The Many Roles of Computational Science in Drug Design and Analysis

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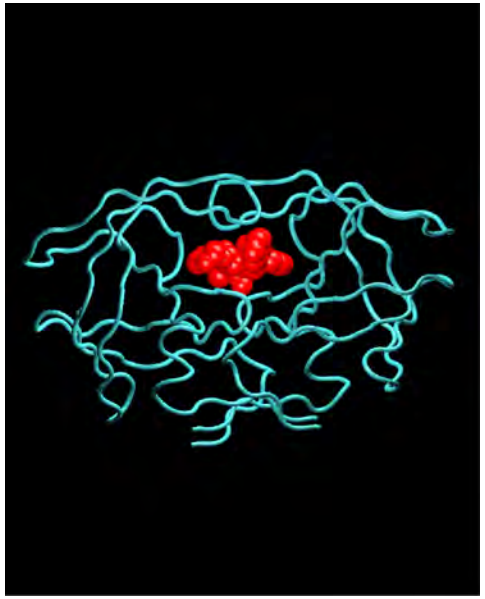
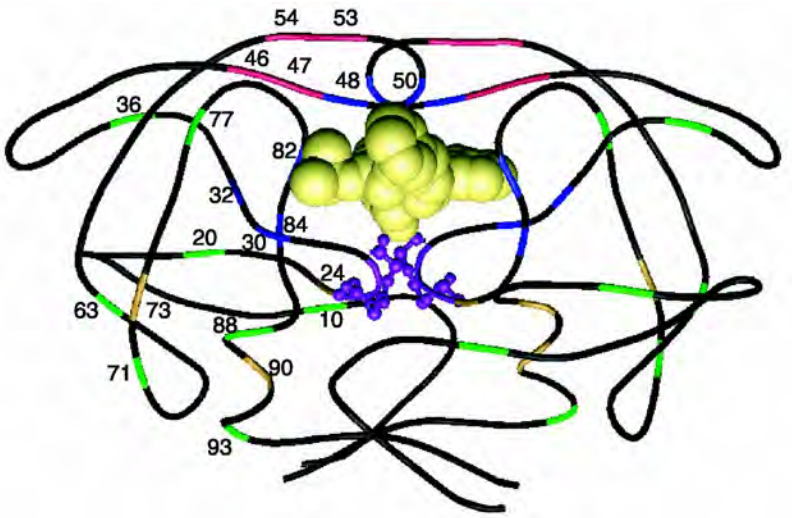
DOE CSGF Fellows Conference, Washington, D.C.



Amprenavir bound to
HIV-1 protease

(HIV)

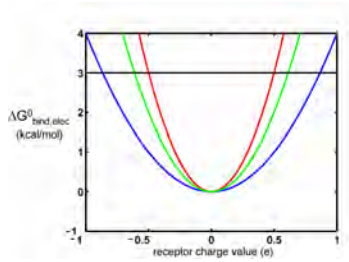
Kim et al, *J. Am . Chem . Soc.* **117**:1181, 1995

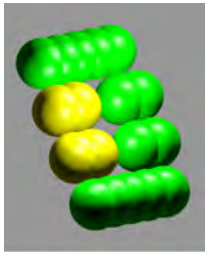


…target rapidly
mutates!

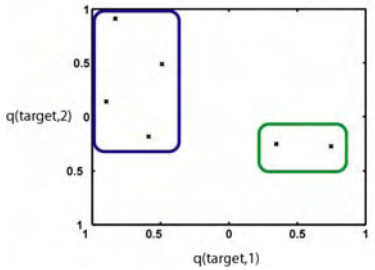
Shafer, *Clinical Microbiology Rev.,* **15**:247, 2002

HIV−1 Protease

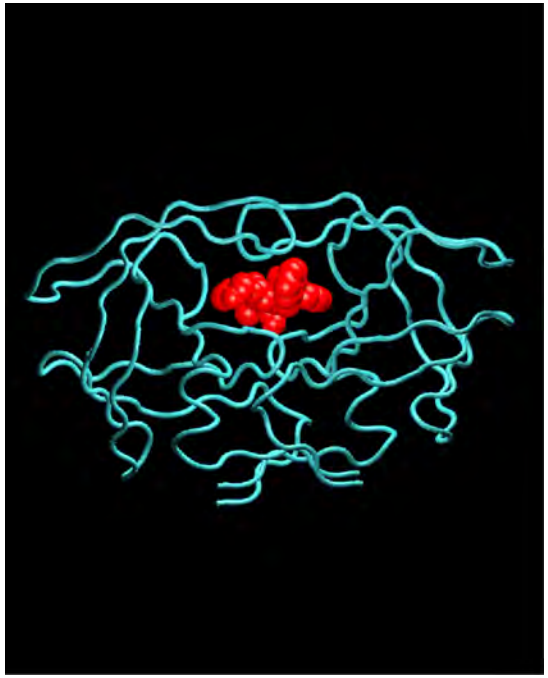


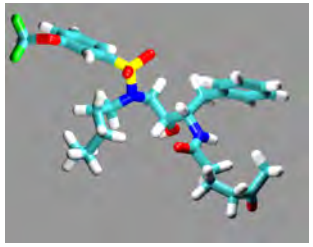


Understanding binding specificity and promiscuity

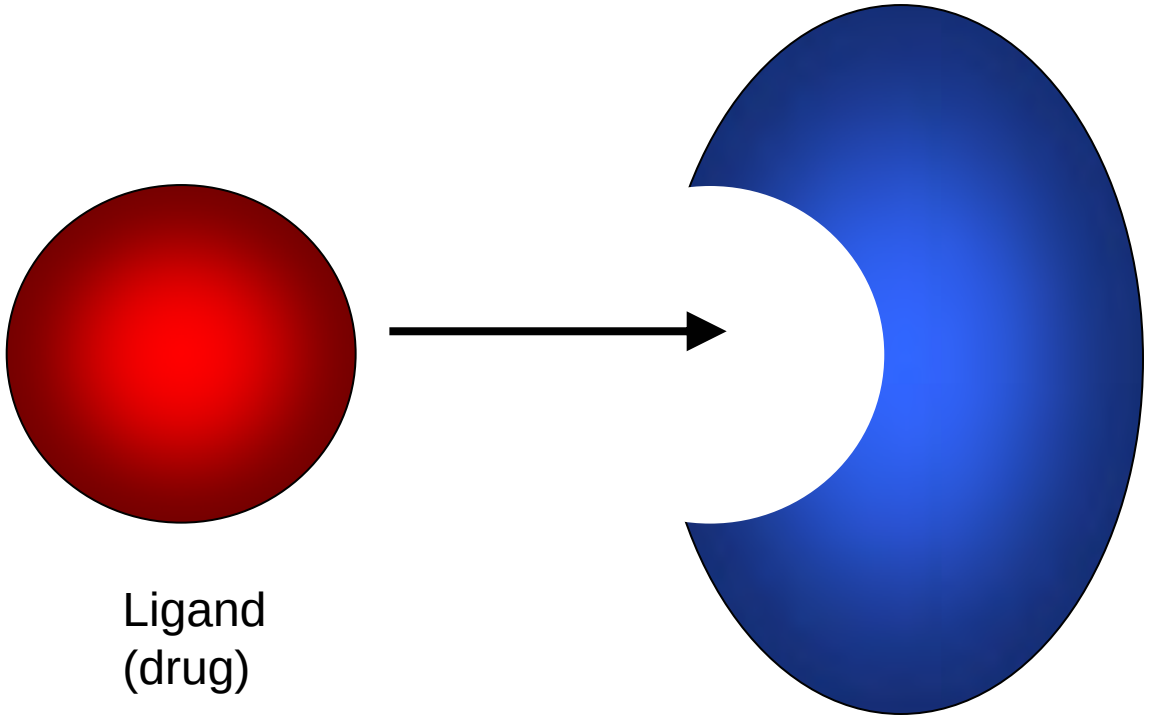


Developing methods for optimal drug cocktail design

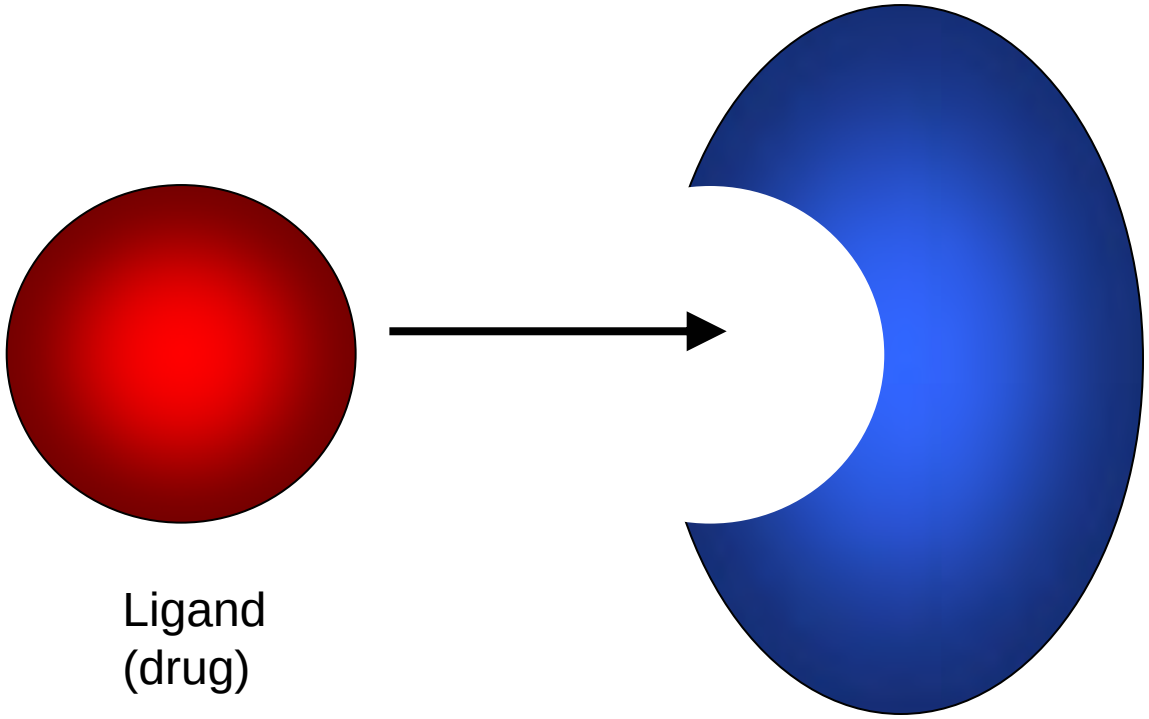




Designing broadly-binding HIV-1 protease inhibitors



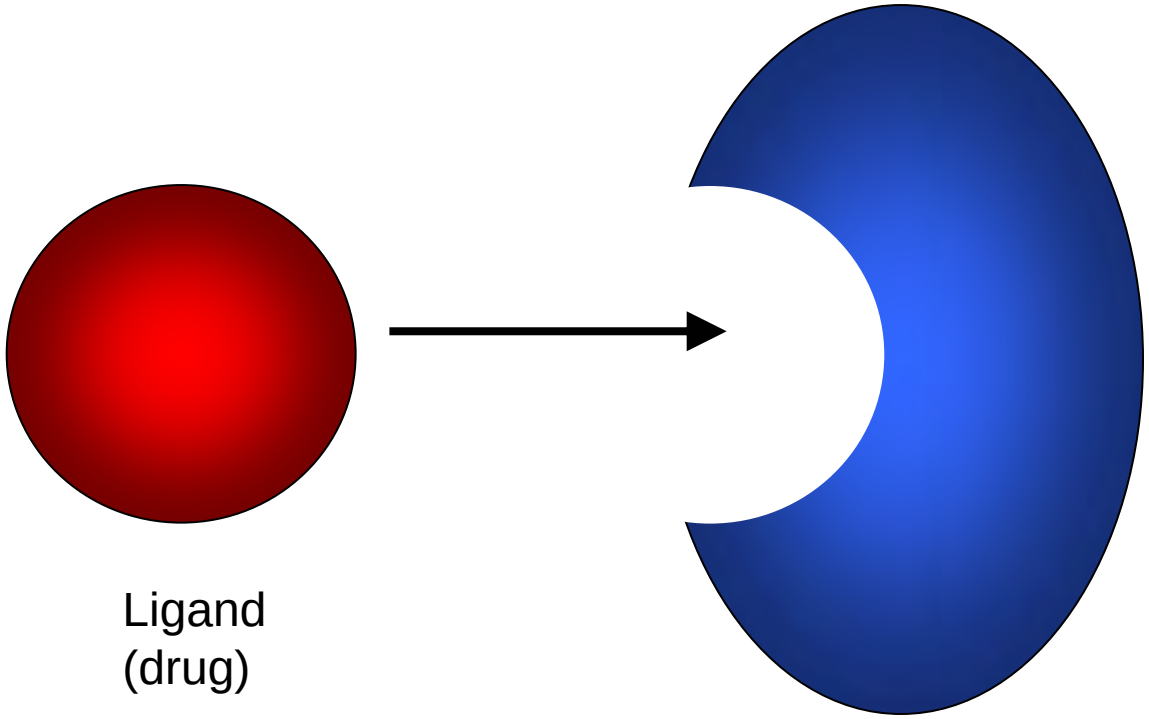
Goal: create a high-affinity interaction ←→ low ΔG



“Reality”:

Quantum mechanics

Statistical Mechanics

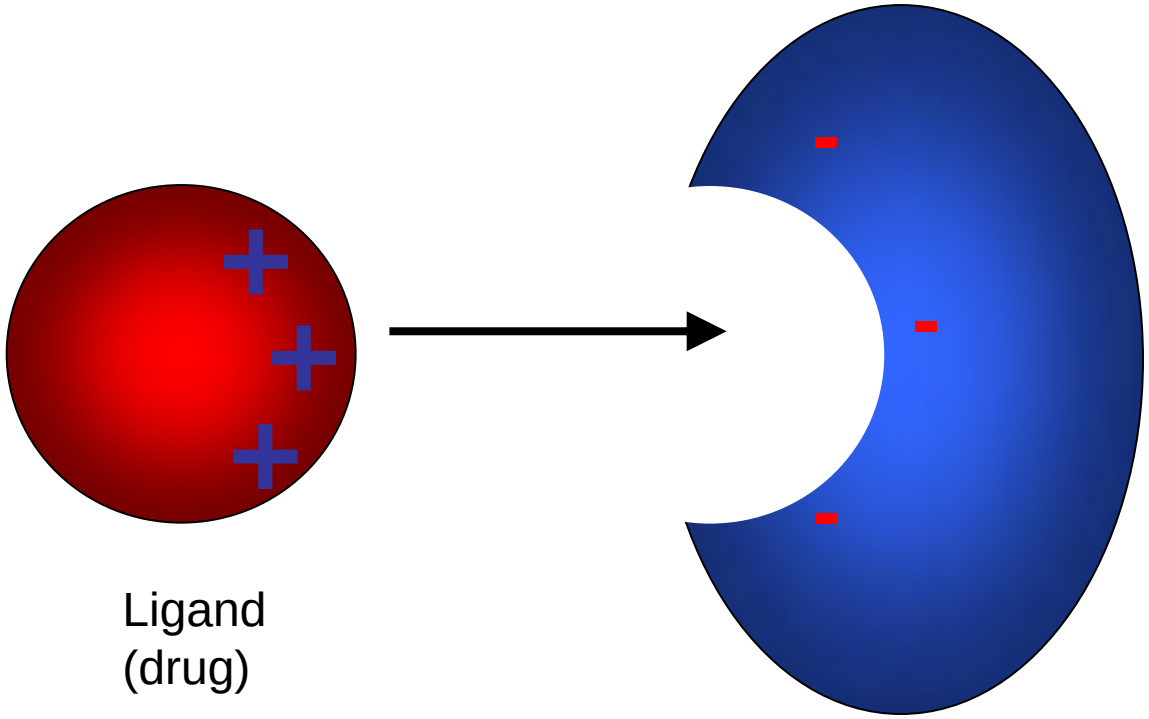


Model:

Atoms as spheres

Point charges

(Rigid Binding)



Model:

Atoms as spheres

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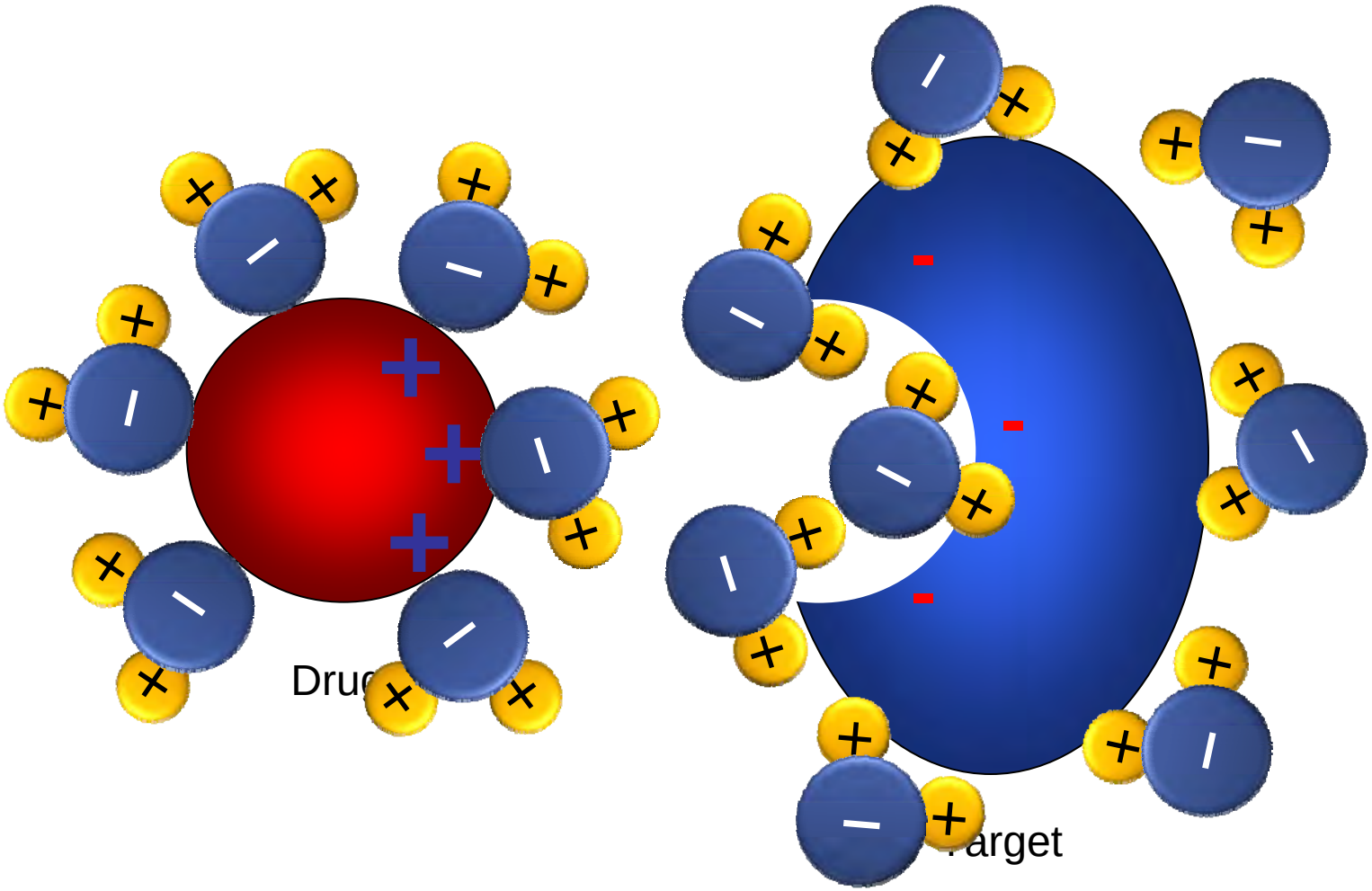
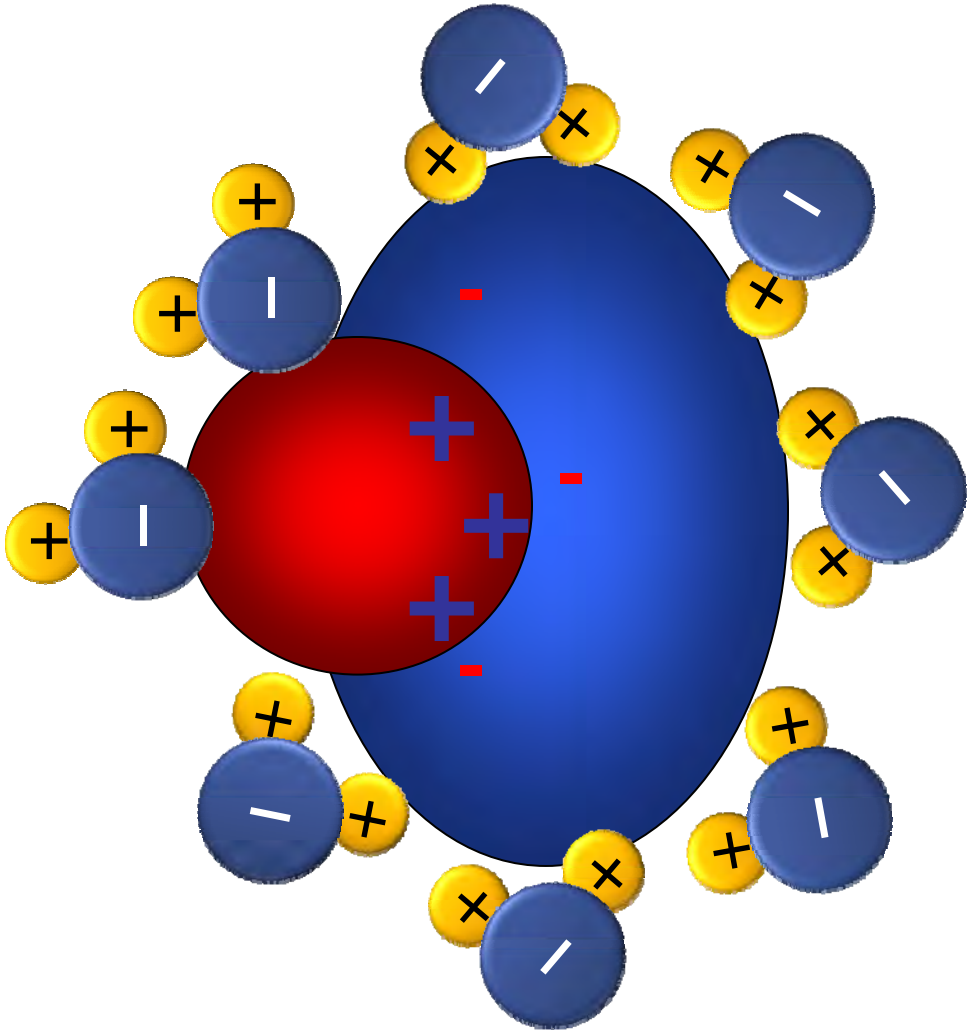


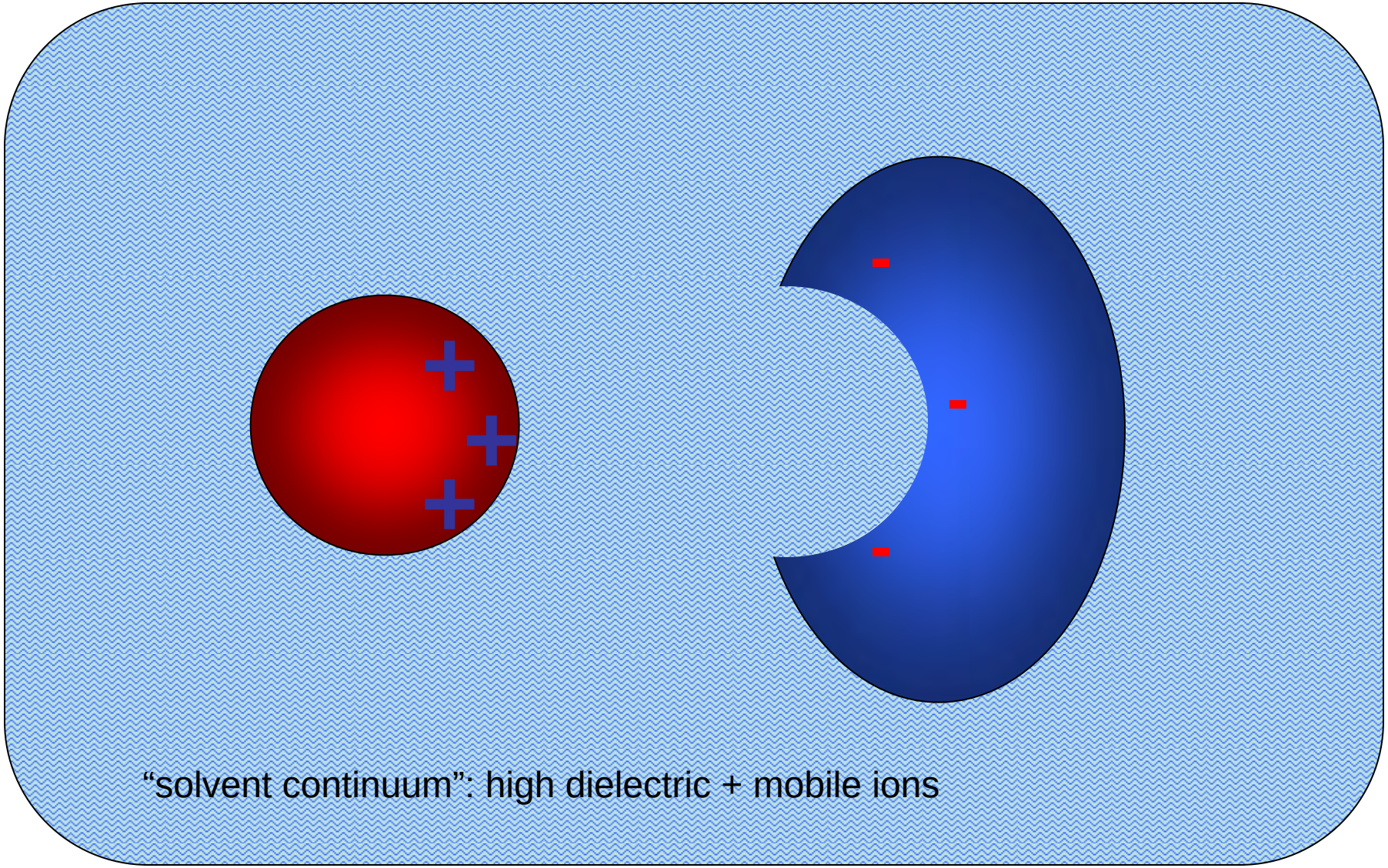
Interactions with solvent



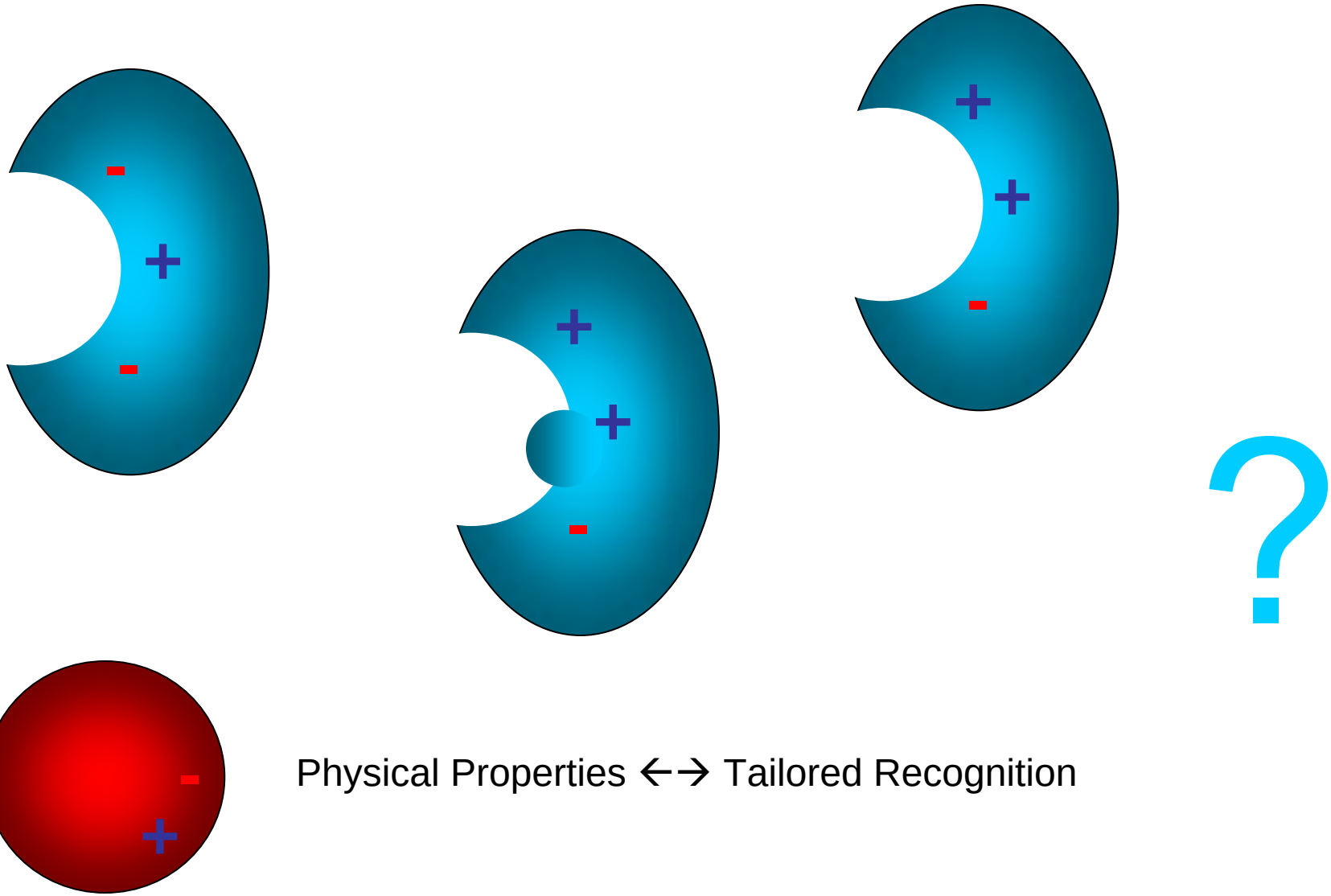
Loss of solvation → FAVORS LOW CHARGE MAGNITUDES

Drug-target interaction → FAVORS HIGH CHARGE MAGNITUDES

Our Model

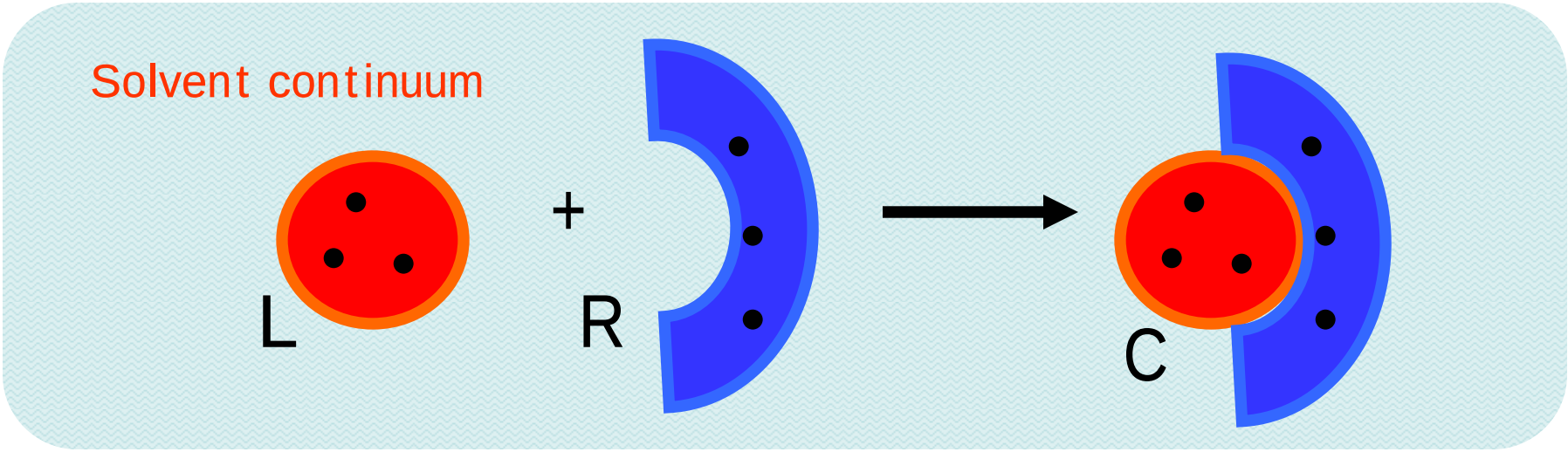


Designing Toward Multiple Targets

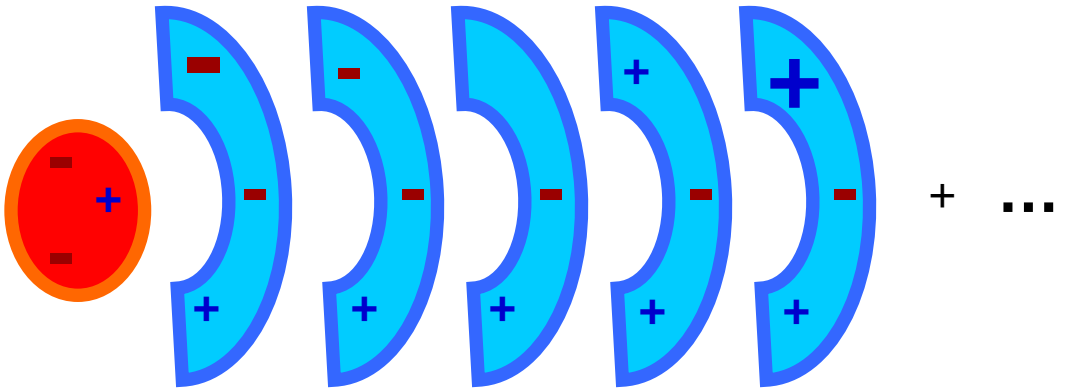


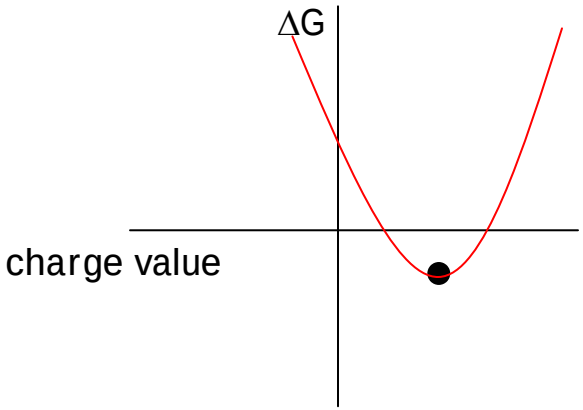
Physical Properties ←→ Tailored Recognition

Theoretical Framework



$$\Delta G_{bind} = vdW + SASA + q_L^T L q_L + q_R^T R q_R + q_R^T C q_L$$

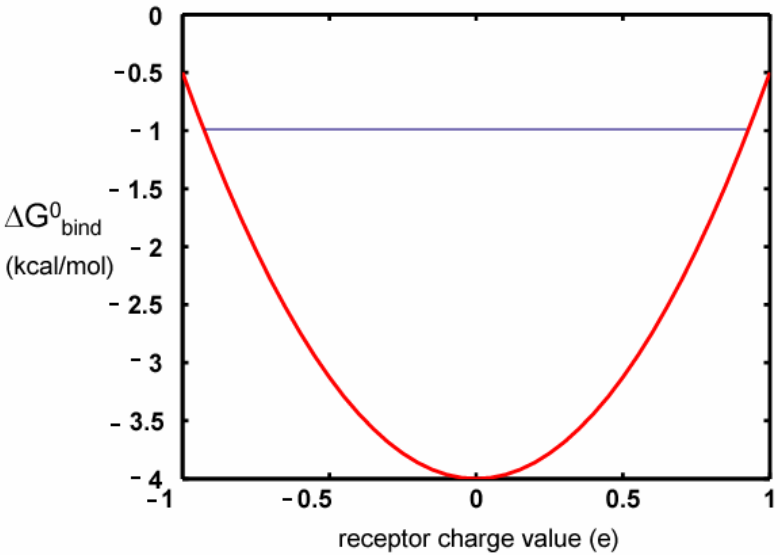




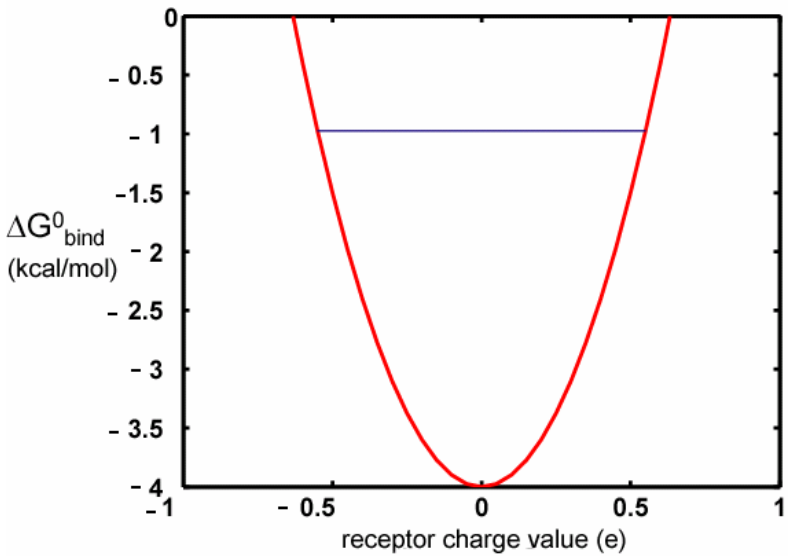
The binding profile looks like a paraboloid.

Kangas and Tidor, *J Chem Phys*, 109:7522-7545, 1998

Theoretical Framework



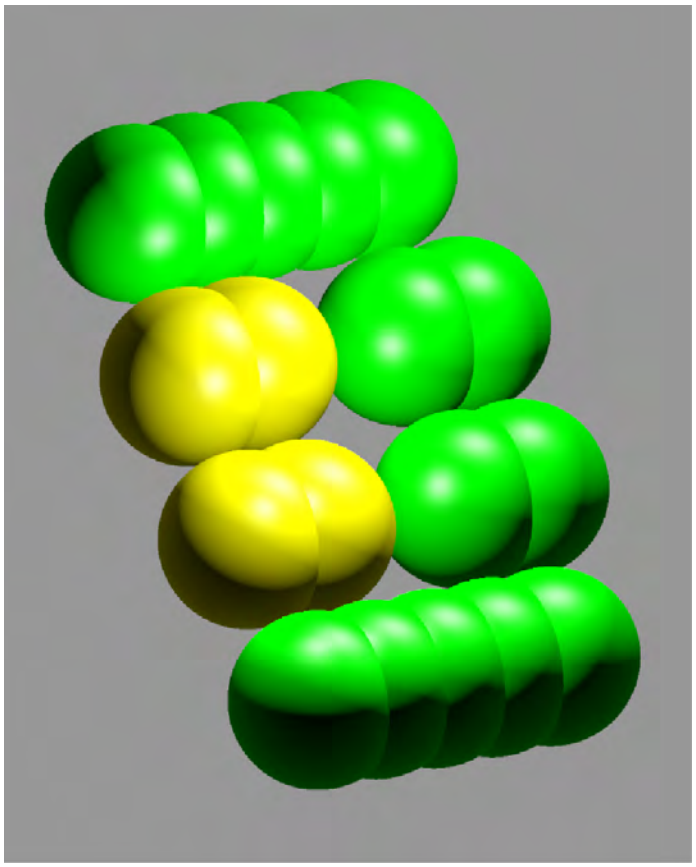
A promiscuous ligand



A specific ligand

Radhakrishnan and Tidor, *J. Phys. Chem. B*, **111**:13419-13435, 2007

Model Systems

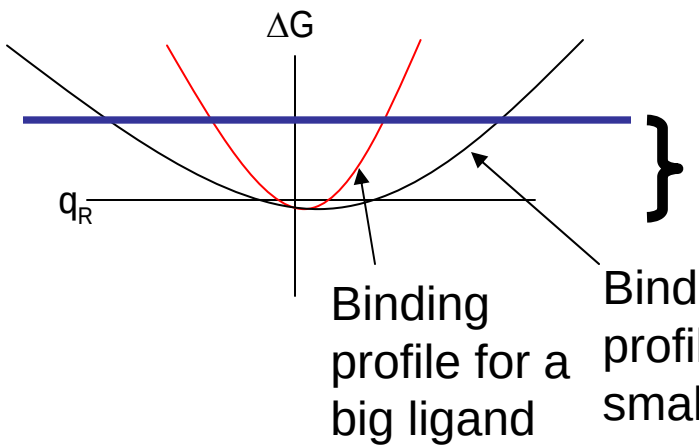


Radhakrishnan and Tidor, *J. Phys. Chem. B*, **111**:13419-13435, 2007

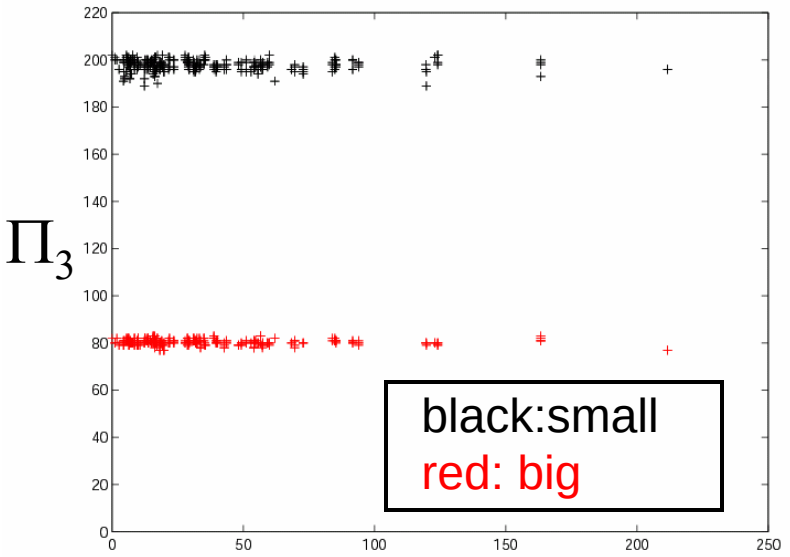
Theory and Model Systems Agree:

- Smaller ligands are more promiscuous than larger ligands

Theory



Numerical Experiment



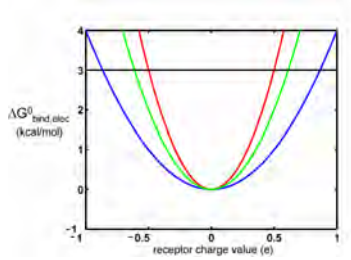
Drug charge distribution

Some Other Insights

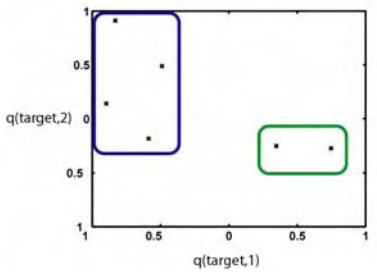
- Smaller ligands are more promiscuous
- Hydrophobic ligands are more promiscuous because they are near the center of biological charge space
- Hydrophobic ligands are more promiscuous because they are not as sensitive to shape differences
- Flexibility makes polar and charged ligands more specific, but allows for greater overall binding affinity to multiple partners.
- Asymmetric groups can lead to increased promiscuity

Radhakrishnan and Tidor, *J. Phys. Chem. B*, **111**:13419-13435, 2007

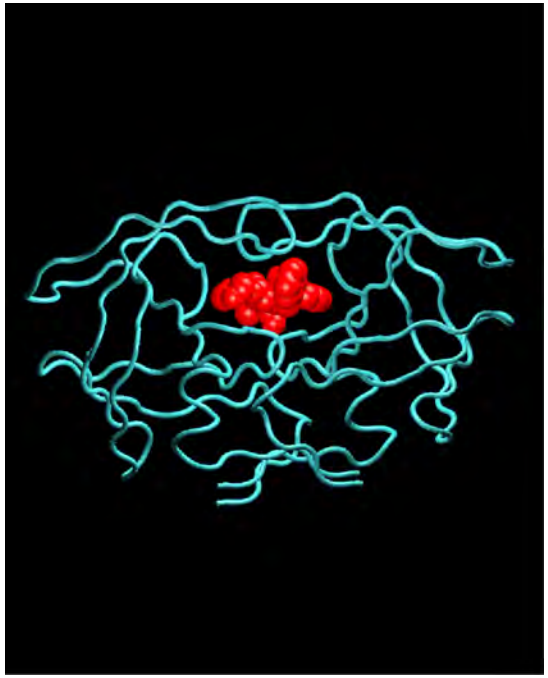
HIV−1 Protease

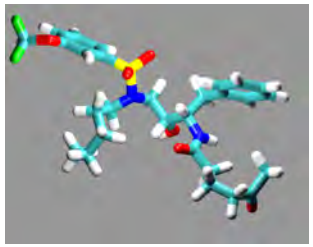


Understanding binding promiscuity



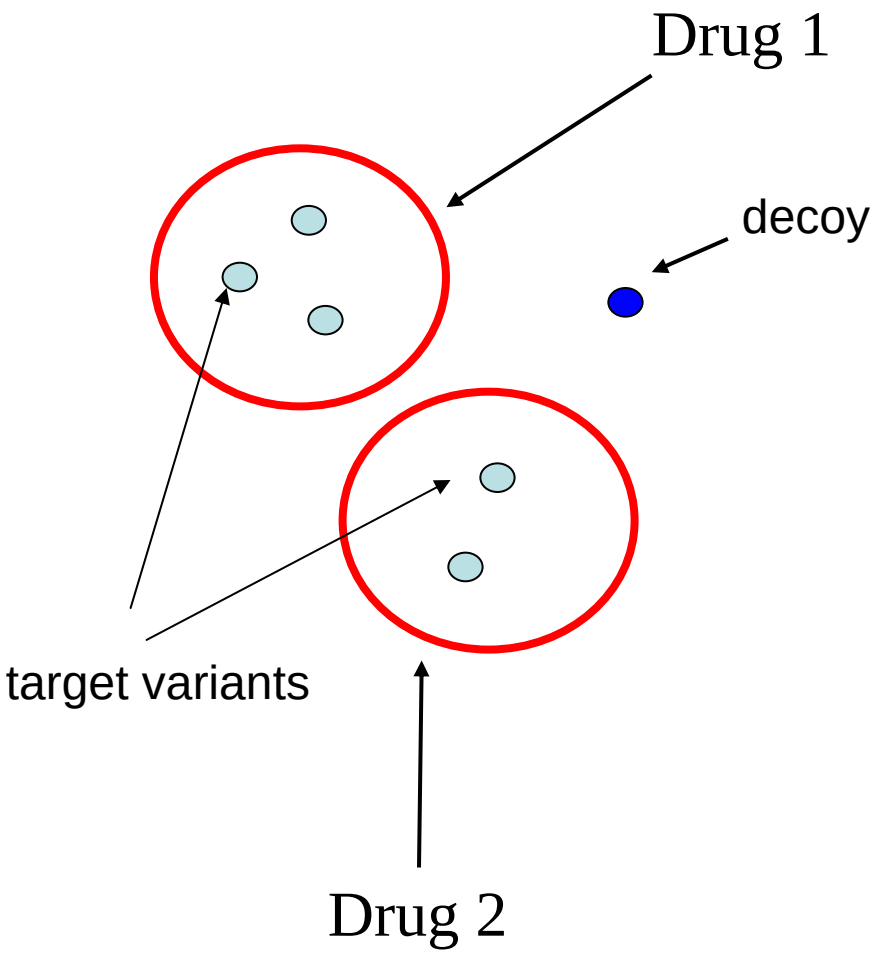
Developing methods for optimal drug cocktail design



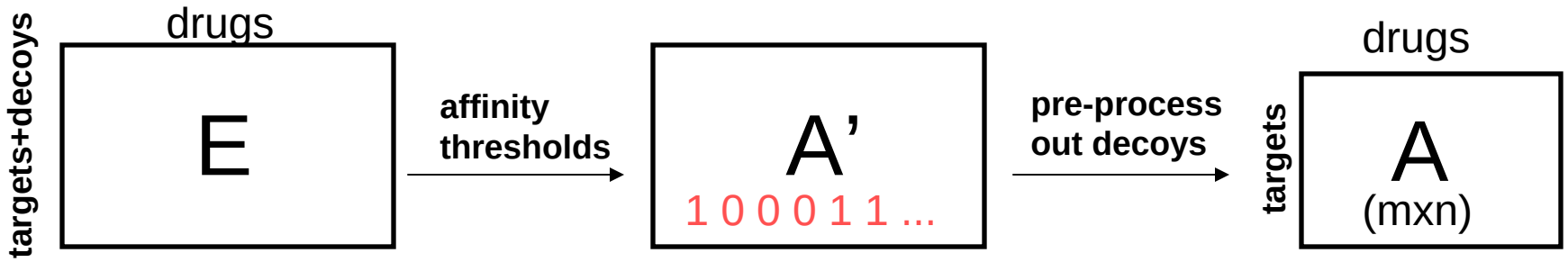


Designing broadly-binding HIV-1 protease inhibitors

Rational Cocktail Design



Cocktail Design as an Optimization Problem



Minimize # drugs in cocktail

All targets covered by at least one drug

IP 1.1

minimize $\sum_j y_j$ subject to

$A\vec{y} \geq \vec{b}$,

$\vec{b}$ is a length-m vector of all ones.

Minimize sum of binding energies

All targets covered by at least one drug

Size of cocktail is optimal

IP 1.3

minimize $\sum_i \sum_j E_{i,j} z_{i,j}$ subject to

$\forall i, \sum_j A_{i,j} z_{i,j} = 1,$

$\forall i, \sum_j z_{i,j} = 1,$

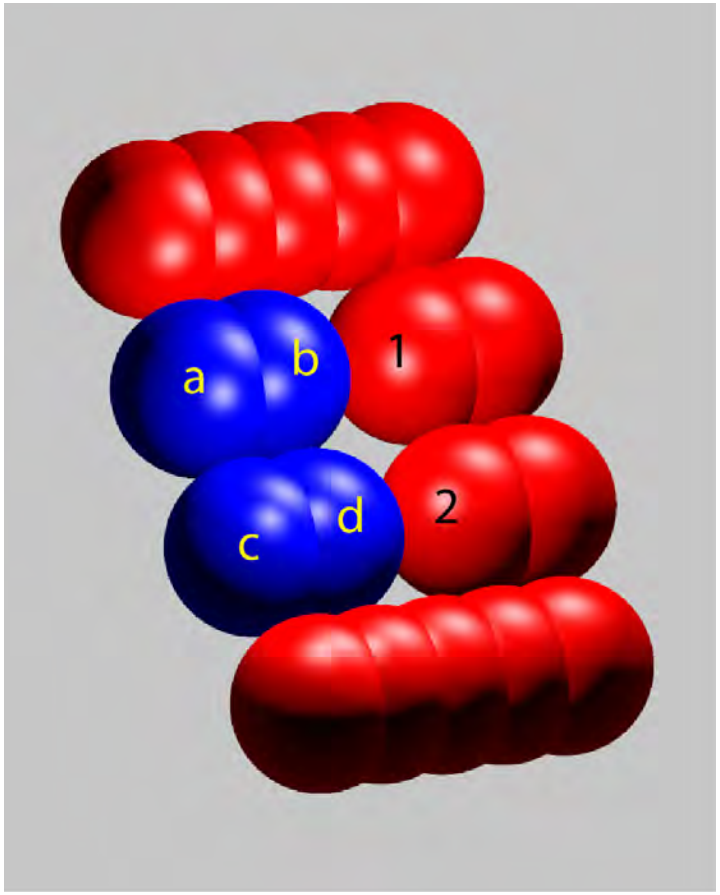
$\forall j, y_j \geq \frac{1}{I} \sum_i z_{i,j},$

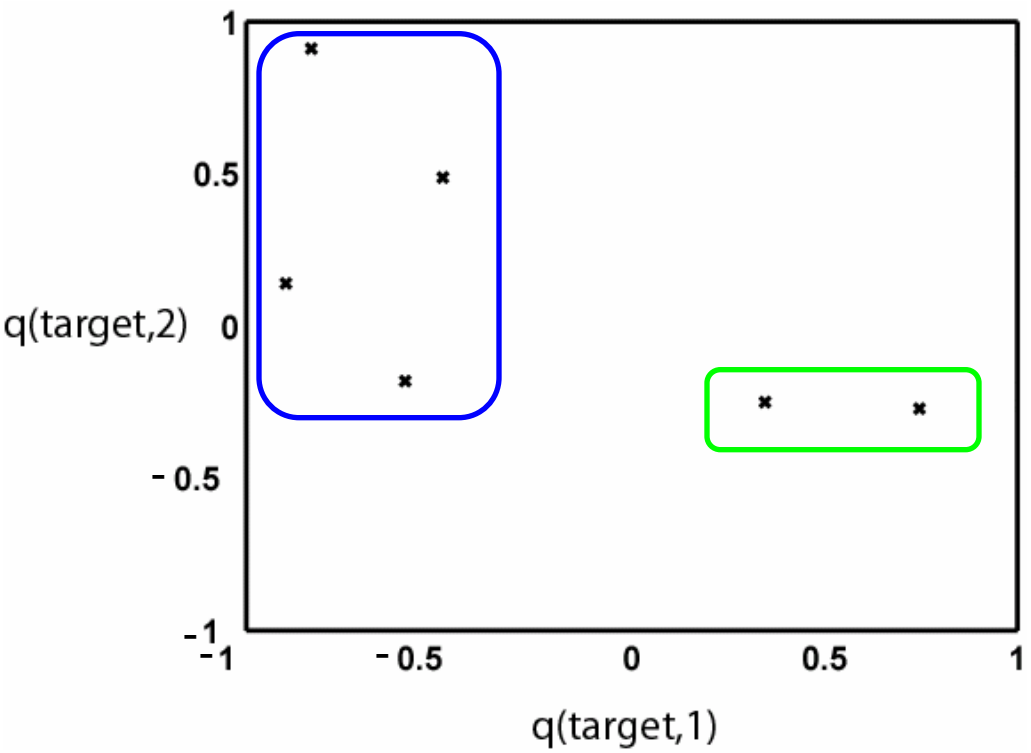
$\sum_j y_j = opt_{1.1},$

where $opt_{1.1}$ is the optimal number of drugs found in IP 1.1.
and I is the number of target variants in the ensemble.

Can also combinatorially design individual molecular members simultaneously

Optimally covering model ensembles



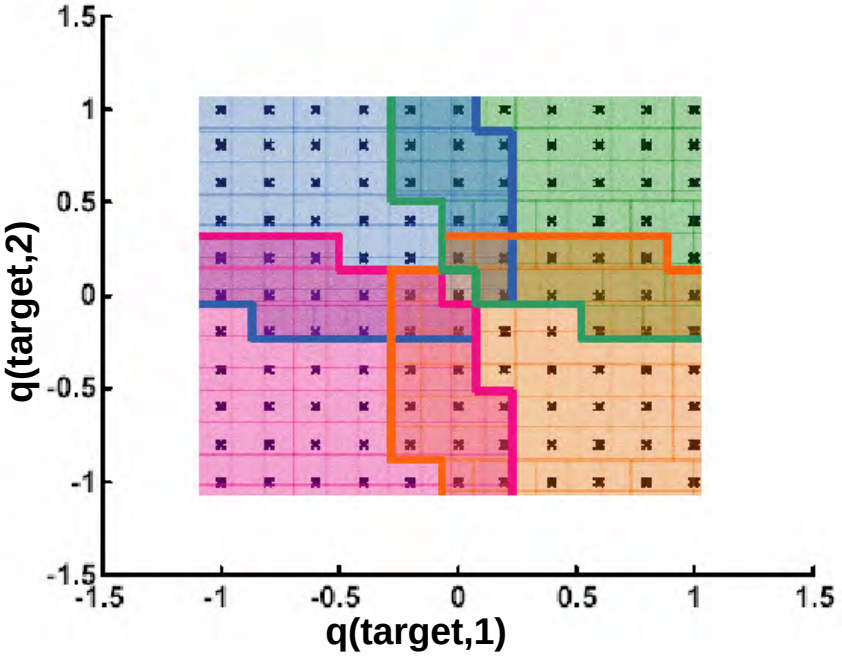


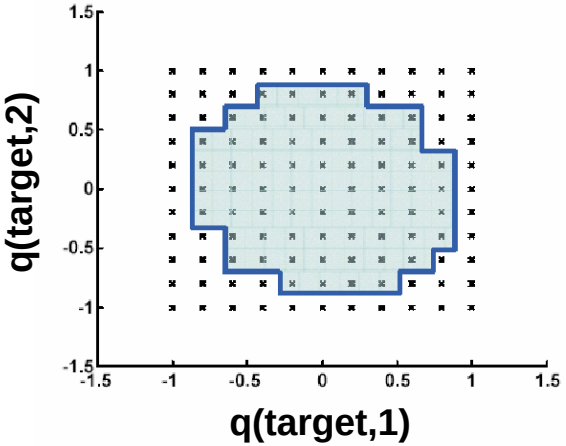
0	0.5
0.5	-0.5

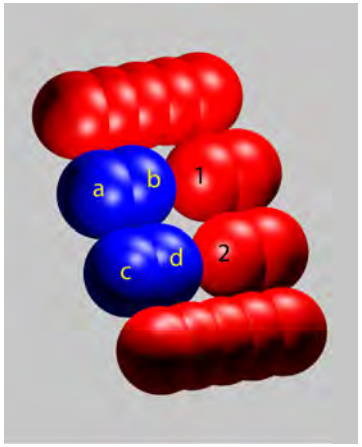
0	-0.5
0	0

Radhakrishnan and Tidor, *J. Chem. Inf. Model* . **48**:1055-1073, 2008

Tiling the Mutation Space







-0.5	0.5
0.5	-0.5

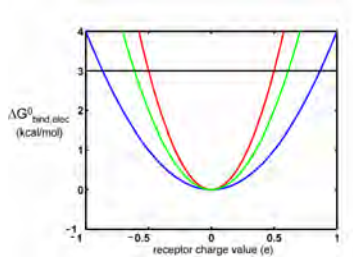
0	-0.5
0	-0.5

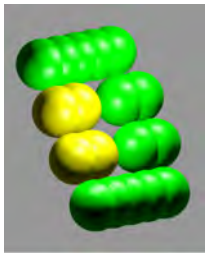
0	0.5
0	0.5

0.5	-0.5
-0.5	0.5

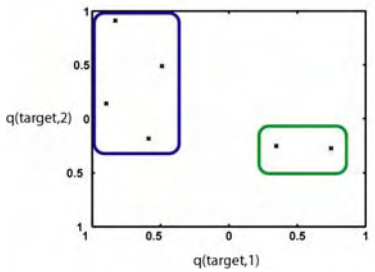
0	0
0	0

HIV−1 Protease

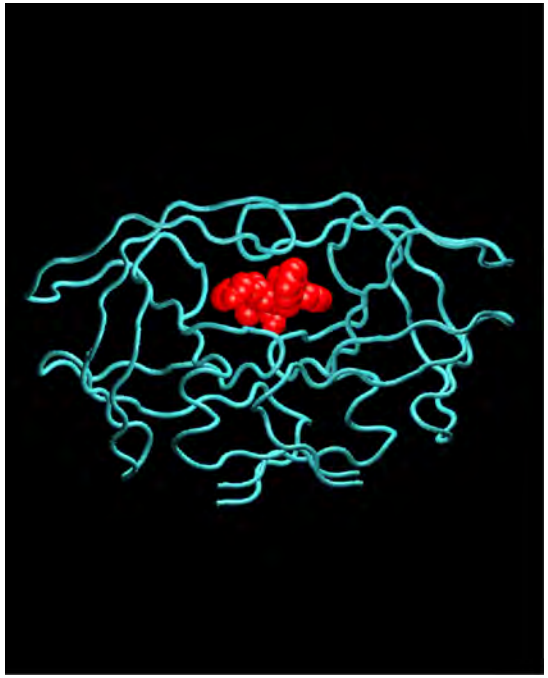


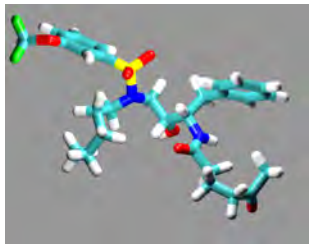


Understanding binding promiscuity



Developing methods for optimal drug cocktail design

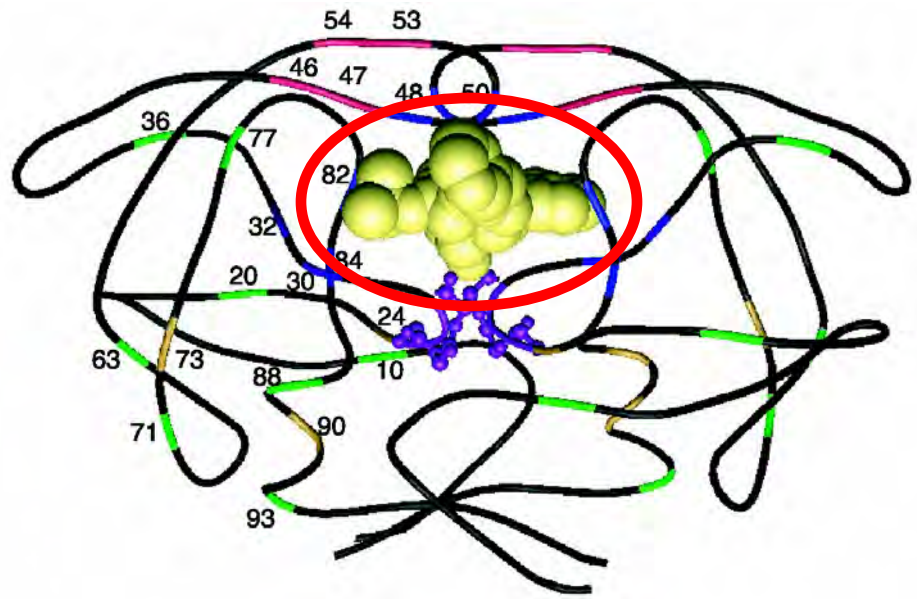




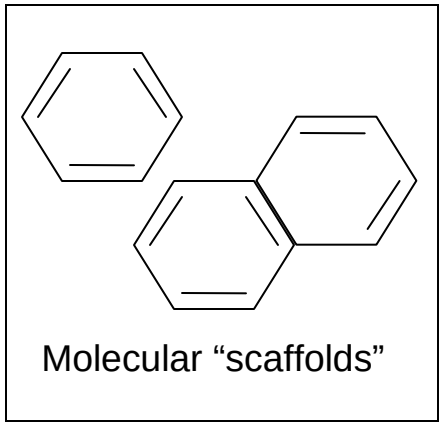
Designing broadly-binding HIV-1 protease inhibitors

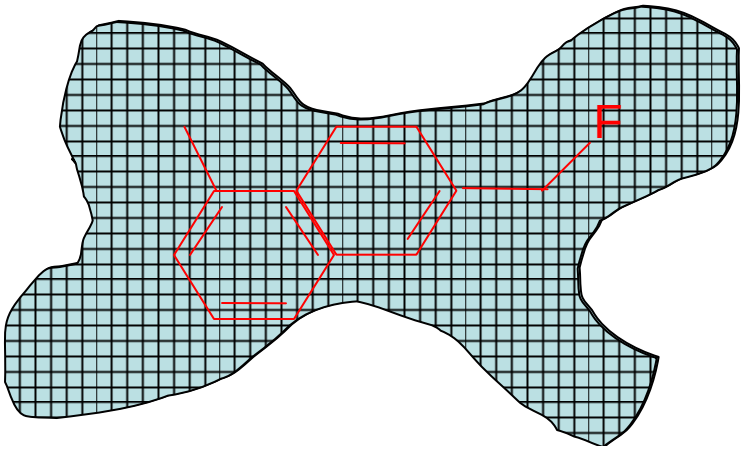
Designing into Multiple Targets: HIV-protease

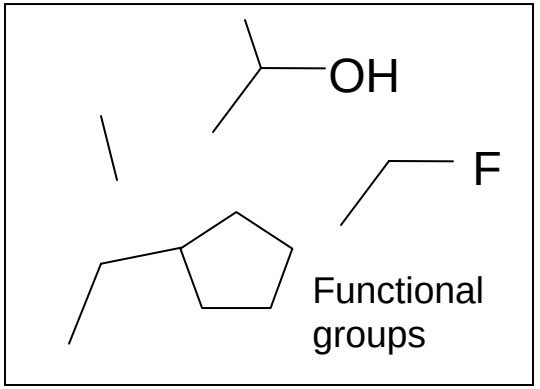
Wild Type
V82A
I84V
D30N
L90M
I50V
L63P, V82T, I84V



Methods:



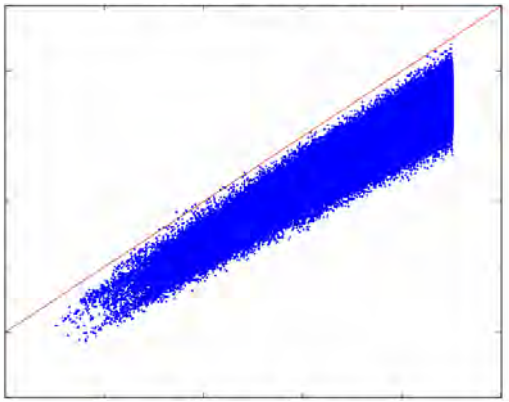




Dead-End Elimination, A*:

List of tight-binding compounds

ΔG, High resolution energy function

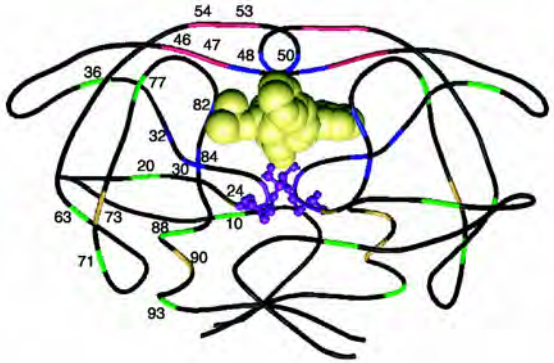


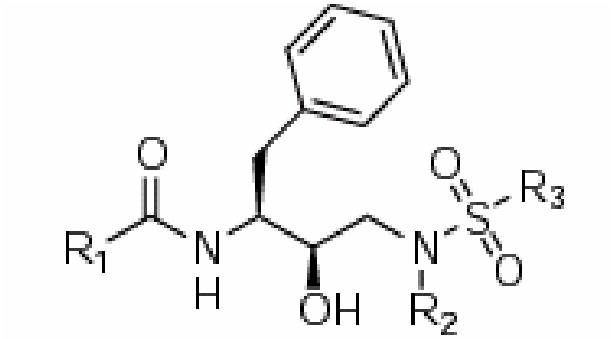
ΔG, fast energy function

Michael Altman *et al. J. Amer. Chem Soc.*, 130: 6099-6113, 2008

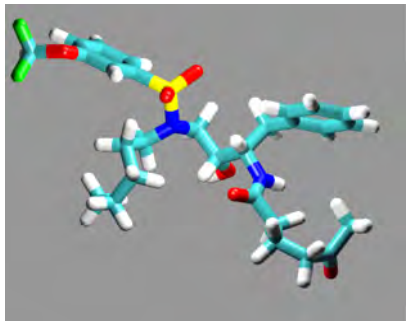
Design of Broadly−Binding HIV−1 Protease Inhibitors

Wild Type
V82A
I84V
D30N
L90M
I50V
L63P, V82T, I84V

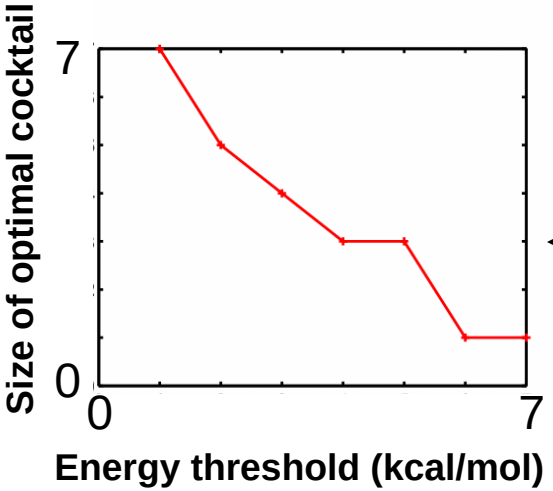




R_1: From Carboxylic Acids (R1-COOH)
R_2: From Primary Amines (R2-NH_2)
R_3: From Sulfonyl Chlorides (R3-SO_2Cl)



Physical Properties



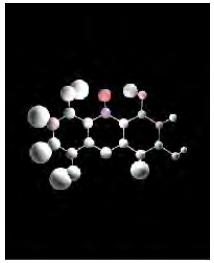
Michael Altman *et al. J. Amer. Chem Soc.*, 130: 6099-6113, 2008

Summary

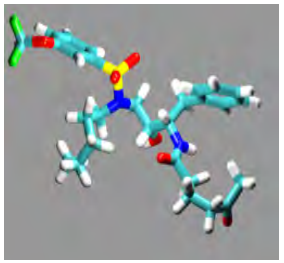
- Physical Framework for Binding Promiscuity and Specificity
- Methods For Designing Toward Target Ensembles
- HIV-1 Protease as a Case Study

The Many Roles of Computation

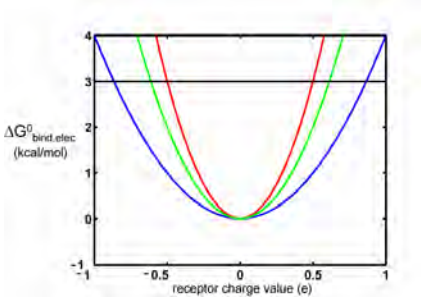
Computation can…



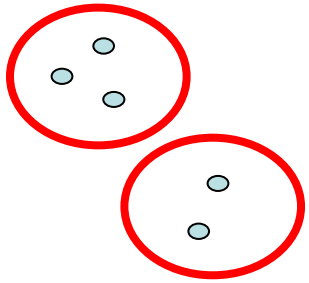
…map out key interactions in a binding site.



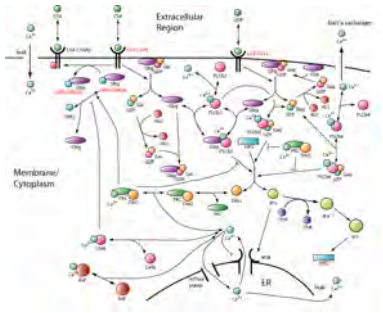
…design drugs.



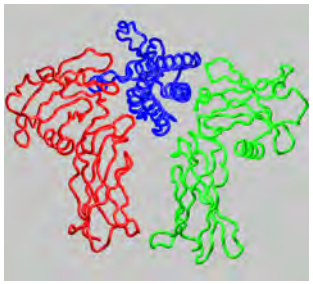
…predict properties that make drugs specific or "promiscuous."



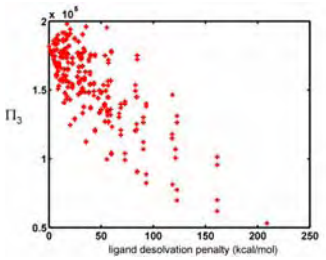
…design drug cocktails.



…model cellular events.



…design novel experimental systems.



…analyze clinical data

…etc. !

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