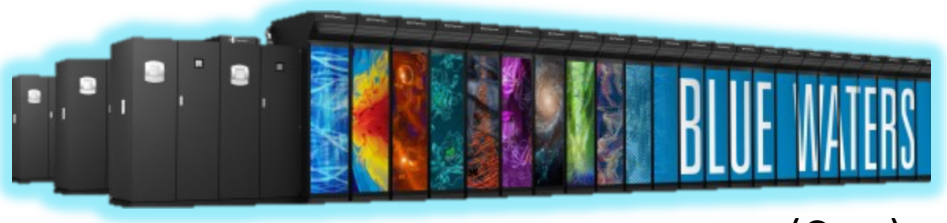
Examples of MD simulations of proteins



Shan et al (2011)
Cancer drug dasatinib binding on Src kinase



Schulten et al (2012)
Folding of the Villin Headpiece protein



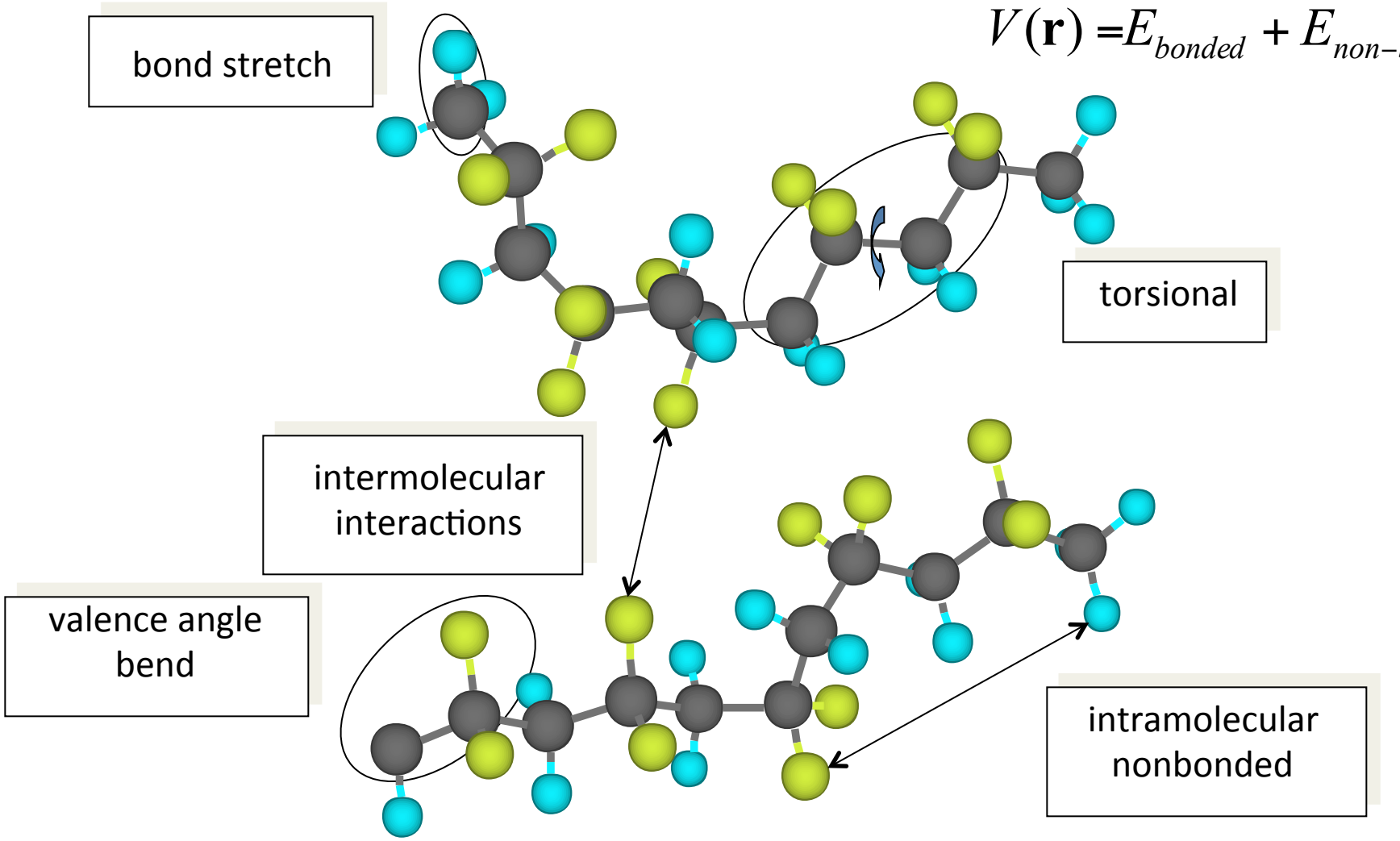
(Cray)

The Potential Energy Function (Force Field)

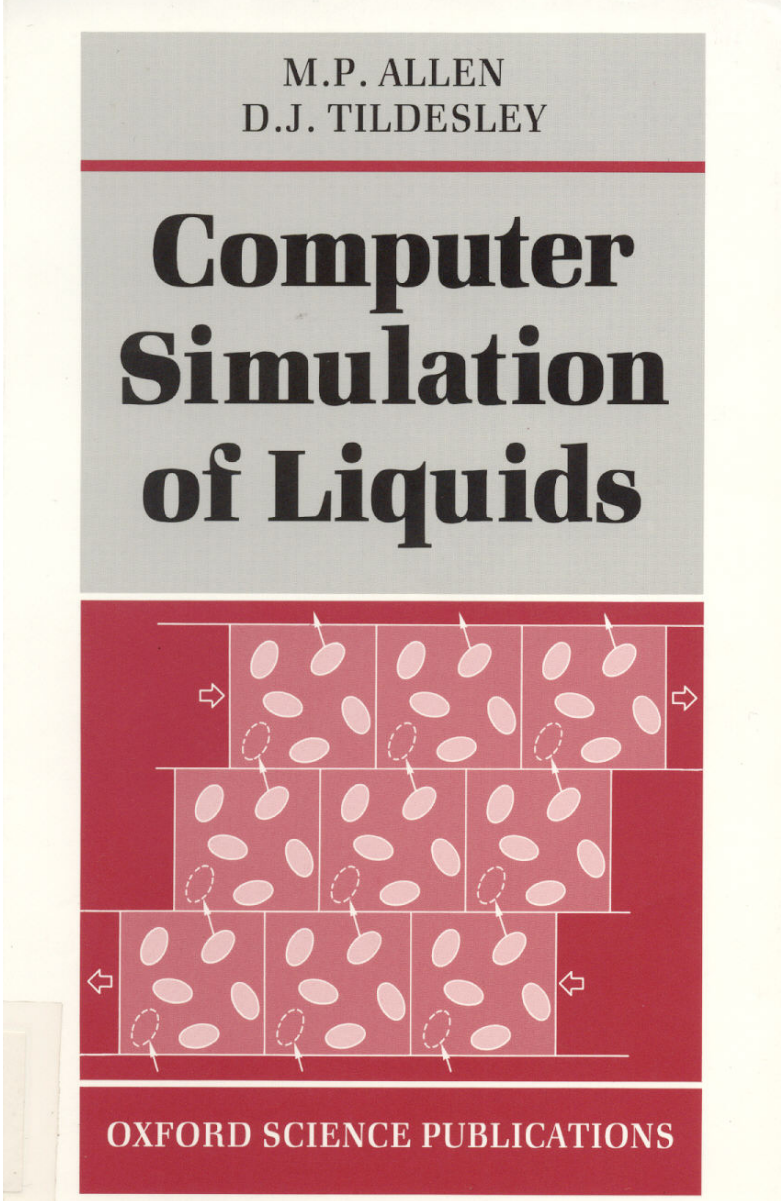
The energy of the system is represented by the Hamiltonian:

$$H = K + V = \frac{1}{2} m\mathbf{v}^2 + V(\mathbf{r})$$

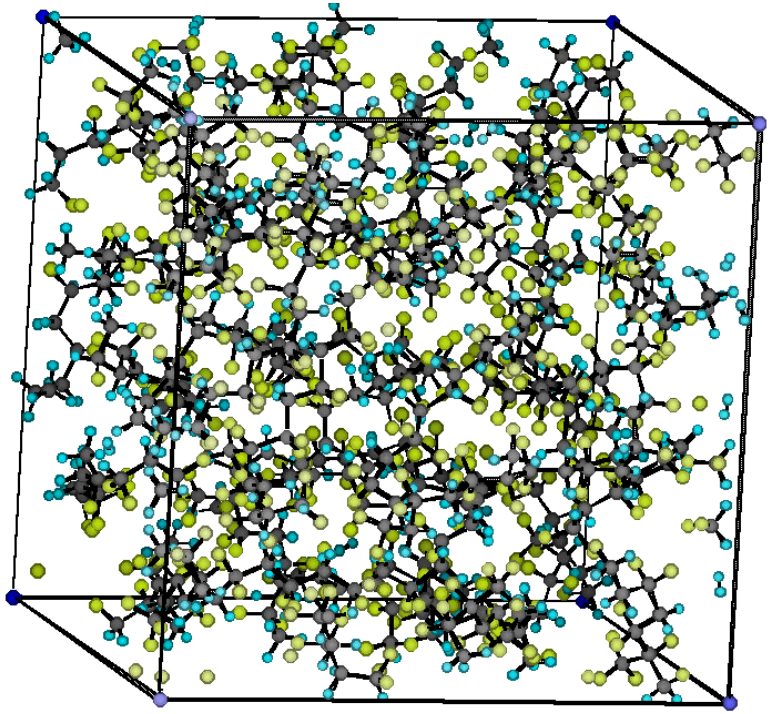
$$V(\mathbf{r}) = E_{bonded} + E_{non-bonded}$$



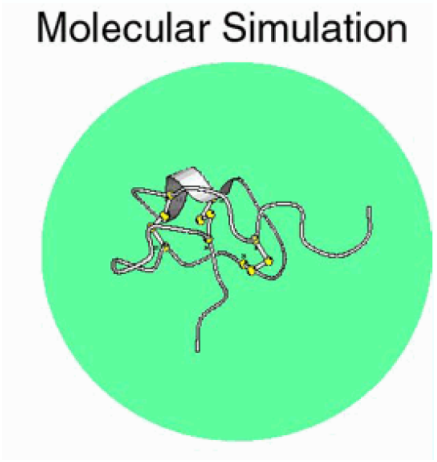
Periodic Boundary Conditions



- *Goal:* To simulate 'infinite' system
- Particles experience forces as if they were in a bulk fluid
- If one molecule leaves the box then it is replaced by an image particle that enters from the opposite side



Statistical Mechanics



Microscopic Description

Macroscopic Description

Quantum Mechanics:
Eigenvalues E_i and eigenfunctions $\Psi(r_1,r_2,\ldots,r_N)$ of Schrodinger's equation

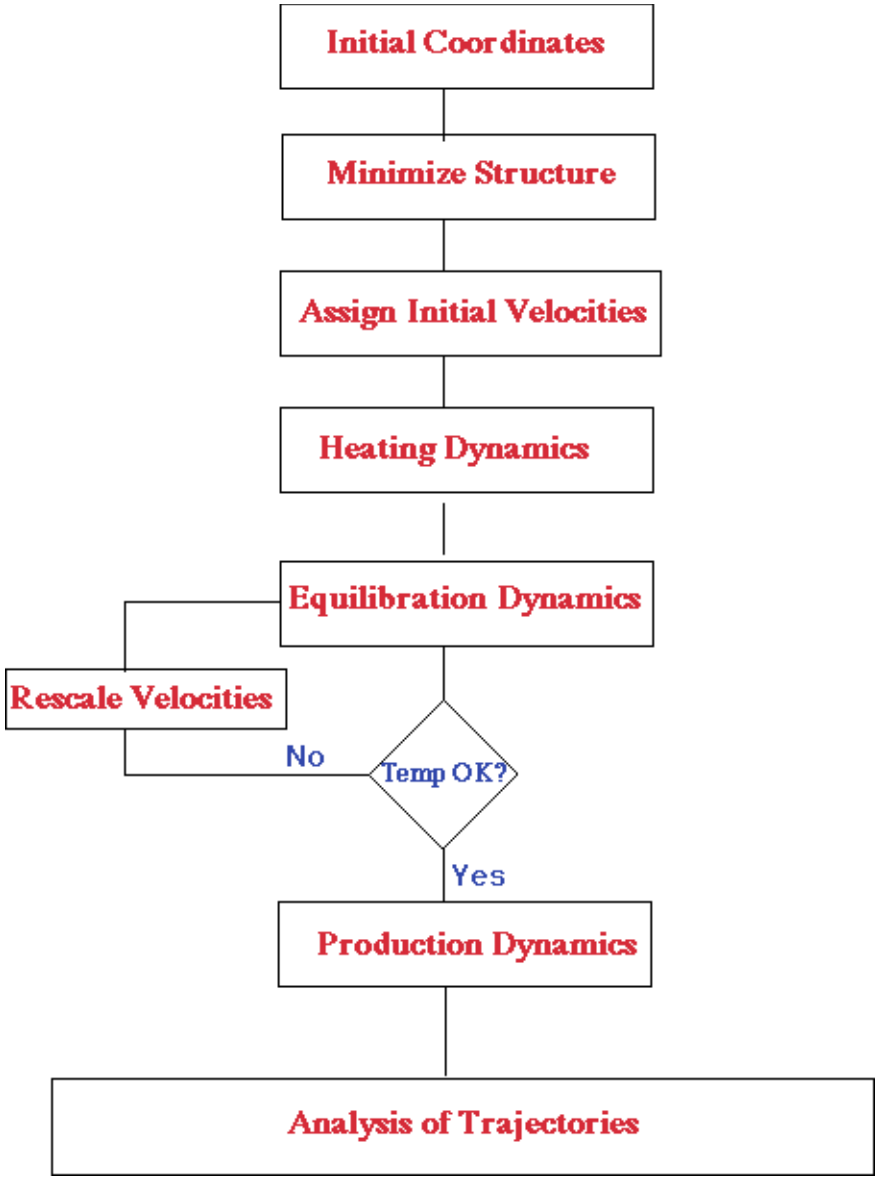
Molecular Mechanics:
Kinetic and Potential energy E(**r,v**)

Thermodynamics:

Relations for the system at equilibrium and non-equilibrium states

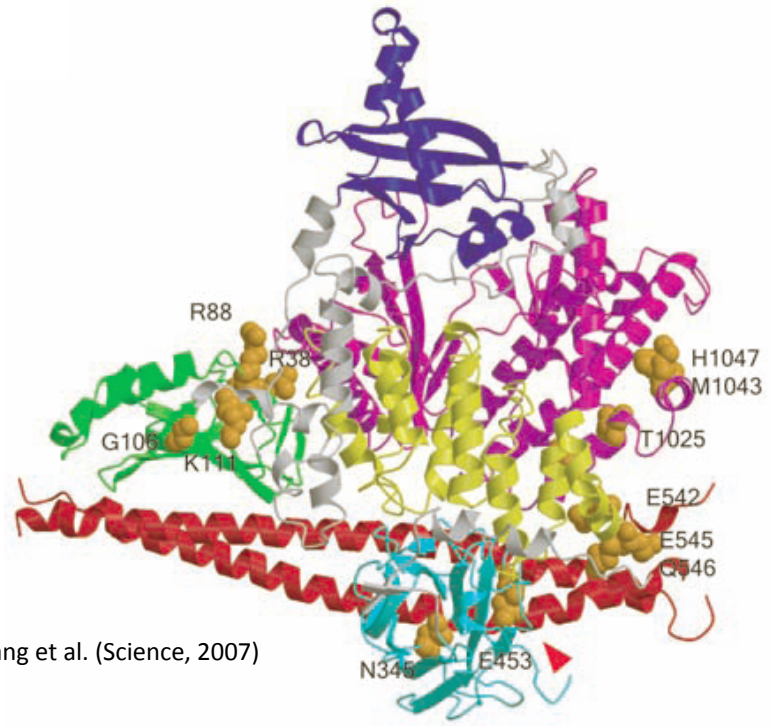
- Use statistical mechanics to derive macroscopic properties from the microscopic picture

Running an MD simulation



Case study: mutated protein PI3Kα

- PI3Ka is a membrane-associated lipid kinase
- Involved in cell growth, proliferation, differentiation
- Most commonly mutated kinase in the human genome ⇒ cancer



Huang et al. (Science, 2007)

80% of all mutations:

Glu545Lys | His1047Arg

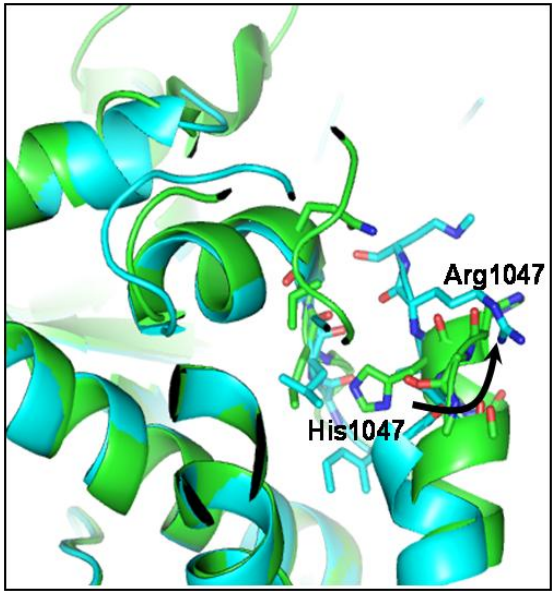
30% of breast cancer patients

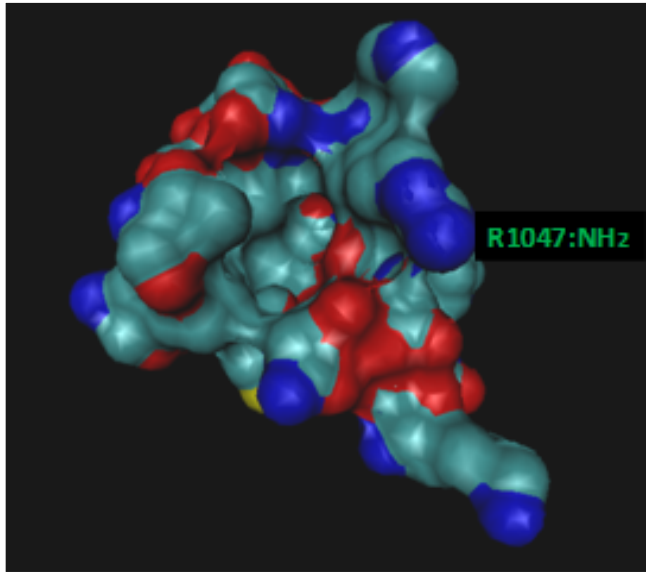
Mechanism of overactivation?

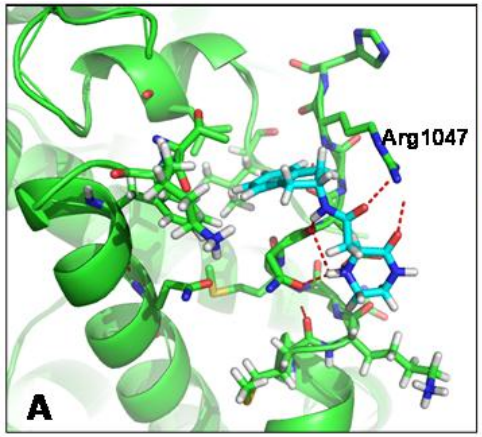
Mutant and isoform specific therapies?

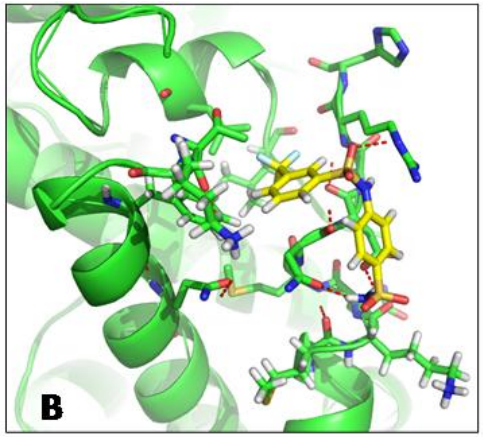
MD Simulations
Virtual screening
Property prediction
***In vitro* & *In vivo* assays**
Lead Optimization

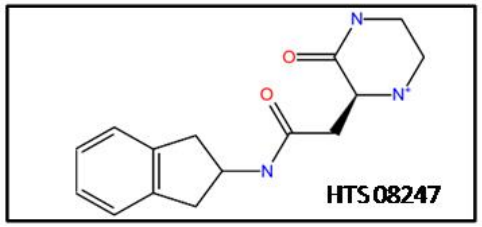
The H1047R mutant of PI3Kα opens up a crevice

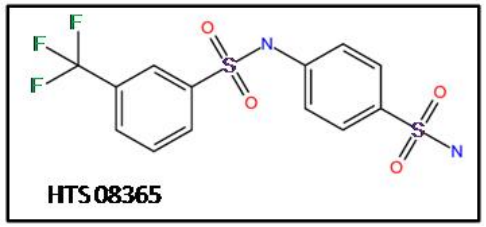




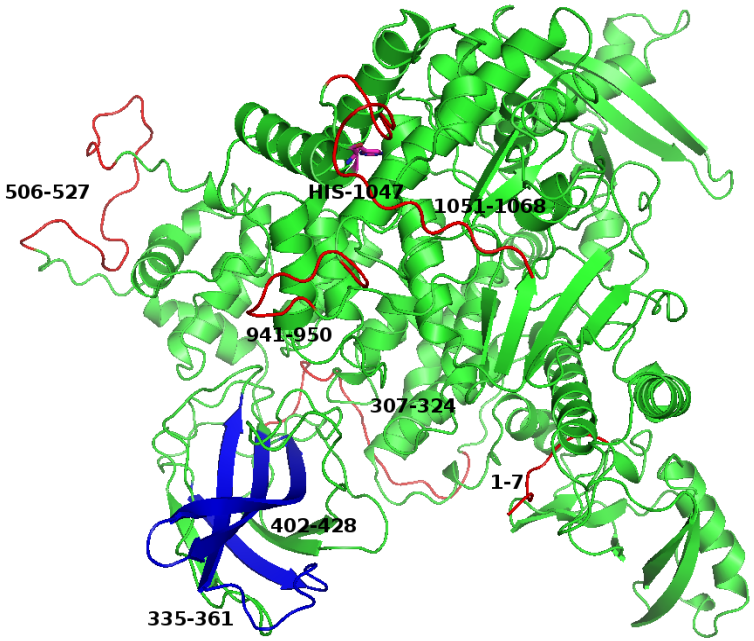




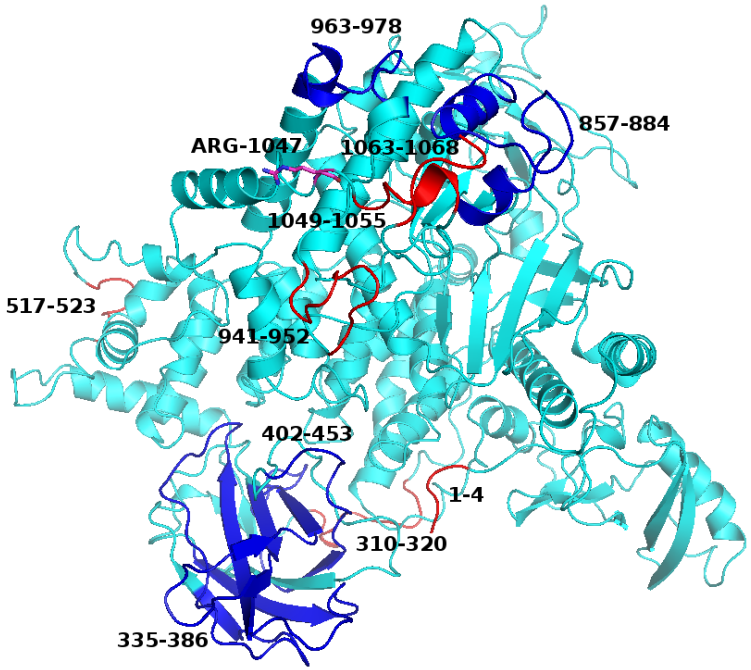




MD Simulations of WT and H1047R PI3Kα



Model of the WT p110a subunit based on 2RD0 X-ray structure

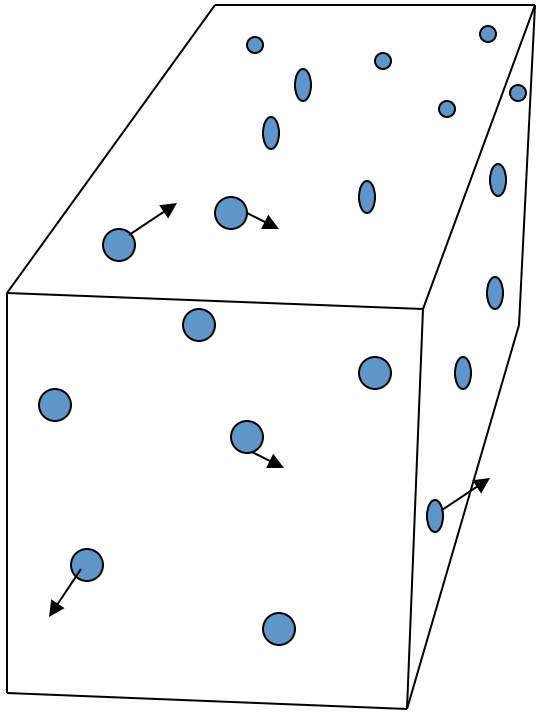


Model of the H1047R p110a subunit based on 3HIZ X-ray structure

- WT and H1047R PI3Kα (modeling of p110α), 300K atoms
- 100-150 ns equilibration, 100 ns production run, NPT, NAMD+CHARMM
- **FIVE** independent MD simulations of each protein
- Total simulation time (~1μs)

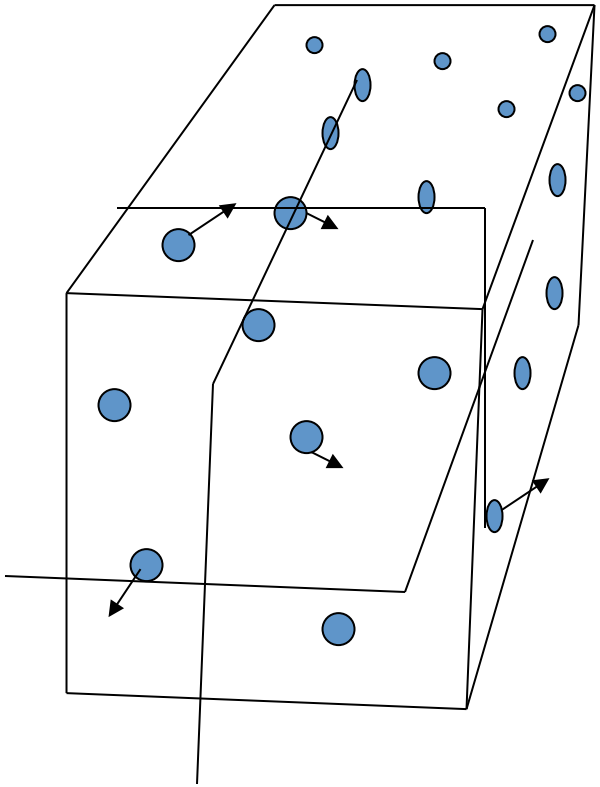
MD Simulator requirements

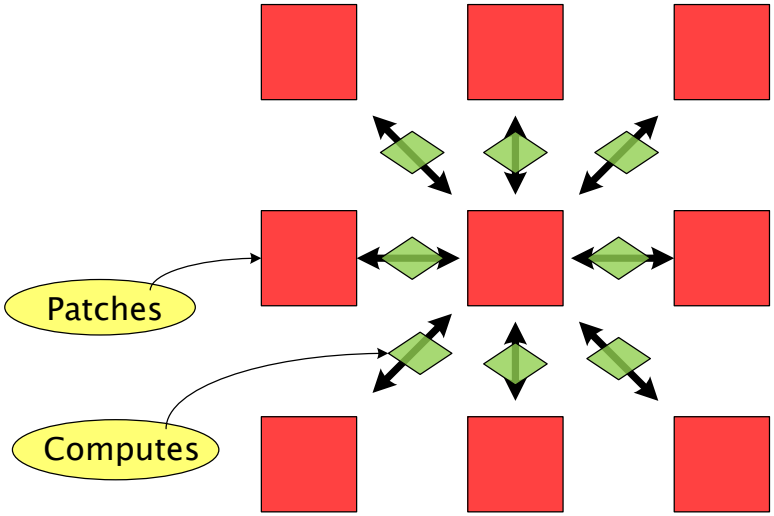
- Parallelization
- (getting an idea of the level of computation needed)
- For every time step, every atom must communicate within its *cutt-off radius* with every other atom.
- A lot of inter-processor communication that can be scaled well is needed.



MD Simulator requirements

- Parallelization
- (getting an idea of the level of computation needed)
- Whole System is broken down into boxes (processing nodes)
- Each node handles the bonded interactions within a cutoff





PRACE

Europe's Supercomputing Research Infrastructure

How many cores should be used?

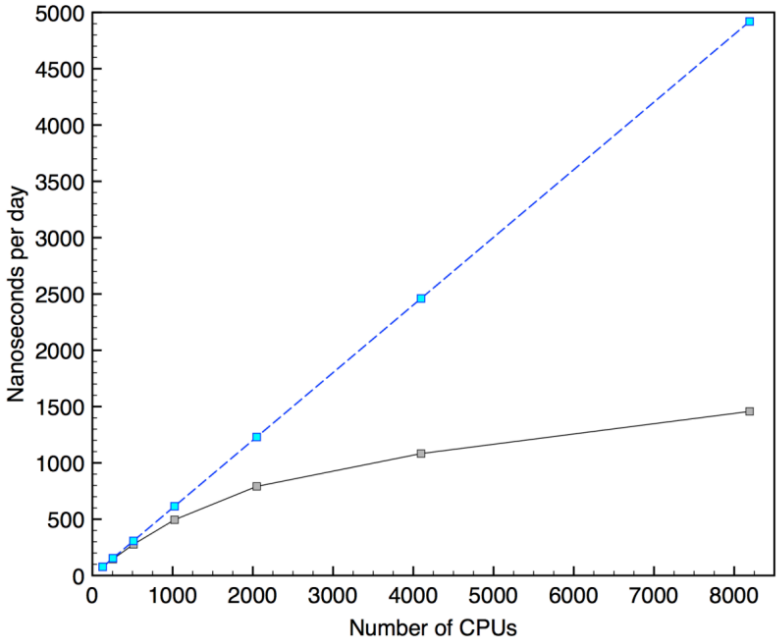
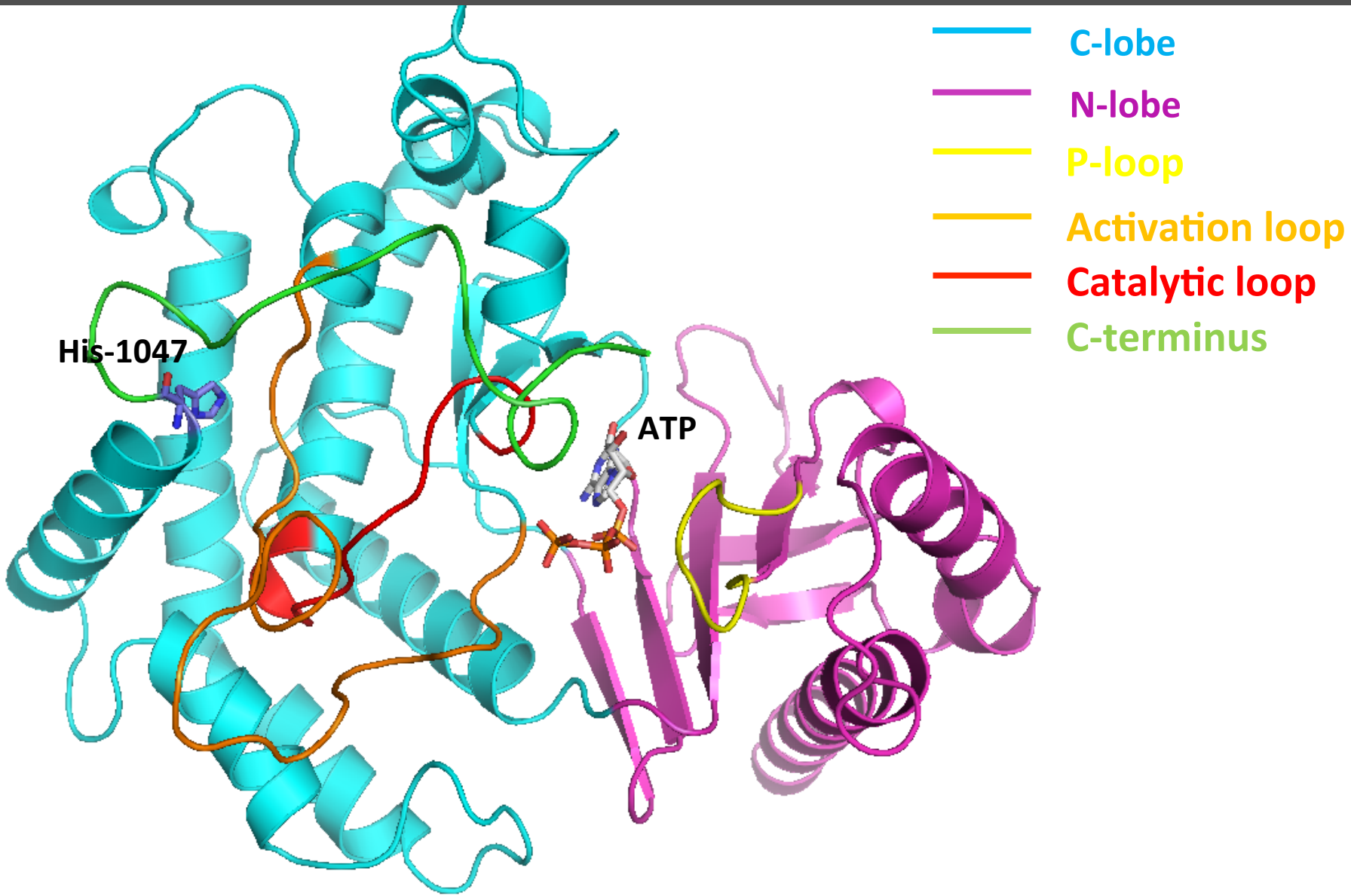


Figure 2: GROMACS performance in CURIE Thin Nodes for a system of 2M particles.

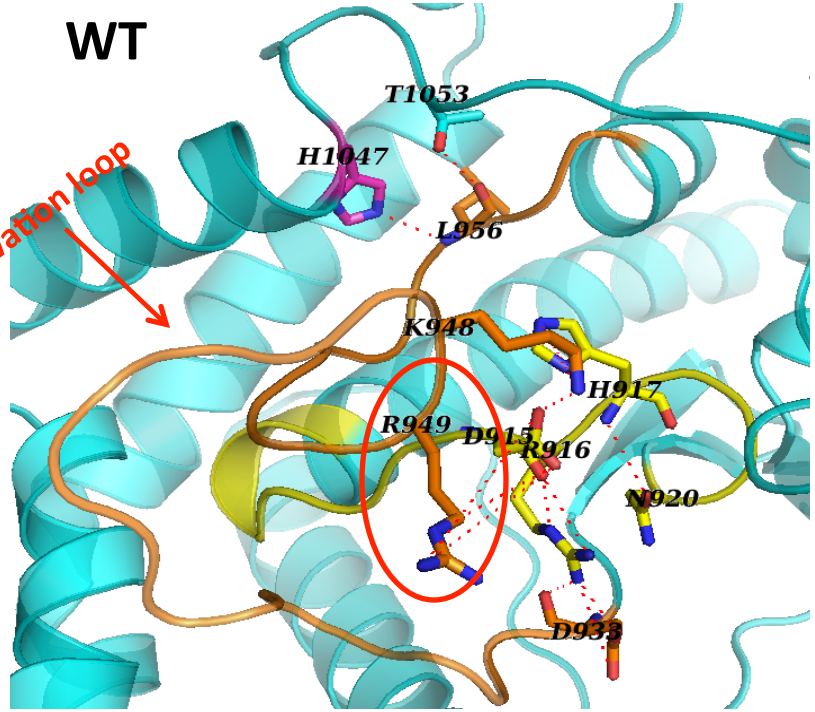
Table 1. Benchmark of a 2M-particle system on Curie Thin Nodes.

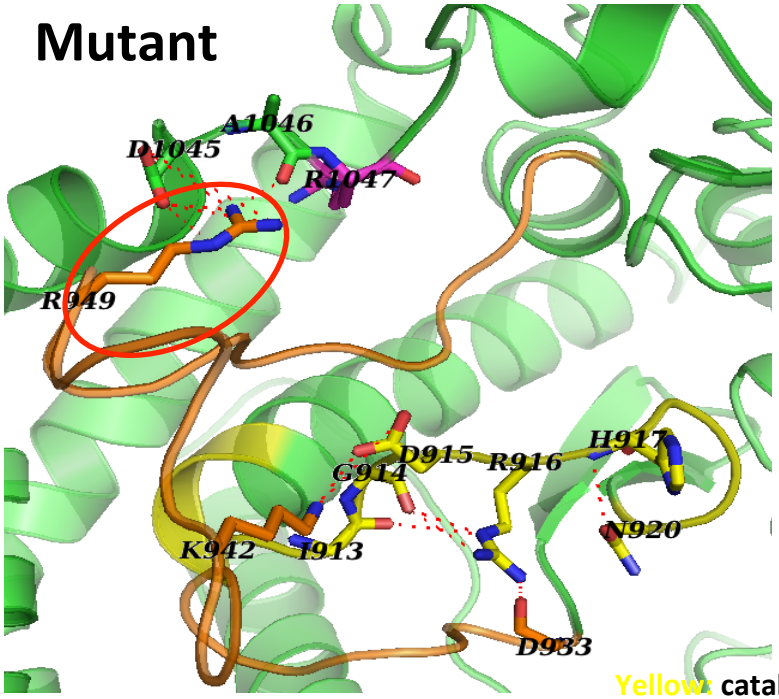
# cores	absolute timing (s)	speedup
128	1124.022	1.0
256	590.897	1.9
512	312.562	3.6
1024	174.532	6.5
2048	109.207	10.3
4096	79.805	14.1
8192	59.291	19.0

Kinase Domain Organization



Hydrogen Bond Analysis



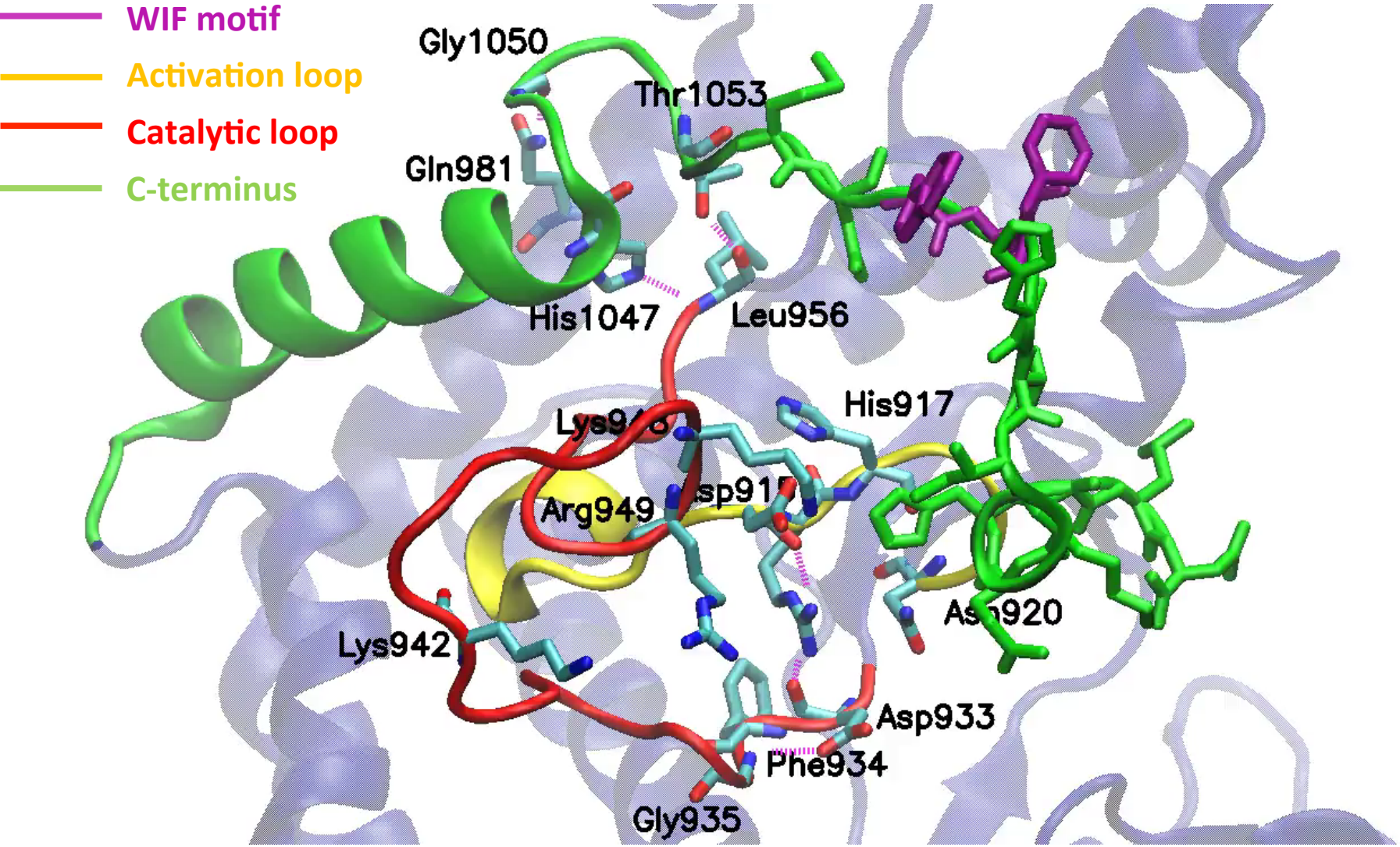


Yellow: catalytic loop
Orange: activation loop
Magenta: residue 1047

- The Hbond between activation loop Leu956 and His1047 breaks
- The α-helix of H1047 partially unfolds in the presence of 1047R
- Displacement of Arg949 creates a different Hbond network in the mutant, which changes the activation and catalytic loop positions

H917, RESPONSIBLE FOR ATP HYDROLYSIS, IS ORIENTED TOWARD THE CATALYTIC POCKET IN THE MUTANT AND AWAY FROM THE POCKET IN THE WT

Simulation of the normal protein



His-917 points away from the active site, while the C-terminus prevents the catalytic loop from reaching the ATP-binding site.

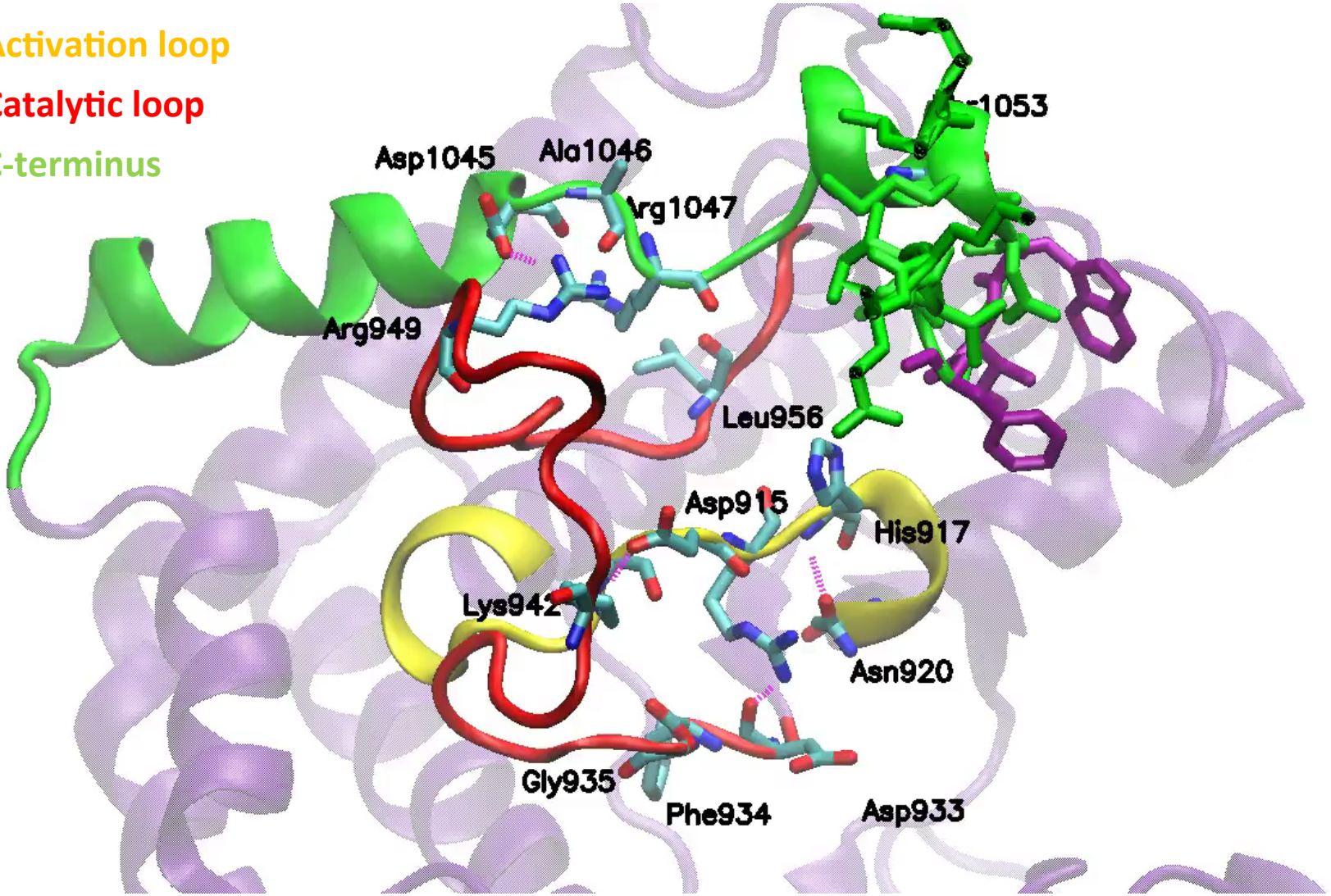
Simulation of the mutated protein

WIF motif

Activation loop

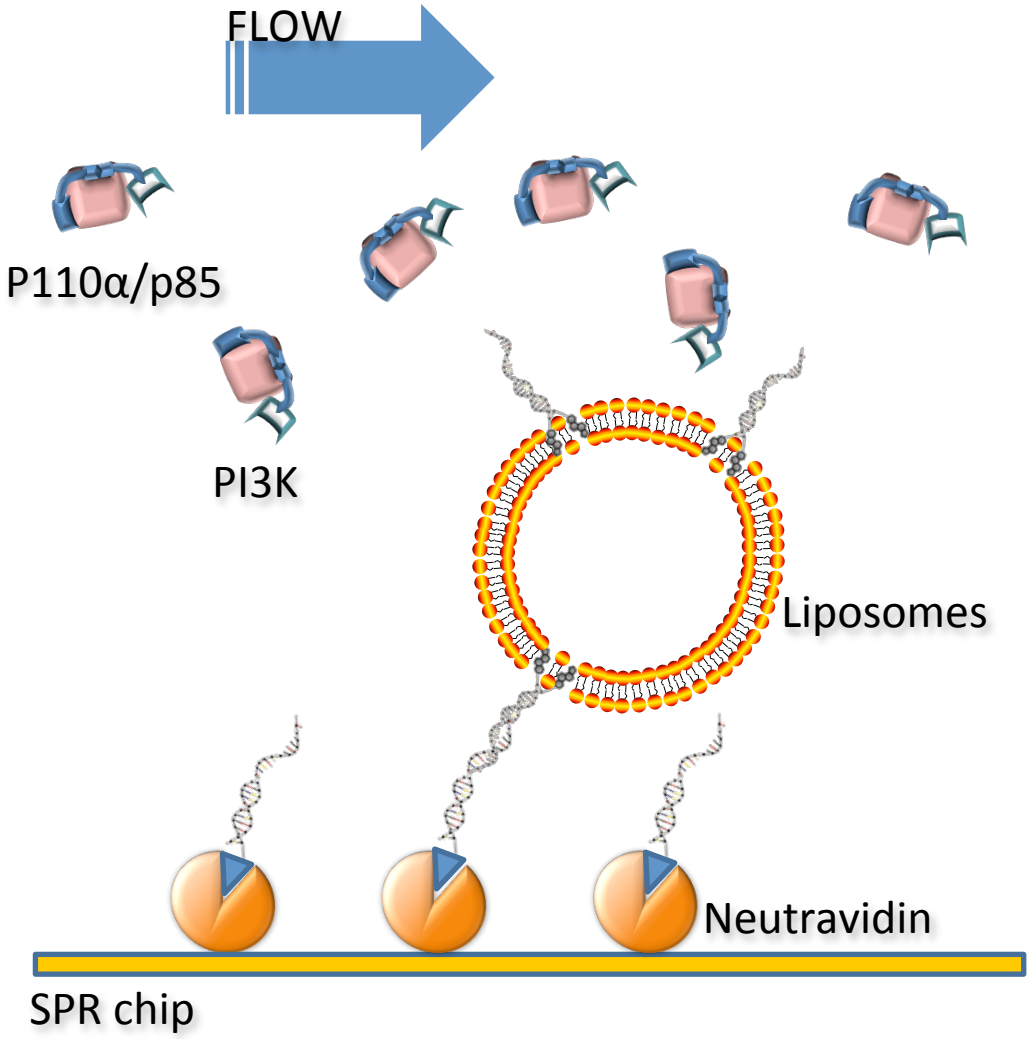
Catalytic loop

C-terminus

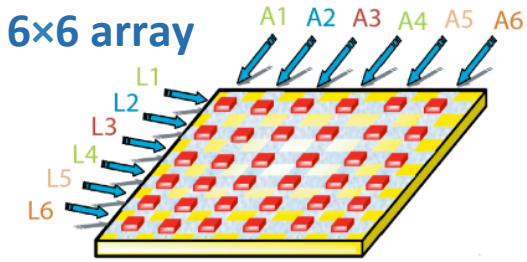


His-917 points towards the active site, while the C-terminus does not interfere with the access of the catalytic loop to the ATP-binding site.

SPR Experiments for membrane-protein binding

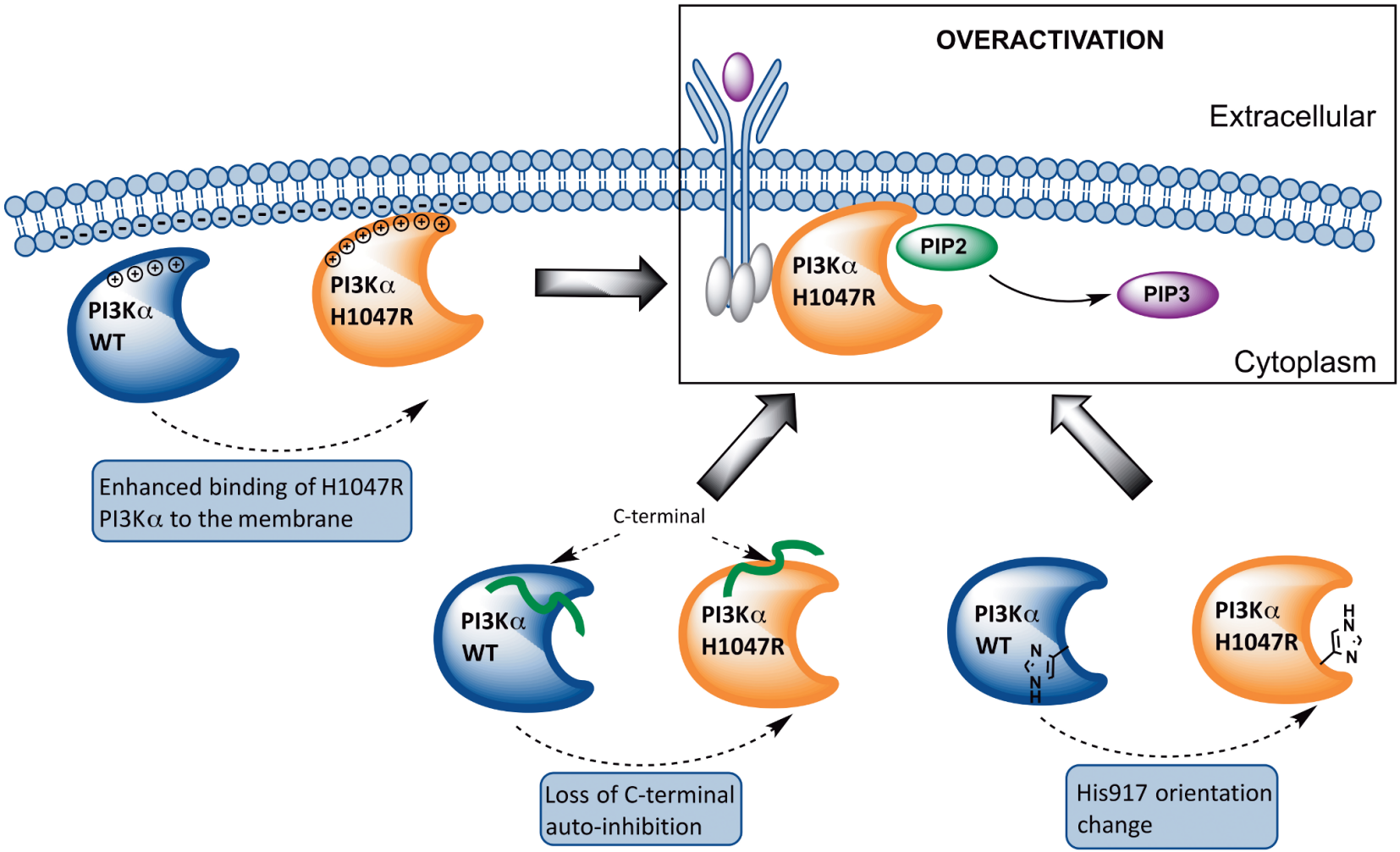


Experiments & Simulations show that the mutated protein binds more to cell membranes than the normal one



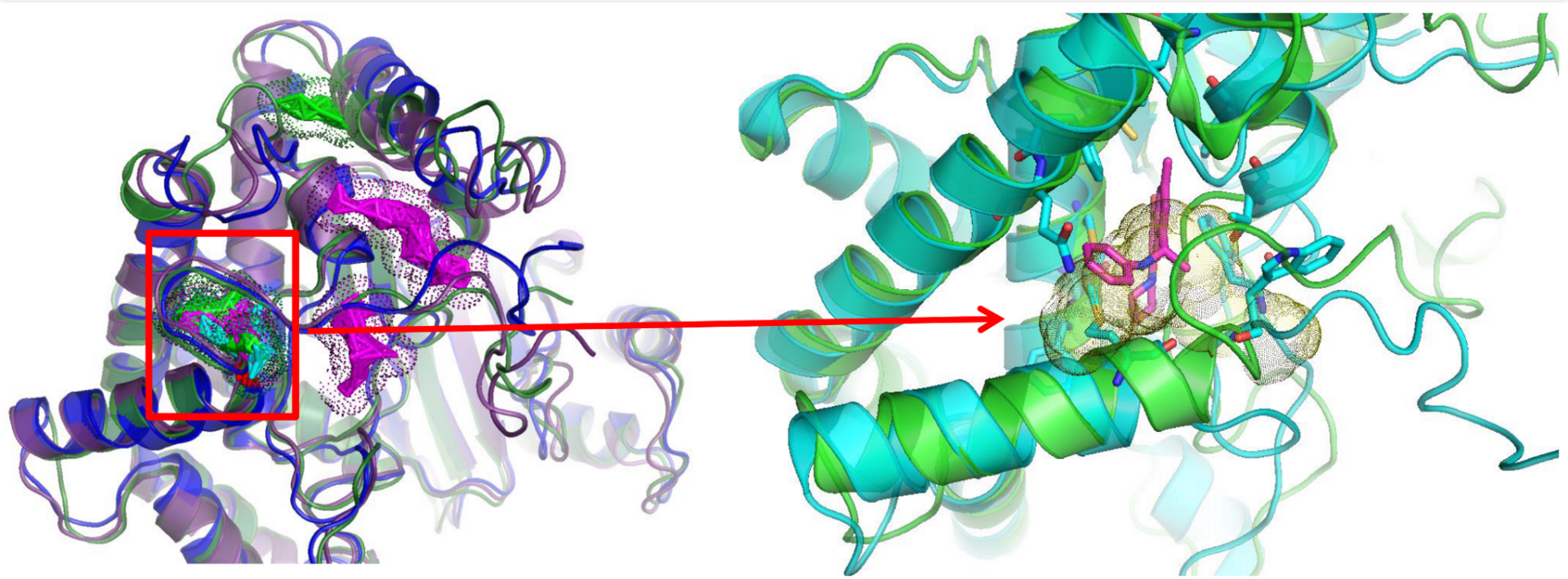
(Agianian lab, University of Thrace, Greece)

Proposed mechanism of H1047R overactivation



Gkeka et al, PLOS Comput Biol (2014)

Binding site identification on PI3Kα conformers



Binding site prediction on PI3Kα representative structures

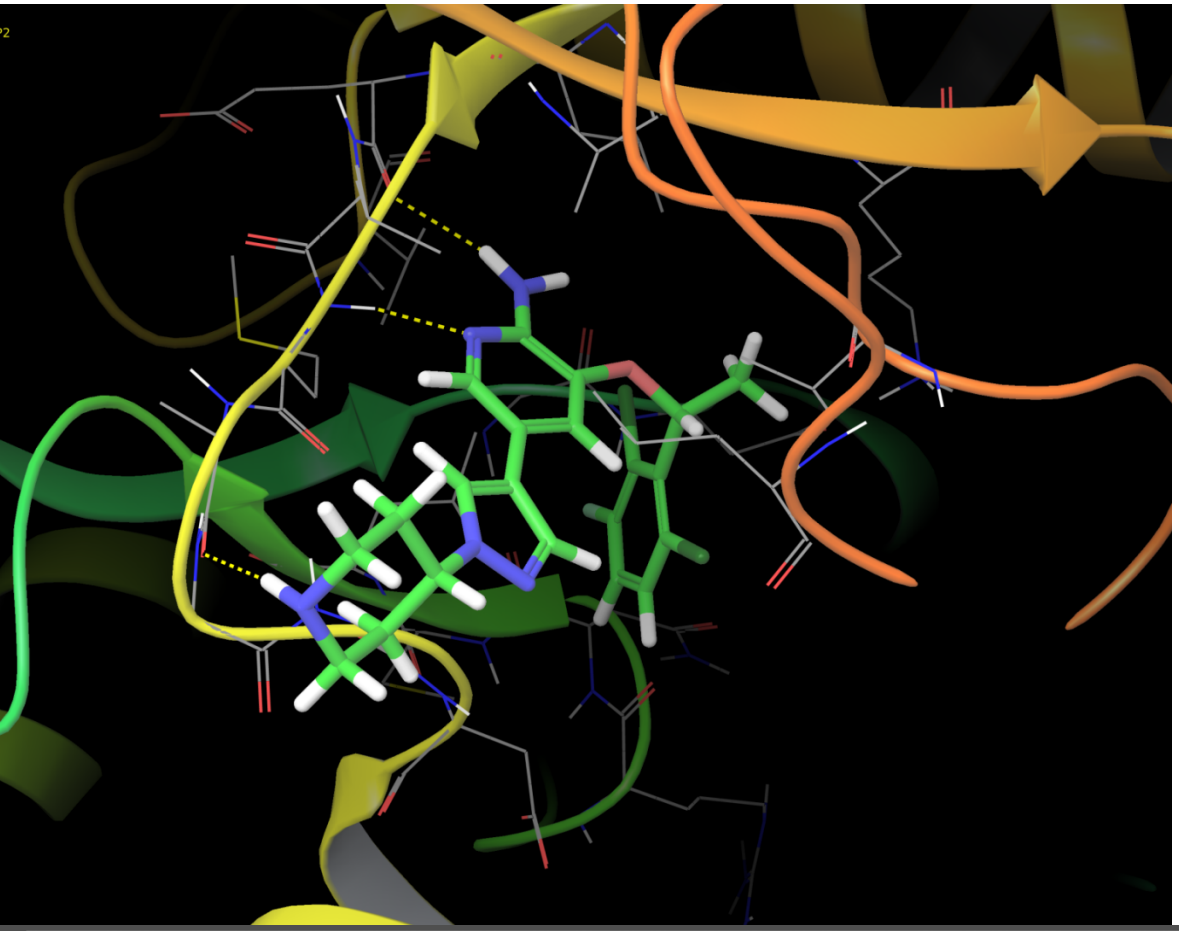
Blue: WT Crystal Structure by Hon et al (2011)

Green: Cluster conformation from MD
Dots: Predicted binding site

Does this binding site also exist in the mutant form and can it be exploited for selective drug design?

Drugs bind on protein pockets through chemical interactions

Structure of the anaplastic lymphoma kinase (ALK)
Complexed with the drug crizotinib – (PDB ID: 2XP2)



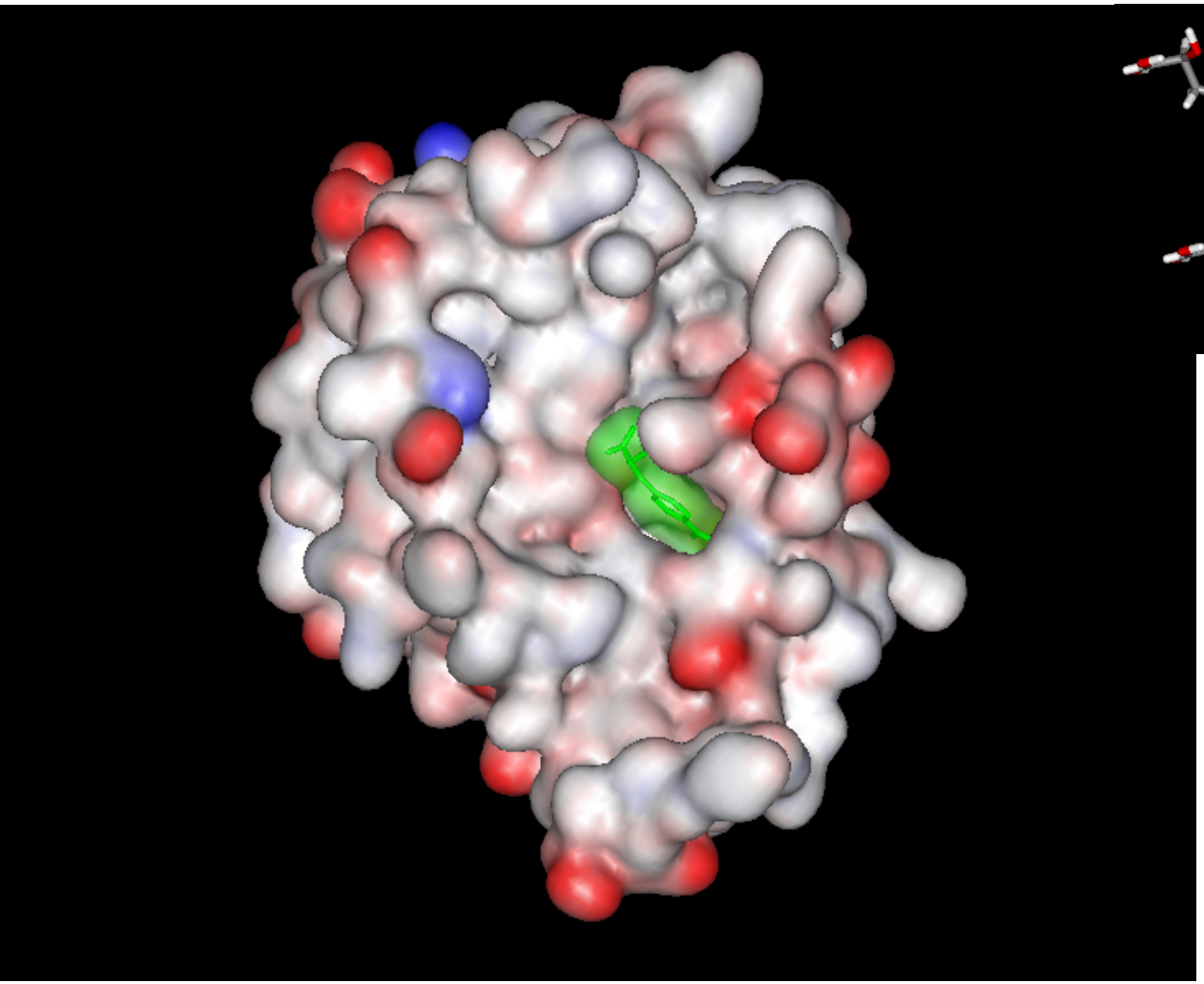
Protein-Ligand interactions:

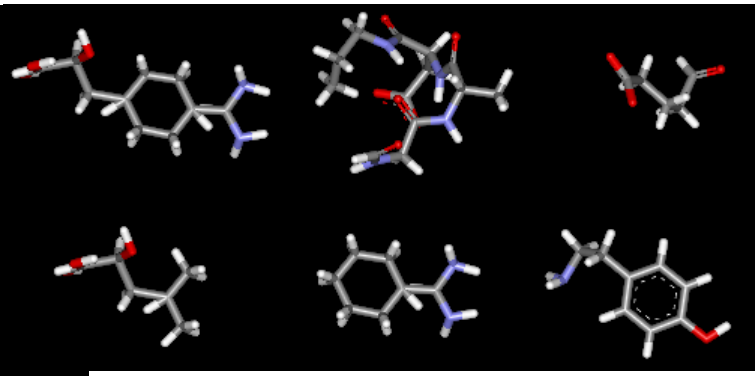
Intermolecular Interactions (Enthalpy)

Hydrogen Bonds
Electrostatic Interactions
van der Waals Forces
π – π Interactions

Entropy

Computing protein-drug structure

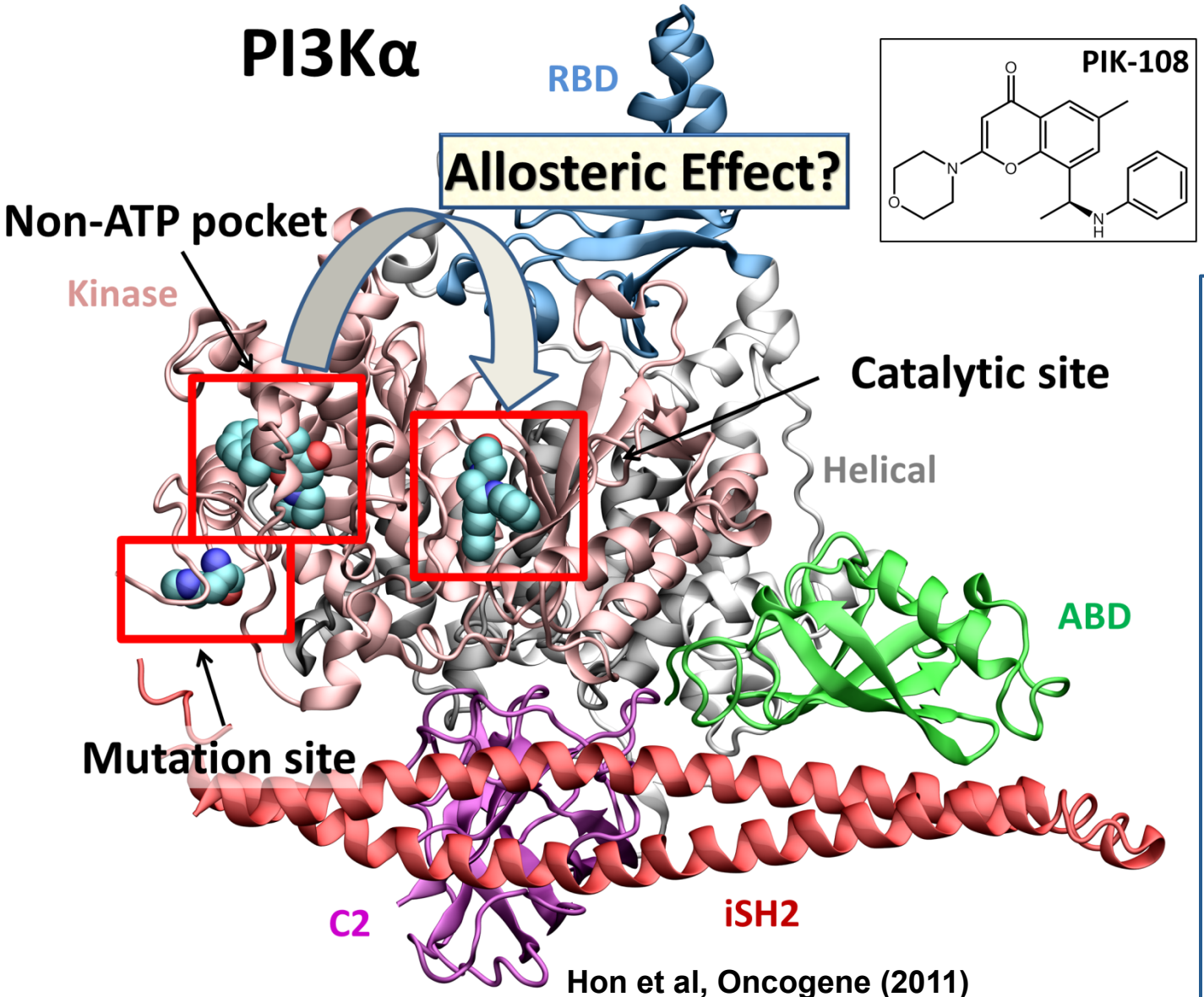




Virtual Screening

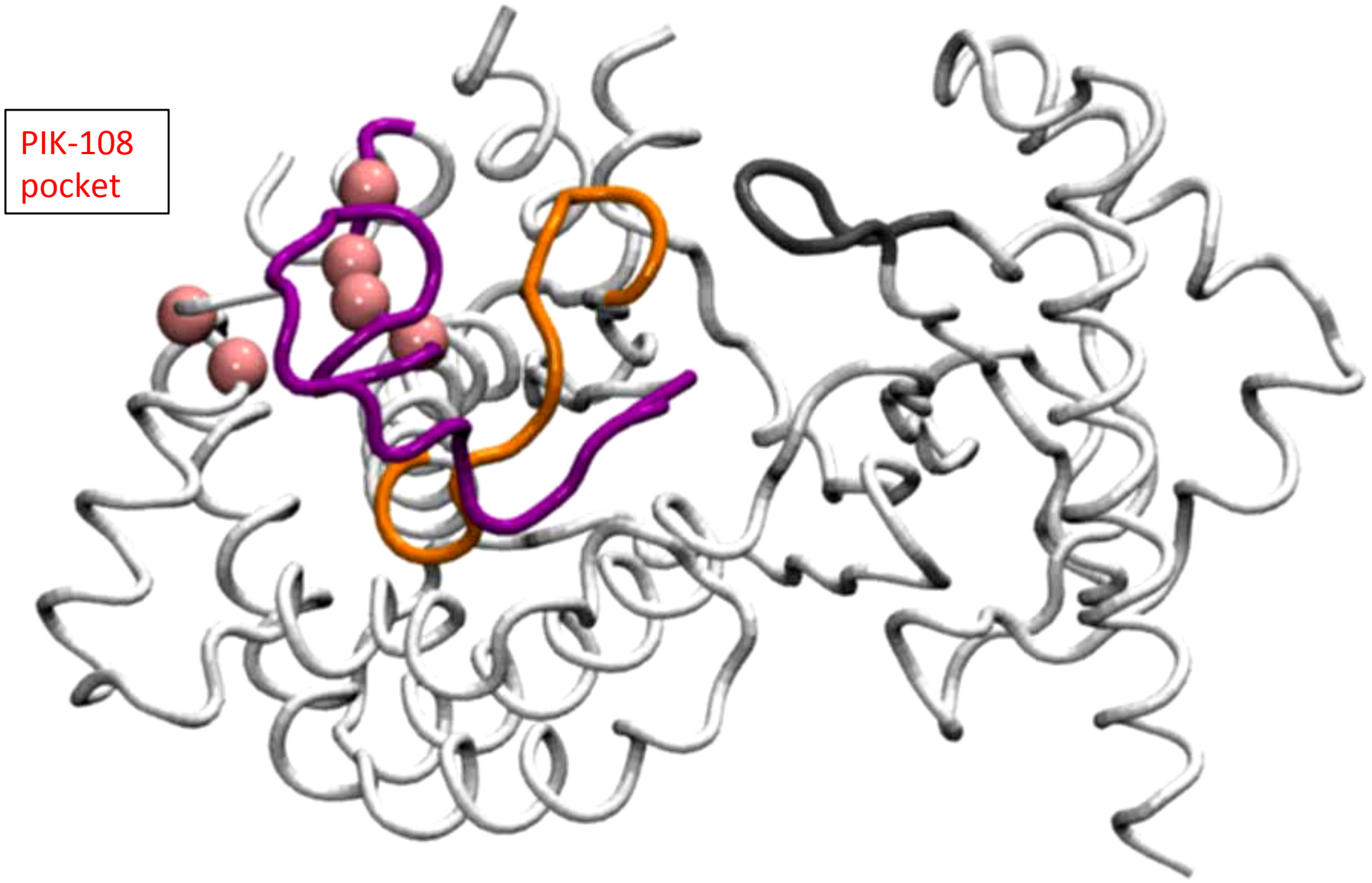
https://www.youtube.com/watch?v=u49k72rUdyc

Mutant-specific drugs in “allosteric” pockets



- Active site and non-ATP pocket occupied by **PIK-108**
- MD simulations of WT, H1047R apo and holo forms (100ns production run)
- Is the non-ATP pocket allosteric?
- **Can we discover allosteric pockets with simulations?**

Assessment of allosteric pockets with PCA



Binding site Prediction

Crystal structure

↓

Molecular Dynamics

↓

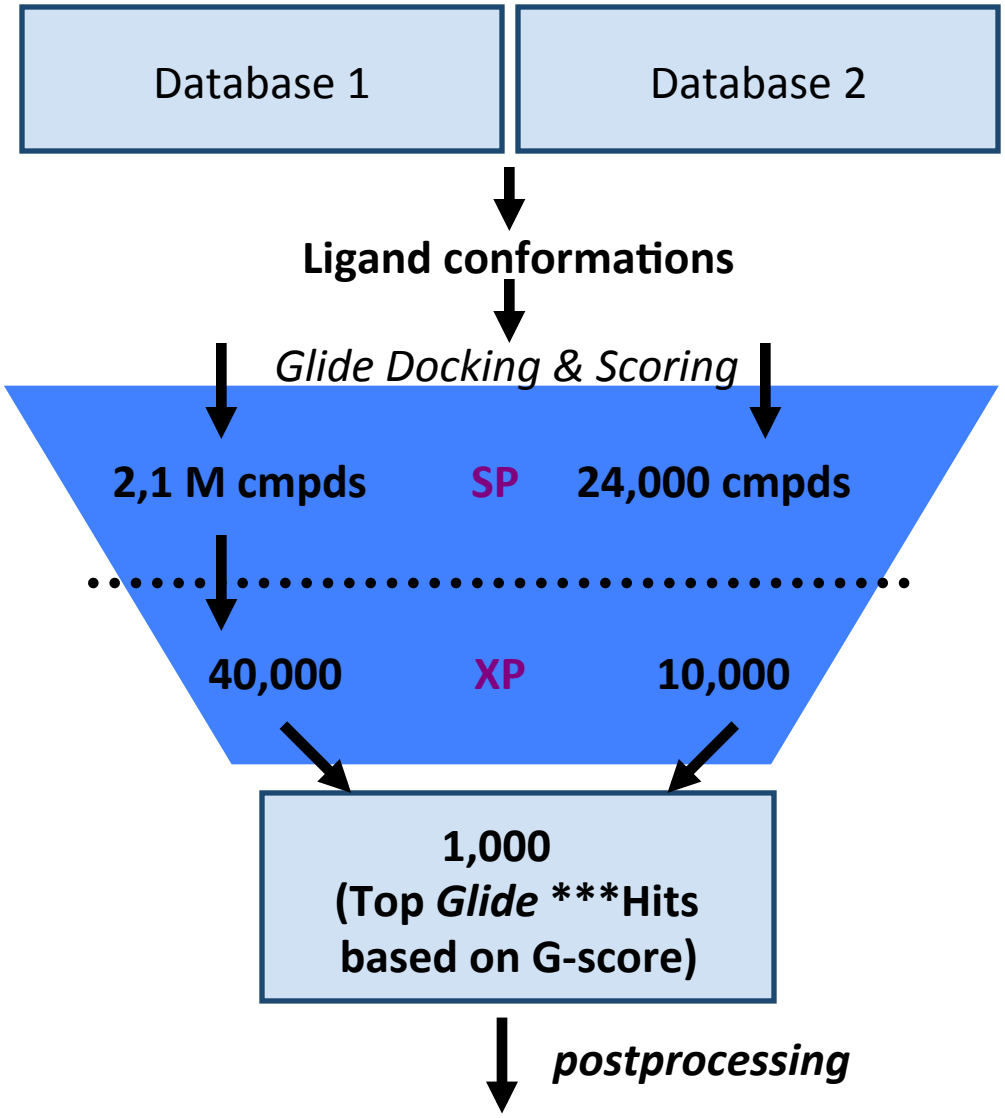
Cluster conformations from trajectory (*RMSD*)

↓

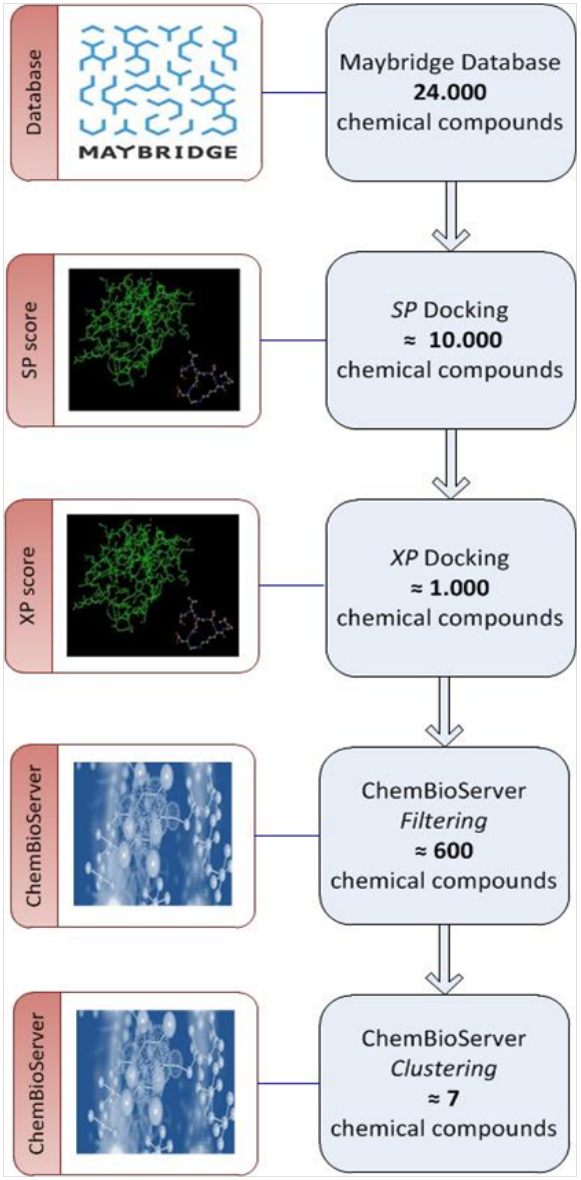
Binding site prediction and *confirmation for allosteric pockets*
(Q-Site Finder, PCA)

Lionta et al, *Curr Top Med Chem* (2014)

Virtual Screening



How are compounds selected for assaying?

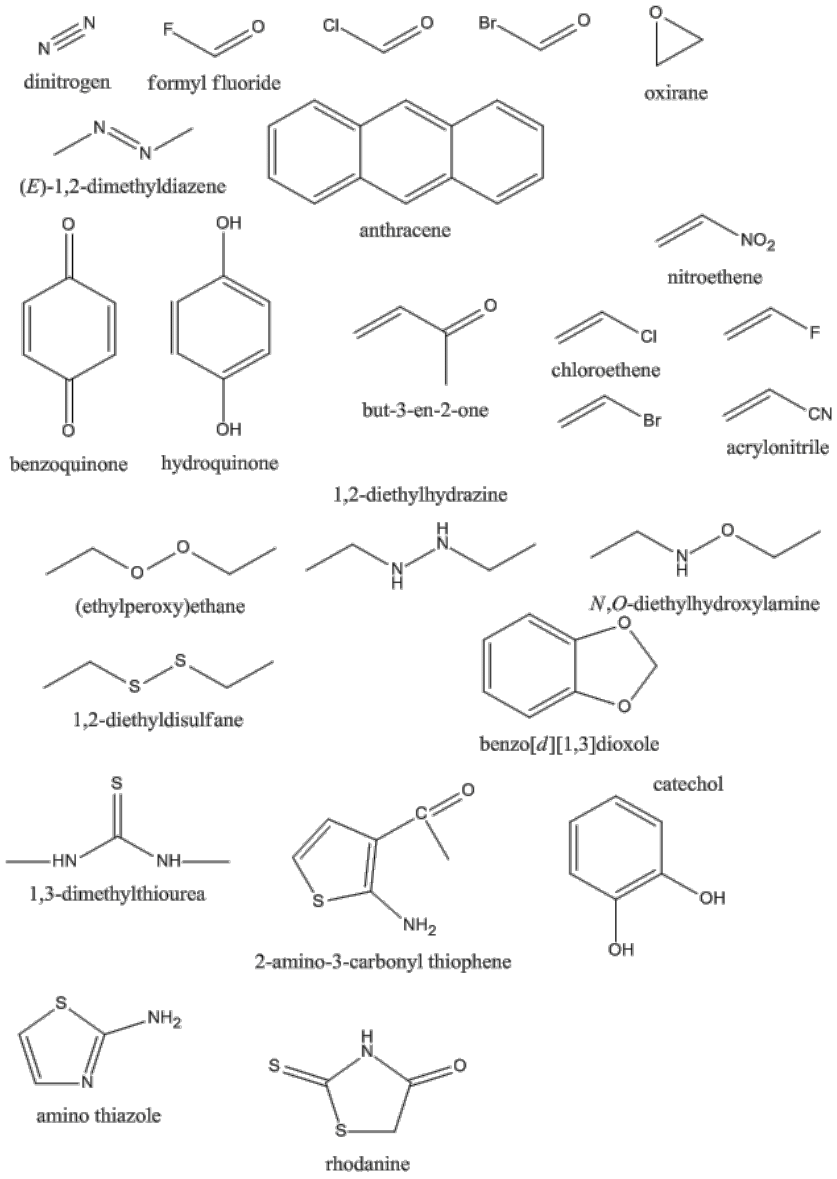


- **Library docking using Glide SP, XP**
- **1000 Top-scored XP compounds**
- **Postprocessing with ChemBioServer**
- **Calculate ADME/tox properties**
- **Check for bad vdW contacts**
- **Hierarchical Clustering**
- **Affinity Propagation (exemplars)**
- **Visualization: check for compound conformations**

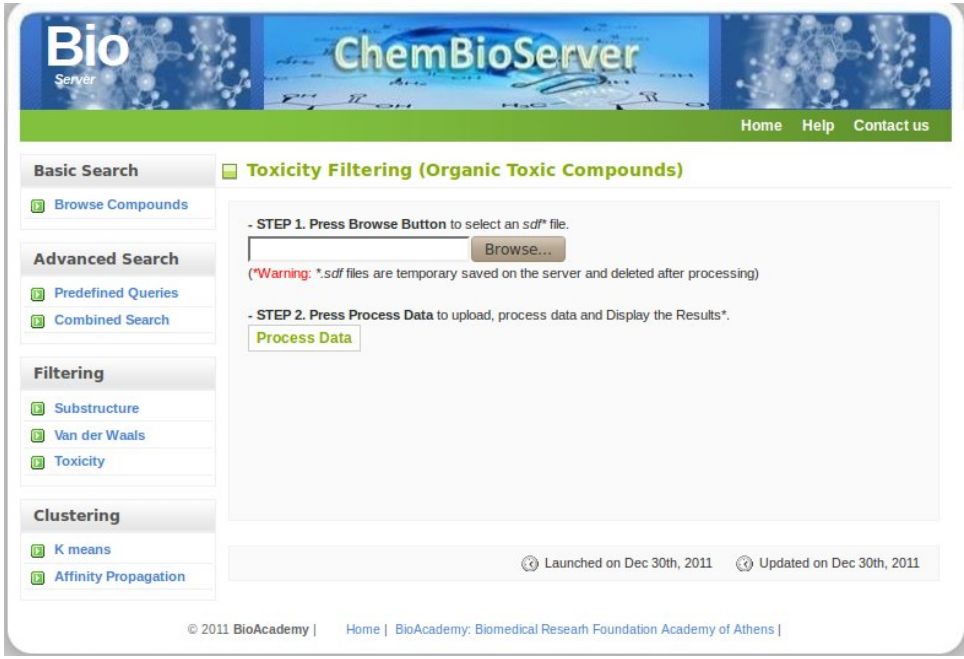
http://bioserver-3.bioacademy.gr/Bioserver/ChemBioServer/

Athanasiadis, Cournia, Spyrou, *Bioinformatics* (2012)

Pre/Postprocessing with ChemBioServer

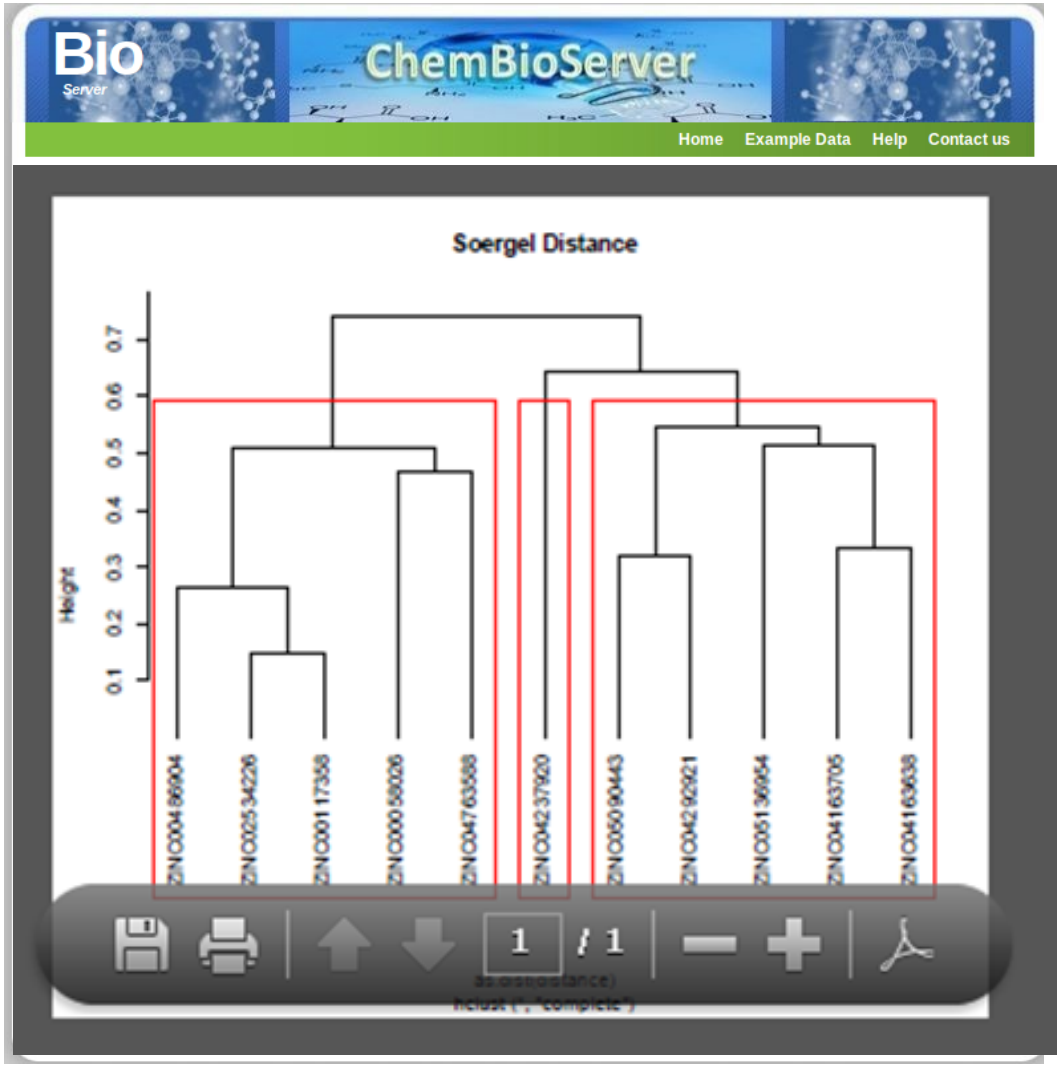


.gr/Bioserver/ChemBioServer/



Clustering and molecular similarity

Similar structures and properties ⇒ similar activity



500- 1,000 compounds

↓

Approximately 15 representative clusters

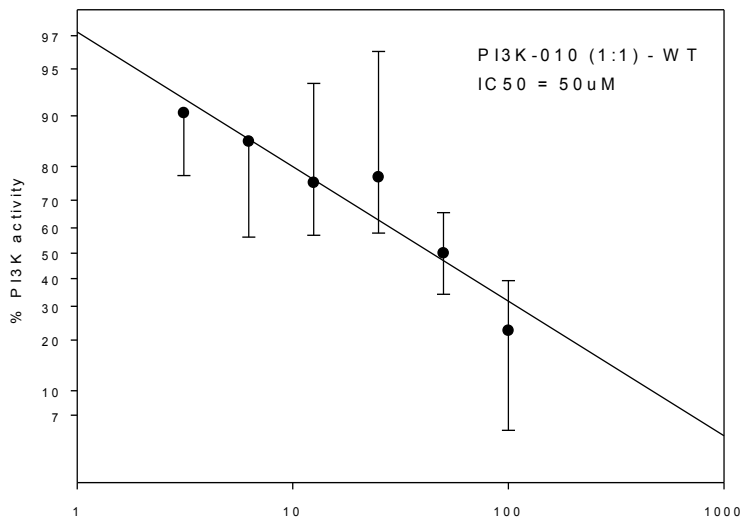
↓

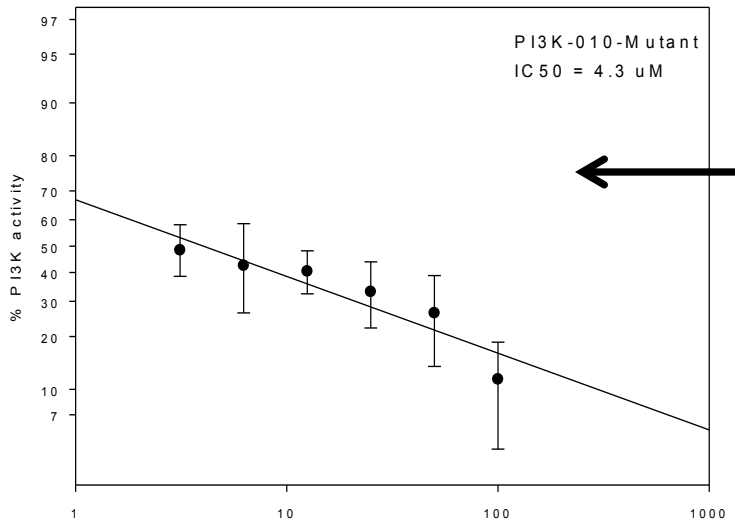
200 exemplars

↓

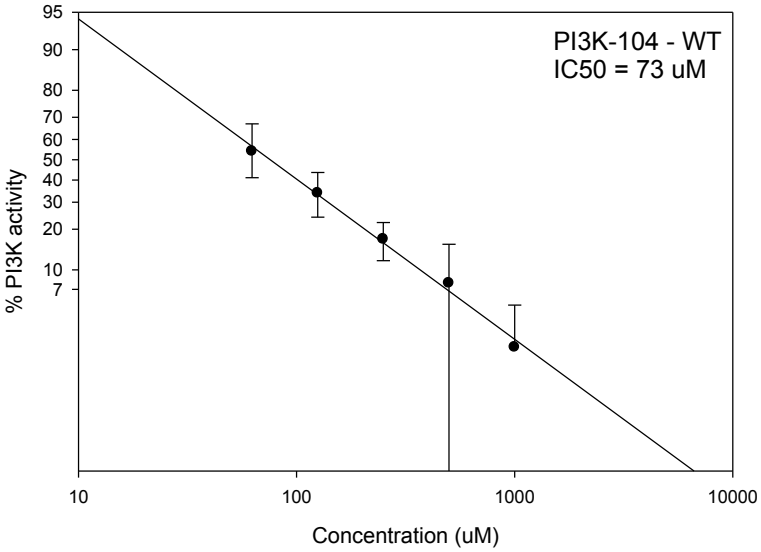
Visualization, purchase ~10 compounds

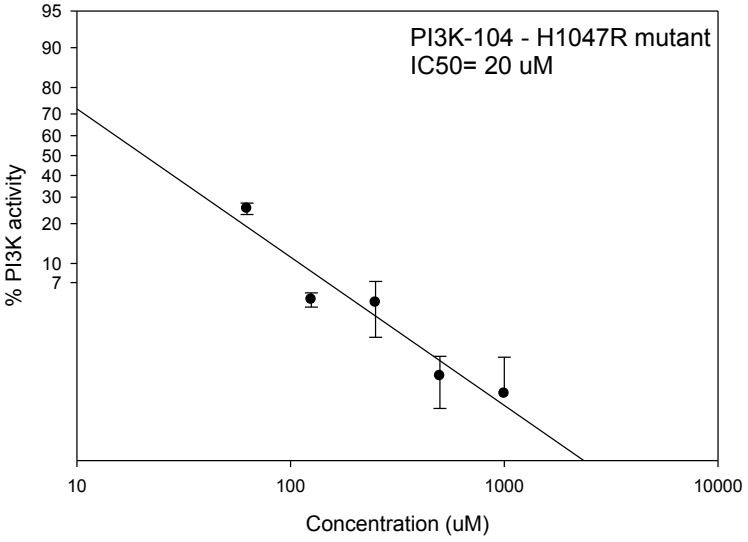
In vitro cell-free assay with cancer liposomes





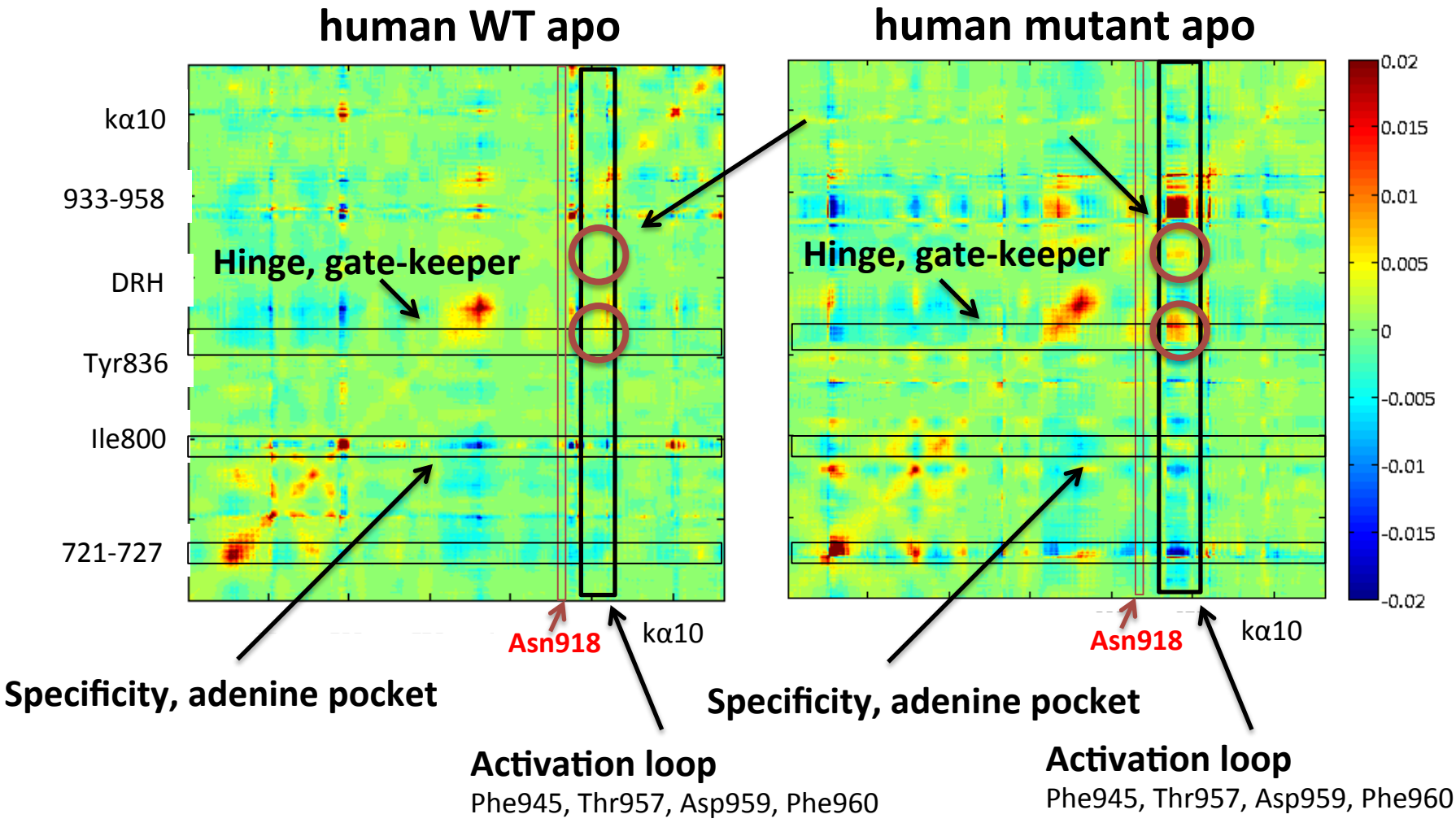
11-fold selectivity of the mutant vs the WT





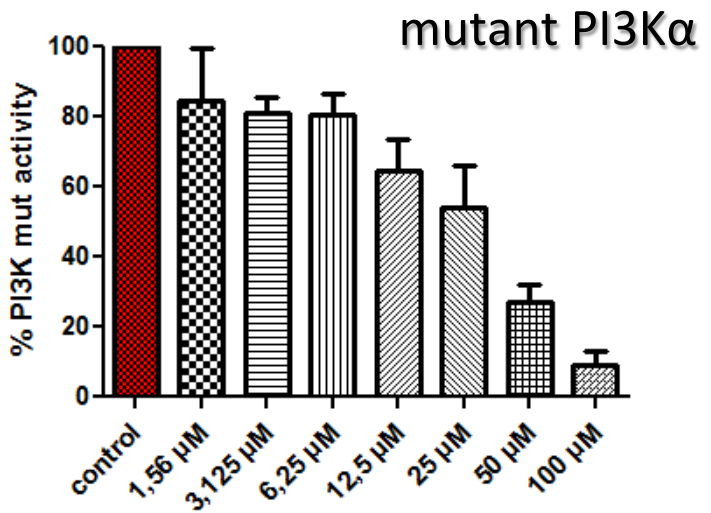
IC50 = the concentration of the compound required to inhibit the protein by 50%

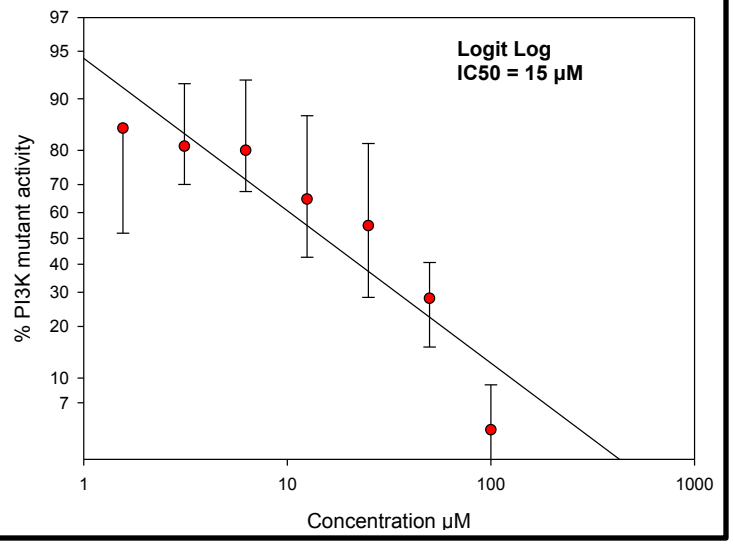
Is PI3K-010 an allosteric (non-competitive) inhibitor?



The motion of the pocket where PI3K-010 resides IS correlated to the motion of the active site.

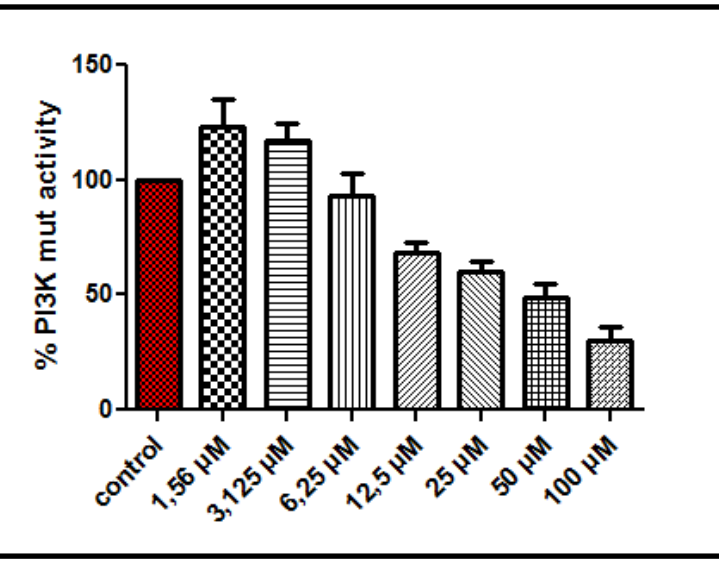
Is PI3K-010 an allosteric (non-competitive) inhibitor?

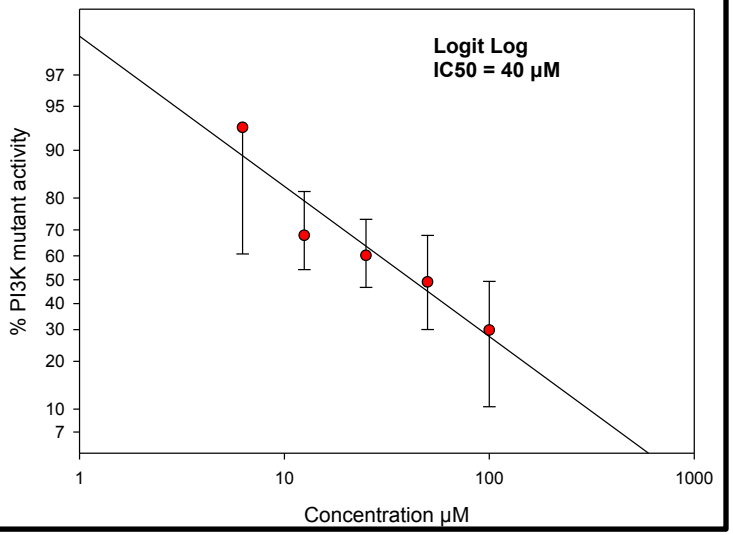




Low ATP (100µM):
IC50 = 15 µM

High ATP (2mM):
IC50 = 40 µM



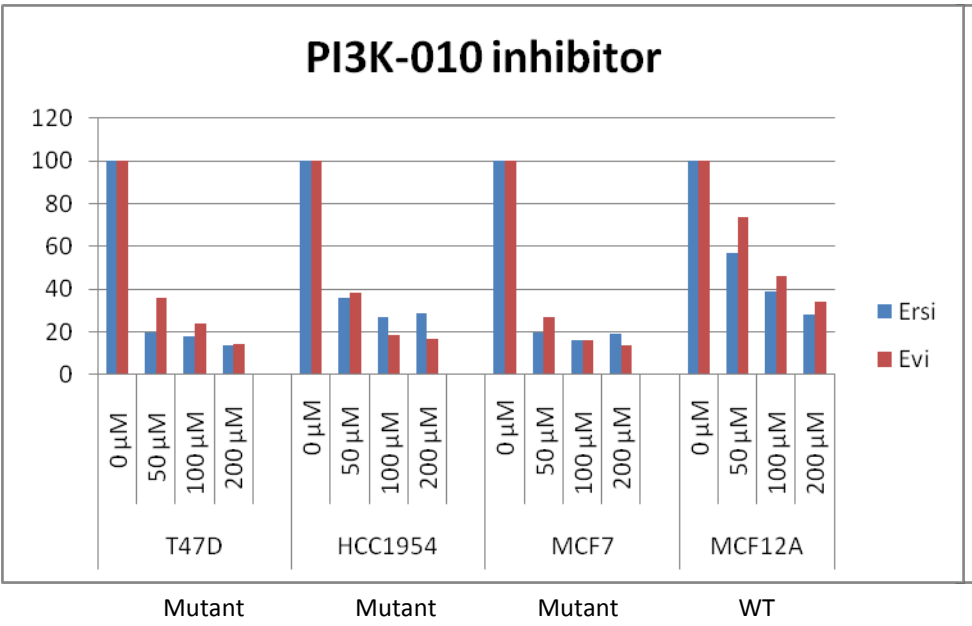


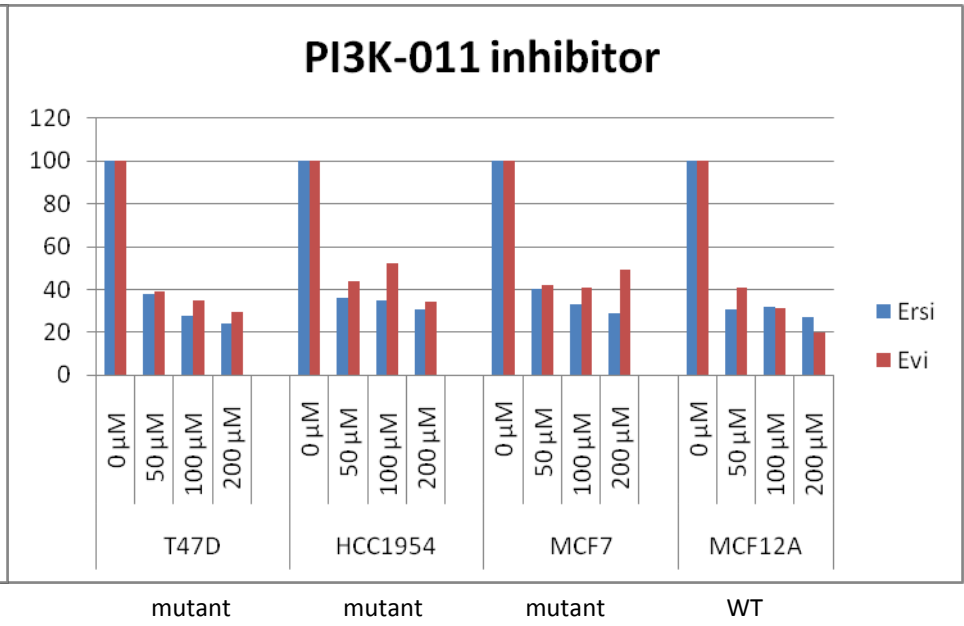
PI3K-010 IC50 is not influenced by ATP concentration

Could be considered allosteric

2 experiments low ATP, 4 experiments high ATP

MTT assay on mutant and WT PI3Kα

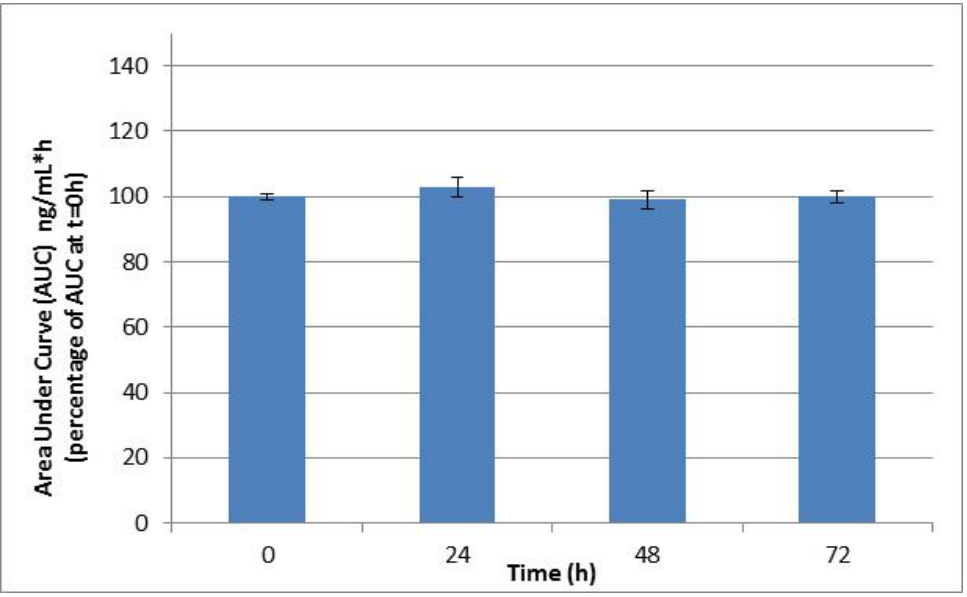




- Mutant-specific inhibition is possible
- IC50 WT = 7uM
- IC50 H1047R = 1uM

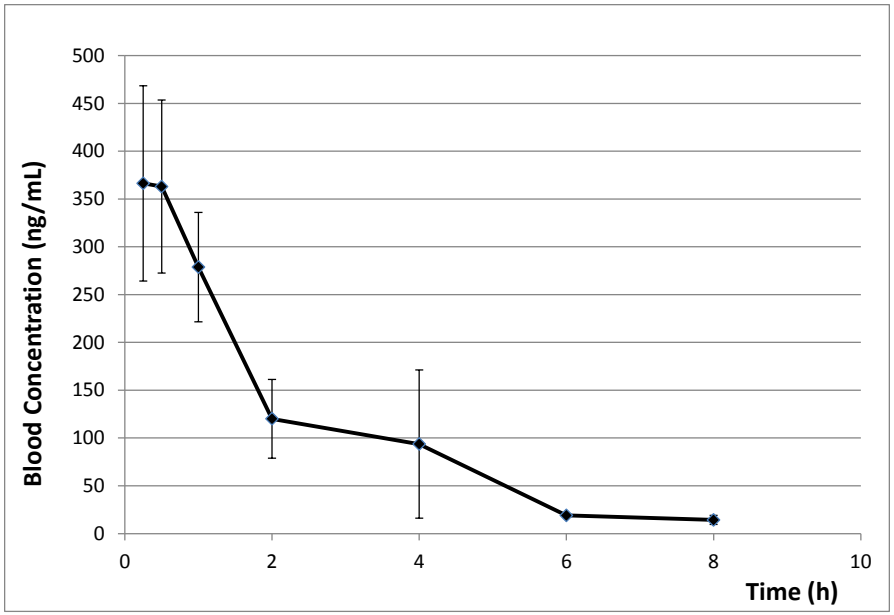
Pharmacokinetic experiments on PI3K-010

Stability of compound PI3K010 in cell conditioned- medium



(Tamvakopoulos lab, BRFAA)

Mean blood concentrations of PI3K010 in corn oil following oral dosing in mice (10 mg/Kg).



Cmax of 396 ng/mL (~ 1 µM)
4 h post-dose - average concentrations of 100 ng/mL (~ 0.3 µM).

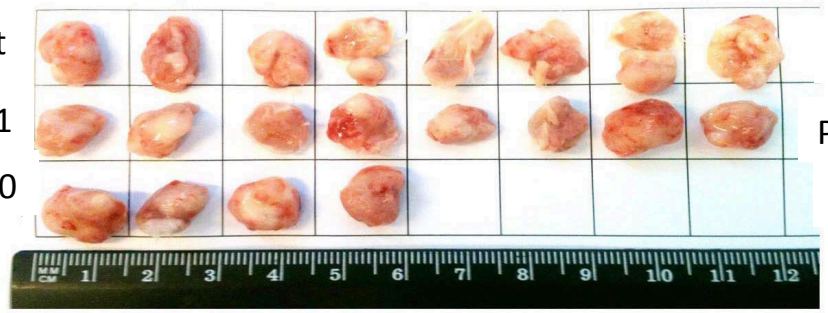
Preclinical study of PI3K-010 (xenografts)

MDA-231-MB (PI3Kα WT)

Solvent

PI3K-021

PI3K-010

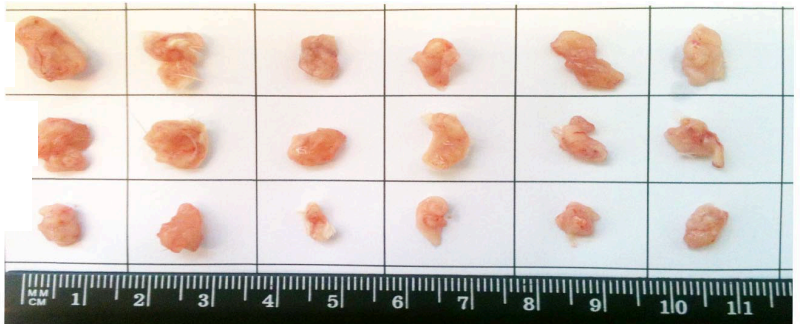


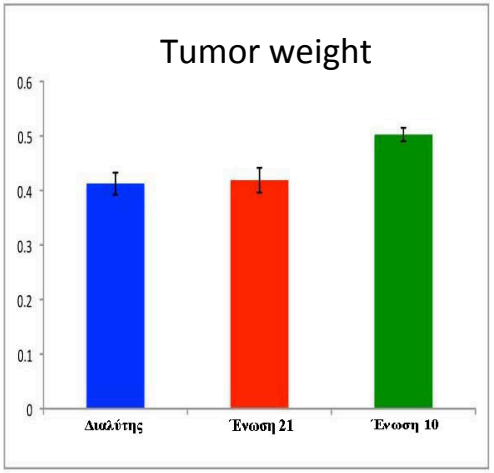
HCC1954 (H1047R PI3Kα mutant)

Solvent

PI3K-021

PI3K-010

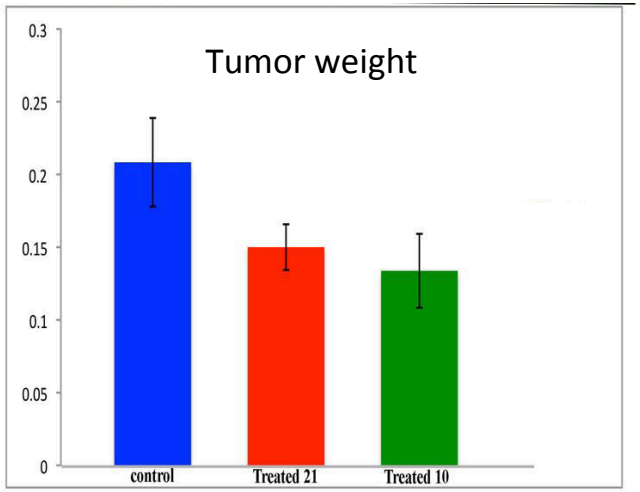




Solvent

PI3K-021

PI3K-010



(D. Stellas, Klinakis & Efstratiadis labs)

PI3K010 in corn oil following oral dosing in mice (100 mg/Kg).

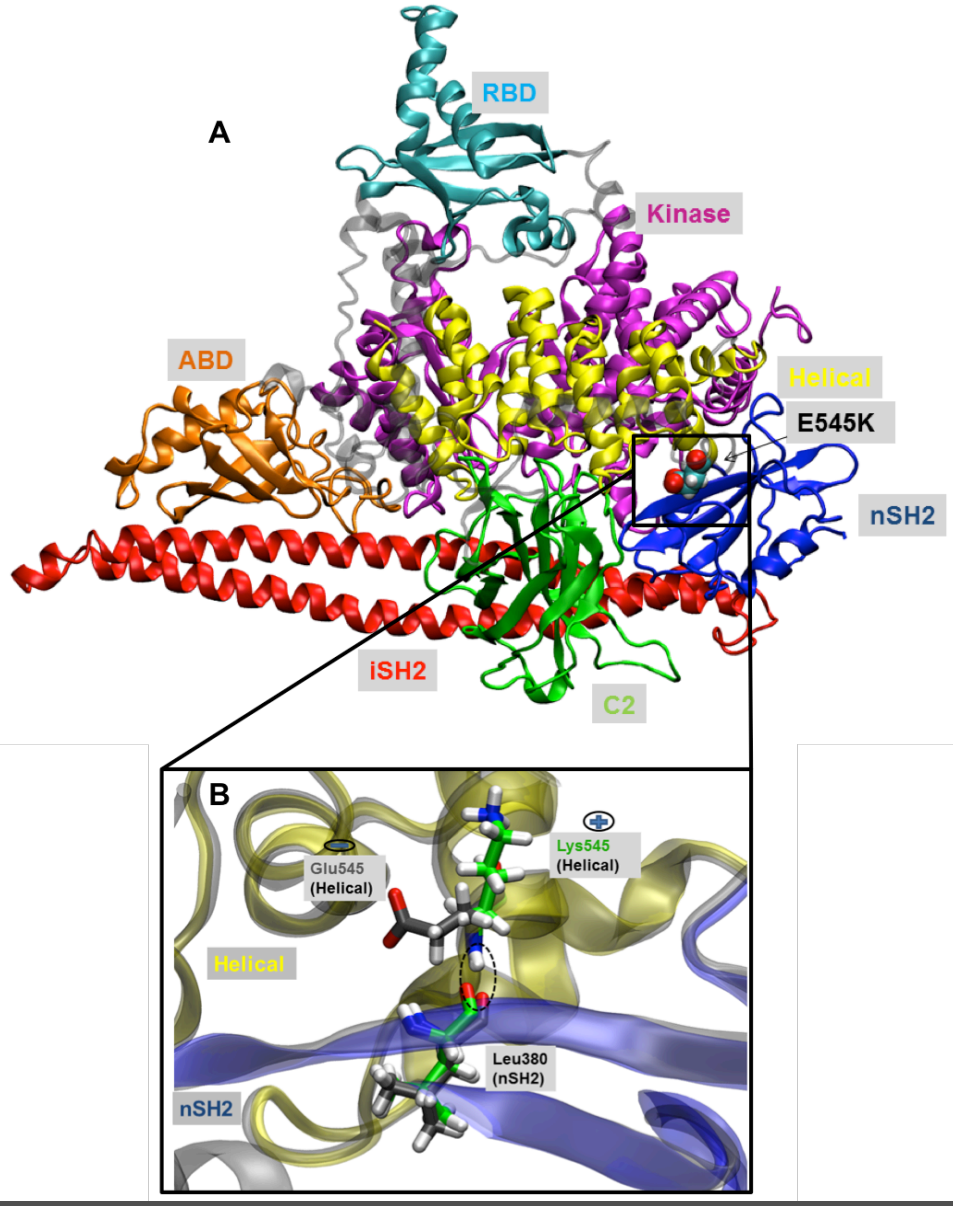
PI3Kα WT and E545K mutant MD simulations

80% of all mutations:

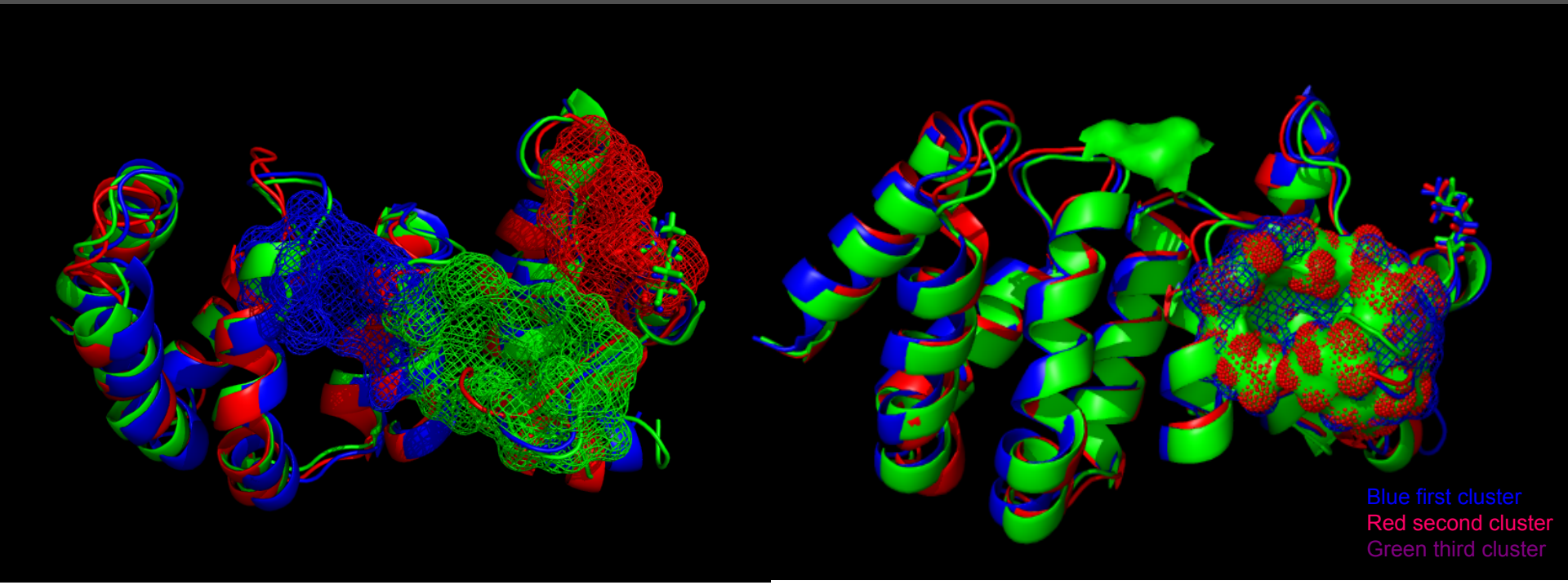
Glu545Lys His1047Arg

System size:
355.000 atoms
(1344 a.a + water+ions)
512 cores => 30 ns/day

Simulation	Time (ns)
WT replica 1	**800**
WT run 1	**900**
Mutant run 1	**900**
Mutant replicate 1	**900**
Mutant replicate 2	**900**
Mutant replicate 3	**900**



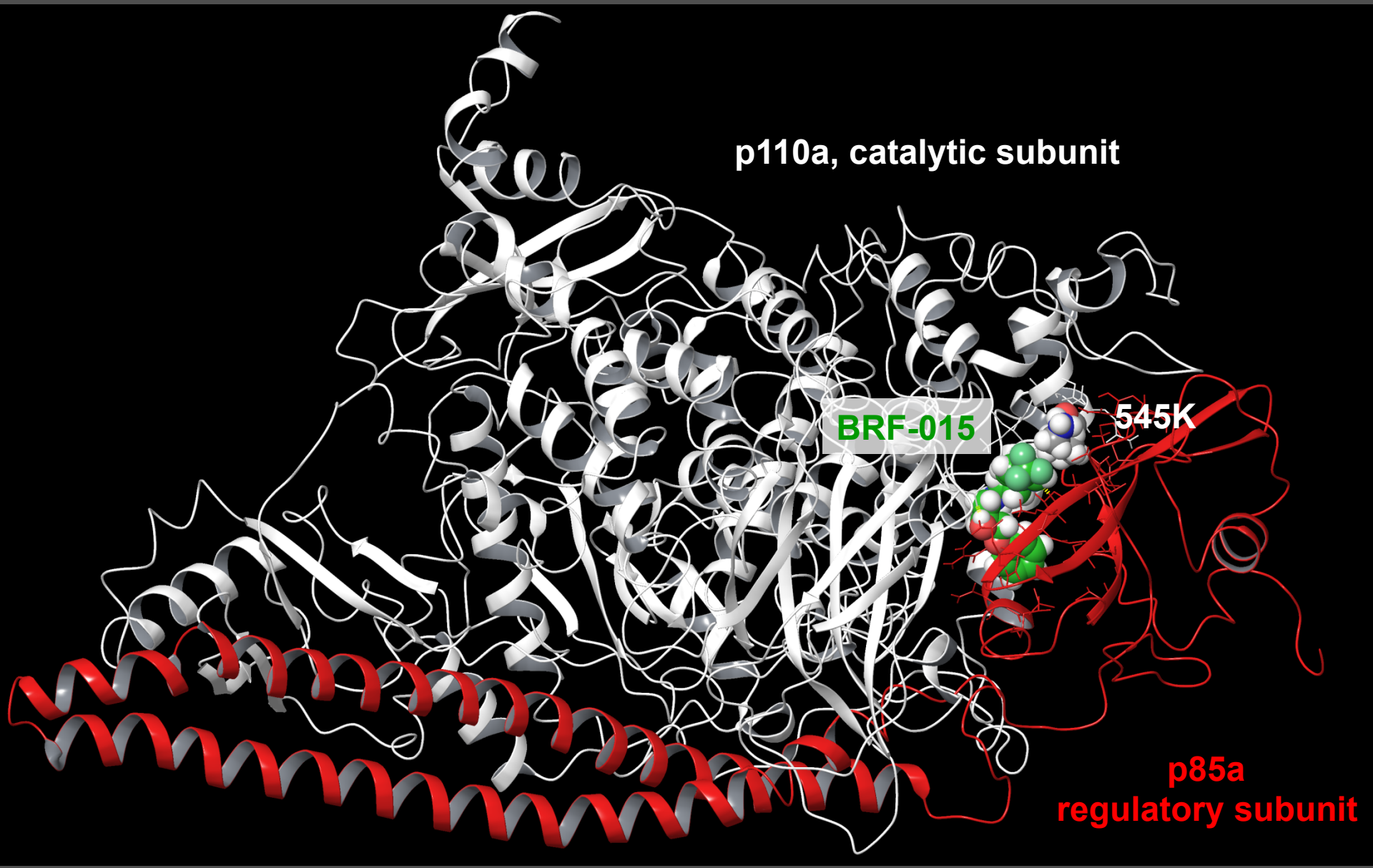
Binding Site Prediction on WT and E545K



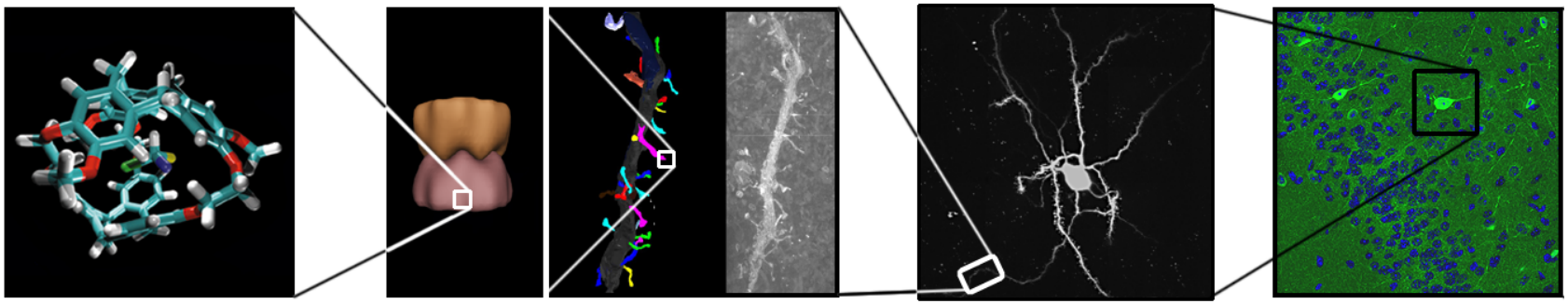
WT Mutant

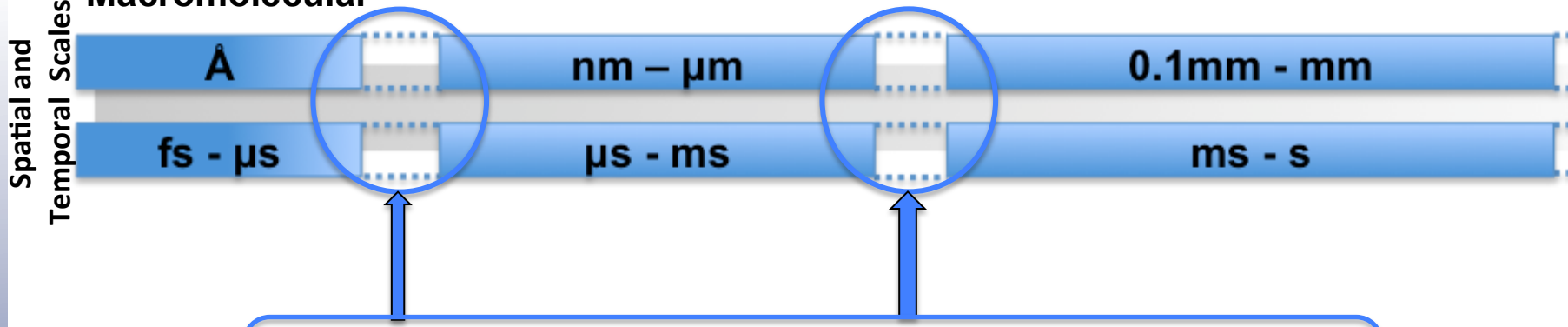
- Cluster analysis was performed
- Binding site prediction on cluster representatives.
- Binding cavities discovered in a region close to the mutation site
- Screening (Glide docking, Maybridge) was performed in the discovered cavity for the WT and Mutant

Targeting the p110a + p85a interface



Mind the Gaps





Challenge areas define the future of computational chemistry & biophysics

e.g., Can we understand the drug target in its real environment? Can we understand the molecular and chemical mechanisms underlying disease?

Source: adapted from Prof. Rommie Amaro

Coarse-graining membranes: MARTINI FF

C - apolar

P - polar

N - nonpolar

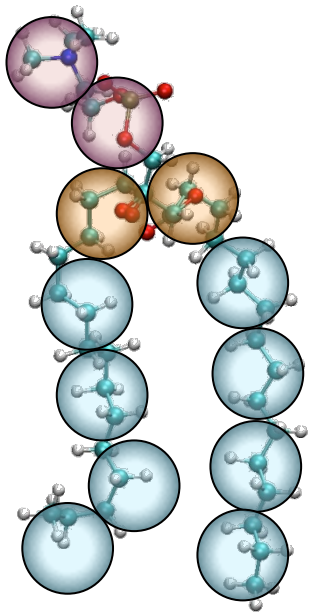
Q - charged

18 subtypes

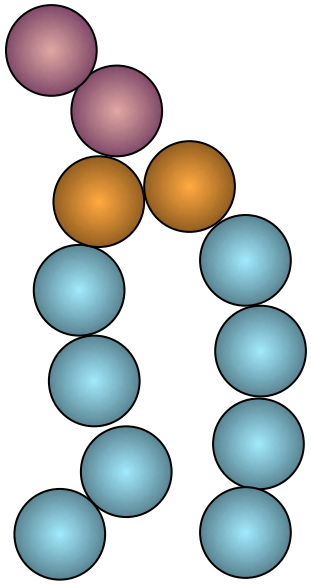
- Hydrogen bond capabilities: d, a, da, 0
- Degree of polarity: 1, low…. 5, high

$$V = V_{bond} + V_{angle} + V_{id} + U_{LJ} + U_{el}$$

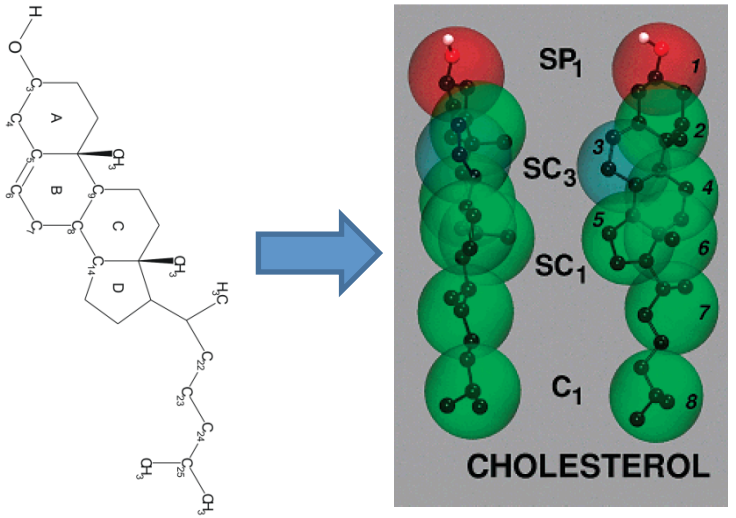
DPPC lipid



130 atoms

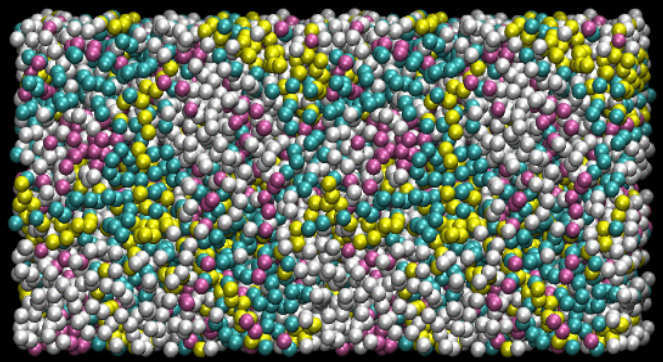


12 particles



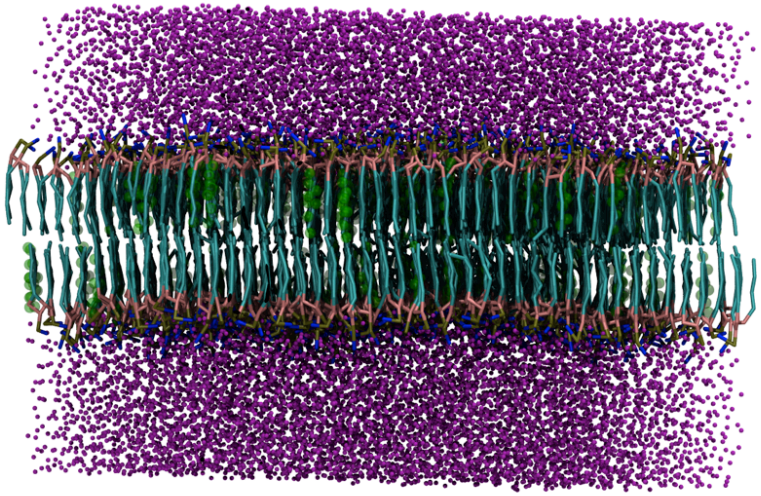
S. J. Marrink *et al.*, *J. Phys. Chem. B,* vol. 111, pp. 7812-7824, 2007.

Lipid bilayer formation

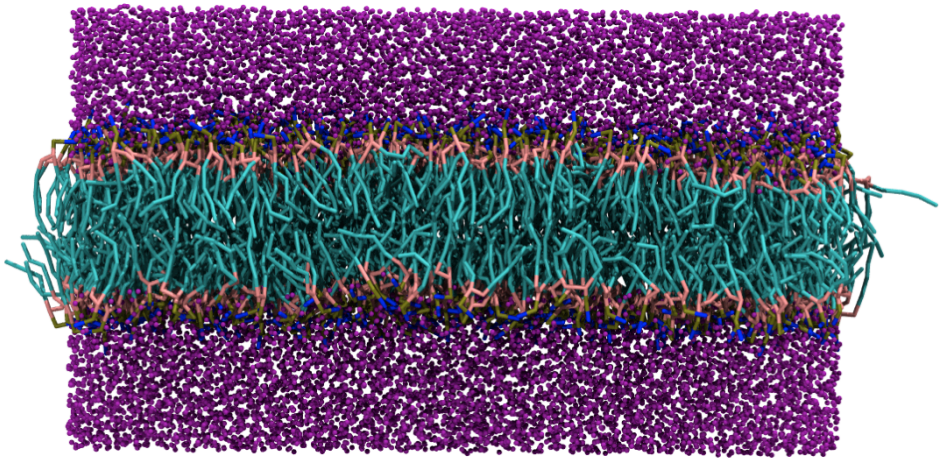


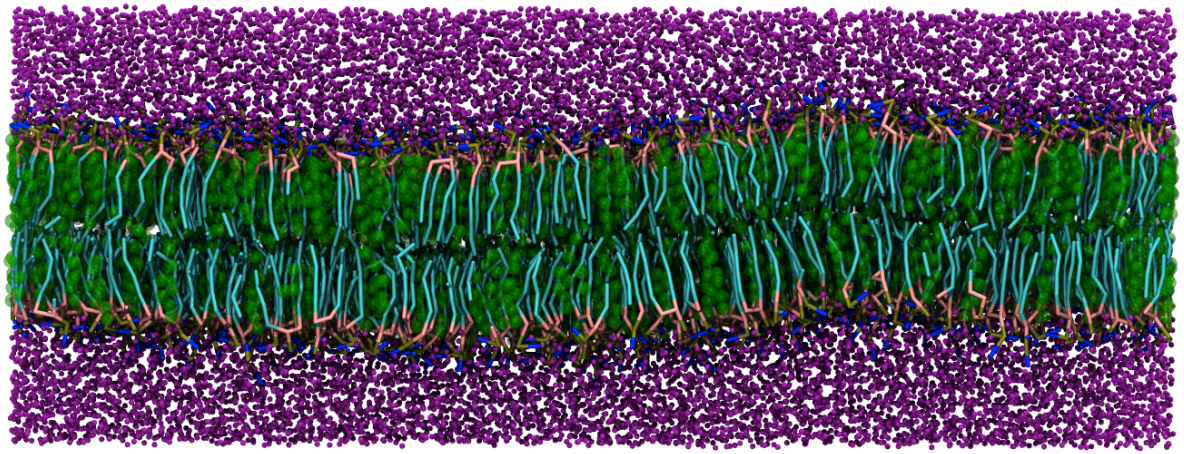
Three lipid bilayer phases observed with CG-MD

Gel phase (T=290K, 10% mol. chol.)



Liquid phase (T=323K, 0% mol. chol.)



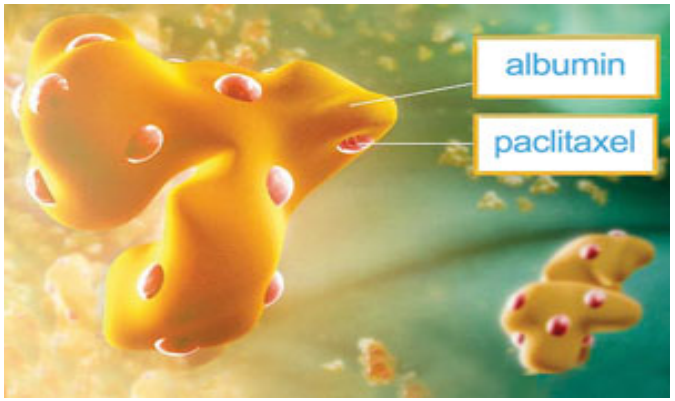


Liquid-ordered
T=323K
50% mol. chol.

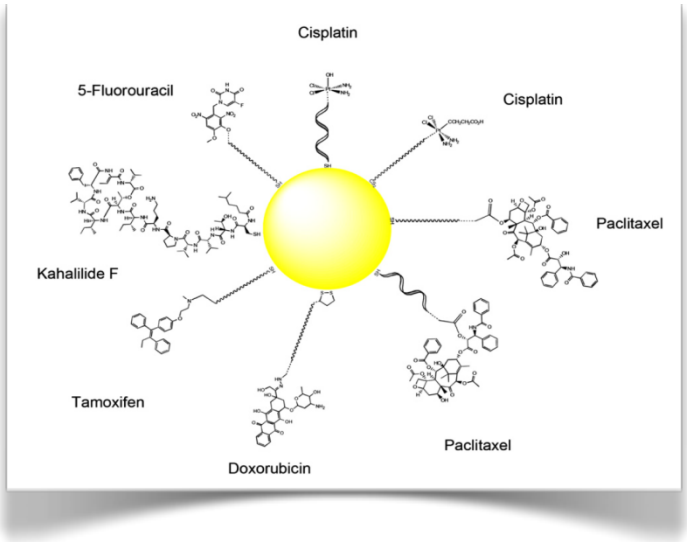
Nanoparticle applications in medicine

Nanoparticle albumin-bound paclitaxel (Abraxane®)

http://www.abraxane.com/



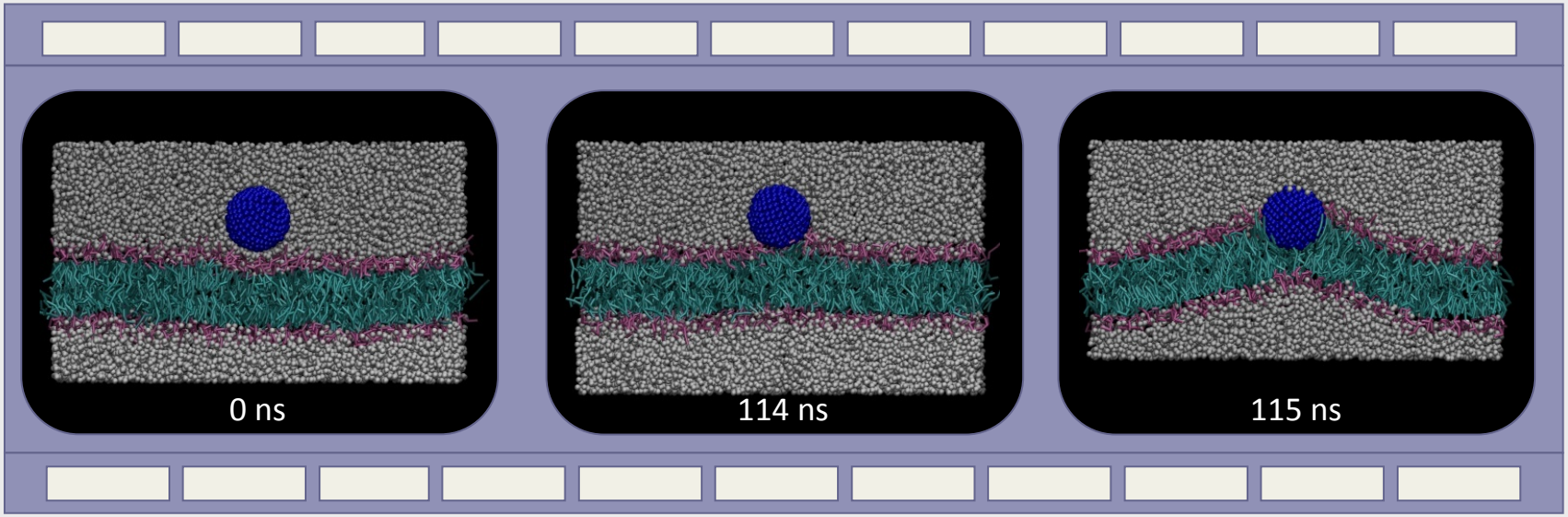
Targeted Drug Delivery

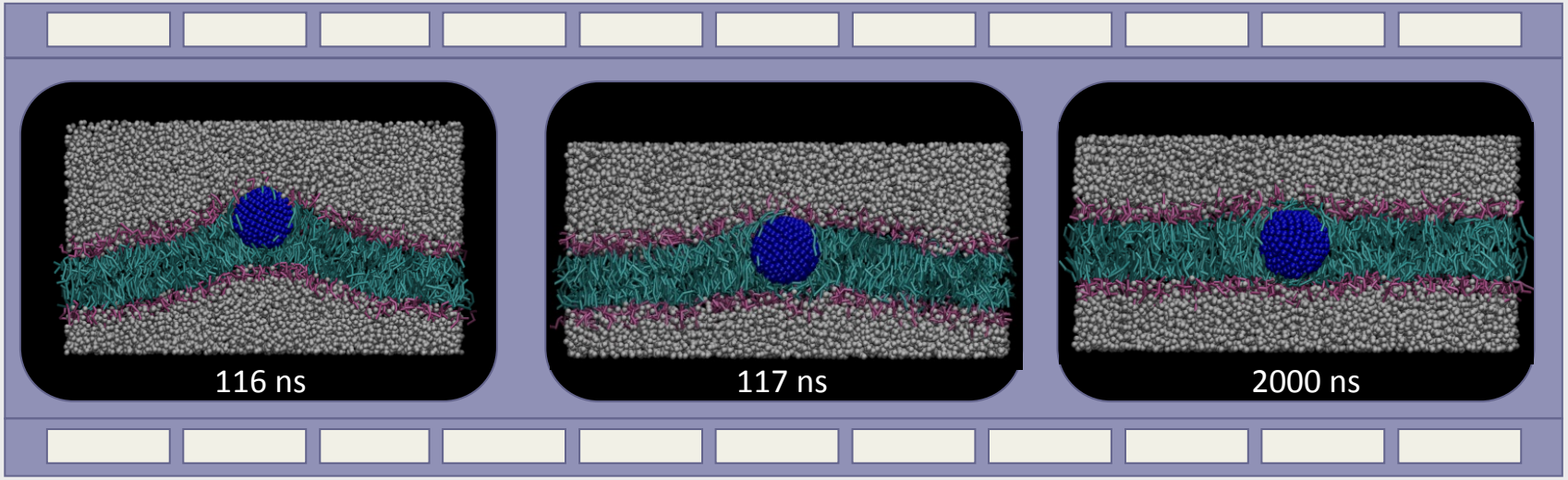


Anticancer drugs covalently conjugated to gold nanoparticles

L. Vigderman, E.R. Zubarev / Advanced Drug Delivery Reviews 65 (2013) 663–676

The fully hydrophobic nanoparticle

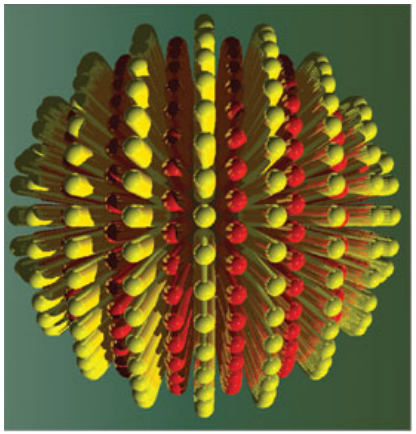




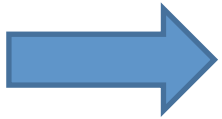
The “hairy” nanoparticle

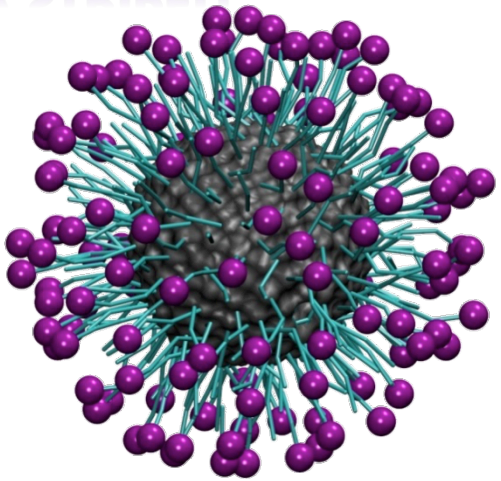
STRIPED NP IS NOT REALLY STRIPED

Evi Gkeka



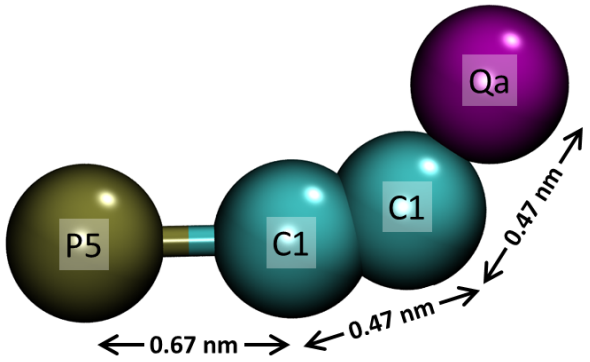
Verma *et al.* Nature Materials 2008



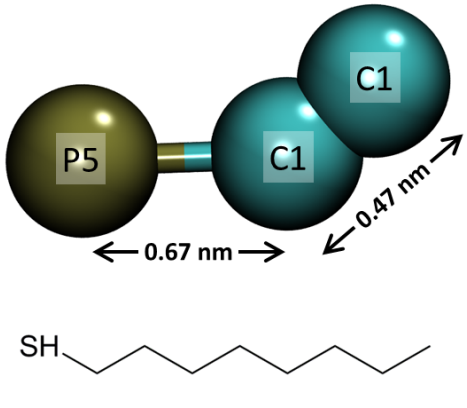


Gkeka et al. PLOS Comput Biol 2014

11-mercapto-1-undecanesulphonate (MUS)



1-octanethiol (OT)



MARTINI modeling of NP surface ligands

Harmonic bond potential

k^{P5-C1}=12,500 kJ mol^{-1}

k^{C1-C1}=1,250 kJ mol^{-1}

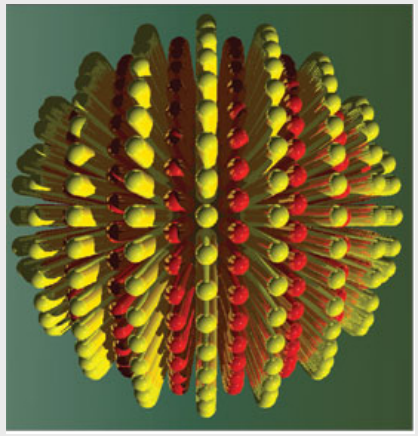
k^{C1-Qa}=1,550 kJ mol^{-1}

Cosine based angle potential

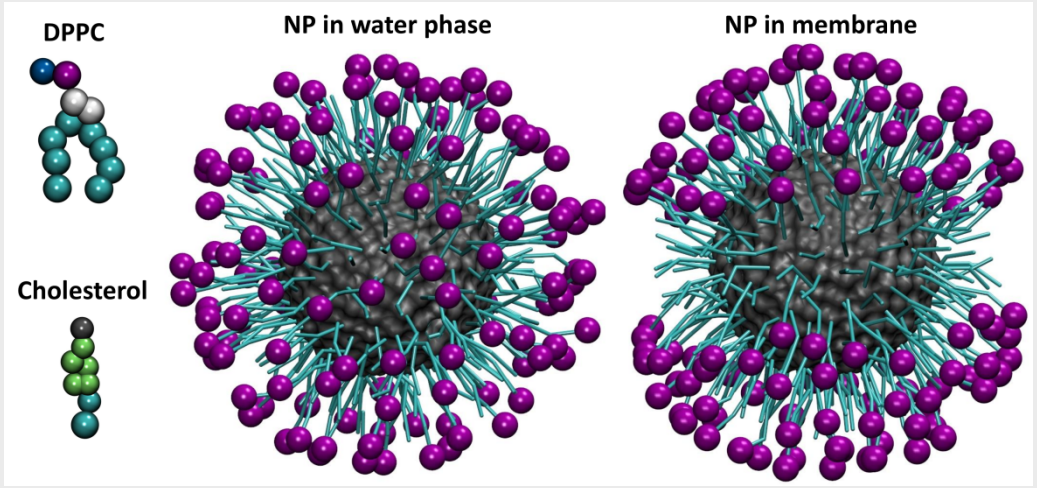
θ_0 =180°

k=25 kJ mol^{-1}

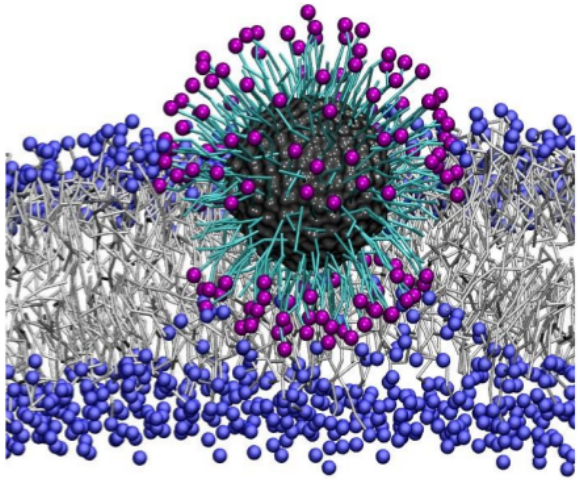
The effect of cholesterol on NP insertion



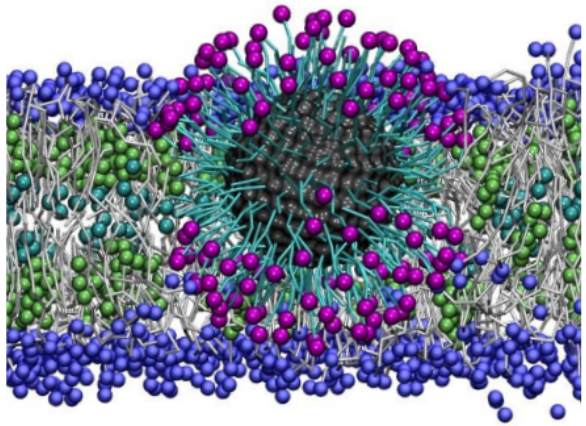
Verma *et al.* Nature Materials 2008



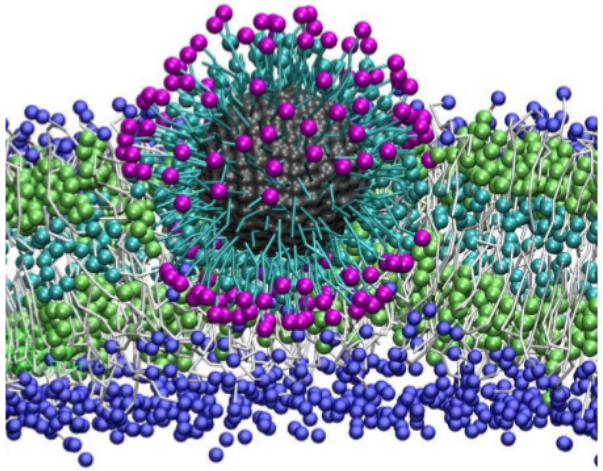
6 different membrane cholesterol concentrations: 0%, 10%, 20%, 30% , 40%, and



0% cholesterol

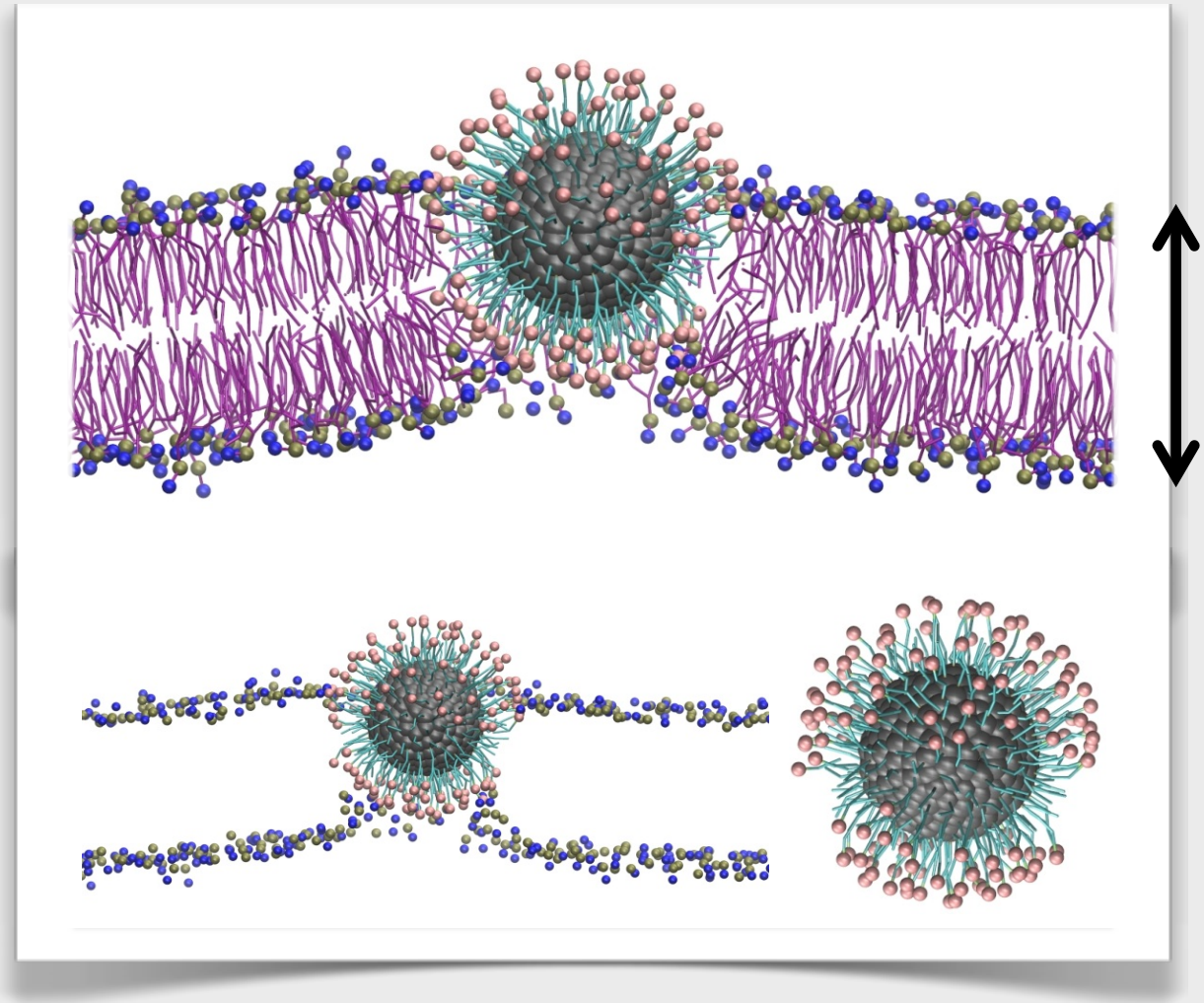


30% cholesterol



50% cholesterol

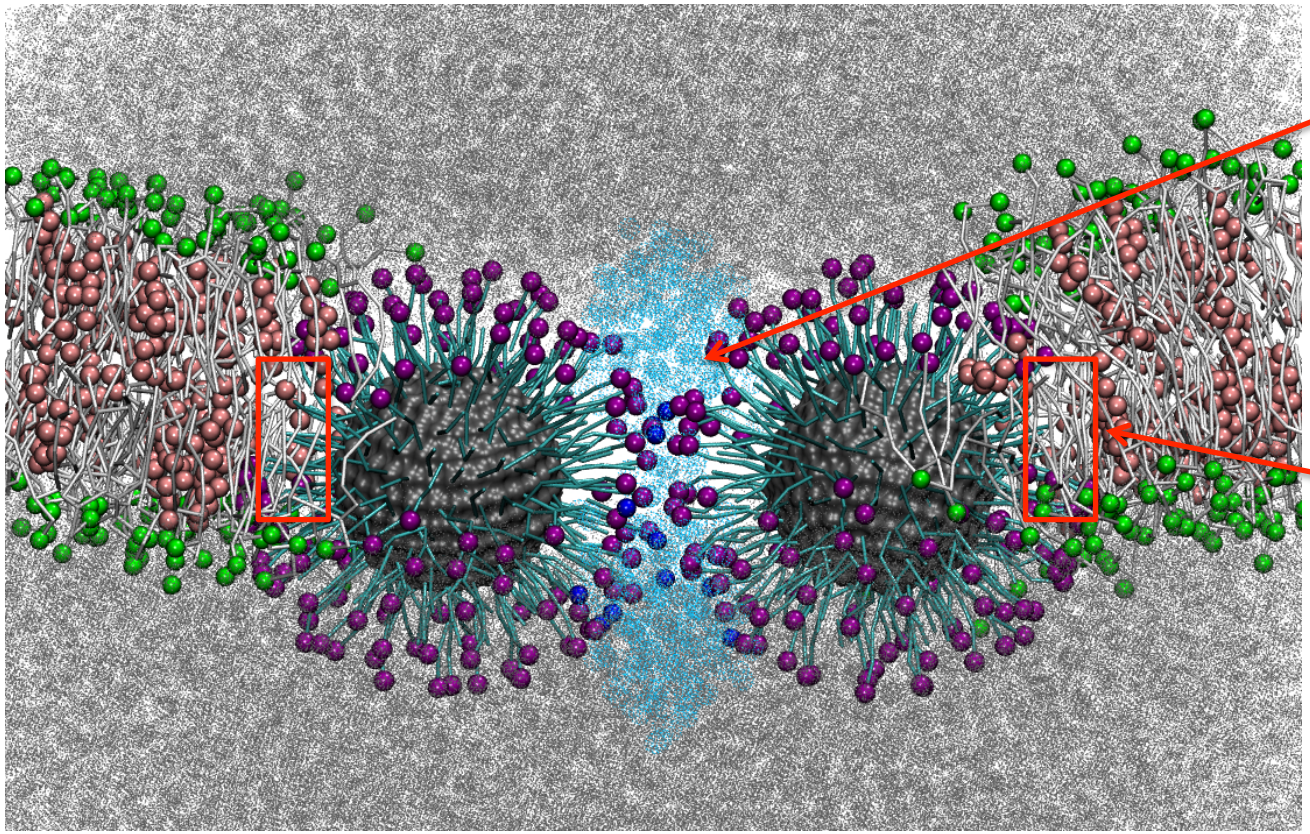
NP is thinning the membrane



Measure the bilayer thickness at the area of NP penetration and in the bulk lipid bilayer

NP-NP interface in the cell membrane

A water pore is formed at the NP-NP interface



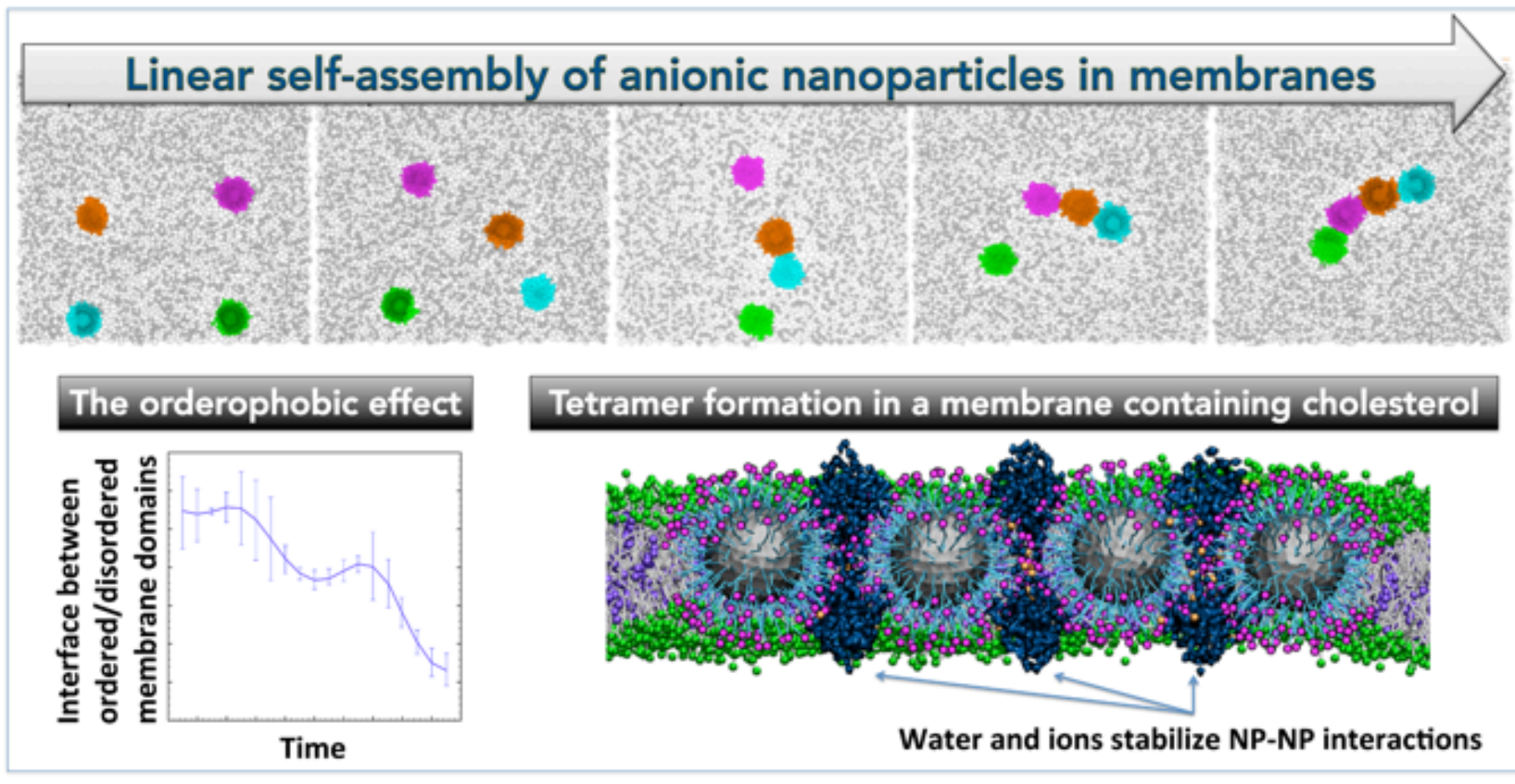
Water and ions lie at the interface between the two NPs

The snorkeling effect is still evident at the side of the NP that is interacting with the cell membrane

Evi Gkeka

NC3 polar ligand ends hydrophobic tails cholesterol water ions

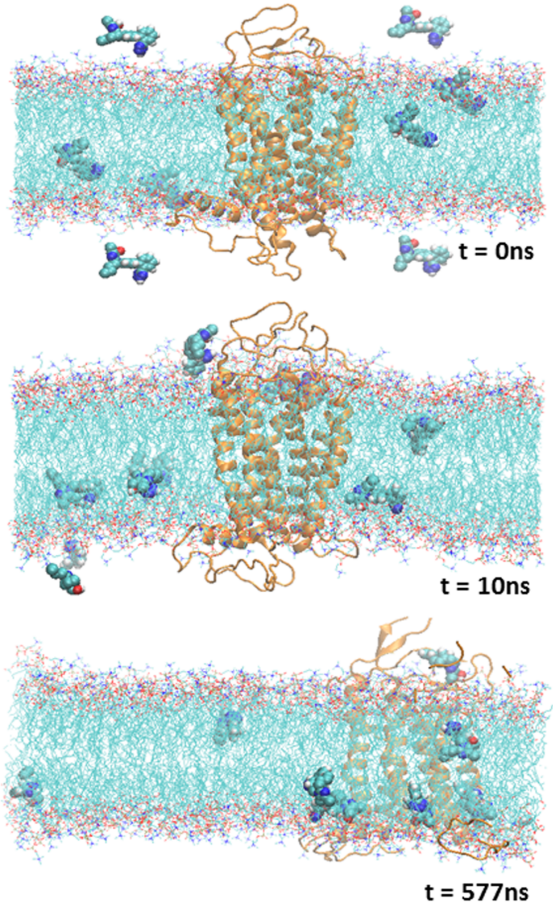
Nanoparticles as drug delivery systems



Angelikopoulos *et al.* submitted

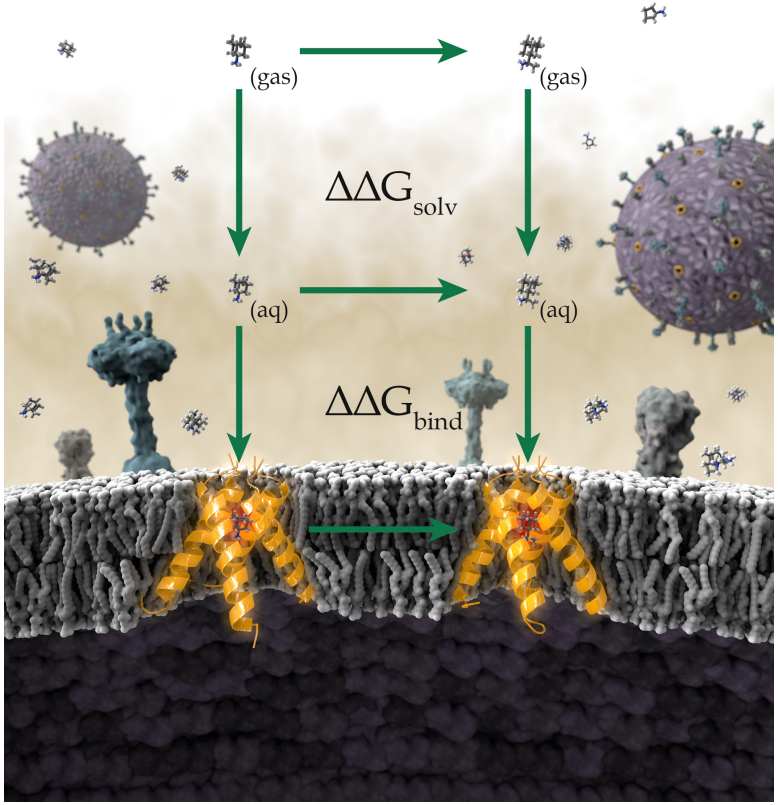
Targeting membranes/membrane interfaces for computer-aided drug design and drug delivery

AT1 receptor



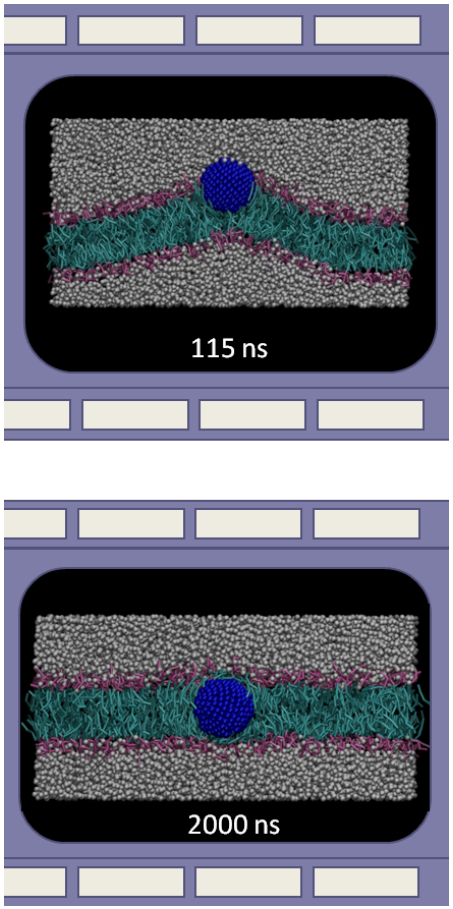
BBA - Biomembranes (2014)

M2TM Influenza A



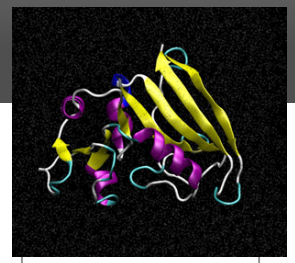
J Chem Theor Comput (2013)

NPs as drug delivery systems

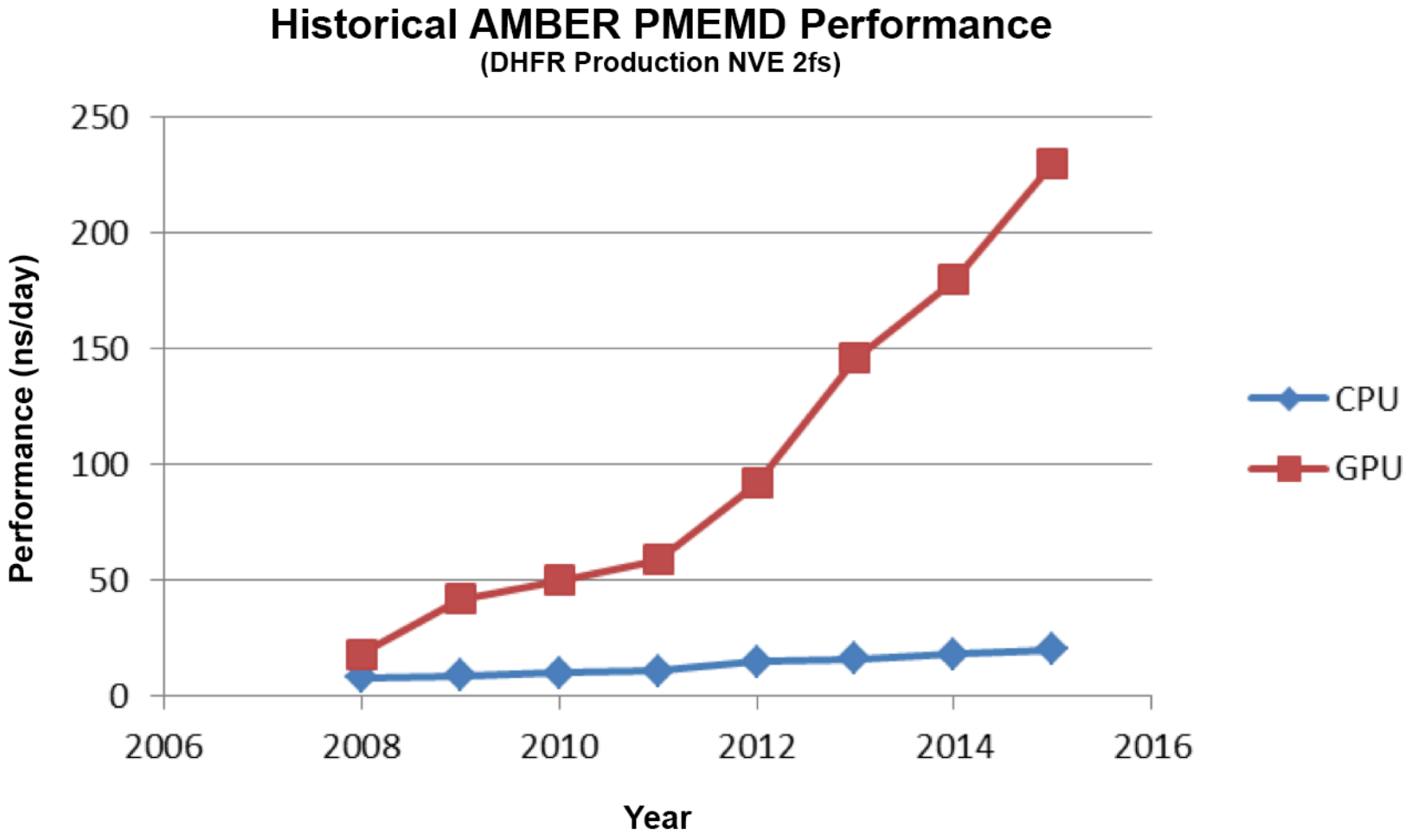


Plos Comput Biol (2014)

The new era: GPU acceleration



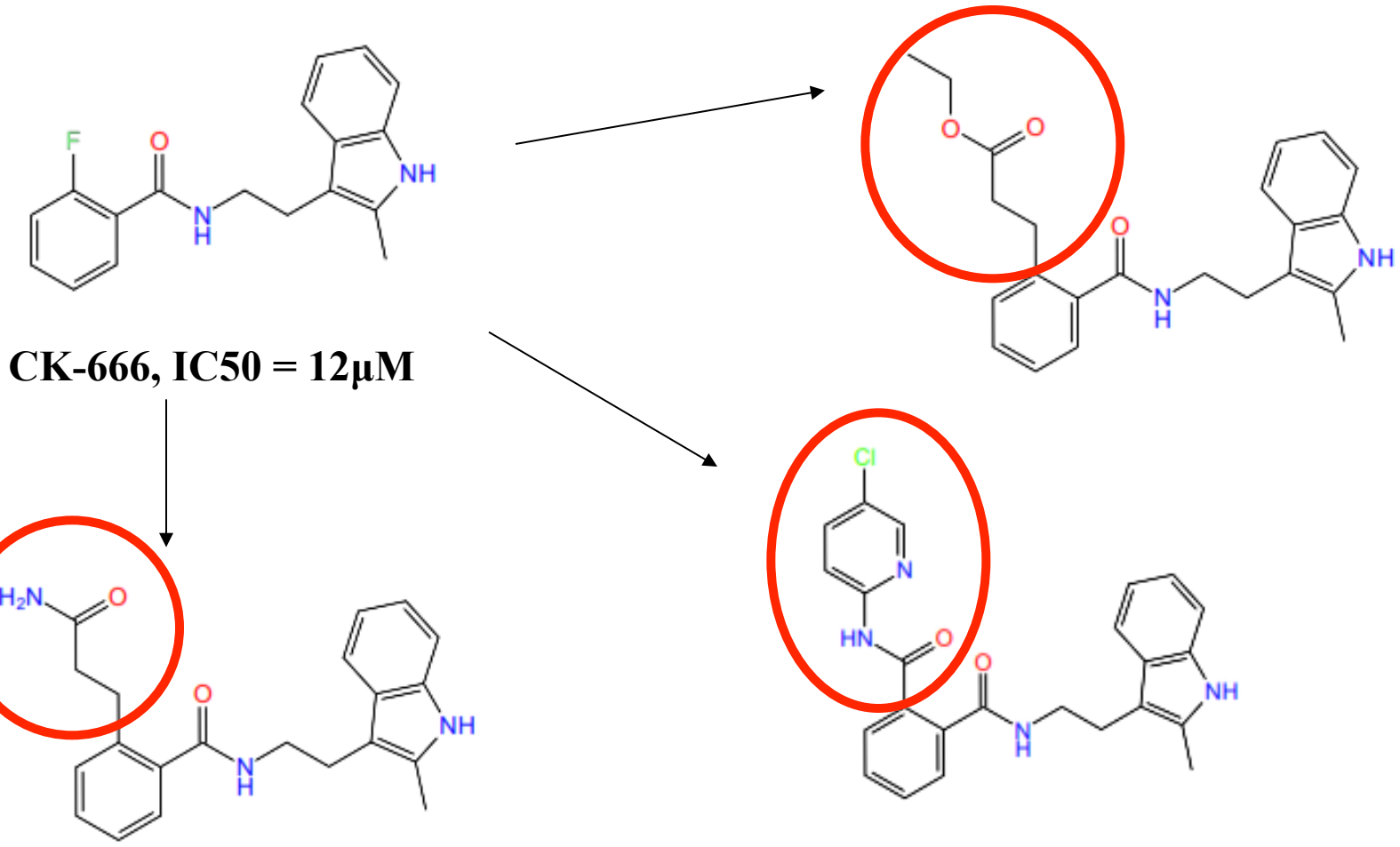
Historical Single Node / Single GPU Performance



Credit: Professor Ross Walker, UCSD Supercomputing Center, AMBER developer

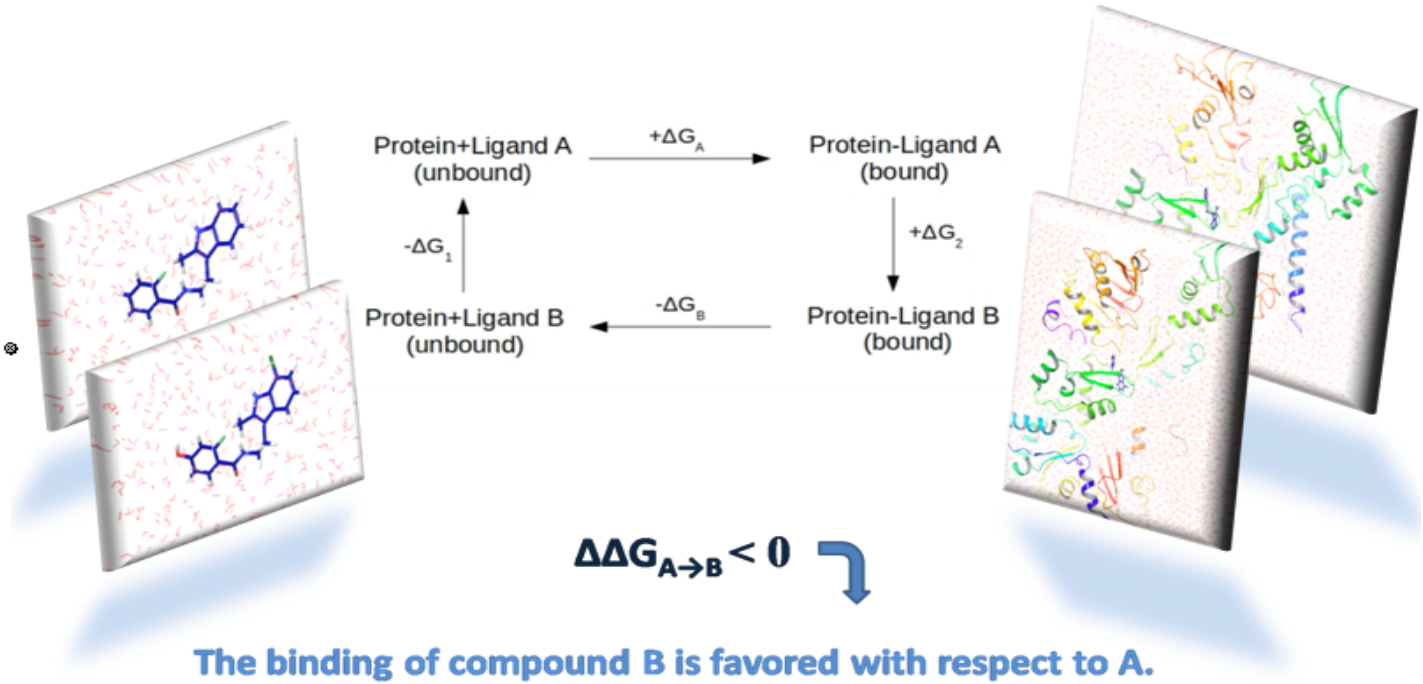
GPU Acceleration: Example on Drug Design

Christina Athanasiou



Free Energy Perturbation Calcualtions

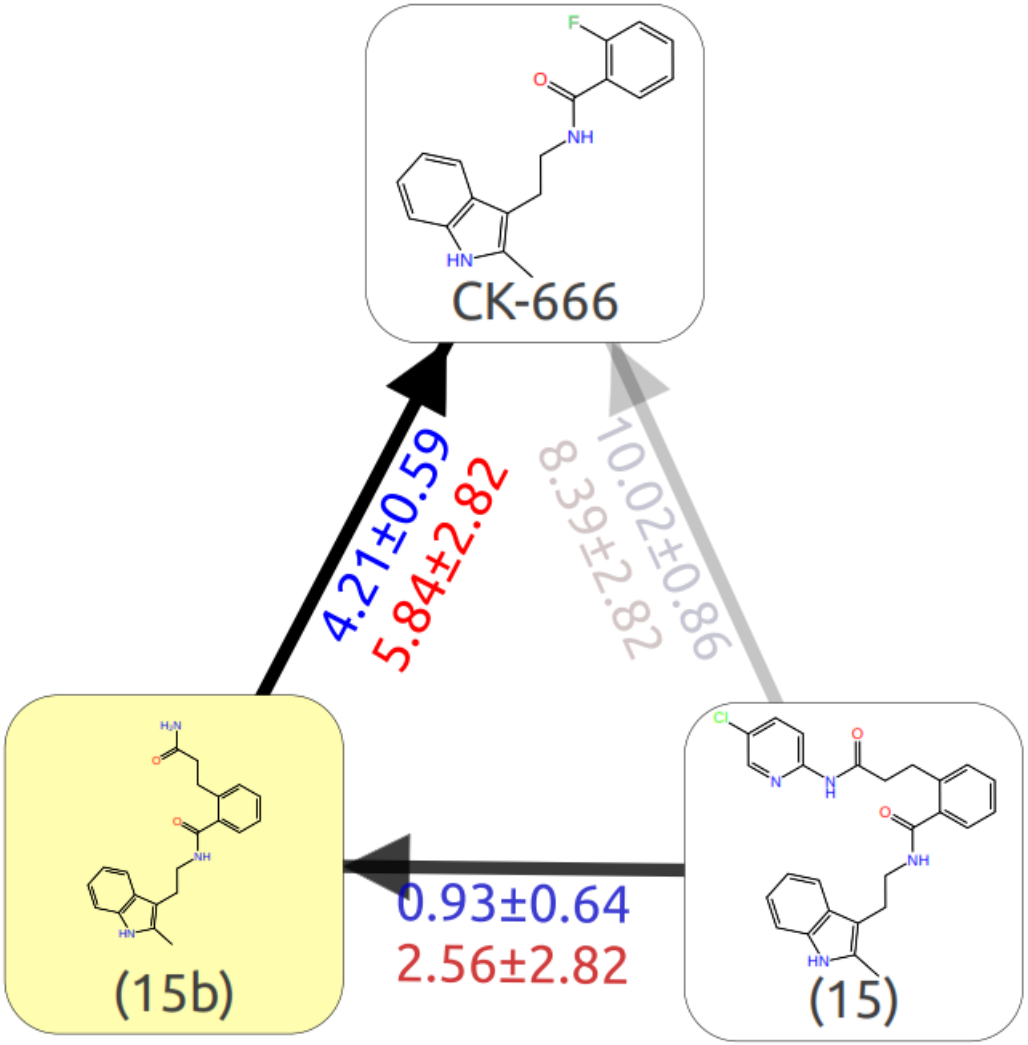
$$\textit{Zwanzig's formula:}\quad \Delta G(A \to B) = G_B - G_A = -kT \ln \left\langle \exp\left(-\frac{V_B - V_A}{kT} \right) \right\rangle_A$$



$$\Delta\Delta G_{binding} = \Delta G_2 - \Delta G_1 = \Delta G_A - \Delta G_B$$

ΔG_A and ΔG_B are the free energies of **transfer** of A and B from the unbound to the bound state.
ΔG_1 and ΔG_2 are the free energy differences of the **mutation of A into B** in solvent and bound to protein

FEP: GPU Acceleration



FEP chemical transformation in protein and in water

CPU: 24 hours on 768 cores per transformation

GPU: 7 hours on 1 GPU per transformation!!

Simulations performed in ARIS - GRNET

Project Team

BRFAA
Cournia lab (MD, drug design, cells)
Dr. Evi Gkeka
Dr. Hari Leontiadou
Thomas Evangelidis

Efstratiadis & Klinakis labs (cells+mice)
Dr. Ersi Tsellou
Dr. Dimitris Stellas

NCSR Demokritos
Couladouros lab
Anna Kapela
Maria Ouzouni

University of Thrace
Agianian lab
Dr. Maria Pavlaki

University of Ioannina
Christoforidis lab (cell-free assays)
Alexandra Papafotika
Dr. Vasiliki Lazani

ARIS

American Association for Cancer Research

Links to the movies I ‘ve shown

Villin headpiece protein folding
https://www.youtube.com/watch?v=sD6vyfTtE4U

A basic introduction to proteins & drugs
https://www.youtube.com/watch?v=u49k72rUdyc

How Does a Drug Molecule Find its Target Binding Site?
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3221467/
(link to .avi file at the end of the article will d/l the movie)

Simulation of the Wild Type PI3Kα protein
http://journals.plos.org/ploscompbiol/article/asset?unique&id=info:doi/10.1371/journal.pcbi.1003895.s031

Simulation of the oncogenic H1047R mutant PI3Kα protein
http://journals.plos.org/ploscompbiol/article/asset?unique&id=info:doi/10.1371/journal.pcbi.1003895.s032