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Computational Methods in Structural Bioinformatics

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Feel free to interrupt if you have questions

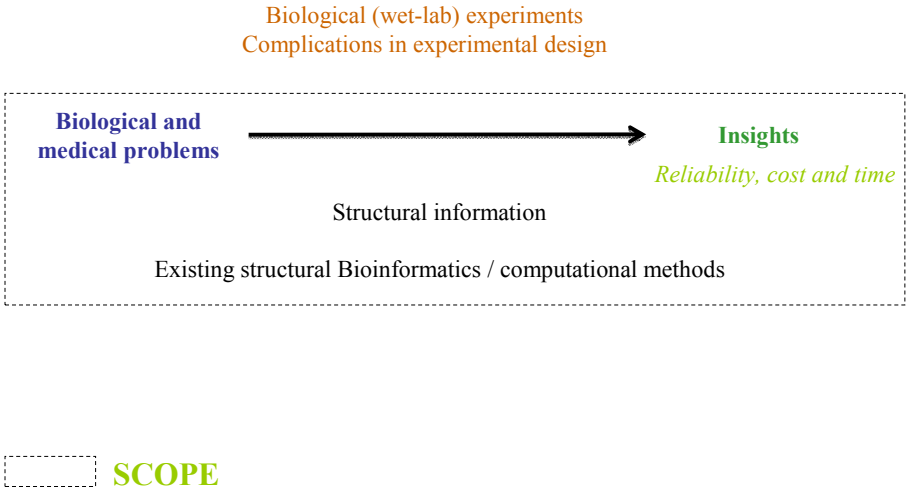
AIM

- Introduce
  - Challenges in structural bioinformatics
  - Some of the computational methods in structural bioinformatics (especially for protein-ligand interactions)
  - What kind of biological insights can we provide using stuctural bioinformatics

Overview

- Background
- Methods (protein-ligand interactions)
- Case study

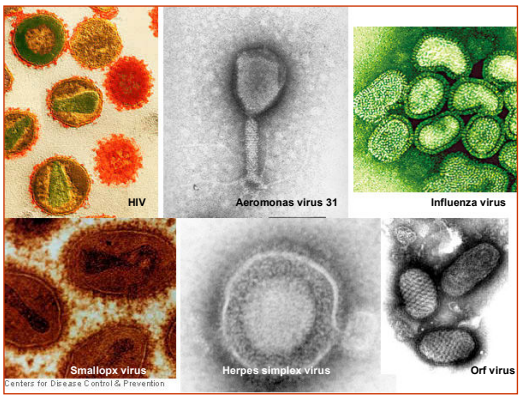
SCOPE



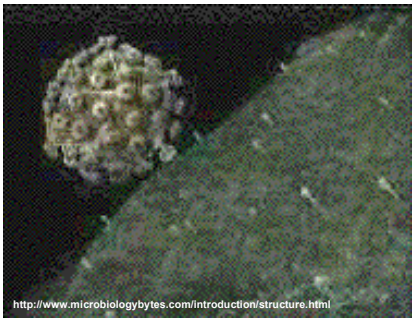
Background

- Human body is constantly invaded by pathogens.
- Proteins on the surface of pathogens are vital in adhesion and proliferation (infection).

Background



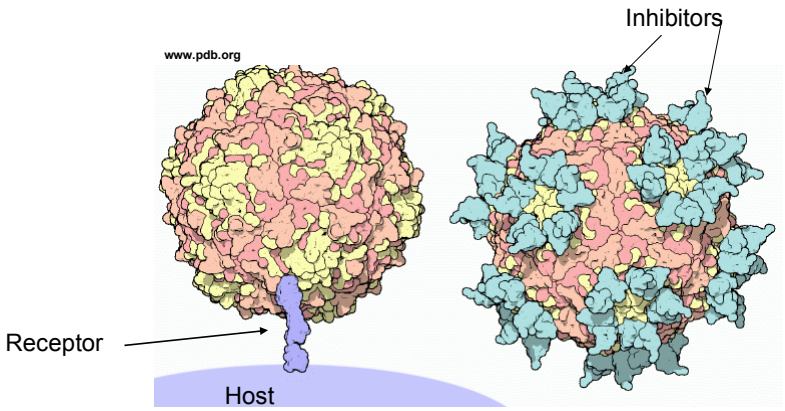
Electron micrographs of viruses.



Background

- Drugs / Inhibitors / ligands
  - Small molecules that prevent the adhesion or proliferation of pathogens.
    - ”Relenza” is the trade name for infuenza virus inhibitors (ligand) that binds to a surface protein of influenza virus that stops proliferation.

Background



Two important properties of a drug
- Affinity
- Specificity

Traditional Drug discovery - THE PROCESS

Available chemicals **10^7**

Screening all 10^7 is seldom — **approx 10^5**

Wet Lab screening

approx 100

Animal models

< 5

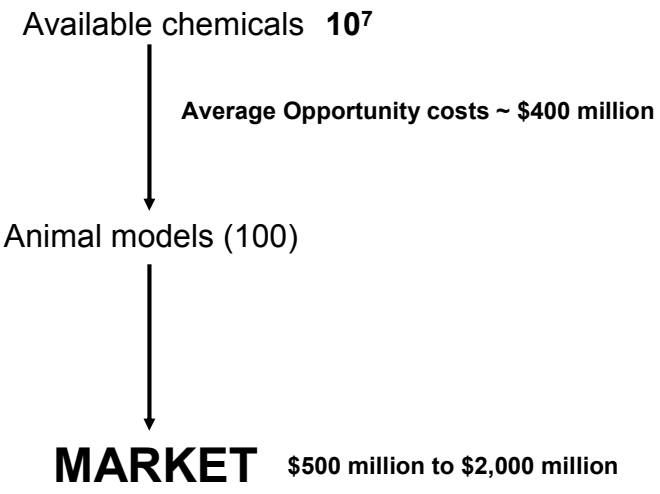
Clinical trails

1

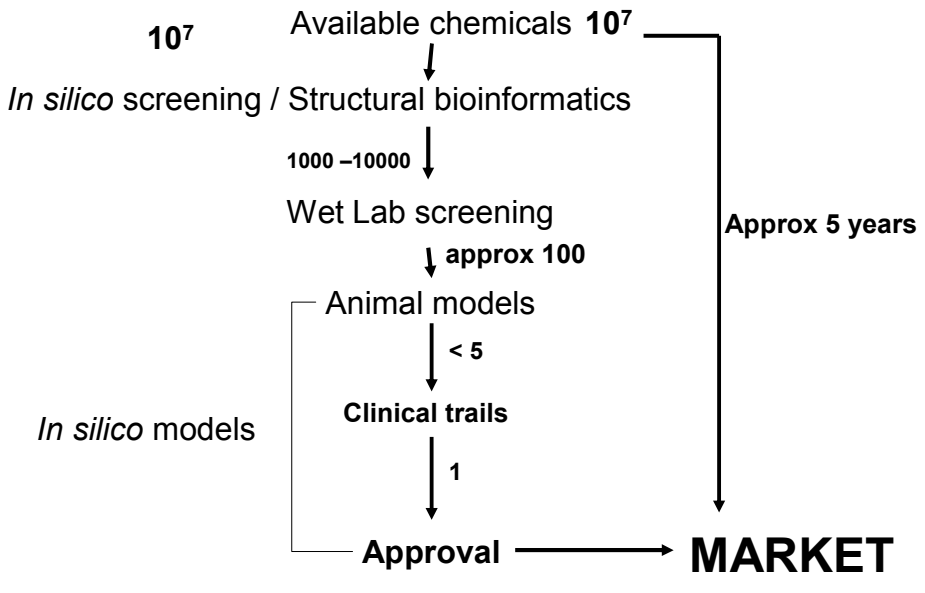
Approval → **MARKET**

Approx. 10 years (?)

Traditional Drug discovery - THE COSTS



Modern drug discovery process



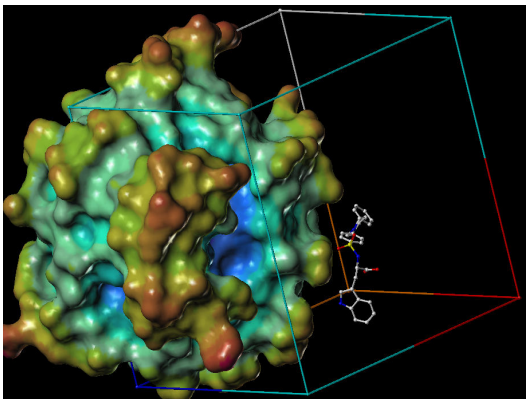
Methods

In silico docking

Problems that can be adressed with *In silico* docking

- How strong does a molecule bind to the target protein
- What is the most possible pose of the drug in the binding site
- What are the main amino acid residues in the protein that interact with the ligand

In silico docking



Conformations of ligands are explored in the proteins active site.

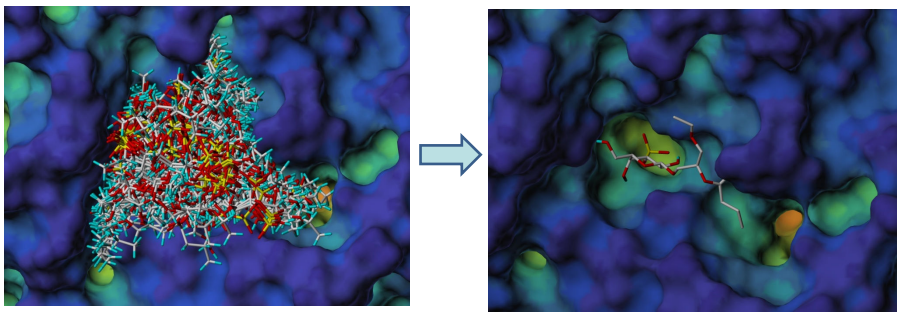
At each step a small random step change is applied to each of the following degrees of freedom of the substrate molecule

- Various algorithms to perform these actions

Docking

Generate conformations

Select the best pose



Selection by a scoring function

Scores normally represent the binding energies

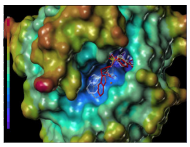
Could be qualitative

Tools: AutoDock, Glide, Hex

In silico virtual screening

A loop of *In silico* docking over a large number of compounds

Available chemicals **Ex. 10^7**



***In silico* virtual screening**

Ranked based on interaction energy

Available docking software

Protein-small molecule docking

AutoDock	Genetic algorithms for generating conformations http://autodock.scripps.edu
Glide	Extensive conformation sampling using ”heuristic” screens Empirical scoring functions Precision modes (SP and XP) Quantum Polarized Ligand Docking (QPLD) http://www.schrodinger.com/productpage/14/5/

Protein-Protein docking

Hex	Shape representation by radial density functions Rotation at fixed distances Scoring steric and electrostatic complementarities http://hex.loria.fr/

Molecular Dynamics (MD) simulations

Molecular Dynamics (MD) simulations

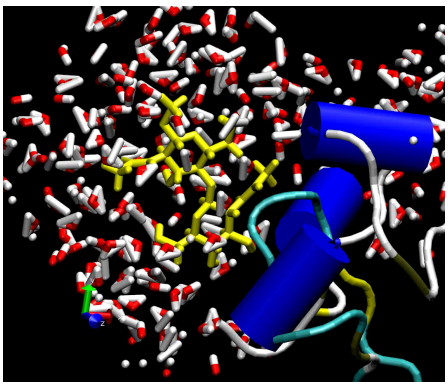
- Simulation of molecules guided by Newton's laws of motion.
- Generates a trajectory of the molecular motions for a period of time.
- Potential energy defined by force field

$$E_{potential} = E_{bond} + E_{angle} + E_{dihedral} + E_{vdW} + E_{electrostatic}$$

$E_{solvation}$ implict and explicit models

Implict models : Generalized Born (GB)
Poisson-Boltzmann (PB)

Molecular Dynamics (MD) simulations



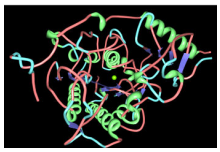
More accurate estimation of binding energies of protein-ligand complexes

Problems that can be adressed with *molecular dynamics* simulations

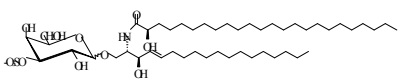
- Behaviour of ligands in proteins active site
- Flexibility of amino acid residues
- Binding energy estimations and many more

Break

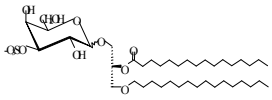
Case study - Docking



- Proteins
  - Arylsulfatase A (ASA) enzyme
- Two glycolipids (sugar with a fatty tail)
  - Sulfogalactosylceramide (SGC)



  - Sulfogalacosylglycerolipid (SGG)



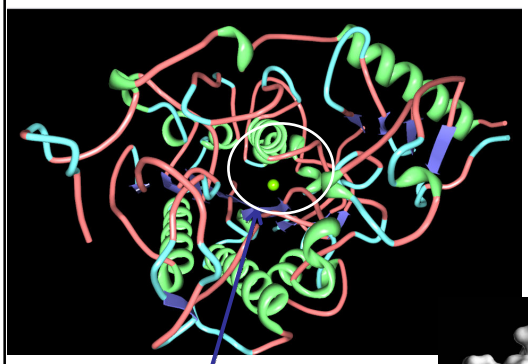
Reference

Schenk M, Koppisetty CA, Santos DC, Carmona E, Bhatia S, Nyholm PG, Tanphaichitr N.
Interaction of arylsulfatase-A (ASA) with its natural sulfoglycolipid substrates: A computational and site-directed mutagenesis study.
Glycoconjugate Journal. 2009 Nov;26(8):1029-45.

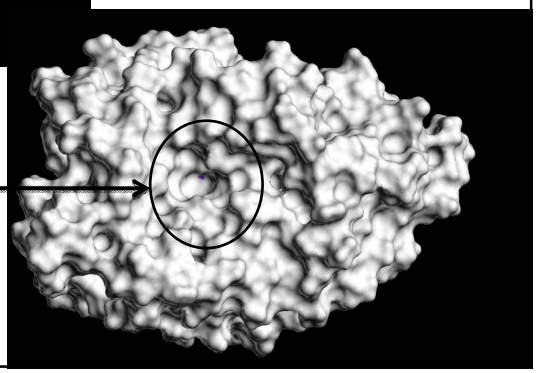
doi: 10.1007/s10719-008-9222-9.

Pubmed: http://www.ncbi.nlm.nih.gov/pubmed/19381802

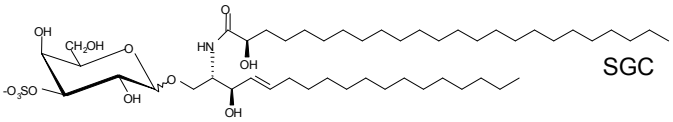
Arylsulfatase A (ASA)

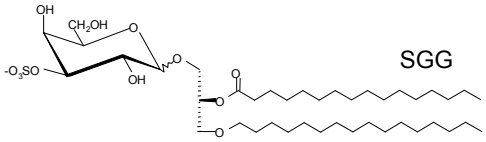


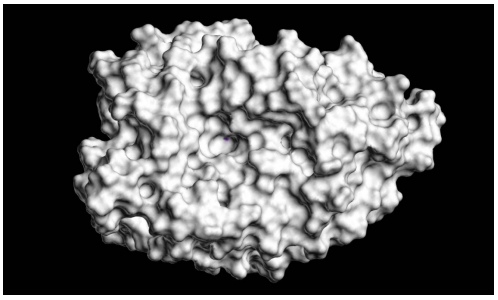
- Possible role in fertilization (Degradation of **SGG**)
- Mutations in ASA causes Metachromatic Leukodystropy (**MLD**)



Main Players







ASA

QUESTIONS

1. How does ASA interact with SGC and SGG ?
2. What are the amino acid residues in ASA that interact with SGC and SGG

GENERAL SOLUTION

Perform X-ray crystallography and analyze the structural details of ASA- SGC and ASA-SGG complexes

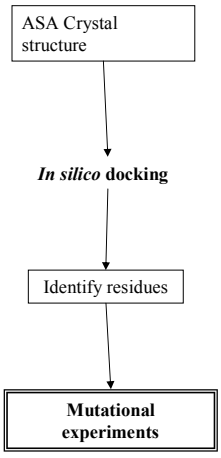
Easy to say, but.....

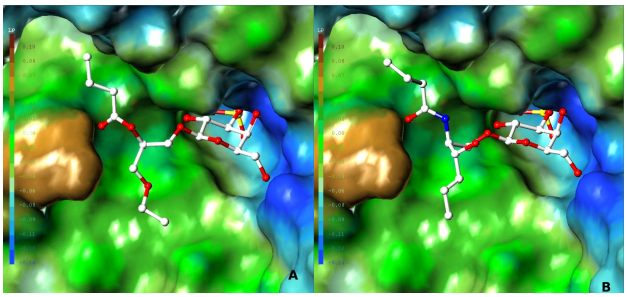
DIFFICULTIES

1. It is known that ASA interacts with SGC and SGG but not known if they exist as a stable complex.
2. Carbohydrates are difficult to co-crystallize with proteins.
3. Other complications in experimental design.

Alternative Solutions with Structural Bioinformatics

Interaction of ASA with SGC and SGG





SGG **SGC**

Involvement of Cys69, Lys302 and Lys123 in binding SGC and SGG was verified by site-directed mutagenesis.

Interaction of ASA with SGC and SGG

1. Structural details on the interaction of SGC and SGG with ASA revealed
2. Computational predictions were verified.
3. SGC and SGG interact with ASA in very similar ways.

Summary

- Challenges in the drug discovery process
- Structural bioinformatics methods
  - Docking and Molecular dynamics
- *In silico* docking could be used for
  - Predicting the protein-ligand interactions
  - Virtual screening of large number of compounds against a protein
- Structural bioinformatics methods aid in reducing the time and costs involved in drug discovery

Thanks for listening !