Chemical properties that affect binding of enzyme-inhibiting drugs to enzymes

Research proposal by Dan Nacu

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Global Pharmaceutical Industry

$400,000,000,000

http://www.who.int/trade/glossary/story073/en/

Drug Development

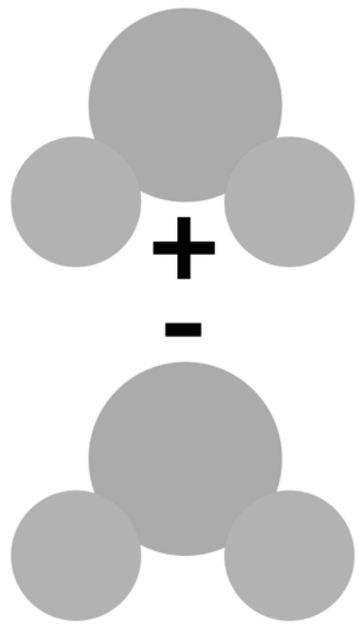
Computer Simulations

How can it be done?

Simulation Models

Shape Complementarity

Chemical Properties



How can it be done?

Chemical Properties

Solvent Accessible Surface Area
Hydrophobicity
Electrostatics
Van Der Waal's Forces
Residue Pair potential
Desolvation Energies
Atomic Contact Energies
Complementary Determining Regions
etc...

A lot of options...

Its been done before... in a different way.

Li et al, 2007

Their Equation

$$\begin{aligned}\text{Score} = {} & w_1 E_{\text{RP}} + w_2 E_{\text{ACE}} + w_3 E_{\text{vdw}}^{\text{attr}} + w_4 E_{\text{vdw}}^{\text{rep}} + w_5 E_{\text{ele}}^{\text{sa}} \\ & + w_6 E_{\text{ele}}^{\text{sr}} + w_7 E_{\text{ele}}^{\text{la}} + w_8 E_{\text{ele}}^{\text{lr}} \ ,\end{aligned}$$

Its been done before...in a different way.

Li et al, 2007

Their Results

Name	Successful structures out of all Structures
Protease/Inhibitor	16/17
Enzyme/Inhibitor	6/6
Antibody/Antigen	18/19
Other	11/15

How will this be different?

Introducing HINT

***H**ydropathic **INT**eractions*

$$b_{ij} = a_i \, a_j \, S_i \, S_j \, T_{ij} \, R_{ij} + r_{ij}$$

The HINT Equation

Why HINT?

Its more true to life

HINT

$$b_{ij} = a_i \, a_j \, S_i \, S_j \, T_{ij} \, R_{ij} + r_{ij}$$

i *j*

two atoms

HINT

$$b_{ij} = a_i \, a_j \, S_i \, S_j \, T_{ij} \, R_{ij} + r_{ij}$$

affinity score
for single interaction

All interactions are summed at end

HINT

$$b_{ij} = a_i\, a_j S_i S_j\, T_{ij}\, R_{ij} + r_{ij}$$

hydrophobic atom constant$_i$ **hydrophobic atom constant$_j$**

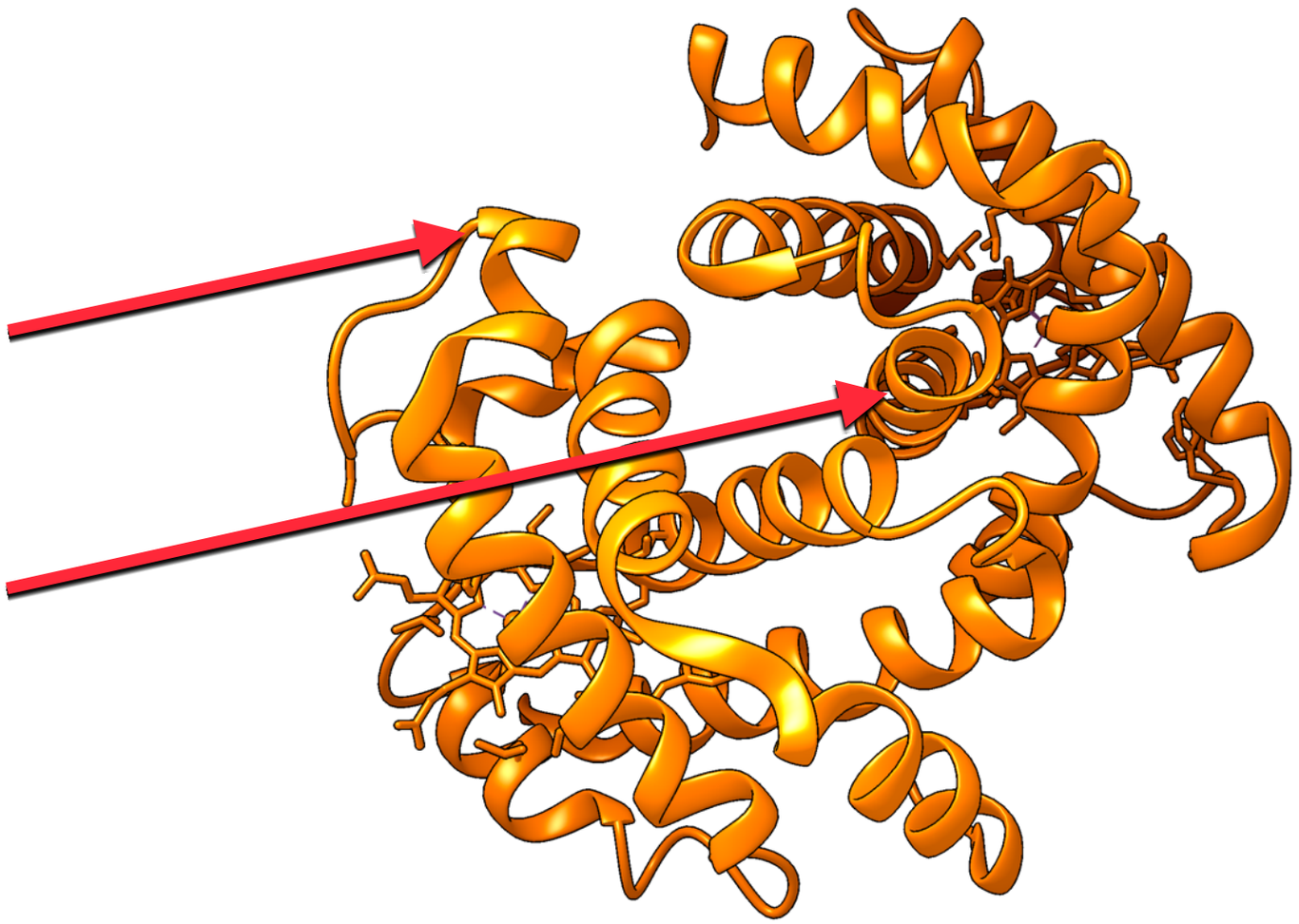
hydrophobic character of interaction

sum

Log P 1-octanol/water

HINT

$$b_{ij} = a_i \, a_j \, S_i \, S_j \, T_{ij} \, R_{ij} + r_{ij}$$



accessible

(inside) non-accessible

HINT

$$b_{ij} = a_i \, a_j \, S_i \, S_j \, T_{ij} \, R_{ij} + r_{ij}$$

Electrostatics

hydrophobic-hydrophobic
hydrophobic-polar
acid-base
hydrogen bond
polar-polar
acid-acid
base-base

returns +1 or -1

HINT

$$b_{ij} = a_i \, a_j \, S_i \, S_j \, T_{ij} \, \boxed{R_{ij}} + r_{ij}$$

Atomic Distance

HINT

$$b_{ij} = a_i \, a_j \, S_i \, S_j \, T_{ij} \, R_{ij} + r_{ij}$$

Lennard-Jones Potential

too close | *too far* | *just right*

What can be done?

By weighing each variable in HINT, the most important chemical property for enzyme/ inhibitor complexes can be found.

$$b_{ij} = (a_i\, a_j)^w\, (S_i\, S_j)^w\, (T_{ij})^w\, (R_{ij})^w + (r_{ij})^w$$

Why exponents?

Why exponents?

Li et al

$$\begin{aligned}\text{Score} = {} & w_1 E_{\text{RP}} + w_2 E_{\text{ACE}} + w_3 E_{\text{vdw}}^{\text{attr}} + w_4 E_{\text{vdw}}^{\text{rep}} + w_5 E_{\text{ele}}^{\text{sa}} \\ & + w_6 E_{\text{ele}}^{\text{sr}} + w_7 E_{\text{ele}}^{\text{la}} + w_8 E_{\text{ele}}^{\text{lr}} \ ,\end{aligned}$$

HINT

$$b_{ij} = (a_i\, a_j)^w\, (S_i\, S_j)^w\, (T_{ij})^w\, (R_{ij})^w + (r_{ij})^w$$

Overview of Experiment

Benchmark 5 PDB File

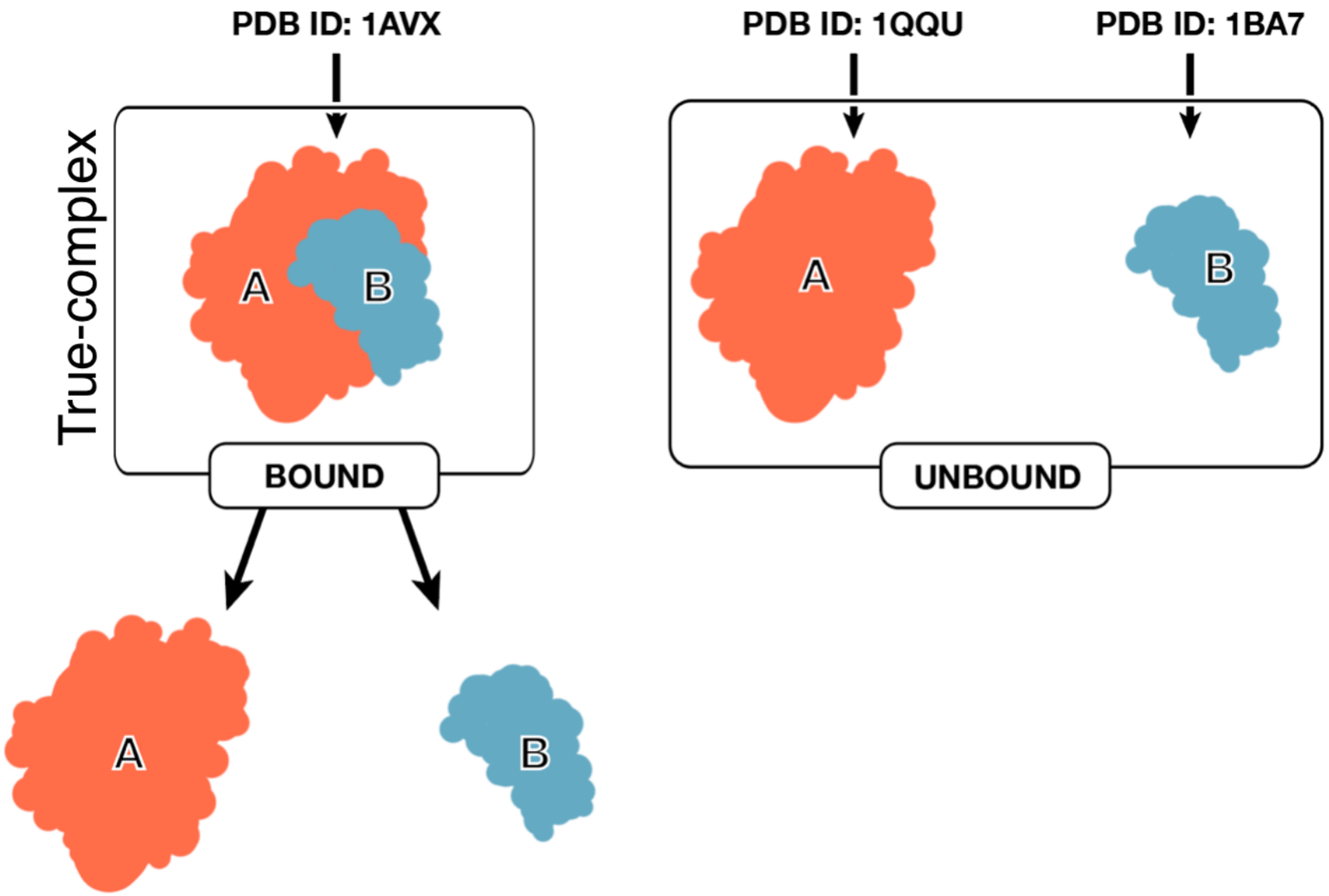
Modified Equation

Similarity to True-Structure

Decision

What's the experiment?

Start with 46 enzyme inhibitor complexes from ***the Benchmark 5.***



What's the experiment?

Bound

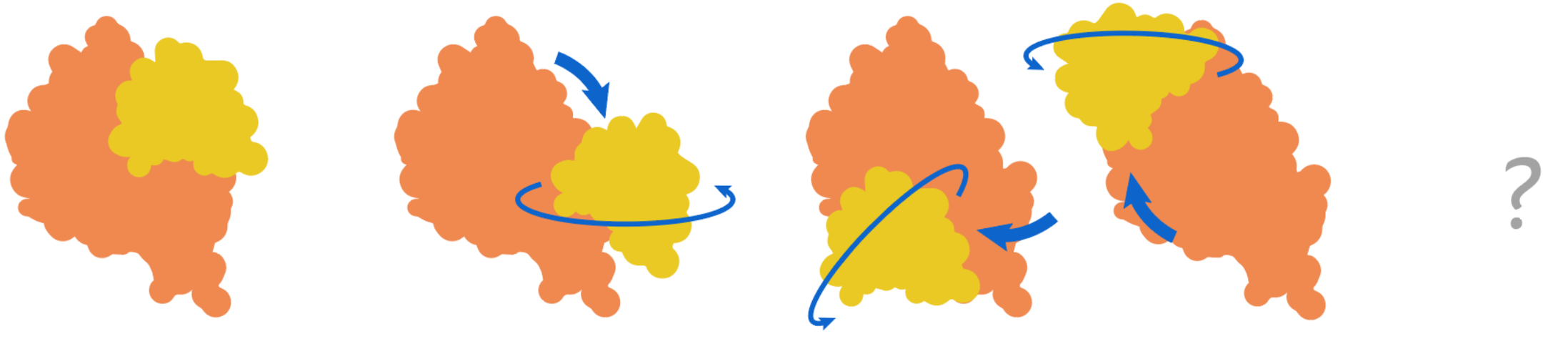
Unbound

FTDock

What's FTDock?

FTDock

Rotation & translation in 3D space to find all possible configurations.



product 1 *product 2* *product 3* *product 4* *etc...*

What's the experiment?

FTDock

Huge list of possible complexes

What's the experiment?

Huge list of possible complexes

L_RMSD Testing

Ligand_Root-Mean-Square-Deviation

What's L_RMSD Testing?

L_RMSD Testing

$$\sqrt{\frac{\sum (\text{atom } x_1 - \text{atom } x_2)^2}{\text{total \# of atoms}}}$$

What's the experiment?

L_RMSD Testing

Top 20 Structures

What's the experiment?

Top 20 Structures

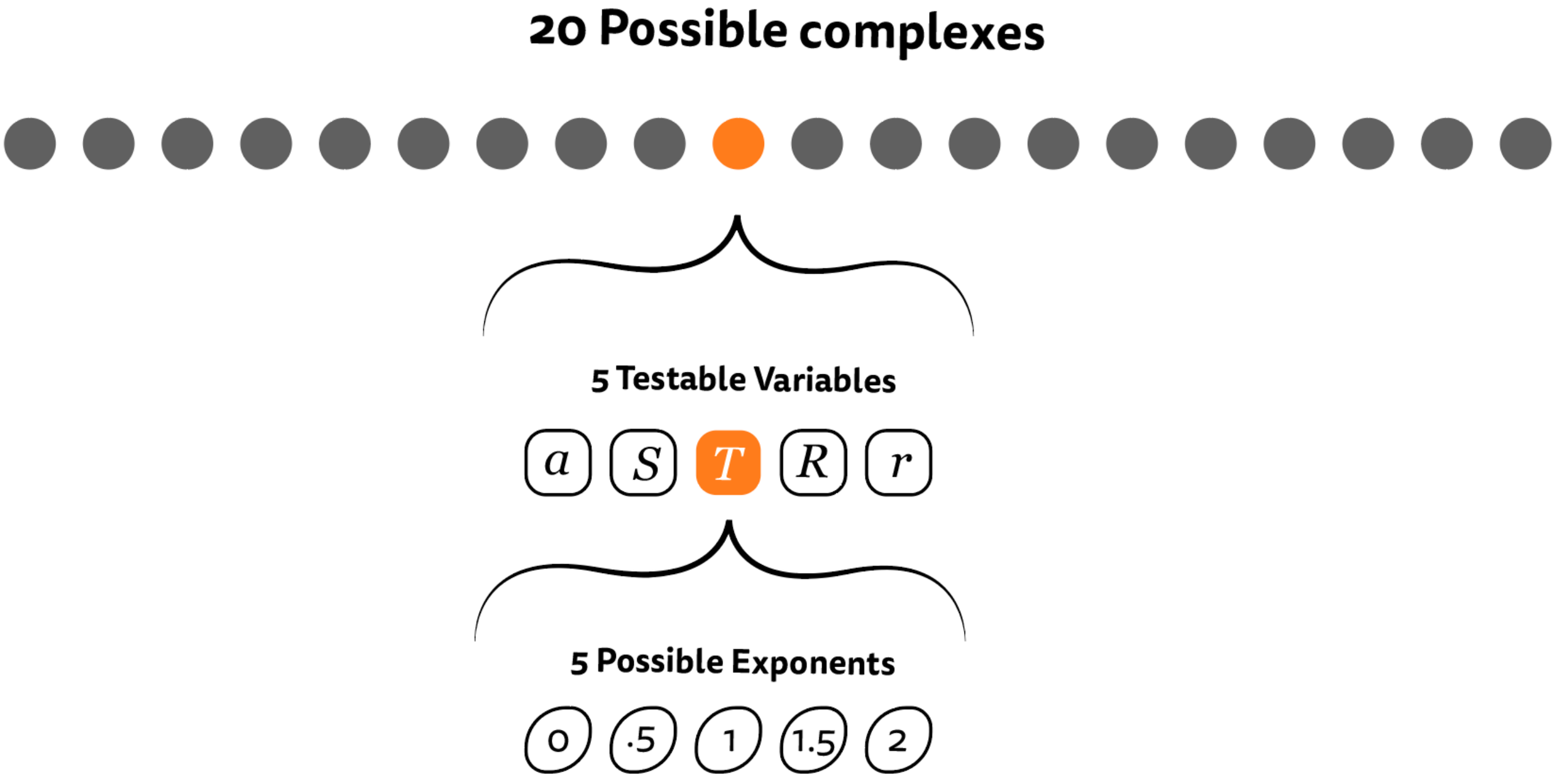
*For **46** complexes =*

***920** simulated structures.*

*For both bound and unbound, **1,840 total***

Lets look at just one

What's the experiment?



Why these exponents?

What's the experiment?

In the end...

23,000 HINT Scores for Bound

23,000 HINT Scores for Unbound

6,325,000 scores

46•20•5•5 = 23,000

What's the experiment?

Highest 50 HINT Scores for each complex

L_RMSD Testing

Find best match for each complex

Interpreting result

Enzyme-Inhibitor Simulated Complex

Best L_RMSD Score: $4\ Å$

HINT weight used: $b_{ij} = a_i\, a_j\, S_i\, S_j\, (T_{ij})^{1.5}\, R_{ij} + r_{ij}$

⬇

Electrostatics

Possible Results

Complex	Final L_RMSD Score	Weighing Used	Significant Chemical Property
#1 Bound	4 Å	$a_i a_j (S_i S_j)^{1.5} T_{ij} R_{ij} + r_{ij}$	Solvent Accessible Surface Area
#1 Unbound	6 Å	$a_i a_j S_i S_j (T_{ij})^2 R_{ij} + r_{ij}$	**Electrostatics**
#2 Bound	2 Å	$a_i a_j S_i S_j T_{ij} (R_{ij})^{0.5} + r_{ij}$	Atomic Distance
#2 Unbound	4 Å	$a_i a_j S_i S_j (T_{ij})^{1.5} R_{ij} + r_{ij}$	**Electrostatics**
#3 Bound	3 Å	$a_i a_j (S_i S_j)^{1.5} T_{ij} R_{ij} + r_{ij}$	Solvent Accessible Surface Area
#3 Unbound	5 Å	$a_i a_j S_i S_j (T_{ij})^{1.5} R_{ij} + r_{ij}$	**Electrostatics**
…	…	…	…
#46 Bound	2 Å	$a_i a_j S_i S_j (T_{ij})^2 R_{ij} + r_{ij}$	**Electrostatics**
#46 Unbound	6 Å	$(a_i a_j)^{0.5} S_i S_j T_{ij} R_{ij} + r_{ij}$	Hydrophobic Atom Constant

Possible Results

Complex	Final L_RMSD Score	Weighing Used	Significant Chemical Property
#1 Bound	4 Å	$a_i a_j (S_i S_j)^1 T_{ij} R_{ij} + r_{ij}$	Solvent Accessible Surface Area
#1 Unbound	6 Å	$a_i a_j S_i S_j (T_{ij})^2 R_{ij} + r_{ij}$	Electrostatics
#2 Bound	2 Å	$a_i a_j S_i S_j T_{ij} (R_{ij})^{0.5} + r_{ij}$	Atomic Distance
#2 Unbound	4 Å	$a_i a_j S_i S_j (T_{ij})^{1.5} R_{ij} + r_{ij}$	Electrostatics
#3 Bound	3 Å	$a_i a_j (S_i S_j)^{1.5} T_{ij} R_{ij} + r_{ij}$	Solvent Accessible Surface Area
#3 Unbound	5 Å	$a_i a_j S_i S_j (T_{ij})^{0.5} R_{ij} + r_{ij}$	Electrostatics
…	…	…	…
#46 Bound	2 Å	$a_i a_j (S_i S_j)^0 T_{ij} R_{ij} + r_{ij}$	Solvent Accessible Surface Area
#46 Unbound	6 Å	$(a_i a_j)^{0.5} S_i S_j T_{ij} R_{ij} + r_{ij}$	Hydrophobic Atom Constant

In the future…

Different models (besides HINT)

Different complexes (besides enzyme/inhibitor)

Questions?

Extras

Electrostatics Table

Table 1. T_{ij} interaction matrix

Atom Type [atom constant]	*H (apolar)* [**a** > 0]	*H (polar)*[1] [**a** > 0]	*C (apolar)* [**a** > 0]	*Polar (N,O,etc.)* [**a** < 0]
H (apolar) [**a** > 0]	+1	-1	+1	+1
H (polar)[1] [**a** > 0]	-1	-1	-1	-1
C (apolar) [**a** > 0]	+1	-1	+1	+1
Polar (N,O,etc.) [**a** < 0]	+1	-1	+1	-1

Notes: green: hydrophobic-hydrophobic; red: hydrophobic-polar; blue: acid-base or hydrogen bond; yellow: polar-polar (horizontal stripes: acid-acid, vertical stripes: base-base).
[1] By convention, all hydrogen atoms have a > 0 [13].

Kellogg and Abraham, 2001