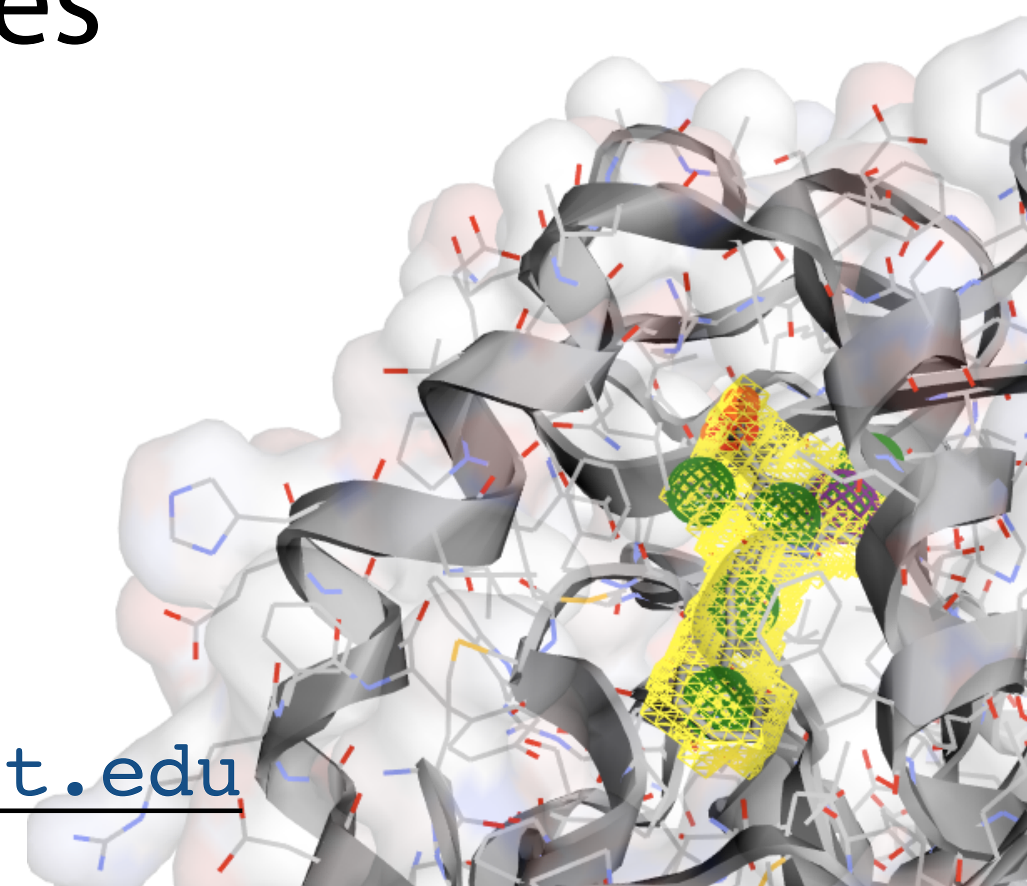
University of Pittsburgh
Department of Computational & Systems Biology

Computational Drug Discovery

David Ryan Koes

11/6/2018



http://bits.csb.pitt.edu

What is a drug?

According to the Food, Drug, and Cosmetic Act (1) **:** a substance recognized in an official pharmacopoeia or formulary (2) **:** a substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease (3) **:** **a substance** other than food **intended to affect the structure or function** of the body (4) **:** a substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device
http://www.merriam-webster.com/dictionary/drug

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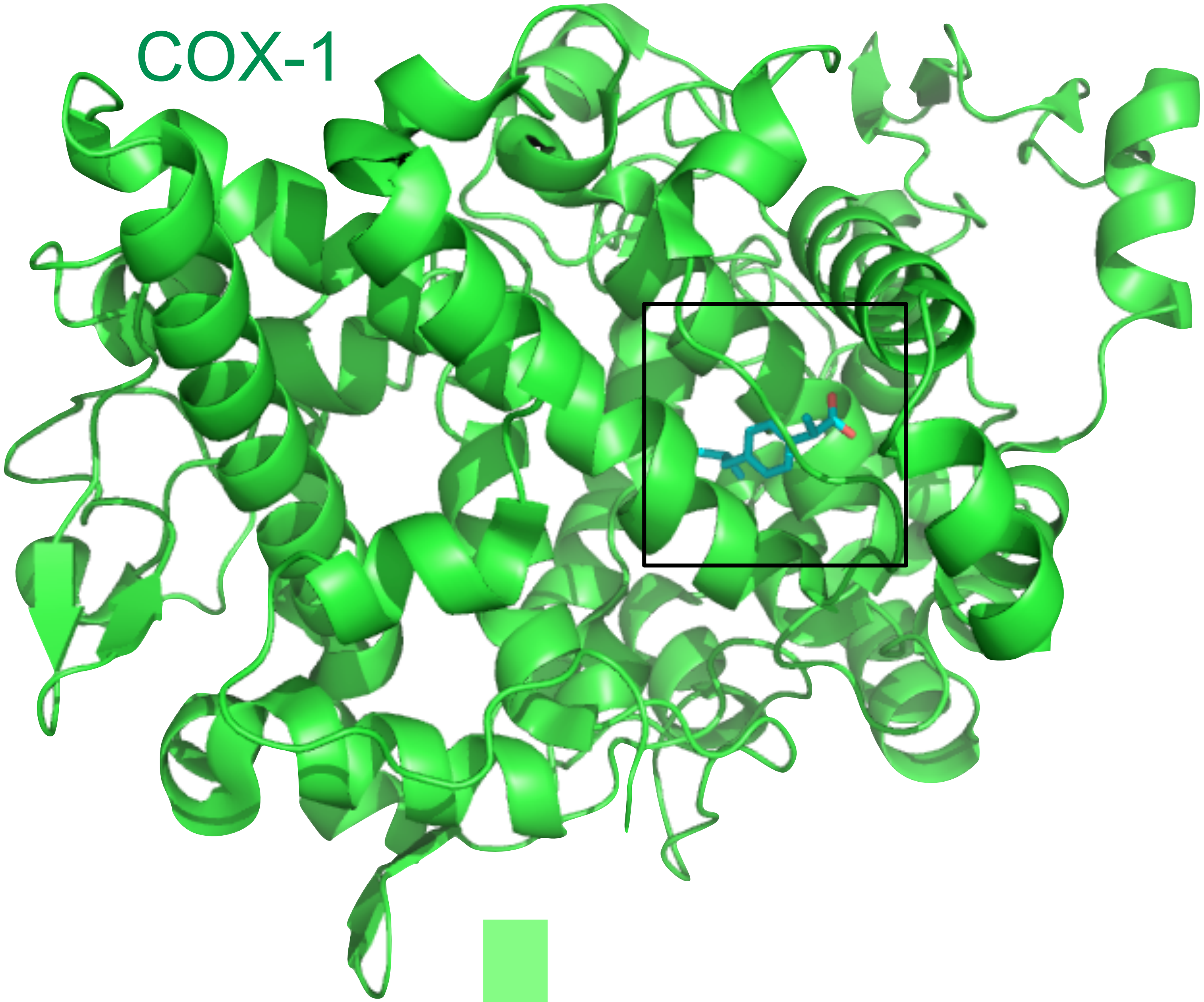
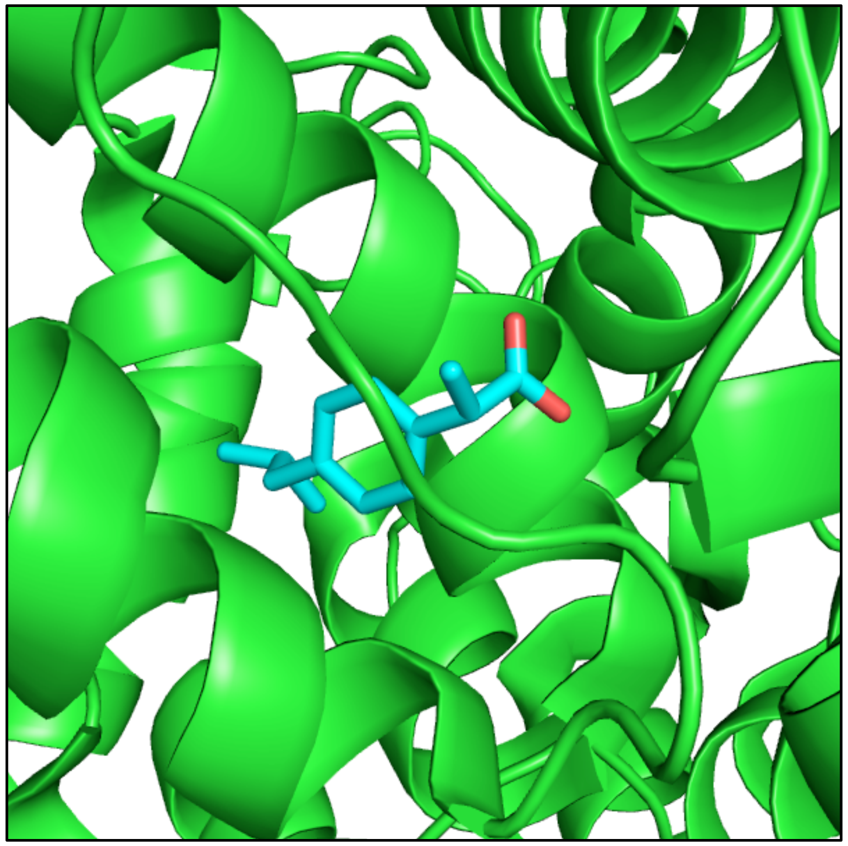
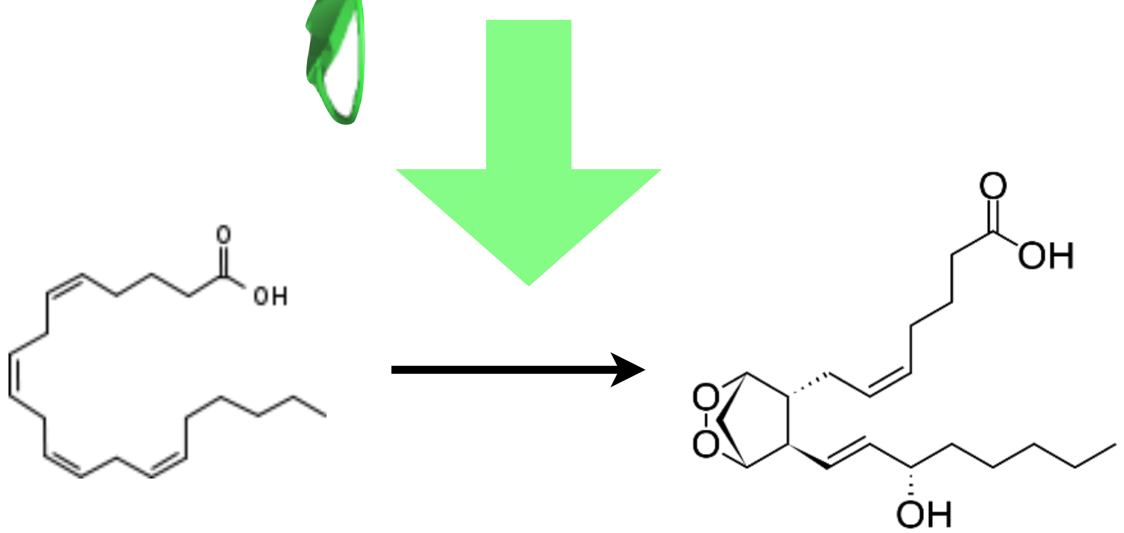
A small molecule intended to affect the structure/function of macromolecules


COX-1

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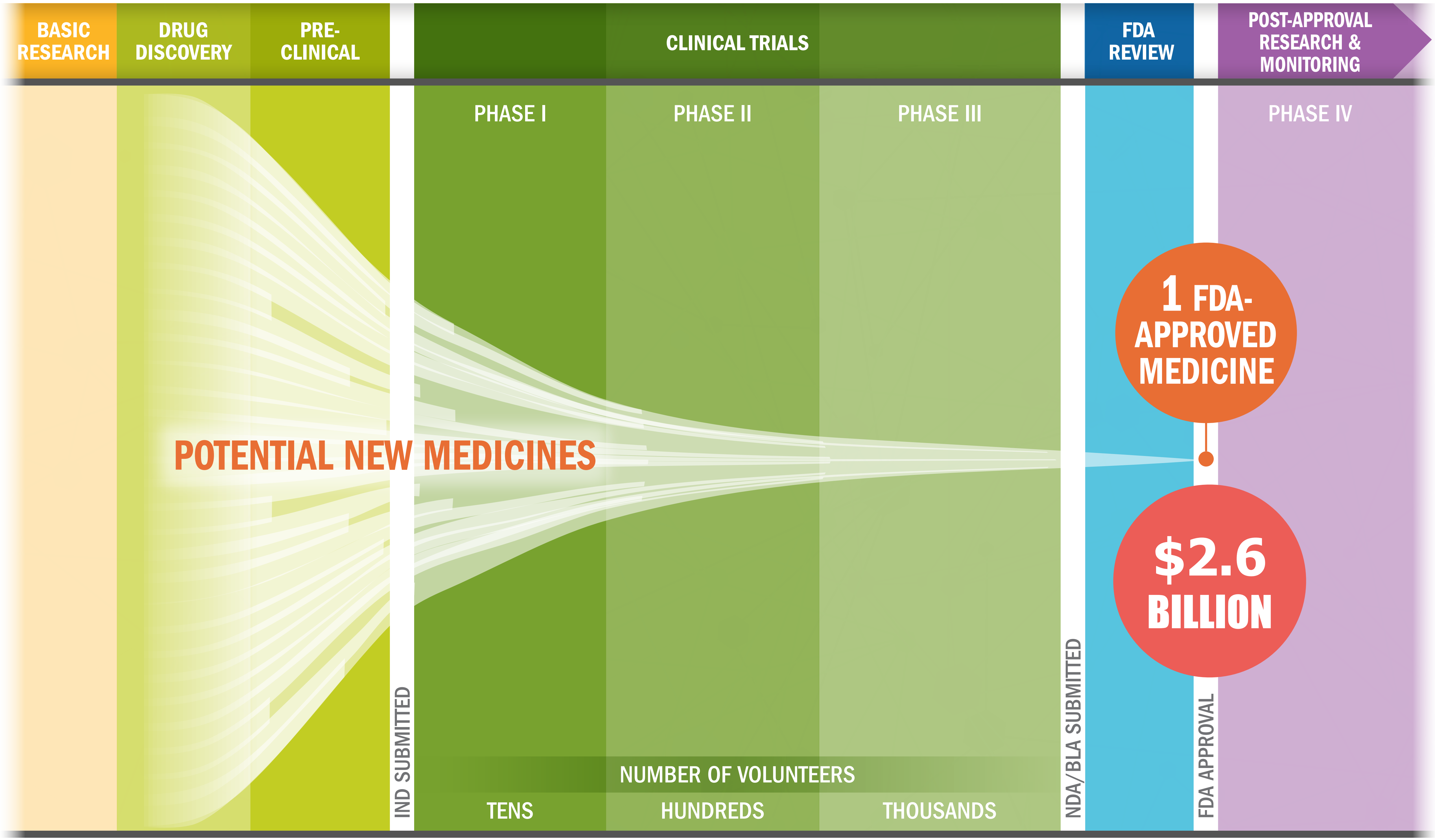
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



Source: Pharmaceutical Research and Manufacturers of America (http://phrma.org)

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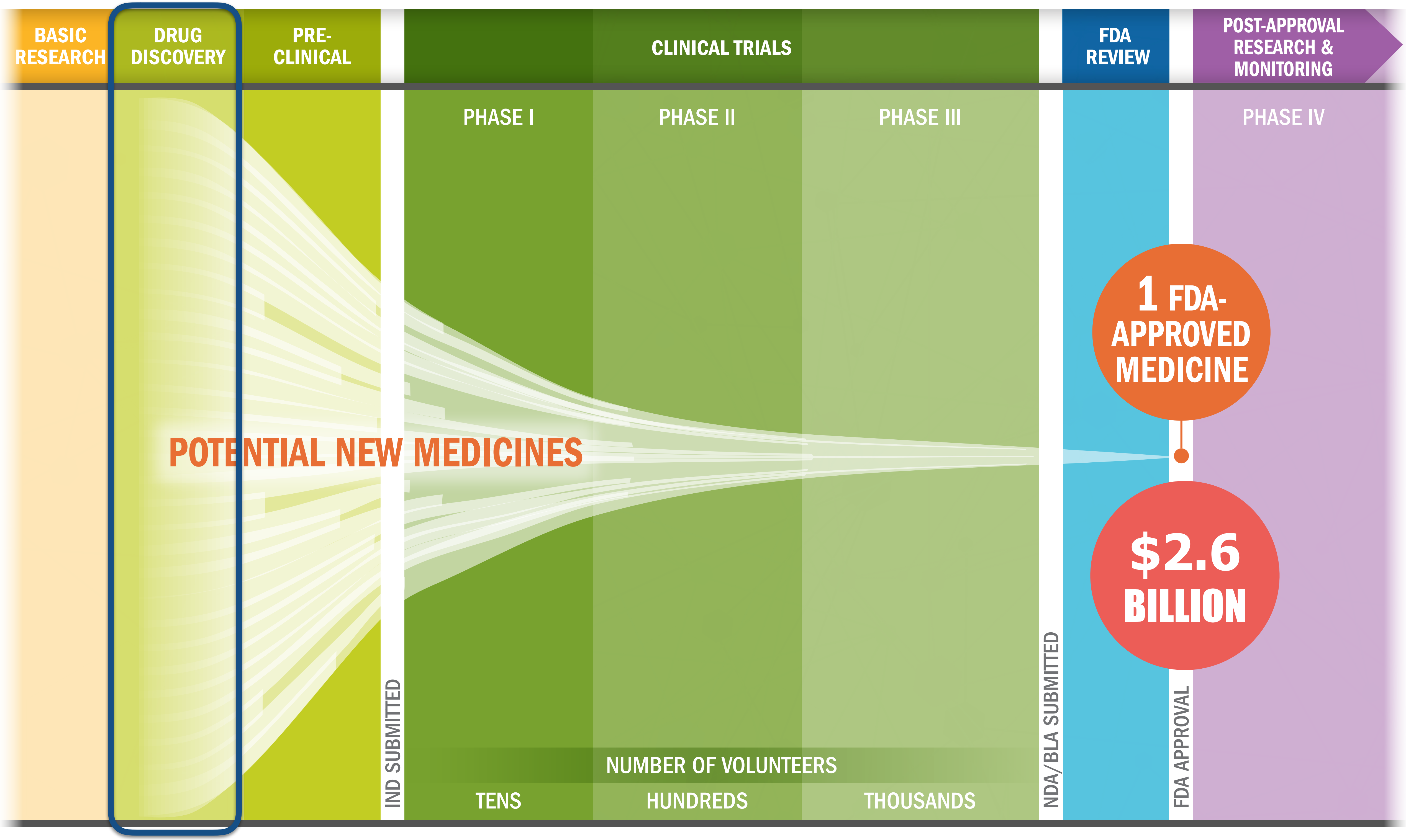

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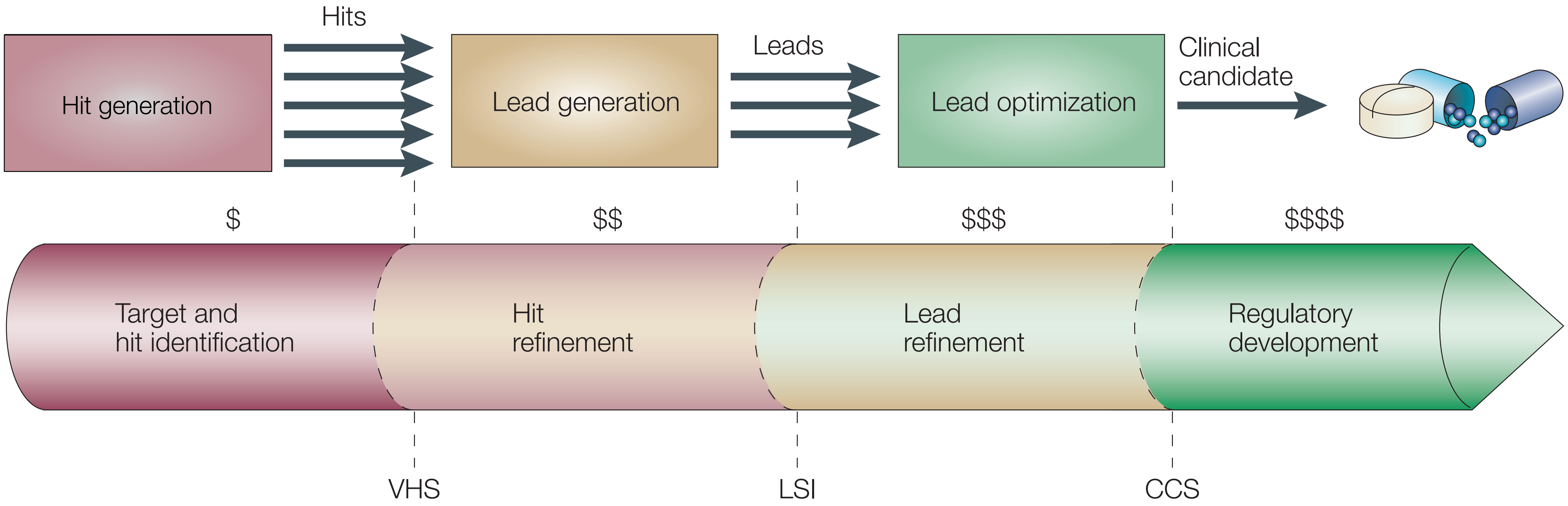
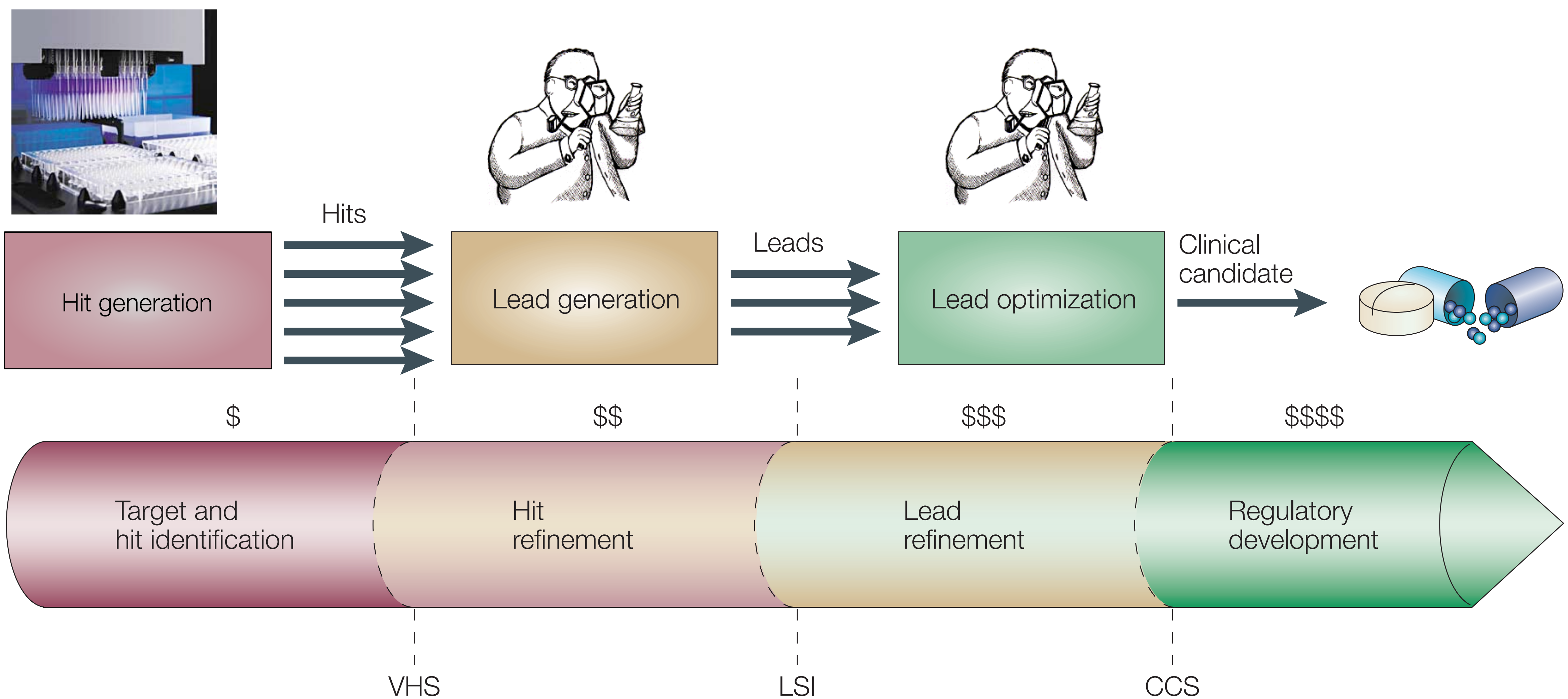
Drug Discovery



Drug Discovery

High Throughput Screening



Drug Discovery

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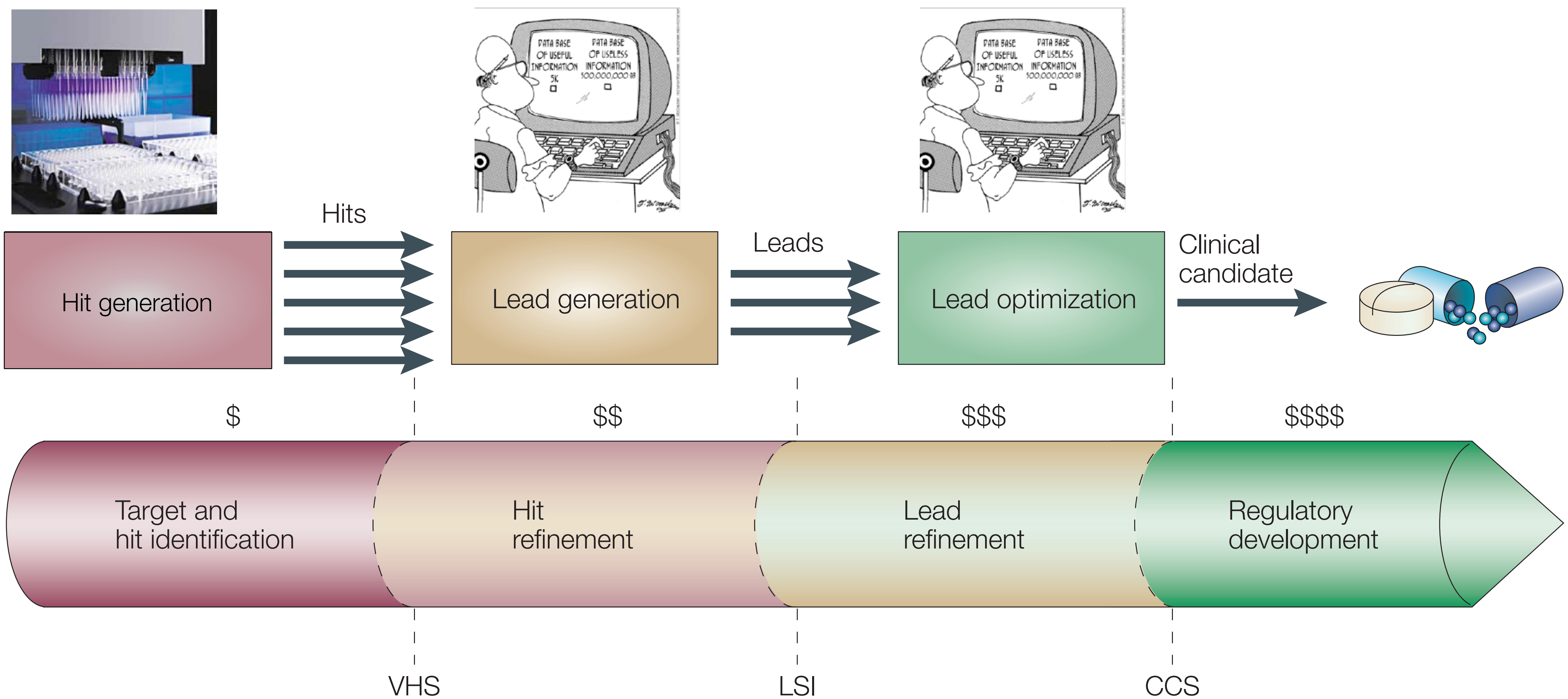
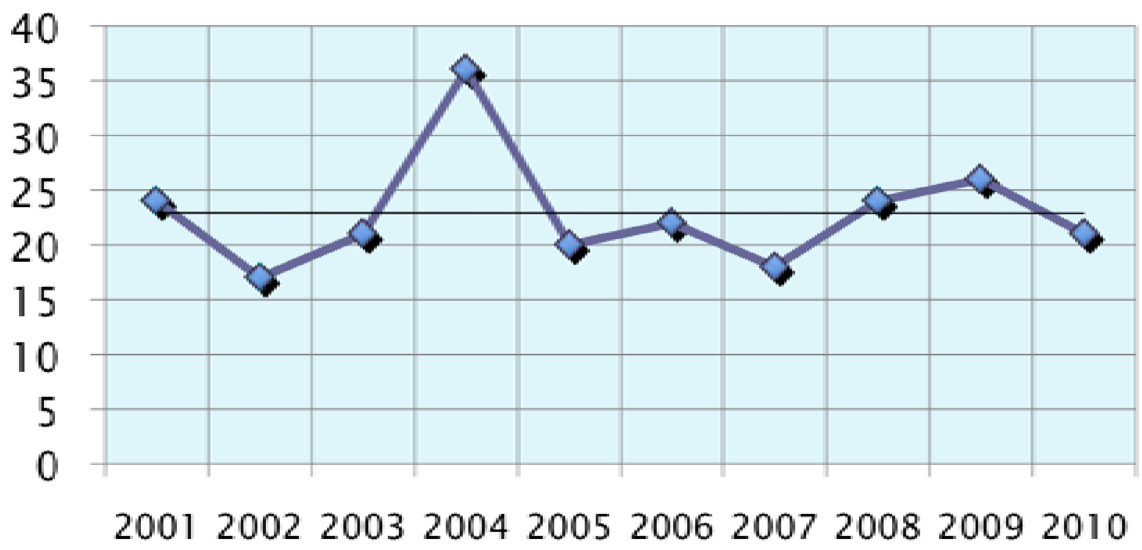
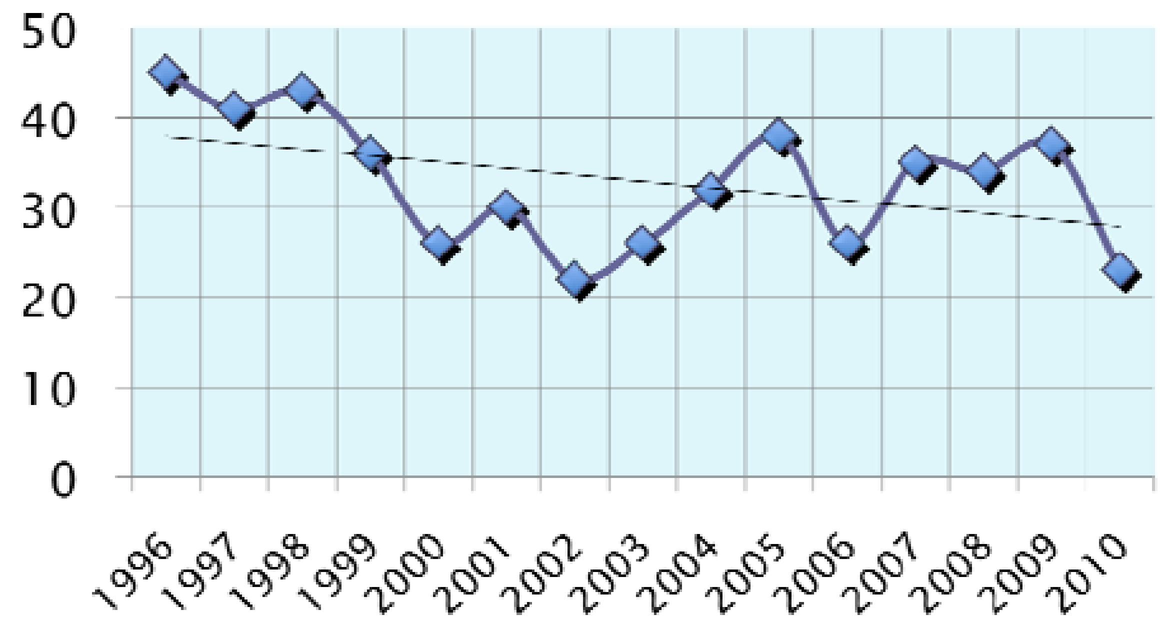


The State of Drug Development

New Drugs Approved



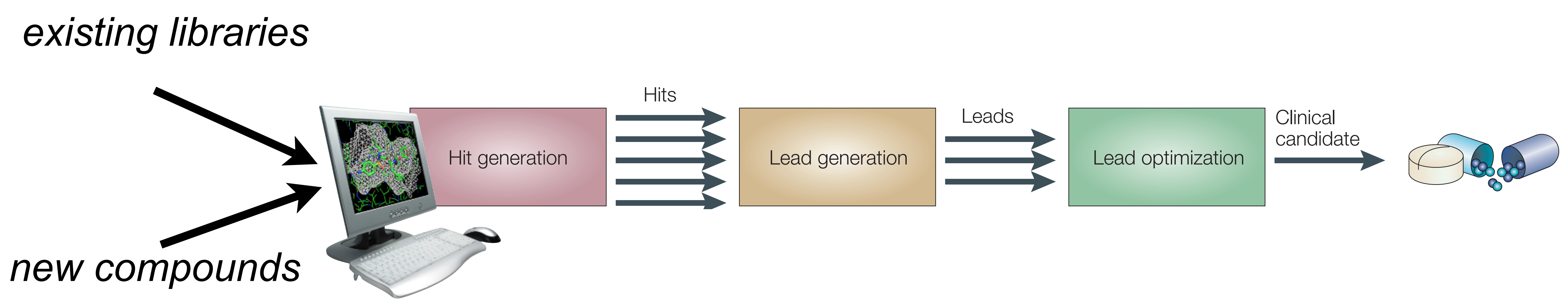
New Drug Applications



http://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM247465.pdf

Computational Drug Discovery

Virtual Screening



Computational Drug Discovery

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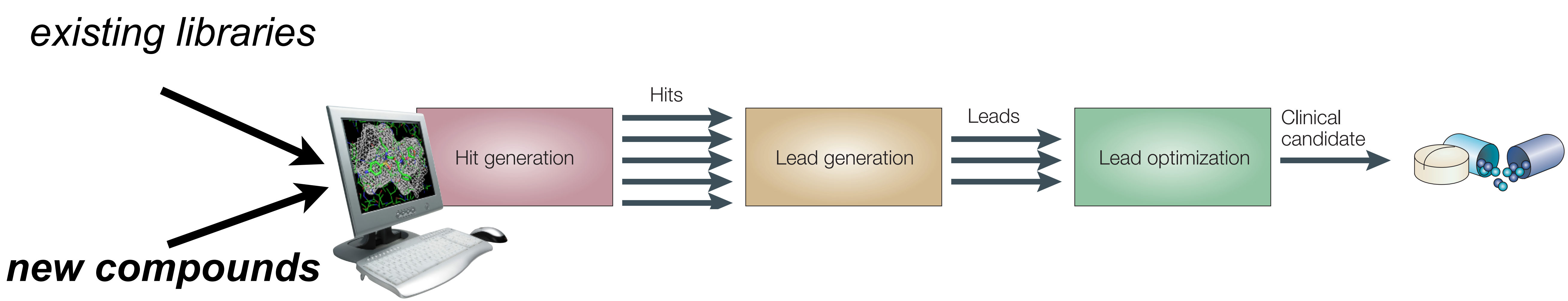
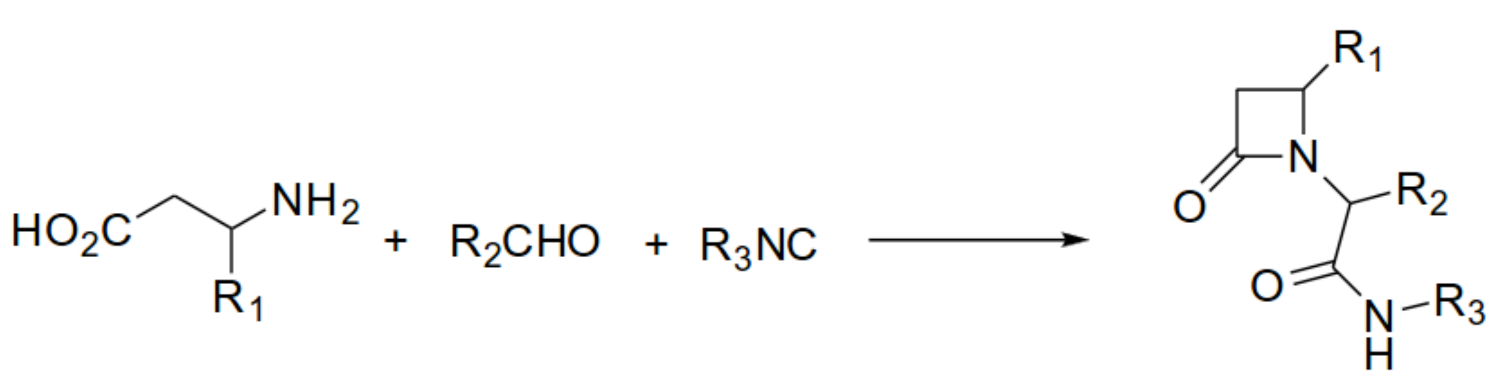
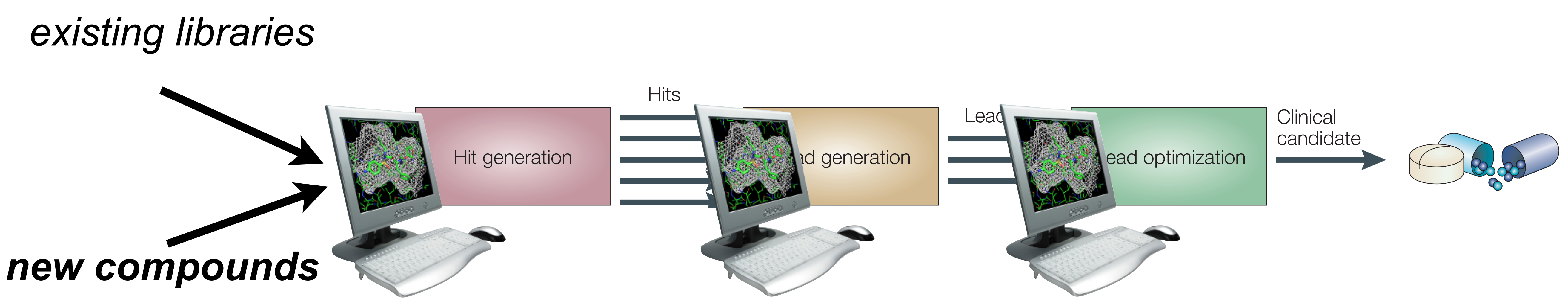
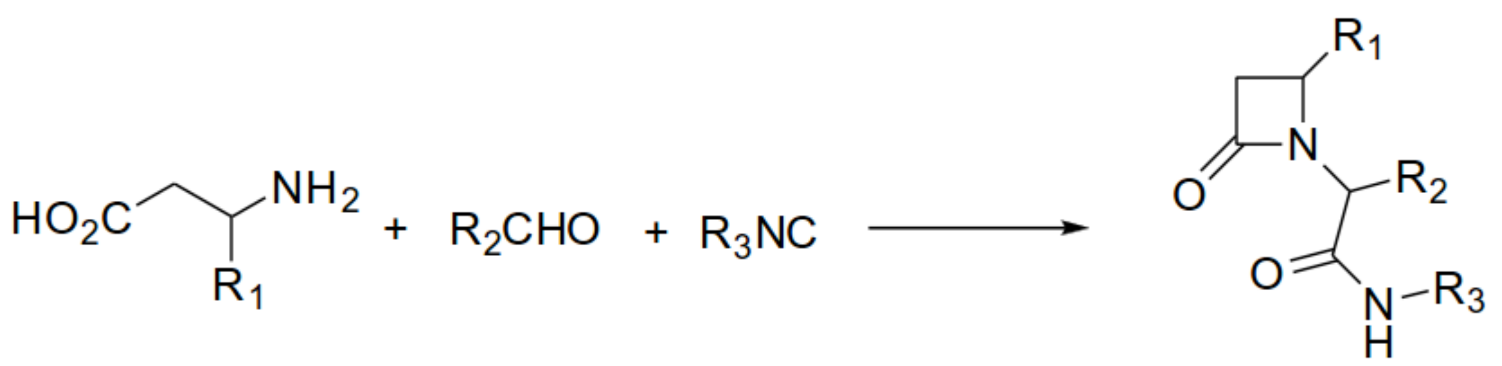




Computational Drug Discovery

Virtual Screening





Kinds of Virtual Screening

ADMET

Ligand Based

- similarity to known binder
- QSAR
- pharmacophore

Receptor Based

- dock and score
- simulation

  MM/GBSA, MM/PBSA, thermodynamic integration, free energy perturbation, Jarzynski, umbrella sampling, Monte Carlo, weighted ensemble, metadynamics…

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Not going to cover today

ADMET

Absorption
Distribution
Metabolism
Excretion
Toxicity

Will this be a usable drug?

Screening for ADMET:
Cytochrome P450 interaction
Lipinksi's Rule of Five
QSPR: Quantitative Structure Property Relationship

Kinds of Virtual Screening

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Ligand Based: Similarity

Fingerprint Methods

- map molecules to a descriptor space:

1D: molecule weight, #h-bonds, etc.
2D: paths, bond distances between atom-pairs

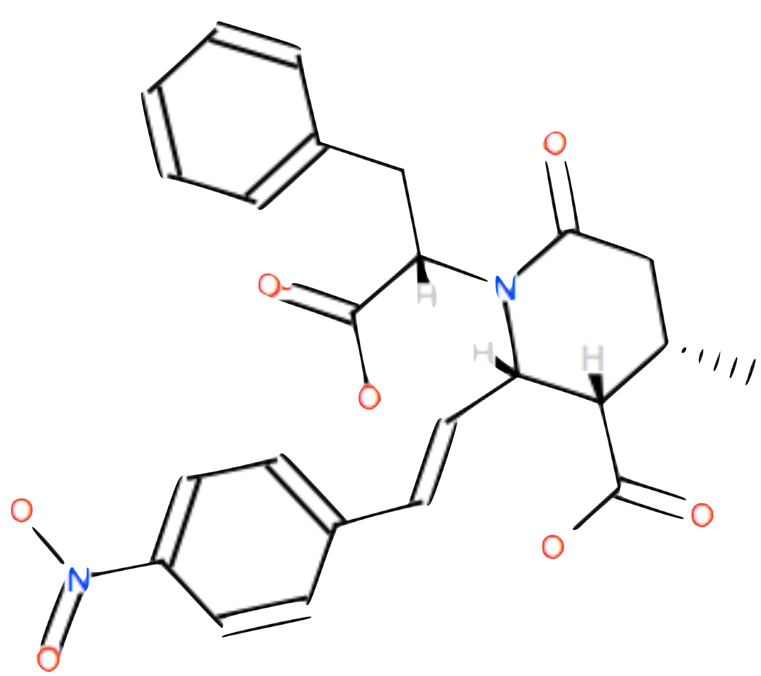
- similarity is "distance" between descriptors
- for bit vectors, Tanimoto distance used

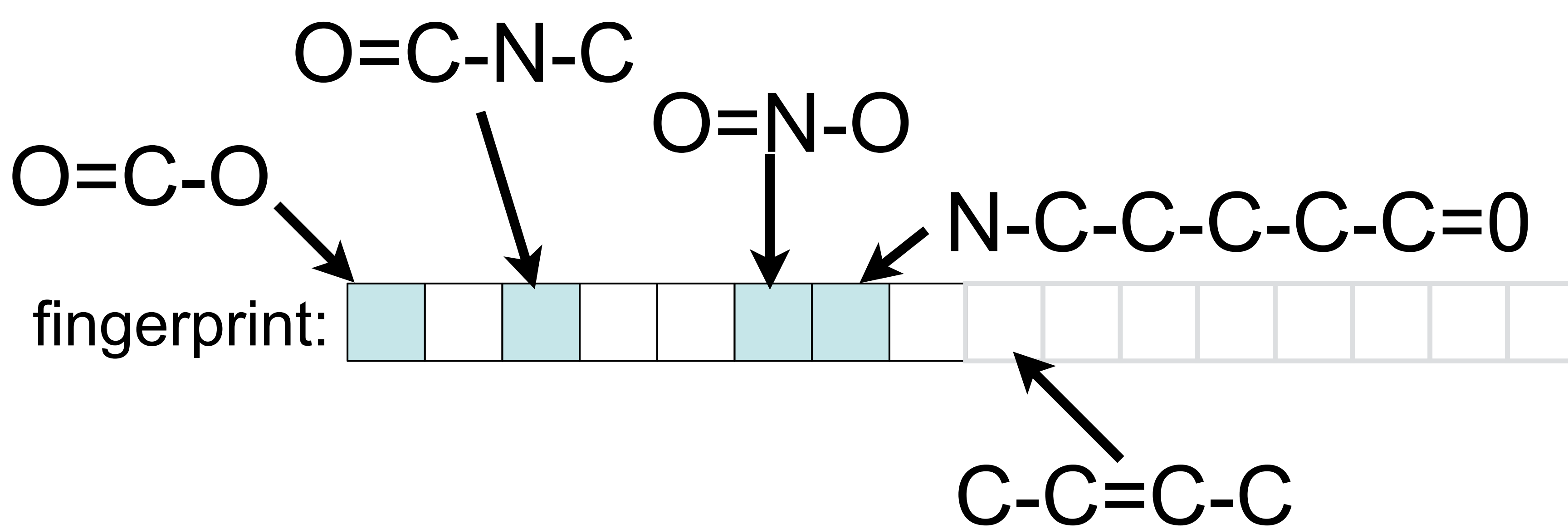
$$T(A,B) = \frac{|A \cap B|}{|A \cup B|}$$

Topological Fingerprints

Daylight/FP2 Fingerprints

- all paths up to 7 bonds long
- each path corresponds to bit position (**hashing**)
- fast similarity checking (Tanimoto)





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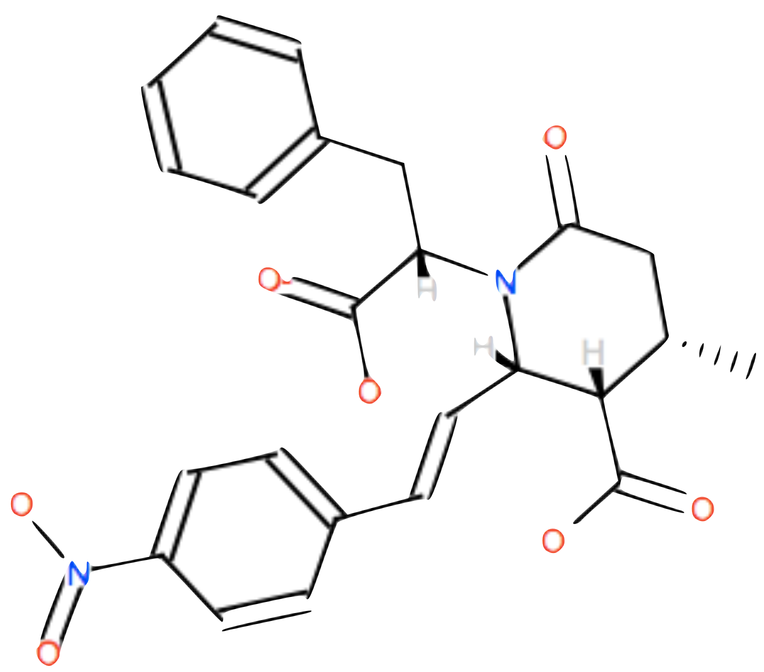
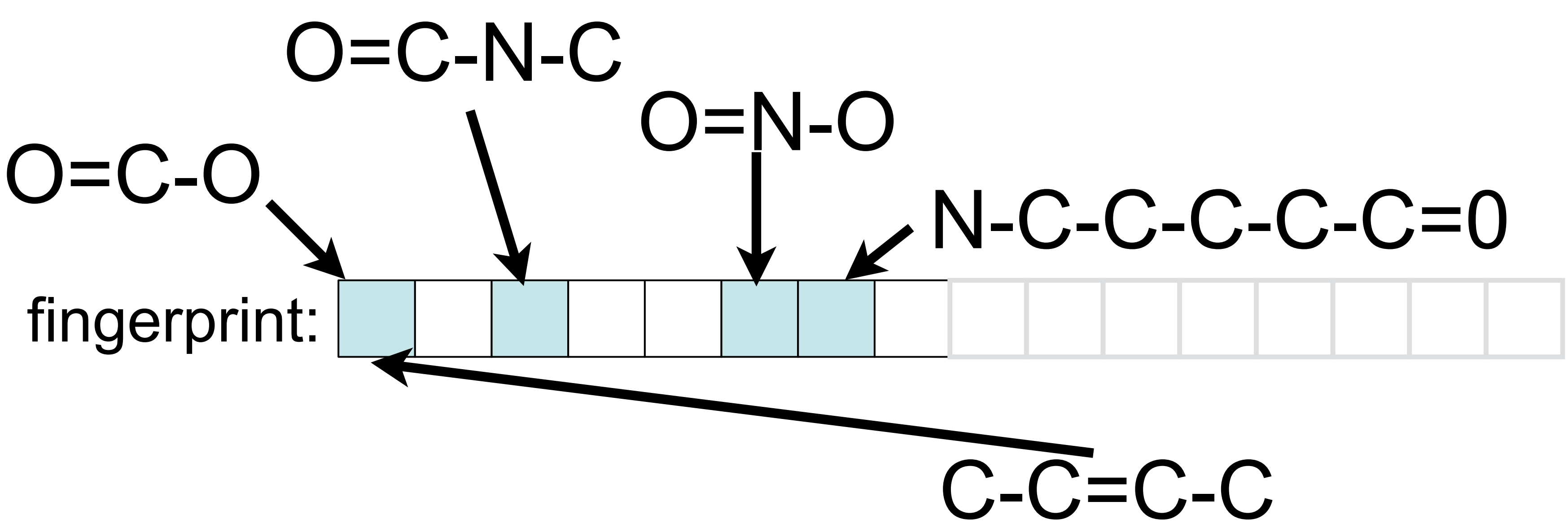
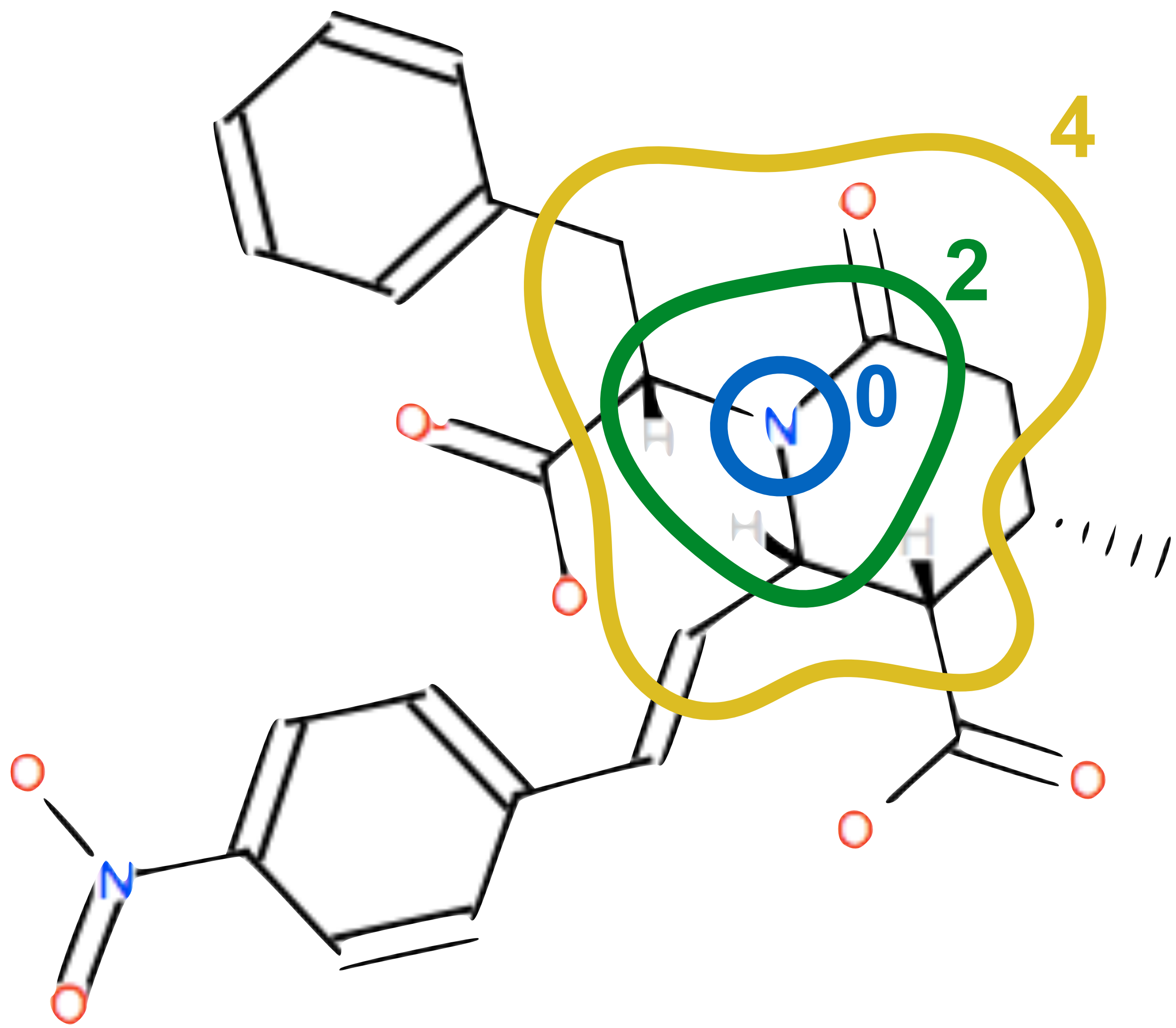




Topological Fingerprints

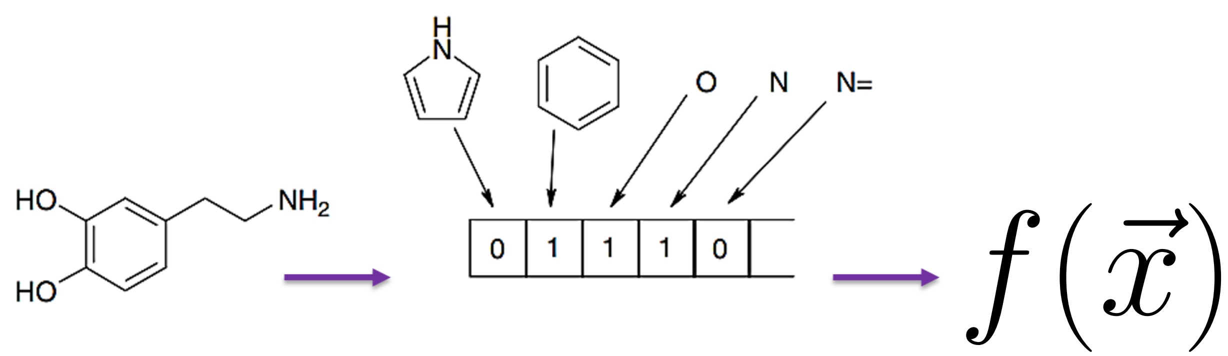
ECFP4

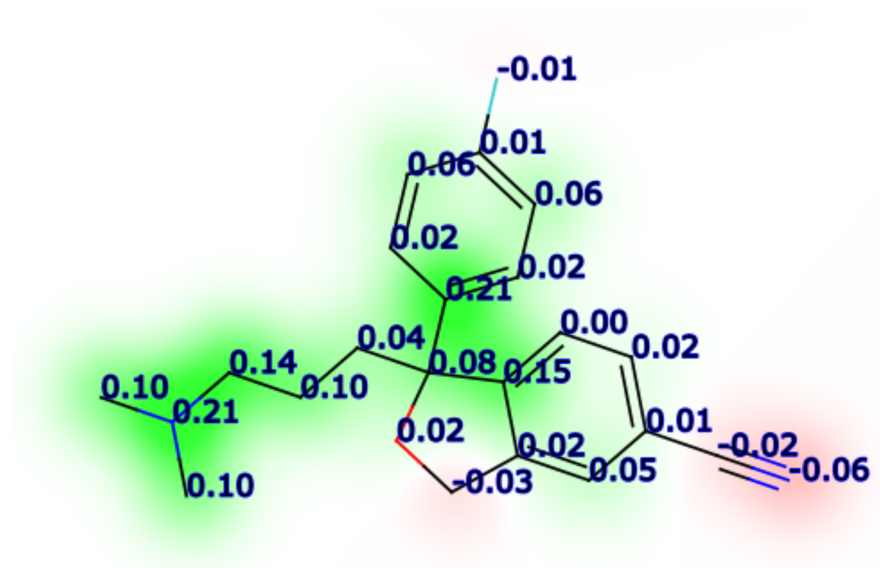
- all substructures with diameter 4 around every atom



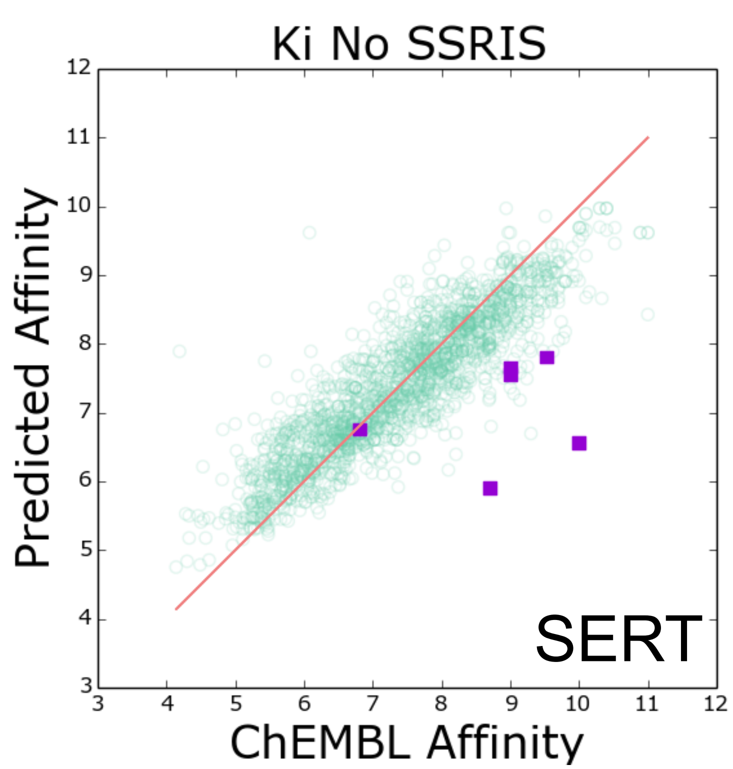
Ligand Based: QSAR

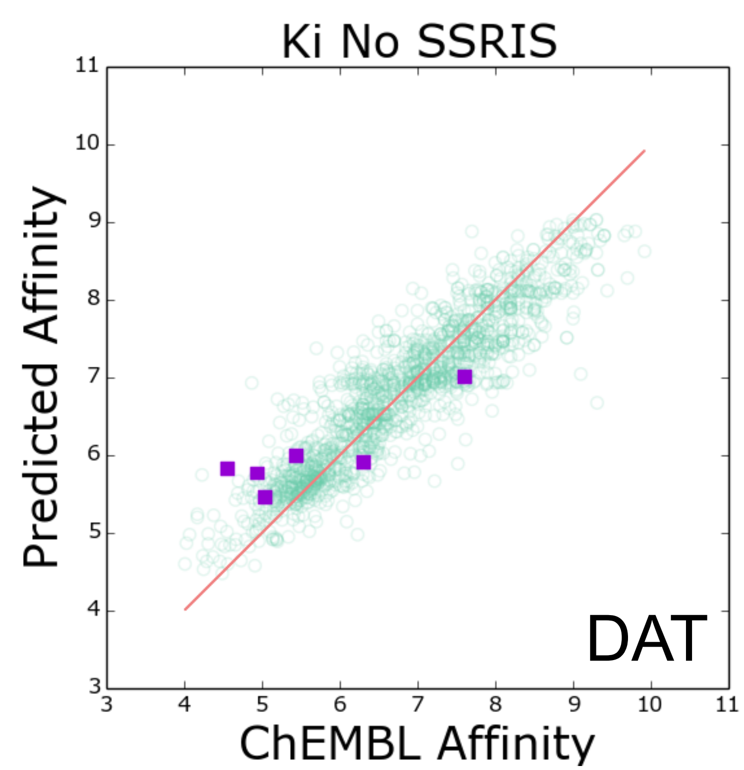
Quantitative Structure/Activity Relationships





$$f(\vec{x}) = w_1\vec{x}_1 + w_2\vec{x}_2 + w_3\vec{x}_3 + \ldots + b$$

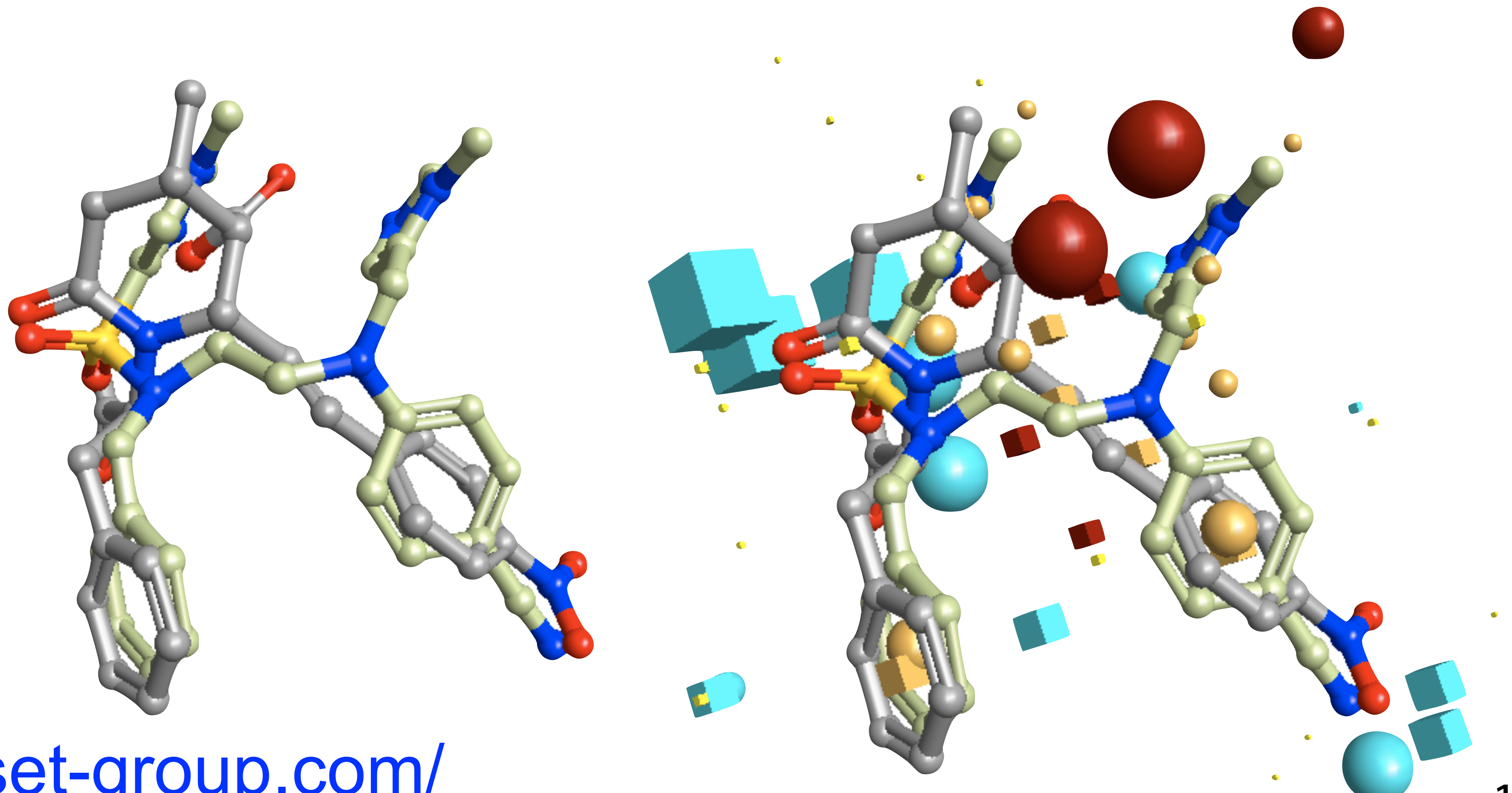




Ligand Based: Similarity

Superposition Methods

- compute "overlap" between molecules
- consider shape, electrostatics, **pharmacophores**

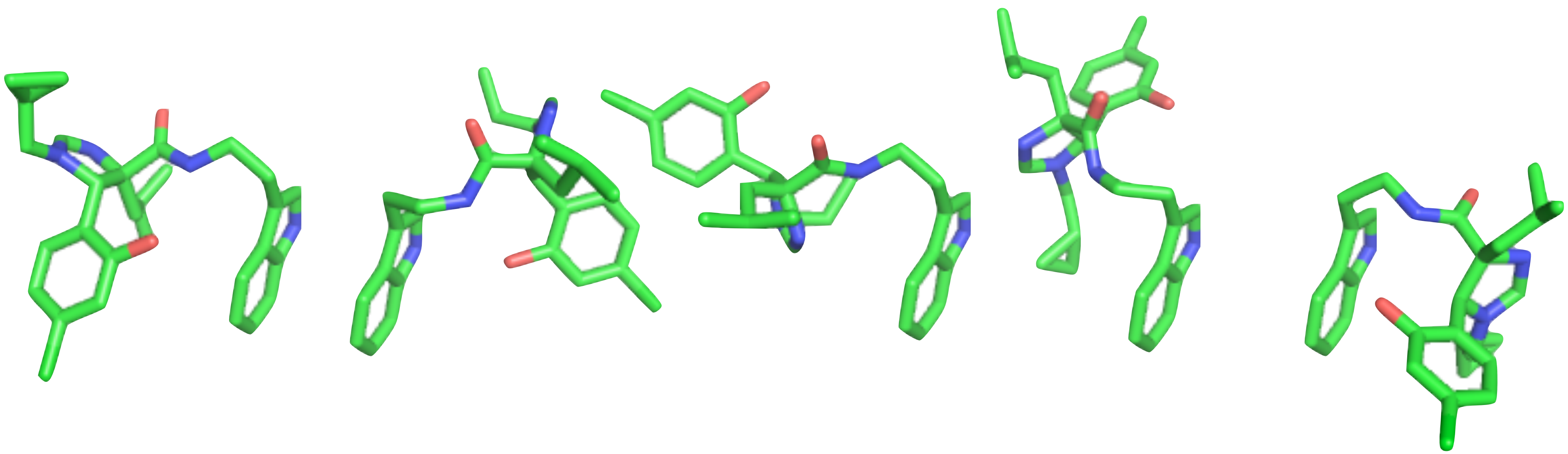


http://www.cresset-group.com/

Representing Compounds

Conformations

A single compound has many different shapes



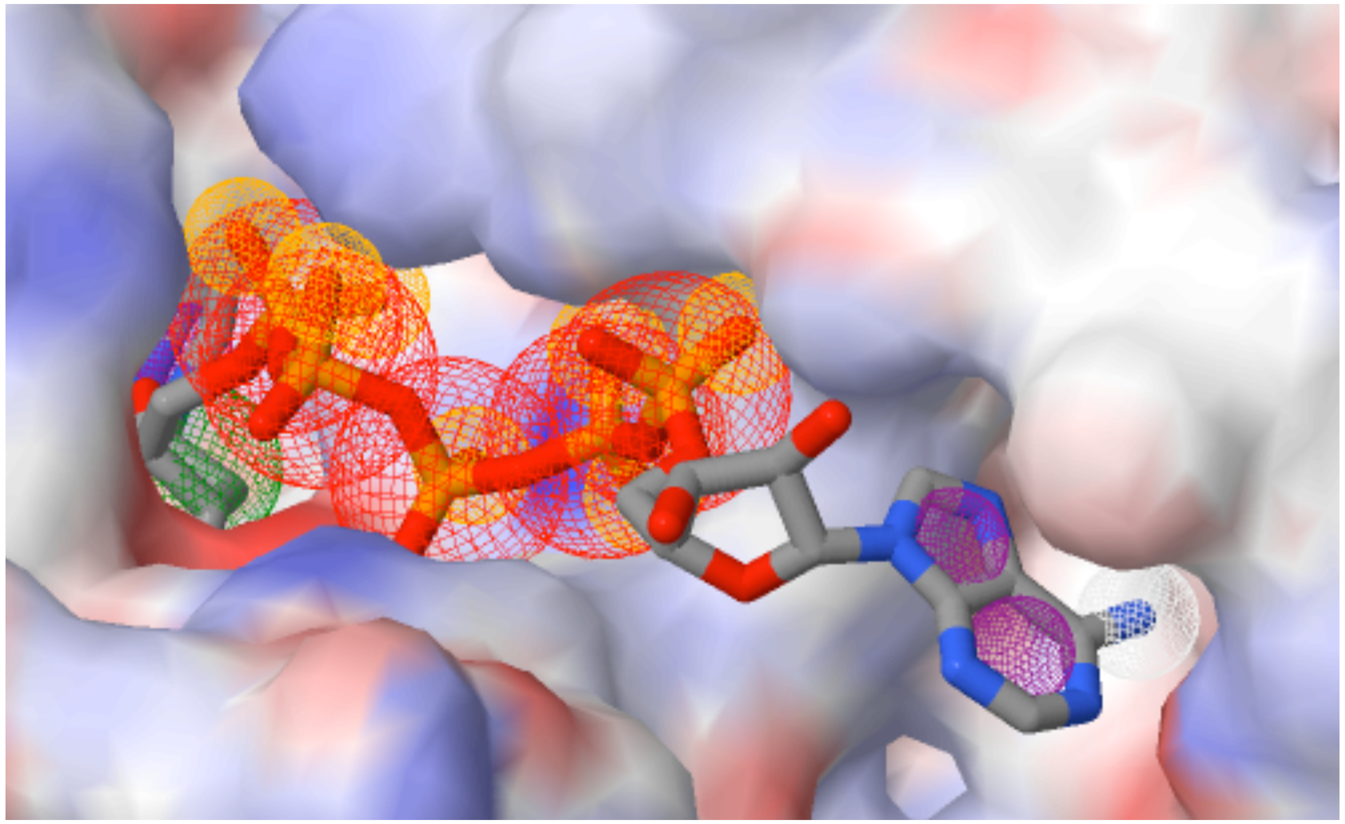
Choices: Store sampling of explicit conformations, search for a good conformation, ignore conformations (2D only)

Ligand Based: Pharmacophore

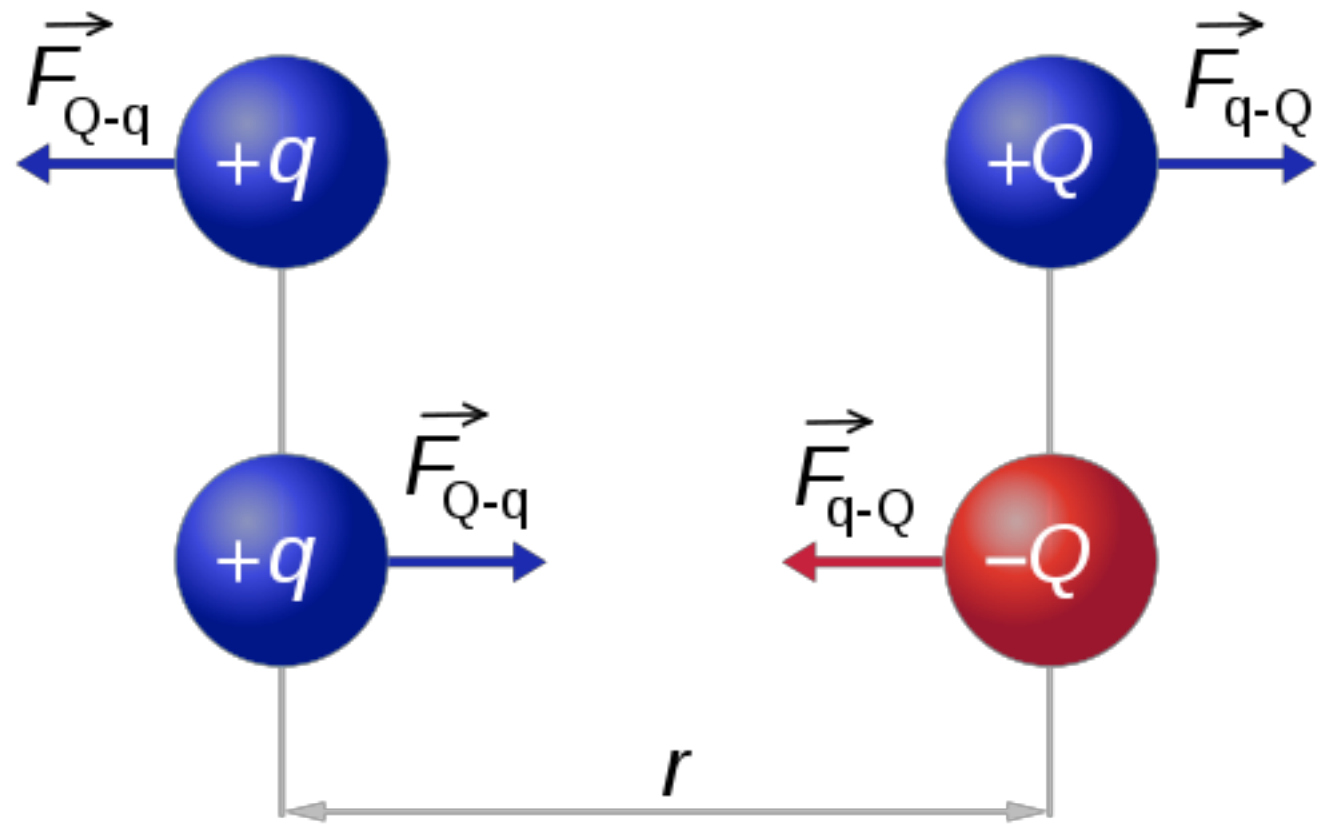
Pharmacophore:

IUPAC: The ensemble of steric and electronic features that is necessary to ensure the optimal supra-molecular interactions with a specific biological target structure and to trigger (or to block) its biological response.

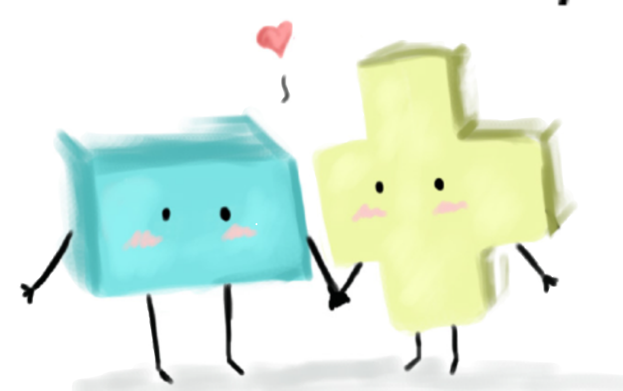
Common Features:
aromatic ring
hydrophobic area
positive ionizable
negative ionizable
hydrogen bond donor
hydrogen bond acceptor



Charge-Charge



$$|\vec{F}_{Q\text{-}q}| = |\vec{F}_{q\text{-}Q}| = k\,\frac{|q \times Q|}{r^2}$$



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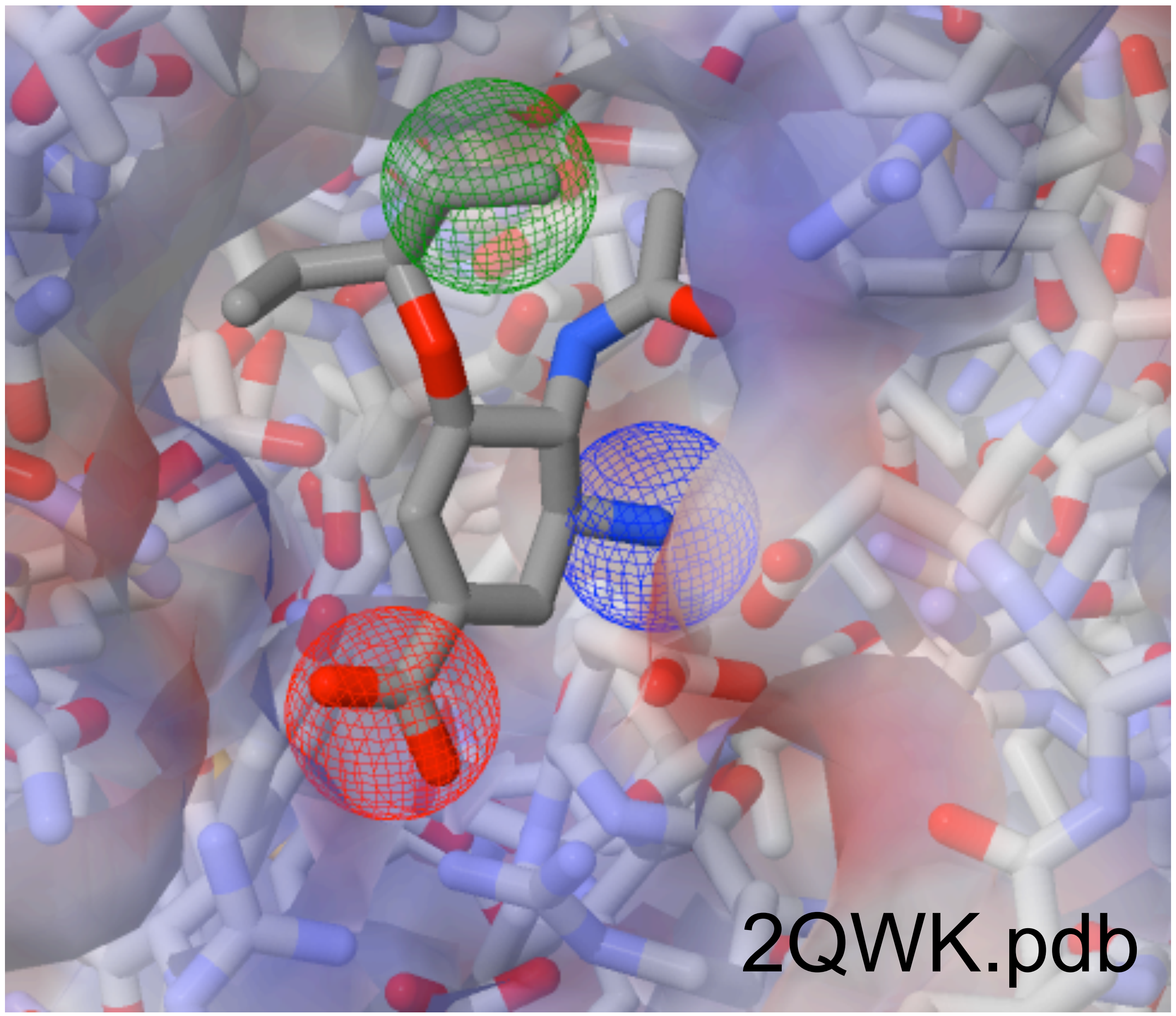
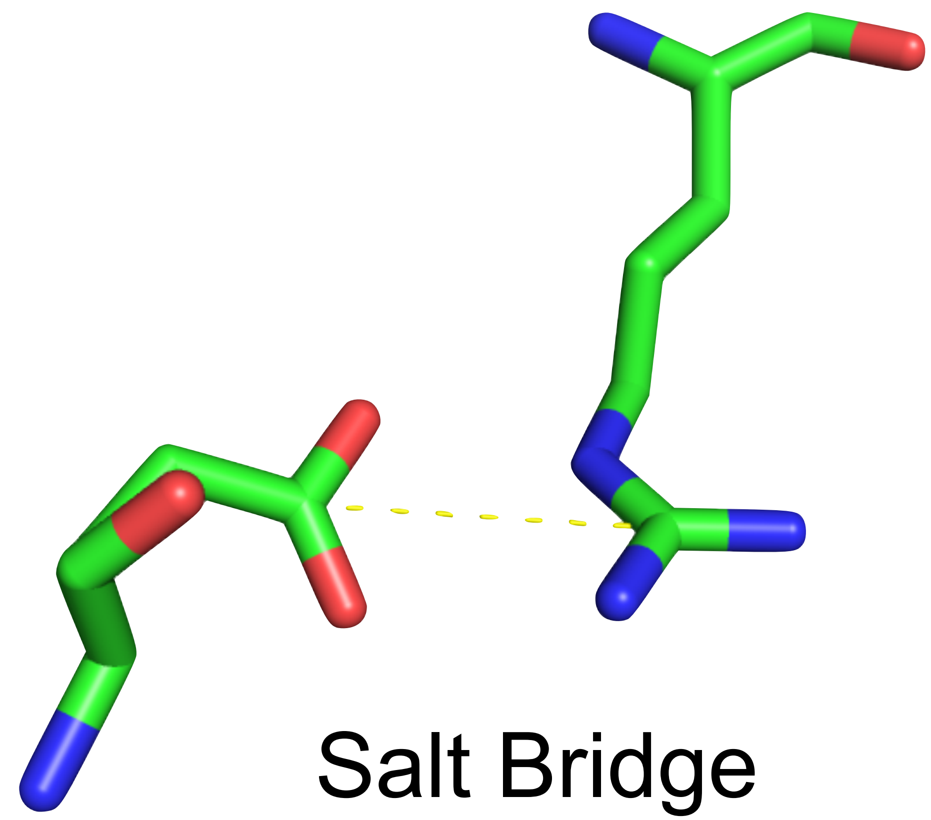
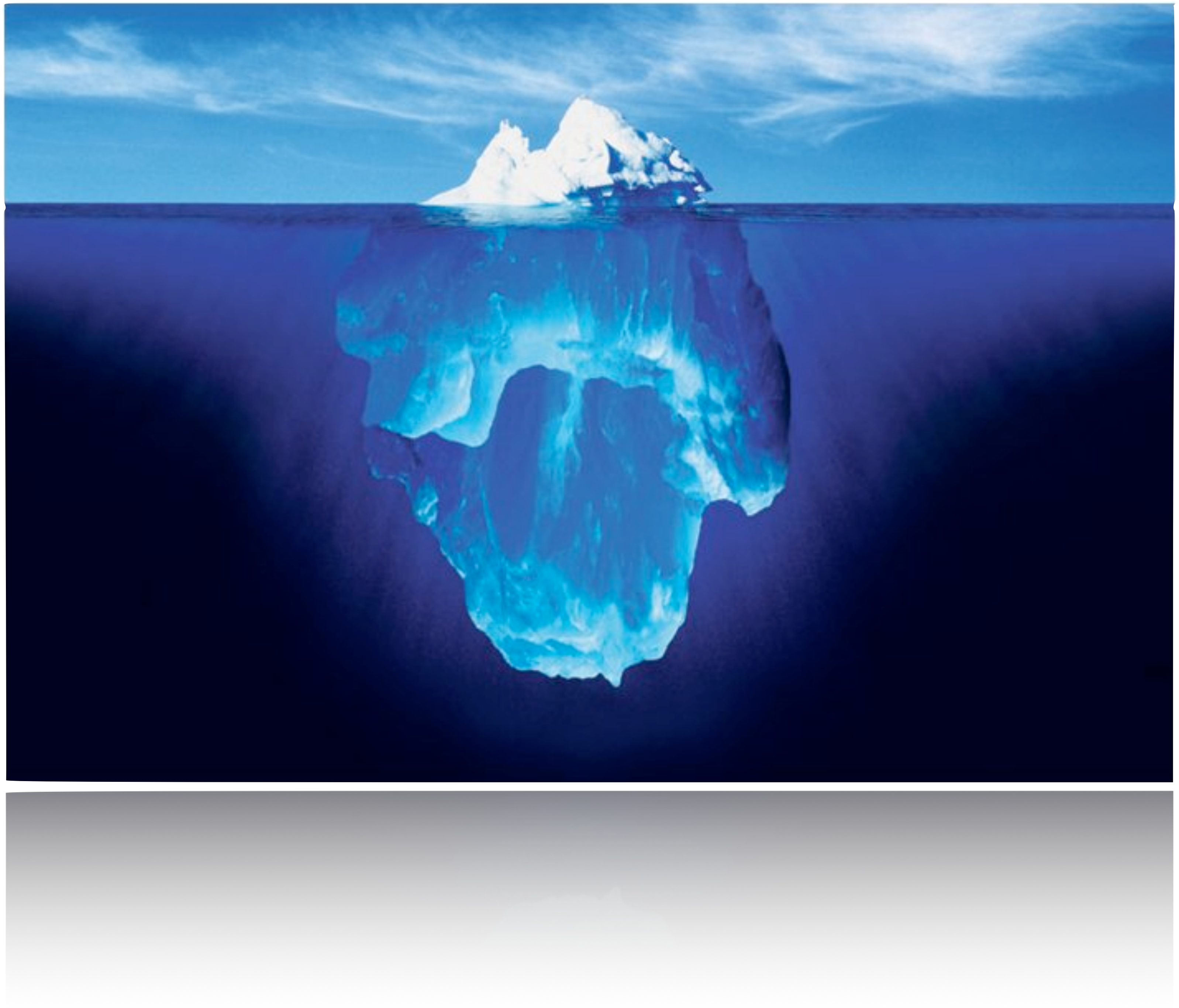
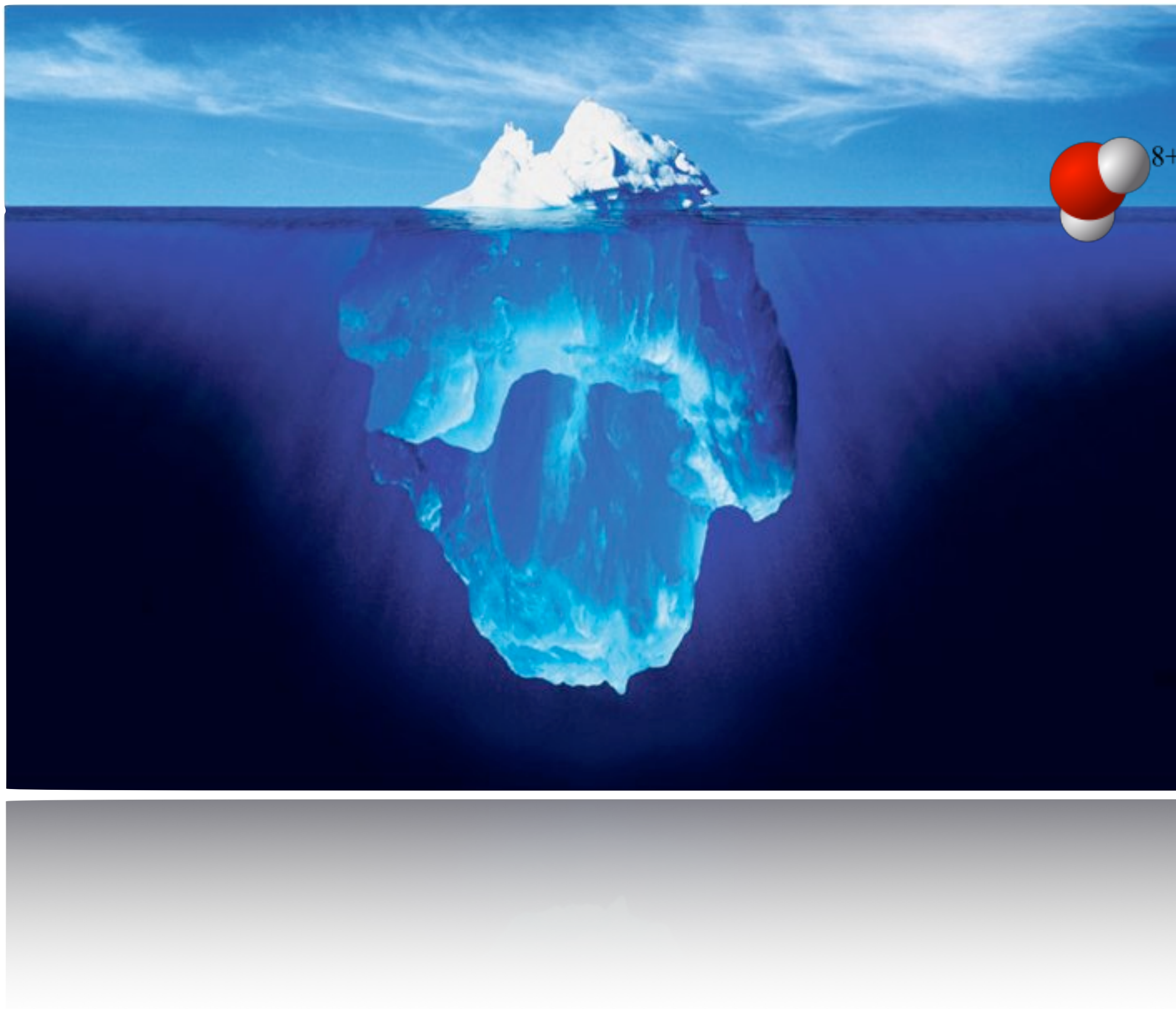


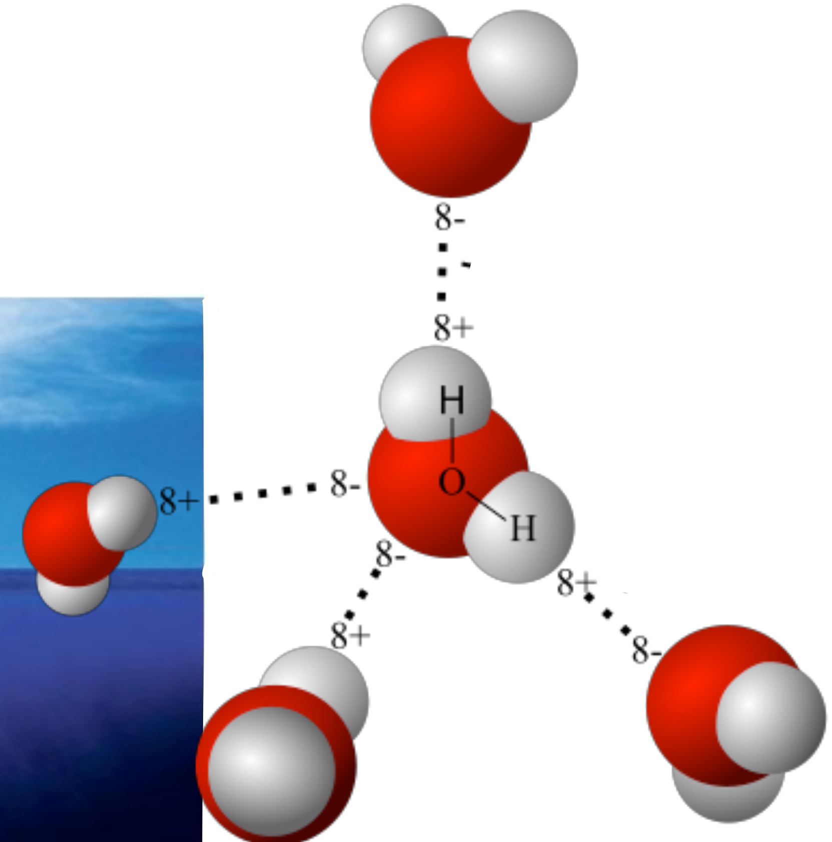


Hydrogen Bond

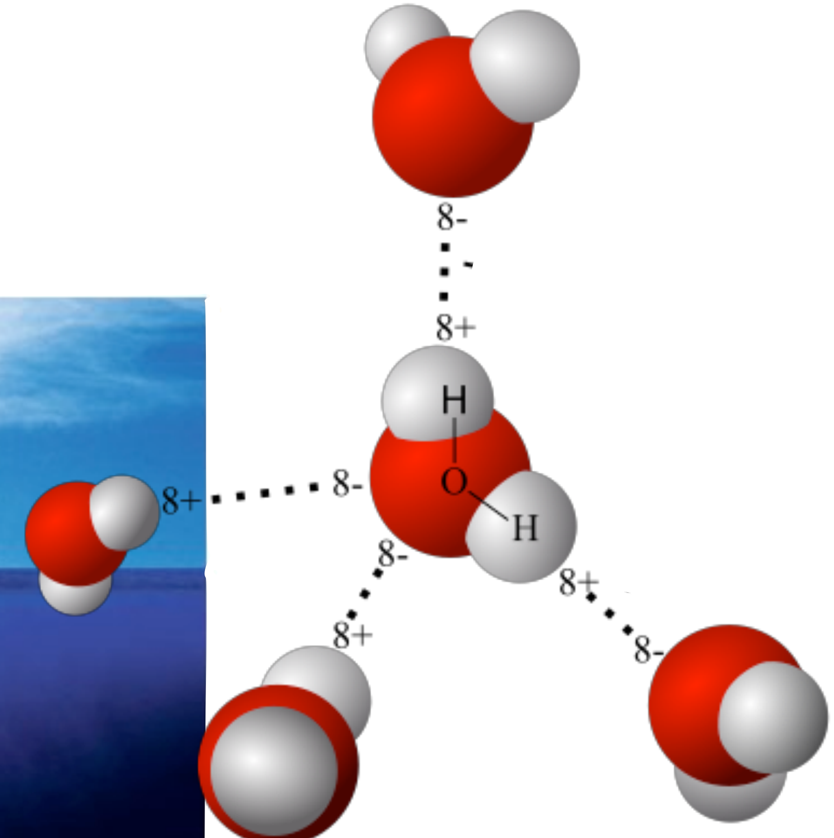


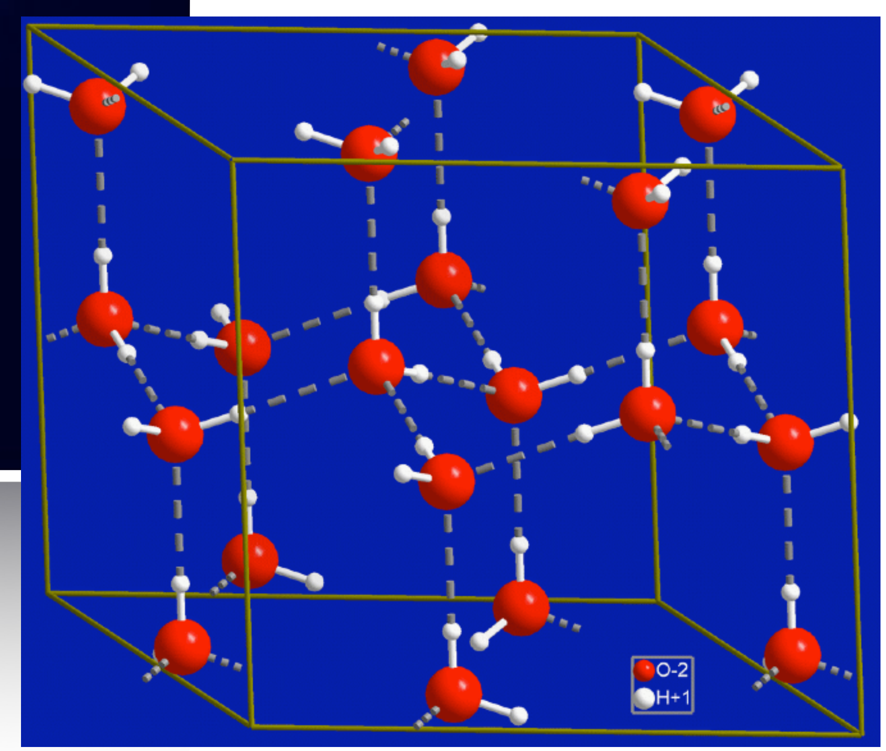
Hydrogen Bond



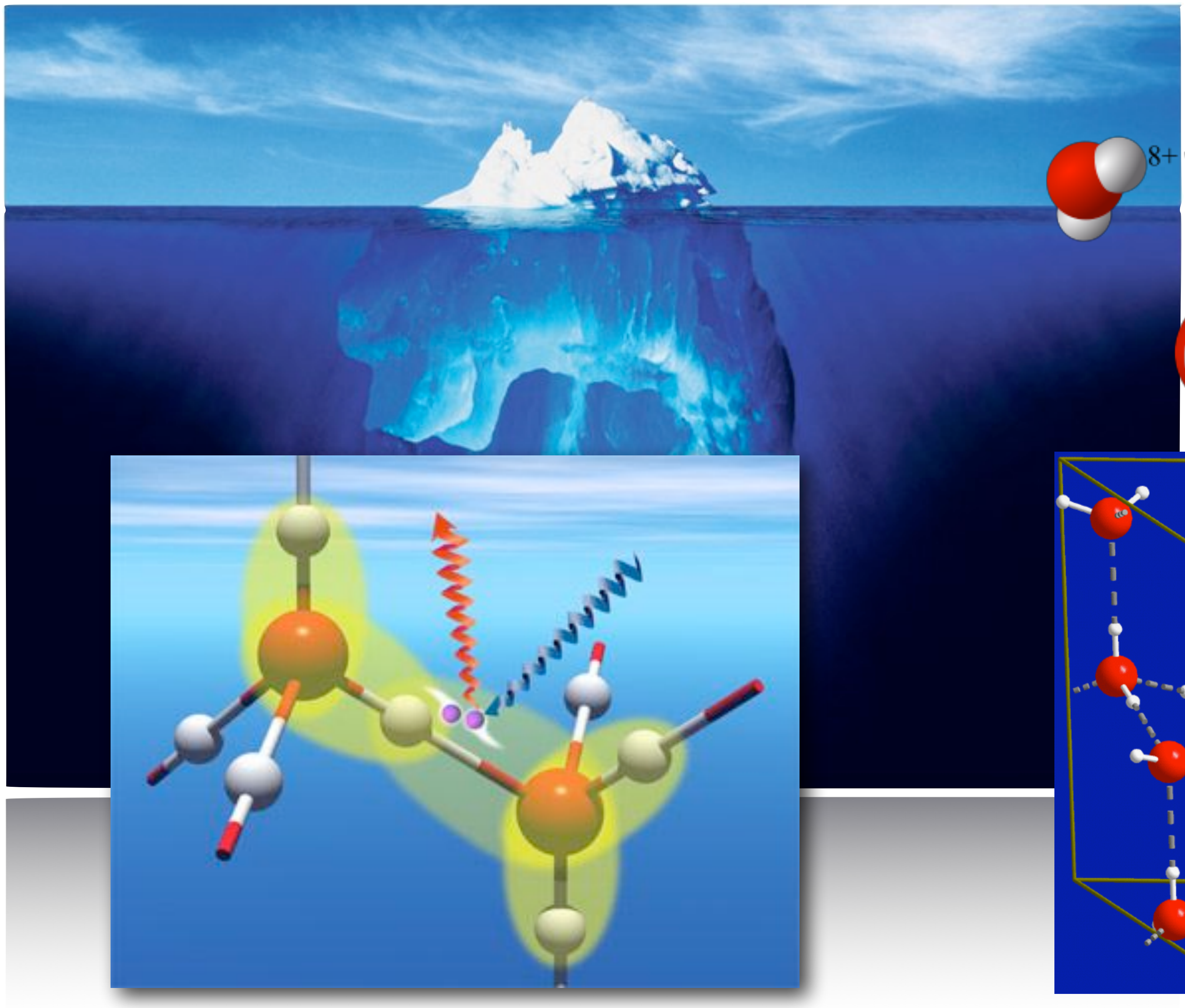


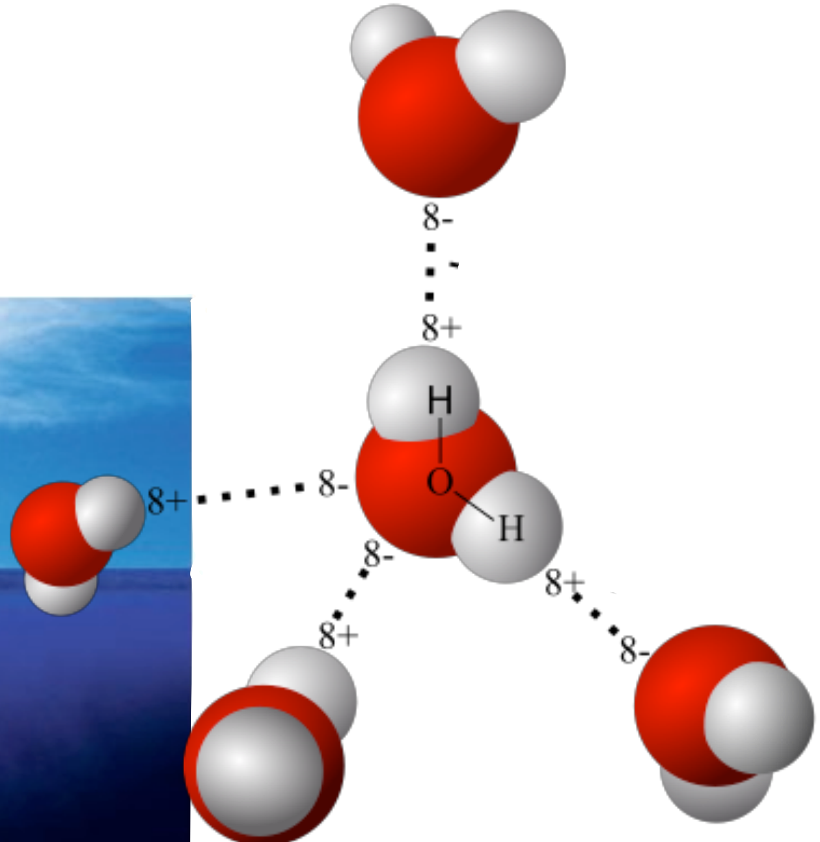
Hydrogen Bond

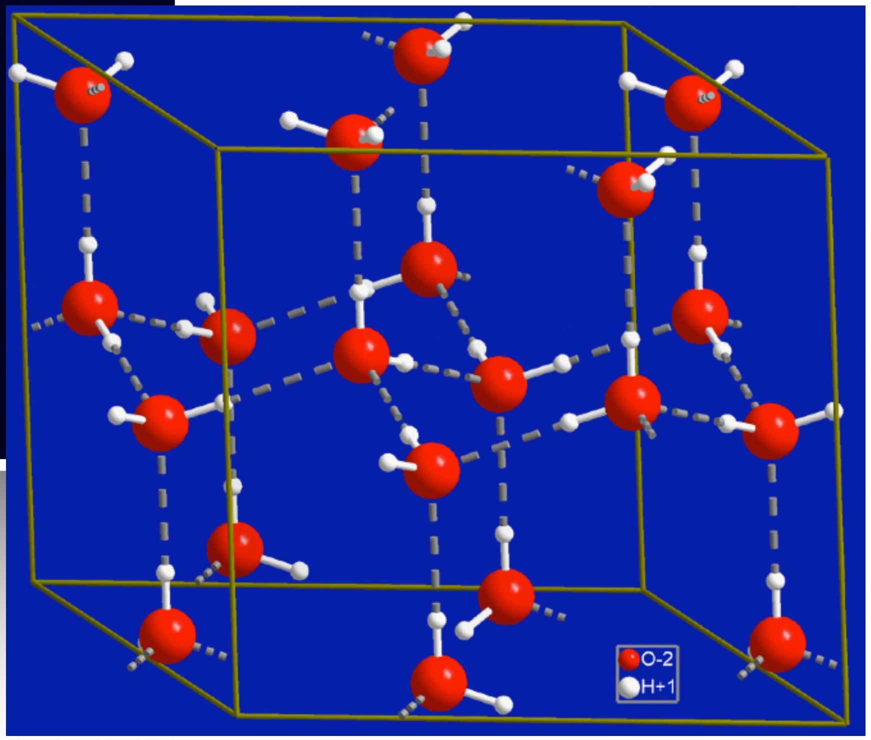


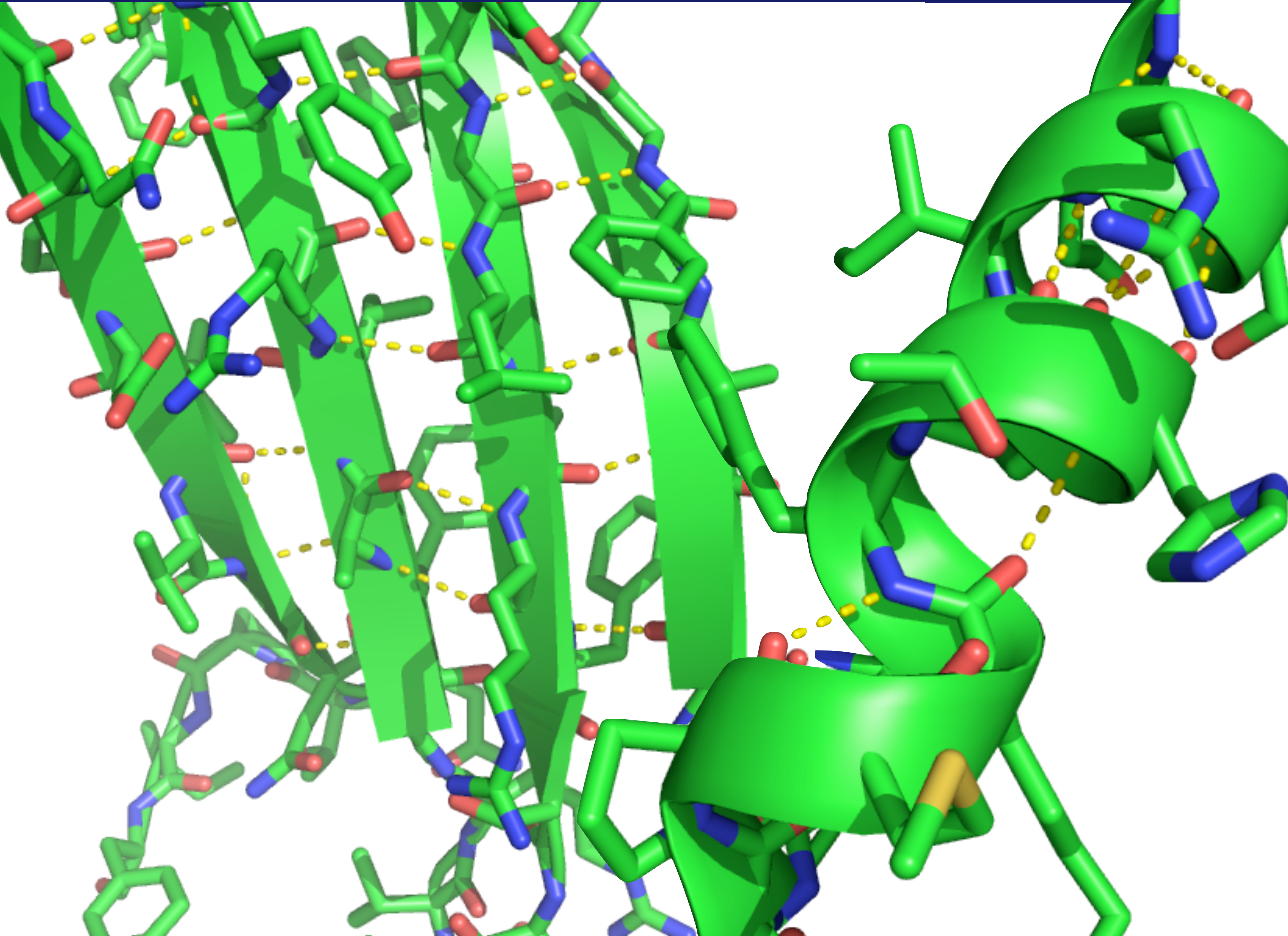


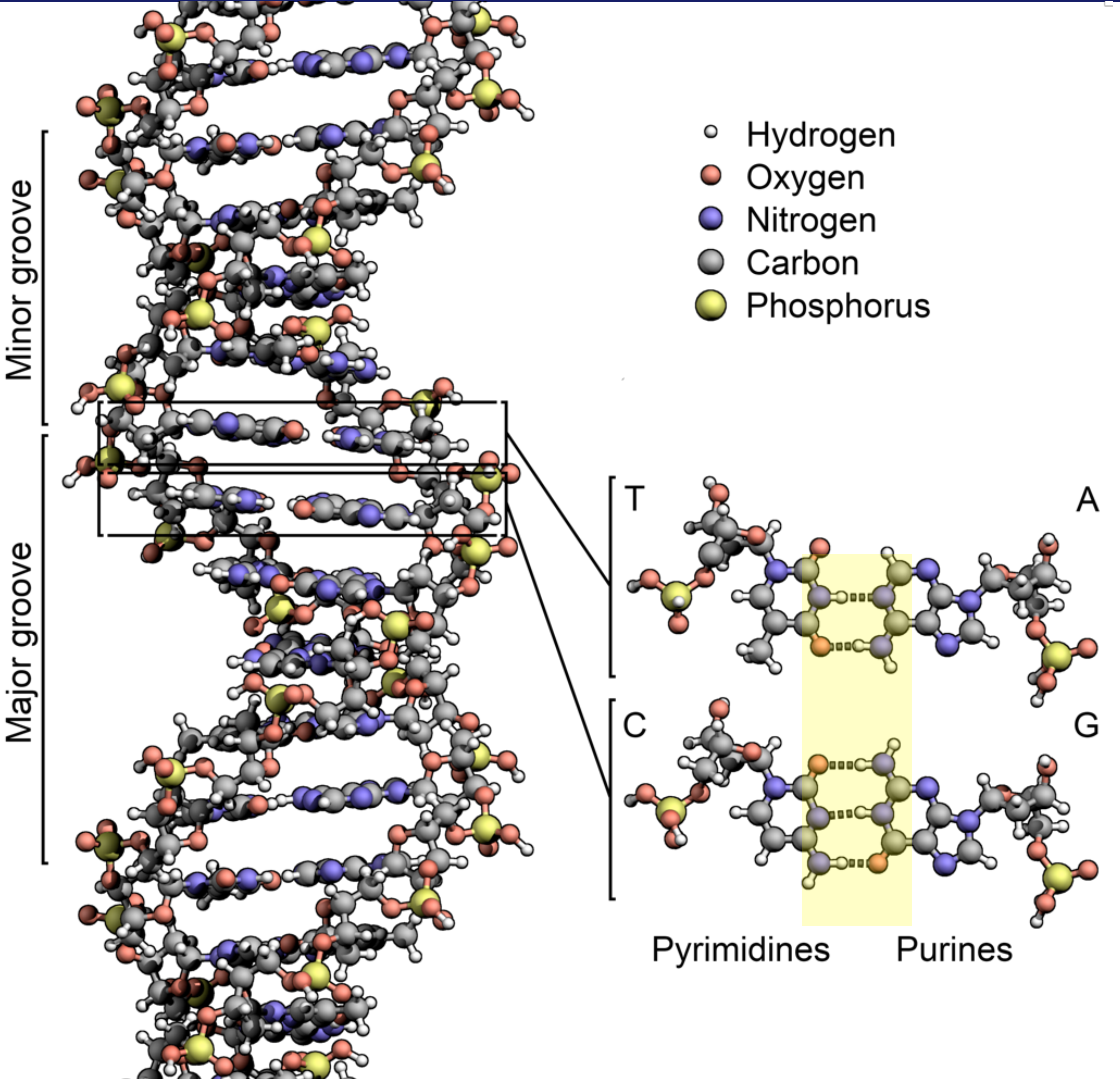
Hydrogen Bond



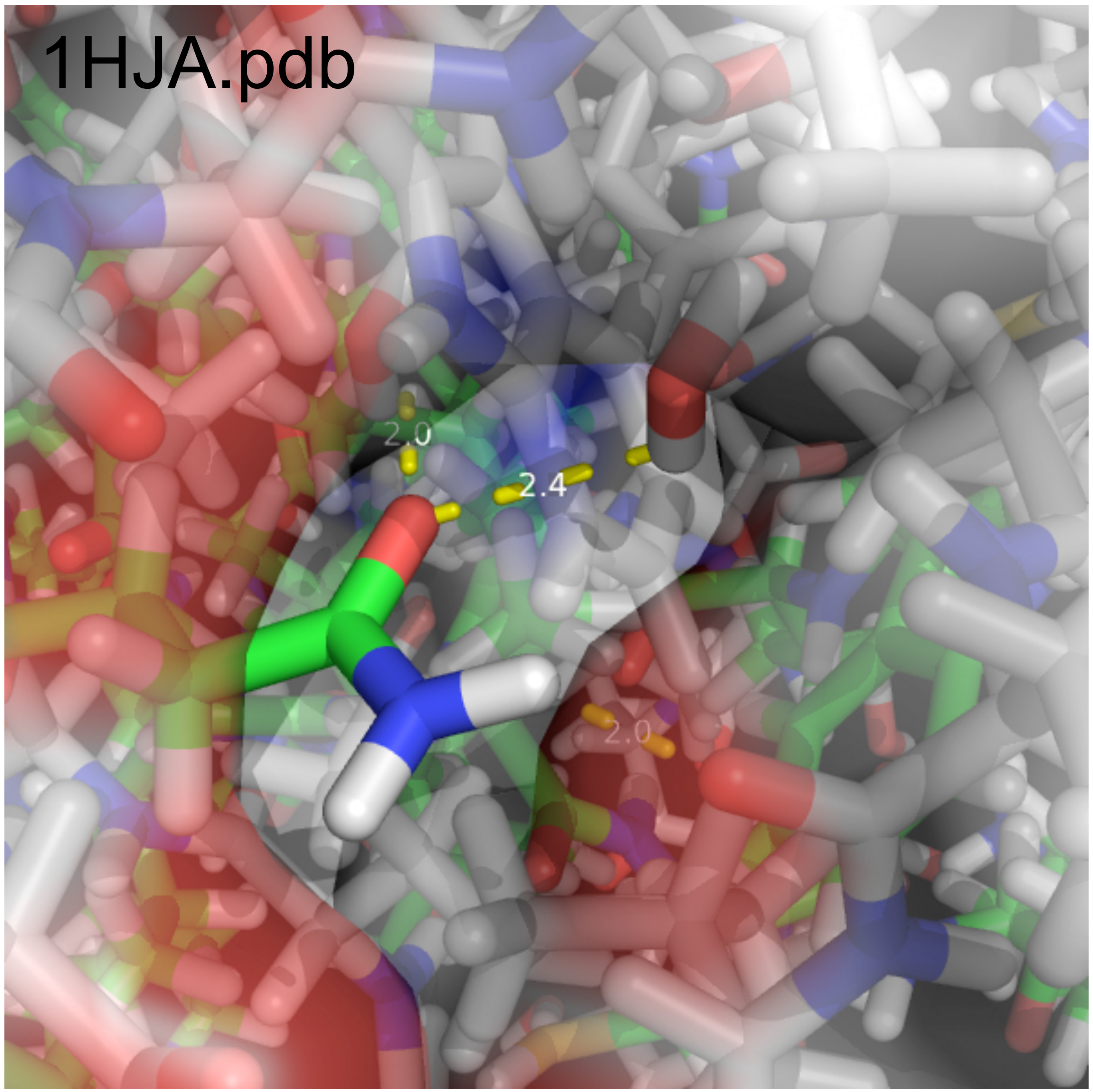







Minor groove
Major groove
Hydrogen
Oxygen
Nitrogen
Carbon
Phosphorus
T
A
C
G
Pyrimidines
Purines

Hydrogen Bond



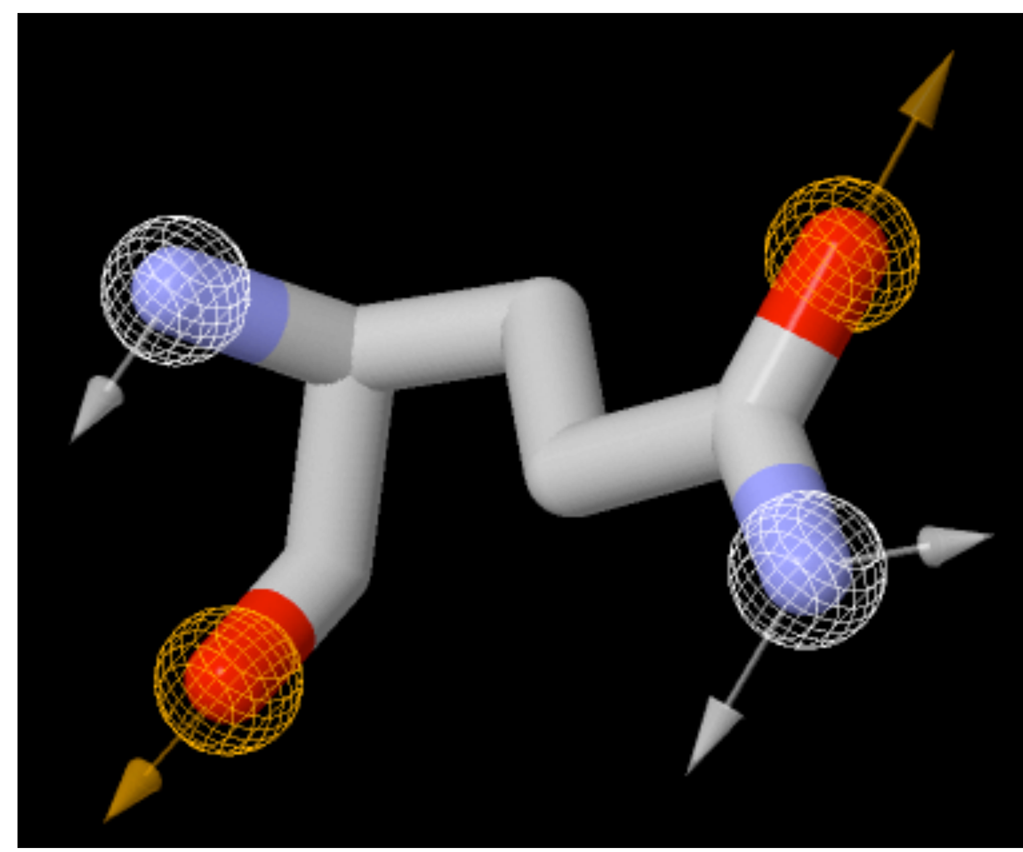
Distance:

D-A: 2.5Å – 3.5Å (4.0Å?)

H-A: 1.5Å – 2.5Å

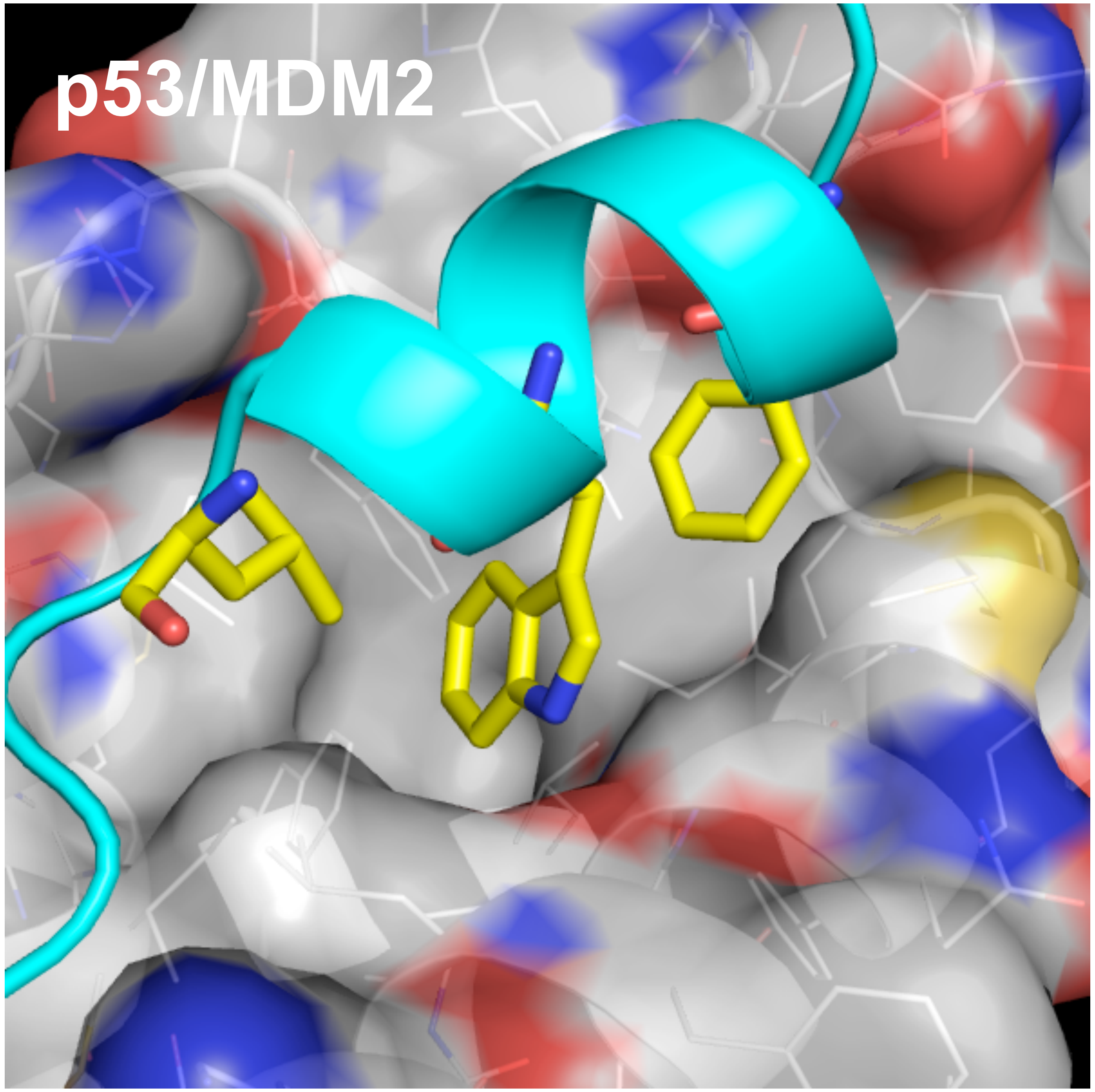
Angle:

Depends on context

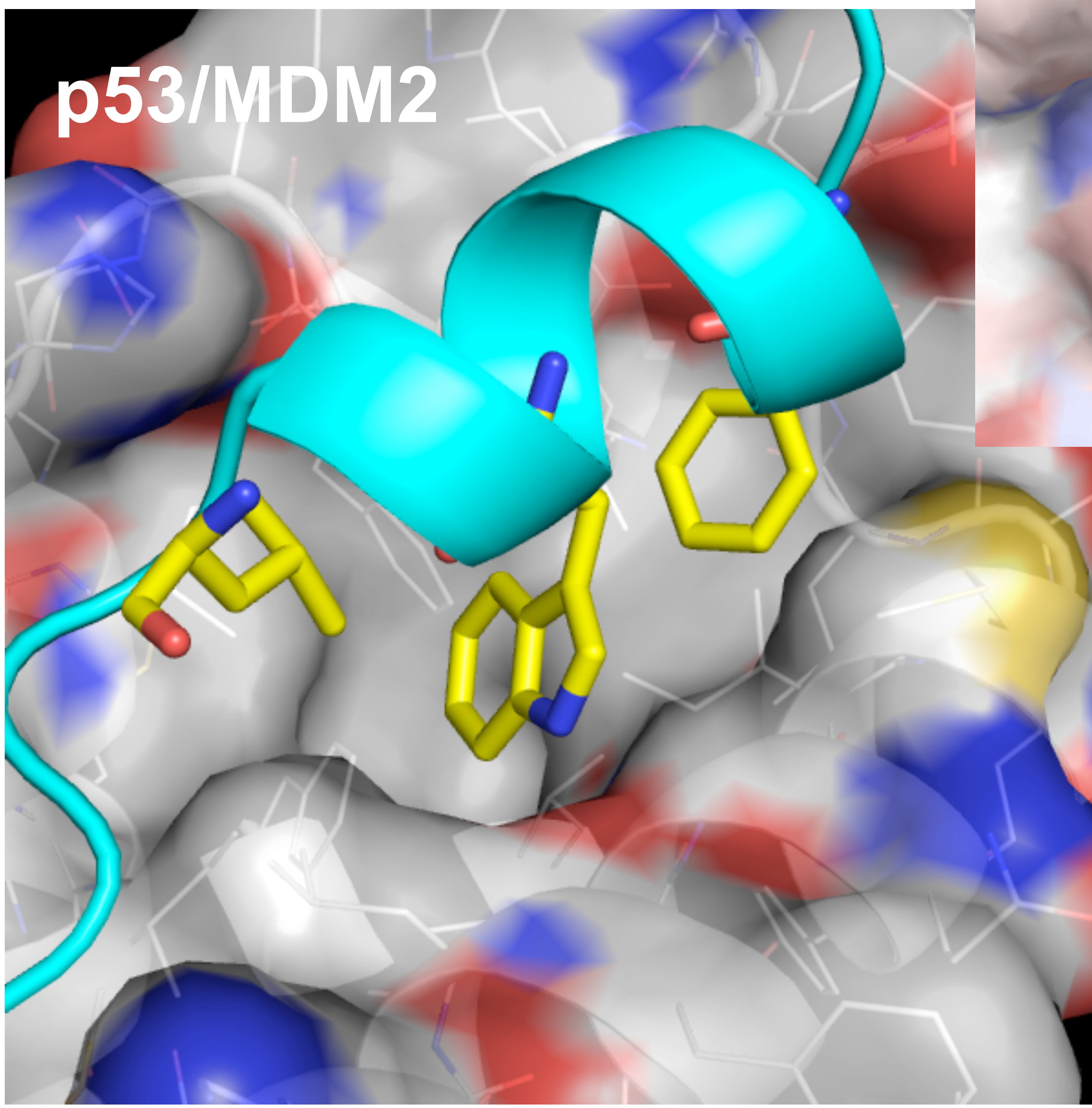


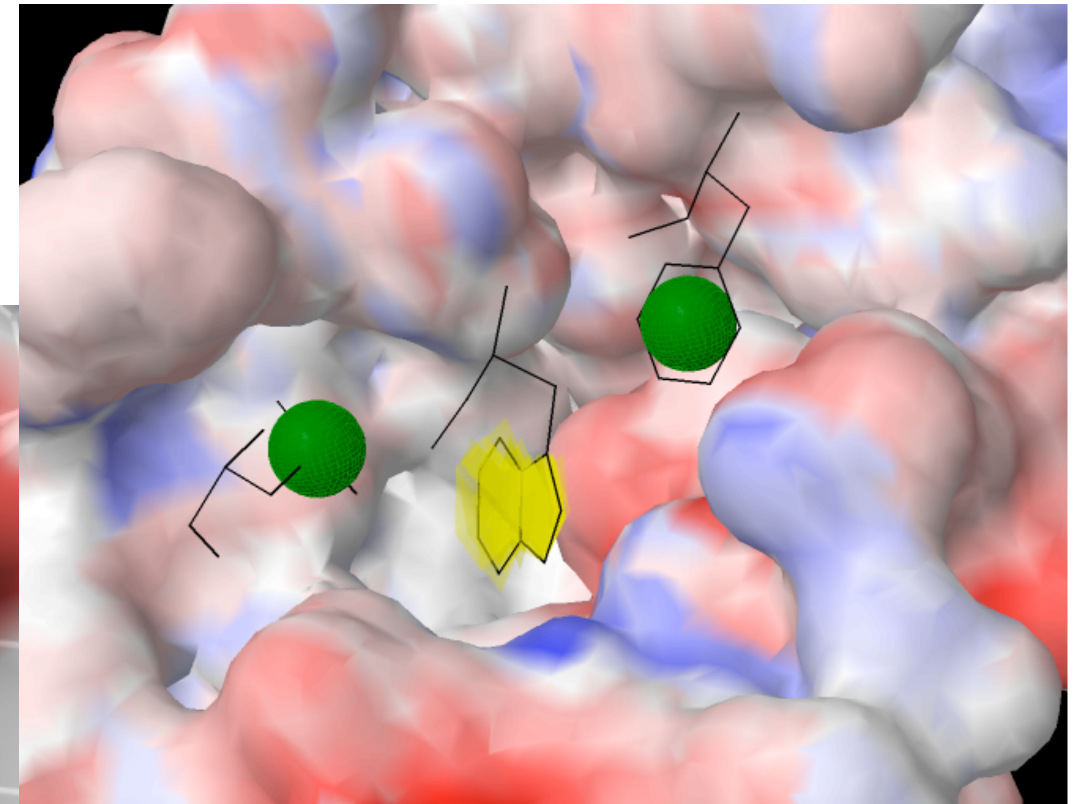
Hydrophobic

Hydrophobic



Hydrophobic





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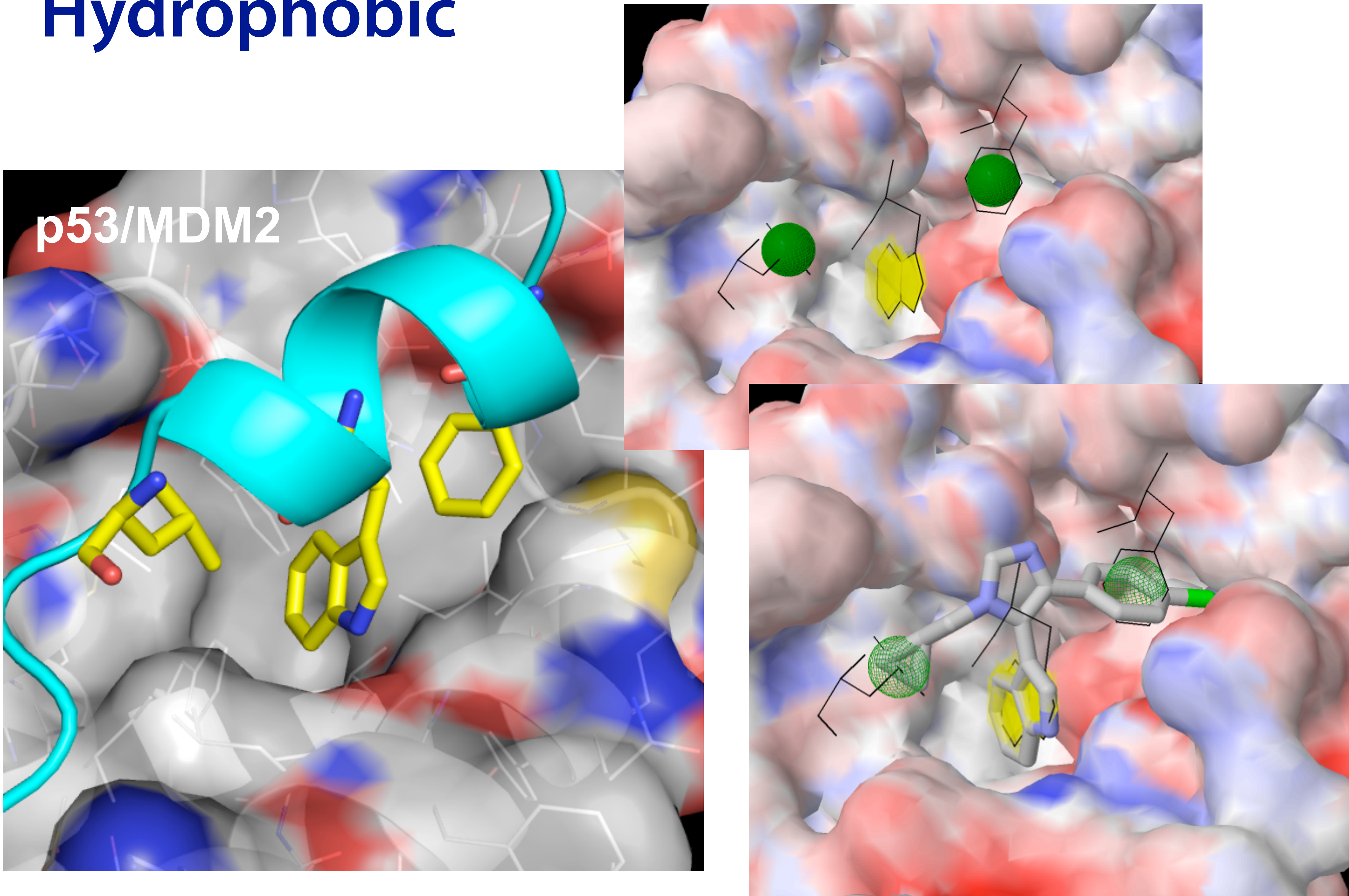
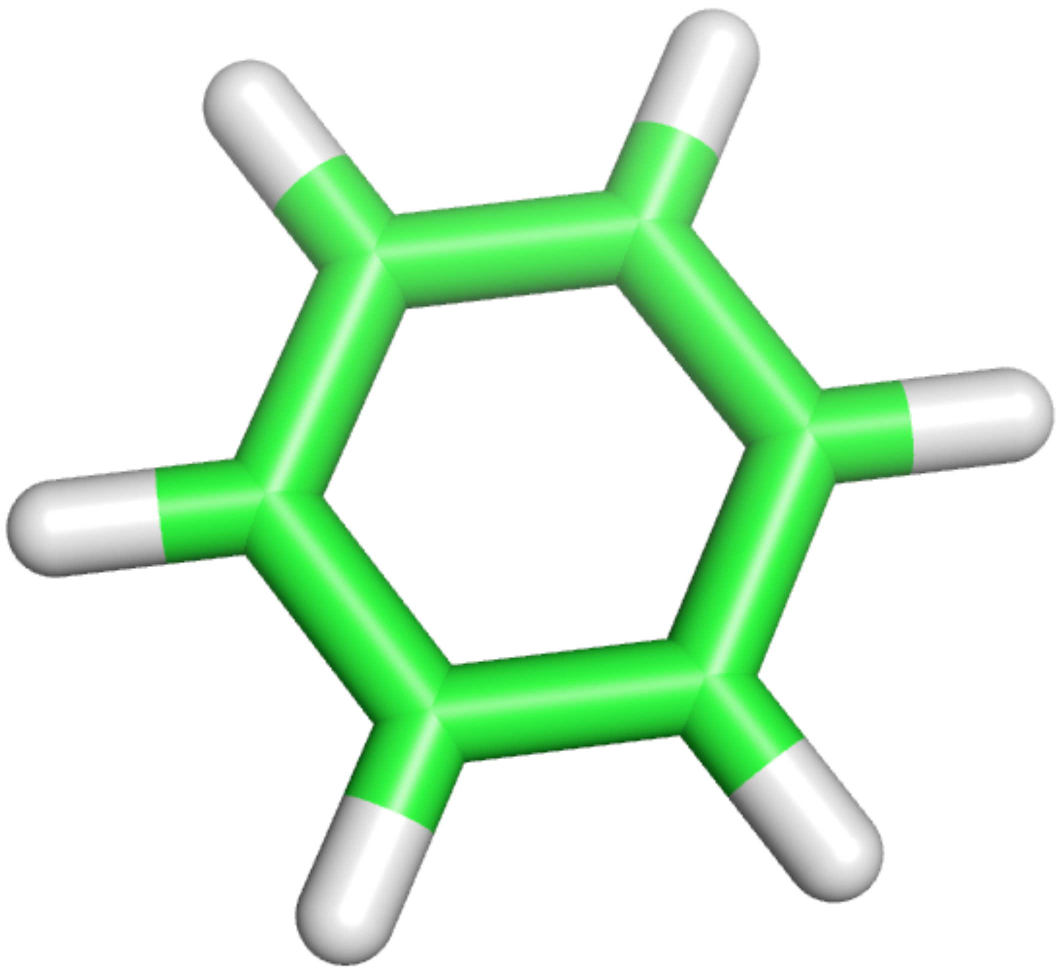
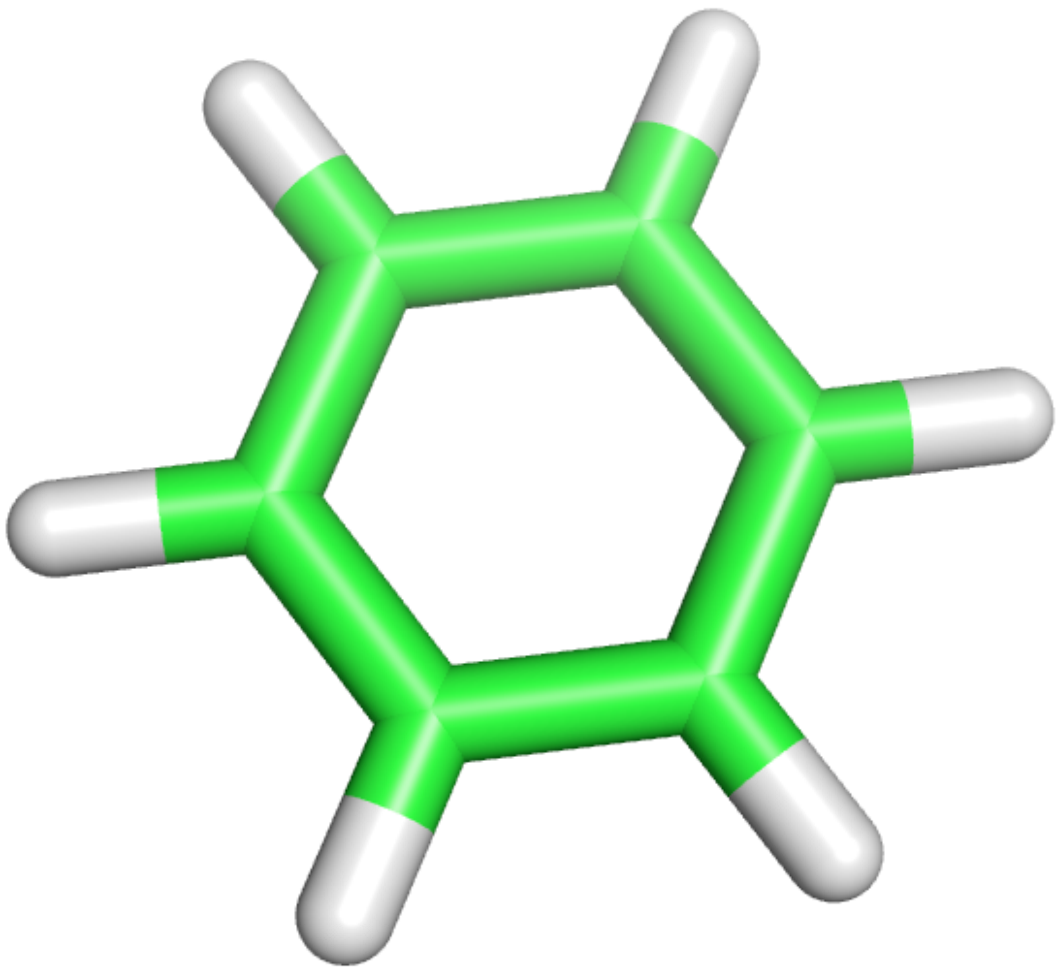


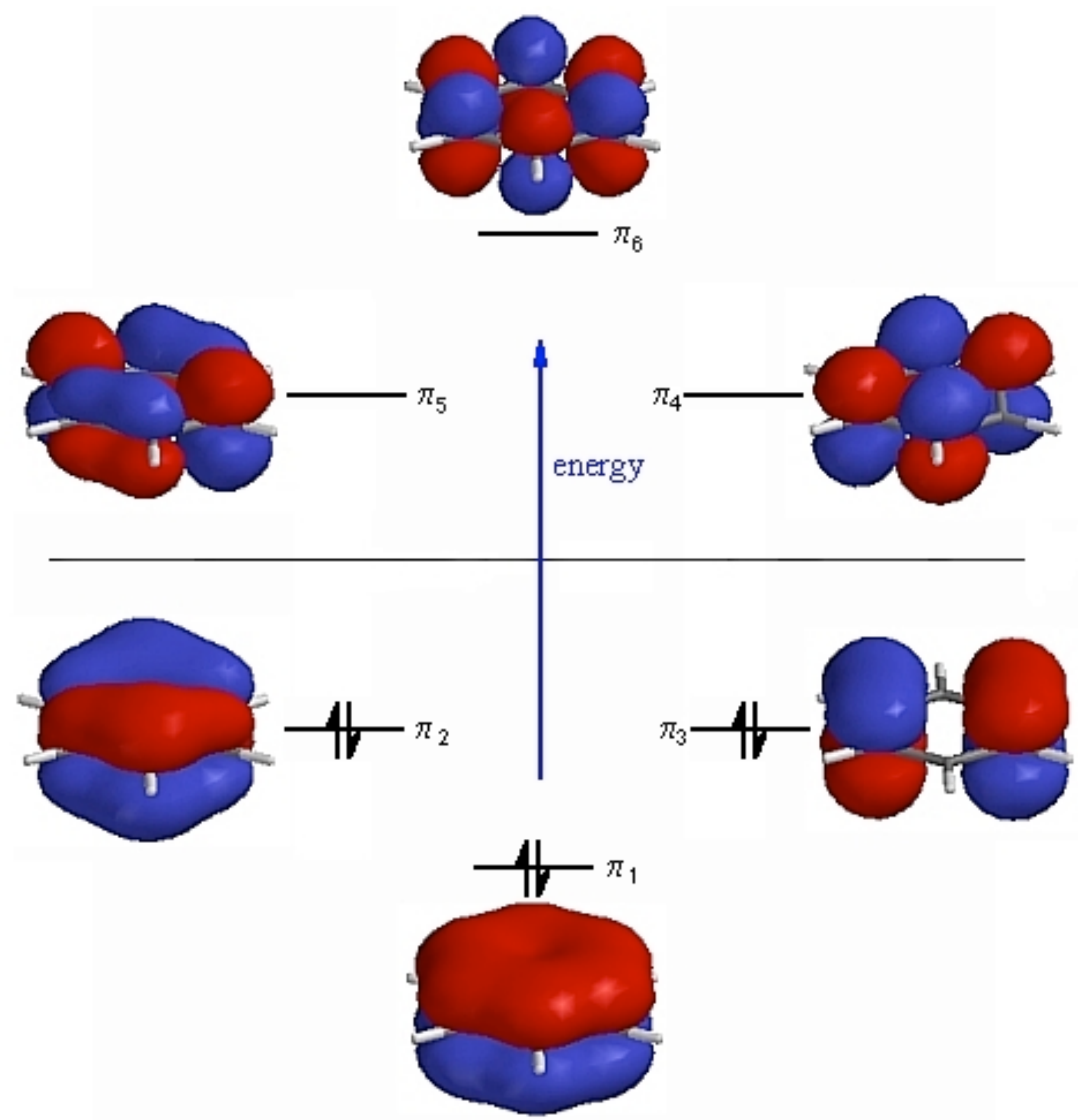
Aromatic



http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch11/benzene-mo.jpg

Aromatic





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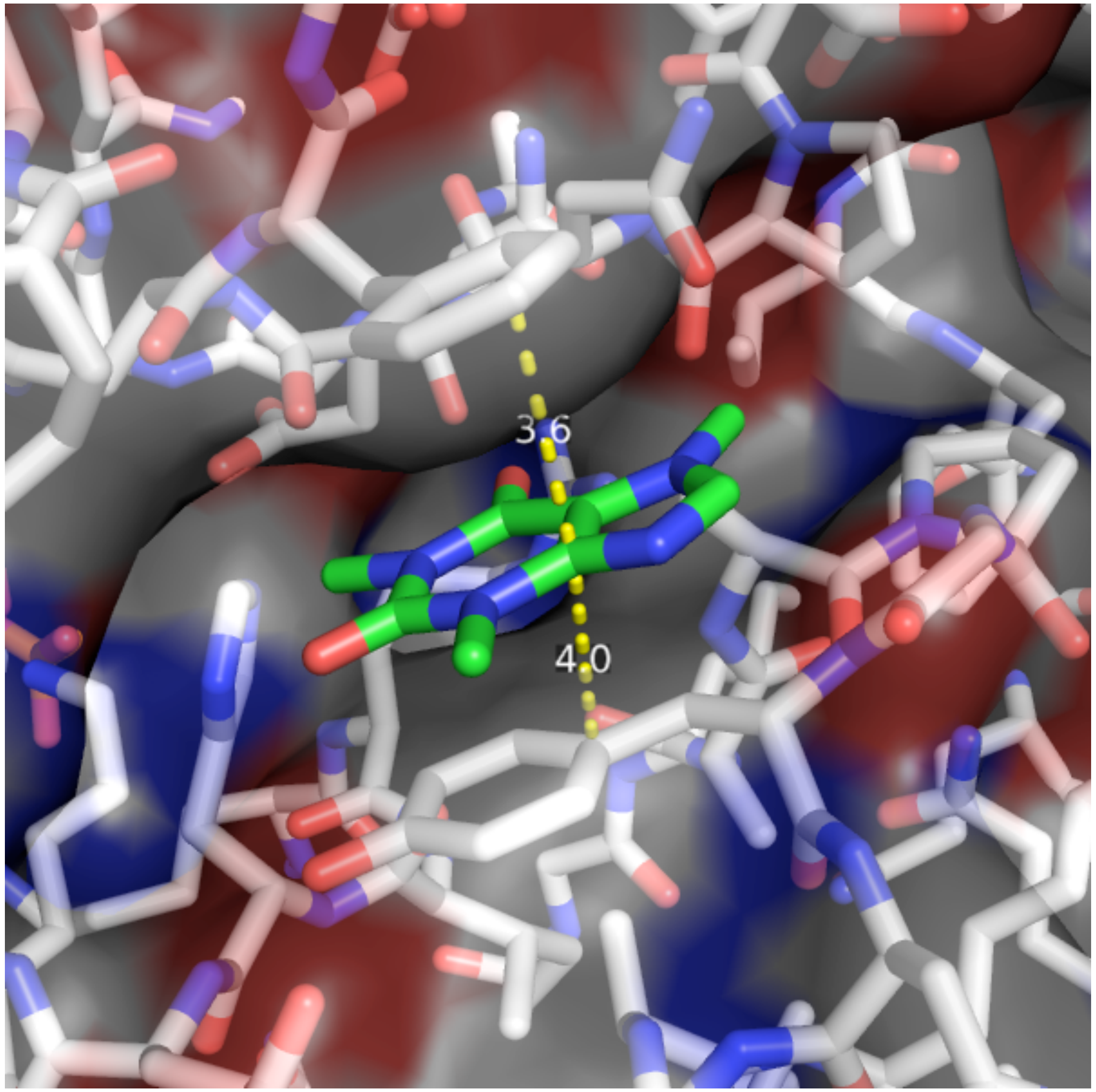
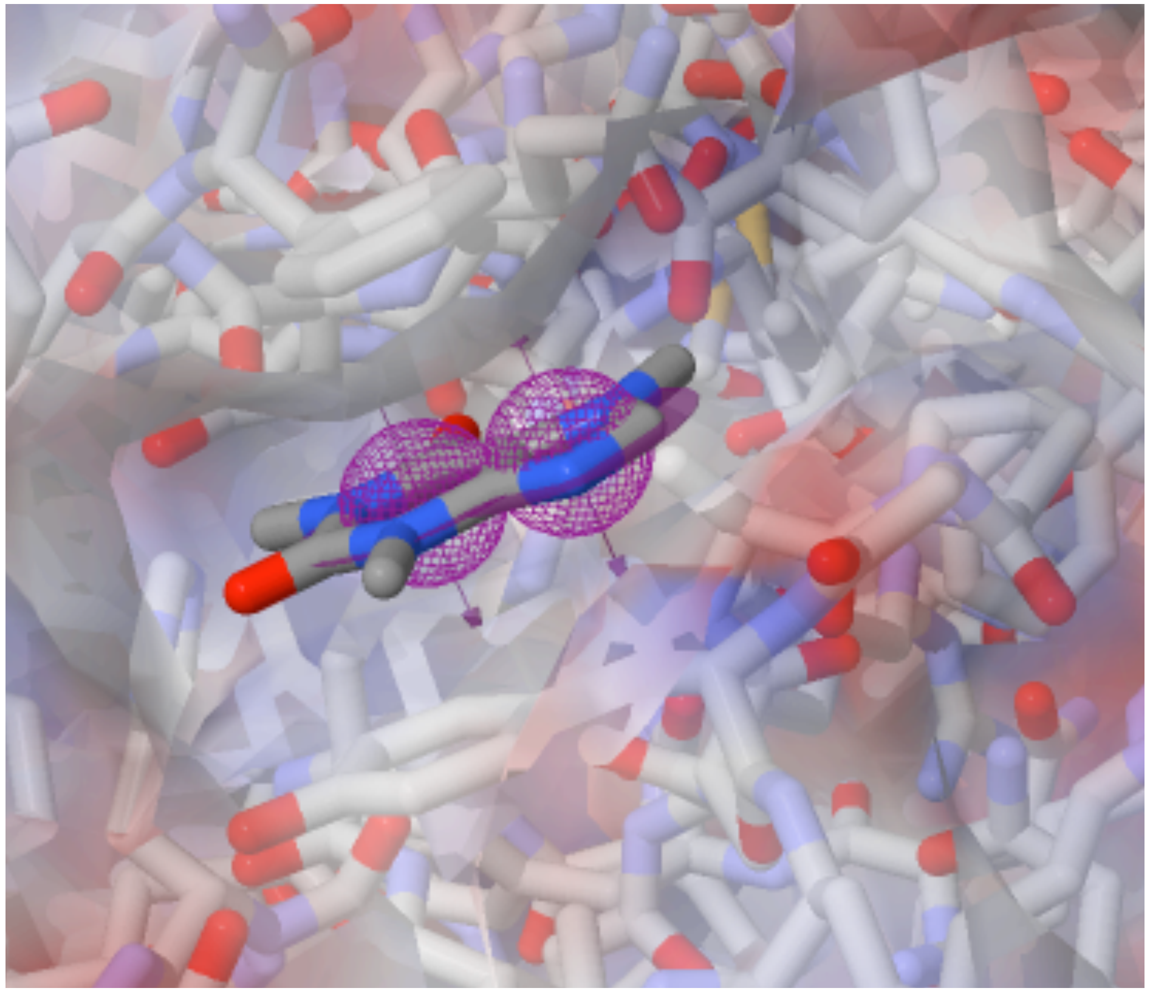
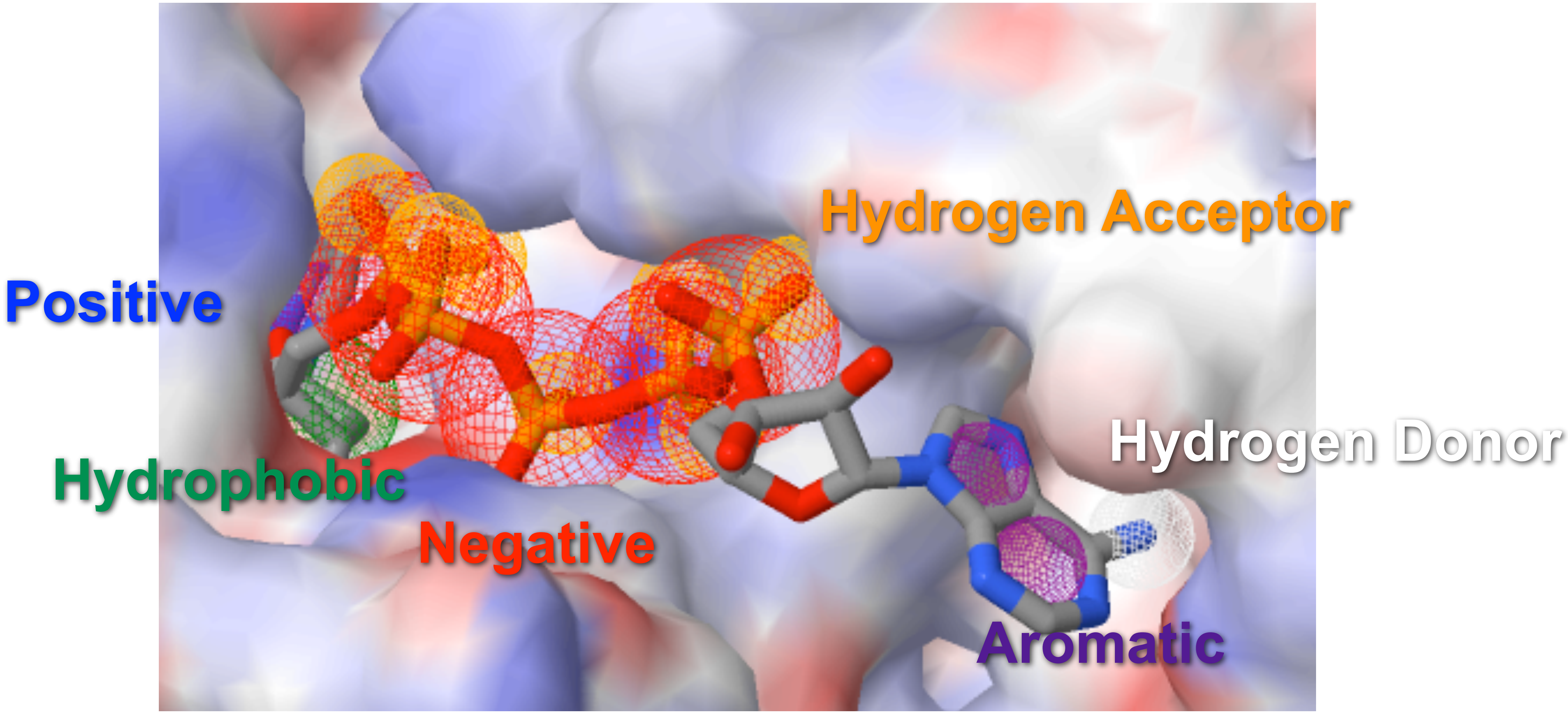
Aromatic



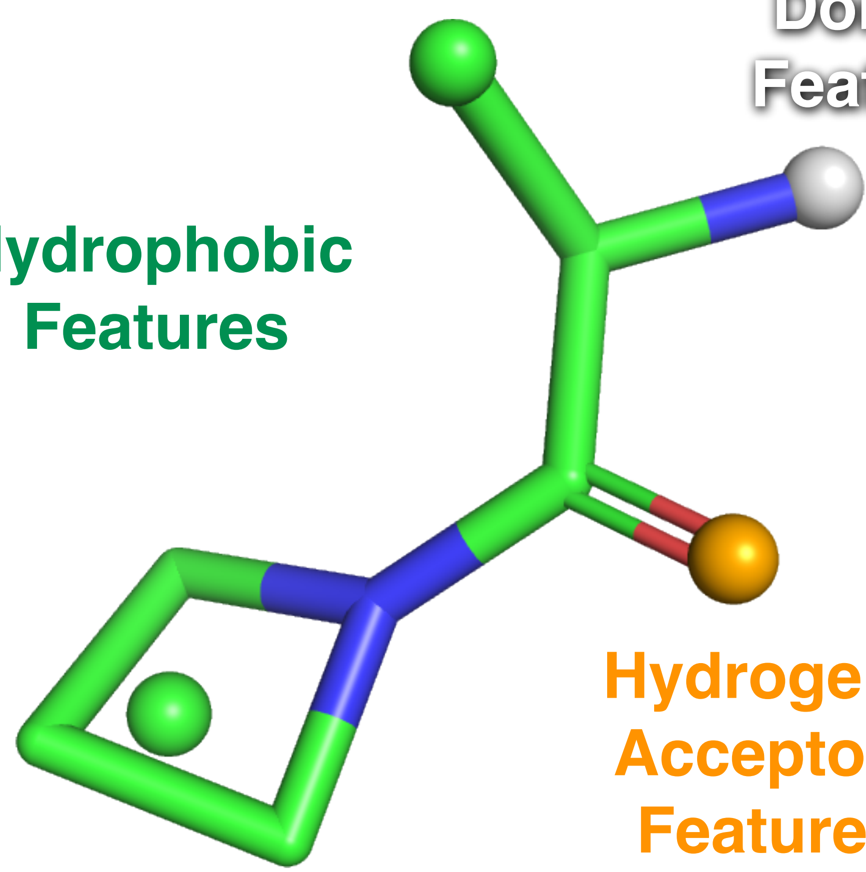
Rings offset
Interplanar distance: 3.3-3.8Å



Pharmacophore Features



Pharmer Efficient and Exact Pharmacophore Search



Pharmacophore

A spatial arrangement of molecular features essential for biological activity

Koes, D. R., & Camacho, C. J. (2011). Pharmer: efficient and exact pharmacophore search. *Journal of Chemical Information and Modeling, 51*(6), 1307-1314. doi:10.1021/ci200097m
Koes, D. R., & Camacho, C. J. (2012). ZINCPharmer: pharmacophore search of the ZINC database. *Nucleic acids research, 40*(Web Server issue), W409-414. doi:10.1093/nar/gks378

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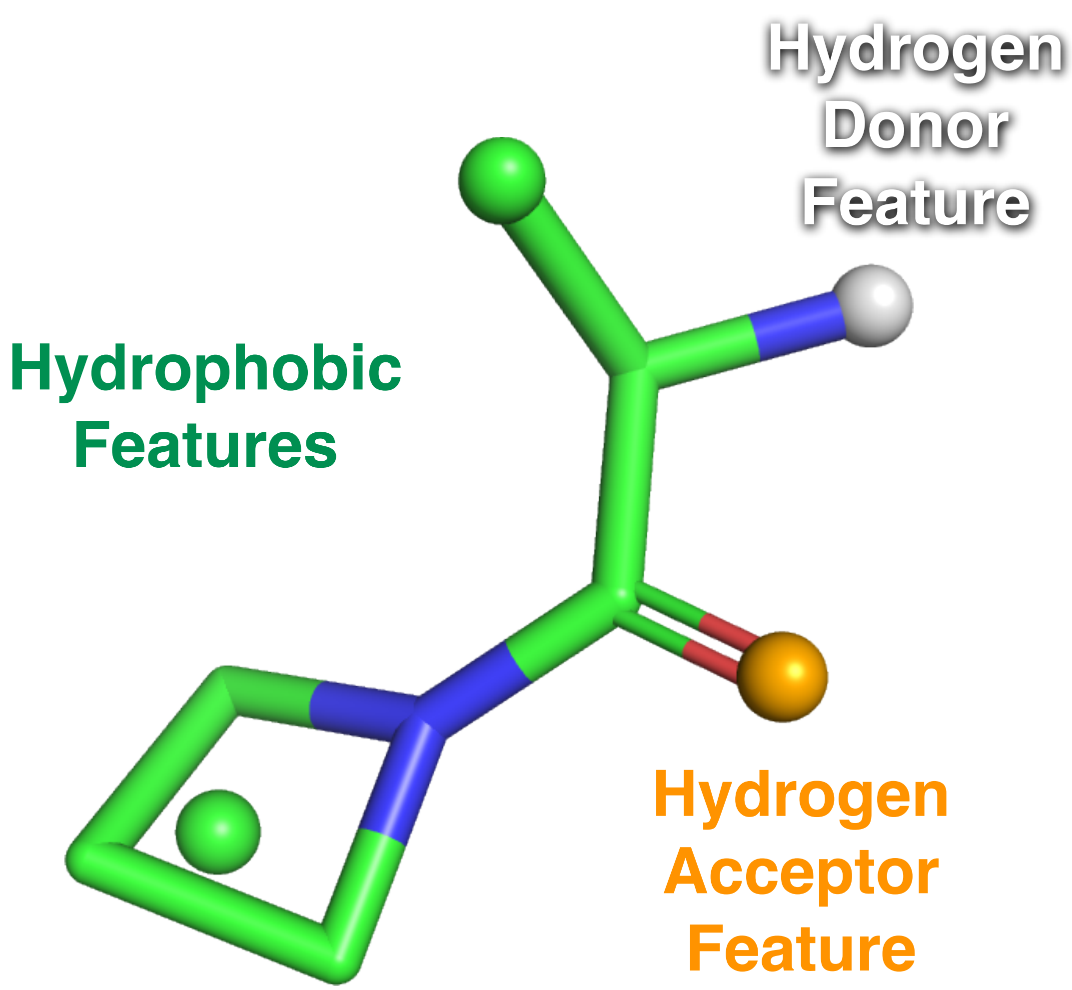

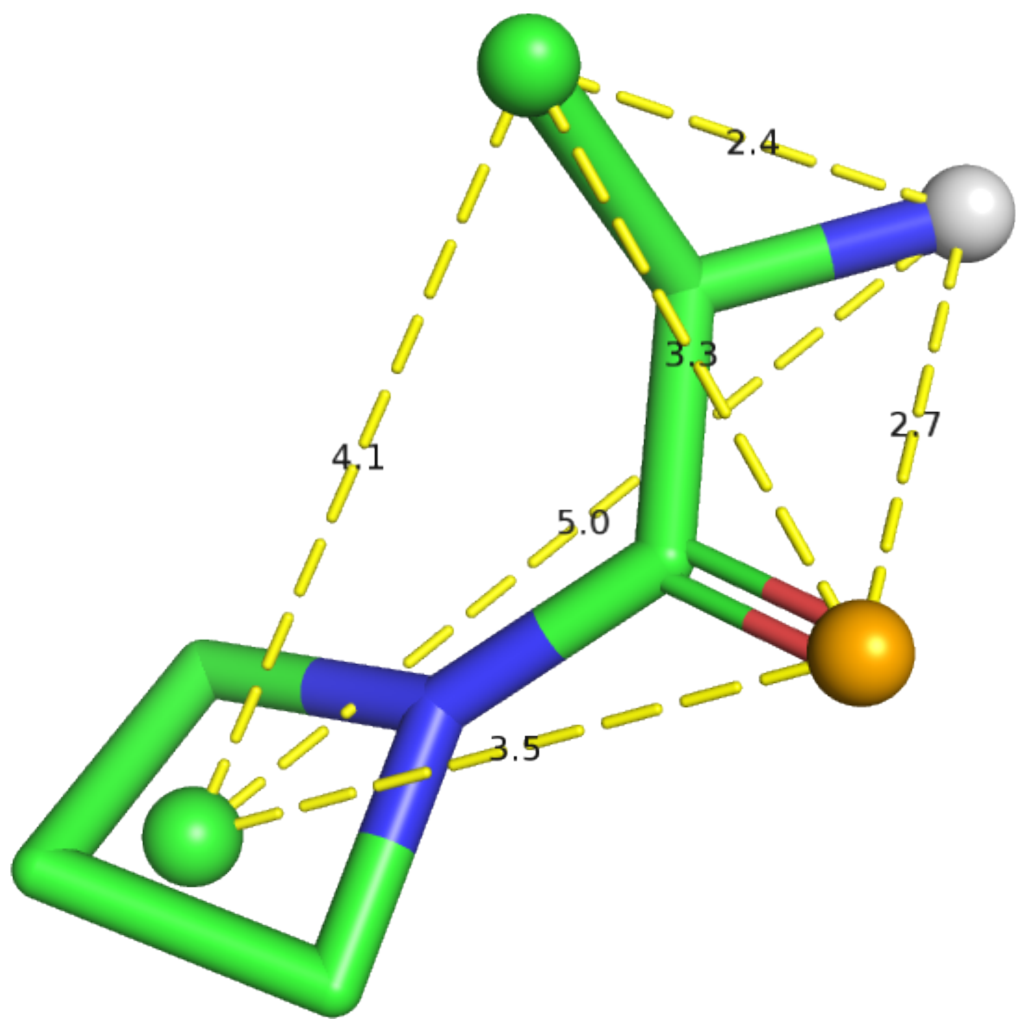

Pharmer

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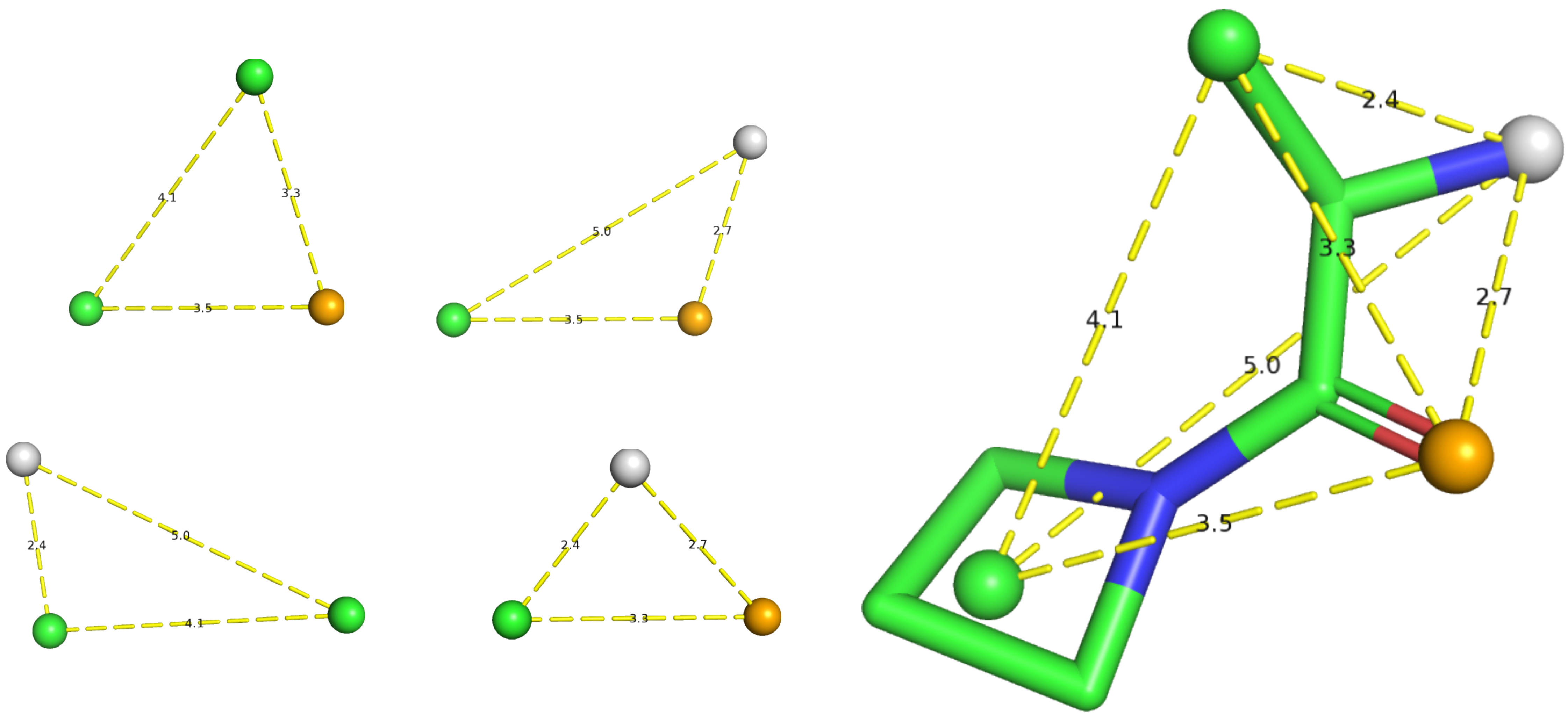

Pharmer

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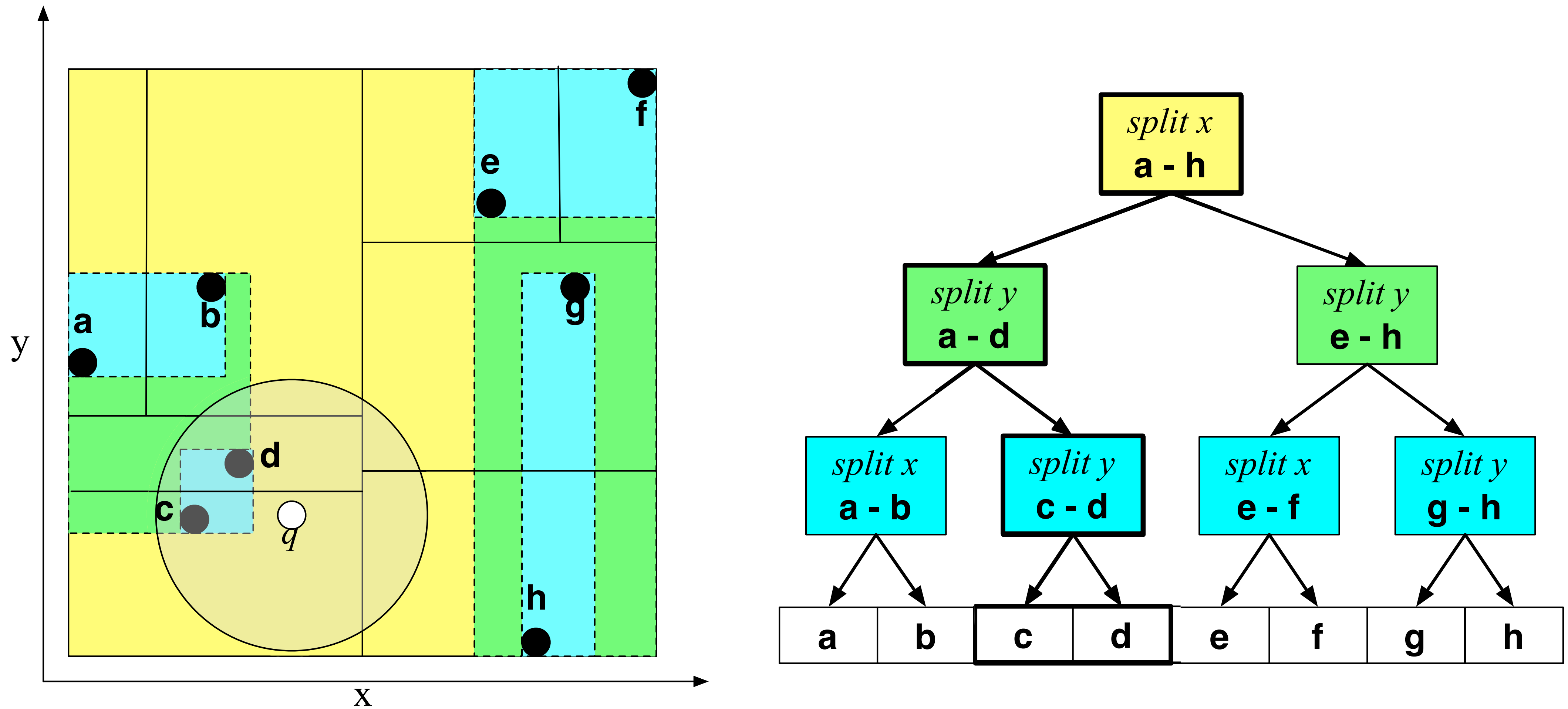

Pharmer

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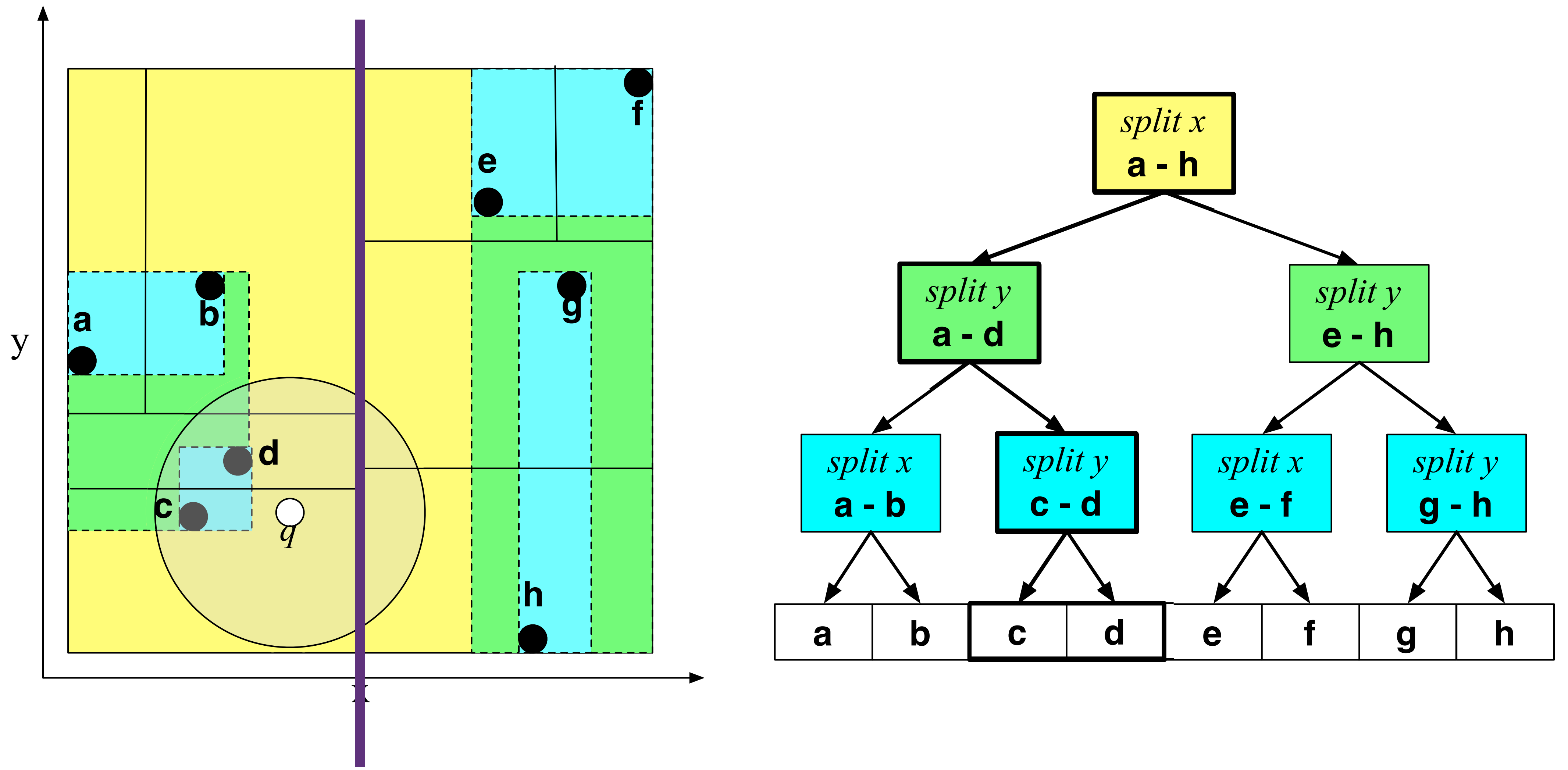
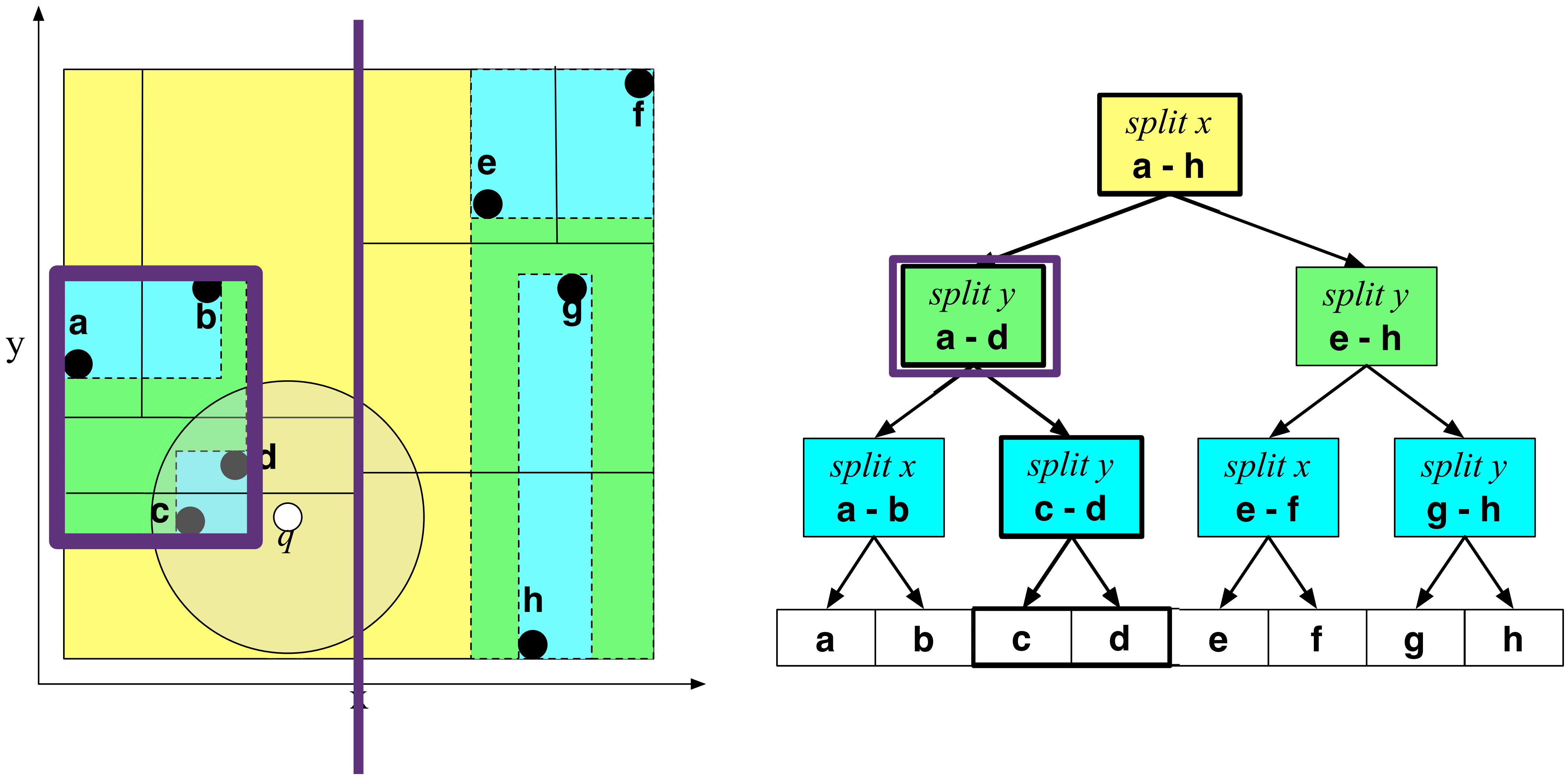


Pharmer

Efficient and Exact Pharmacophore Search



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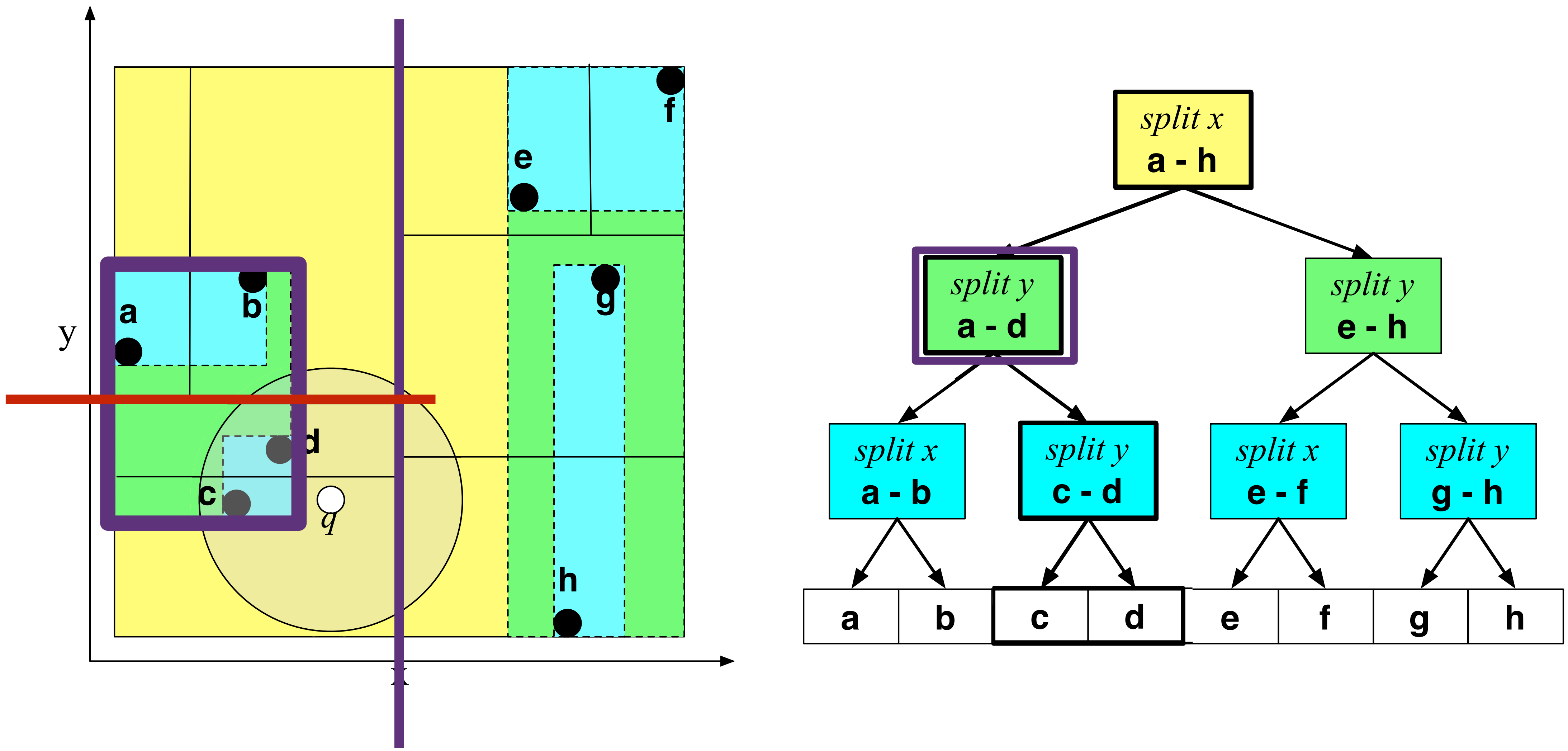

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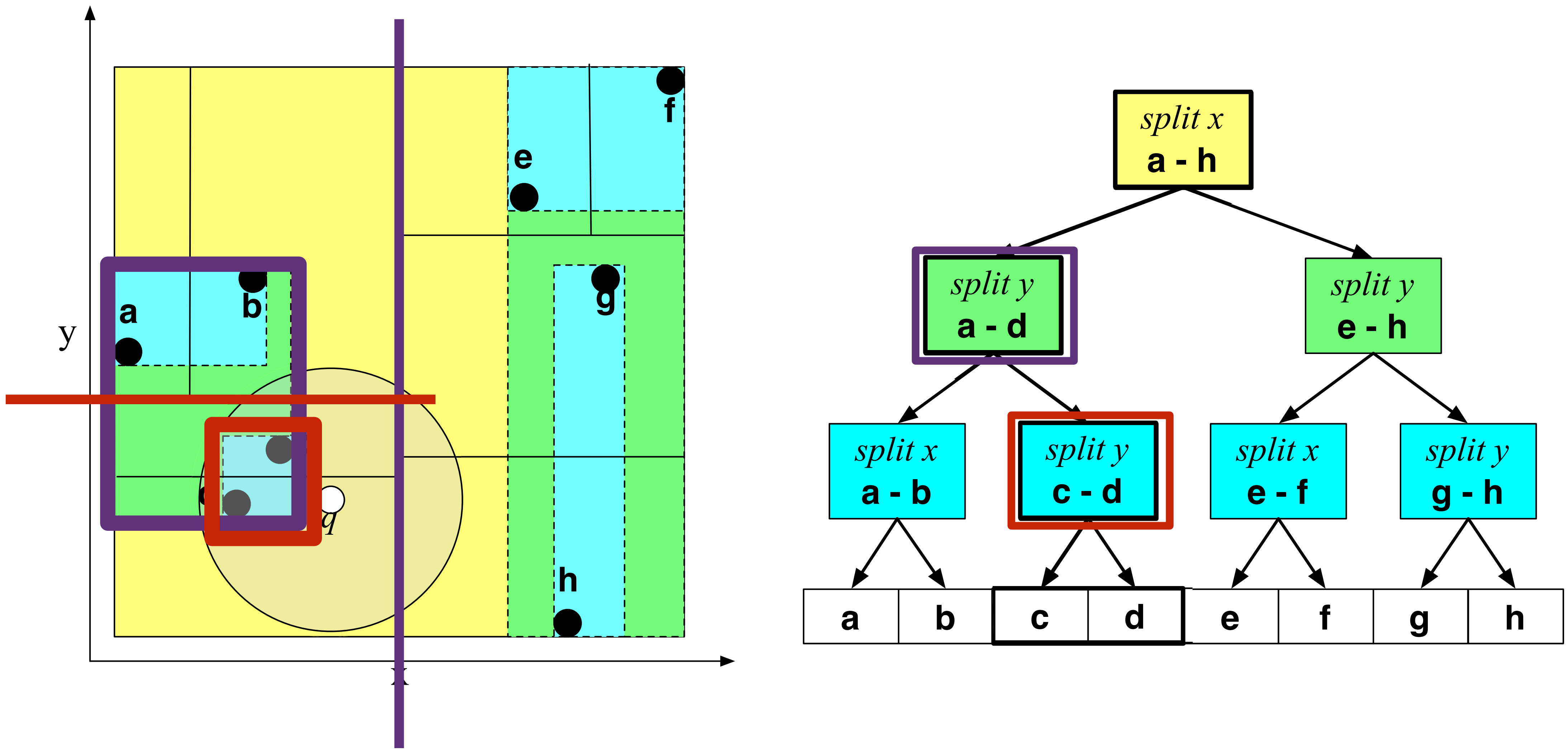

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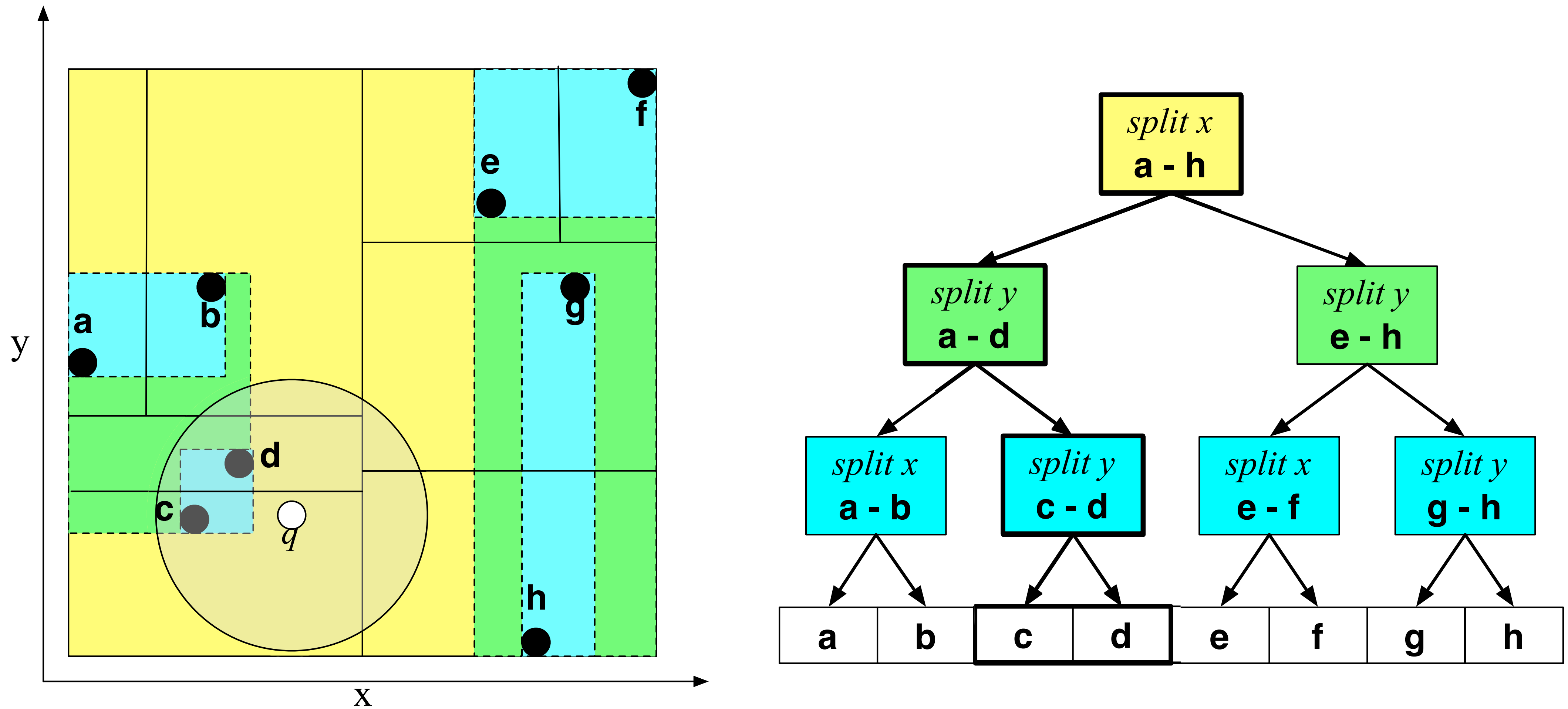

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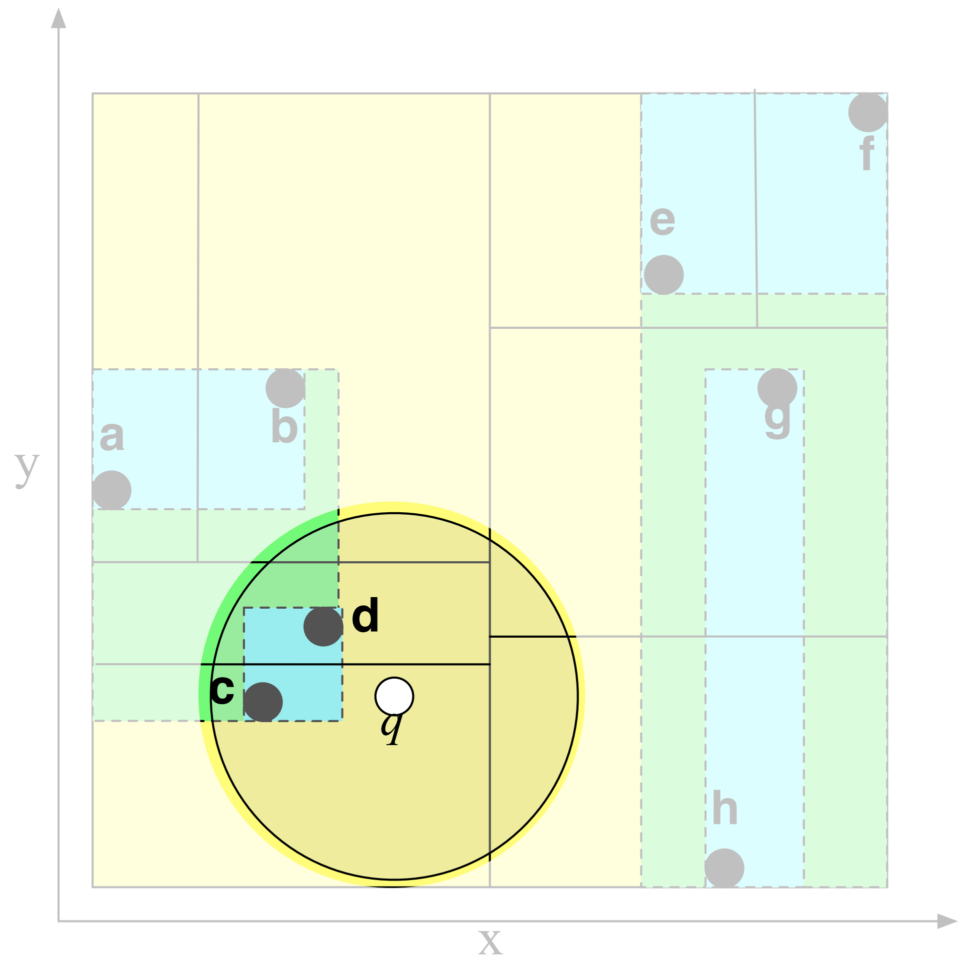

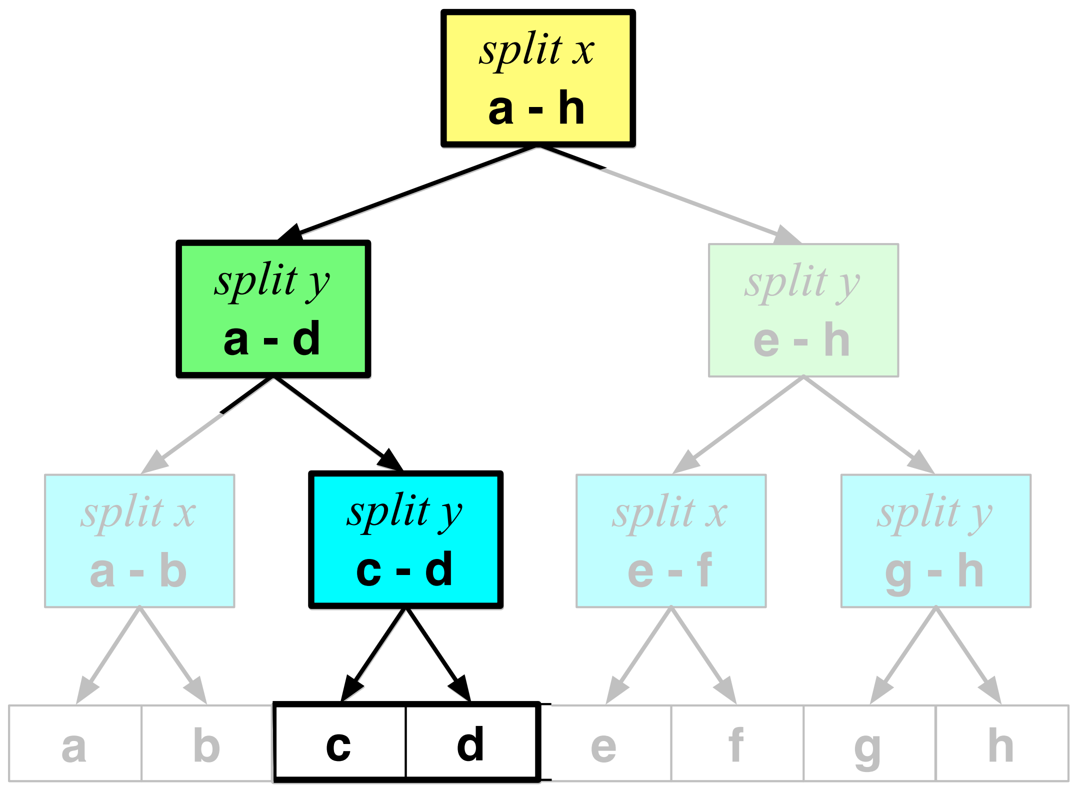

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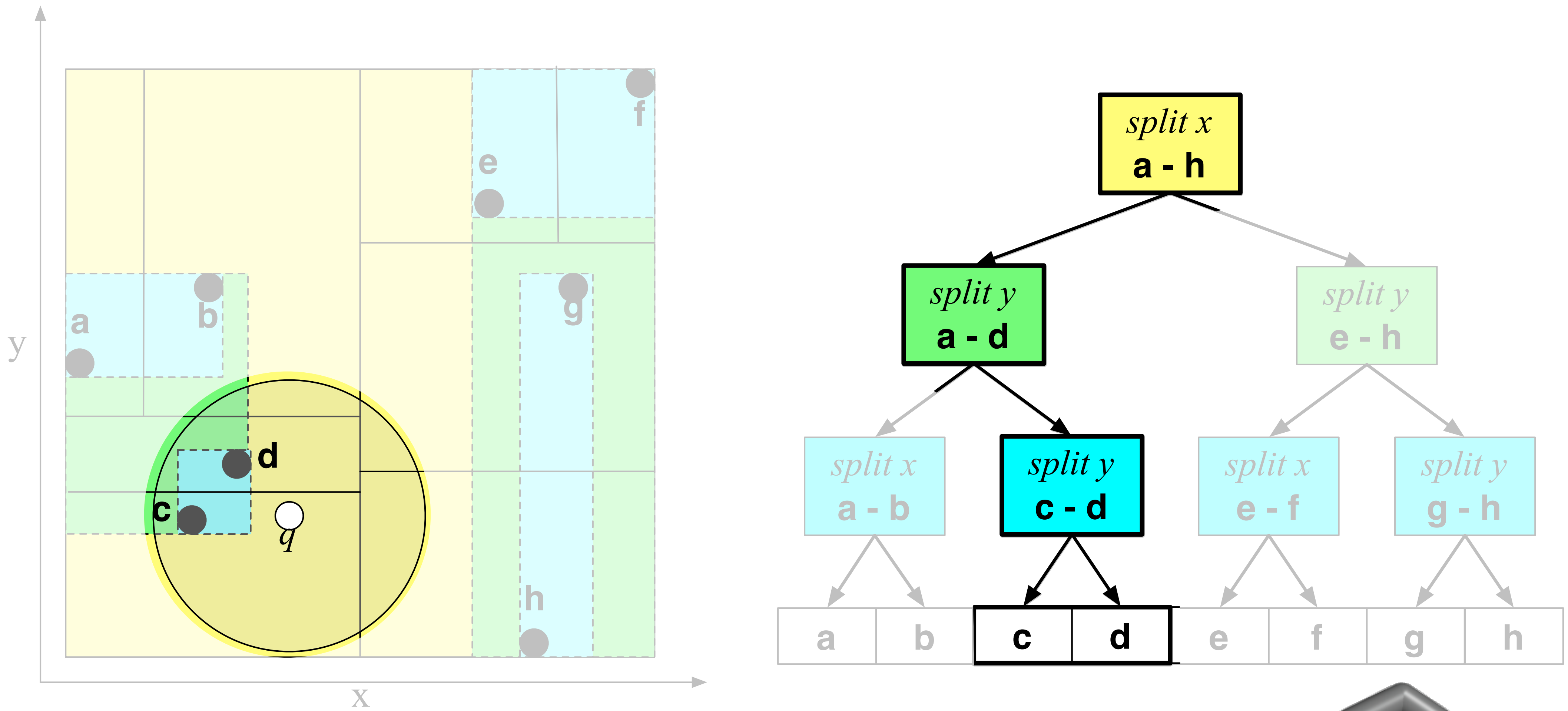

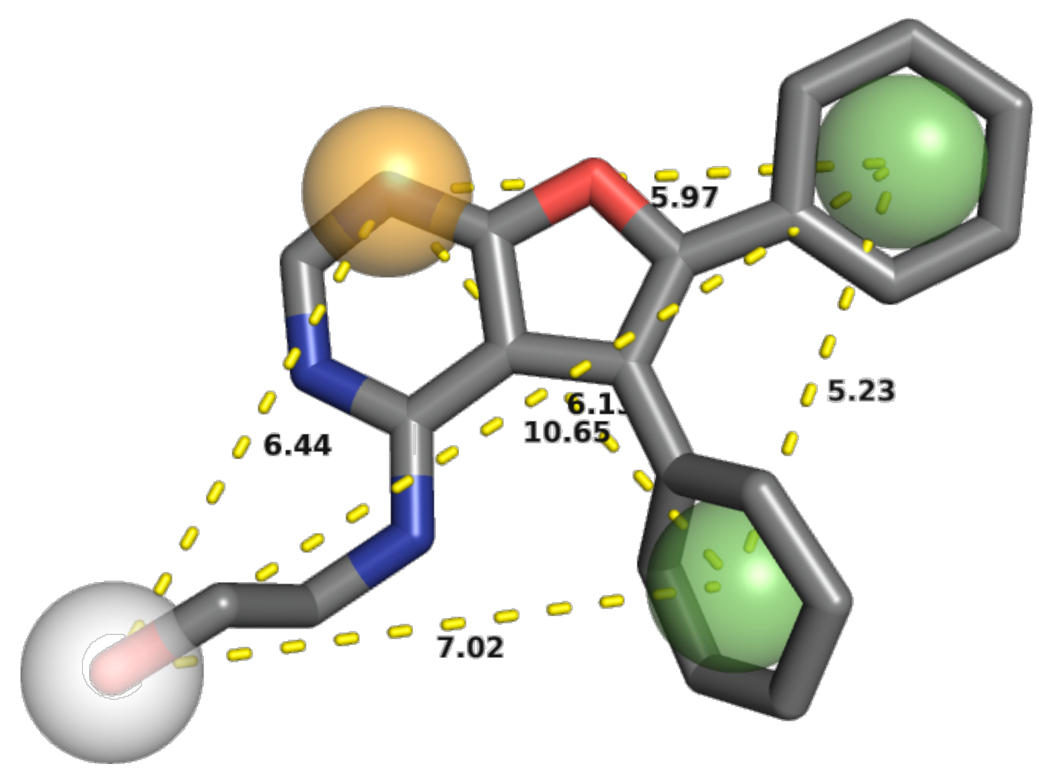

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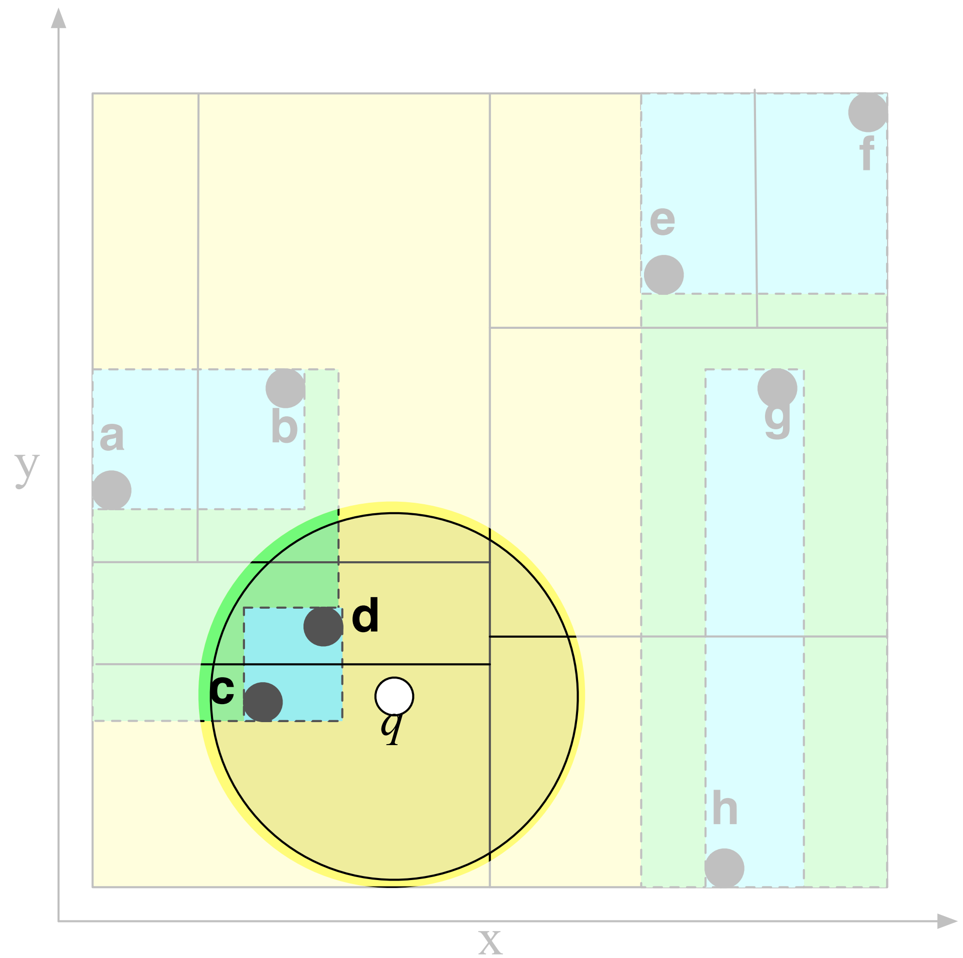

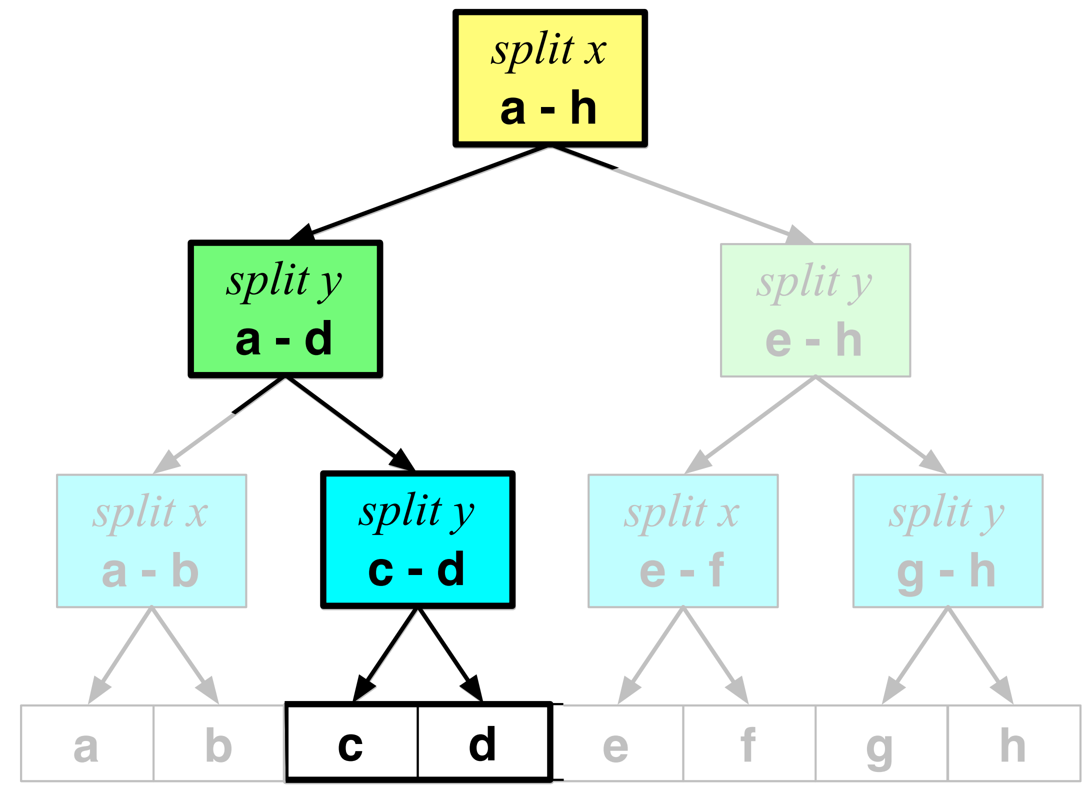

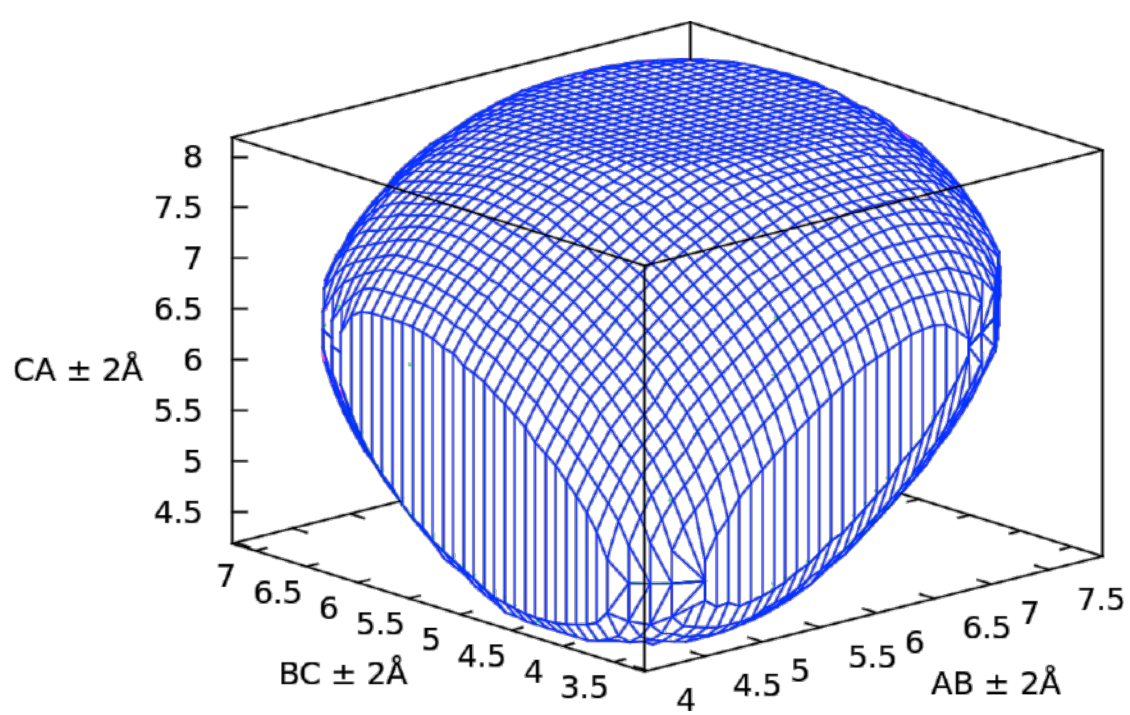

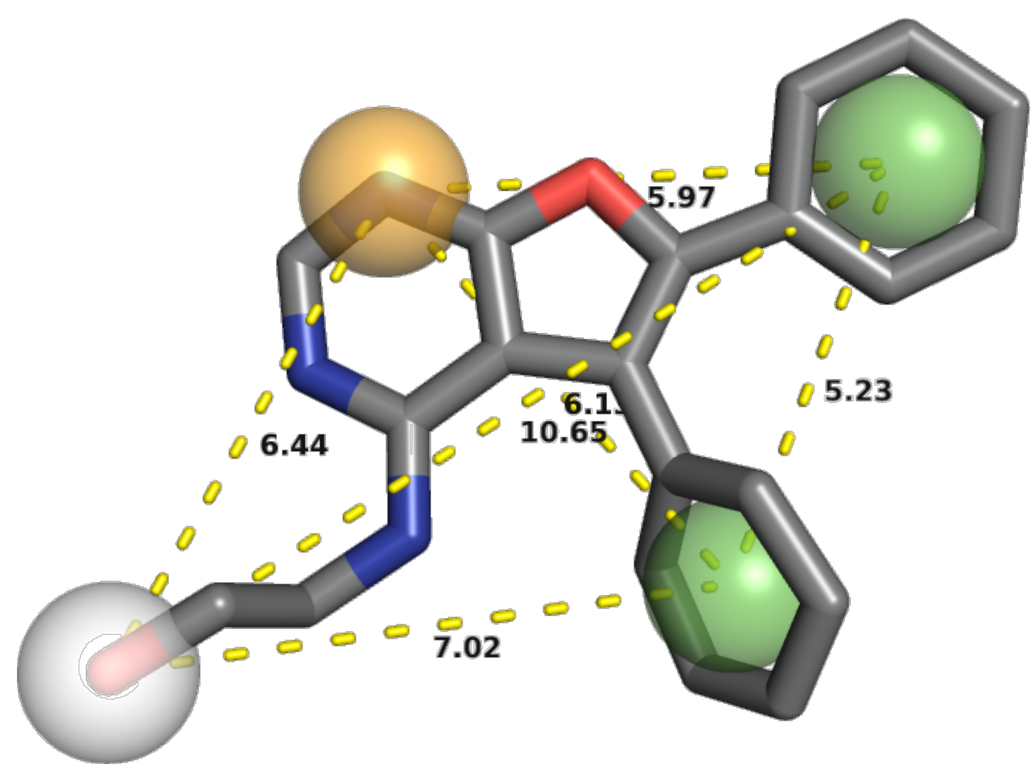

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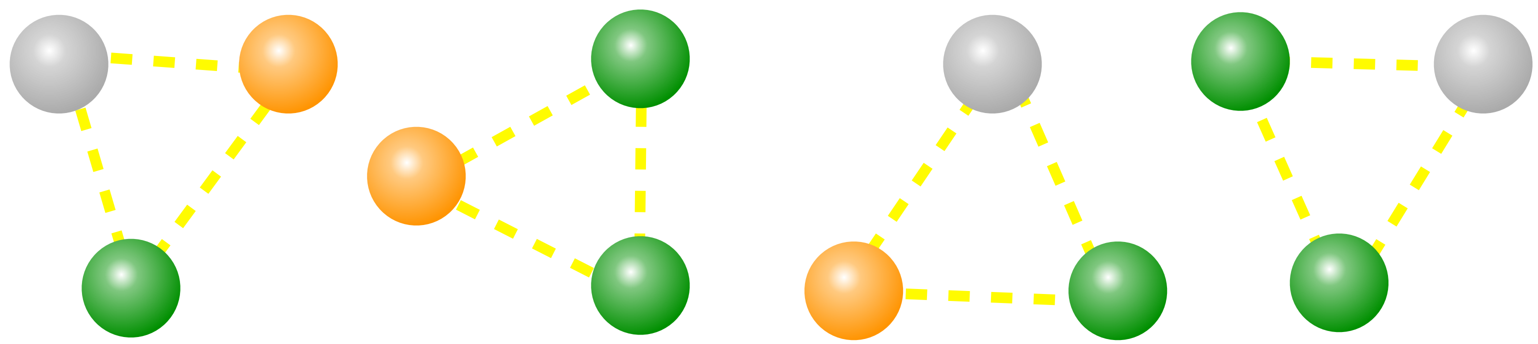

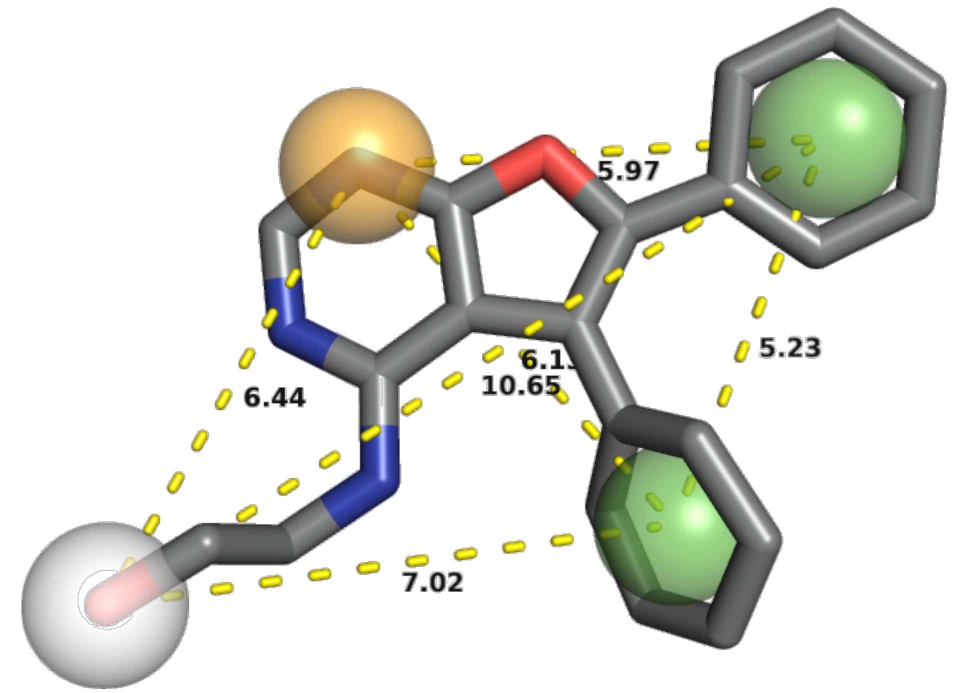

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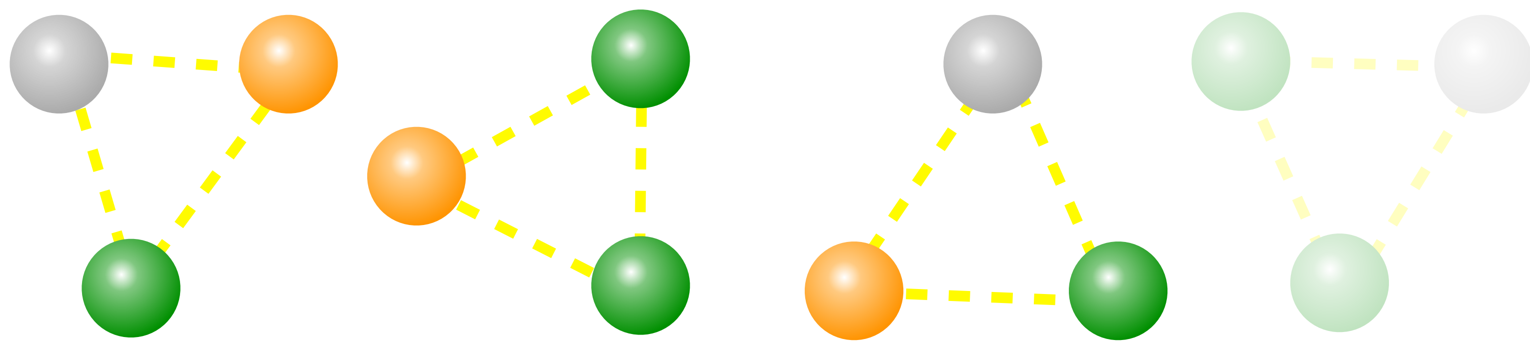
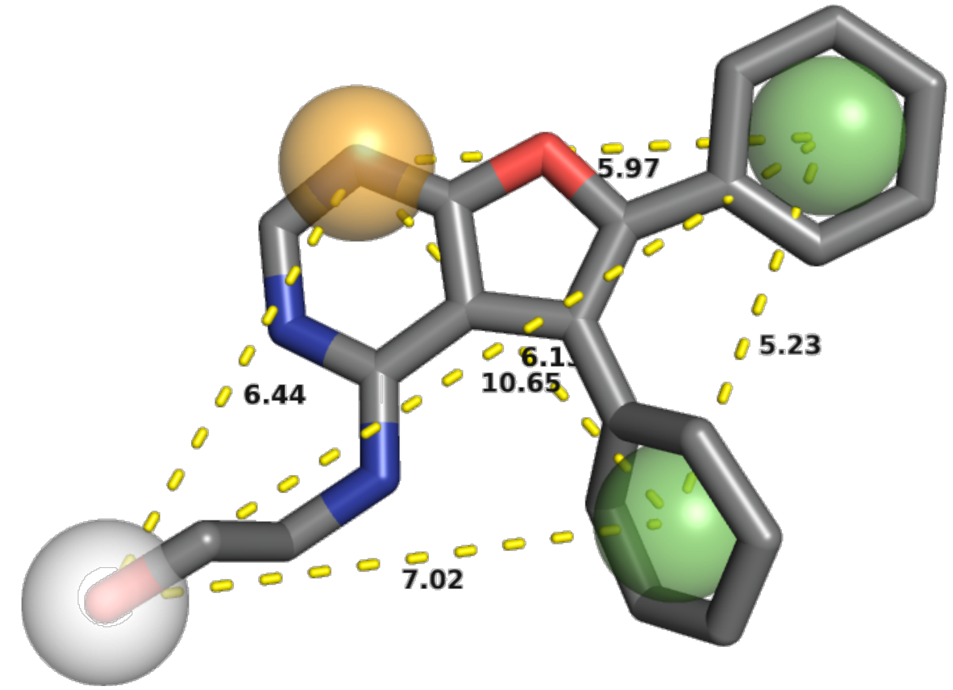
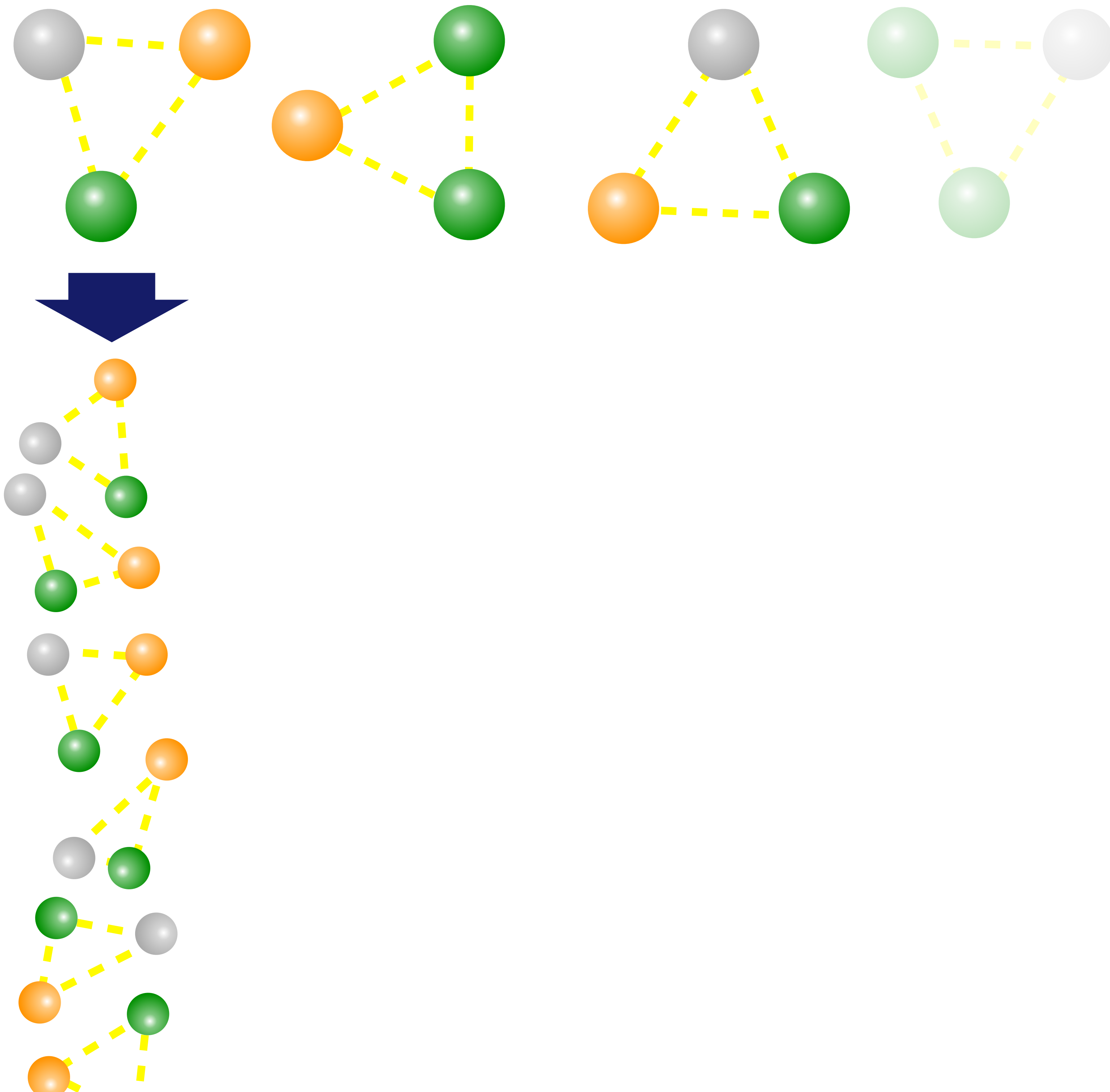
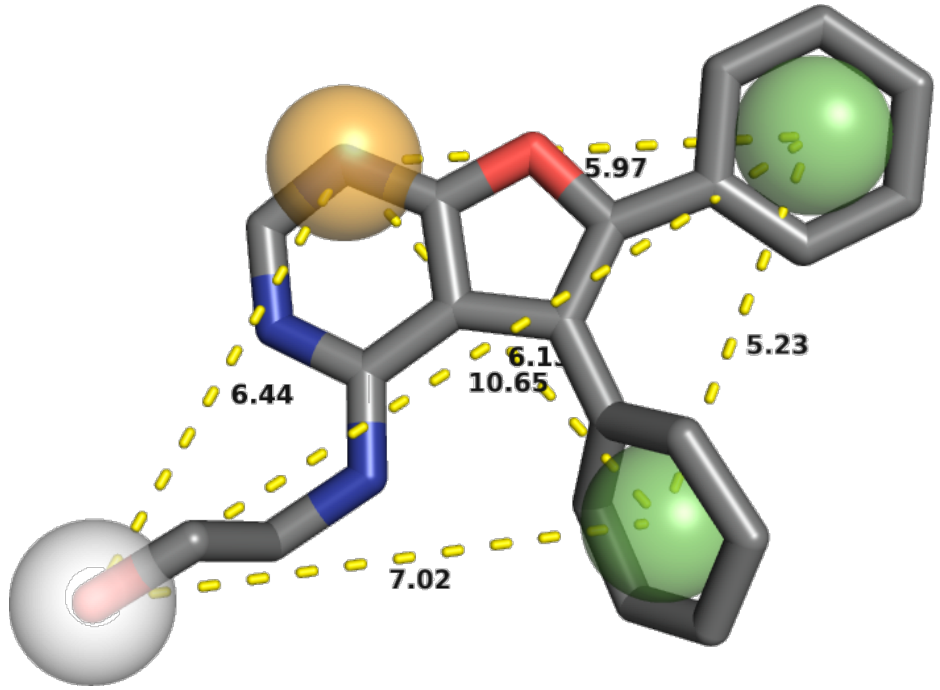




Pharmer

Efficient and Exact Pharmacophore Search





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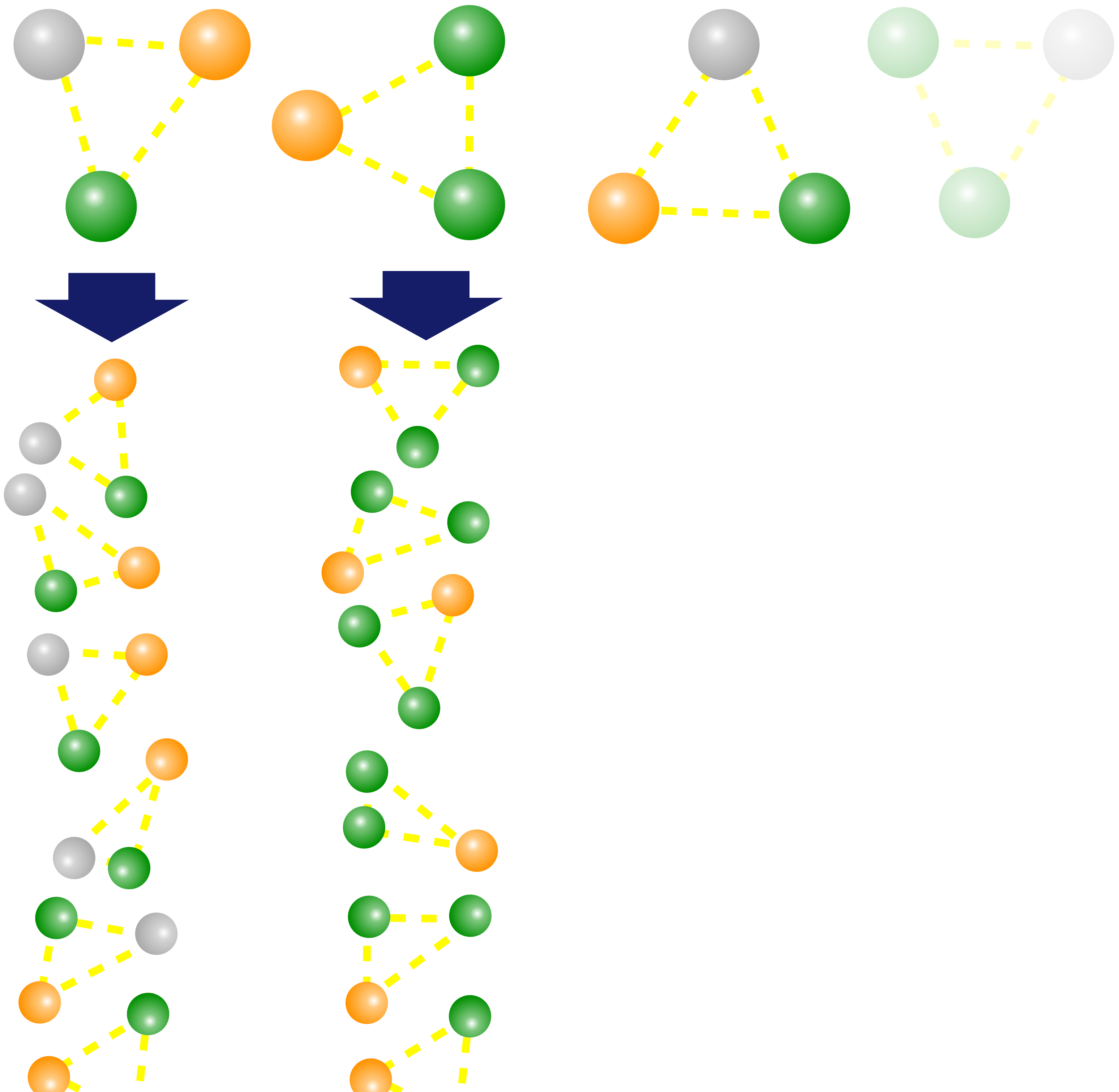

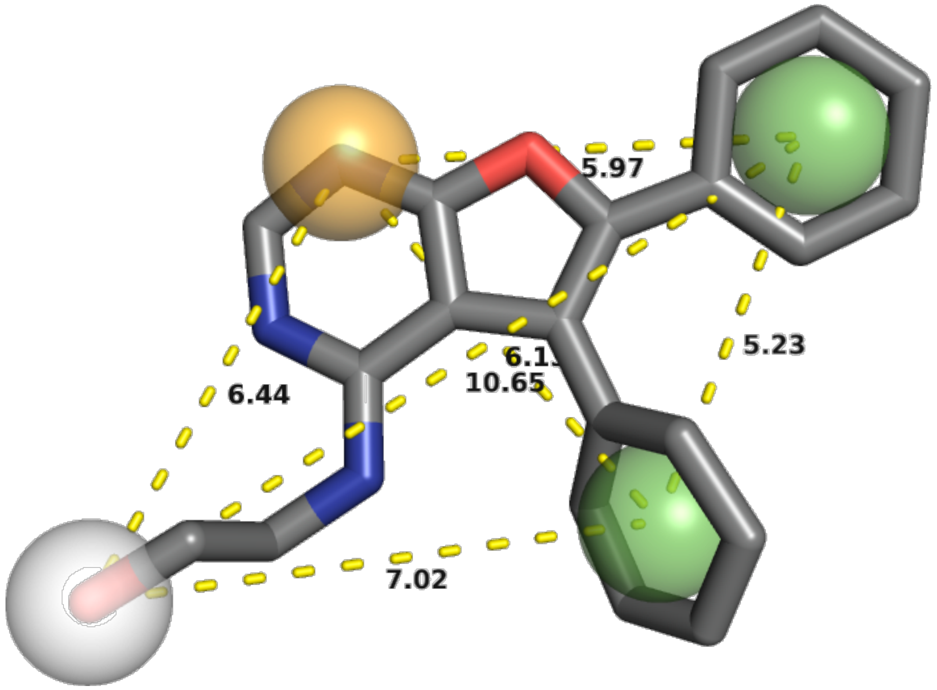

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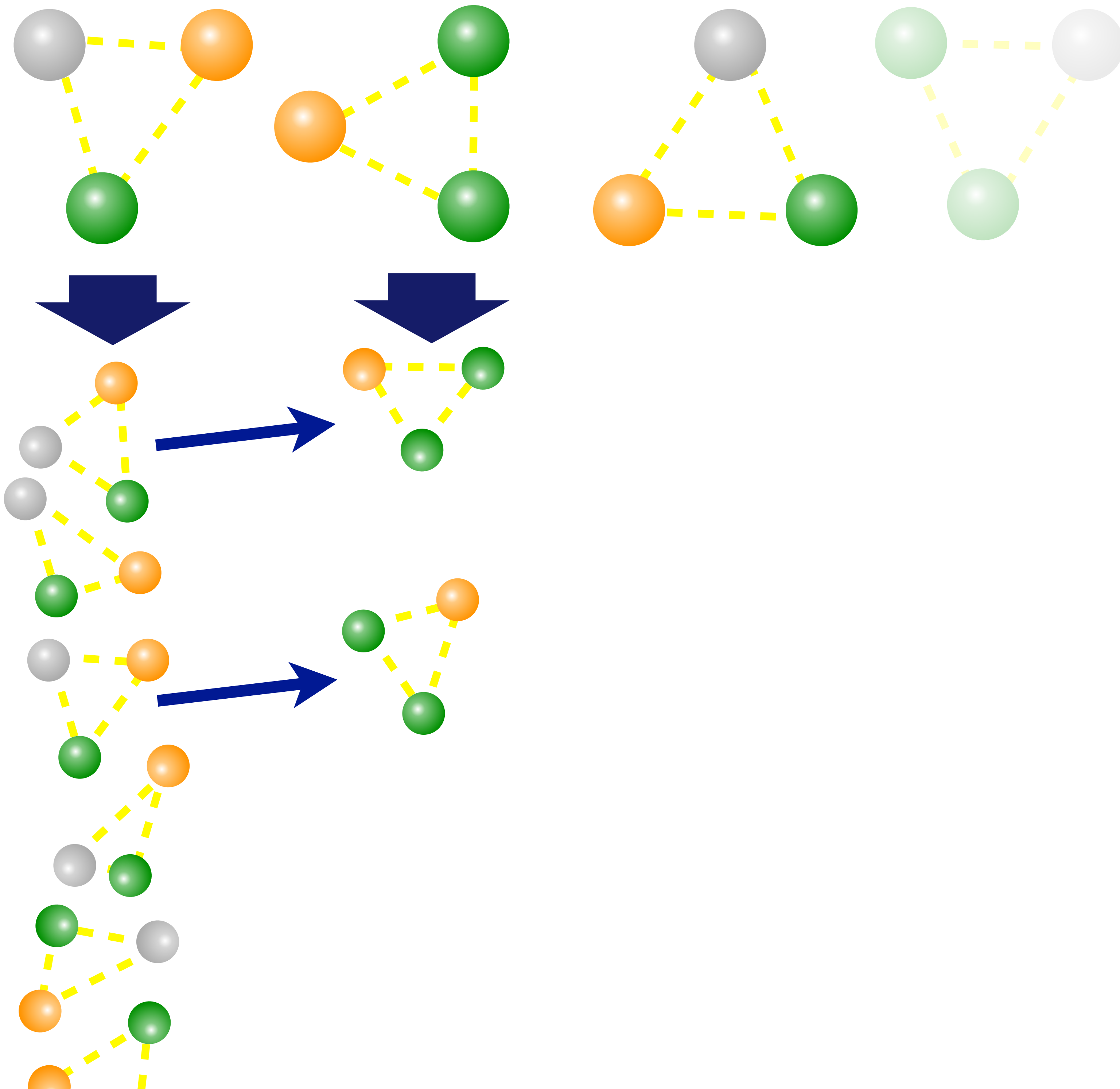
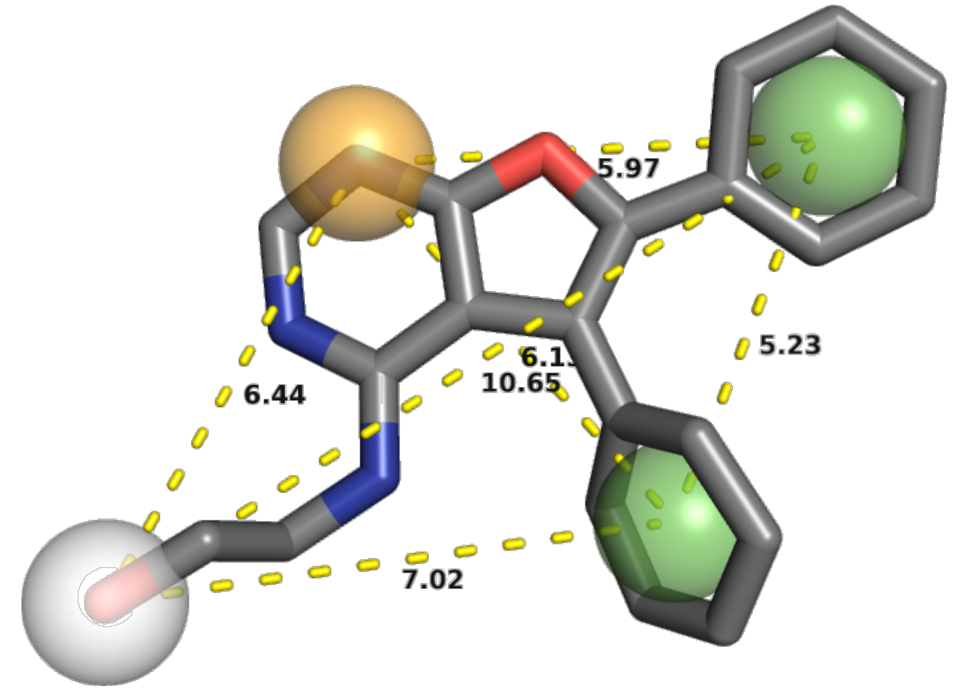
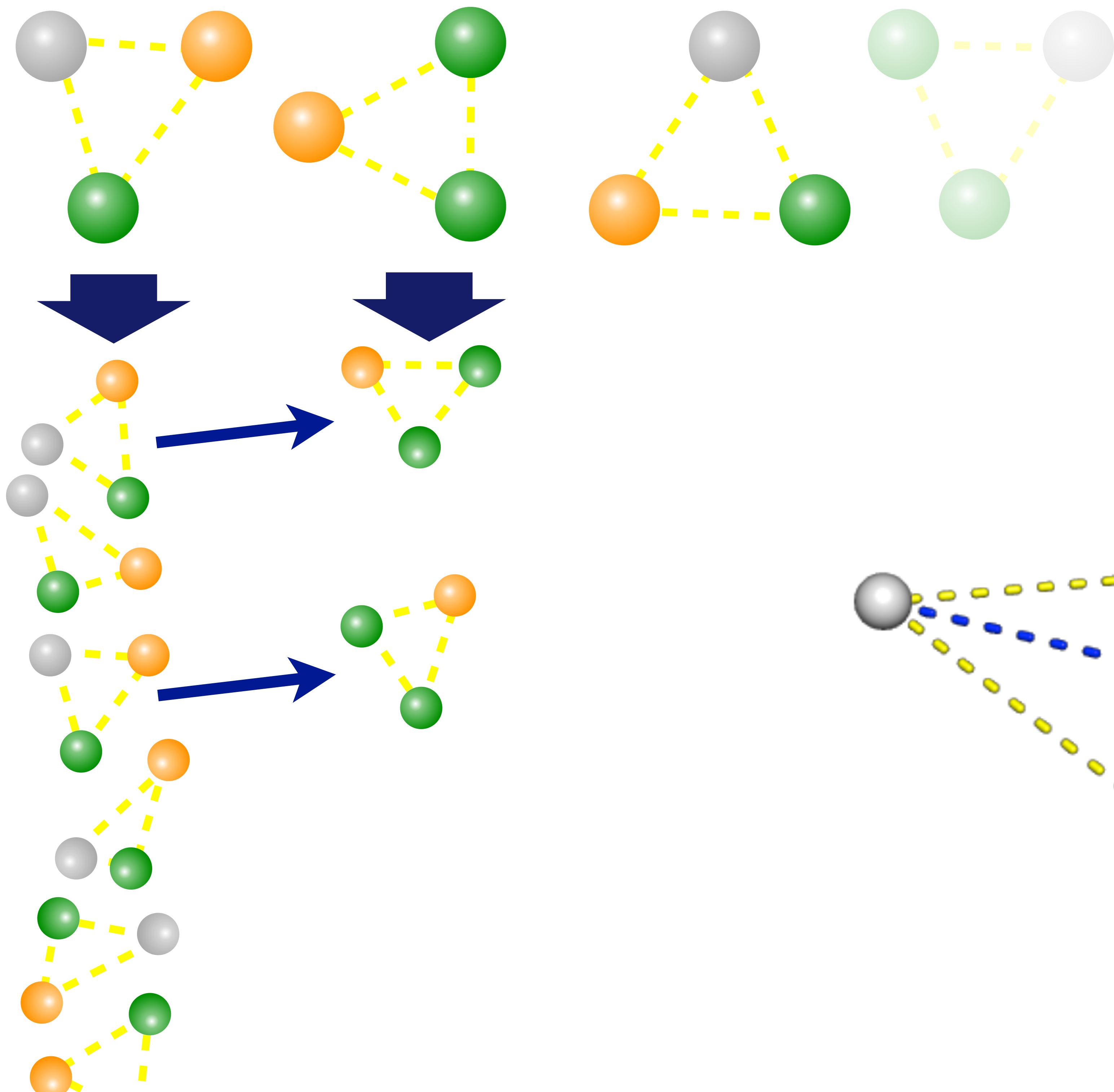
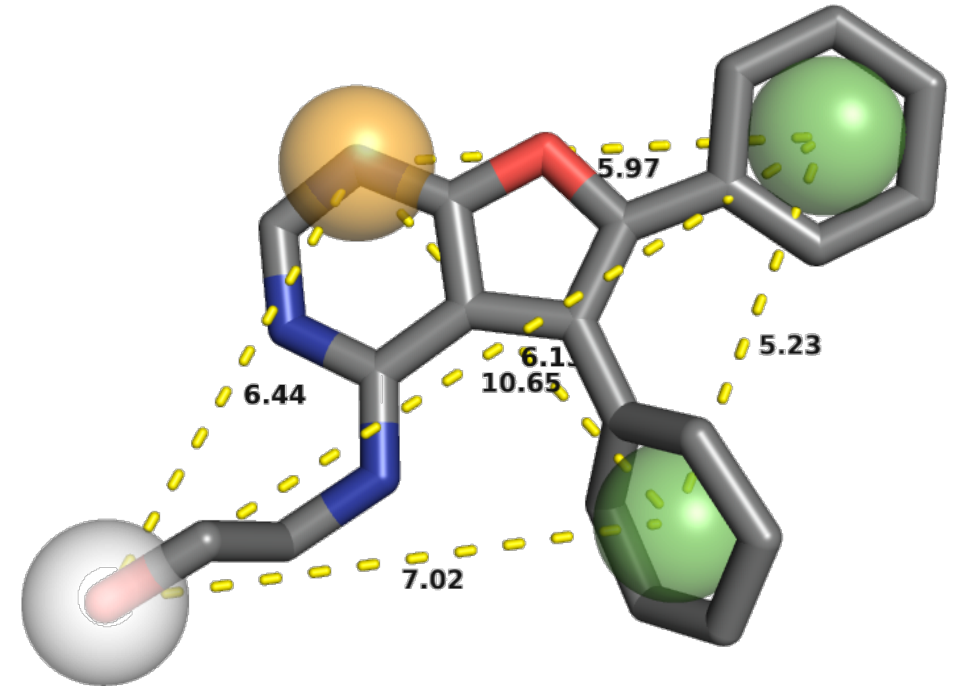
Efficient and Exact Pharmacophore Search

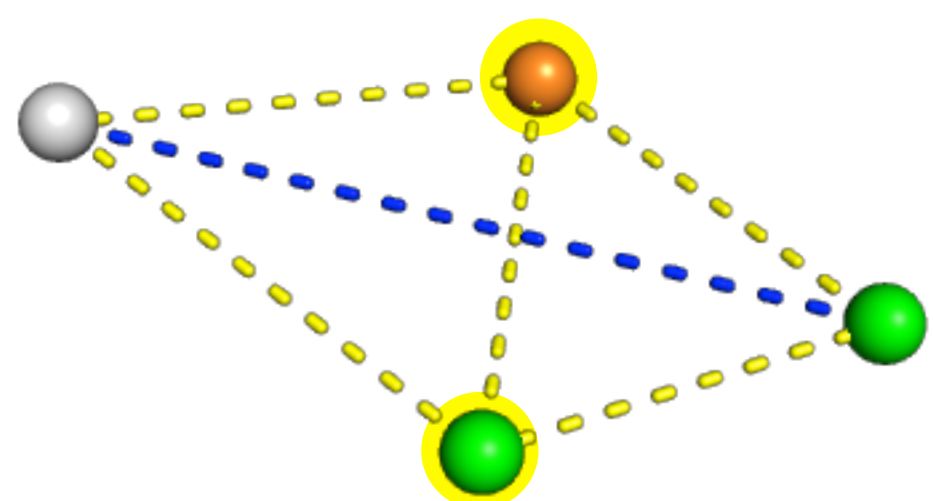




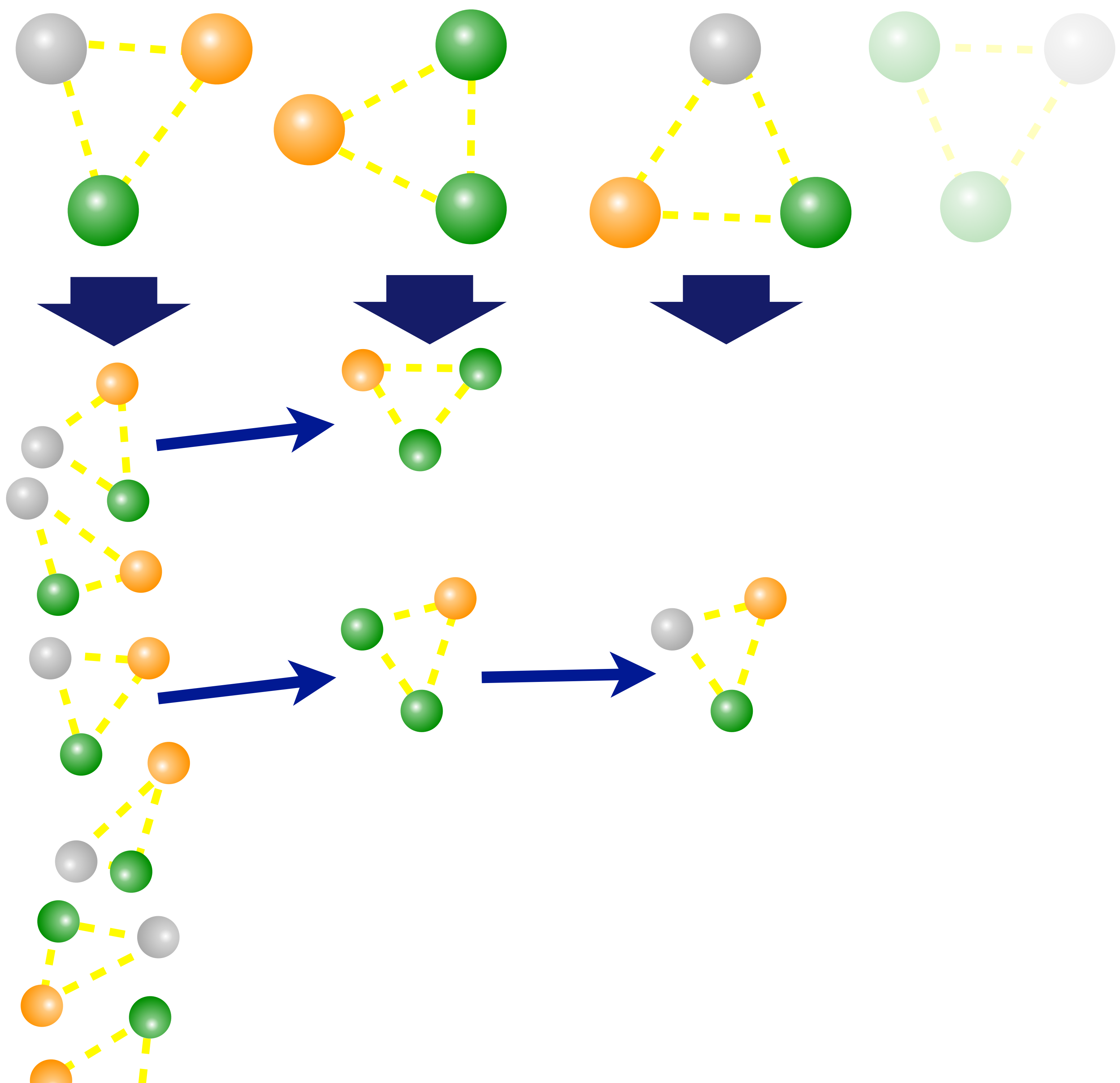
Pharmer Efficient and Exact Pharmacophore Search

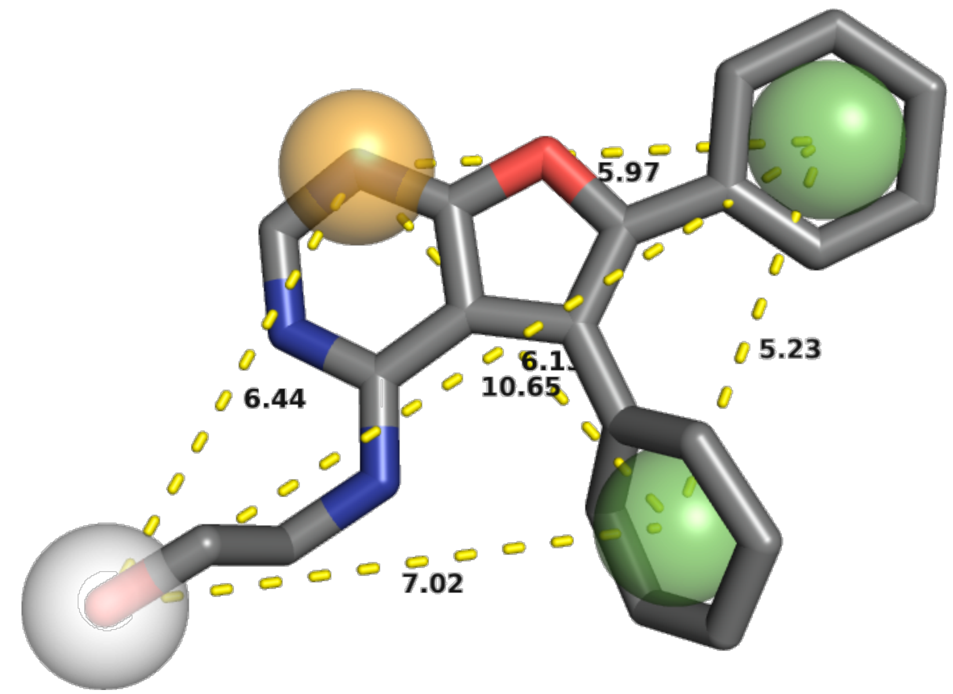






Pharmer Efficient and Exact Pharmacophore Search





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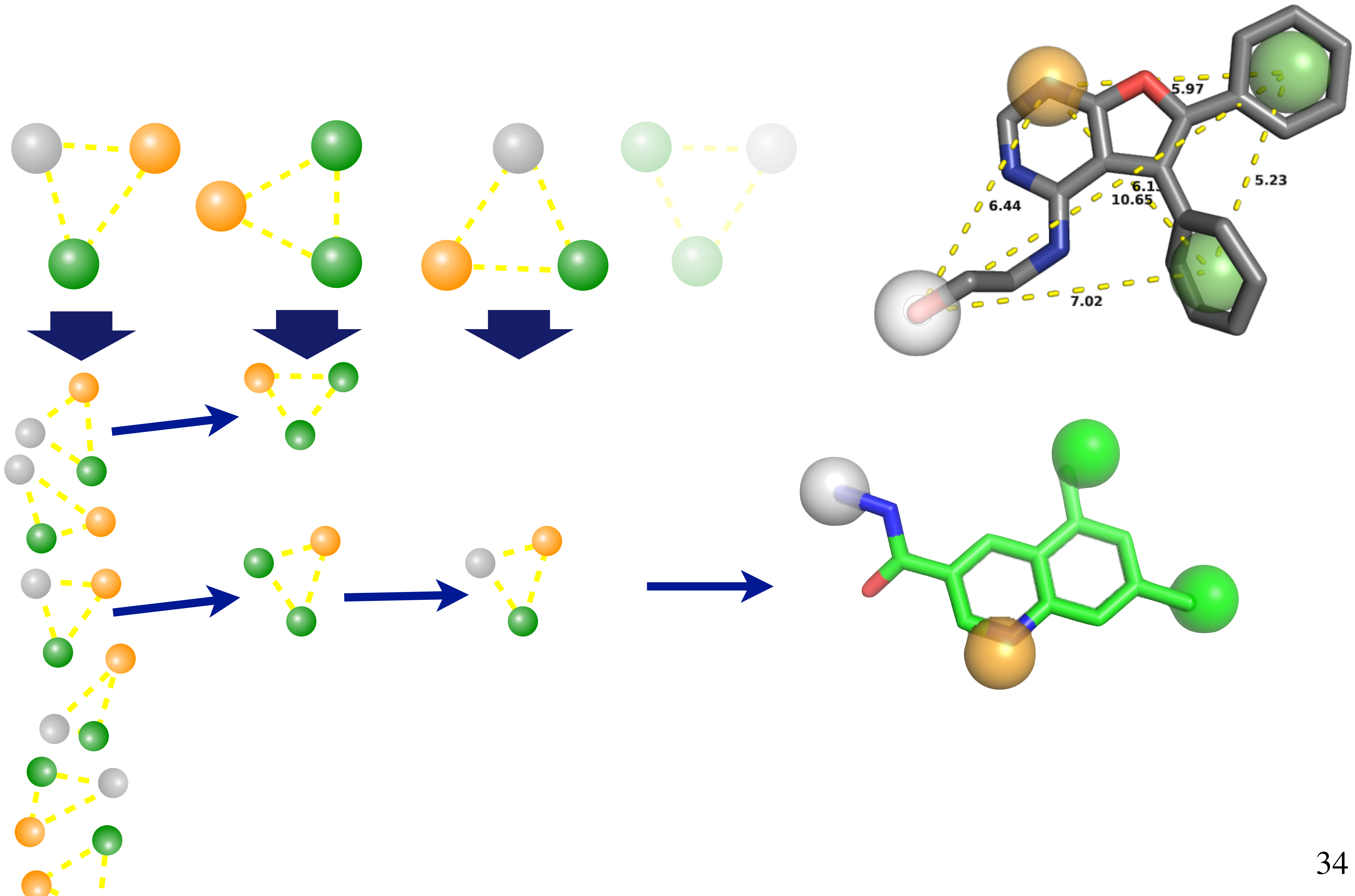

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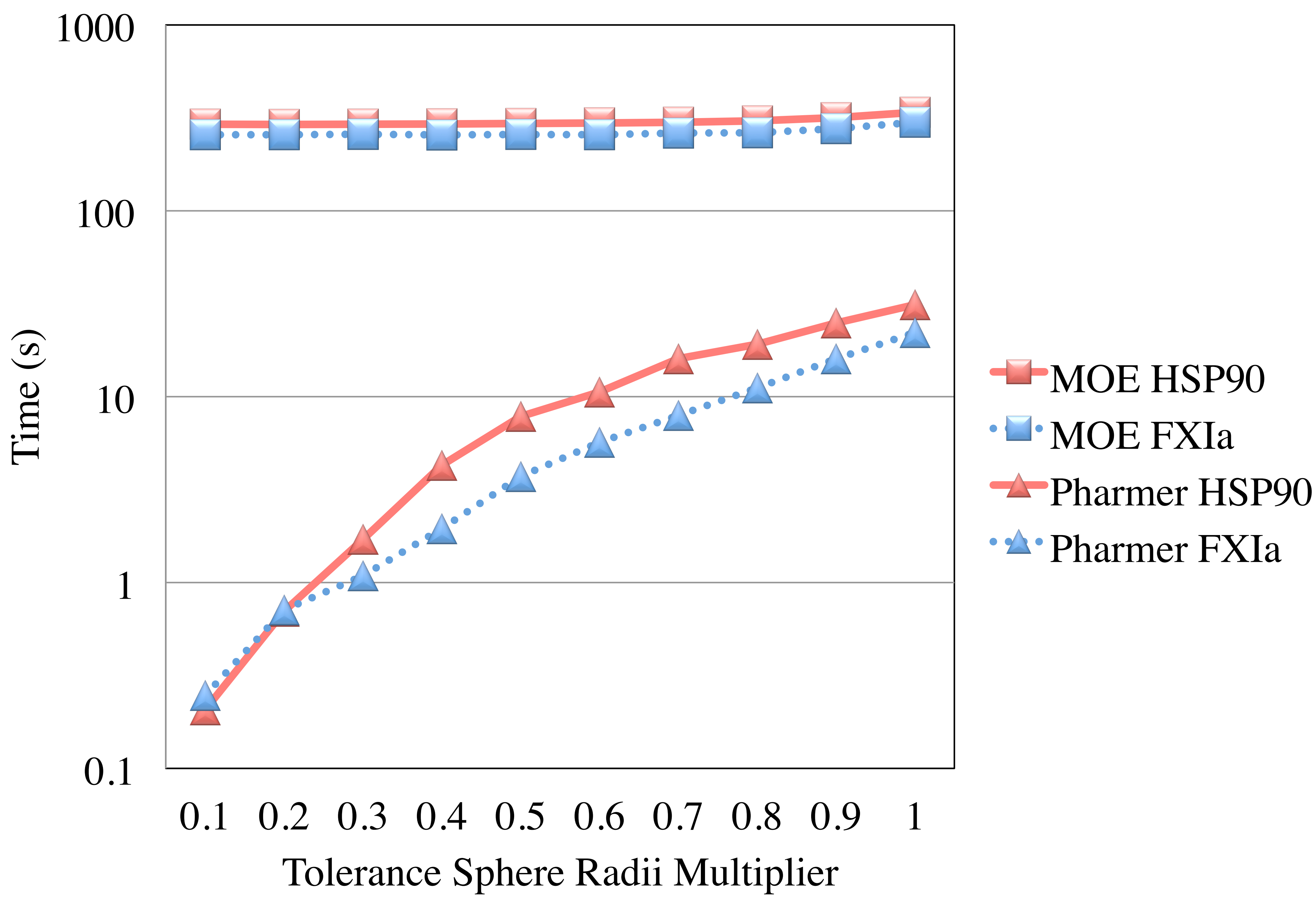
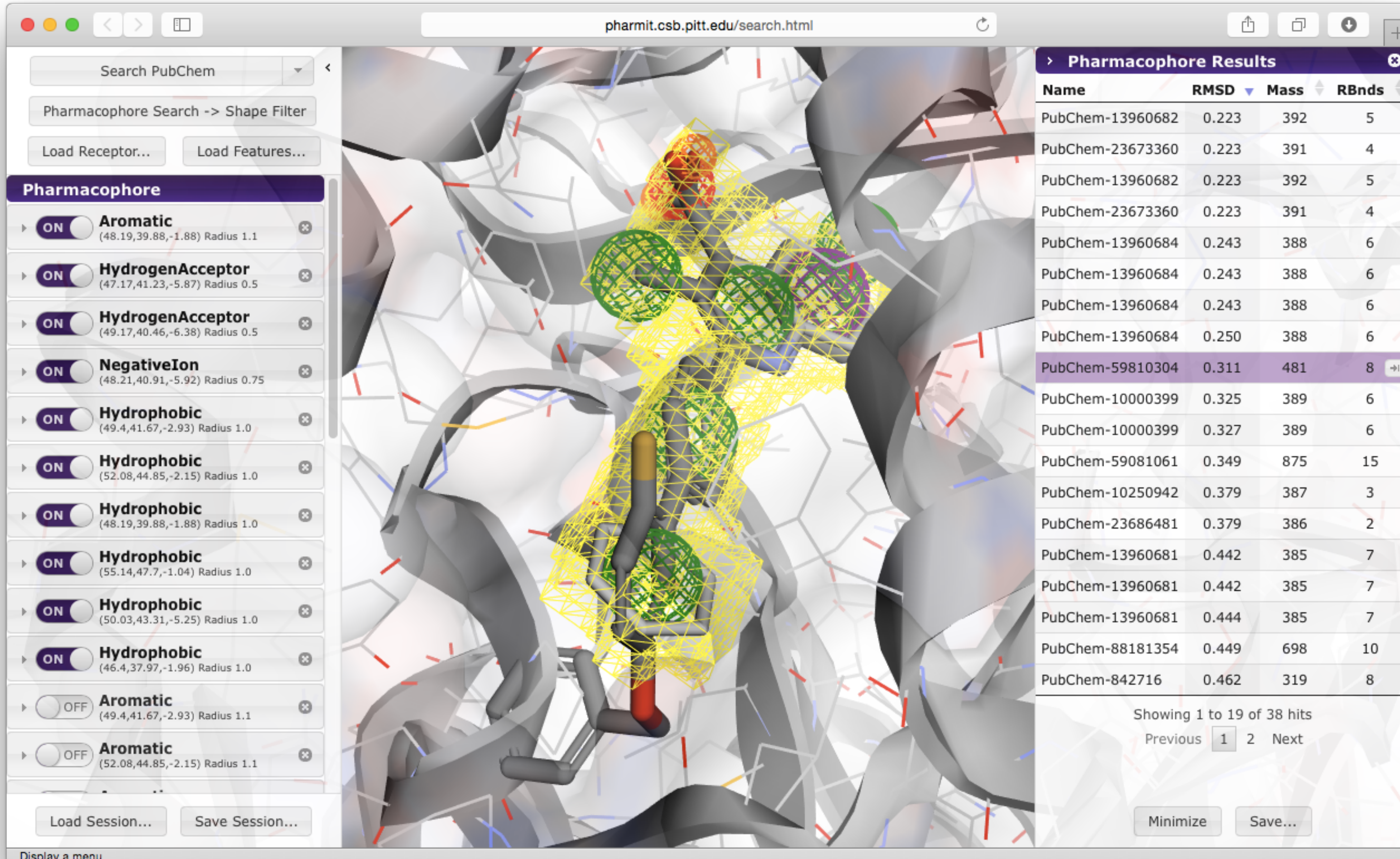
Efficient and Exact Pharmacophore Search





http://pharmit.csb.pitt.edu

Kinds of Virtual Screening

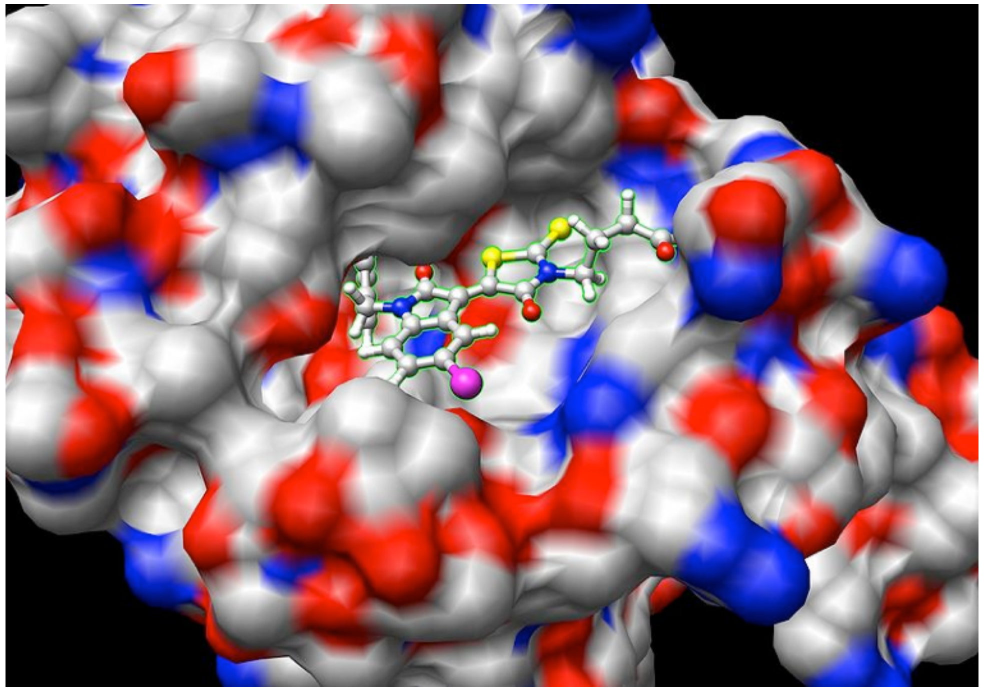
ADMET

Ligand Based

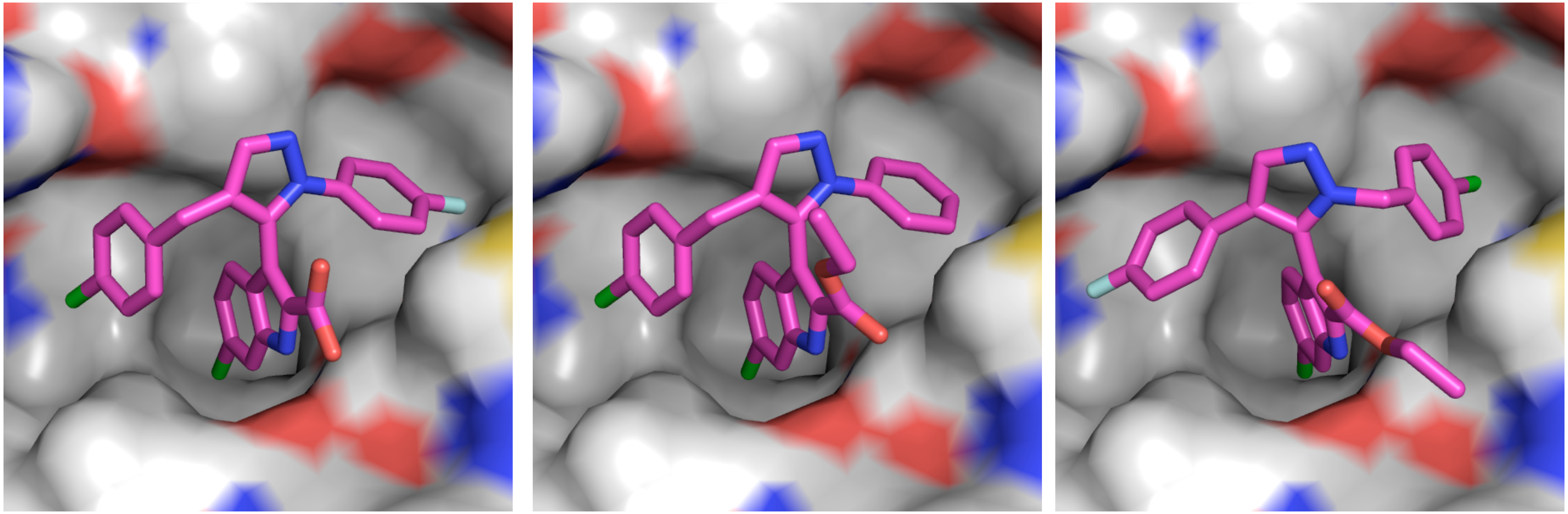
- similarity to known binder
- QSAR
- pharmacophore

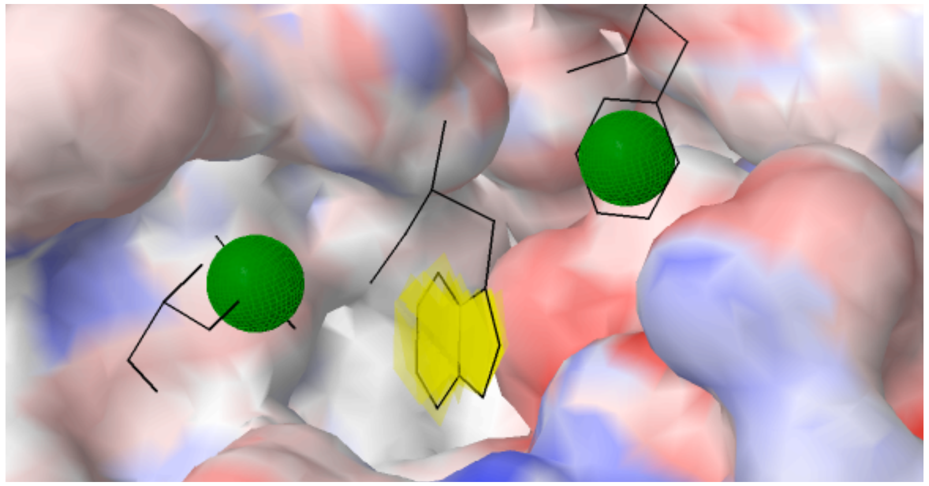
Receptor Based

- **dock and score**

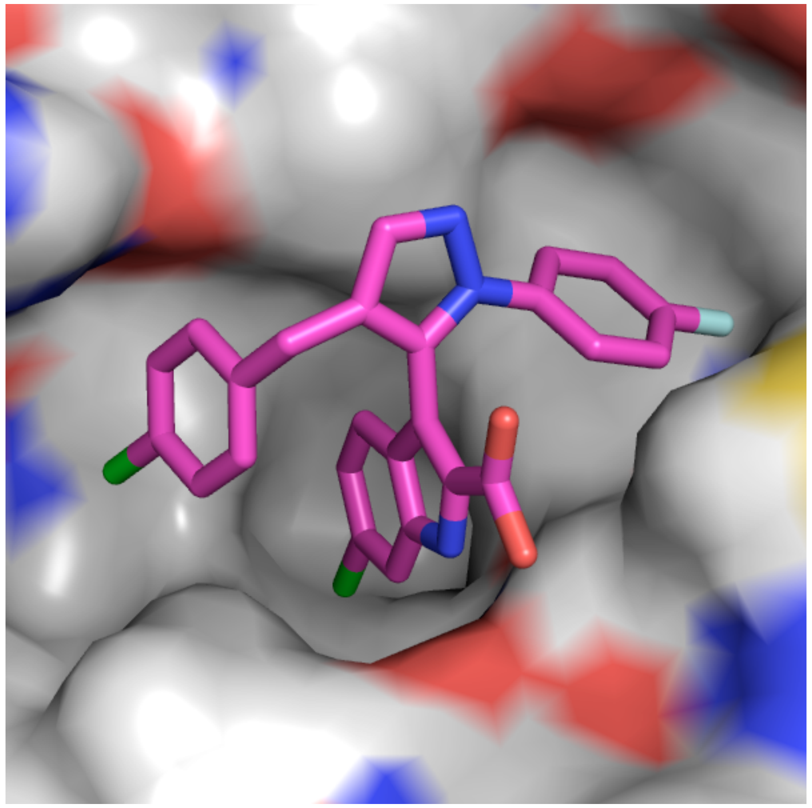


Pharmacophores Aren't Enough

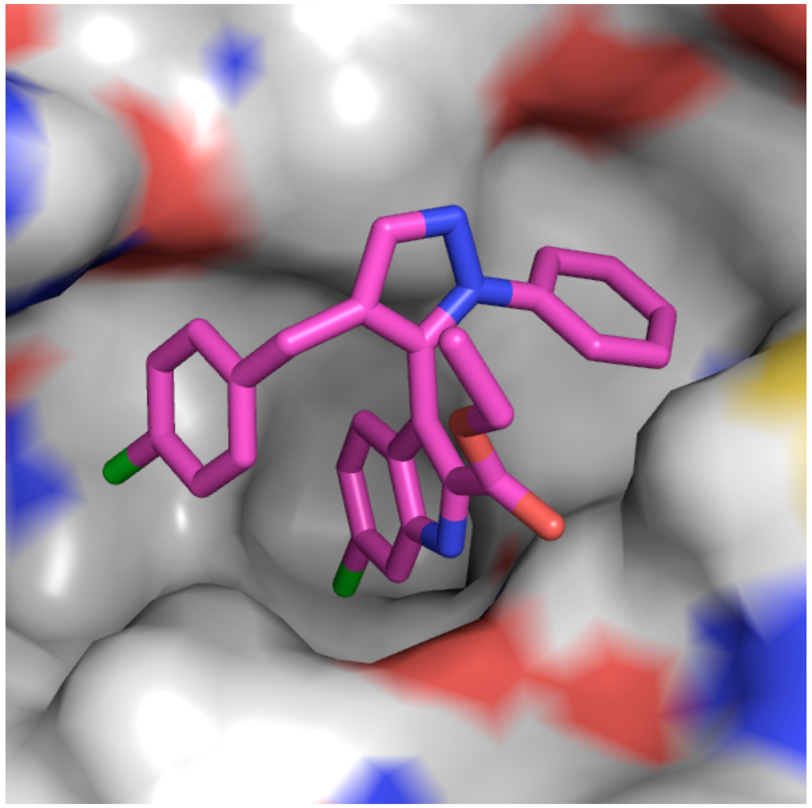




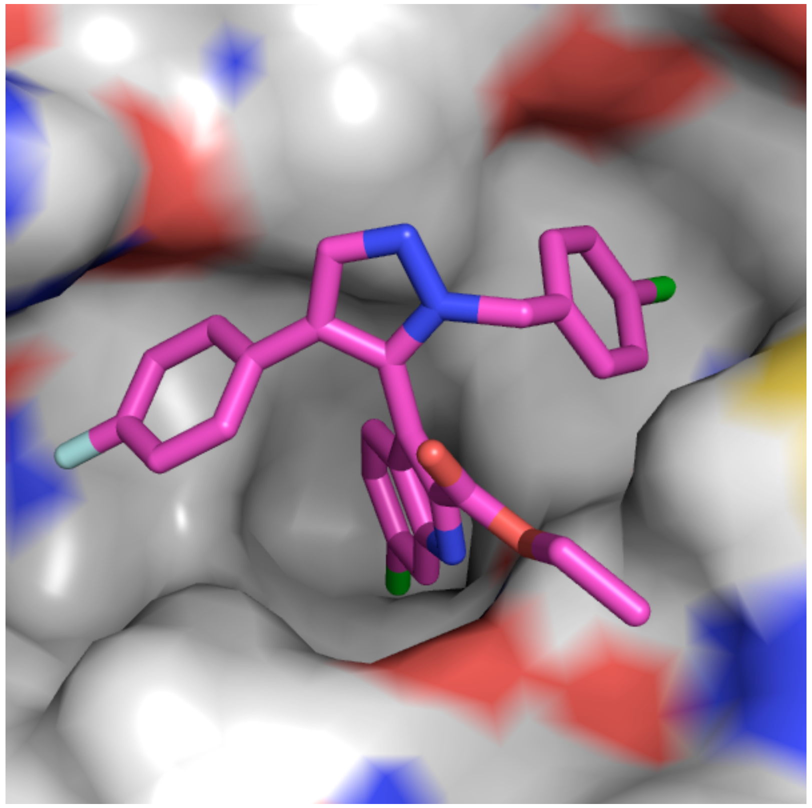
Pharmacophores Aren't Enough



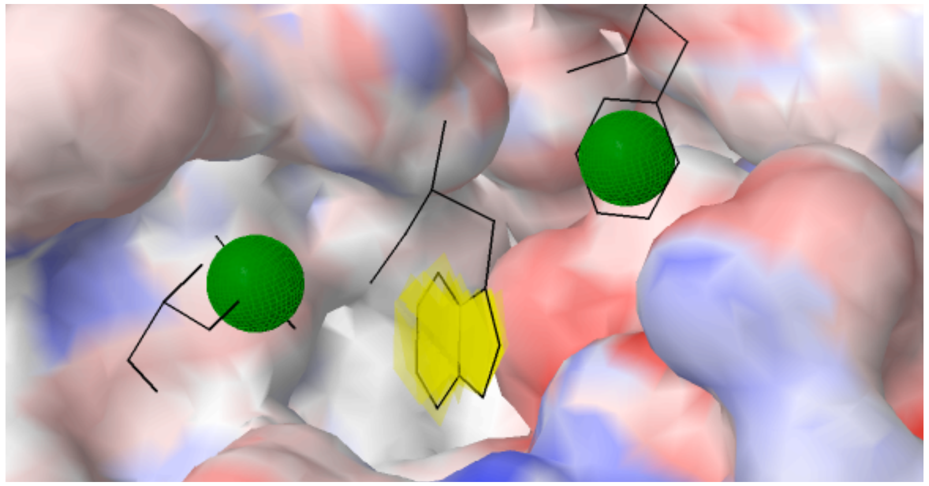
.2µM



50µM



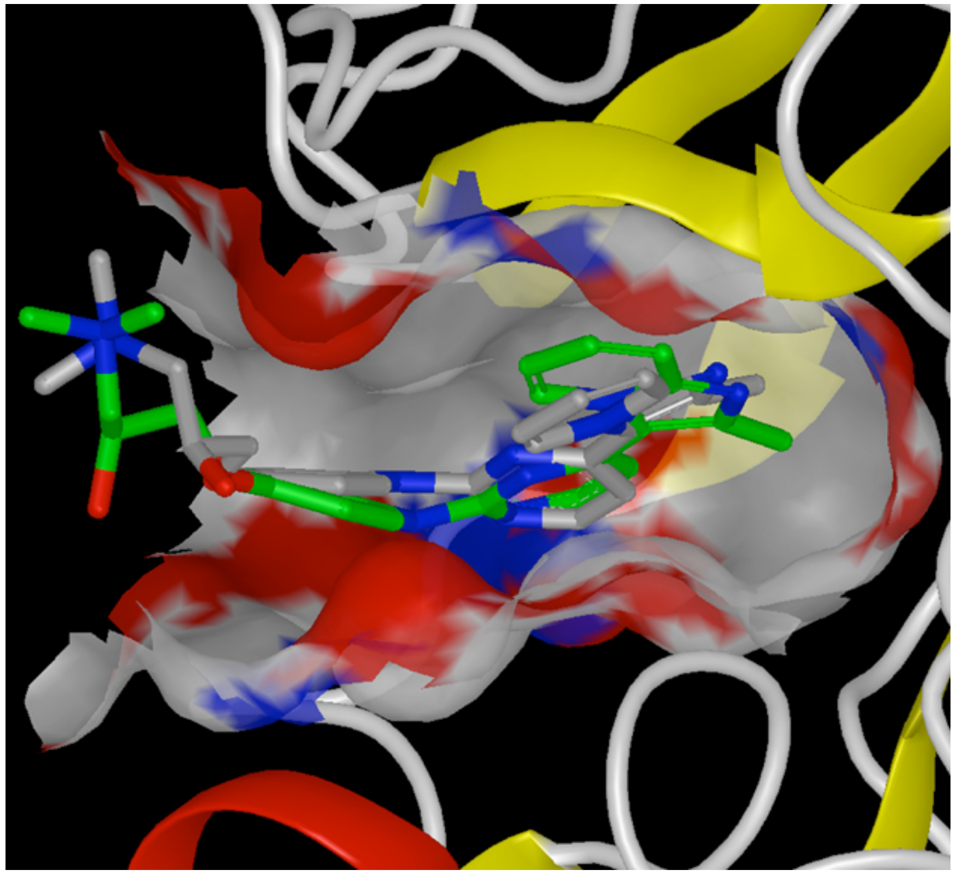
n.i.



Docking

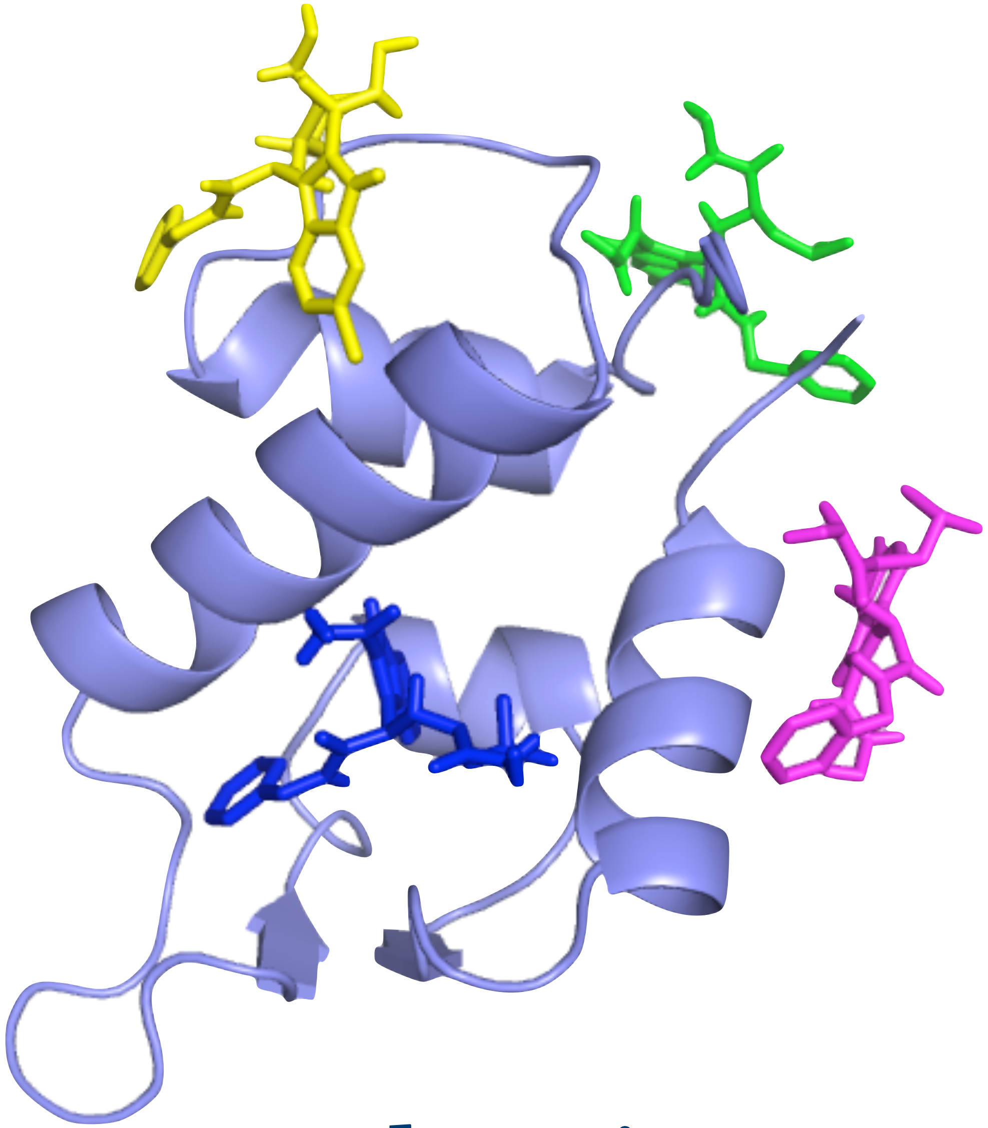
Determine the **conformation** and **pose** of a ligand at a docking site

Challenge is to find conformation and pose with the best **score**



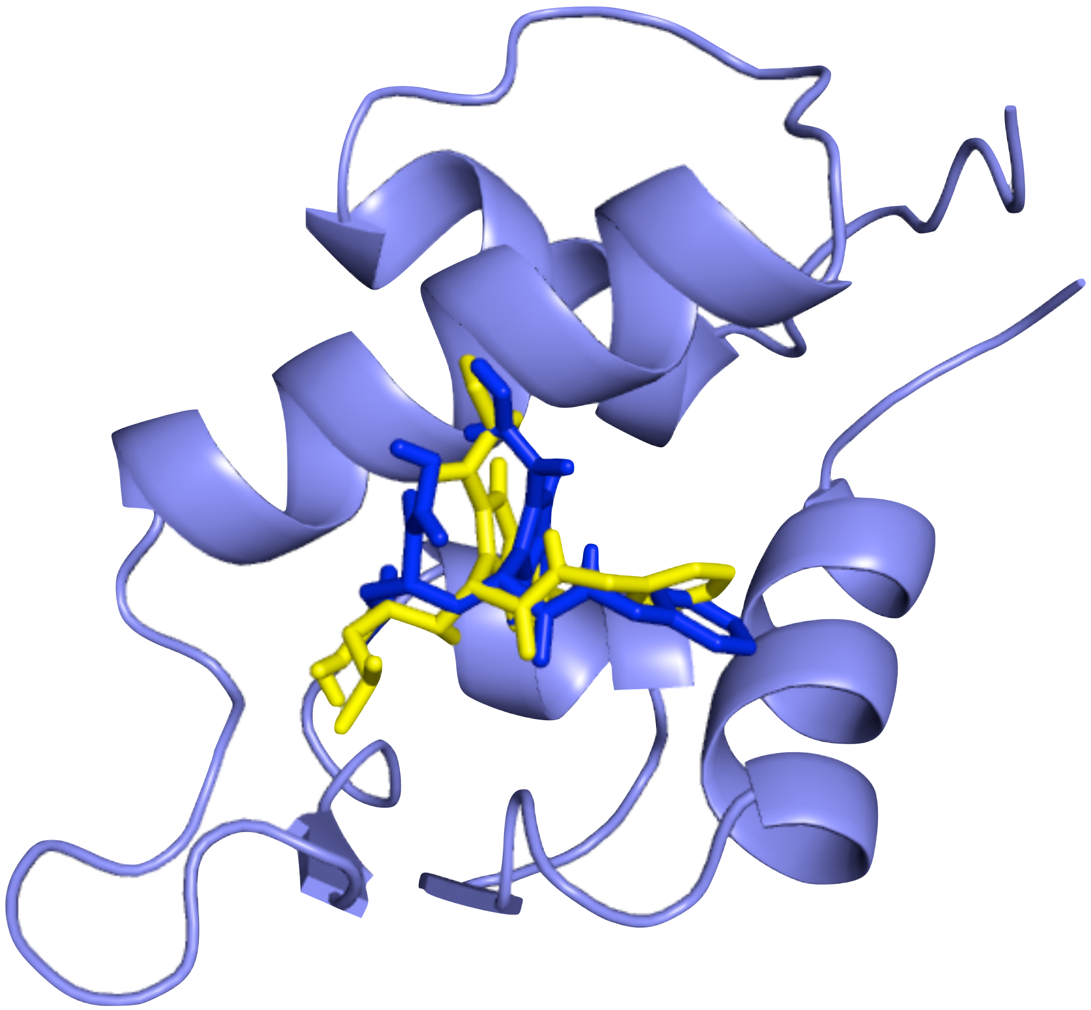
Two Phase Docking

1. Global Pose Estimation



Stochastic

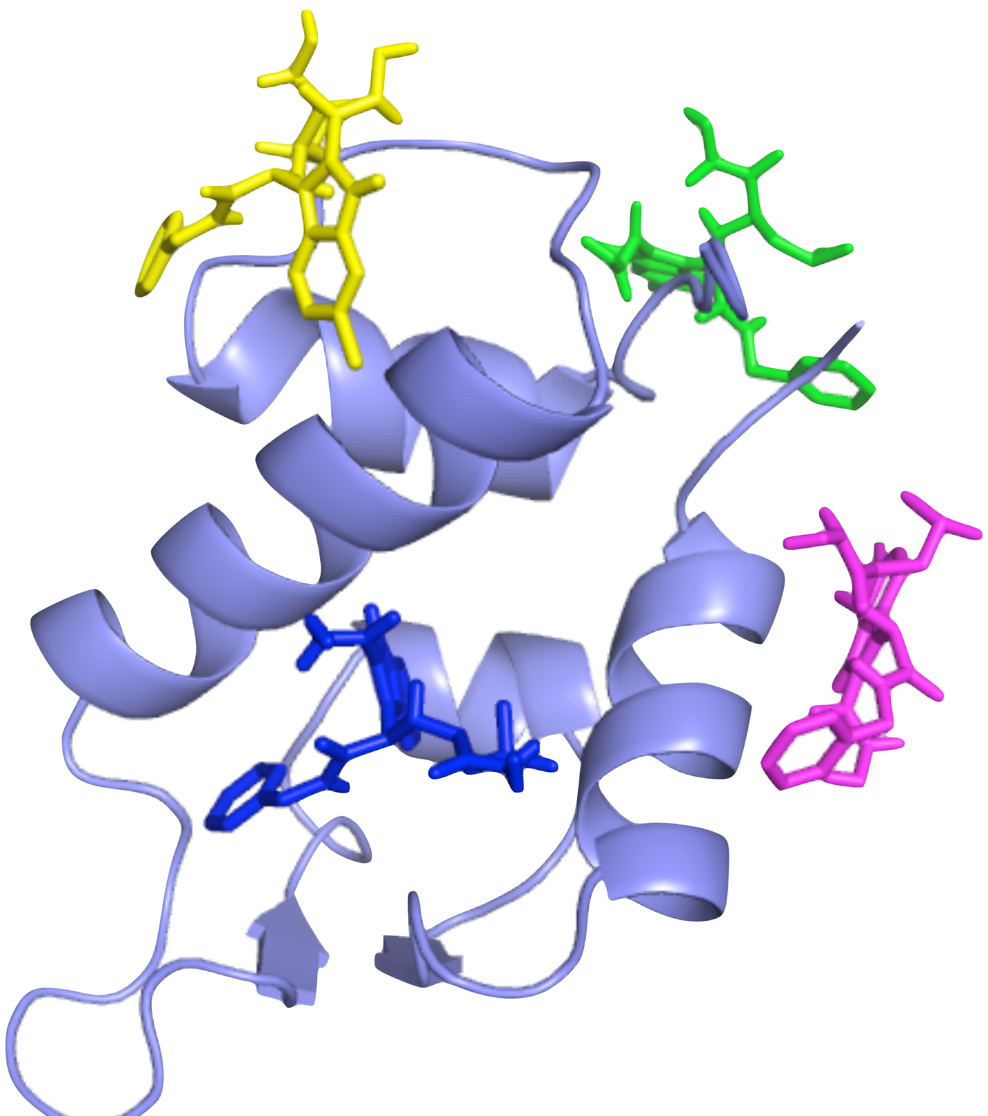
2. Local Refinement



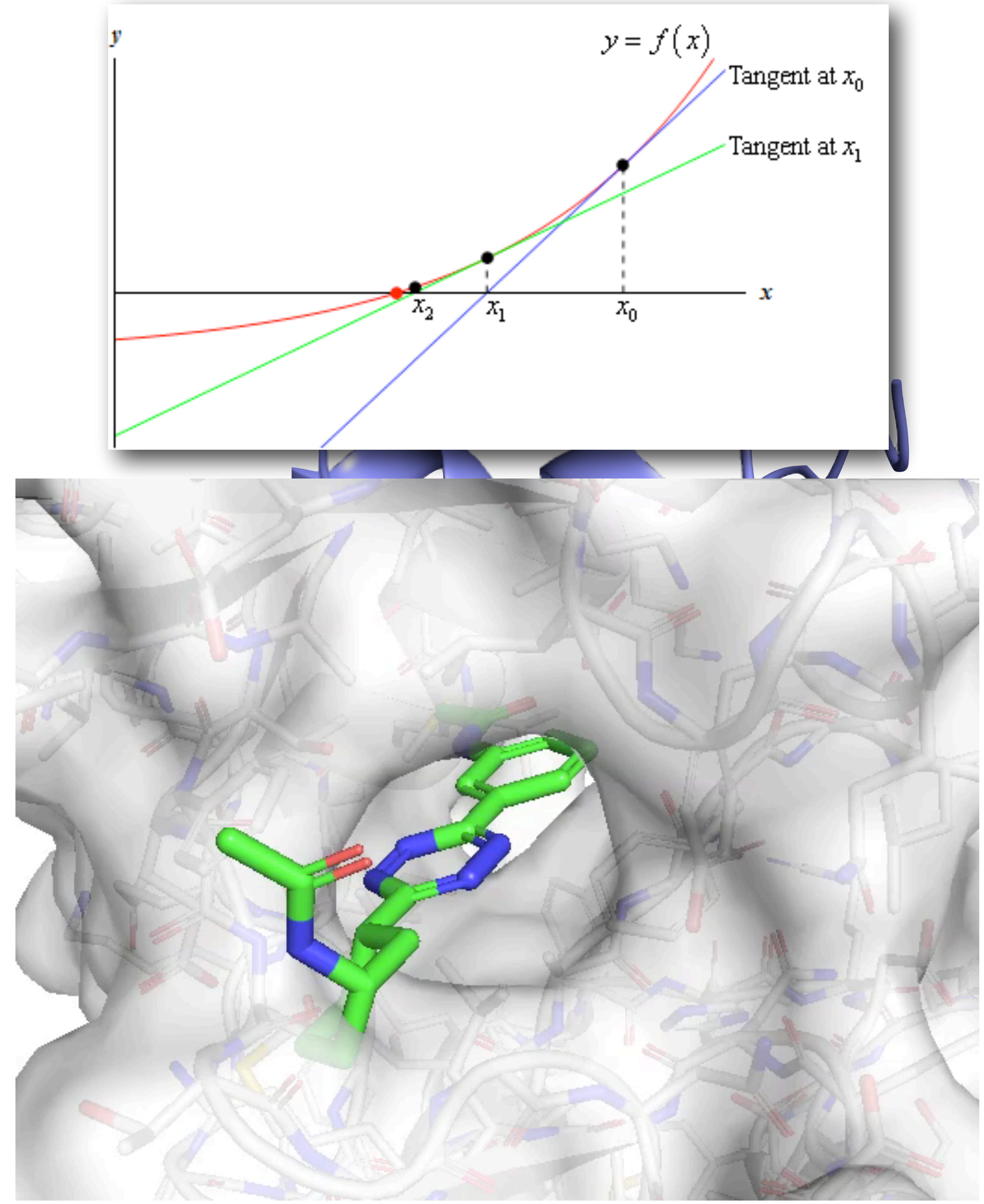
Minimization

Two Phase Docking

1. Global Pose Estimation



Stochastic



Minimization

Scoring Goals

Affinity Prediction

-how well does it bind?

Inactive/Active Discrimination

-does it bind?

Pose Prediction

-how does it bind?

Scoring Goals

Affinity Prediction

-how well does it bind?

Inactive/Active Discrimination

-does it bind?

Pose Prediction

-how does it bind?

Speed

Scoring Goals

Affinity Prediction

-how well does it bind?

Inactive/Active Discrimination

-does it bind?

Pose Prediction

-how does it bind?

Speed

Approximations:
Rigid or semi-rigid receptor
Implicit water model

Scoring Types

Force-field based

- inter- and intra- molecular forces
- van der Waals, electrostatic, torsional

Empirical

- parameterized function is fit to binding energy data

Knowledge based

- scoring function based on known structure, not physical principles

Consensus

Force Field Scoring

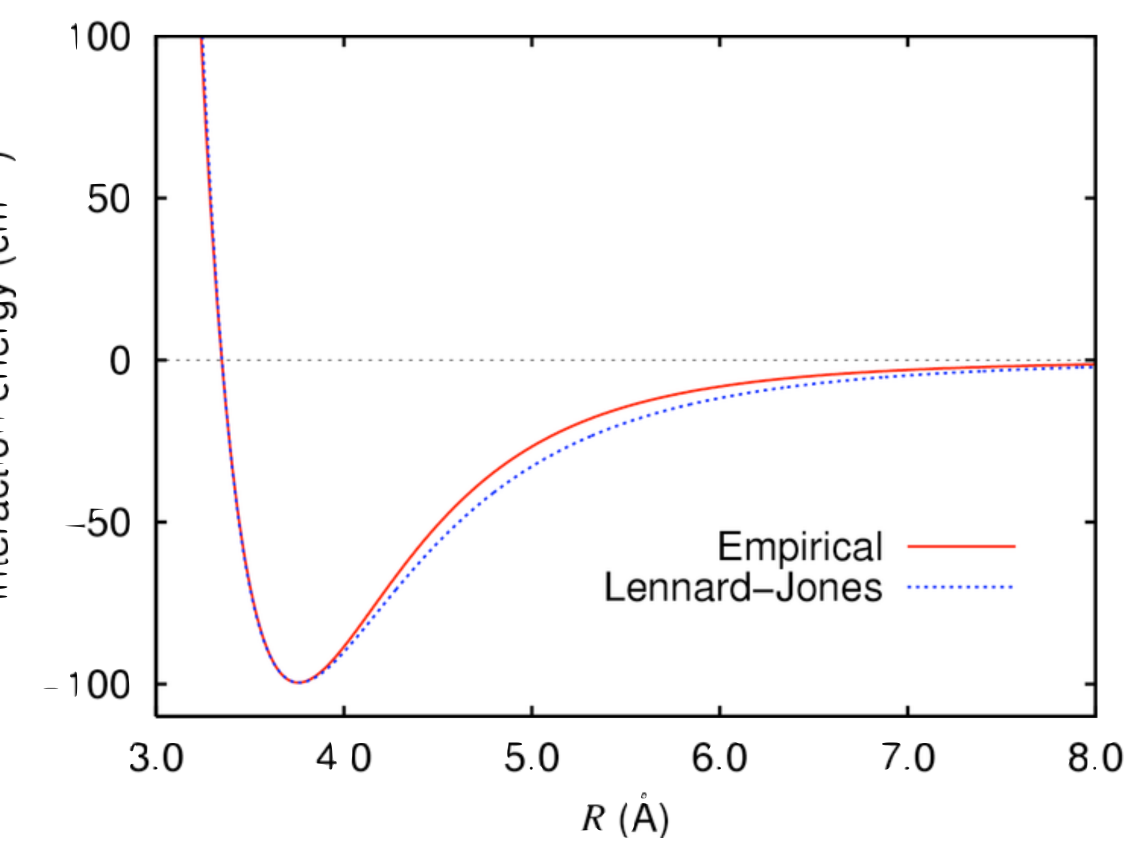
	Protein–ligand	Internal ligand
G-Score	$E_{vdW} + E_{H-bond} = \sum_{prot}\sum_{lig}\left[\left(\frac{A_{ij}}{d_{ij}^{8}} - \frac{B_{ij}}{d_{ij}^{4}}\right) + (E_{da} + E_{ww}) - (E_{dw} + E_{aw})\right]$	$E_{vdw} + E_{torsion} = \sum_{lig}\left(\frac{C_{ij}}{d_{ij}^{12}} - \frac{D_{ij}}{d_{ij}^{6}}\right) + \sum_{lig}\frac{1}{2}V\left[1 + \frac{n}{\lvert n\rvert}\cos(\lvert n\rvert\omega)\right]$
D-Score	$E_{vdW} + E_{electrostatic} = \sum_{prot}\sum_{lig}\left[\left(\frac{A_{ij}}{d_{ij}^{12}} + \frac{B_{ij}}{d_{ij}^{6}}\right) + 332.0\frac{q_i q_j}{\in(d_{ij})d_{ij}}\right]$	
Gold	$E_{vdW} + E_{electrostatic} = \sum_{prot}\sum_{lig}\left[\left(\frac{A_{ij}}{d_{ij}^{a}} + \frac{B_{ij}}{d_{ij}^{b}}\right) + 332.0\frac{q_i q_j}{\in(d_{ij})d_{ij}}\right]$	$E_{vdW} + E_{electrostatic} = \sum_{lig}\left[\left(\frac{A_{ij}}{d_{ij}^{a}} + \frac{B_{ij}}{d_{ij}^{b}}\right) + 332.0\frac{q_i q_j}{\in(d_{ij})d_{ij}}\right]$ $+ \text{optional } E_{H-bond}$
AutoDock	$E_{vdW} + E_{H-bond} + E_{electrostatic} = \sum_{prot}\sum_{lig}\left[\left(\frac{A_{ij}}{d_{ij}^{12}} - \frac{B_{ij}}{d_{ij}^{6}}\right) + E(t)\times\left(\frac{C_{ij}}{d_{ij}^{12}} - \frac{D_{ij}}{d_{ij}^{10}}\right) + 332.0\frac{q_i q_j}{\in(d_{ij})d_{ij}}\right]$ $E(t) = \text{angular weight factor}$	$E_{vdW} + E_{H-bond} + E_{electrostatic} = \sum_{lig}\left[\left(\frac{A_{ij}}{d_{ij}^{12}} - \frac{B_{ij}}{d_{ij}^{6}}\right) + E(t)\left(\frac{C_{ij}}{d_{ij}^{12}} - \frac{D_{ij}}{d_{ij}^{10}}\right) + 332.0\frac{q_i q_j}{4(d_{ij})d_{ij}}\right]$ $E(t) = \text{angular weight factor}$
DOCK (v4.0)	$E_{vdW} + E_{electrostatic} = \sum_{prot}\sum_{lig}\left[\left(\frac{A_{ij}}{d_{ij}^{a}} + \frac{B_{ij}}{d_{ij}^{b}}\right) + 332.0\frac{q_i q_j}{\in(d_{ij})d_{ij}}\right]$	

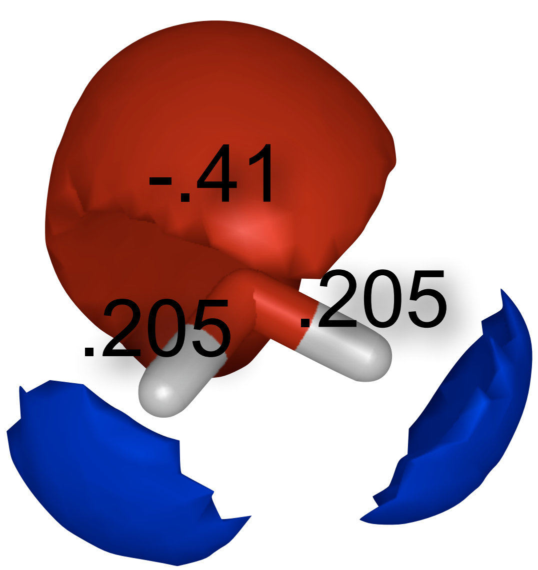
Dock 4.0

Coulomb's Law
q: partial charges
D: dielectrict constant

$$E = \sum_{i=1}^{lig} \sum_{j=1}^{rec} \left(\frac{A_{ij}}{r_{ij}^{a}} - \frac{B_{ij}}{r_{ij}^{b}} + 332 \frac{q_i q_j}{D r_{ij}} \right)$$

van der Waals
a = 12, b = 6
Lennard-Jones potential





Empirical Scoring

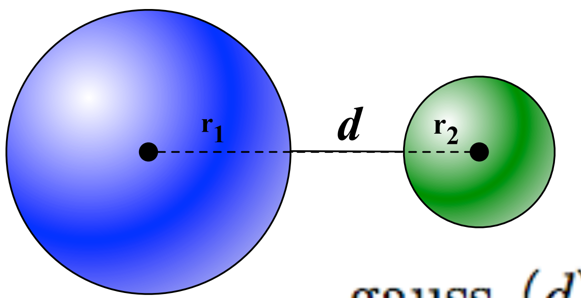
	Functional form
LUDI	$\Delta G_{bind} = \Delta G_{H-bond} \sum_{H-bond} f(\Delta R, \Delta\alpha) + \Delta G_{ionic} \sum_{ionic} f(\Delta R, \Delta\alpha) + \Delta G_{hydrophobic} \sum_{hydrophobic} \lvert A_{hydrophobic} \rvert + \Delta G_{rotor} N_{rotor} + \Delta G_0$ $A_{hydrophobic}$ = molecular surface area
F-Score	$\Delta G_{bind} = \Delta G_{H-bond} \sum_{H-bond} f(\Delta R, \Delta\alpha) + \Delta G_{ionic} \sum_{ionic} f(\Delta R, \Delta\alpha) + \Delta G_{aromatic} \sum_{aromatic} f(\Delta R, \Delta\alpha) + \Delta G_{contact} \sum_{contact} f(\Delta R, \Delta\alpha) + \Delta G_{rotor} N_{rotor} + \Delta G_0$
Chem-Score	$\Delta G_{bind} = \Delta G_{H-bond} \sum_{H-bond} f(\Delta R, \Delta\alpha) + \Delta G_{metal} \sum_{metal} f(\Delta R, \Delta\alpha) + \Delta G_{lipo} \sum_{lipo} f(\Delta R) + \Delta G_{rotor} \sum_{rotor} f(P_{nl}, P'_{nl}) + \Delta G_0$

Empirical Scoring

	Functional form
LUDI	$\Delta G_{bind} = \Delta G_{H-bond} \sum_{H-bond} f(\Delta R, \Delta\alpha) + \Delta G_{ionic} \sum_{ionic} f(\Delta R, \Delta\alpha) + \Delta G_{hydrophobic} \sum_{hydrophobic} \lvert A_{hydrophobic} \rvert + \Delta G_{rotor} N_{rotor} + \Delta G_0$ $A_{hydrophobic} = \text{molecular surface area}$
F-Score	$\Delta G_{bind} = \Delta G_{H-bond} \sum_{H-bond} f(\Delta R, \Delta\alpha) + \Delta G_{ionic} \sum_{ionic} f(\Delta R, \Delta\alpha) + \Delta G_{aromatic} \sum_{aromatic} f(\Delta R, \Delta\alpha) + \Delta G_{contact} \sum_{contact} f(\Delta R, \Delta\alpha) + \Delta G_{rotor} N_{rotor} + \Delta G_0$
Chem-Score	$\Delta G_{bind} = \Delta G_{H-bond} \sum_{H-bond} f(\Delta R, \Delta\alpha) + \Delta G_{metal} \sum_{metal} f(\Delta R, \Delta\alpha) + \Delta G_{lipo} \sum_{lipo} f(\Delta R) + \Delta G_{rotor} \sum_{rotor} f(P_{nl}, P'_{nl}) + \Delta G_0$

regression coefficient

AutoDock Vina



$$\mathrm{gauss}_1(d) = w_{\mathrm{guass}_1} e^{-(d/0.5)^2}$$

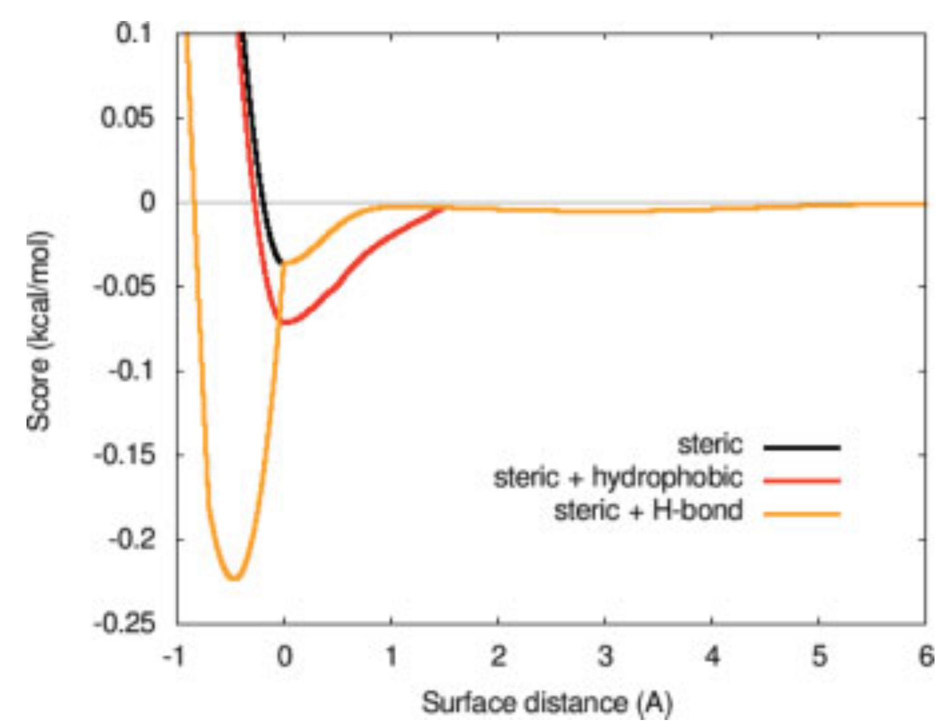
$$\mathrm{gauss}_2(d) = w_{\mathrm{guass}_2} e^{-((d-3)/2)^2}$$

$$\mathrm{repulsion}(d) = \begin{cases} w_{\mathrm{repulsion}} d^2 & d < 0 \\ 0 & d \geq 0 \end{cases}$$

$$\mathrm{hydrophobic}(d) = \begin{cases} w_{\mathrm{hydrophobic}} & d < 0.5 \\ 0 & d > 1.5 \\ w_{\mathrm{hydrophobic}}(1.5 - d) & otherwise \end{cases}$$

$$\mathrm{hbond}(d) = \begin{cases} w_{\mathrm{hbond}} & d < -0.7 \\ 0 & d > 0 \\ w_{\mathrm{hbond}}(-\frac{10}{7} d) & otherwise \end{cases}$$

Weight	Term
−0.0356	gauss_1
−0.00516	gauss_2
0.840	Repulsion
−0.0351	Hydrophobic
−0.587	Hydrogen bonding
0.0585	N_{rot}

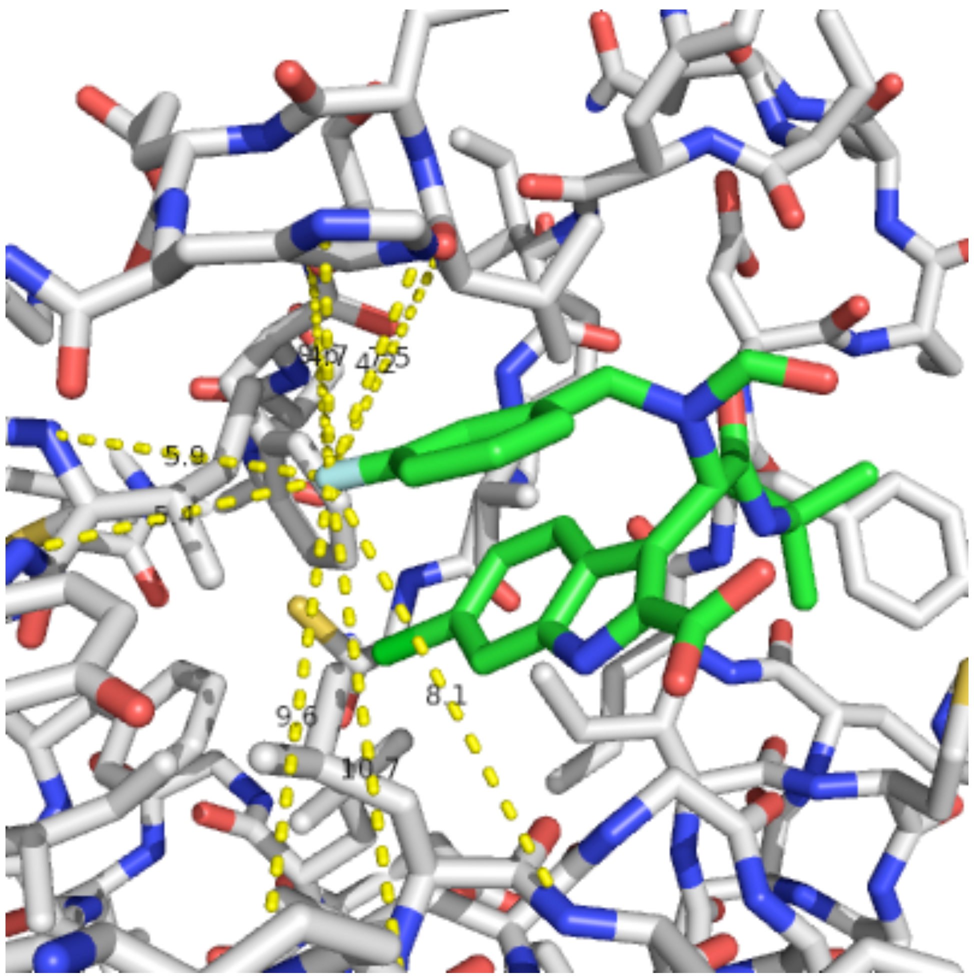


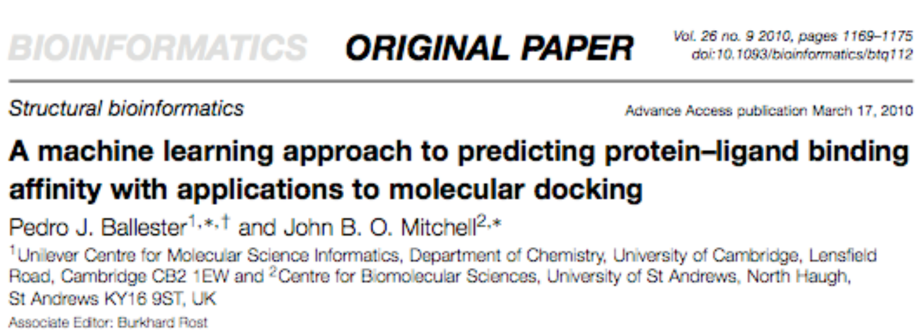
Knowledge Based

	Functional form
PMF	Parametrized pairwise potential PMF score: $PMF = \sum_{prot}\sum_{lig} A_{ij}(d_{ij}) \quad A_{ij}(d_{ij}) = -k_B T \ln\left[f_{Vol\_corr}^{j}(r) \frac{\rho_{seg}^{ij}(r)}{\rho_{bulk}^{ij}} \right]$ where k_B is the Boltzmann constant, $f_{Vol\_corr}^{j}(r)$ is a ligand volume correction factor and $\frac{\rho_{seg}^{ij}(r)}{\rho_{bulk}^{ij}}$ indicates a radial distribution function for a protein atom i and a ligand atom j.
DrugScore (v1.2)	$\Delta W = \gamma \sum_{prot}\sum_{lig} \Delta W_{ij}(r) + (1-\gamma) \times \left[\sum_{lig} \Delta W_i(SAS, SAS_0) + \sum_{prot} \Delta W_j(SAS, SAS_0) \right]$ SAS = Solvent accessible surface area terms, W_{ij} = distance dependent pairwise potential
SMoG	$G = \sum_{ij} g_{ij}\Delta_{ij}; \qquad \Delta_{ij} = \begin{cases} 0 & \text{(i, j more than 5 Å)} \\ 1 & \text{(i, j within 5 Å)} \end{cases}; \qquad g_{ij} = -kT \log\left[\frac{p_{ij}}{\overline{p}}\right];$ p_{ij} an $\overline{p}$ are interatomic and averaged interactomic interactions

RF-Score

Pairwise Distance Counts (<12Å)

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doi:10.1093/bioinformatics/btq112

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A machine learning approach to predicting protein–ligand binding affinity with applications to molecular docking

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Associate Editor: Burkhard Rost

Protein

Ligand

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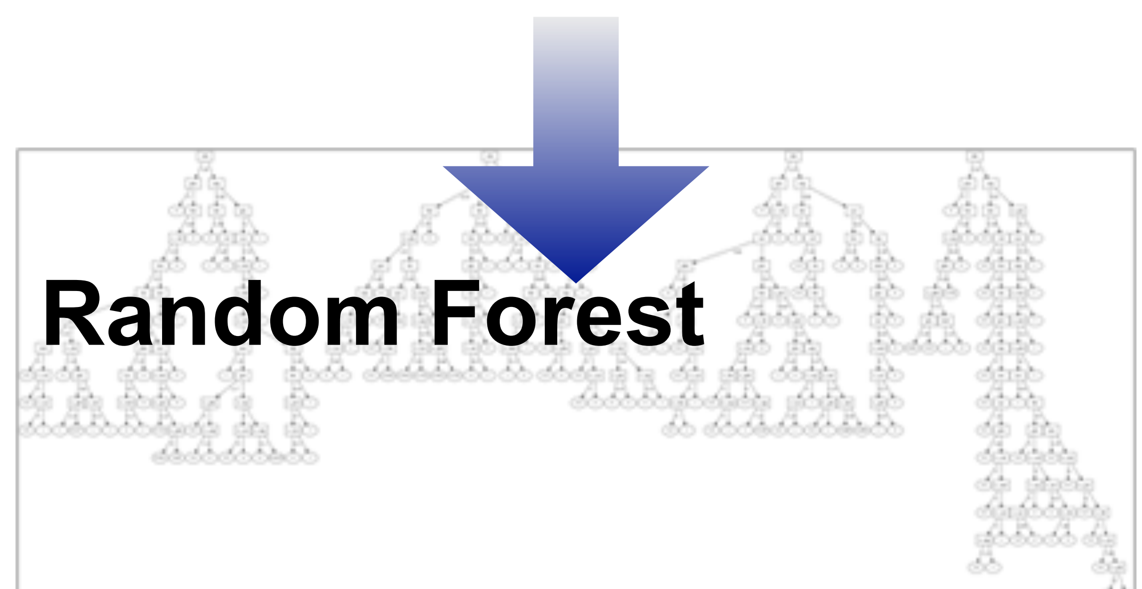
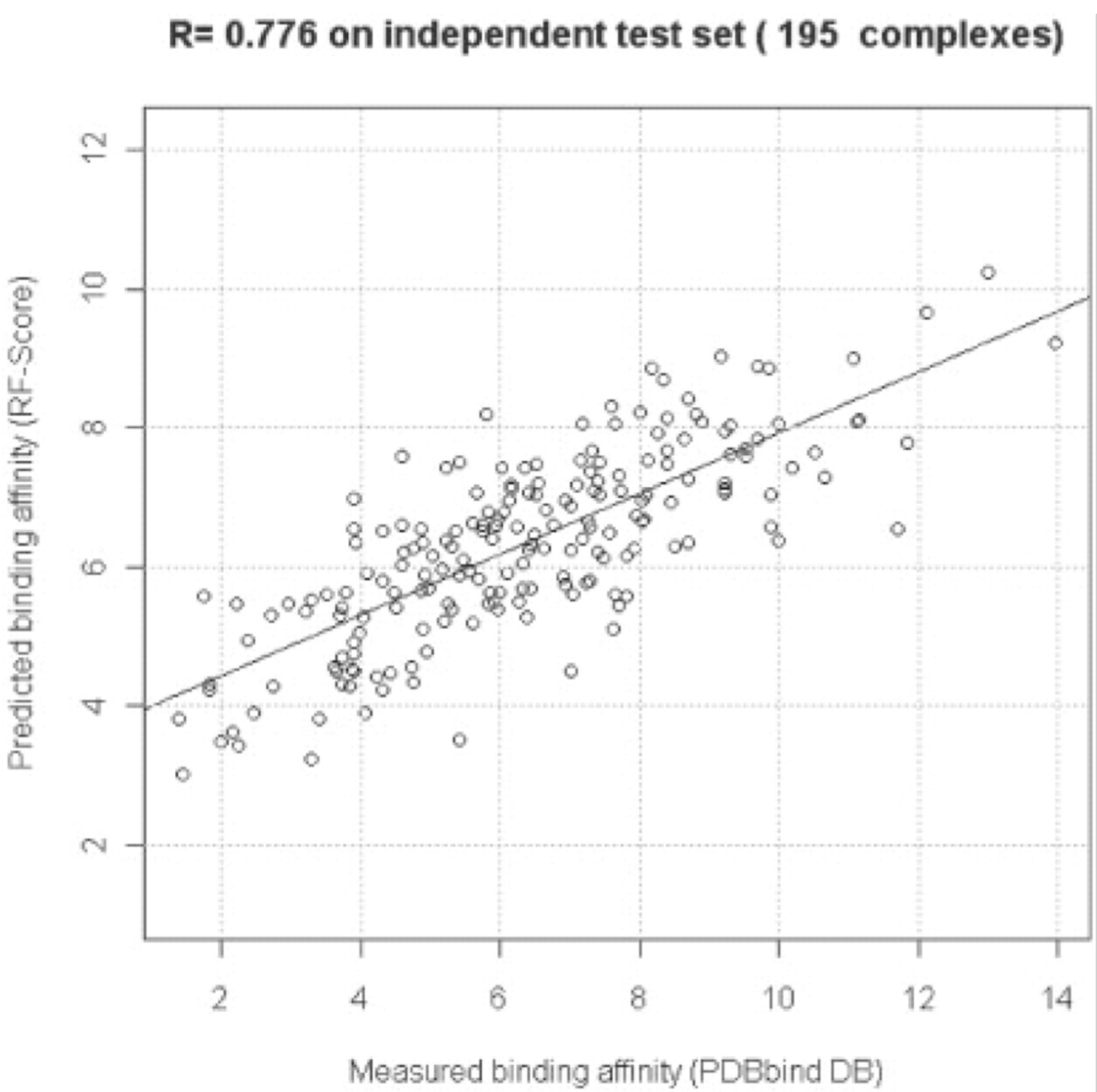


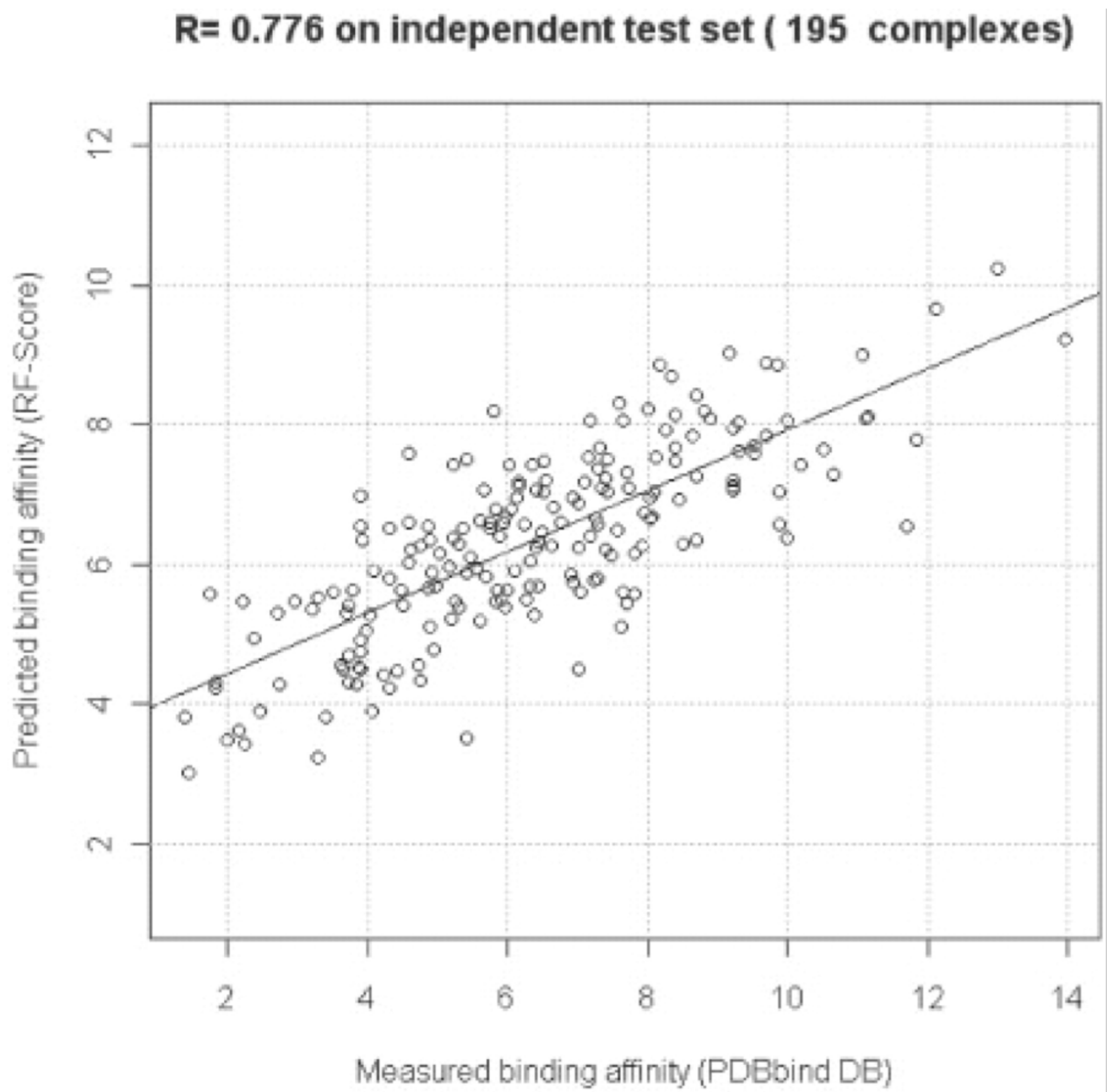
RF-Score Output



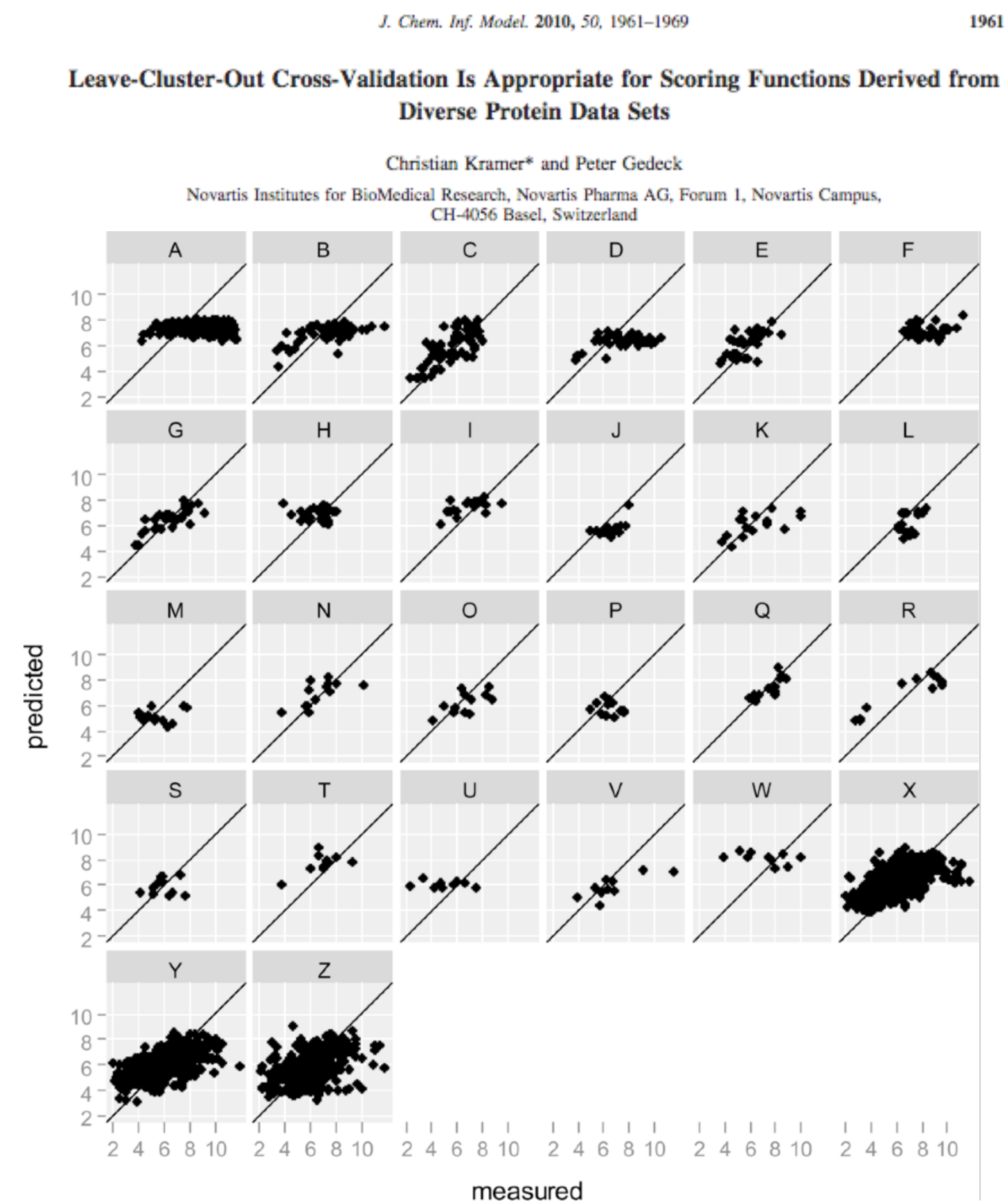
RMSE = 1.58

Scoring function	*R*	*Rs*	RMSE
RF-Score	**0.776**	**0.762**	**1.58**
X-Score::HMScore	0.644	0.705	1.83
DrugScore^{CSD}	0.569	0.627	1.96
SYBYL::ChemScore	0.555	0.585	1.98
DS::PLP1	0.545	0.588	2
GOLD::ASP	0.534	0.577	2.02
SYBYL::G-Score	0.492	0.536	2.08
DS::LUDI3	0.487	0.478	2.09
DS::LigScore2	0.464	0.507	2.12
GlideScore-XP	0.457	0.435	2.14
DS::PMF	0.445	0.448	2.14
GOLD::ChemScore	0.441	0.452	2.15
SYBYL::D-Score	0.392	0.447	2.19
DS::Jain	0.316	0.346	2.24
GOLD::GoldScore	0.295	0.322	2.29
SYBYL::PMF-Score	0.268	0.273	2.29
SYBYL::F-Score	0.216	0.243	2.35

RF-Score Output



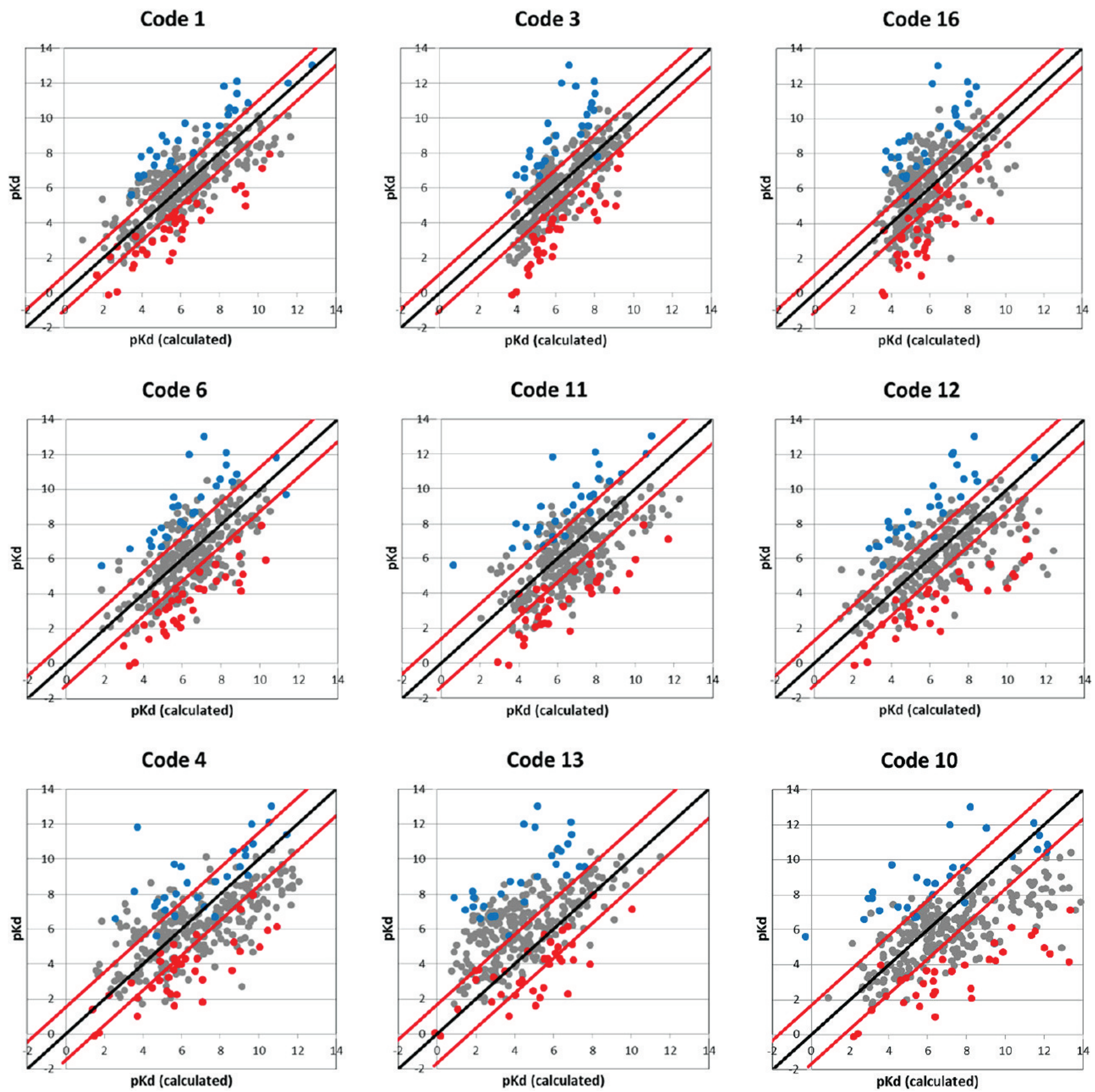
RMSE = 1.58



R = 0.46; RMSE = 1.6

Scoring

Ideally, score would equal affinity – but this is an unsolved problem.



http://www.csardock.org/

Scoring

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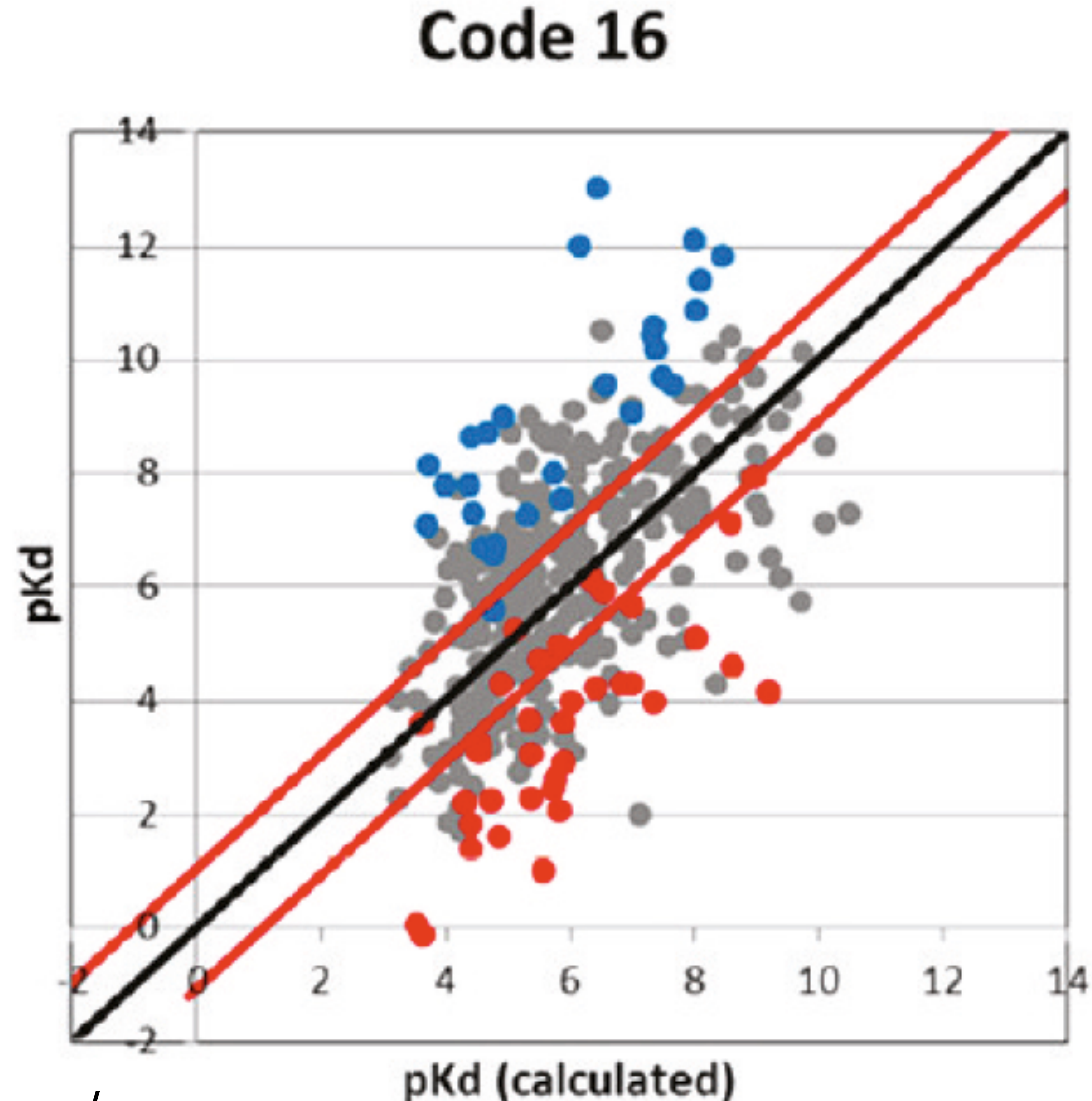

$R^2 = 0.28$
RMSE = 1.9

http://www.csardock.org/

Scoring

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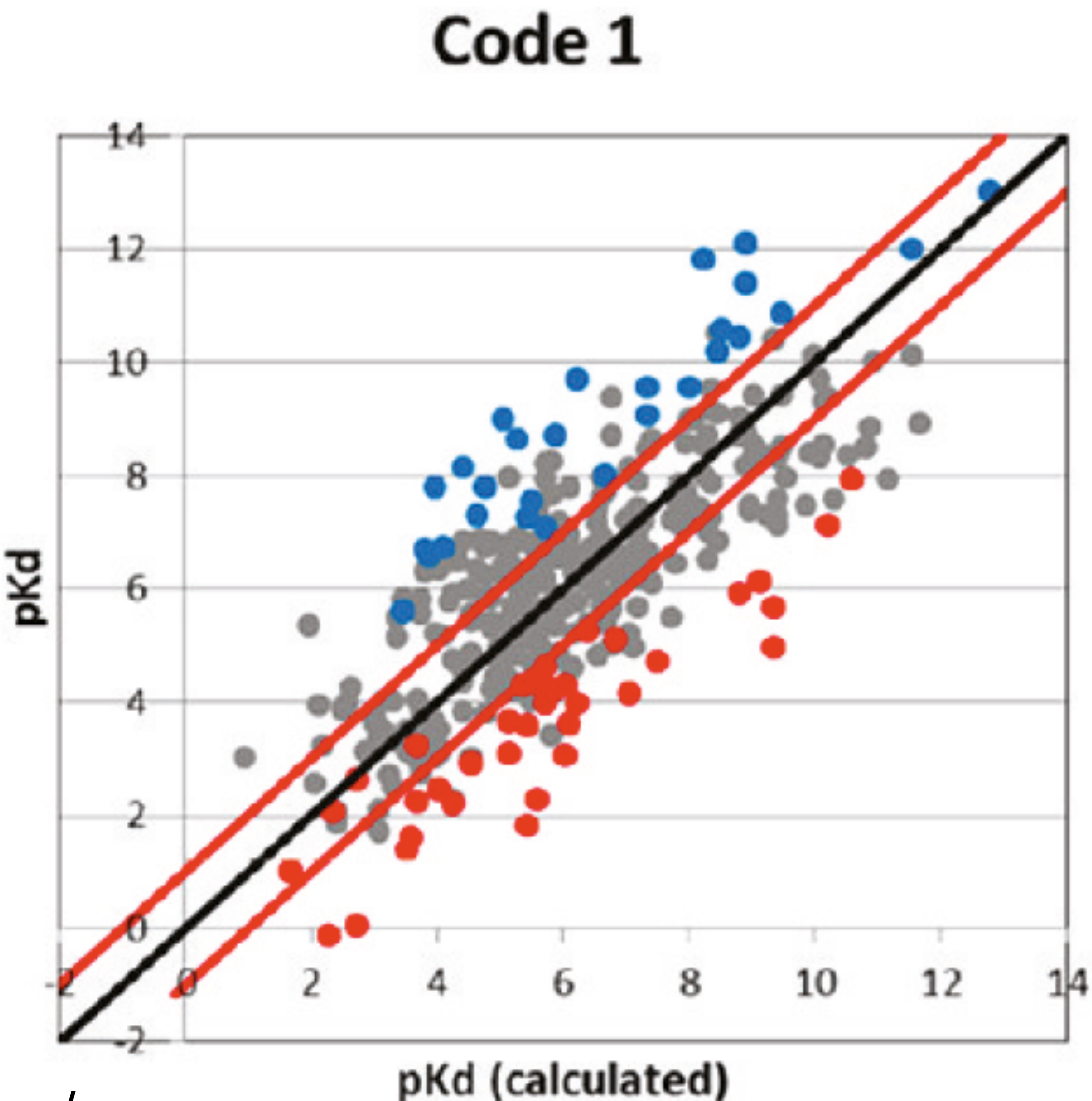
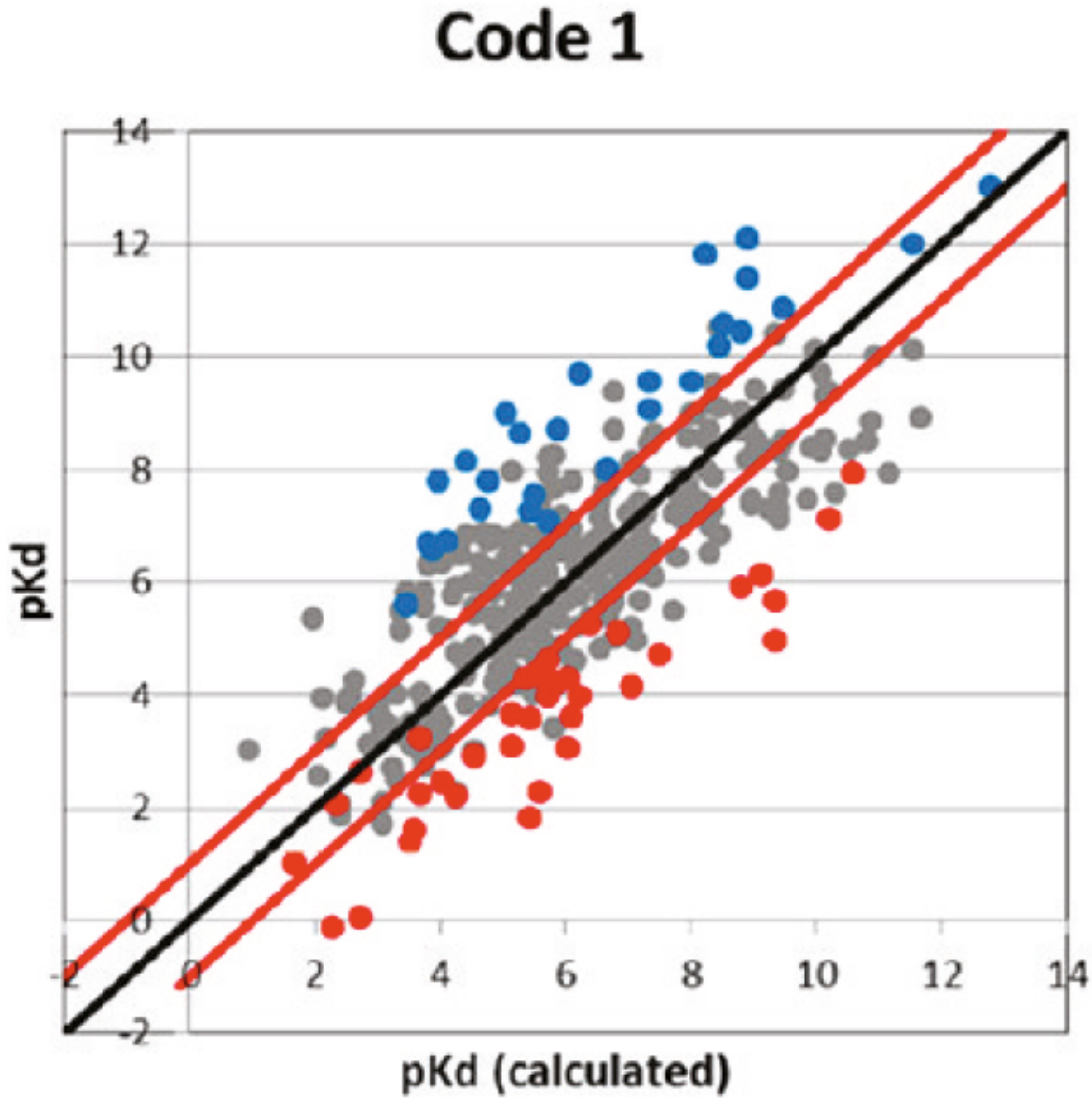


$R^2 = 0.58$
RMSE = 1.51

http://www.csardock.org/

Scoring

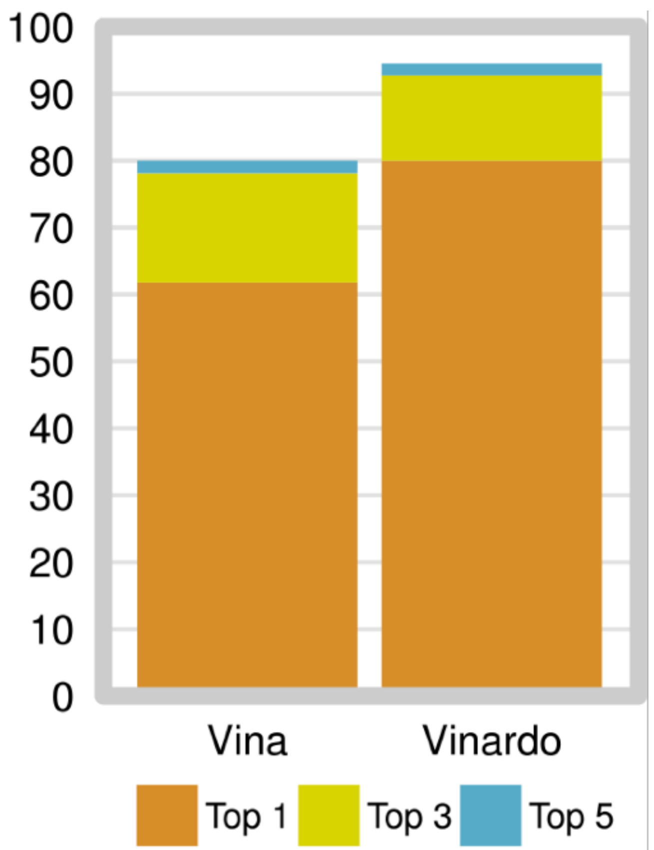
Ideally, score would equal affinity – but this is an unsolved problem.

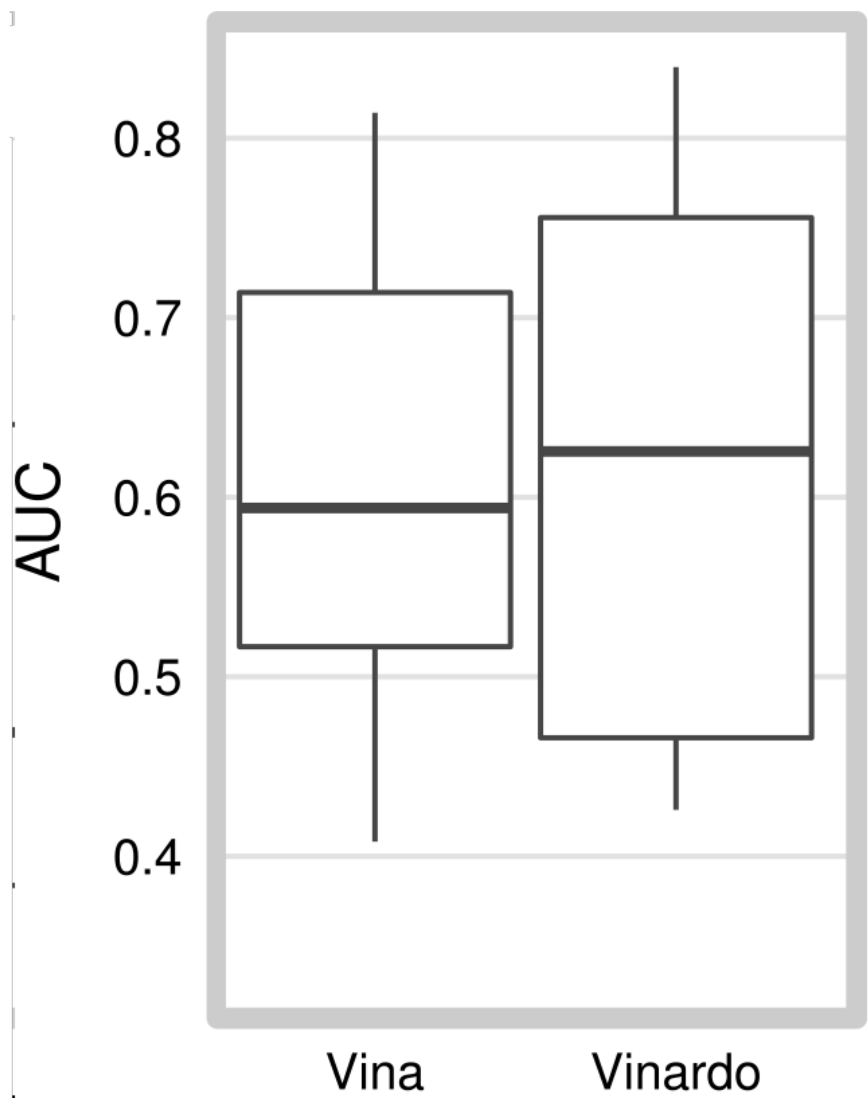


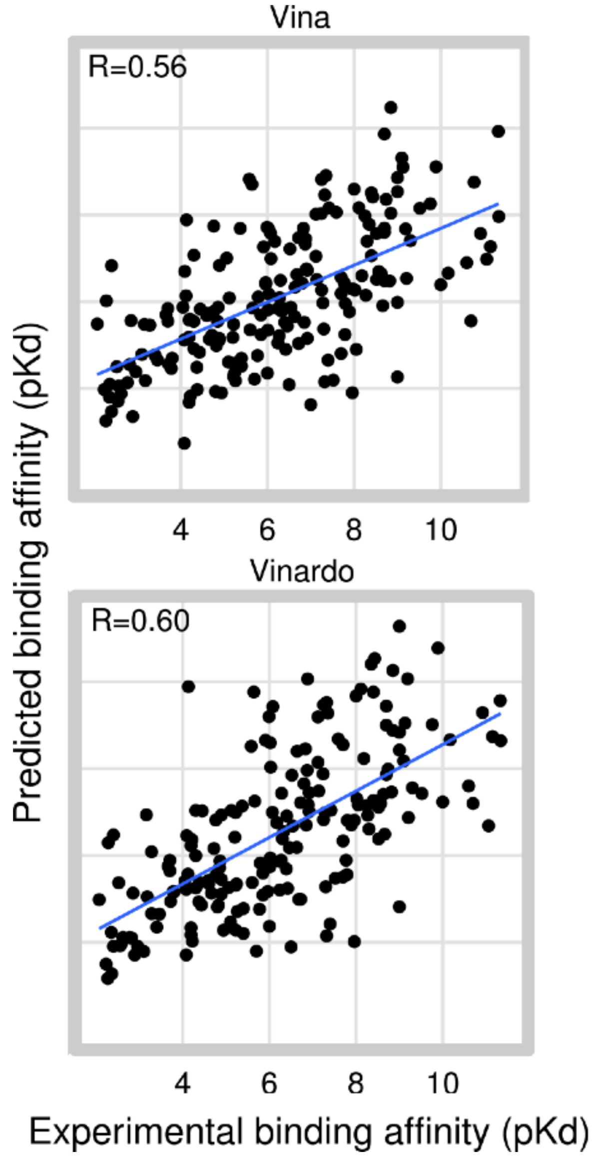
$R^2 = 0.58$
RMSE = 1.51

http://www.csardock.org/

Scoring State of the Art







Pose Prediction | Binding Discrimination | Affinity Prediction

Quiroga R, Villarreal MA (2016) Vinardo: A Scoring Function Based on Autodock Vina Improves Scoring, Docking, and Virtual Screening. *PLoS ONE* 11(5): e0155183. doi:10.1371/journal.pone.0155183

Can we do better?

Accurate pose prediction, binding discrimination, **and** affinity prediction without sacrificing performance?

Can we do better?

Accurate pose prediction, binding discrimination, **and** affinity prediction without sacrificing performance?

Key Idea: Leverage "big data"

231,655,275 bioactivities in PubCher

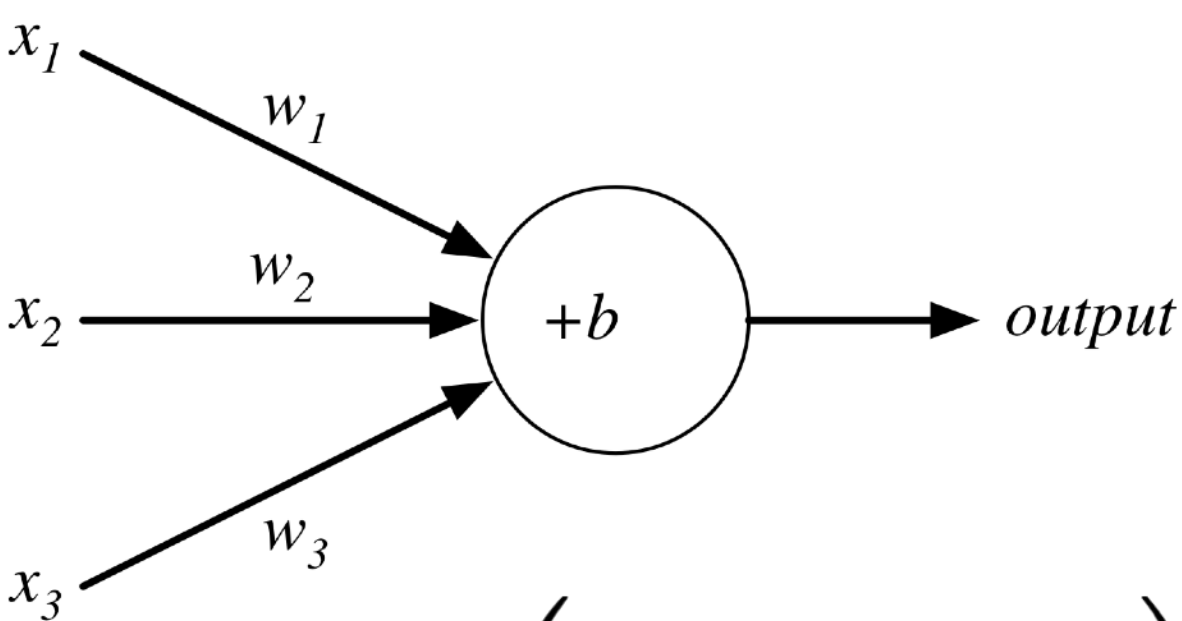
125,526 structures in the PDB

16,179 annotated complexes in PDBbind

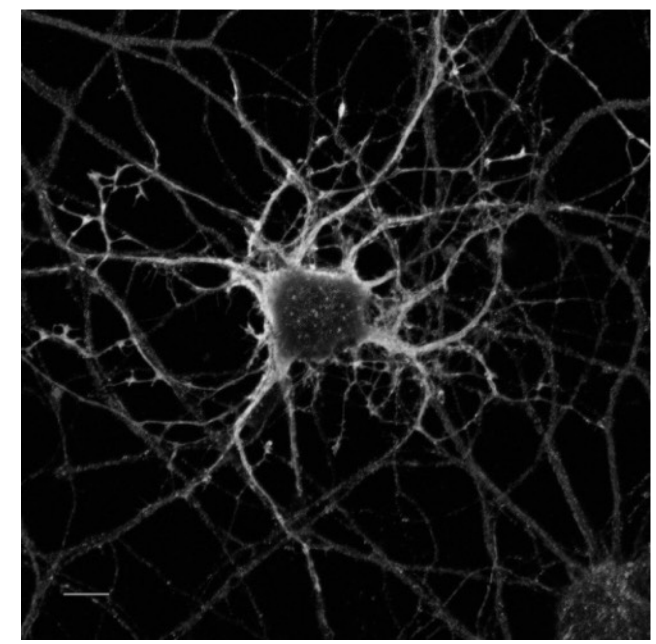
Machine Learning

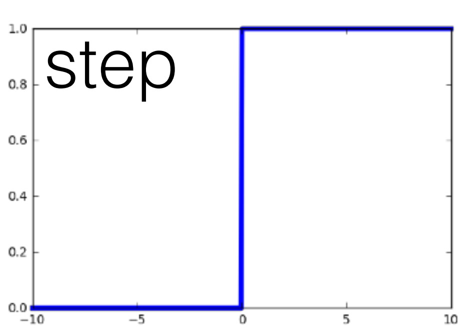
Features $X \rightarrow$ **Model** $\rightarrow y$ Prediction

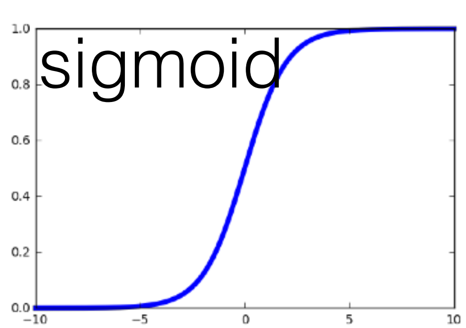
Neural Networks

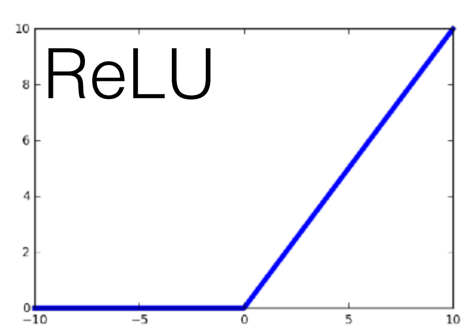


$$output = \sigma\left(\sum_i w_i x_i + b\right)$$

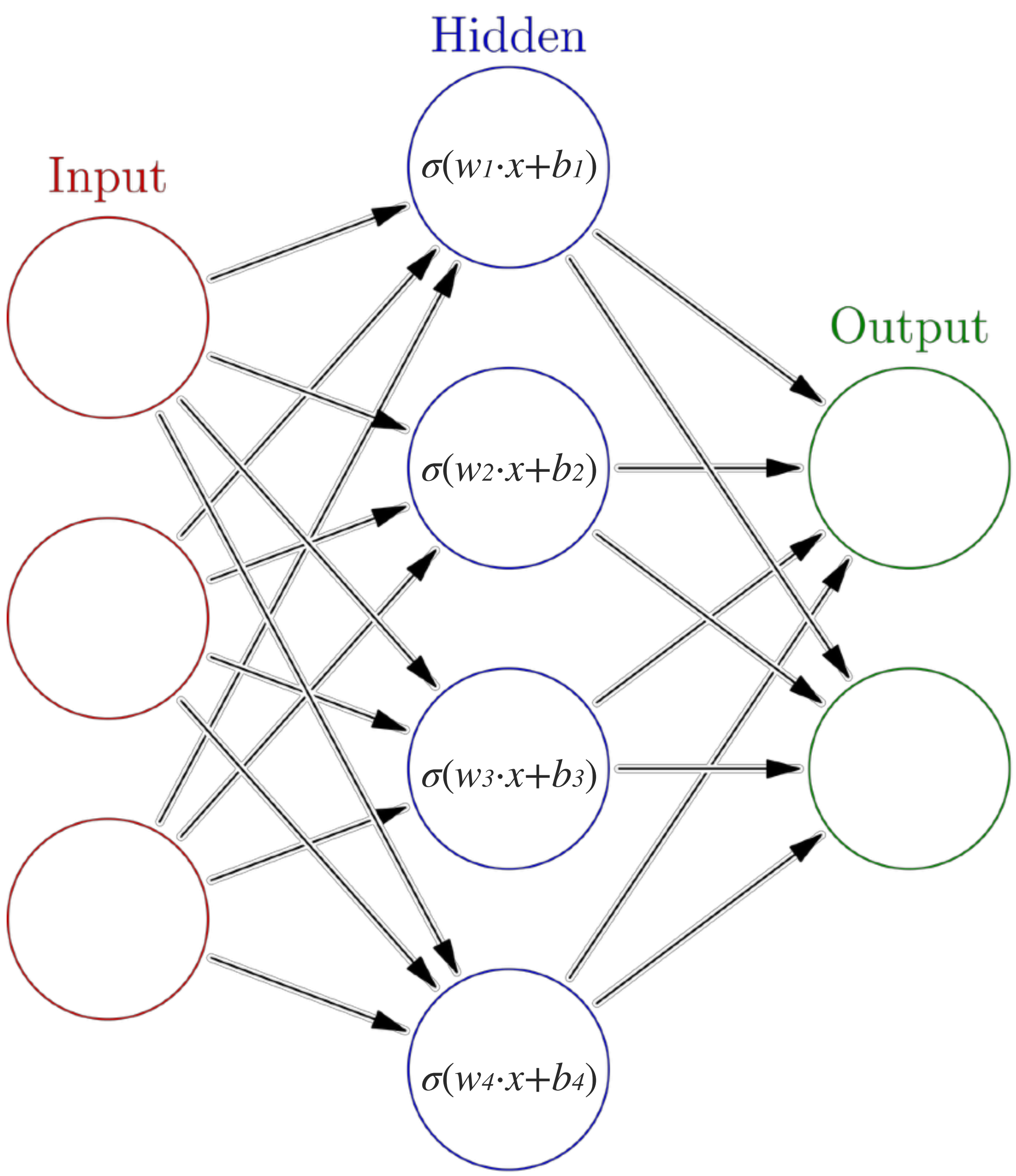


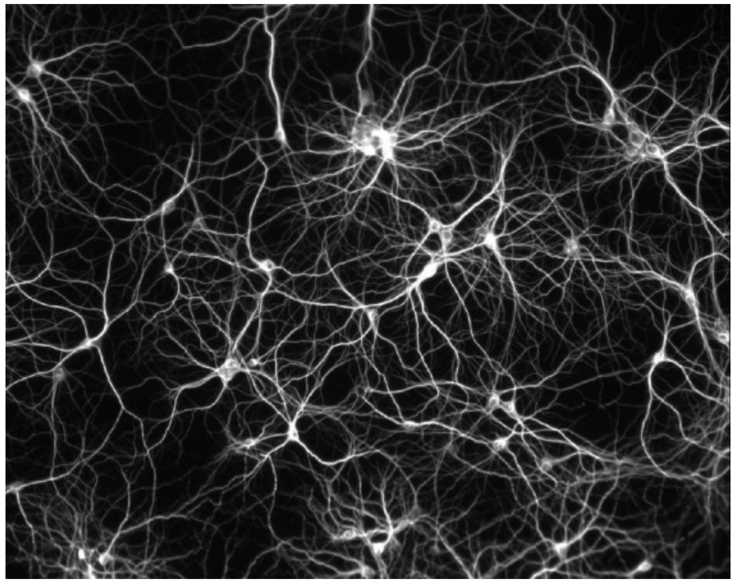






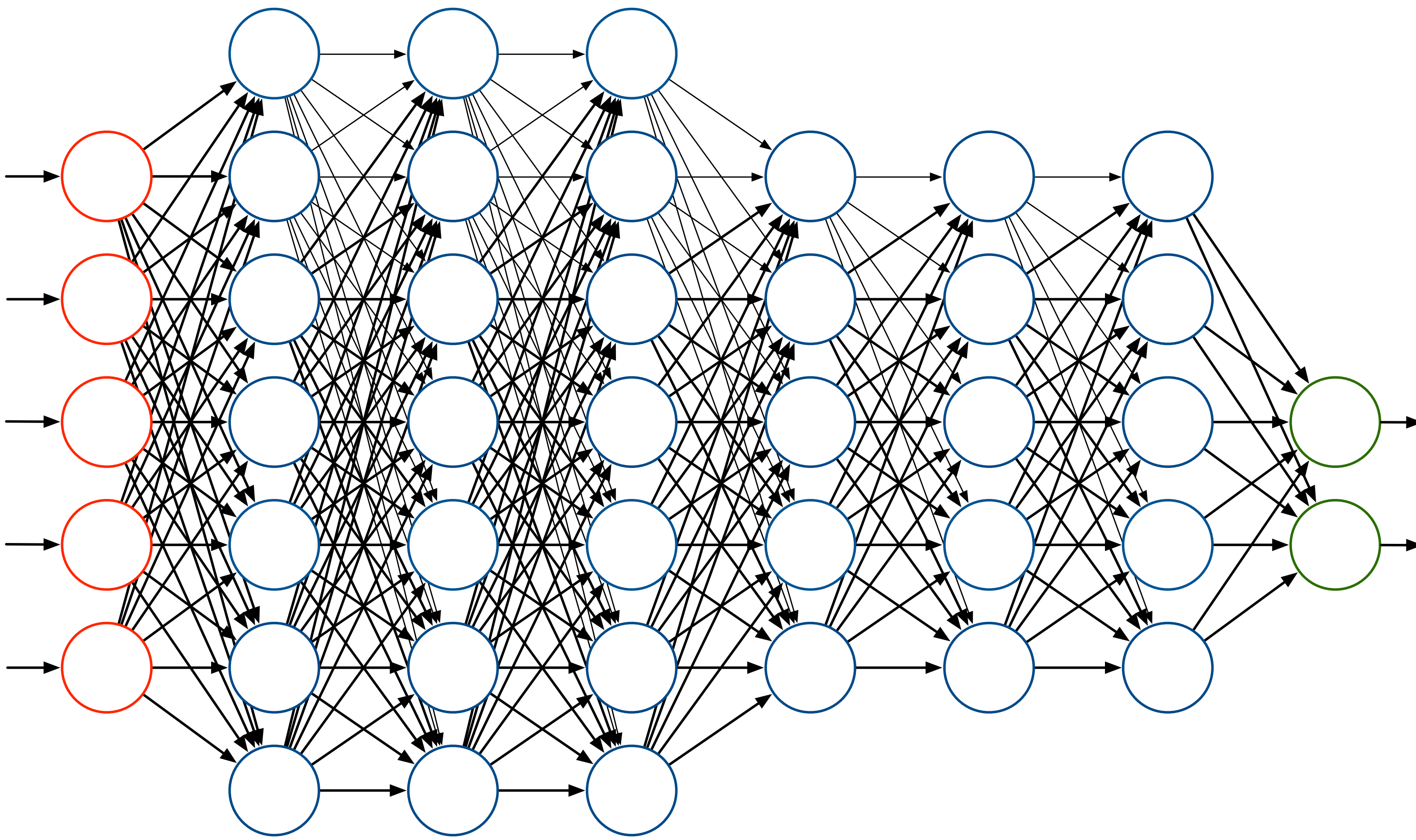
Neural Networks



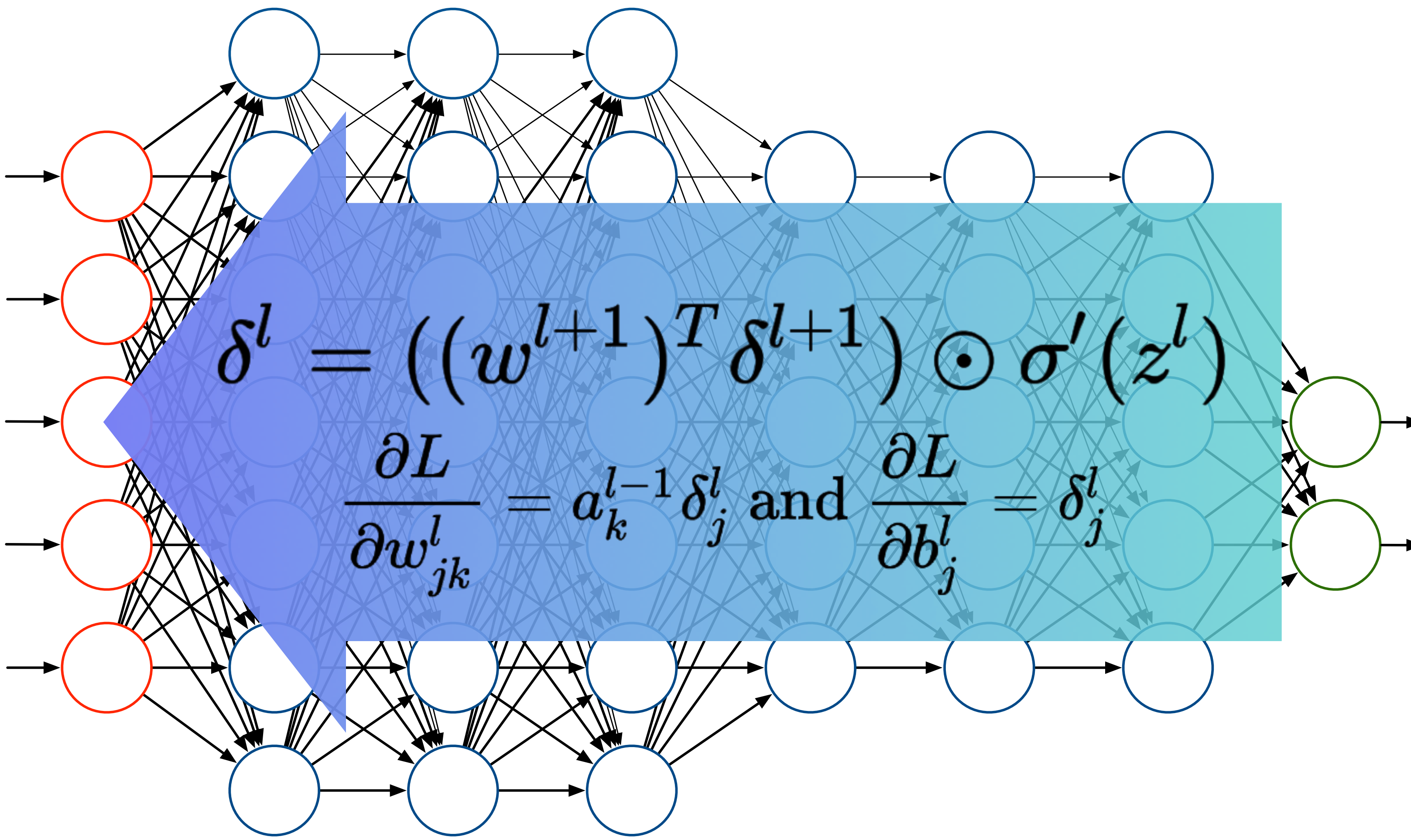


The **universal approximation theorem** states that, under reasonable assumptions, a feedforward **neural network** with a finite number of nodes **can approximate any continuous** function to within a given error over a bounded input domain.

Deep Learning

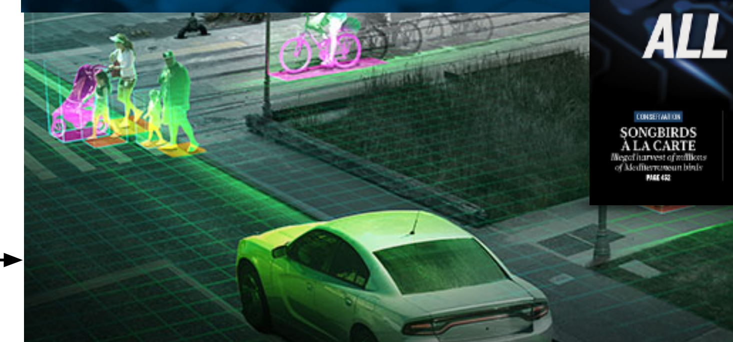


Deep Learning



$$\delta^l = ((w^{l+1})^T \delta^{l+1}) \odot \sigma'(z^l)$$

$$\frac{\partial L}{\partial w^l_{jk}} = a^{l-1}_k \delta^l_j \text{ and } \frac{\partial L}{\partial b^l_j} = \delta^l_j$$



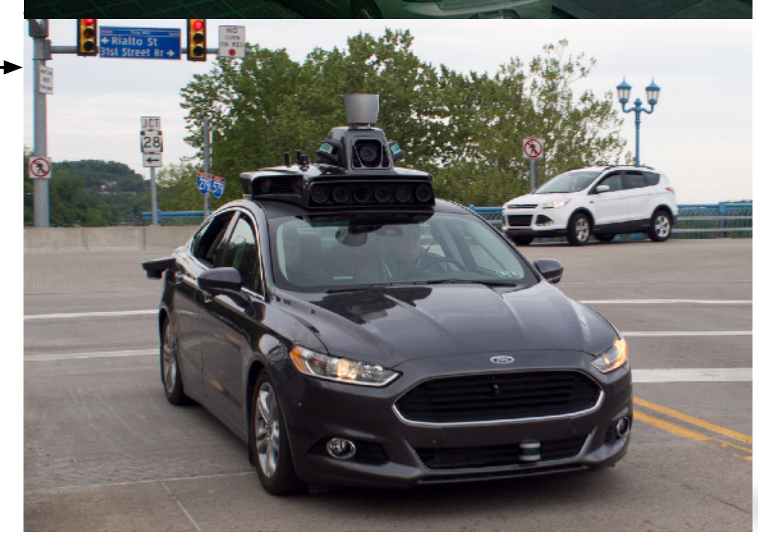
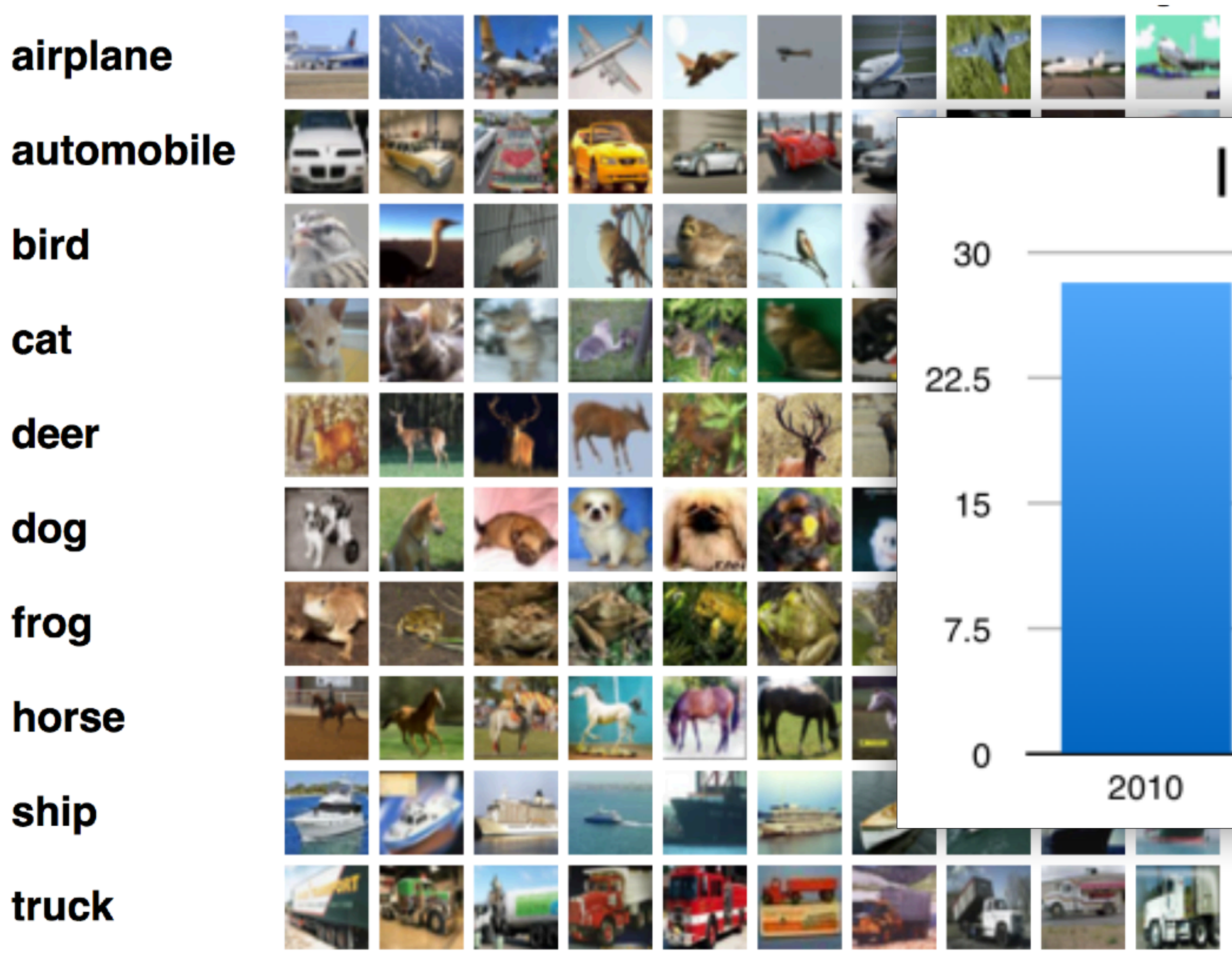
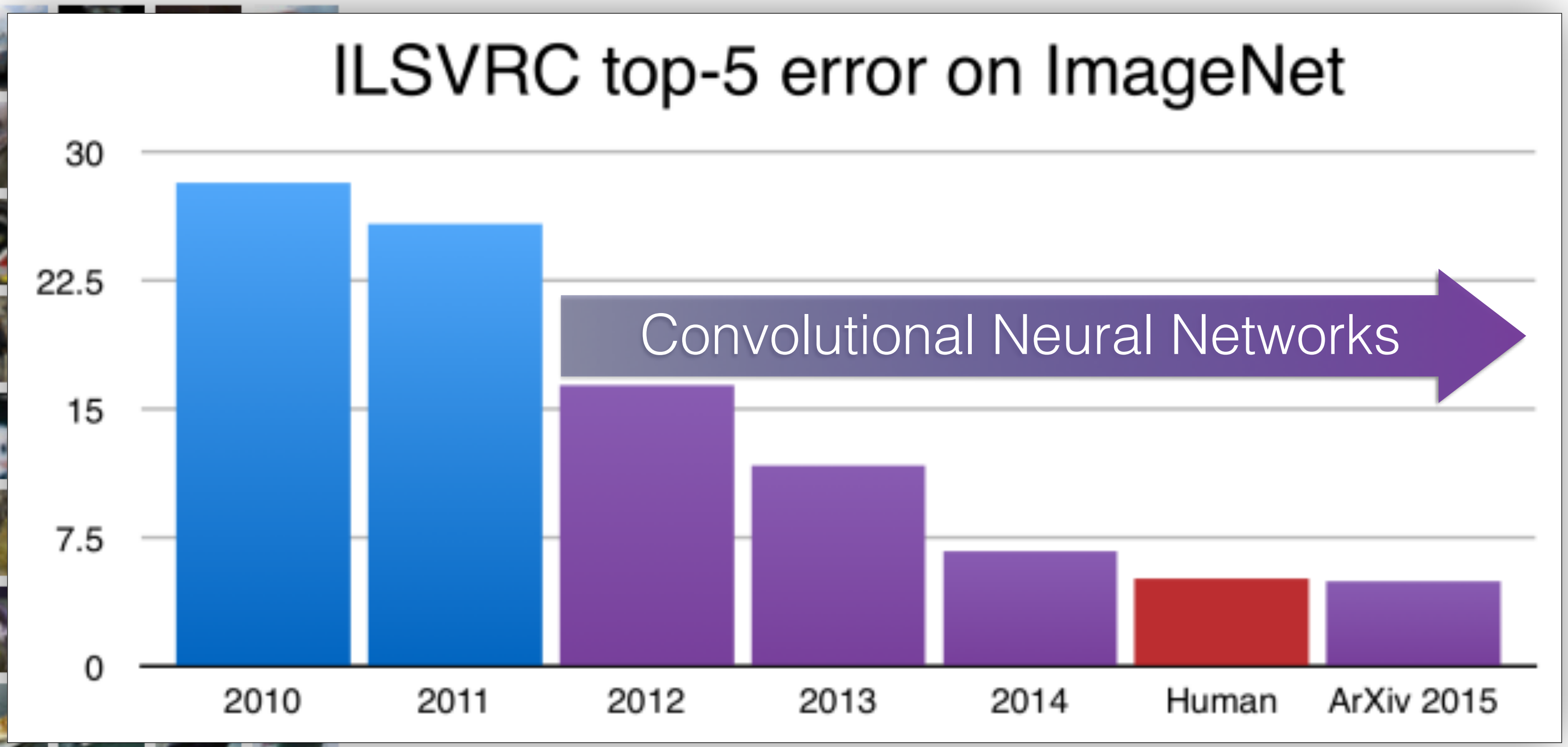


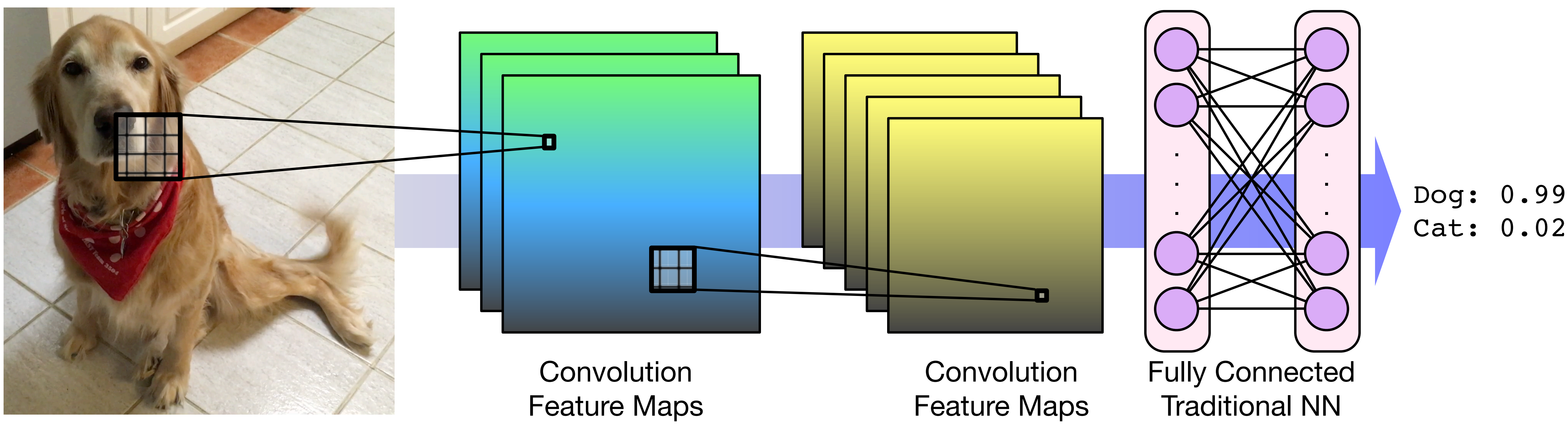
Image Recognition

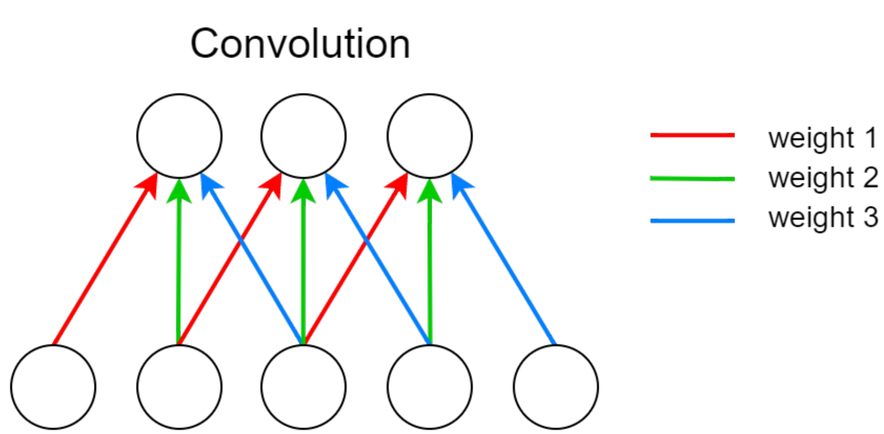


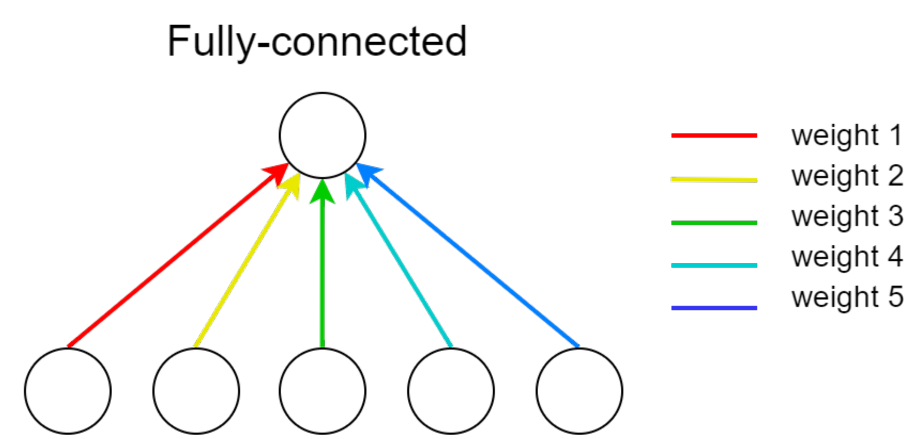


https://devblogs.nvidia.com

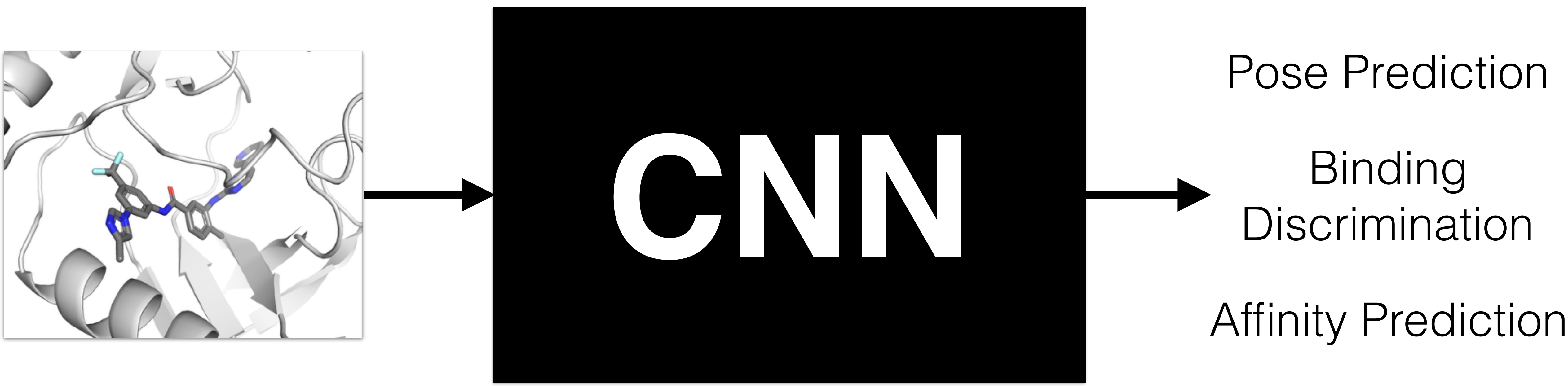
Convolutional Neural Networks



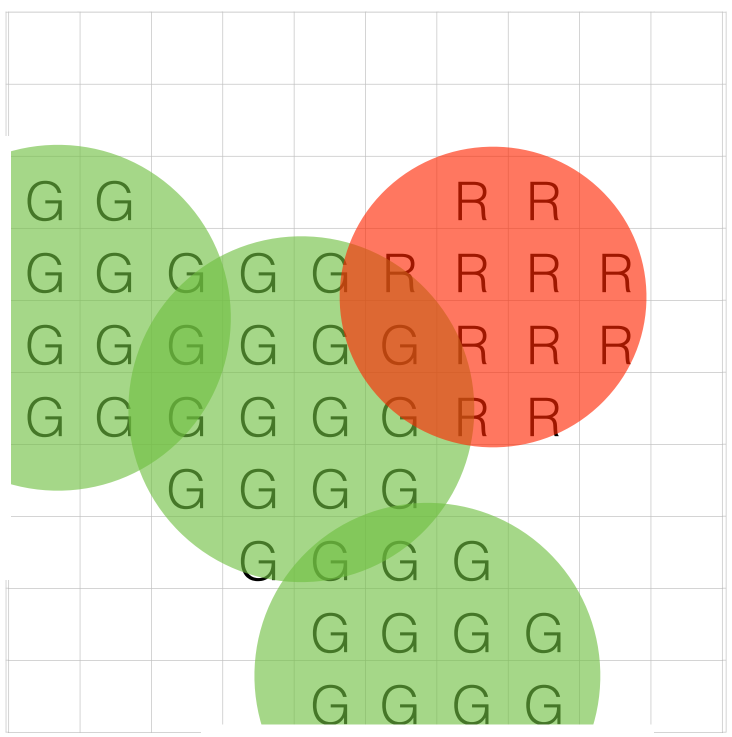




CNNs for Protein-Ligand Scoring

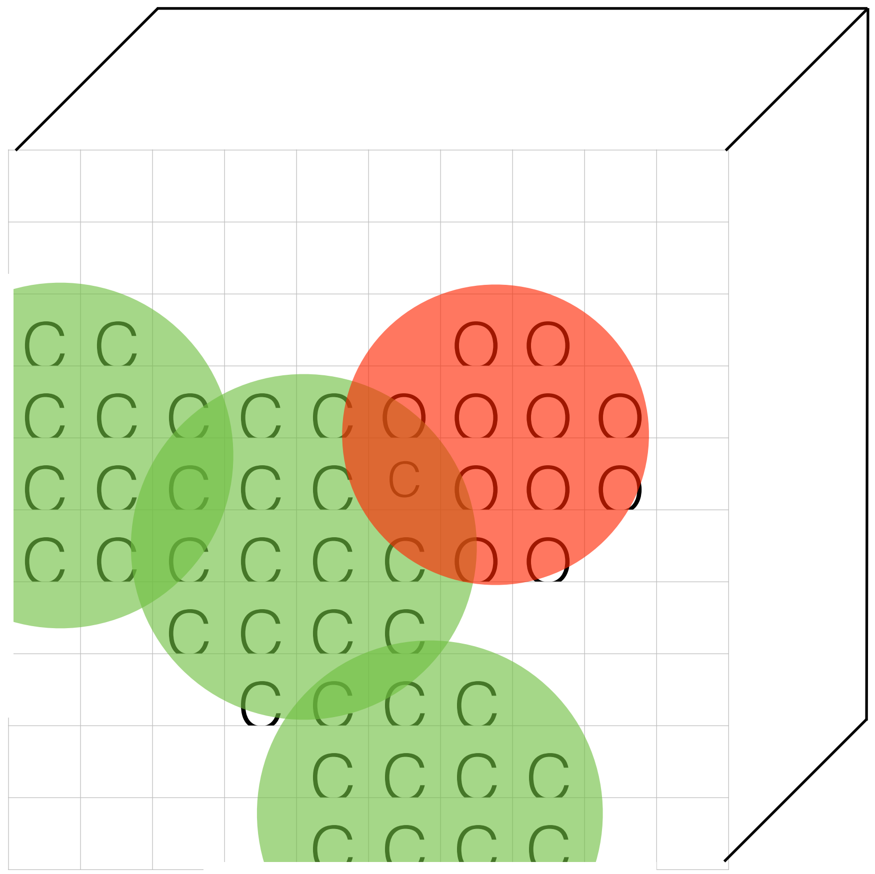


Protein-Ligand Representation



(R,G,B) pixel

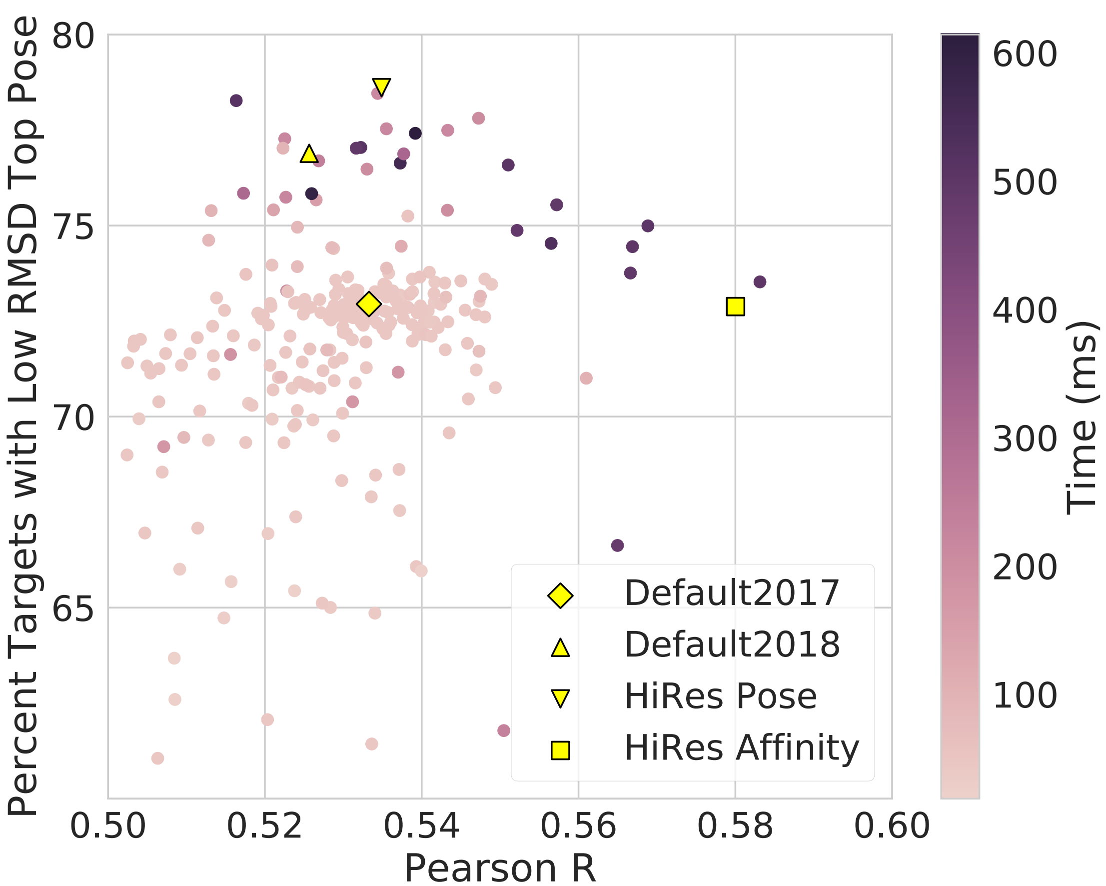
Protein-Ligand Representation

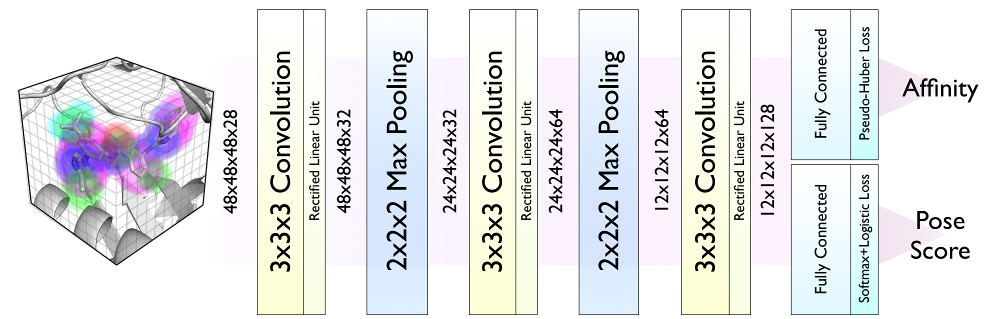


(R,G,B) pixel → (Carbon, Nitrogen, Oxygen,…) **voxe**

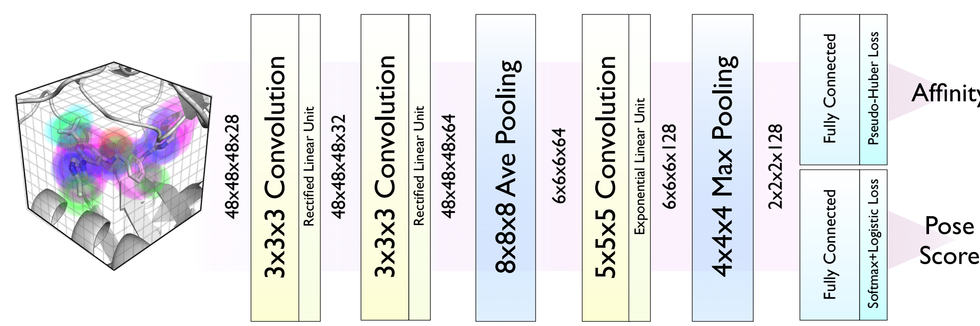
The only parameters for this representation are the choice of **grid resolution**, **atom density**, and **atom types**.

Optimized Models



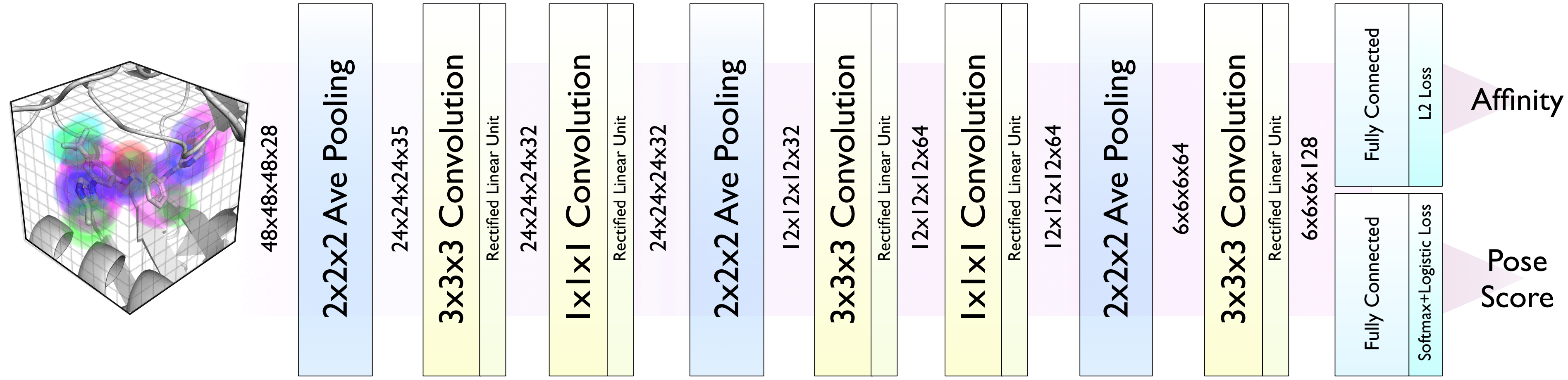


HiRes Pose

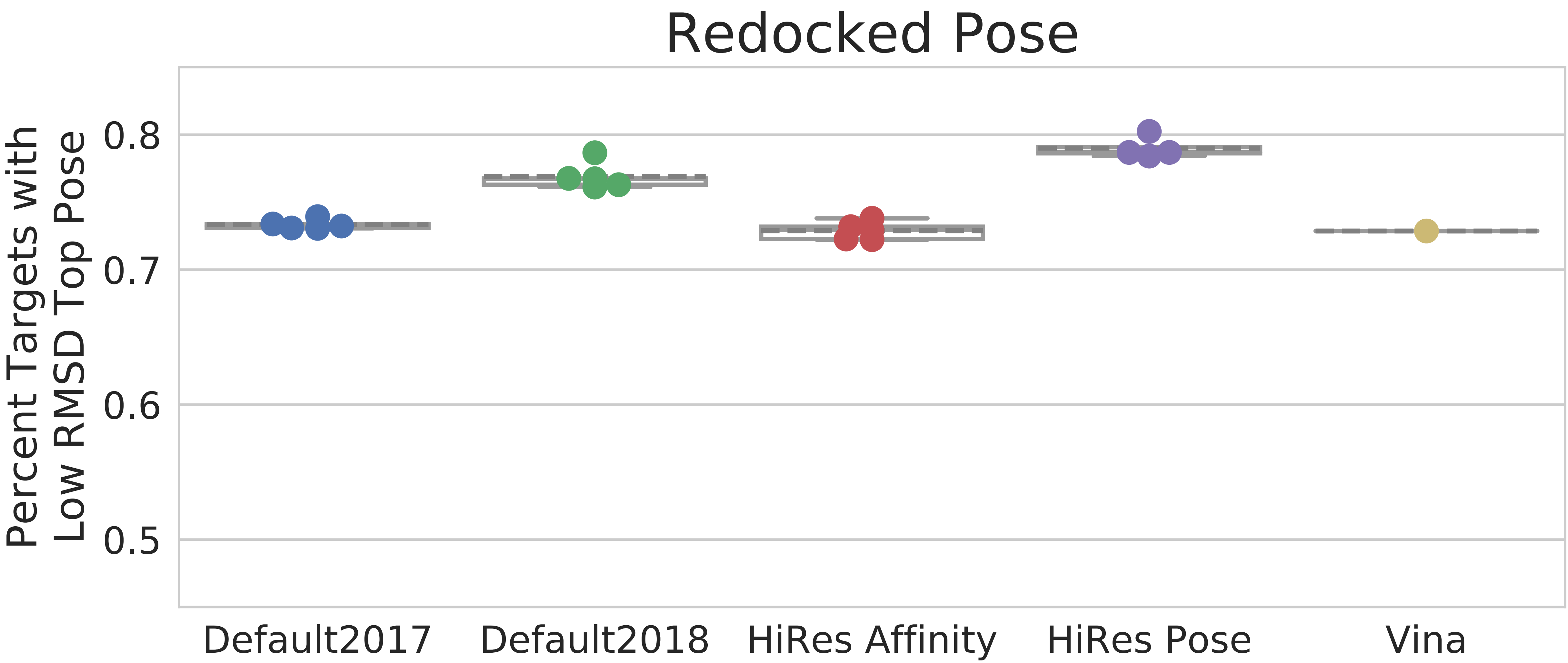


HiRes Affinity

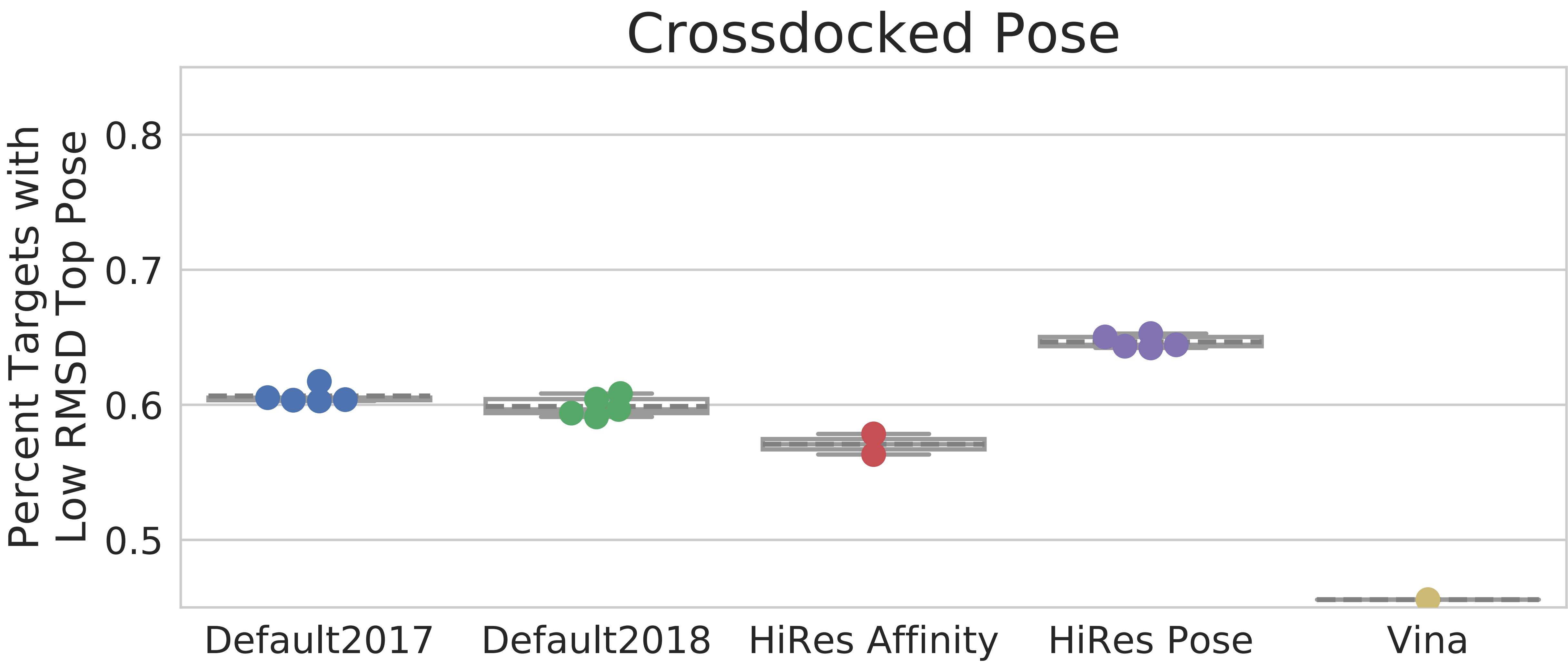
Default2018



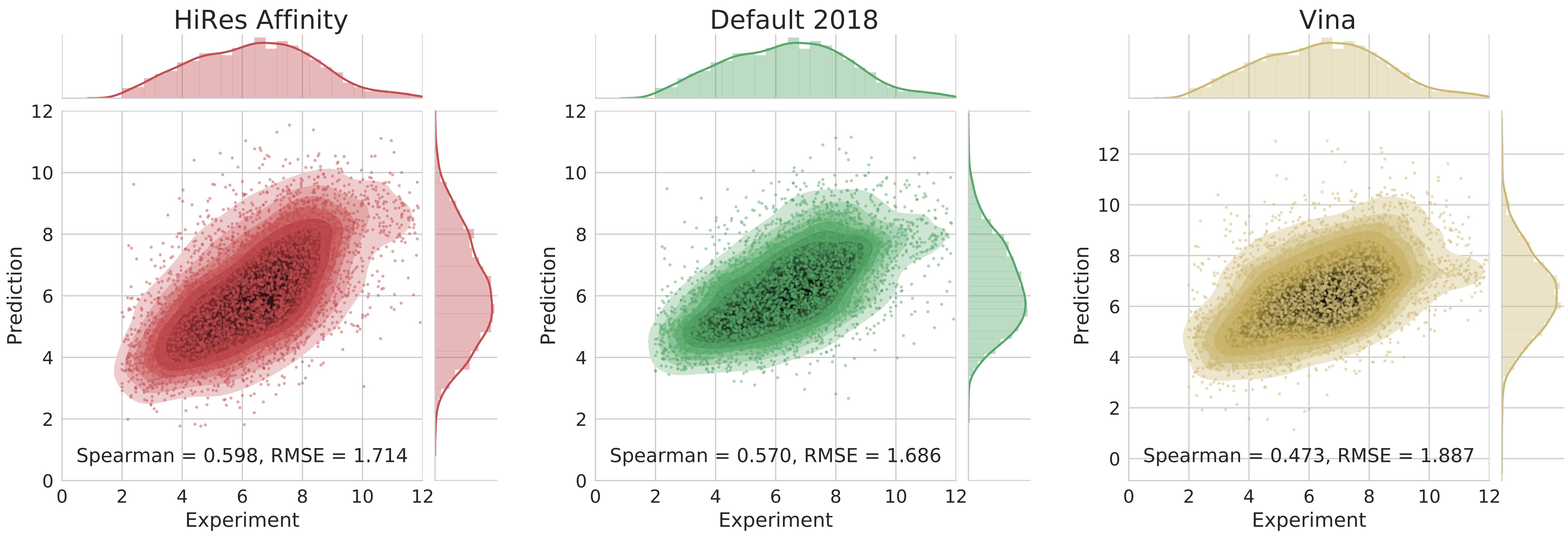
Pose Results



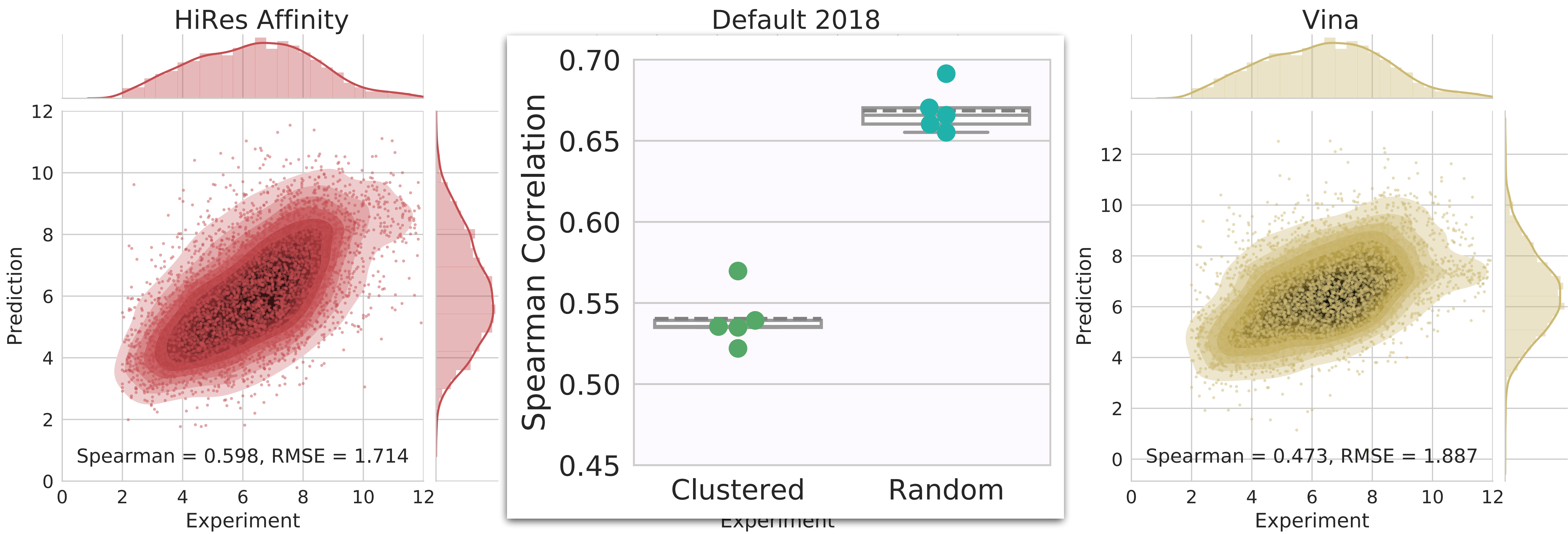
Pose Results



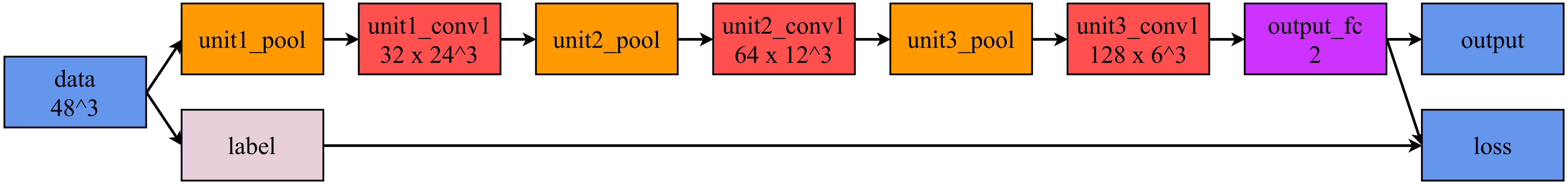
Affinity Results



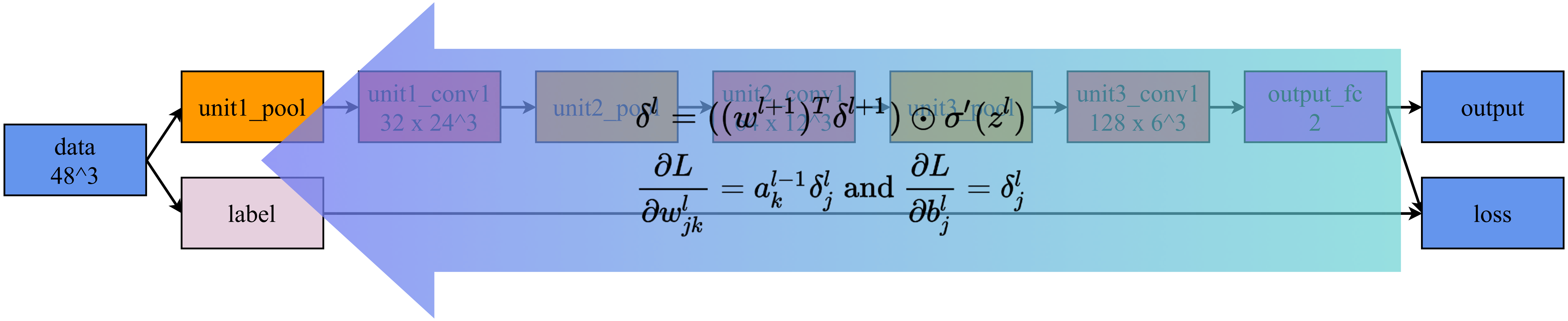
Affinity Results



Beyond Scoring



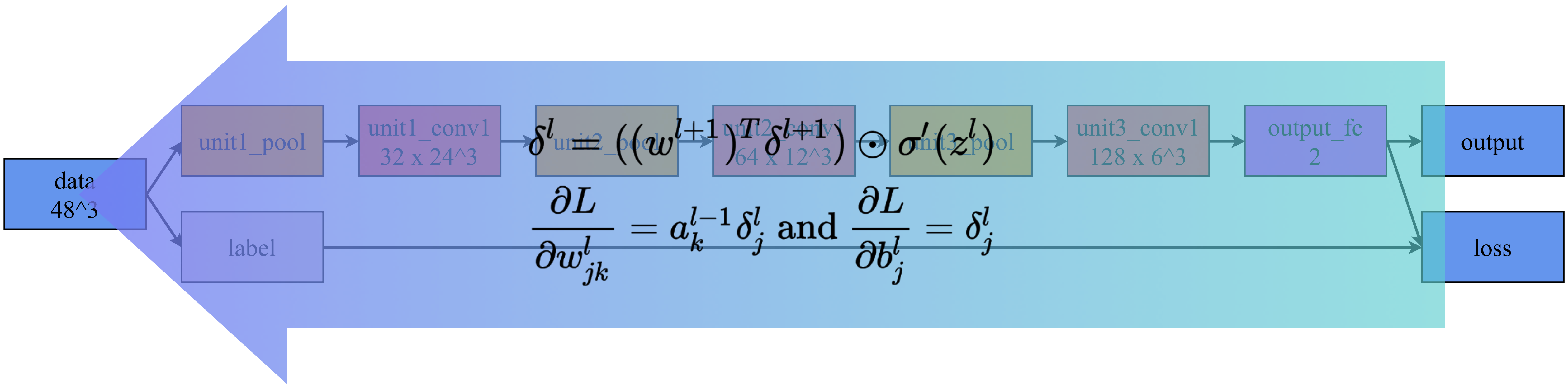
Beyond Scoring



$$\delta^l = ((w^{l+1})^T \delta^{l+1}) \odot \sigma'(z^l)$$

$$\frac{\partial L}{\partial w^l_{jk}} = a^{l-1}_k \delta^l_j \text{ and } \frac{\partial L}{\partial b^l_j} = \delta^l_j$$

Beyond Scoring



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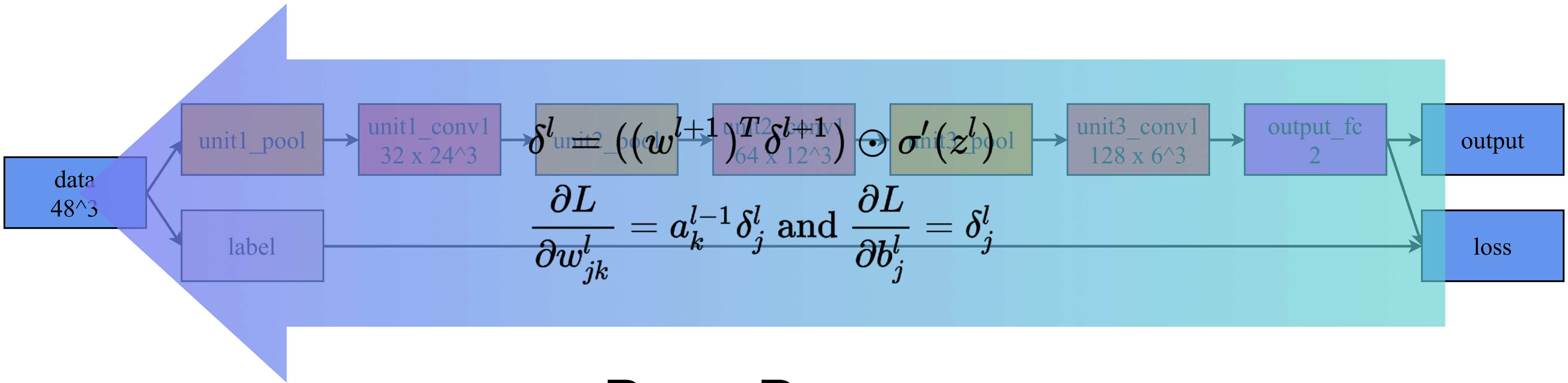

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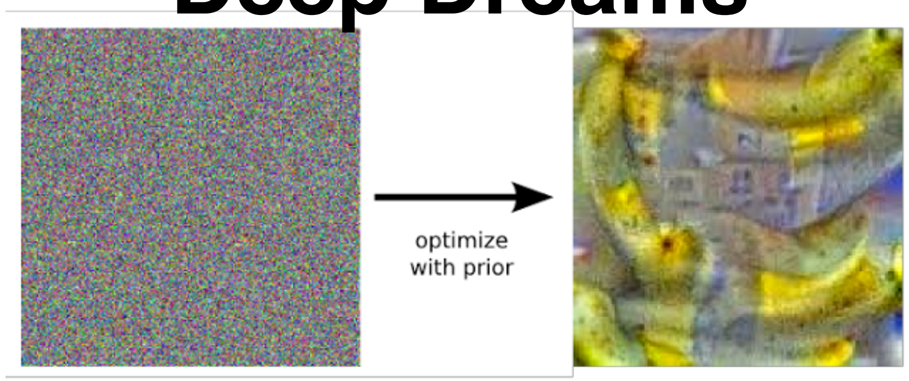
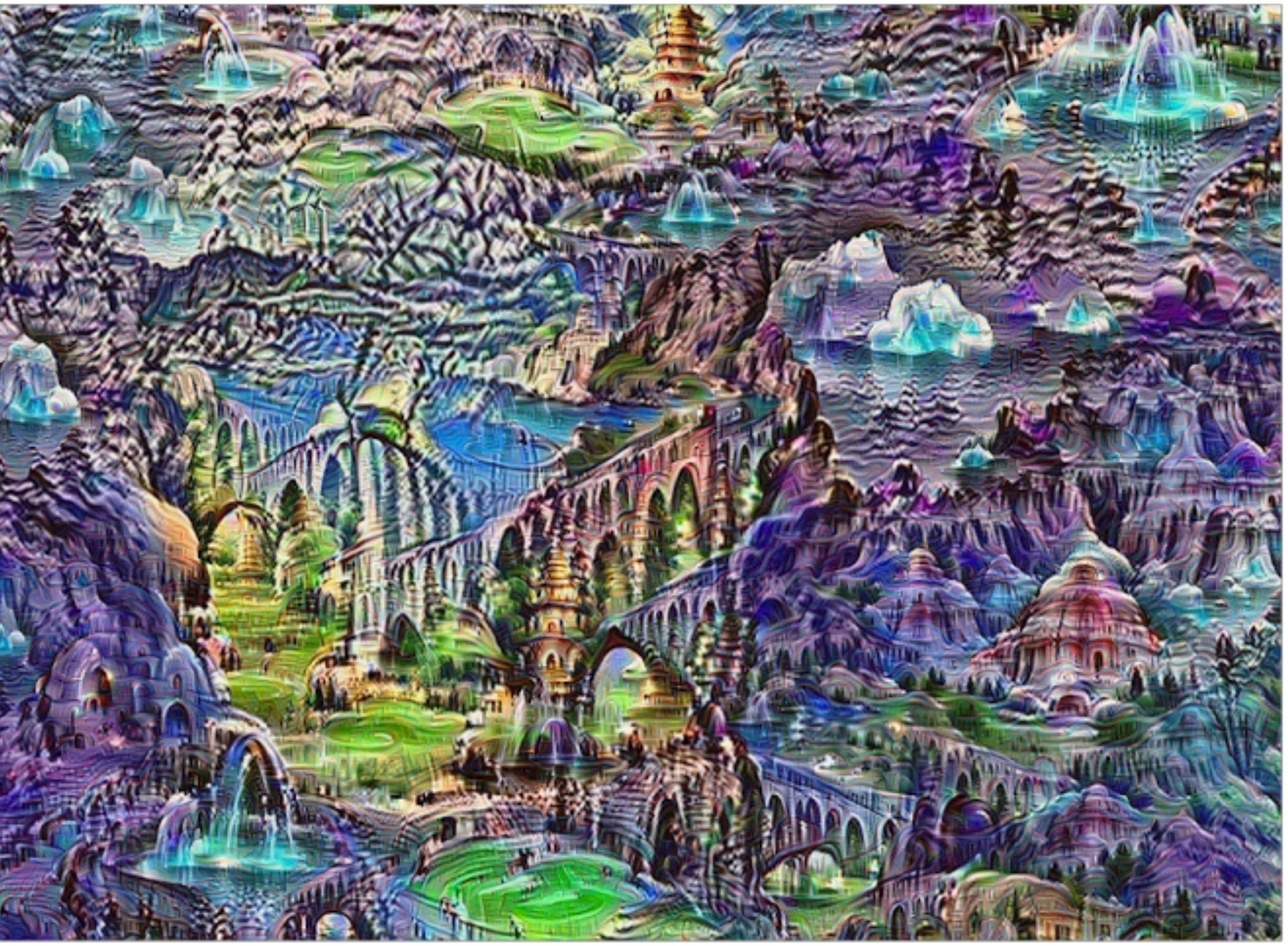
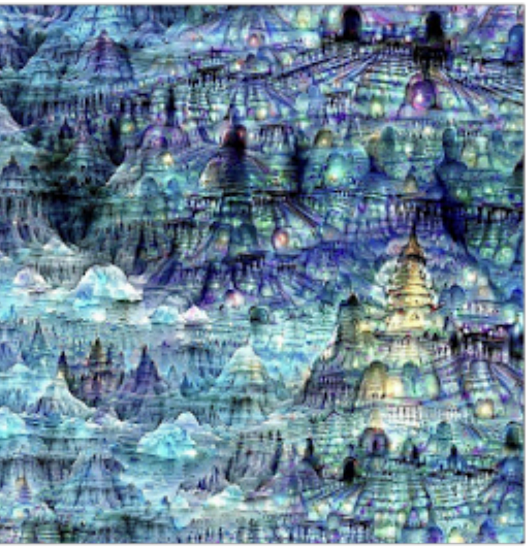
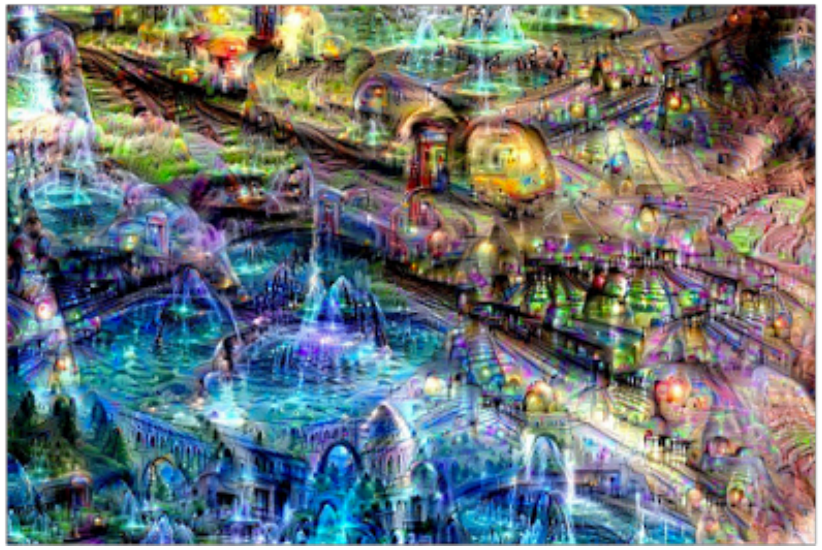
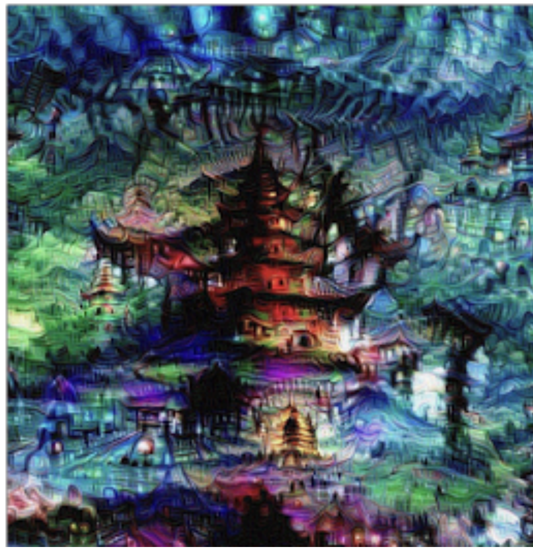
Deep Dreams



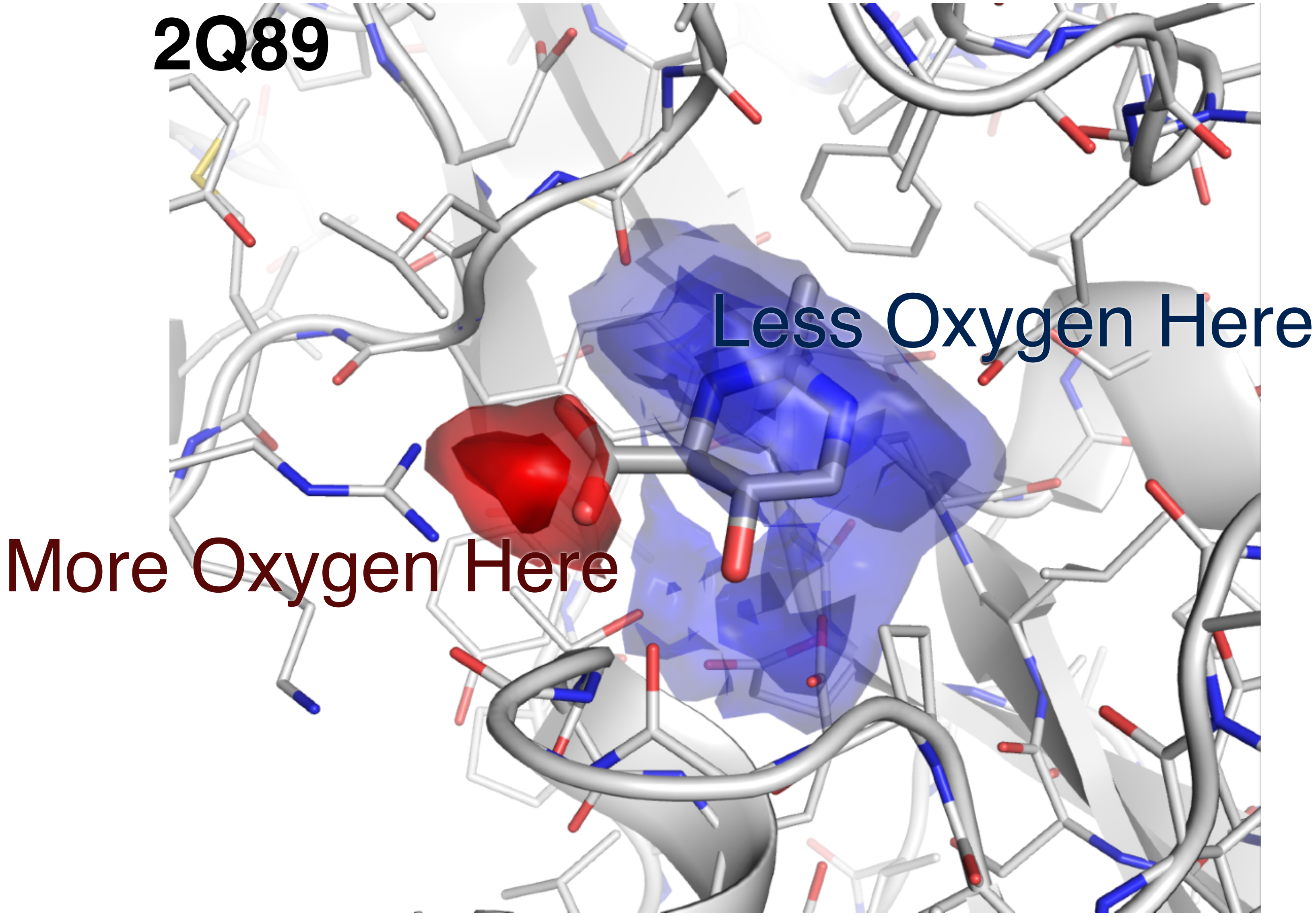
https://research.googleblog.com/2015/06/inceptionism-going-deeper-into-neural.html



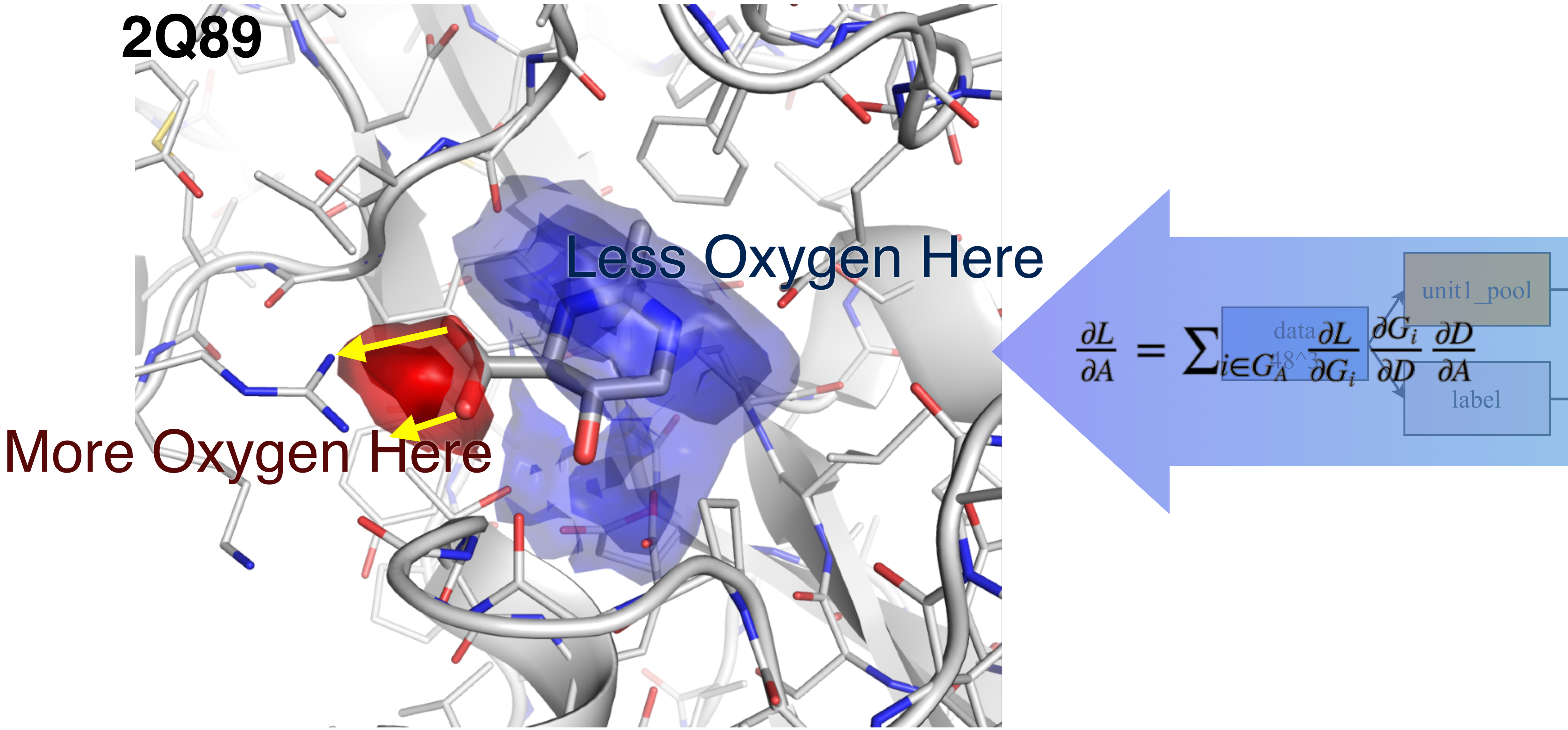



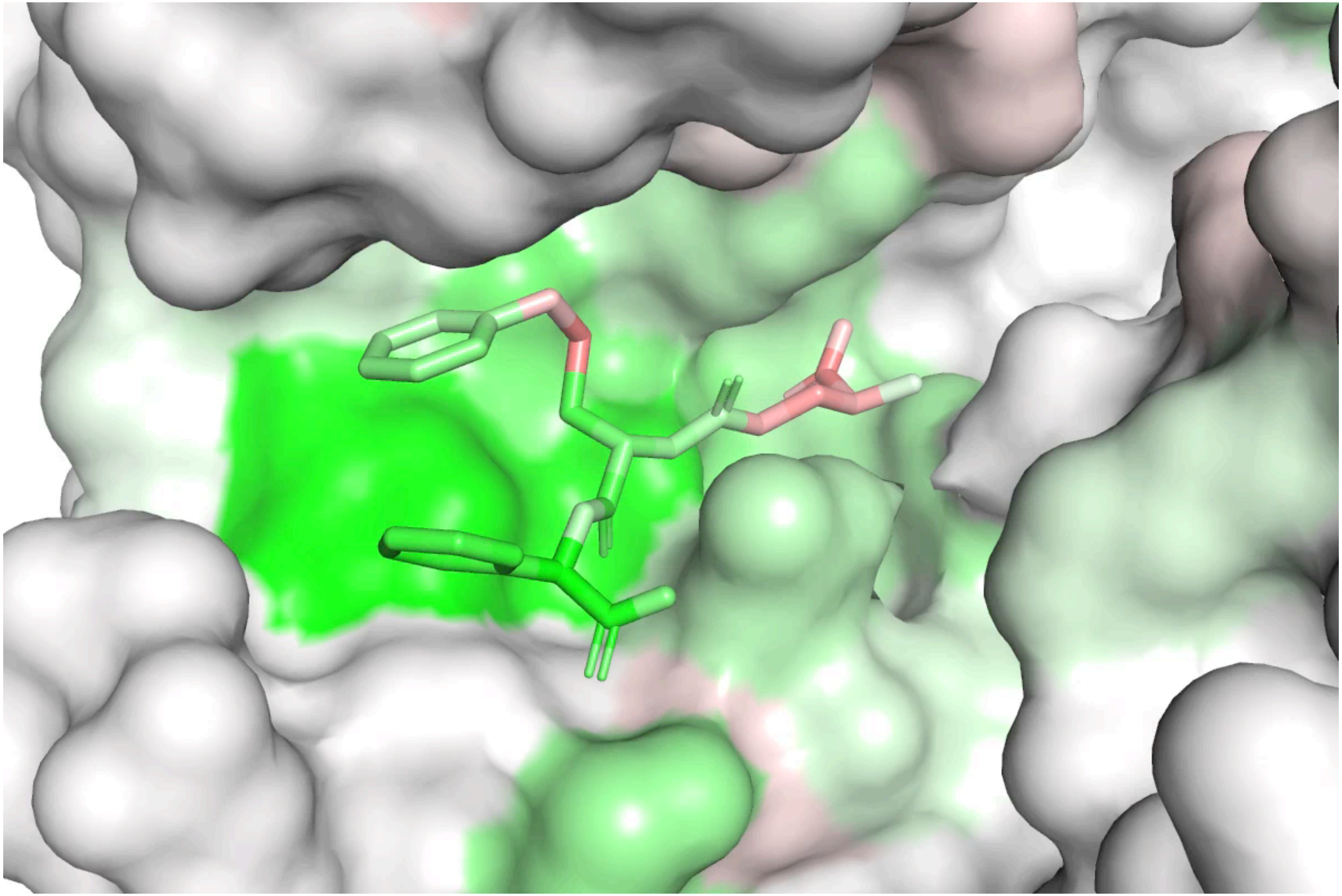


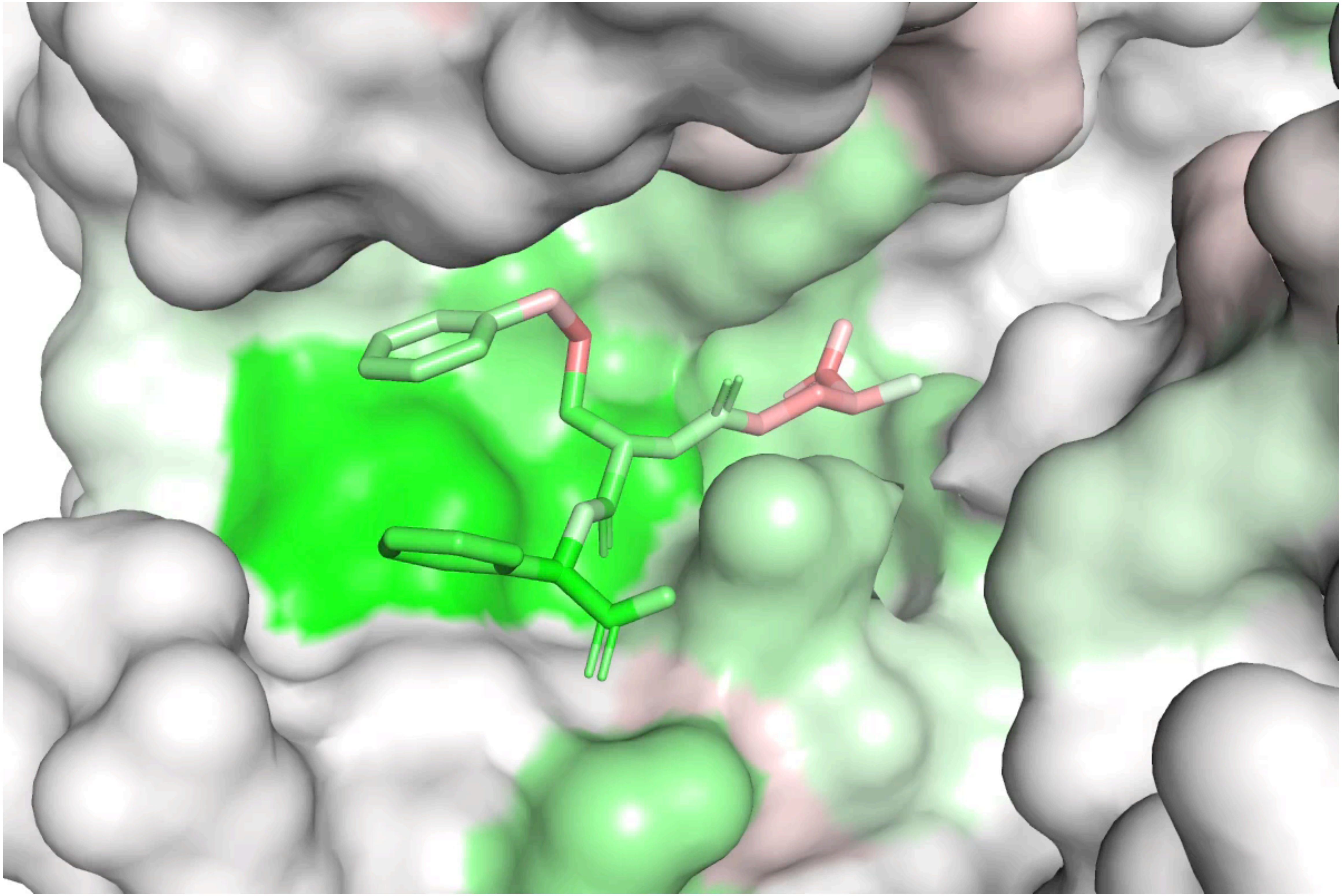
Beyond Scoring

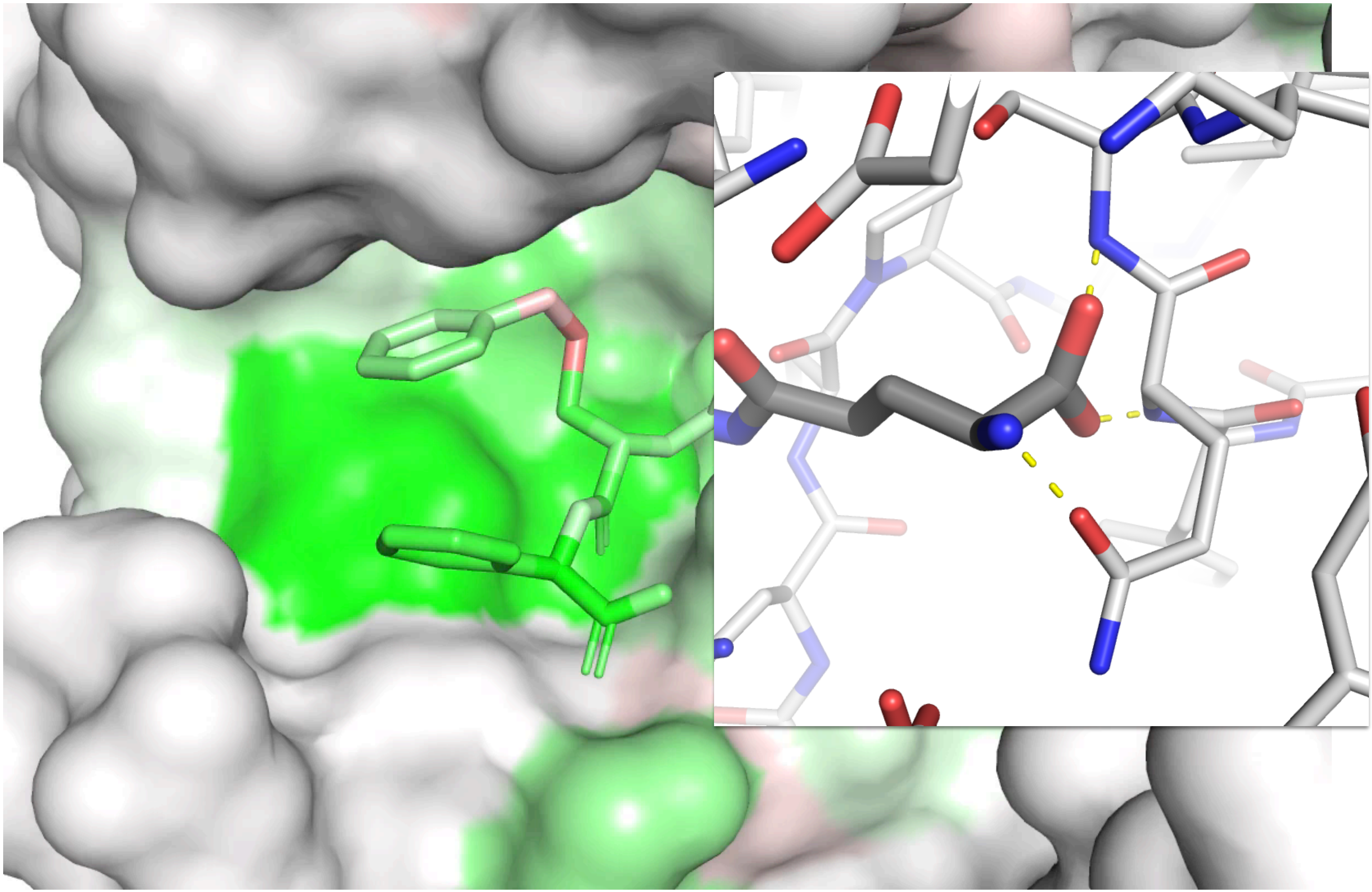


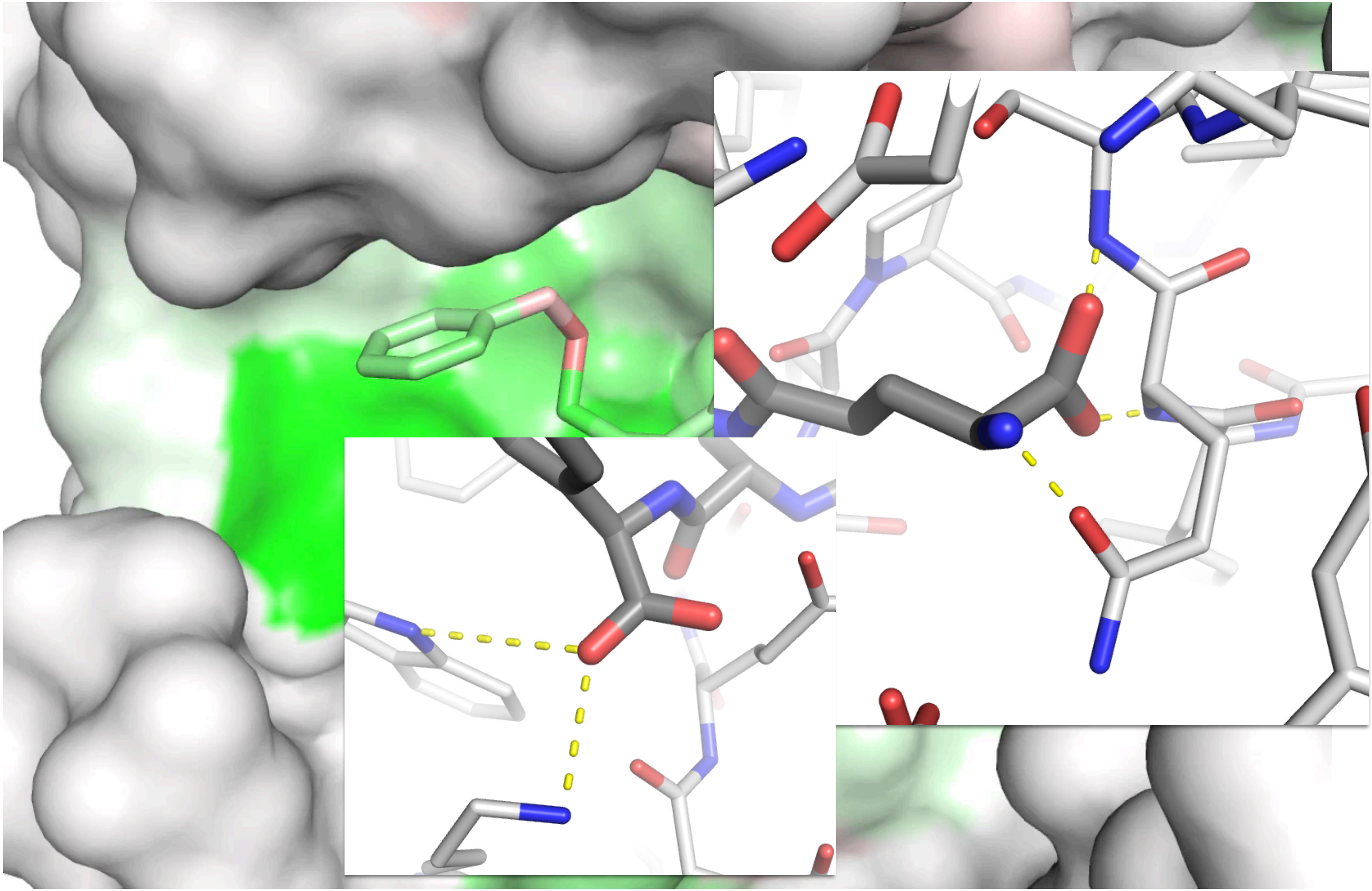
Beyond Scoring



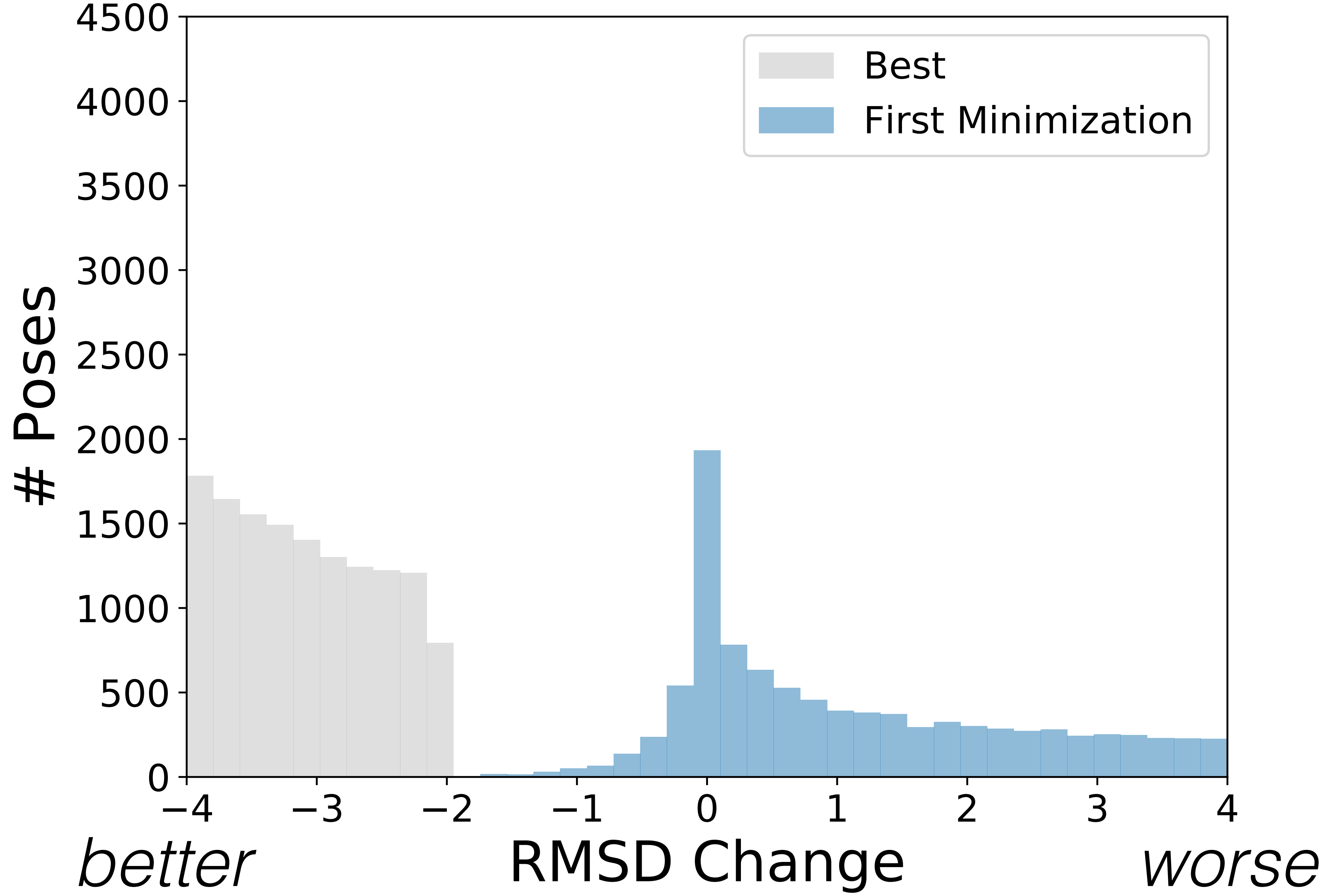


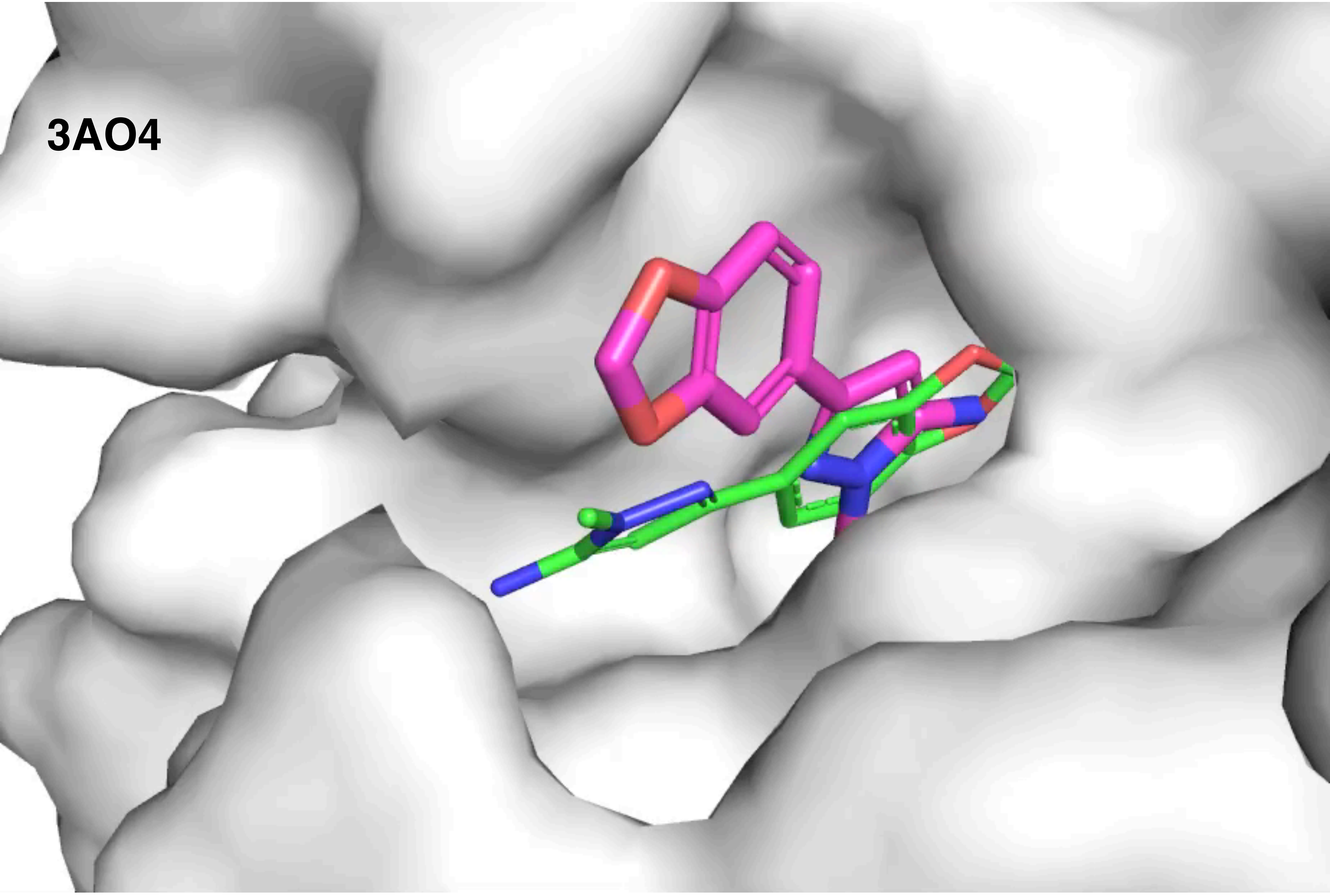


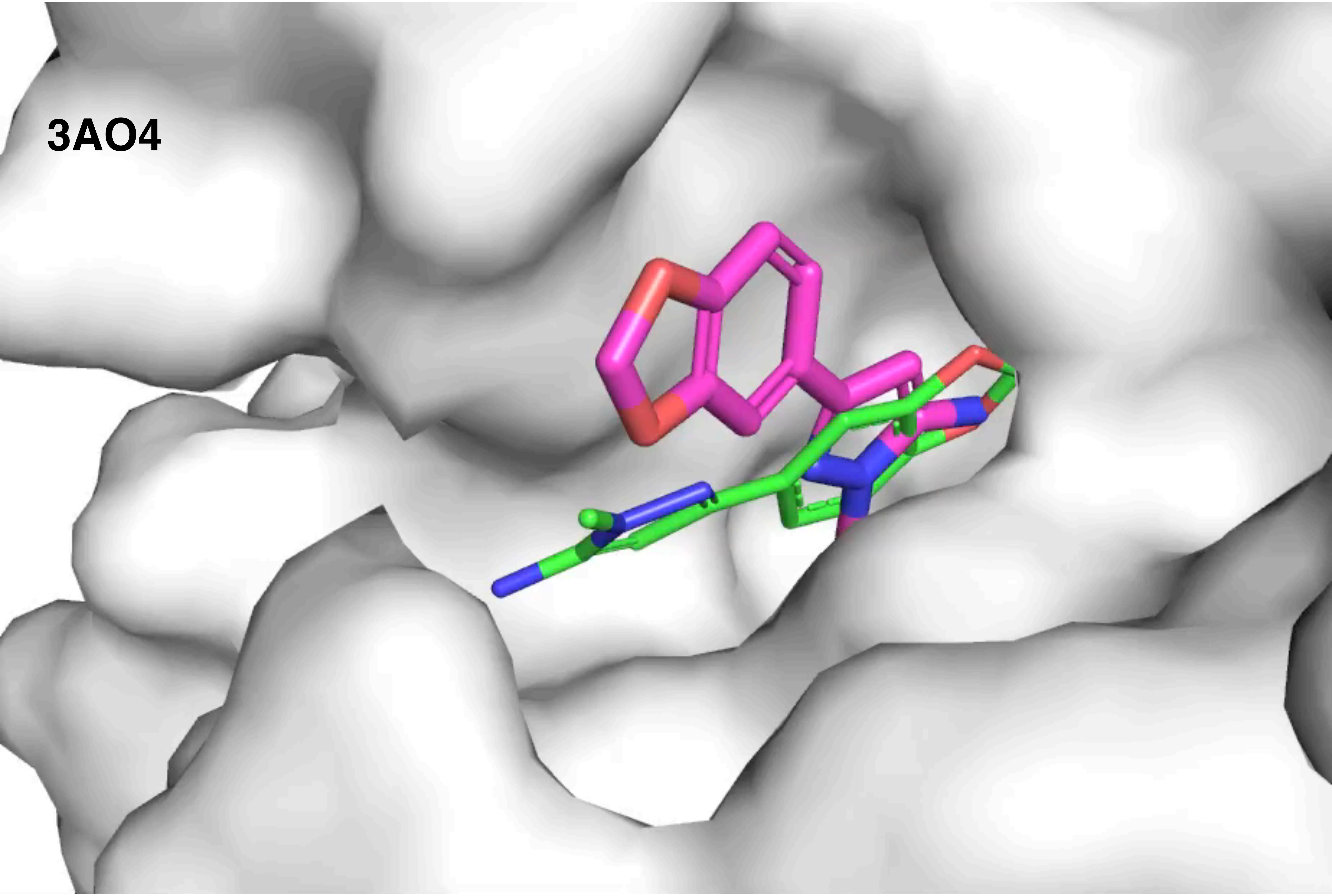




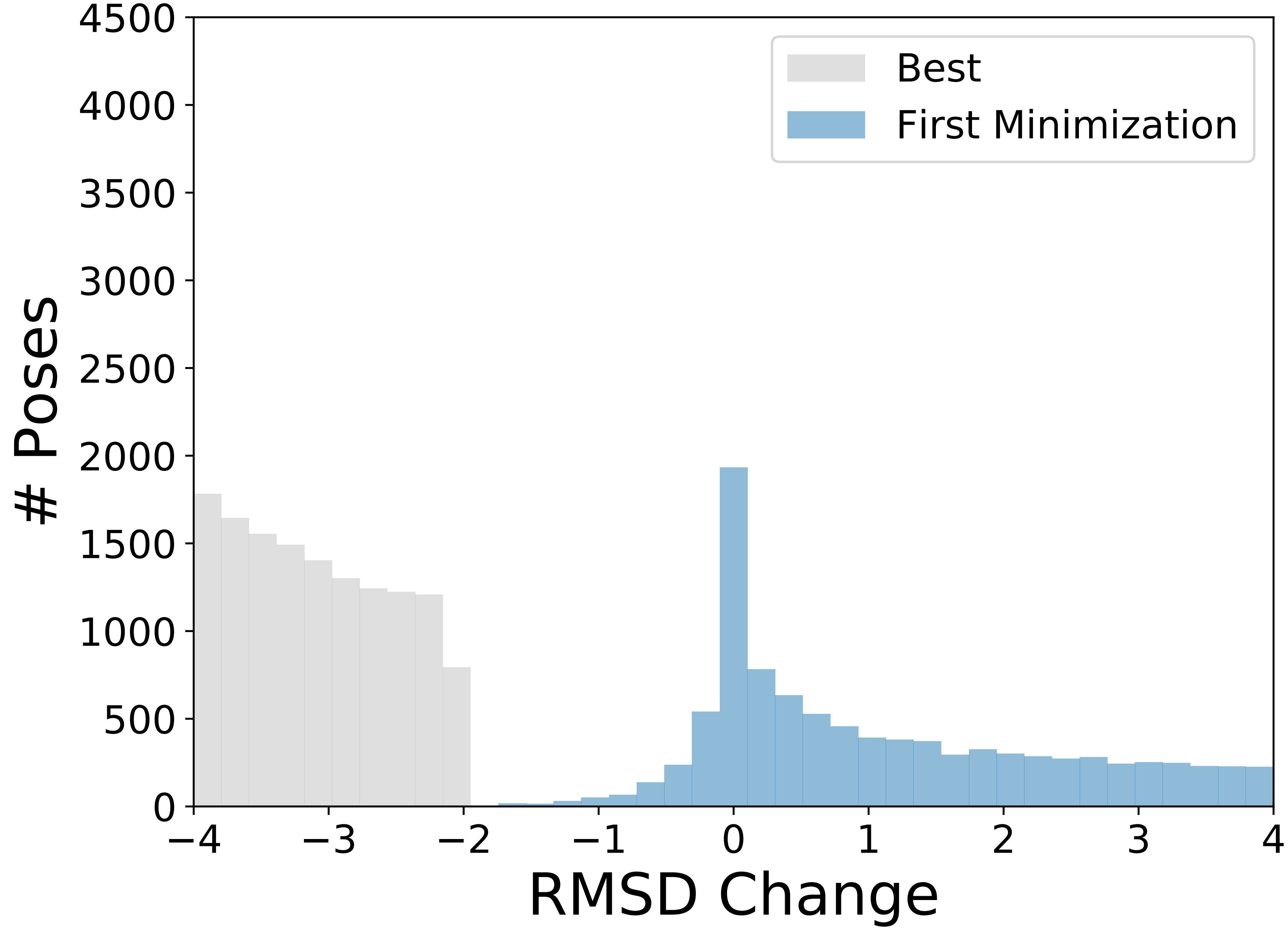
Minimizing Low RMSD Poses



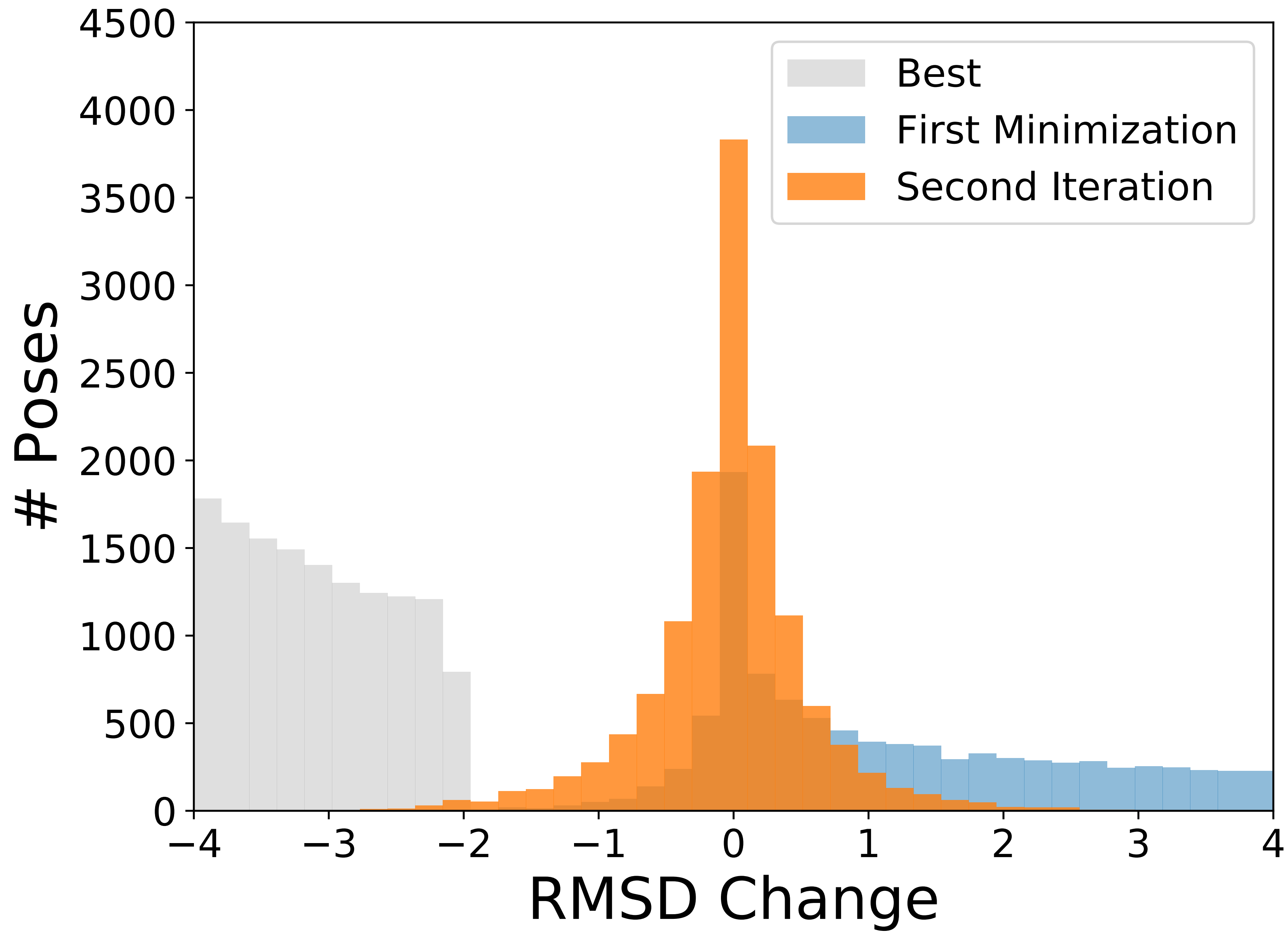

3AO4


3AO4

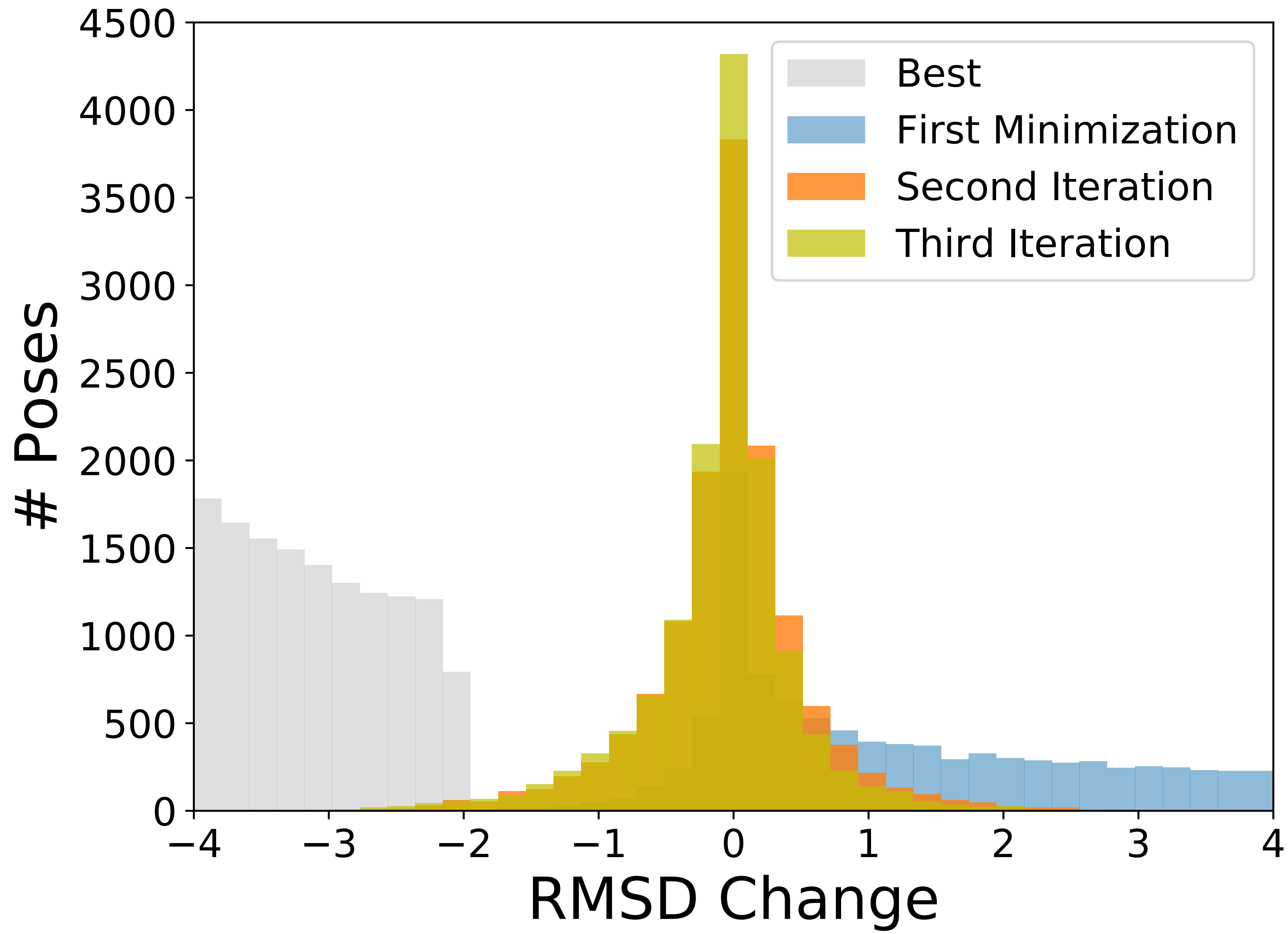
Iterative Refinement

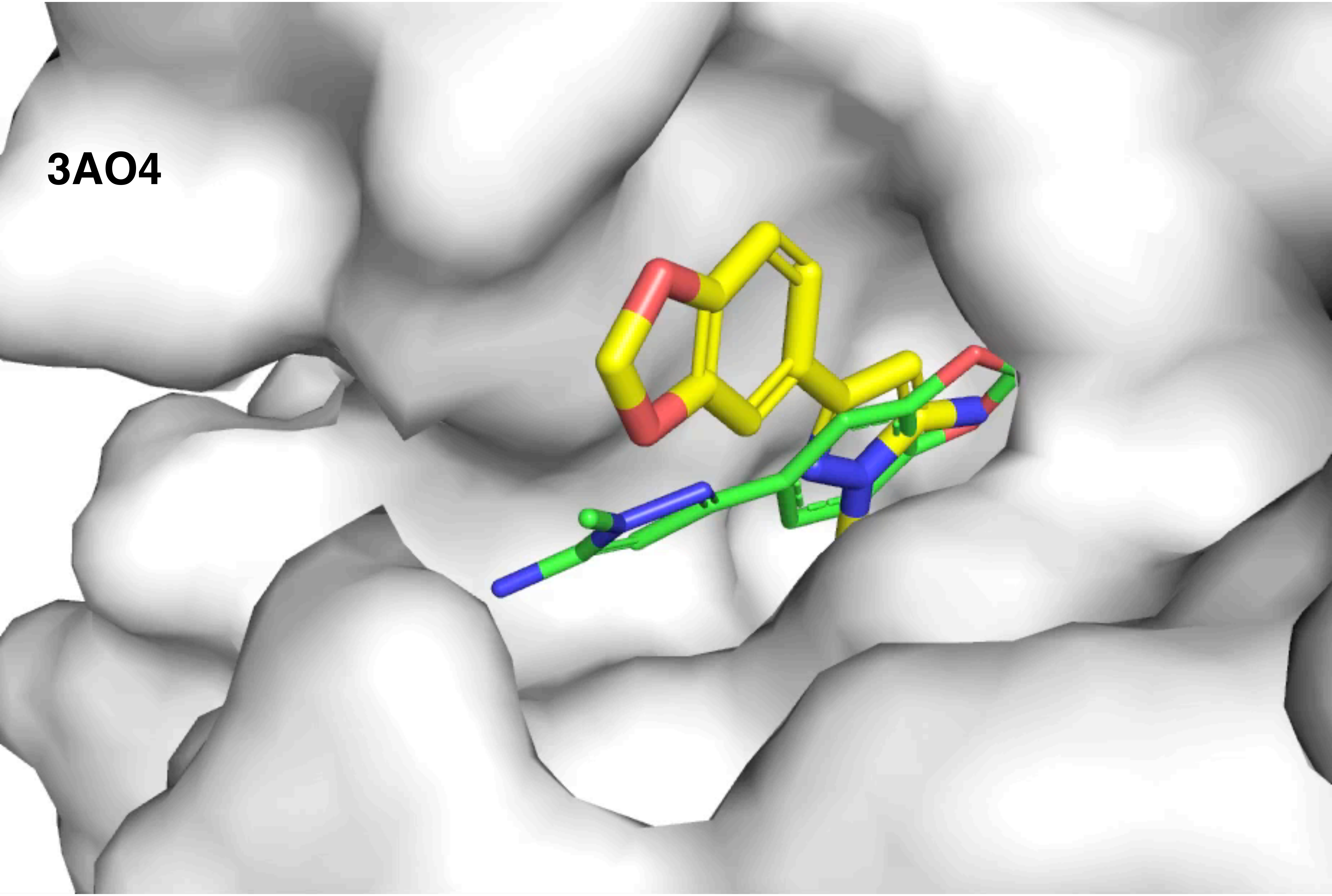


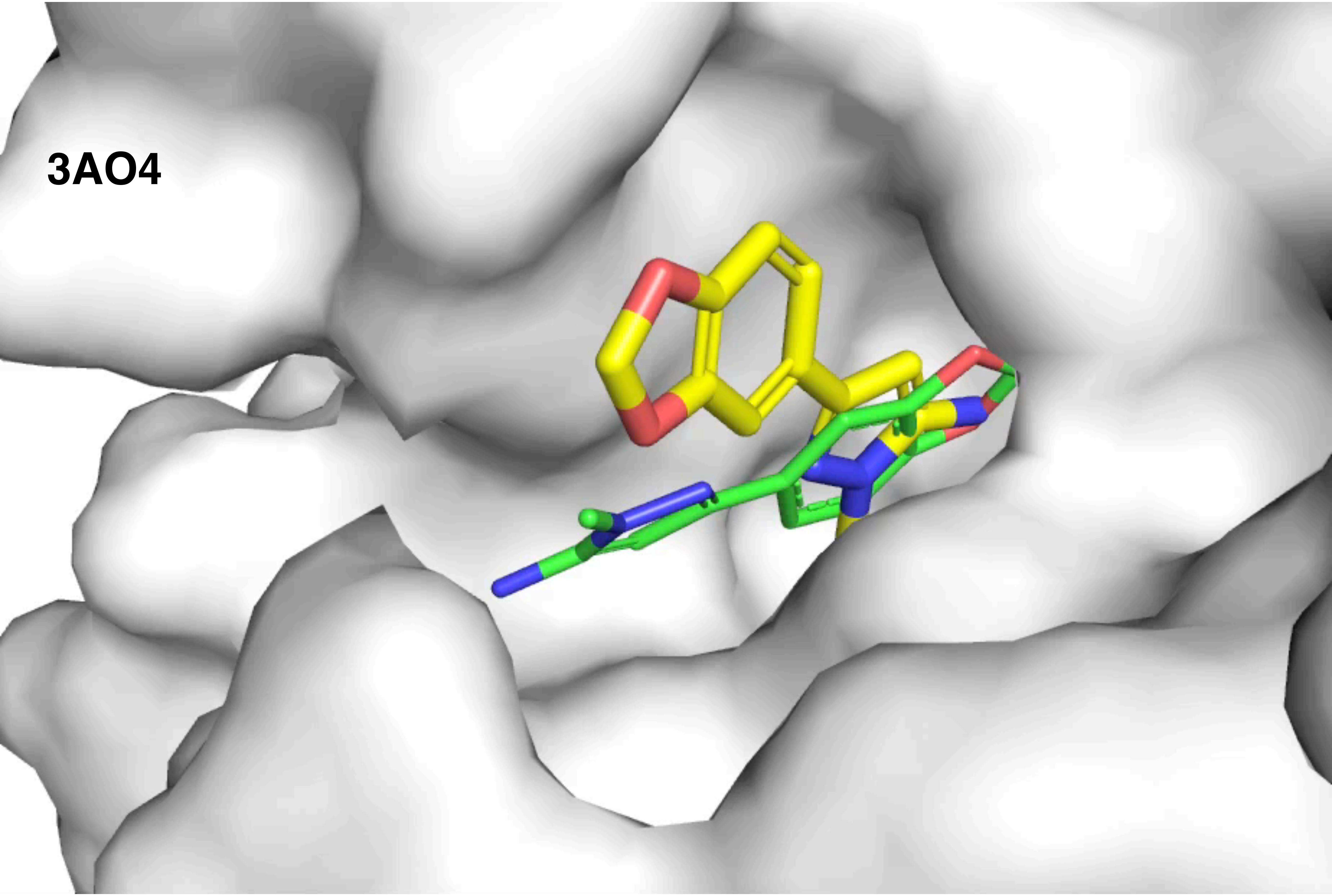
Iterative Refinement



Iterative Refinement




3AO4


3AO4

Related Work

MolecuLeNet: A continuous-filter convolutional neural network for modeling quantum interactions

Kristof T. Schütt, Pieter-Jan Kindermans, Huziel E. Sauceda, Stefan Chmiela, Alexandre Tkatchenko, Klaus-Robert Müller

(Submitted on 26 Jun 2017)

Automatic chemical design using a data-driven continuous representation of molecules

Rafael Gómez-Bombarelli, David Duvenaud, José Miguel Hernández-Lobato, Jorge Aguilera-Iparraguirre, Timothy D. Hirzel, Ryan P. Adams, Alán Aspuru-Guzik

(Submitted on 7 Oct 2016 (v1), last revised 6 Jan 2017 (this version, v2))

AtomNet: A Deep Convolutional Neural Network for Bioactivity Prediction in Structure-based Drug Discovery

Izhar Wallach, Michael Dzamba, Abraham Heifets

(Submitted on 10 Oct 2015)

ANI-1: An extensible neural network potential with DFT accuracy at force field computational cost

Justin S. Smith, Olexandr Isayev, Adrian E. Roitberg

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Convolutional Networks on Graphs for Learning Molecular Fingerprints

David Duvenaud, Dougal Maclaurin, Jorge Aguilera-Iparraguirre, Rafael Gómez-Bombarelli, Timothy Hirzel, Alán Aspuru-Guzik, Ryan P. Adams

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Atomic Convolutional Networks for Predicting Protein-Ligand Binding Affinity

Joseph Gomes, Bharath Ramsundar, Evan N. Feinberg, Vijay S. Pande

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Deep Architectures and Deep Learning in Chemoinformatics: The Prediction of Aqueous Solubility for Drug-Like Molecules

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Low Data Drug Discovery with One-shot Learning

Han Altae-Tran, Bharath Ramsundar, Aneesh S. Pappu, Vijay Pande

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Massively Multitask Networks for Drug Discovery

Bharath Ramsundar, Steven Kearnes, Patrick Riley, Dale Webster, David Konerding, Vijay Pande

(Submitted on 6 Feb 2015)

Protein–Ligand Scoring with Convolutional Neural Networks

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