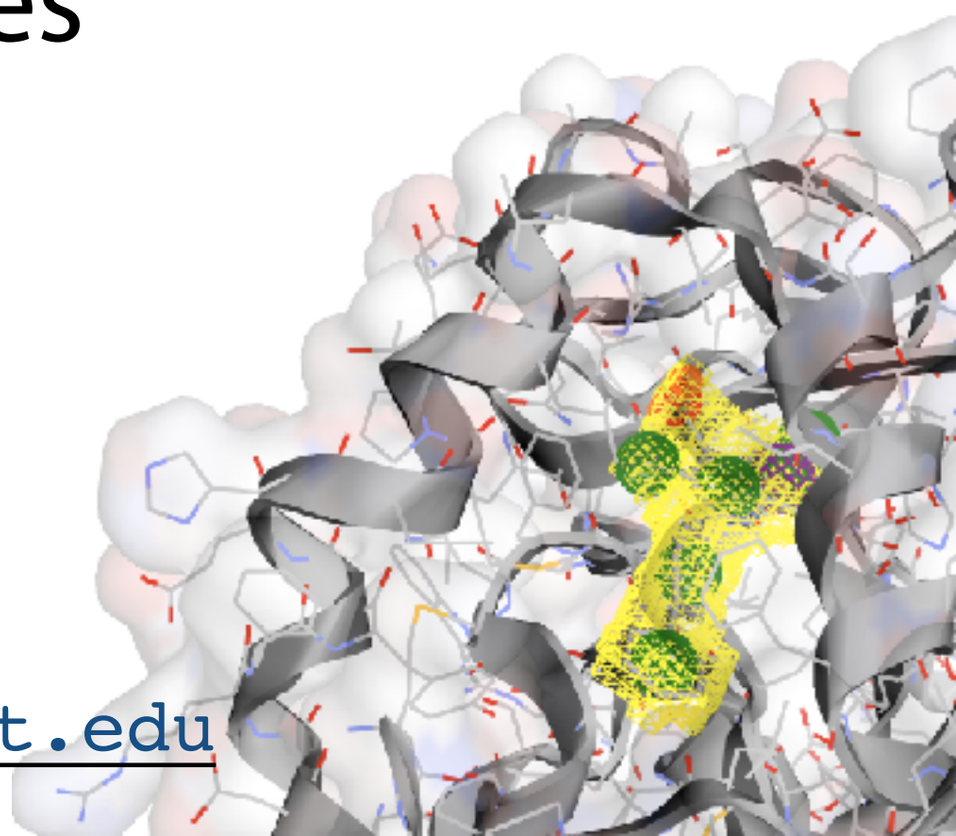
Computational Drug Discovery

David Ryan Koes

11/19/2017



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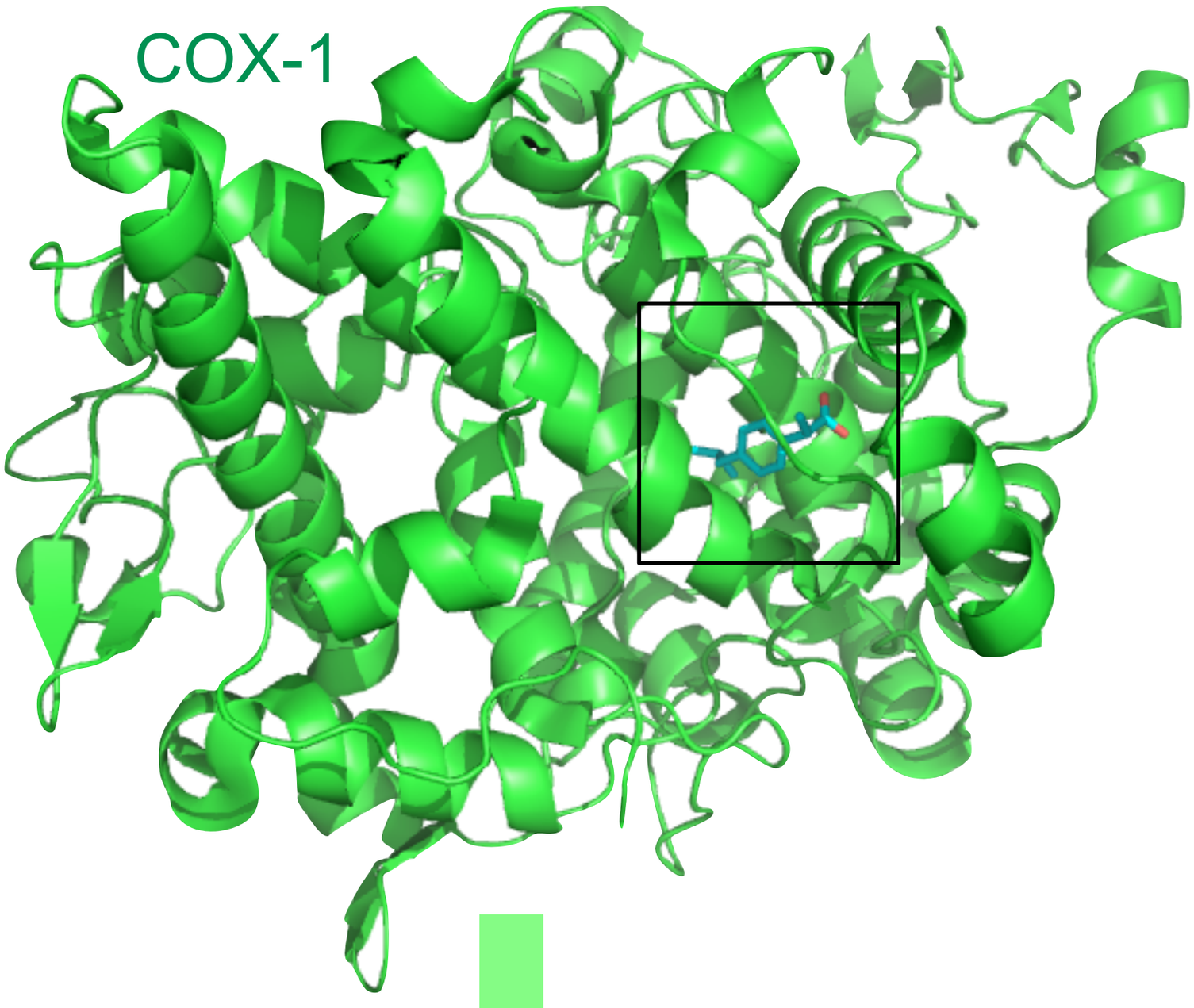
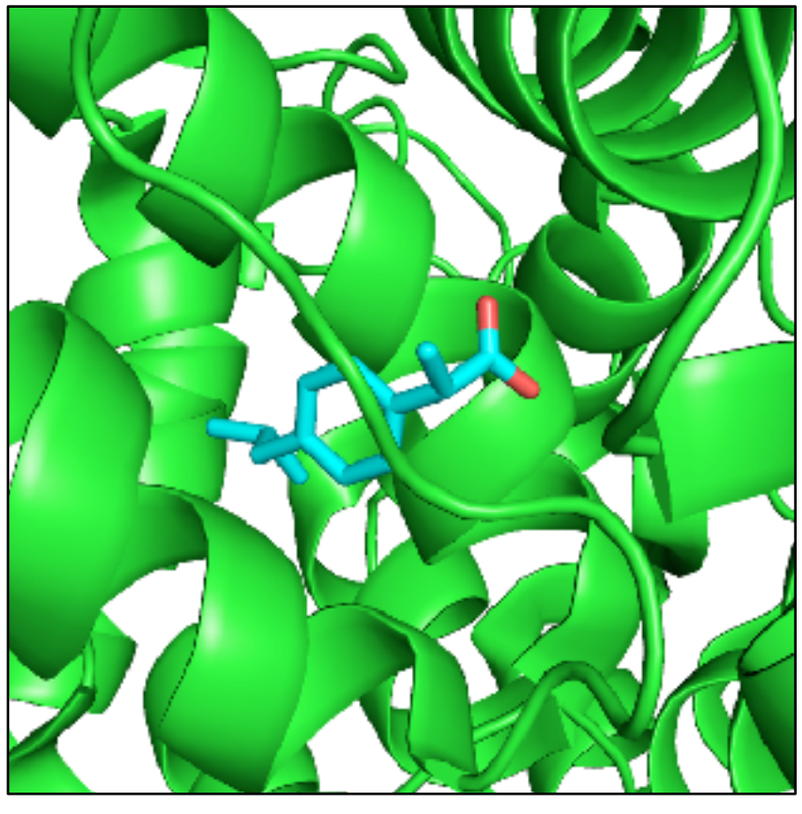
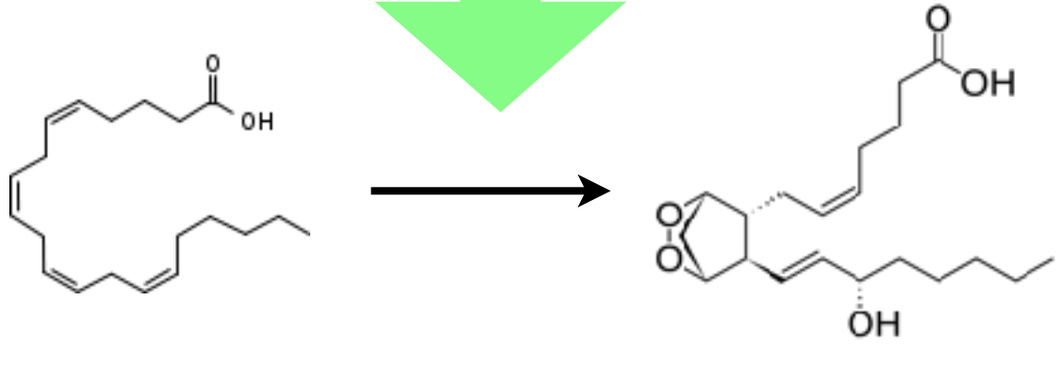
A small molecule intended to affect the structure/function of macromolecules


COX-1




OH
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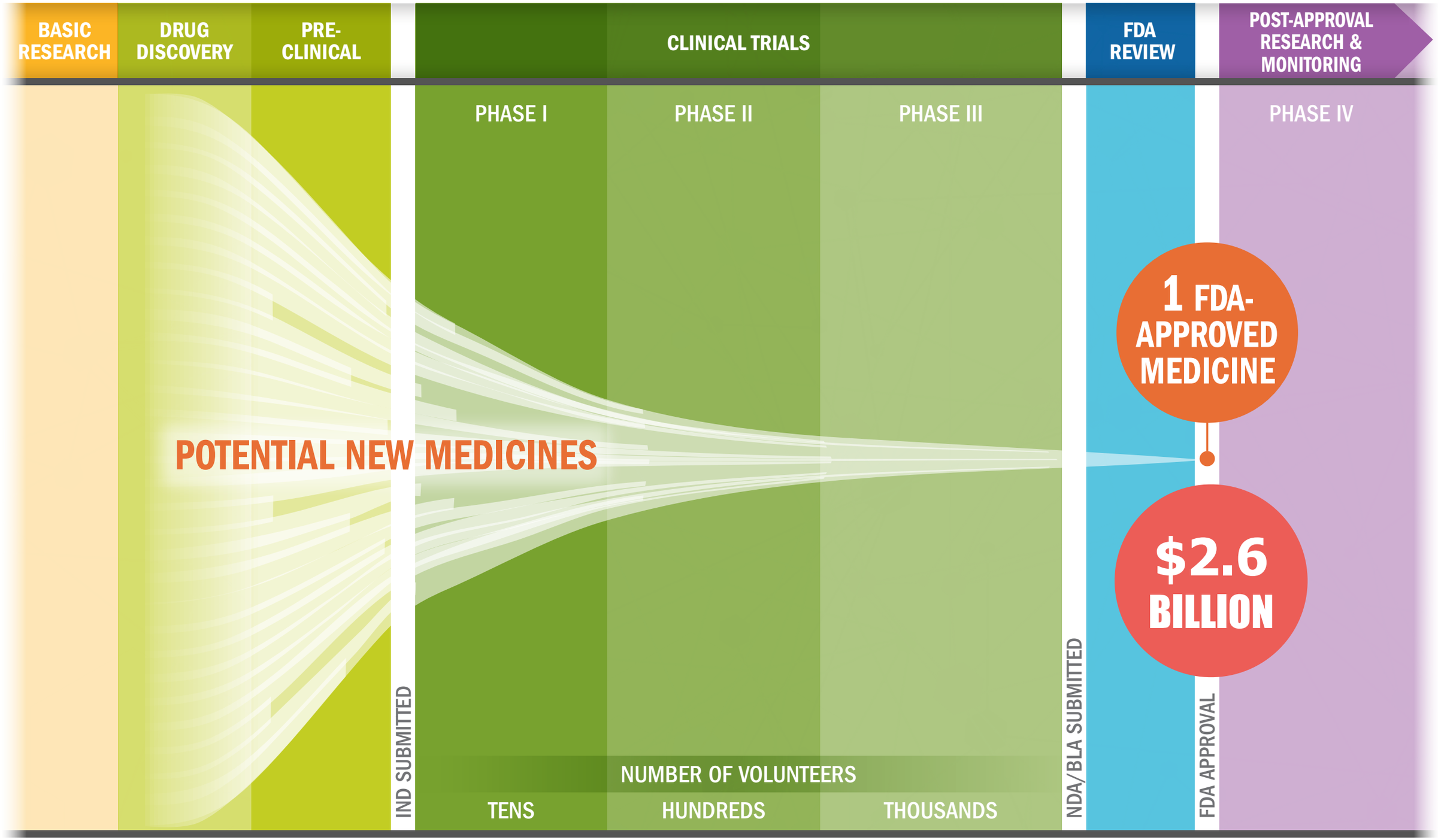
OH

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



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

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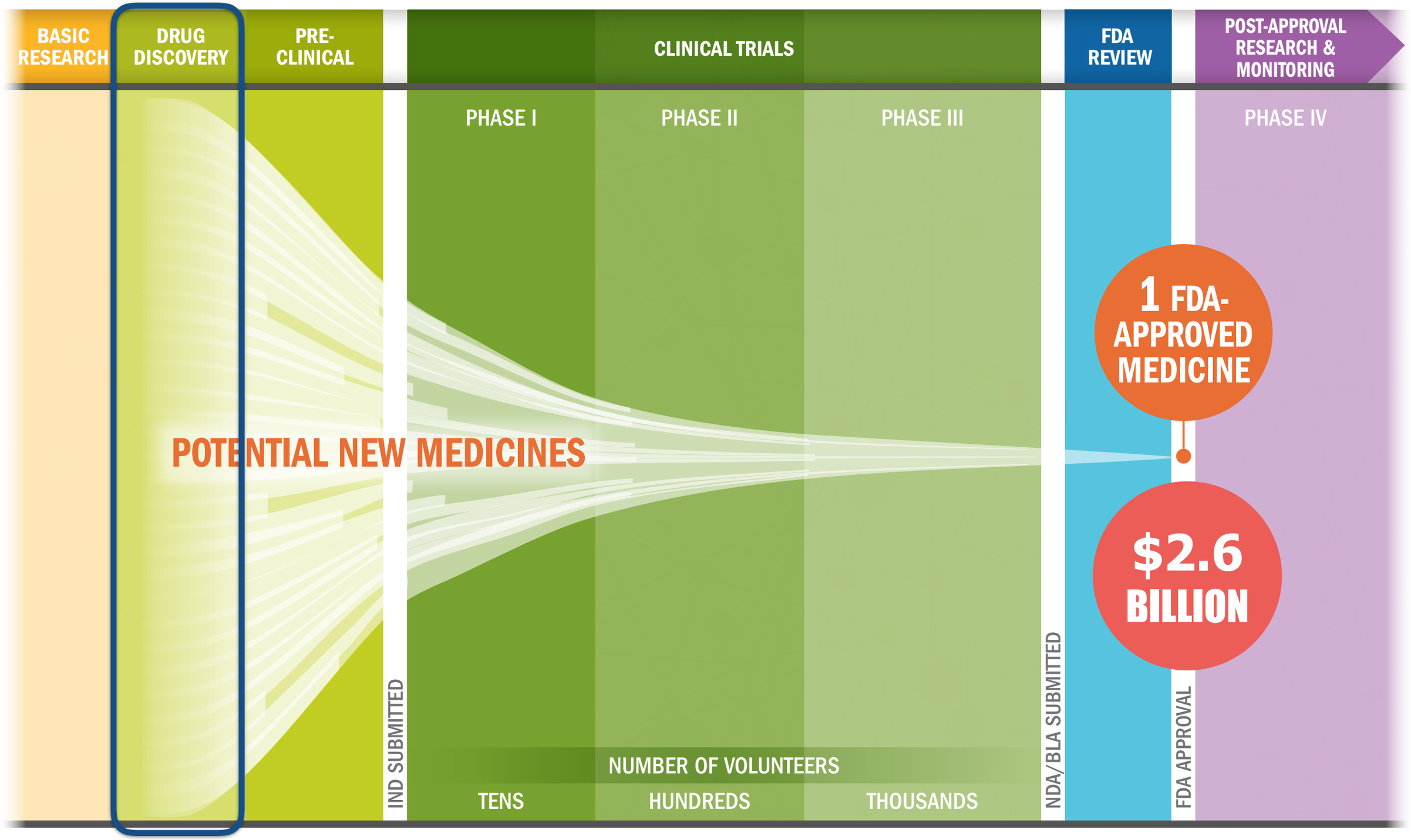

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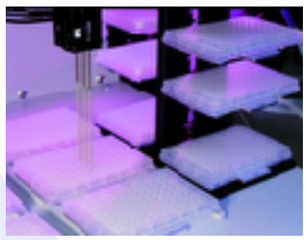
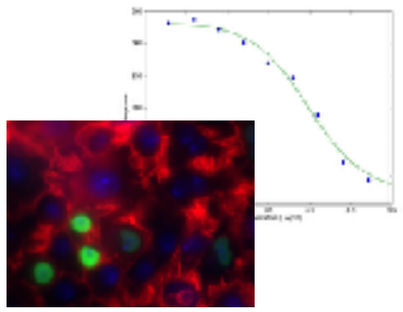
1. Does the compound do what you want it to?
2. Does the compound **not** do what you **don't** want it to?
3. Is what you want it to do the right thing?

Drug Discovery

Target Identification



Screening



Lead Identification

Lead Optimization

Compounds **Hits** **Leads** **Clinical Candidates**

Cost

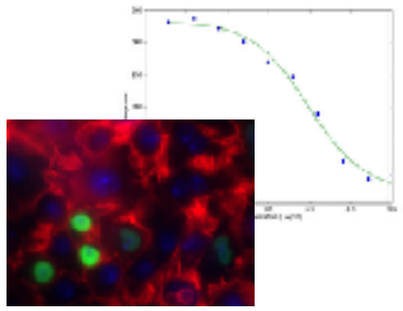
Computational Drug Discovery

Omics

Target Identification

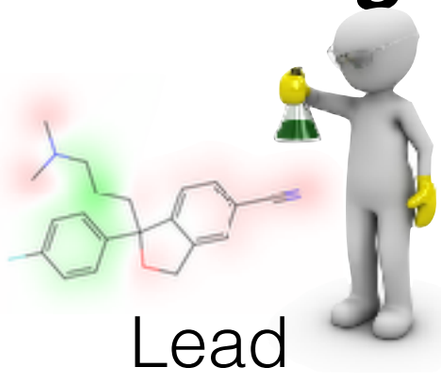
Virtual

Screening



Lead Identification

Modeling



Lead Optimization

Compounds **Hits** **Leads** **Clinical Candidates**

Cost

Kinds of Virtual Screening

ADMET

Ligand Based

- similarity to known binder
- QSAR
- pharmacophore

Receptor Based

- dock and score
- simulation

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

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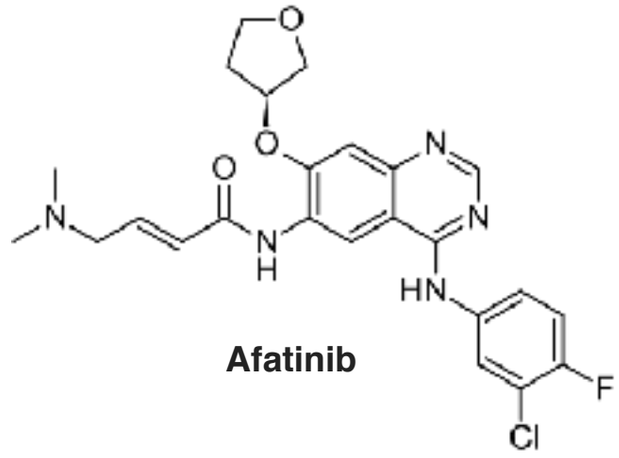
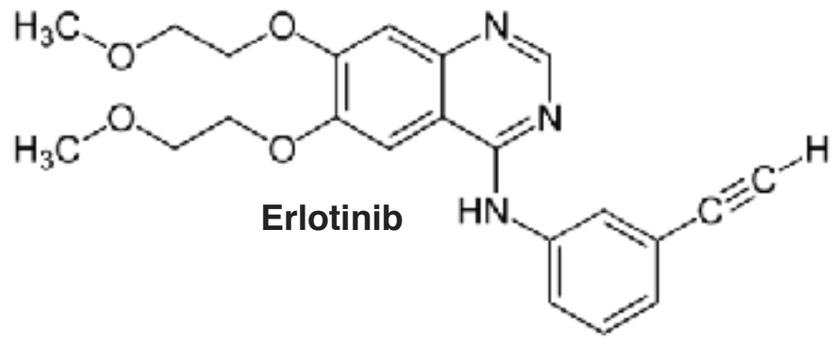
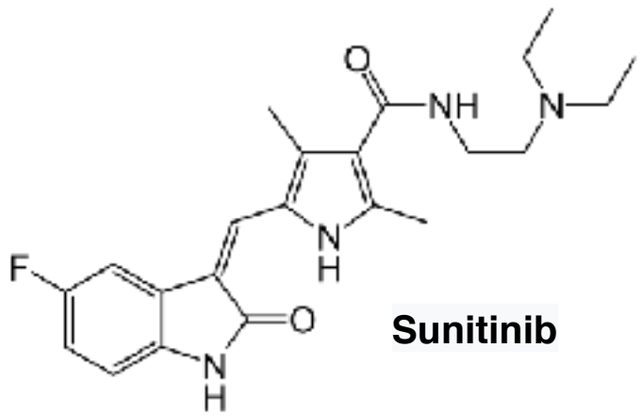


Afatinib



Erlotinib



Sunitinib

Ligand Based: Similarity

Fingerprint Methods

- map molecules to a descriptor space:

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

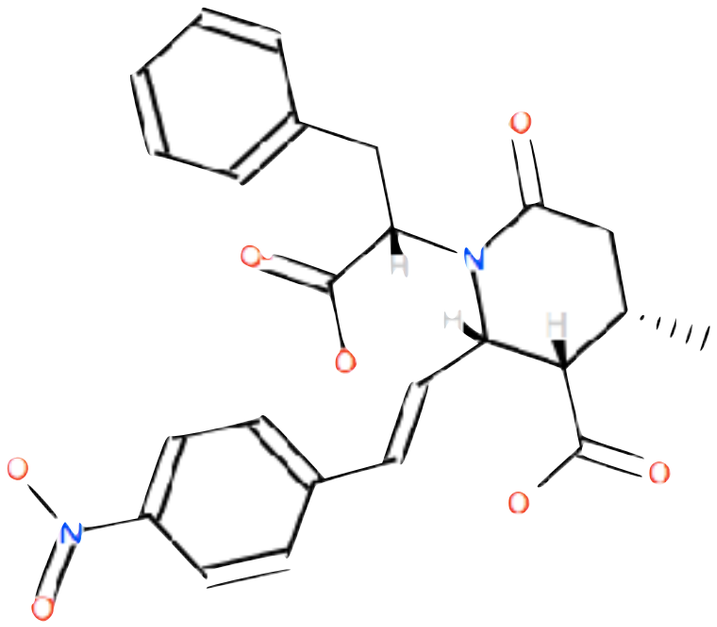
- similarity is “distance” between descriptors
- for bit vectors, Tanimoto distance used

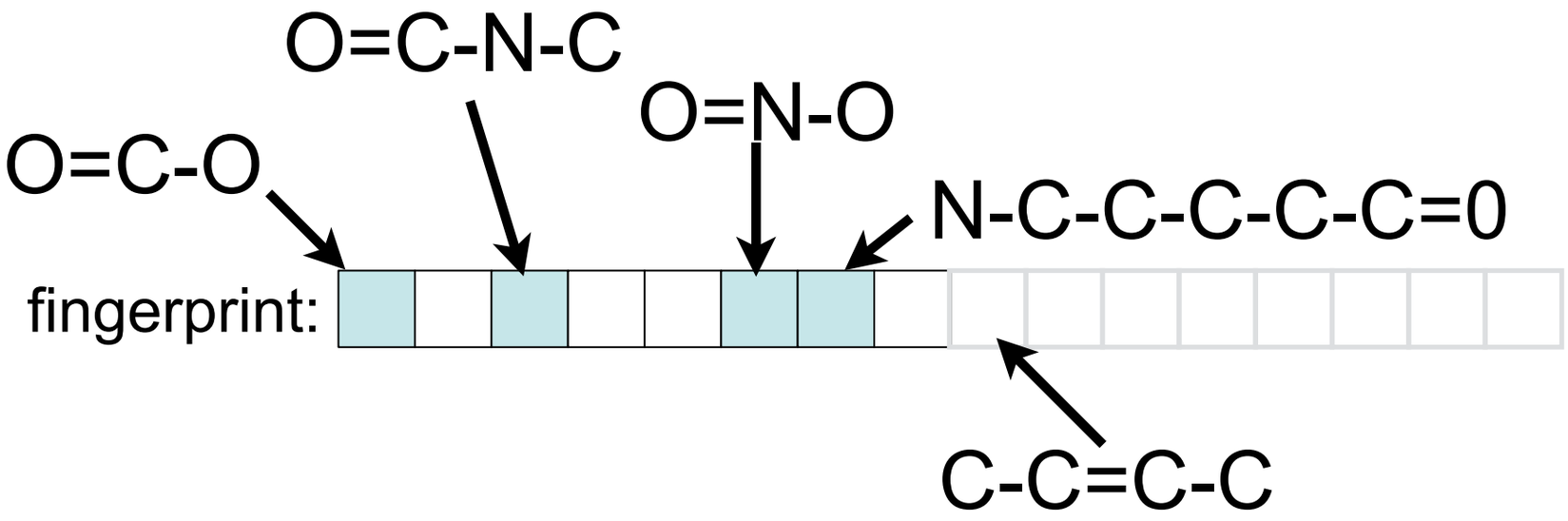
$$T(A,B) = \frac{|A \cap B|}{|A \cup B|}$$

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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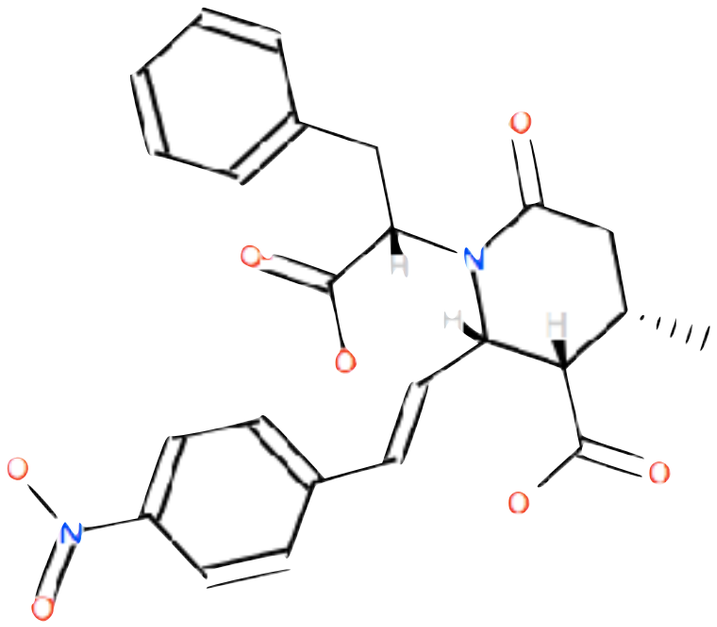
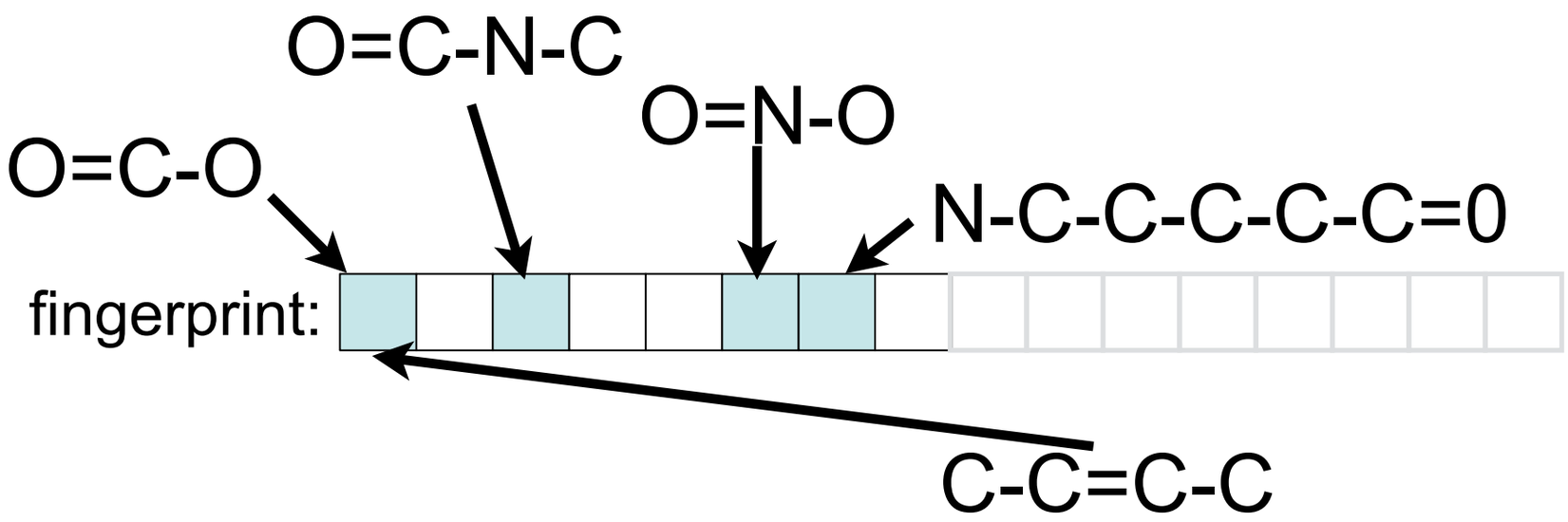


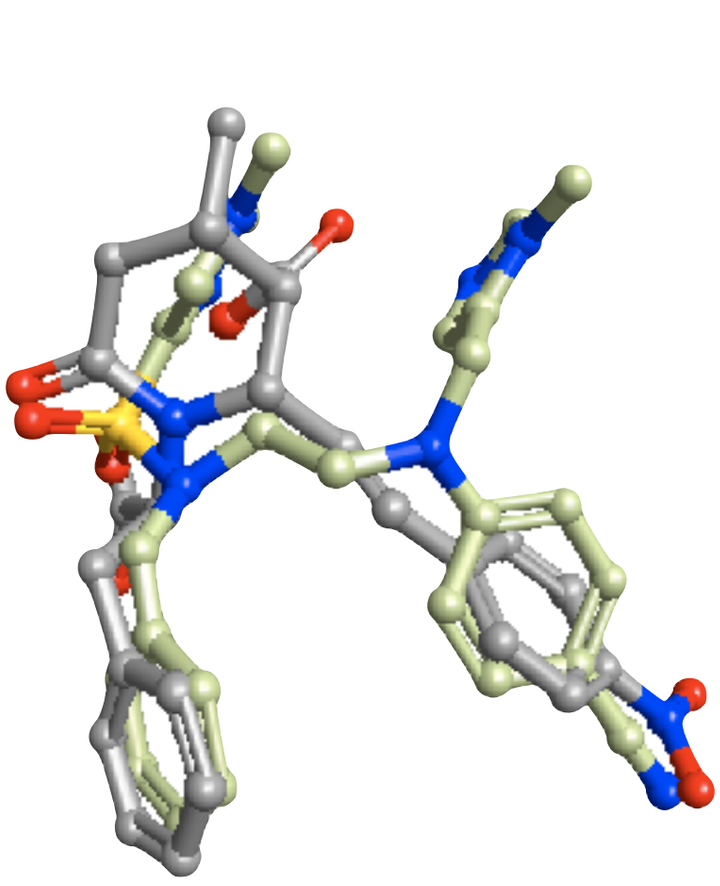


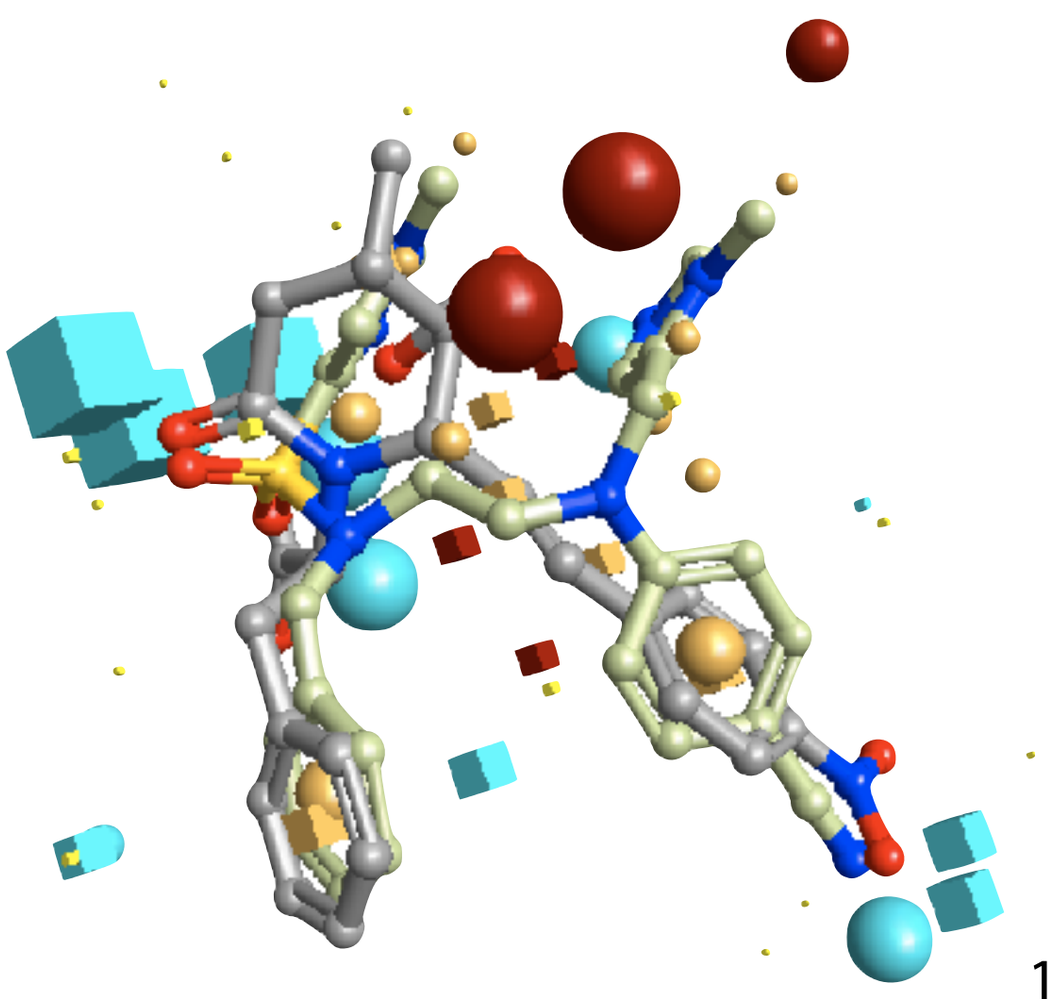
Ligand Based: Similarity

Superposition Methods

- compute "overlap" between molecules

- consider shape, electrostatics, **pharmacophores**



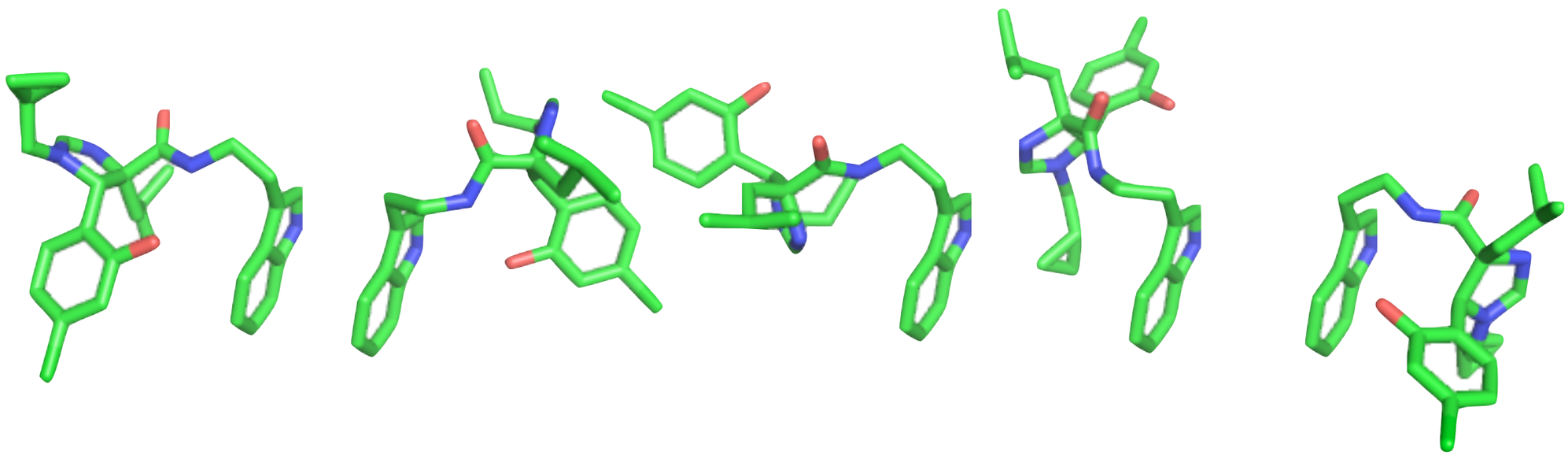


http://www.cresset-group.com/

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: QSAR

Quantitative Structure/Activity Relationships

Properties

Compounds

Cmpd Number	Cmpd Name	X	Log EC_{50}	π	Calculated Log EC_{50}	Residual
1	6a	H	1.07	0	0.79	0.28
2	6b	Cl	0.09	0.71	0.21	-0.12
3	6d	NO_2	0.66	-0.28	1.02	-0.36
4	6e	CN	1.42	-0.57	1.26	0.16
5	6f	C_6H_5	-0.62	1.96	-0.81	0.19
6	6g	$N(CH_3)_2$	0.64	0.18	0.65	-0.01
7	6h	I	-0.46	1.12	-0.12	-0.34

Biological Activity = Learned ~~linear~~ function of properties

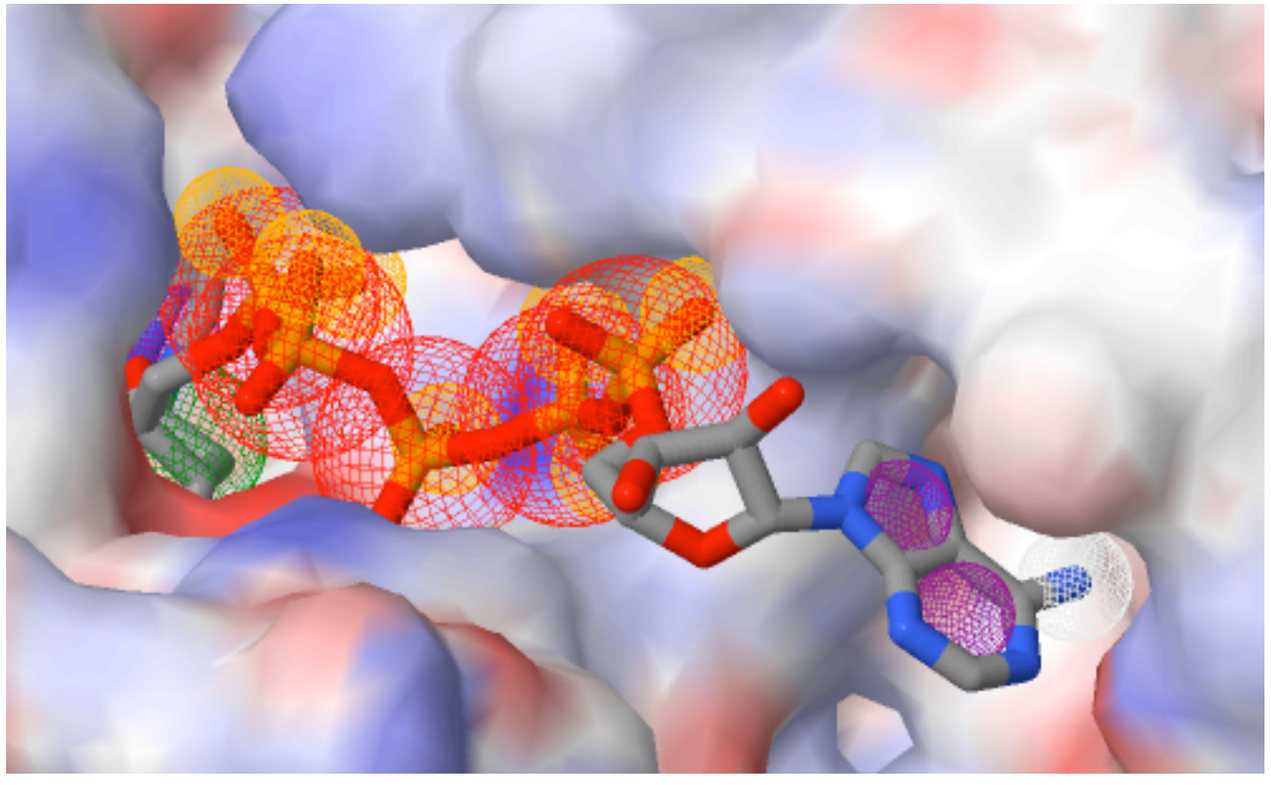
3D-QSAR: includes geometric/structural properties

Ligand/Receptor Based: Pharmacophore

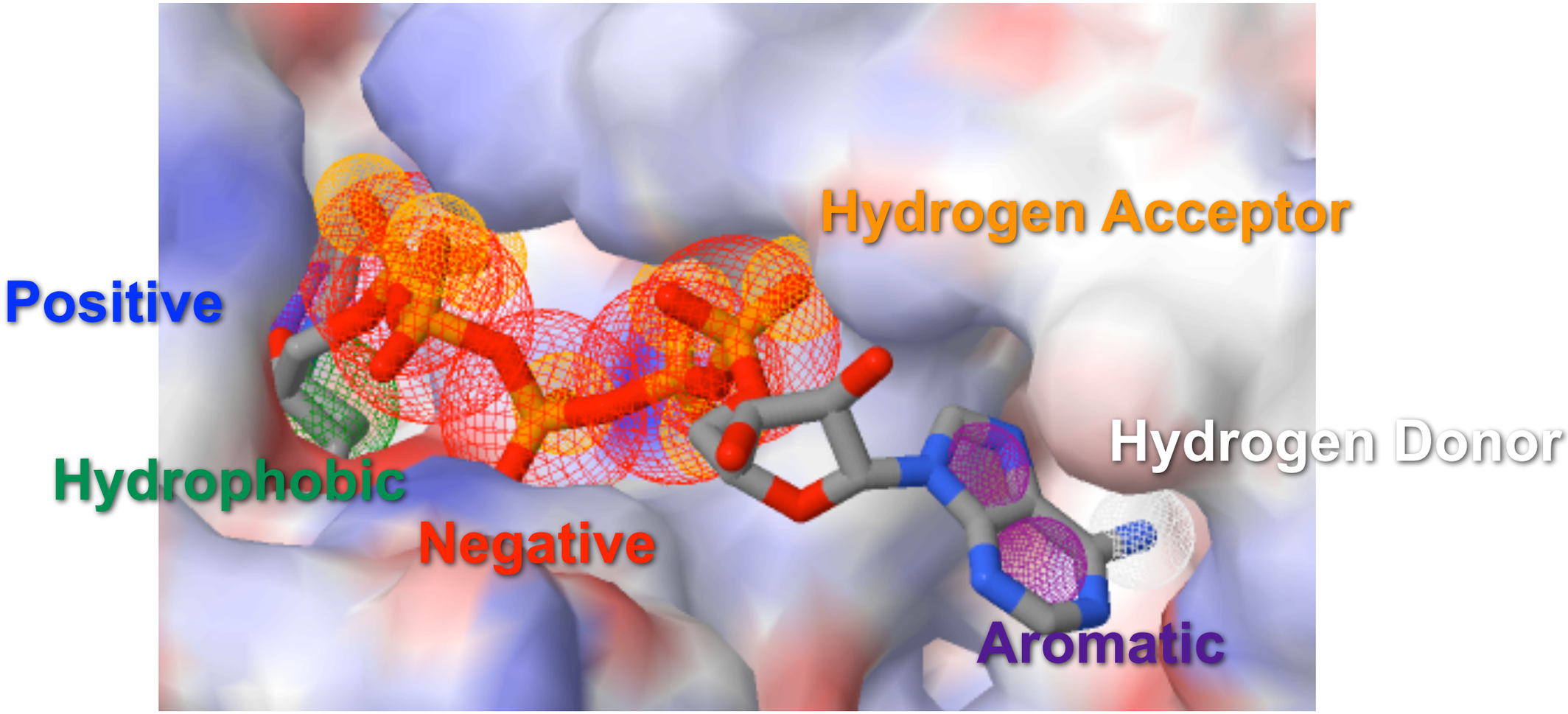
Pharmacophore:

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.

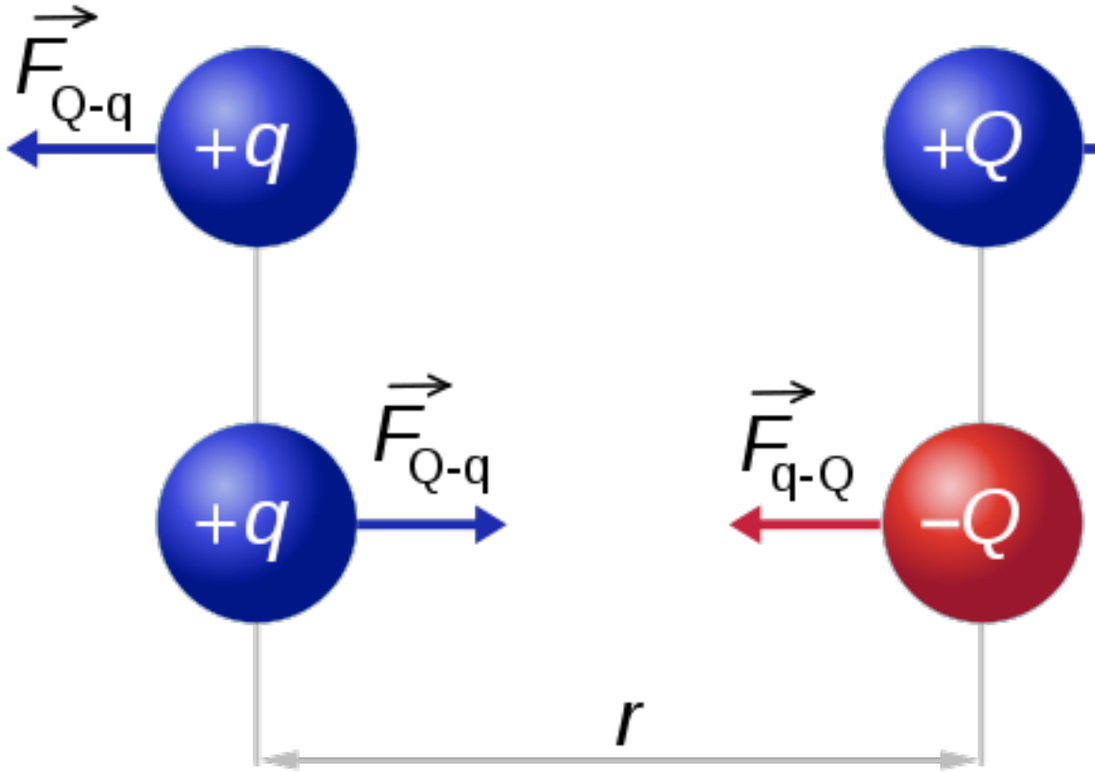
Common Features:
aromatic ring
hydrophobic area
positive ionizable
negative ionizable
hydrogen bond donor
hydrogen bond acceptor



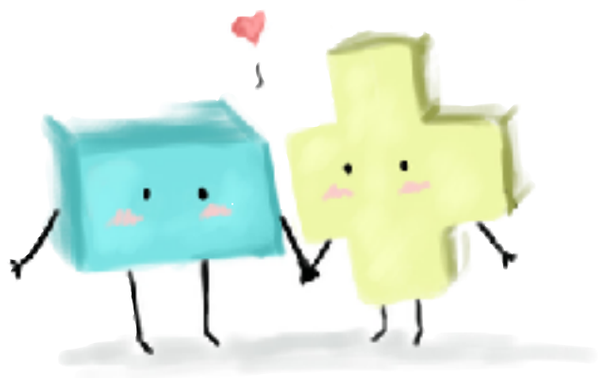
Pharmacophore Features



Charge-Charge



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



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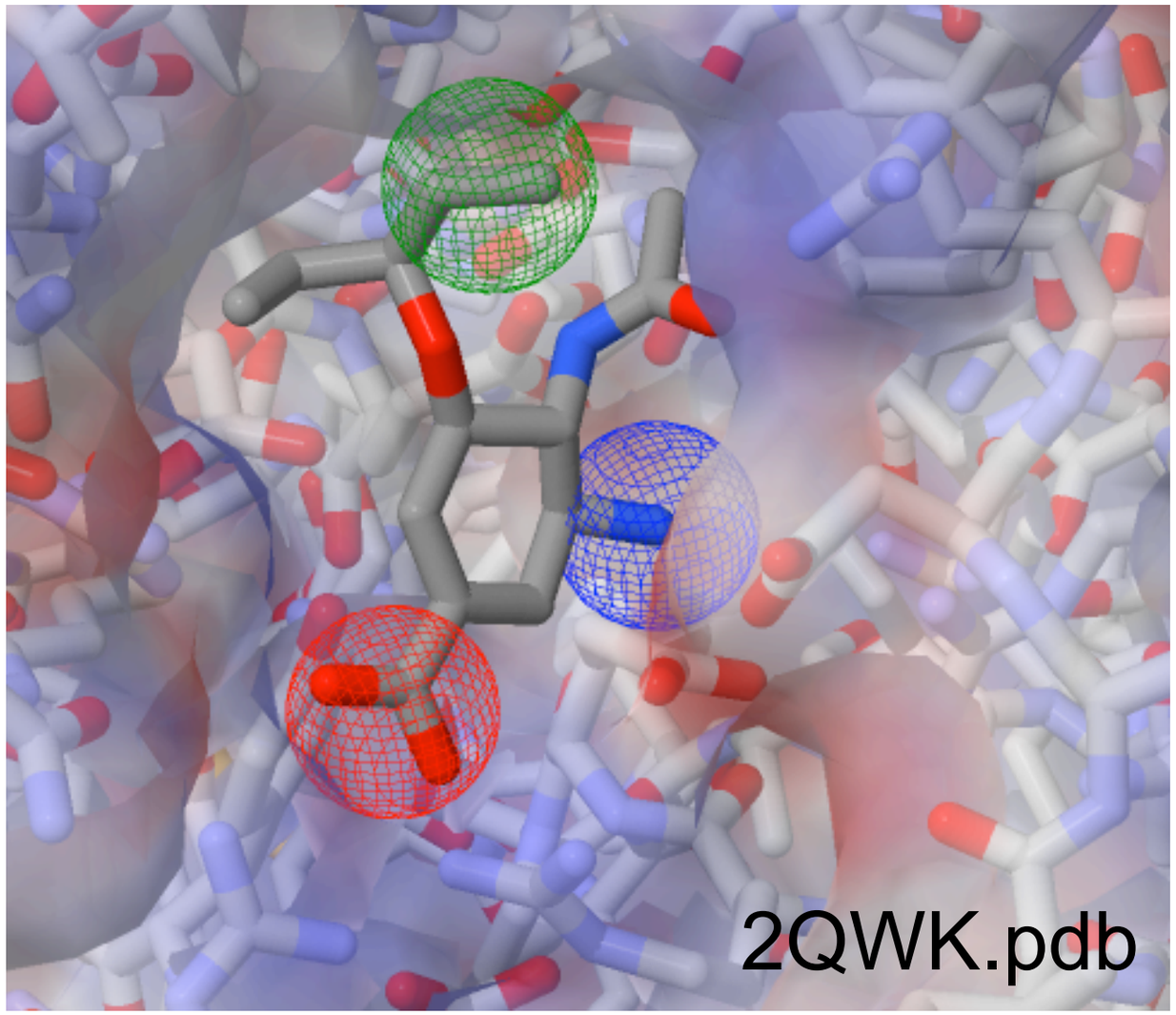
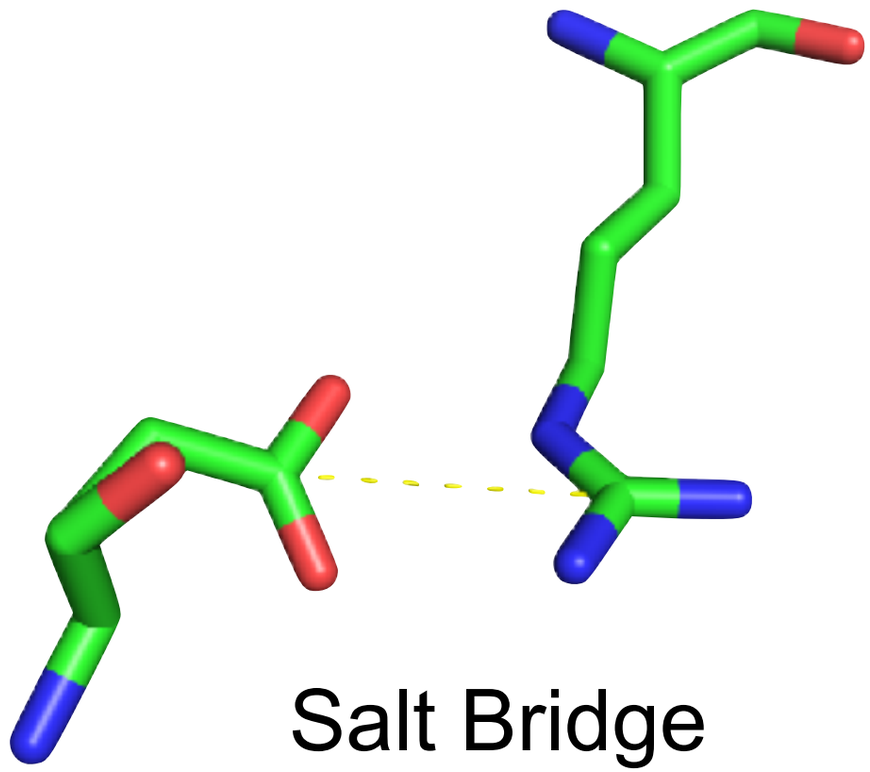
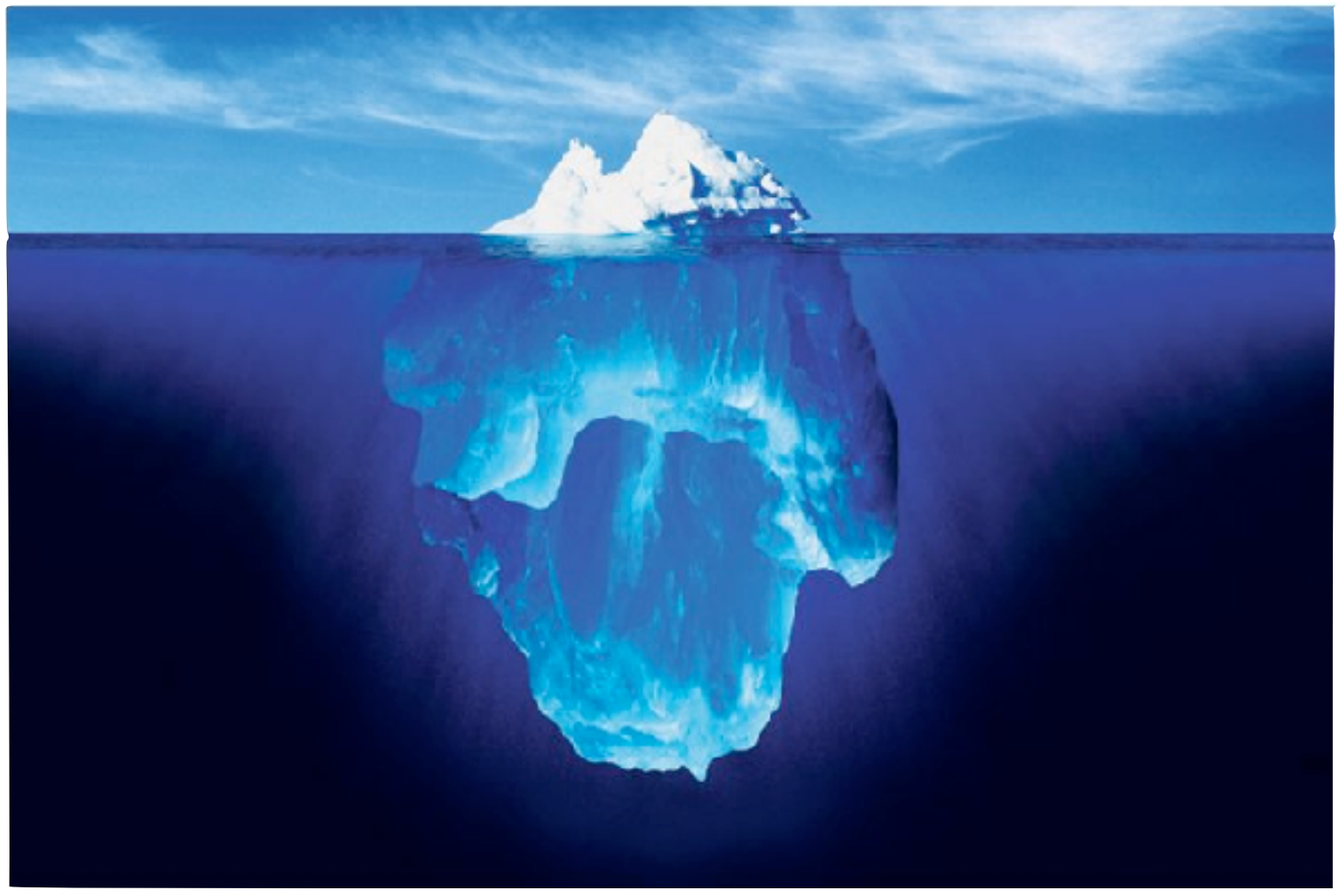


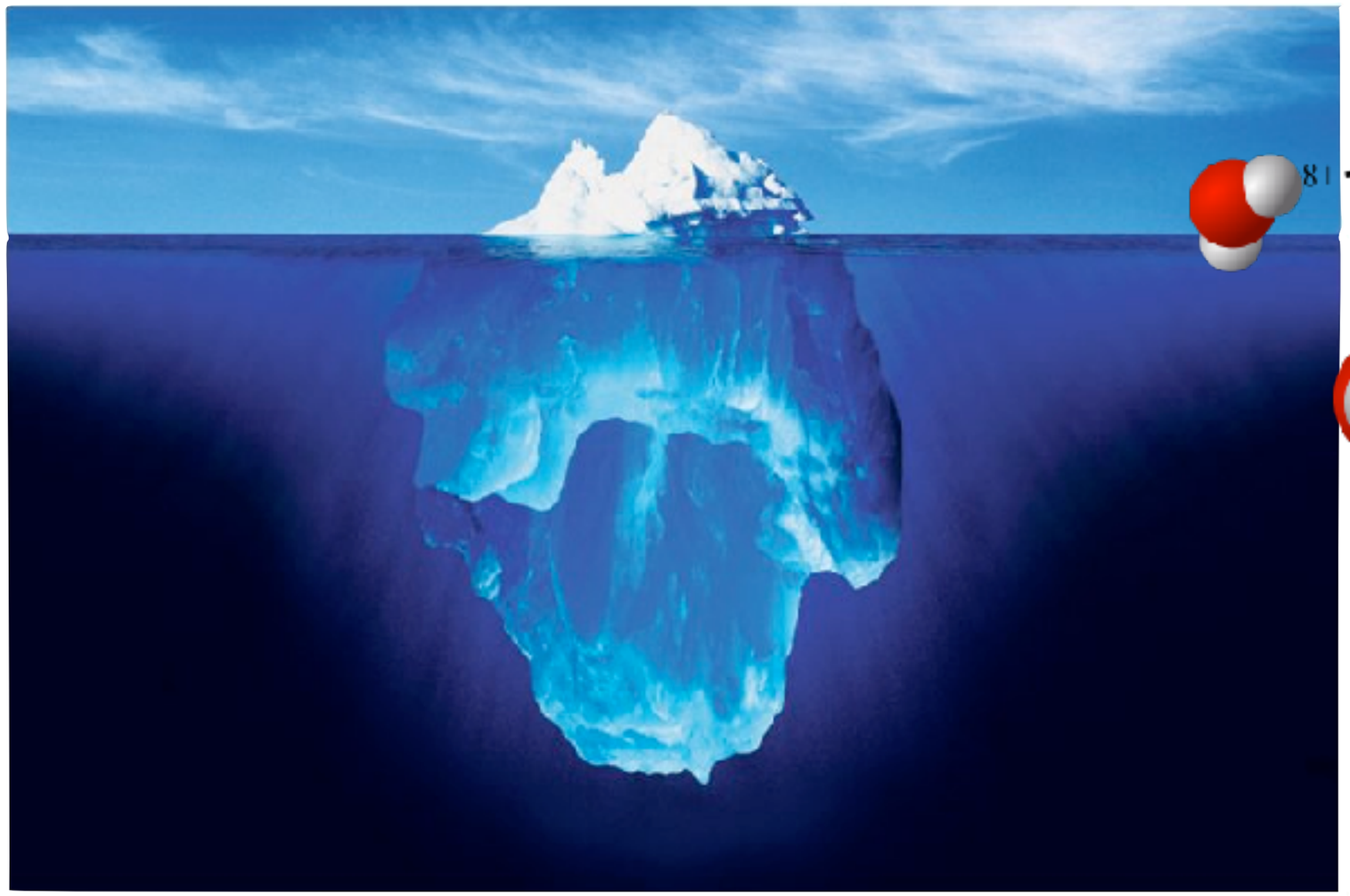


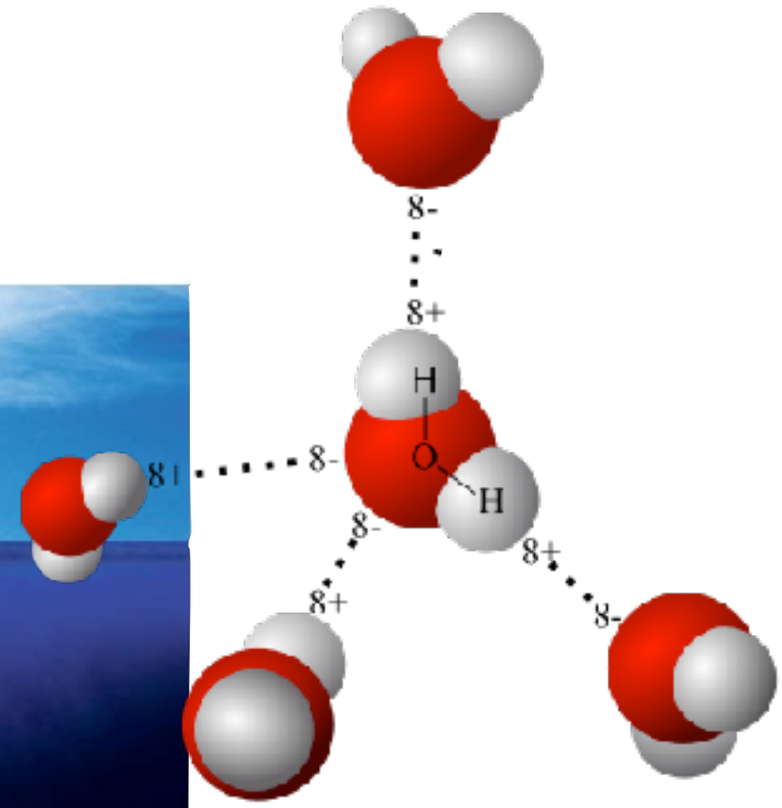
Inhibitor of the influenza virus neuraminidase (antiviral agent)

Hydrogen Bond

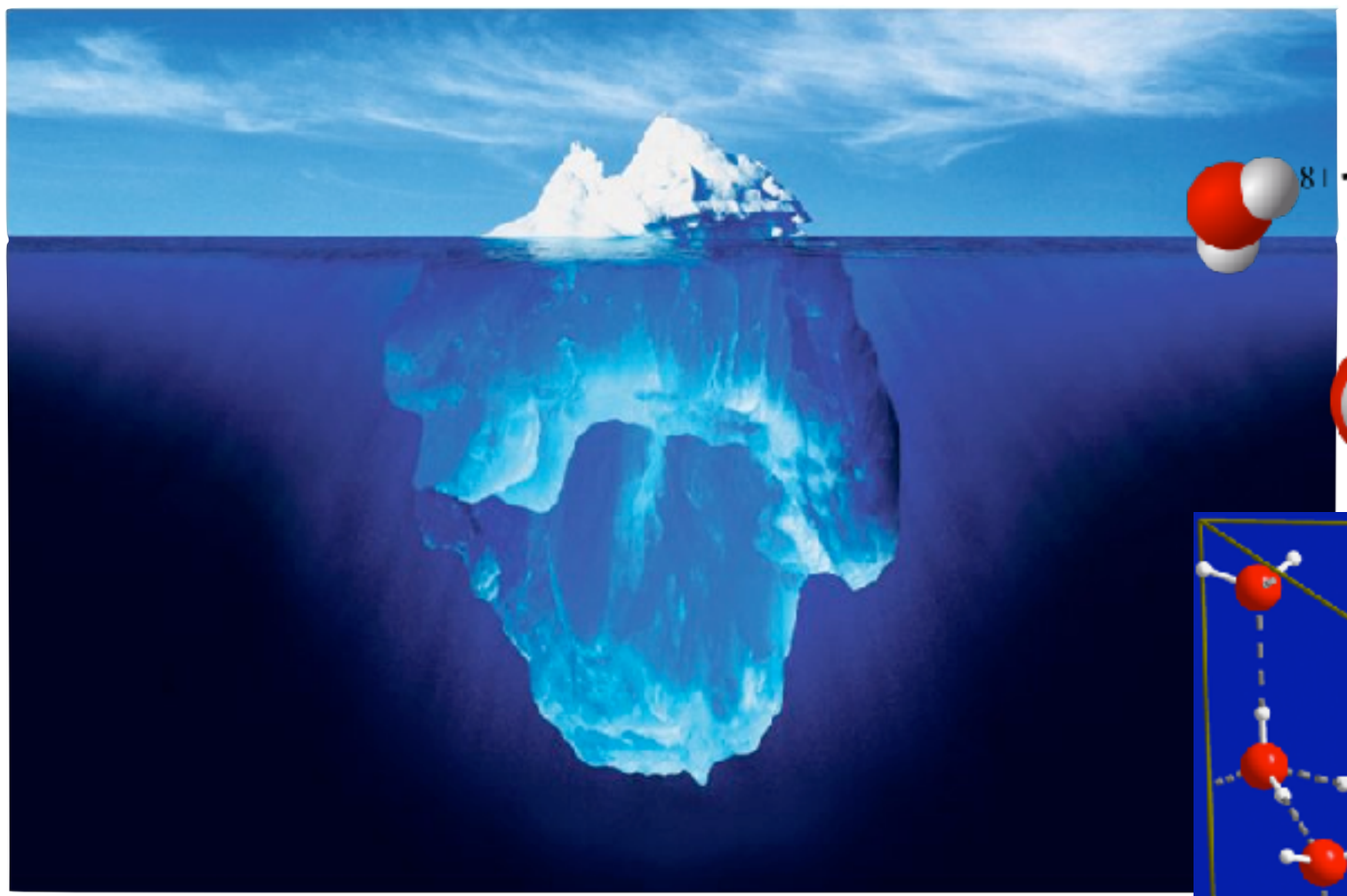


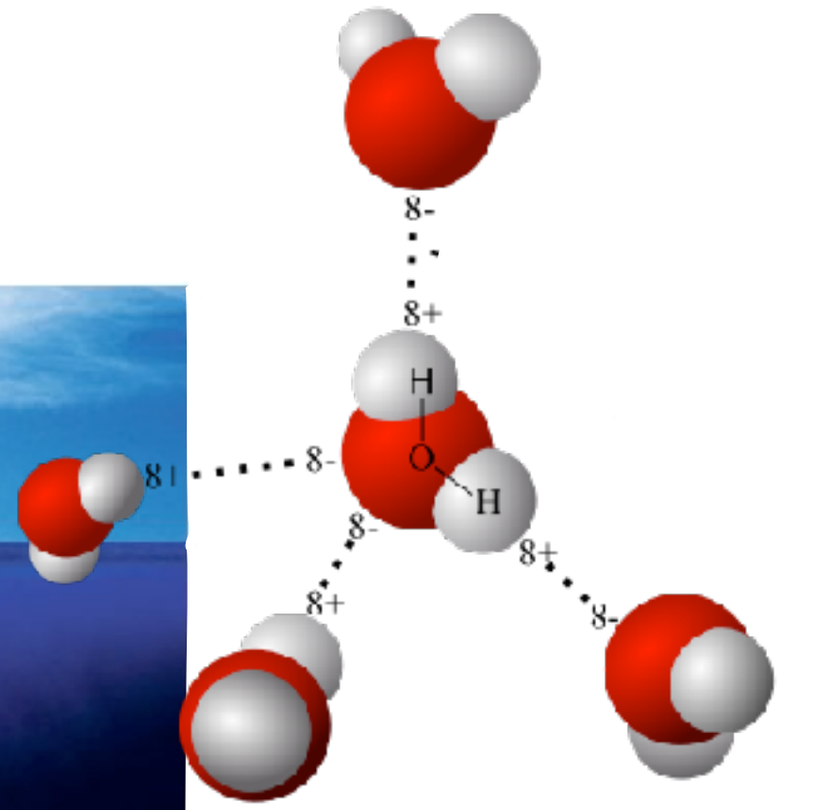
Hydrogen Bond

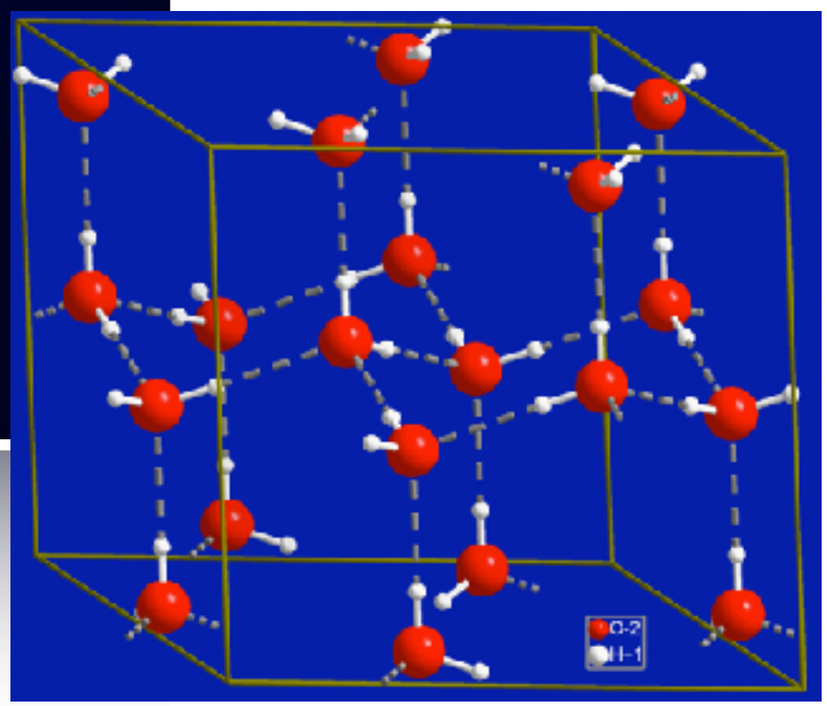




Hydrogen Bond







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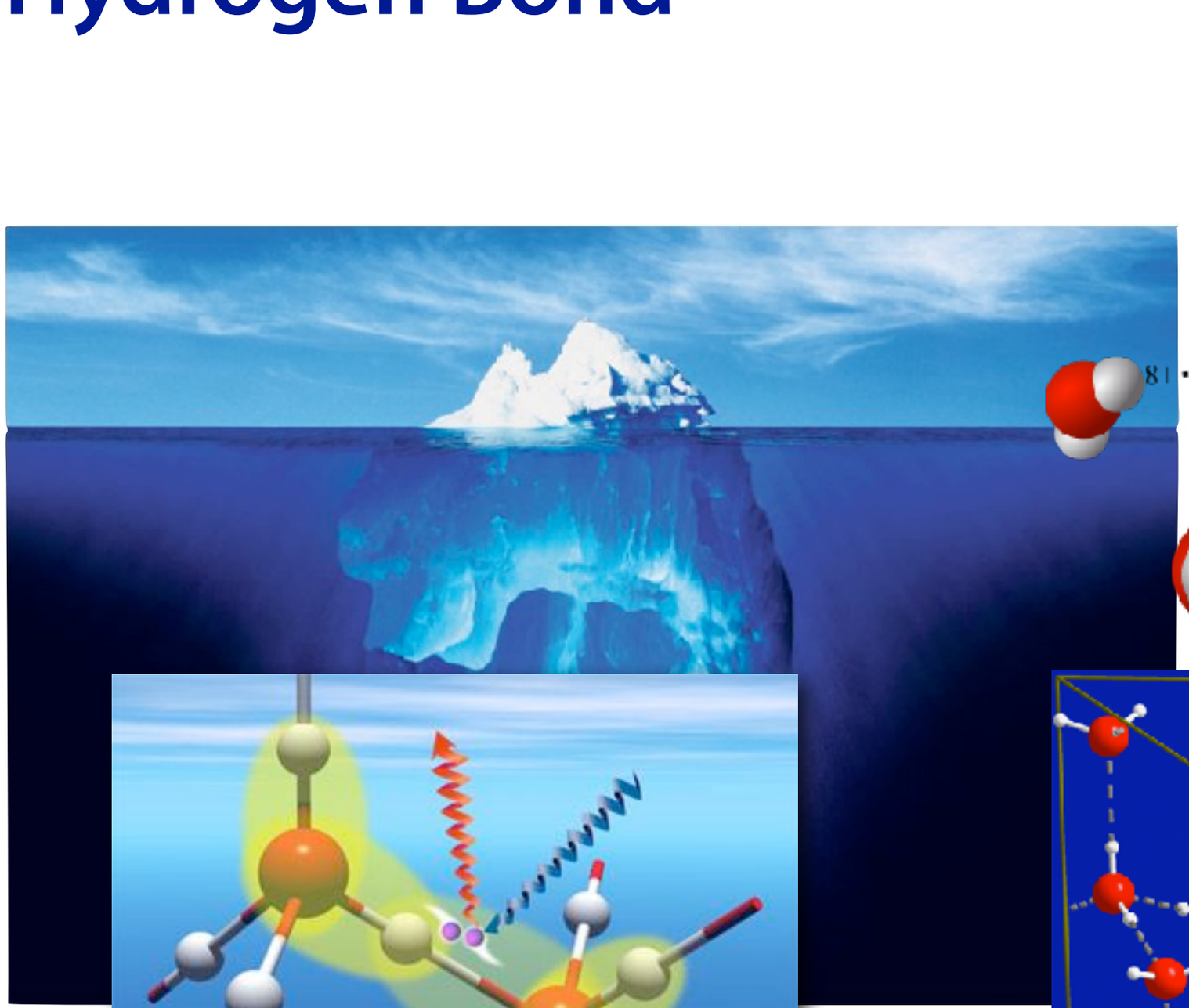

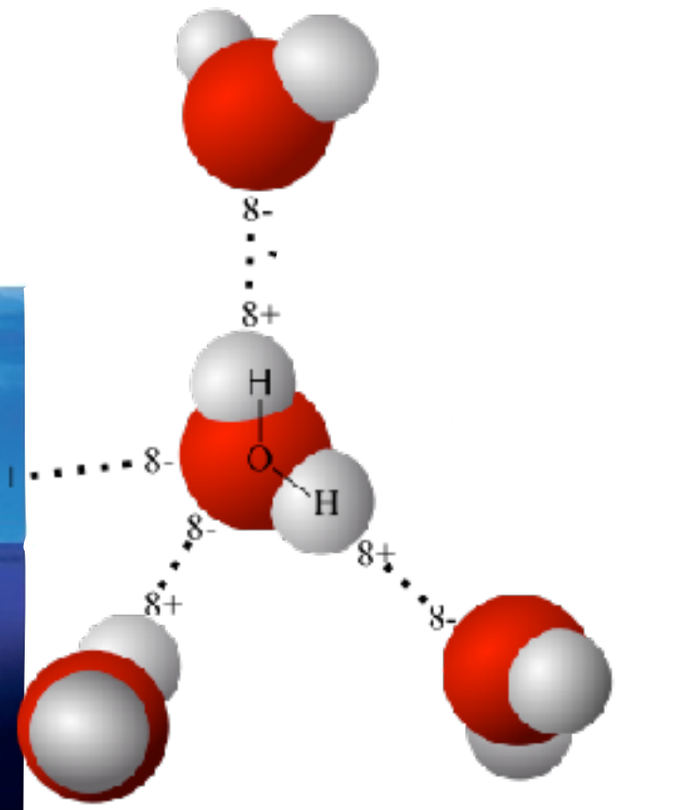

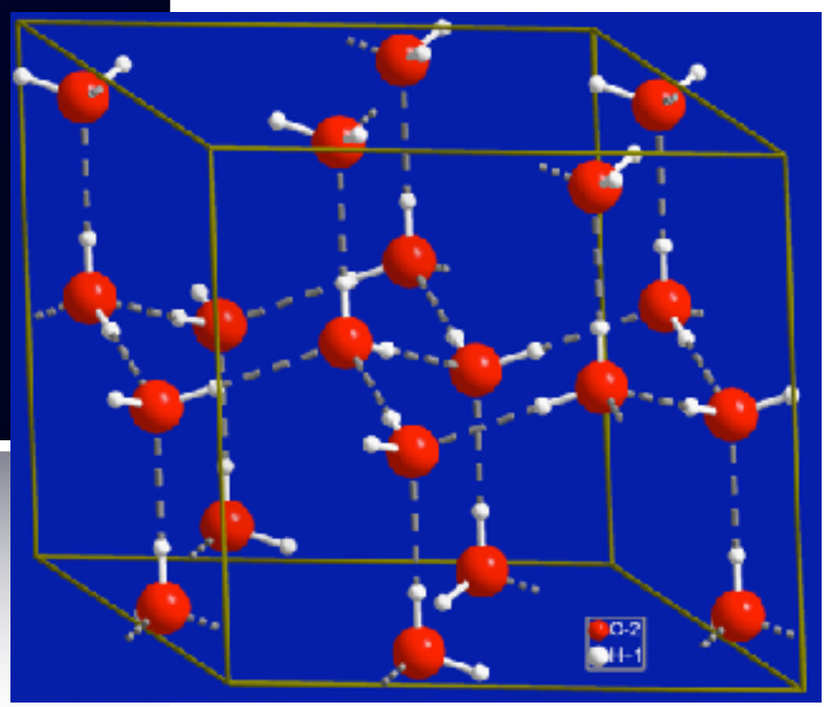

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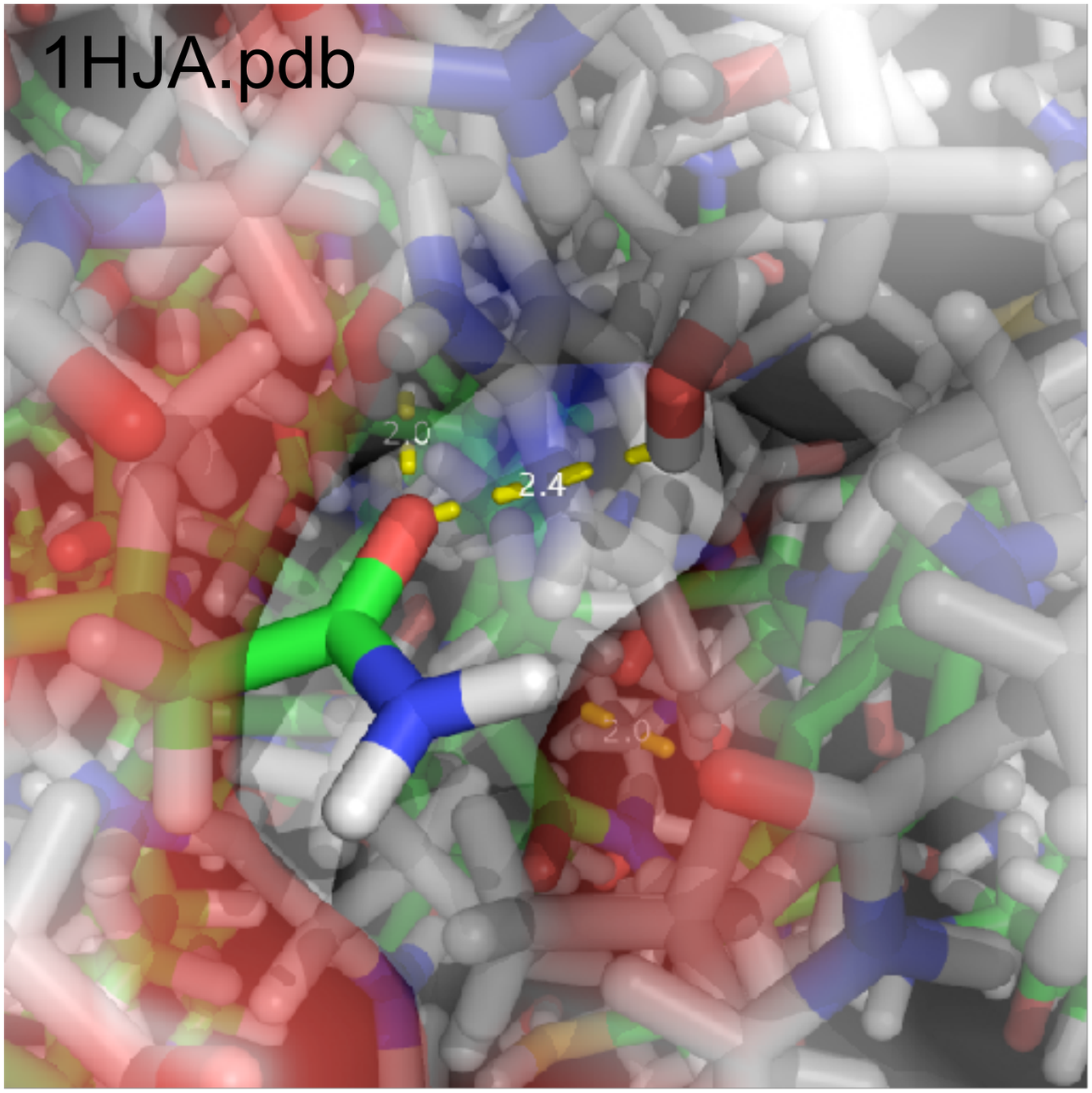
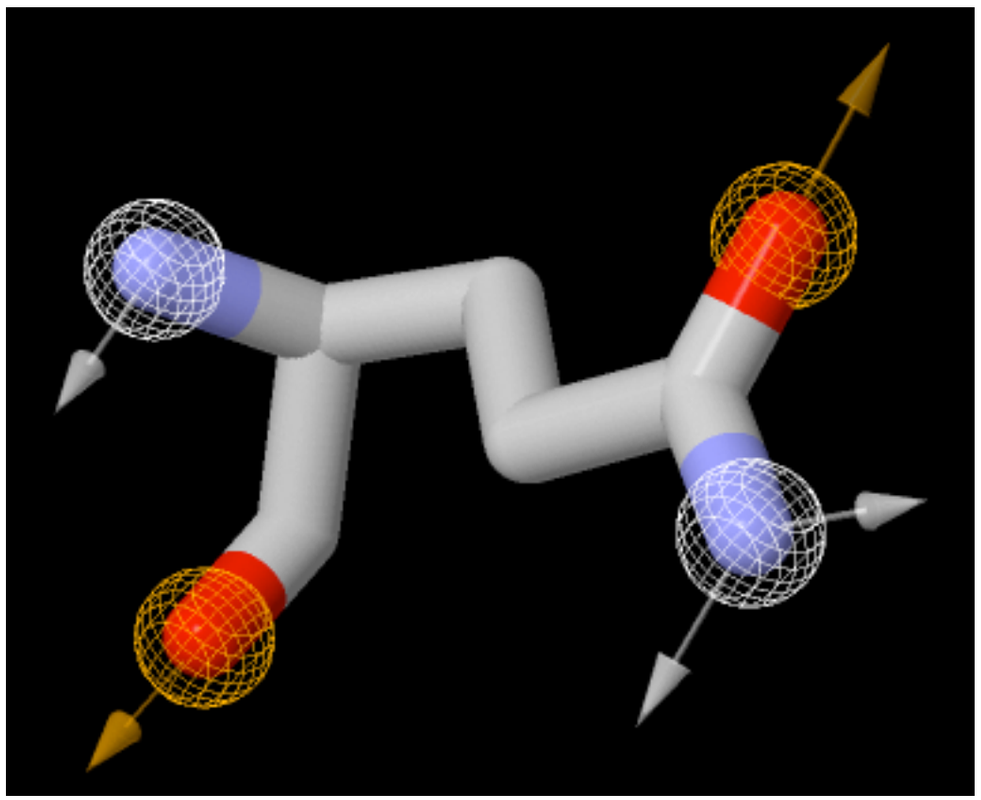


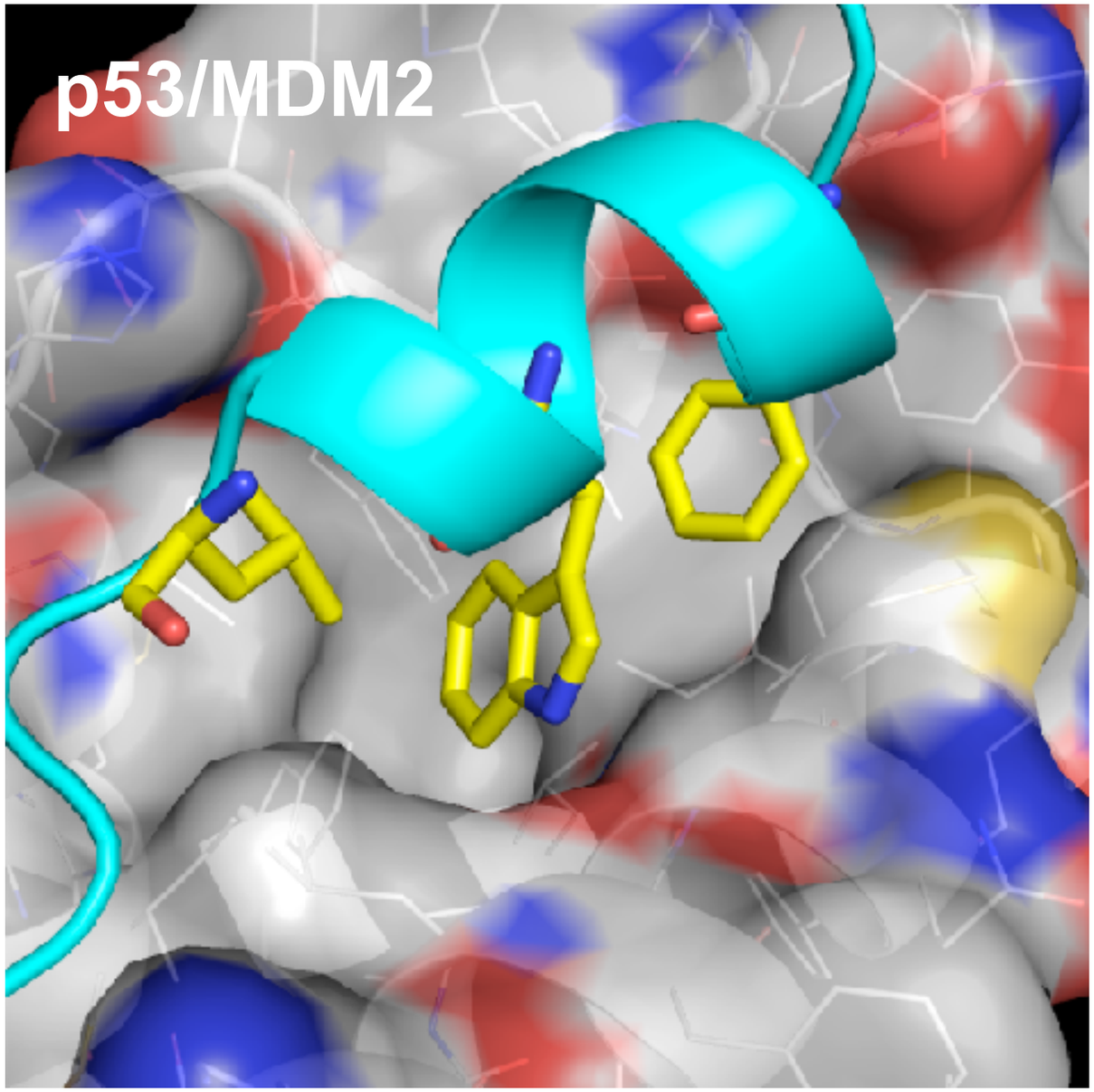
Distance:
D-A: 2.5Å – 3.5Å (4.0Å?)
H-A: 1.5Å – 2.5Å
Angle:
Depends on context



Turkey Ovomucoid Inhibitor

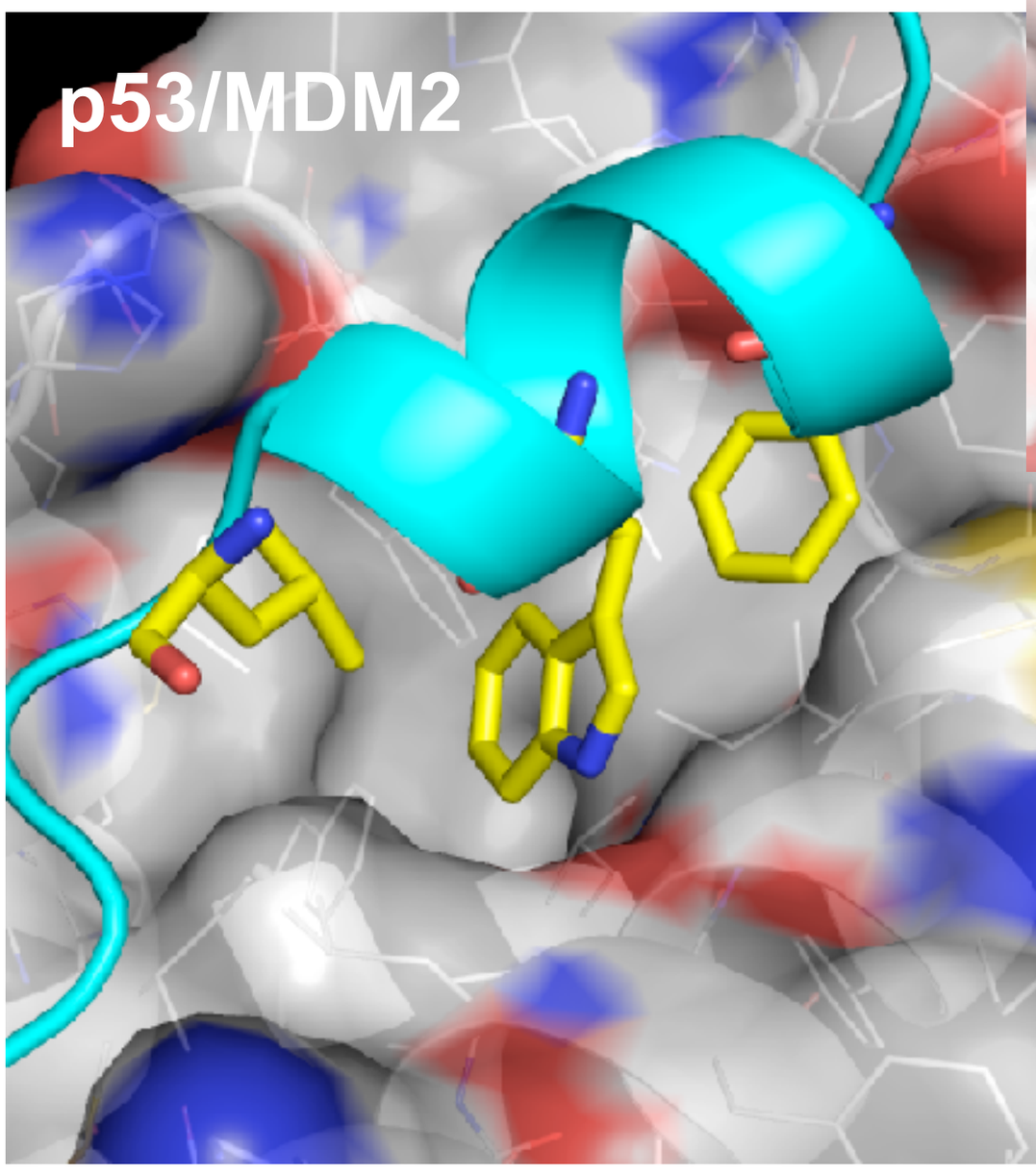
Hydrophobic

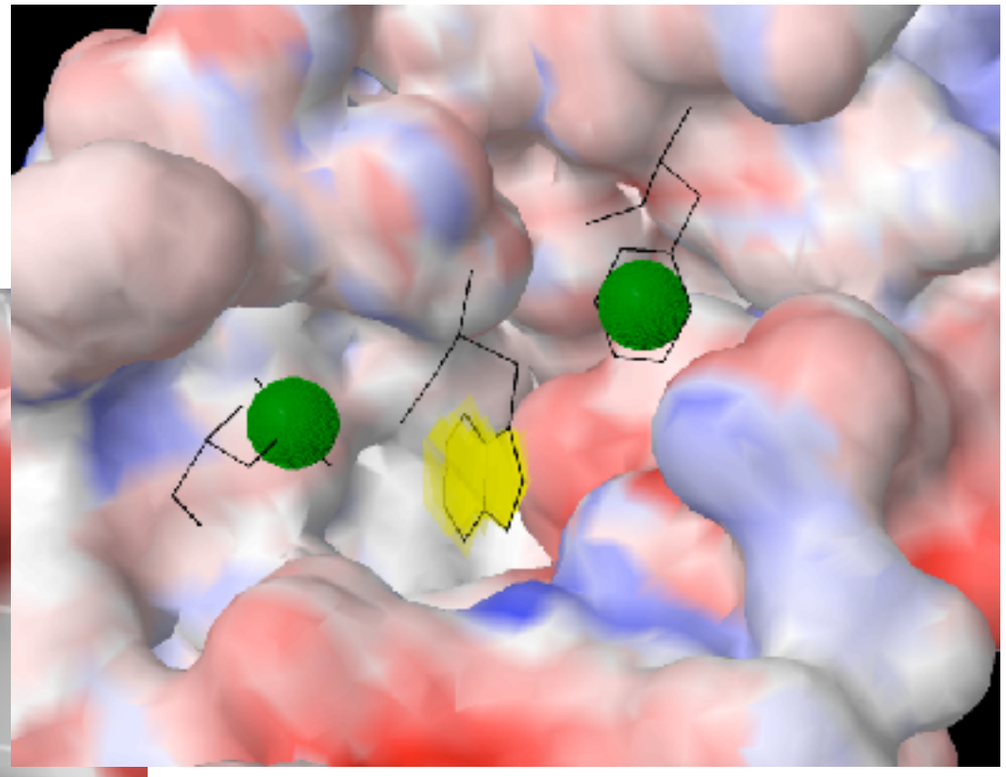
Hydrophobic



MDM2 (over expressed in >50% of cancers) down-regulates p53 (guardian of the genome)

Hydrophobic





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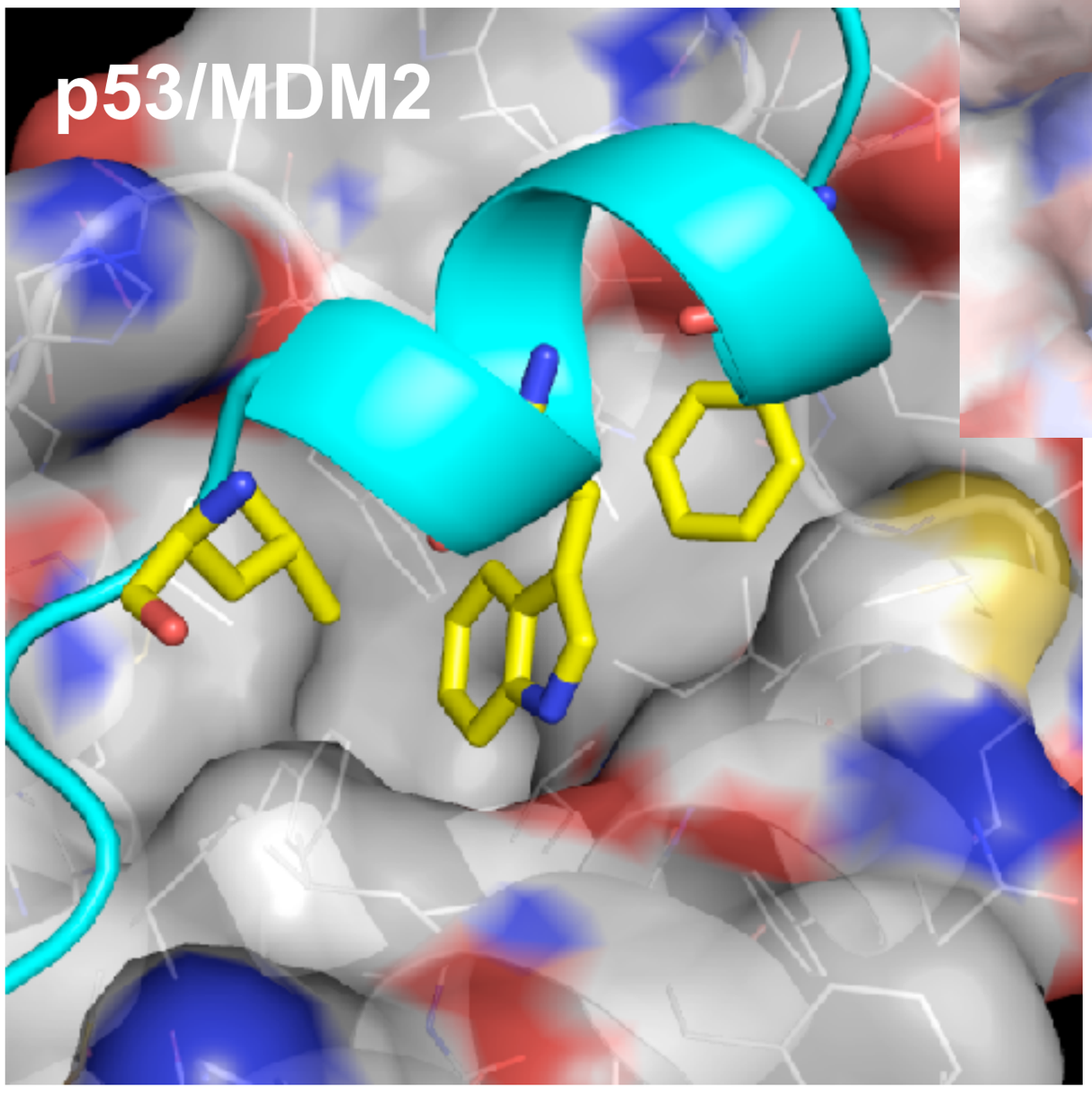

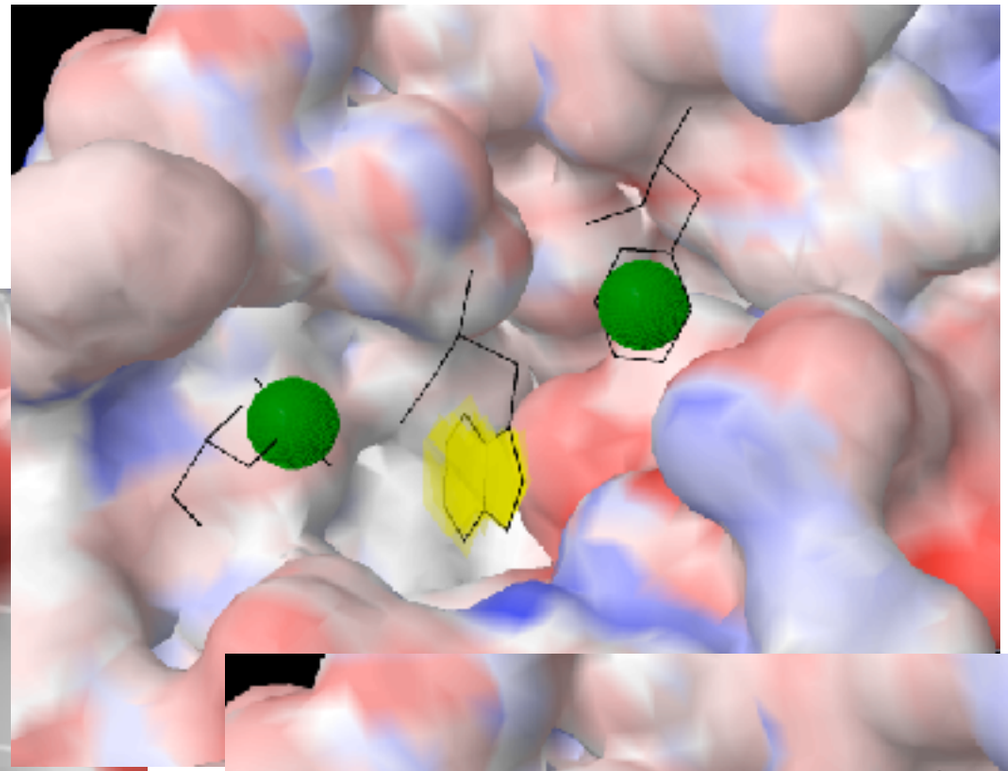

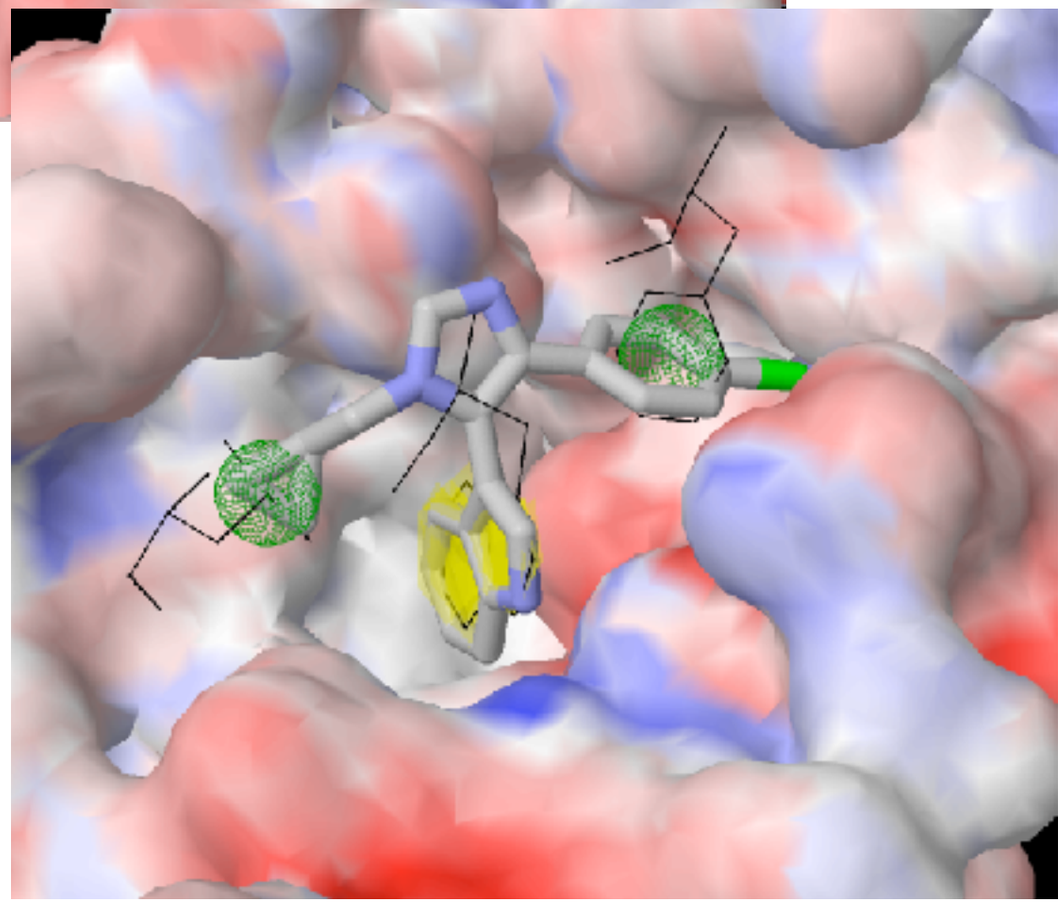

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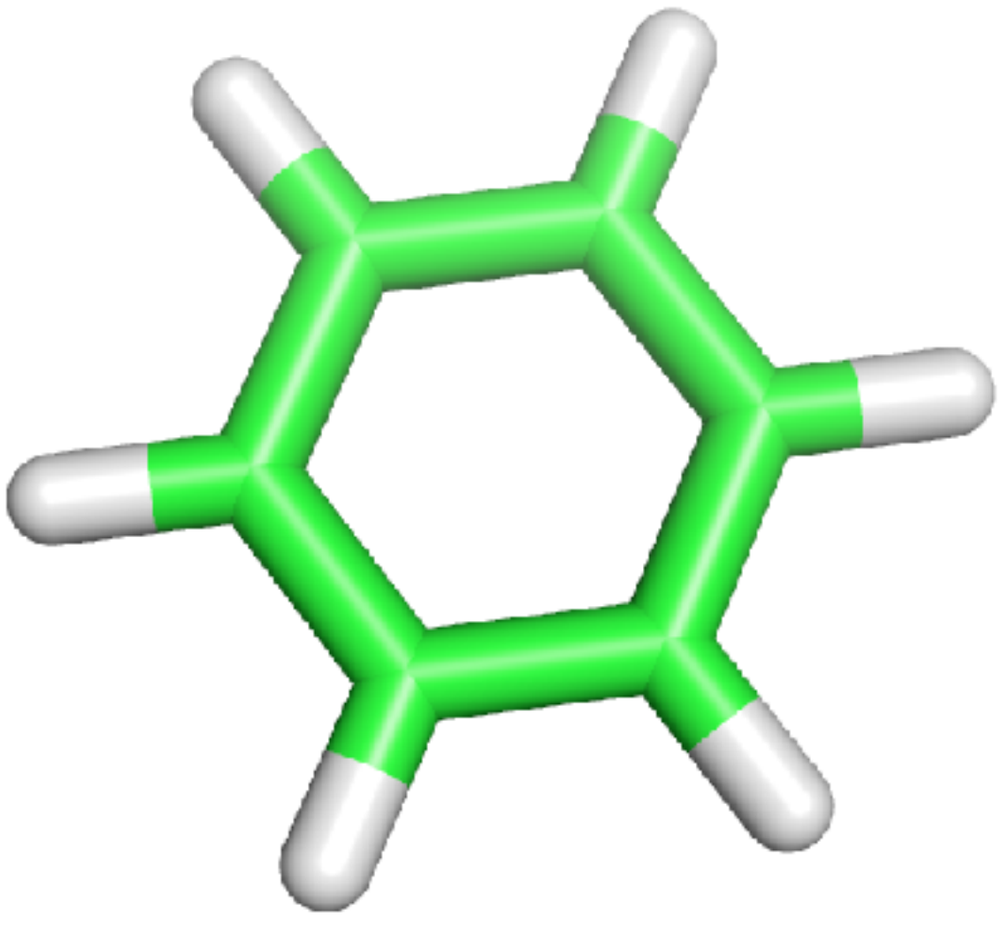
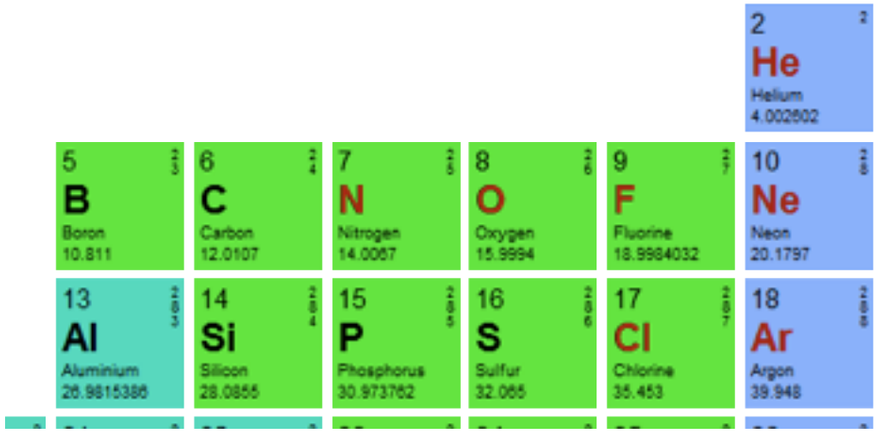
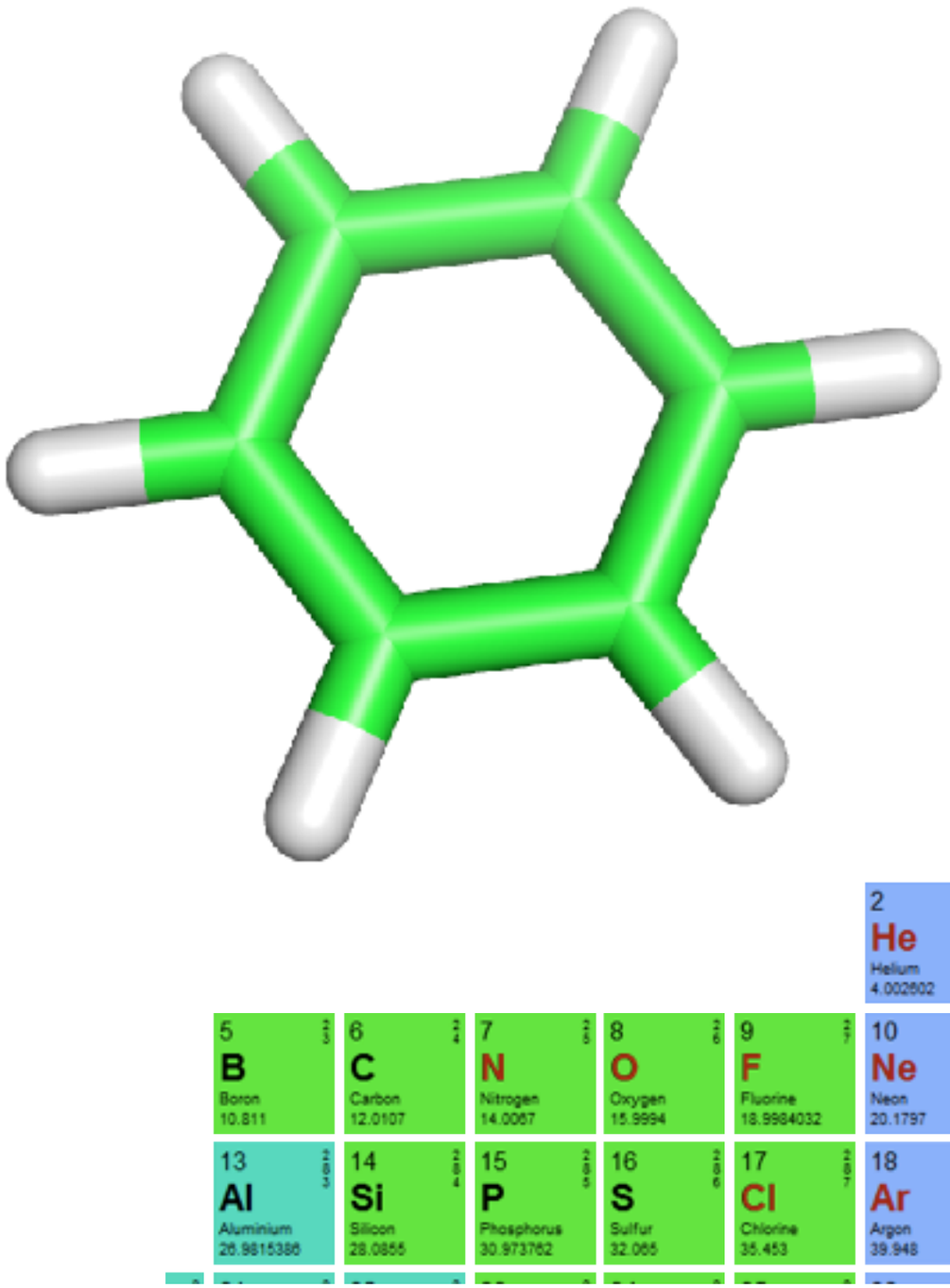
Aromatic

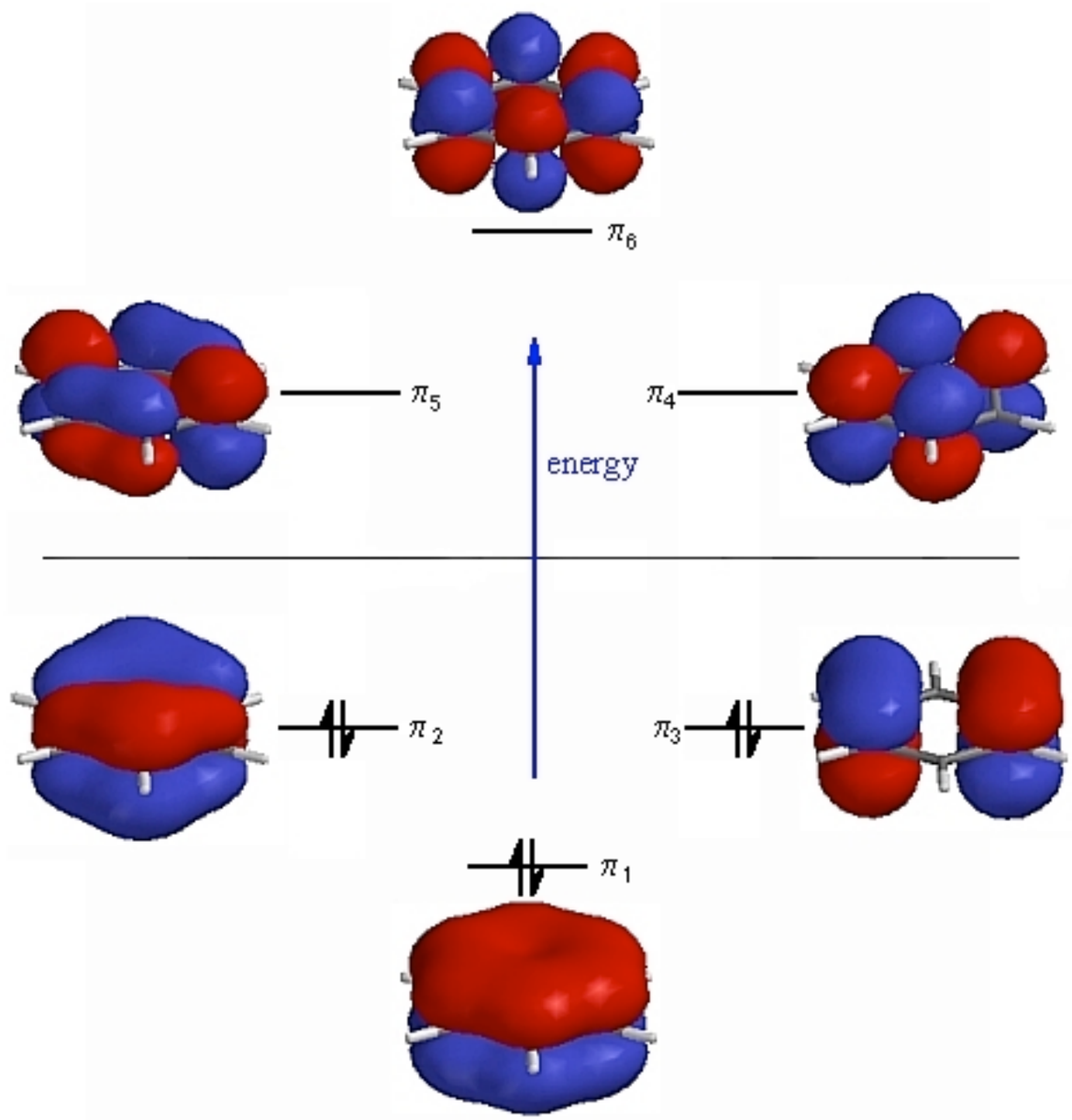




http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch11/benzene-mo.jpg

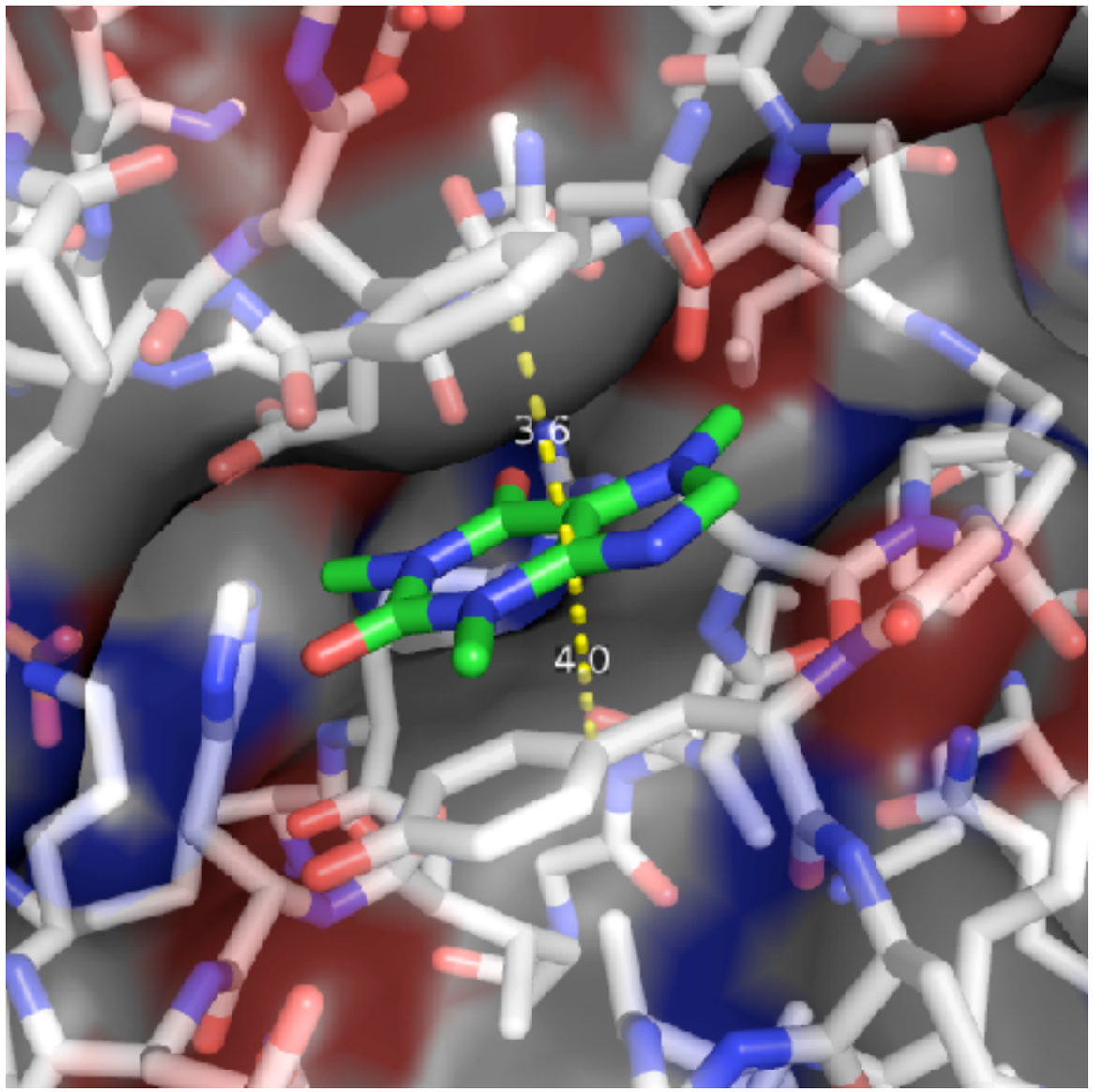
Aromatic



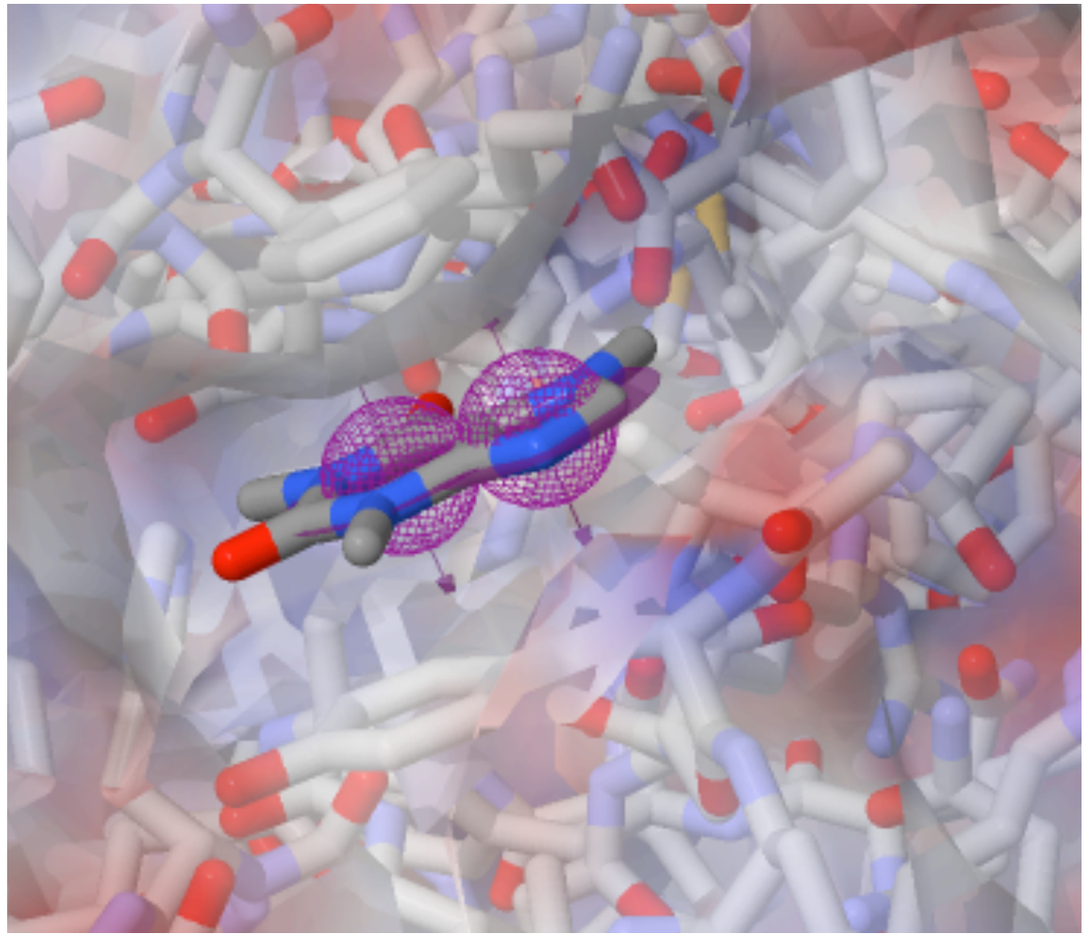


http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch11/benzene-mo.jpg

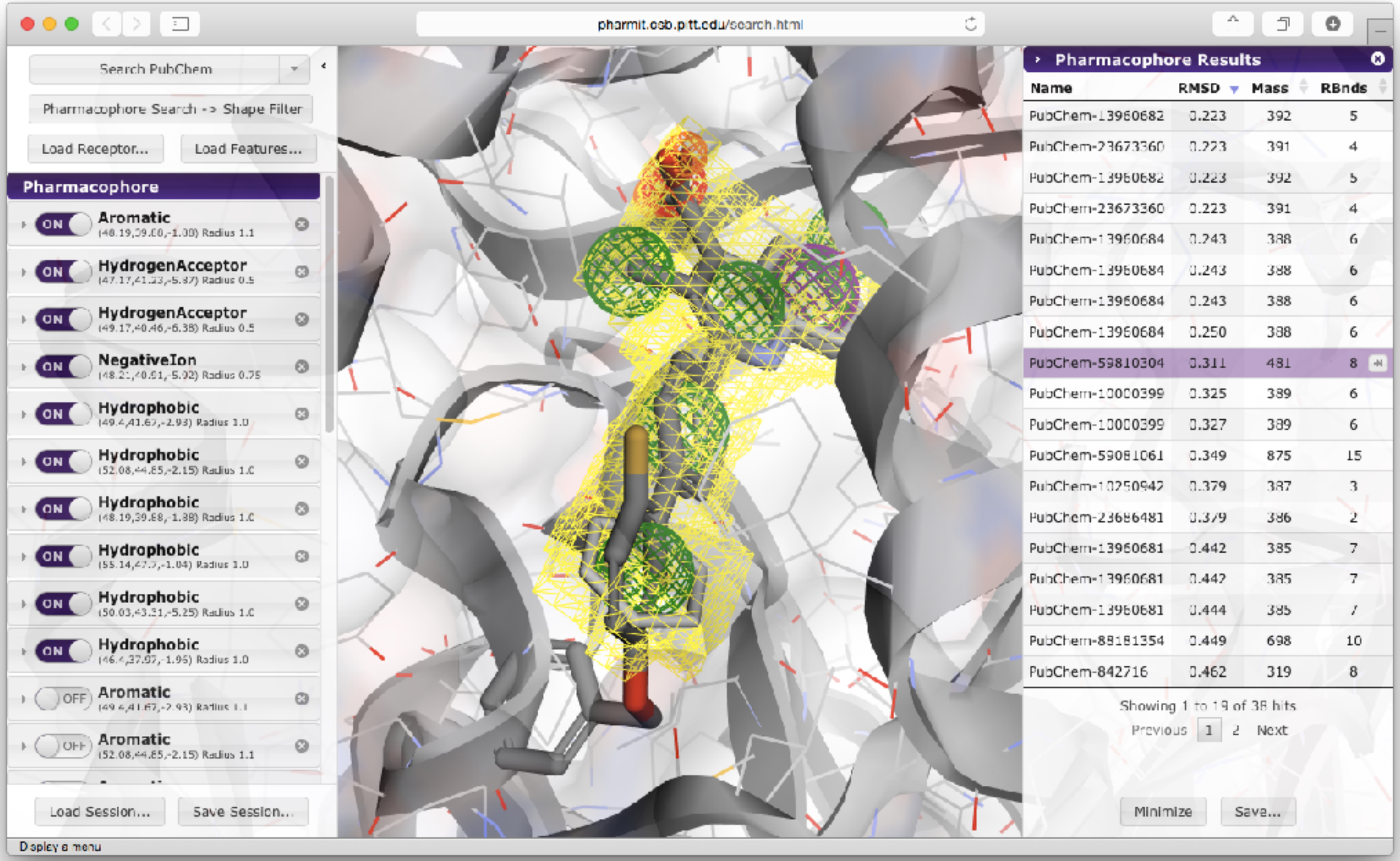
Aromatic



Rings offset
Interplanar distance: 3.3-3.8Å



Human liver glycogen phosphorylase a complexed with caffeine



http://pharmit.csb.pitt.edu

Kinds of Virtual Screening

ADMET

Ligand Based

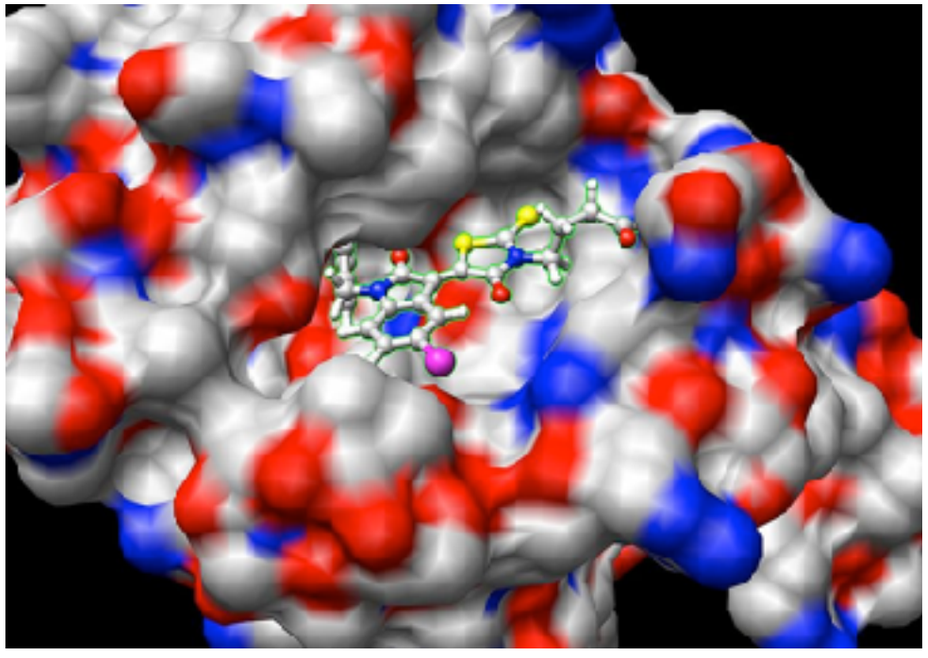
- similarity to known binder

- QSAR

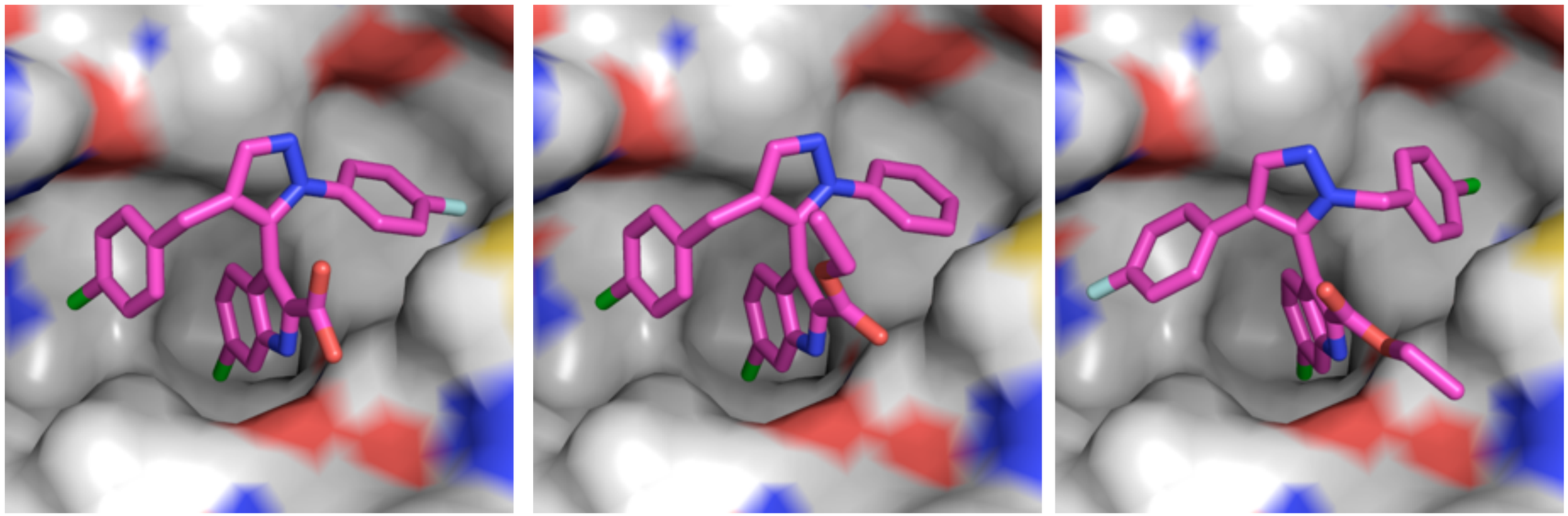
- pharmacophore

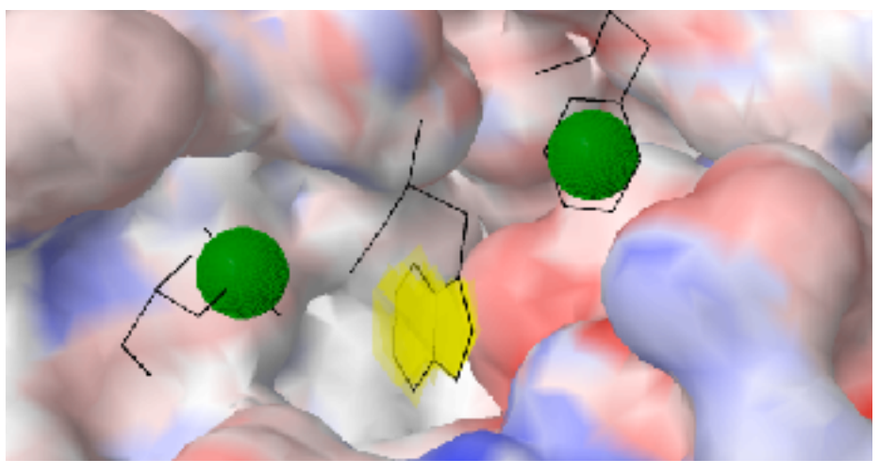
Receptor Based

- dock and score

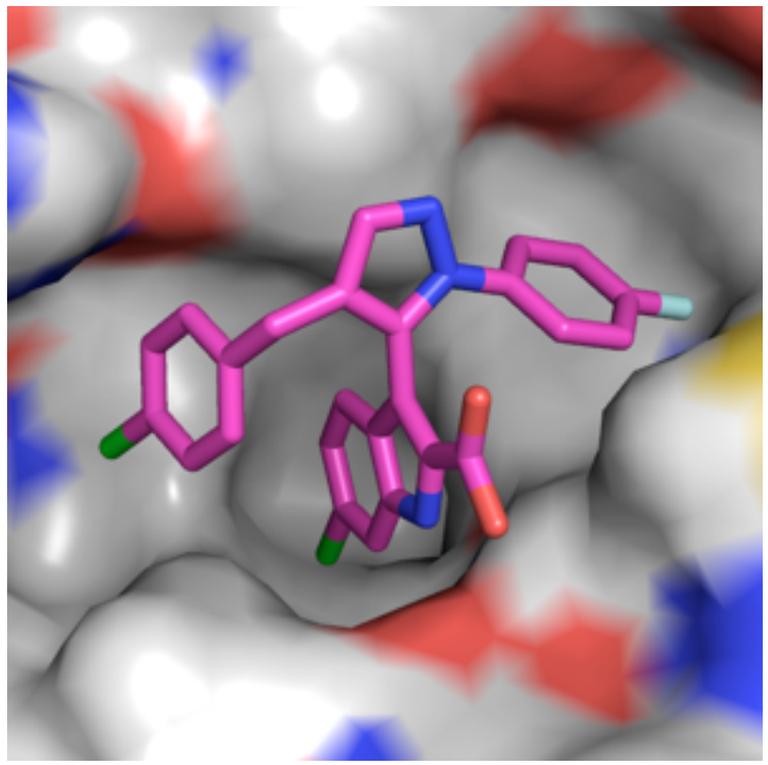


Pharmacophores Aren't Enough

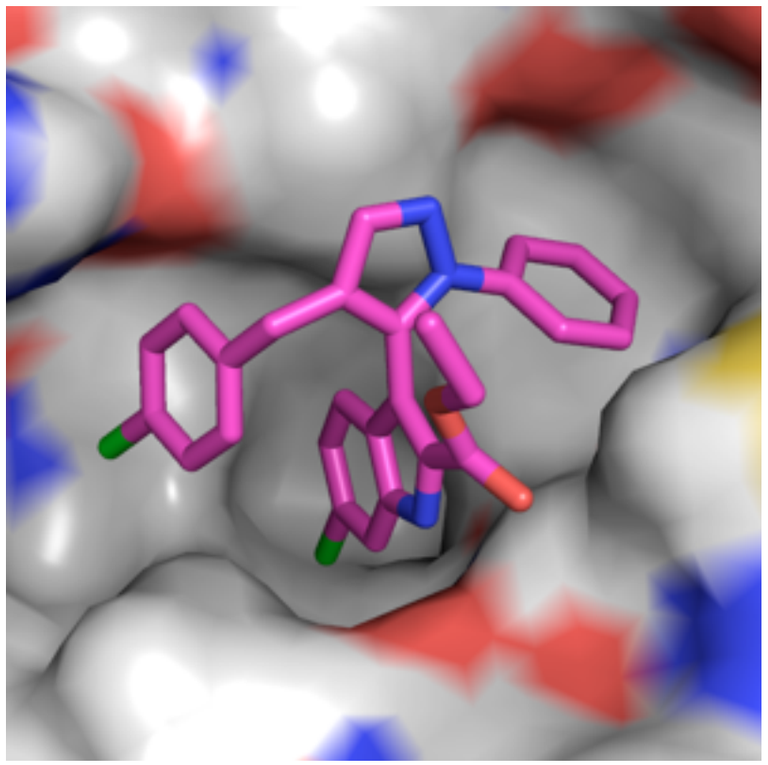




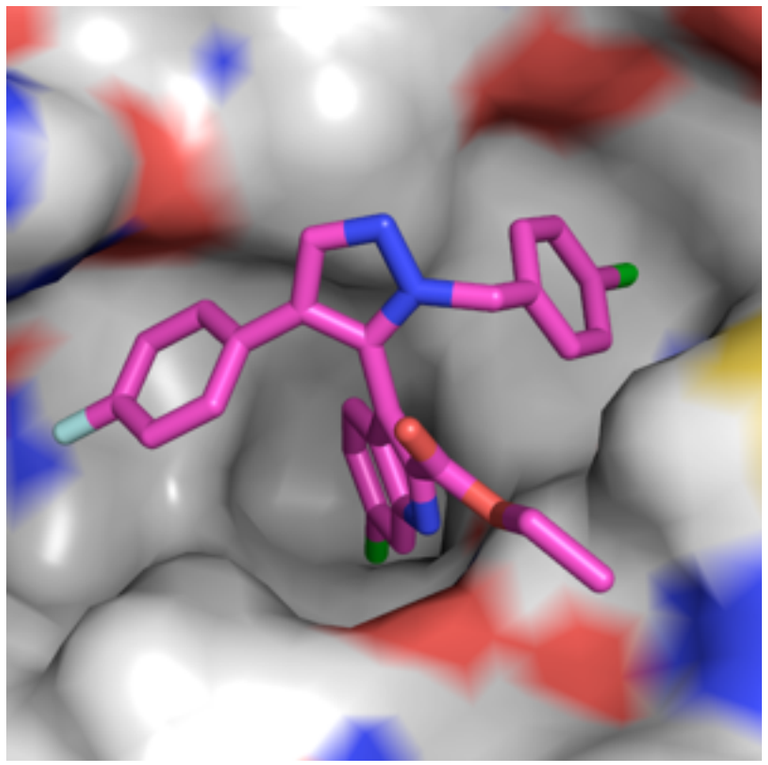
Pharmacophores Aren't Enough



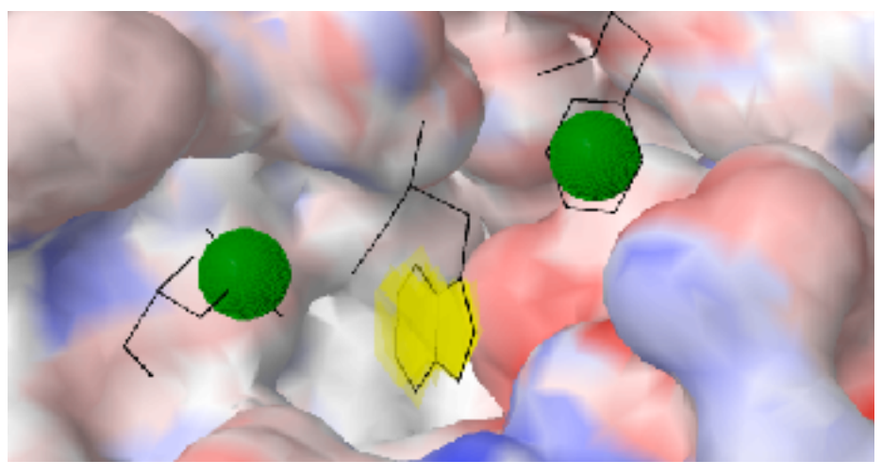
.2μM



50μM



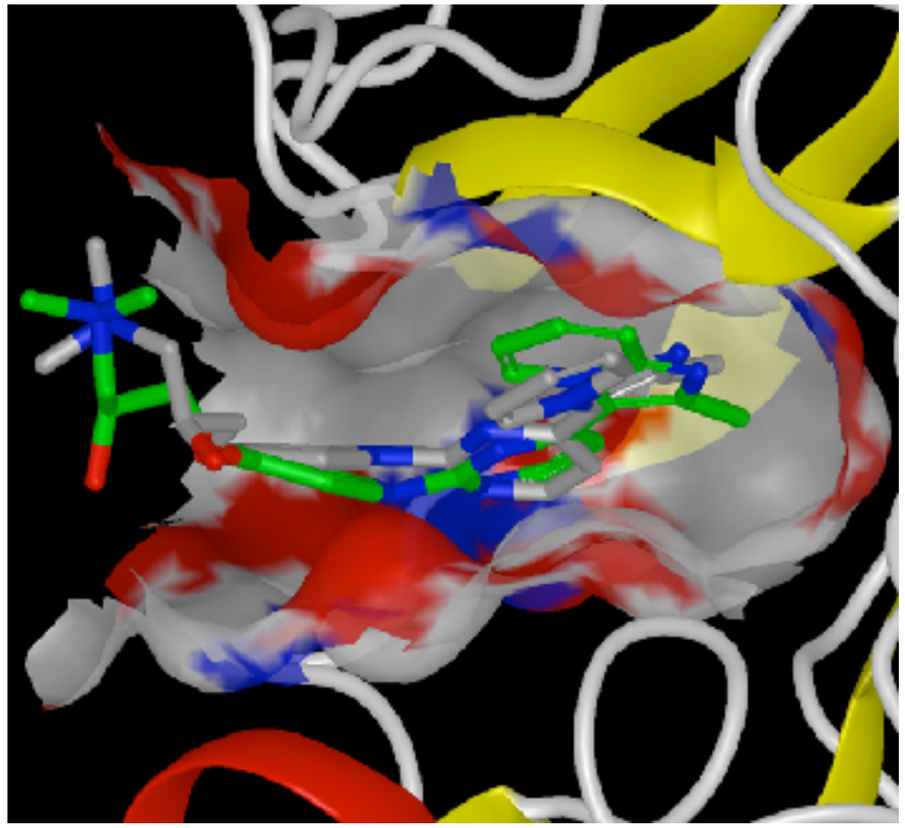
n.i.



Docking

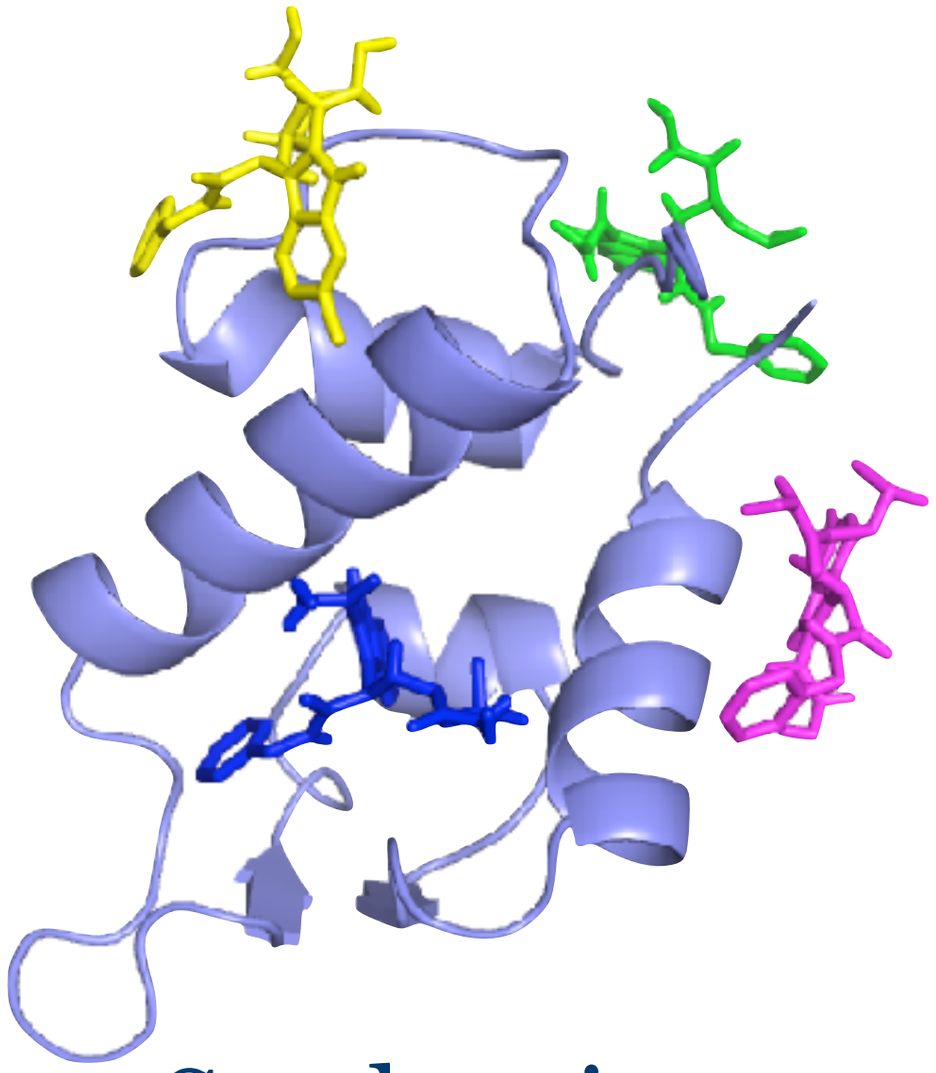
Determine the **conformation** and **pose** of a ligand at a docking site

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



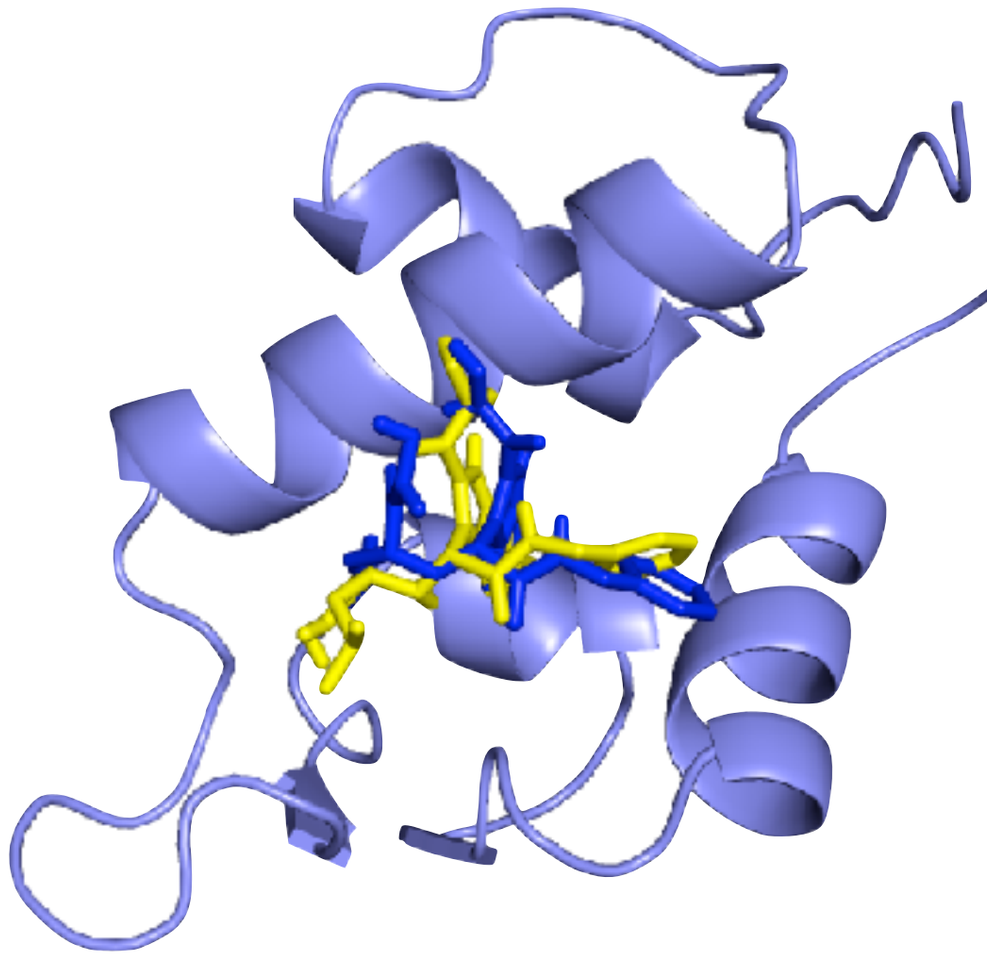
Two Phase Docking

1. Global Pose Estimation



Stochastic

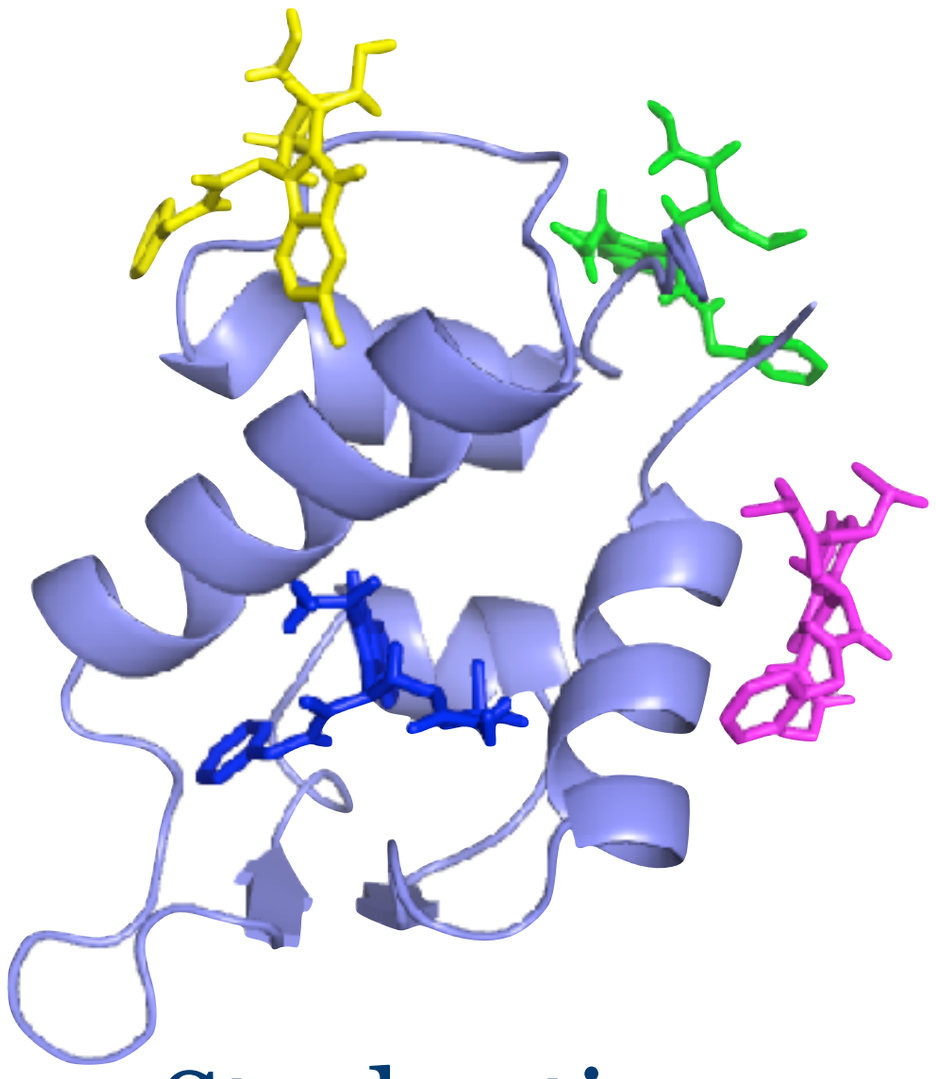
2. Local Refinement



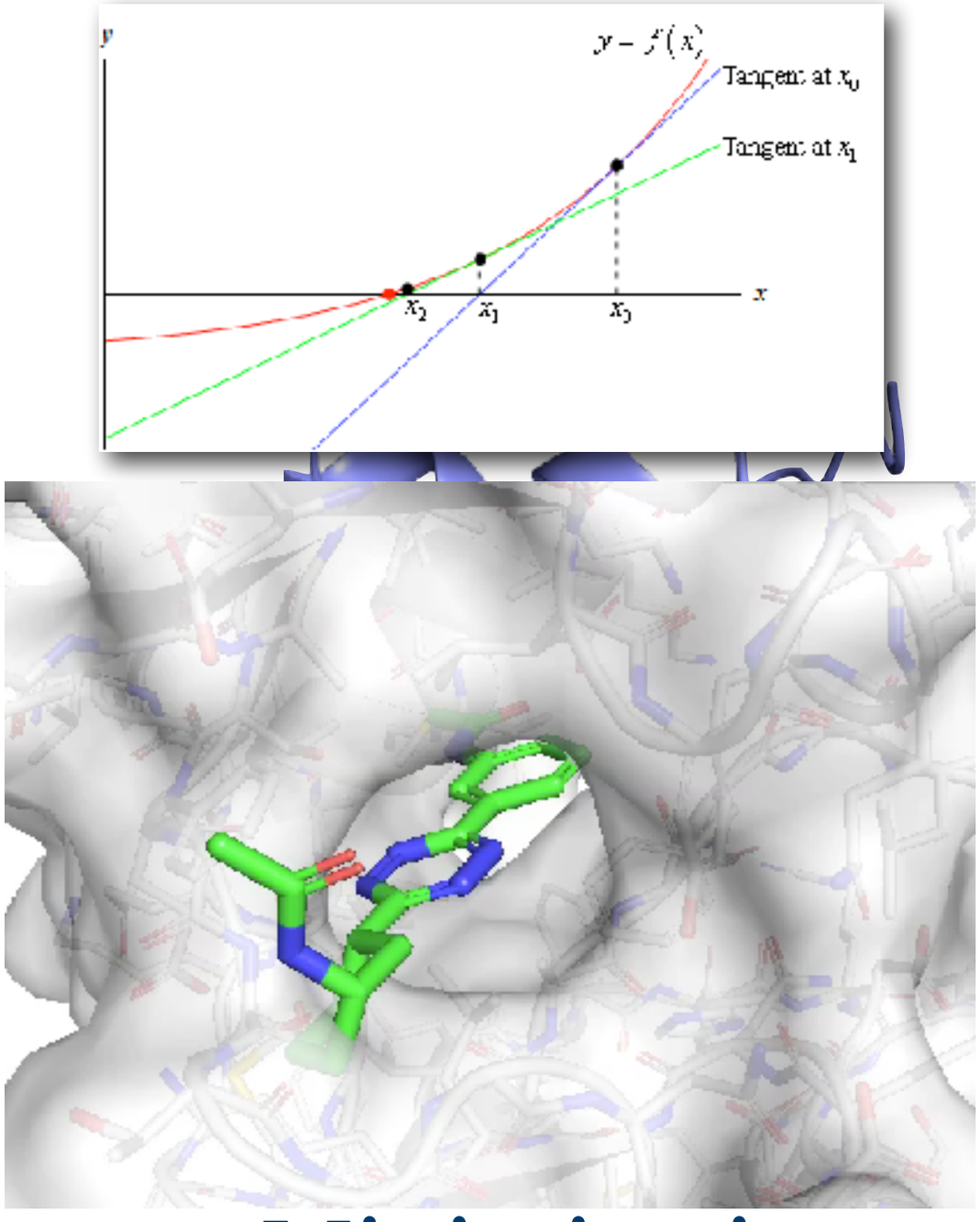
Minimization

Two Phase Docking

1. Global Pose Estimation



Stochastic



Minimization

Scoring Goals

Affinity Prediction

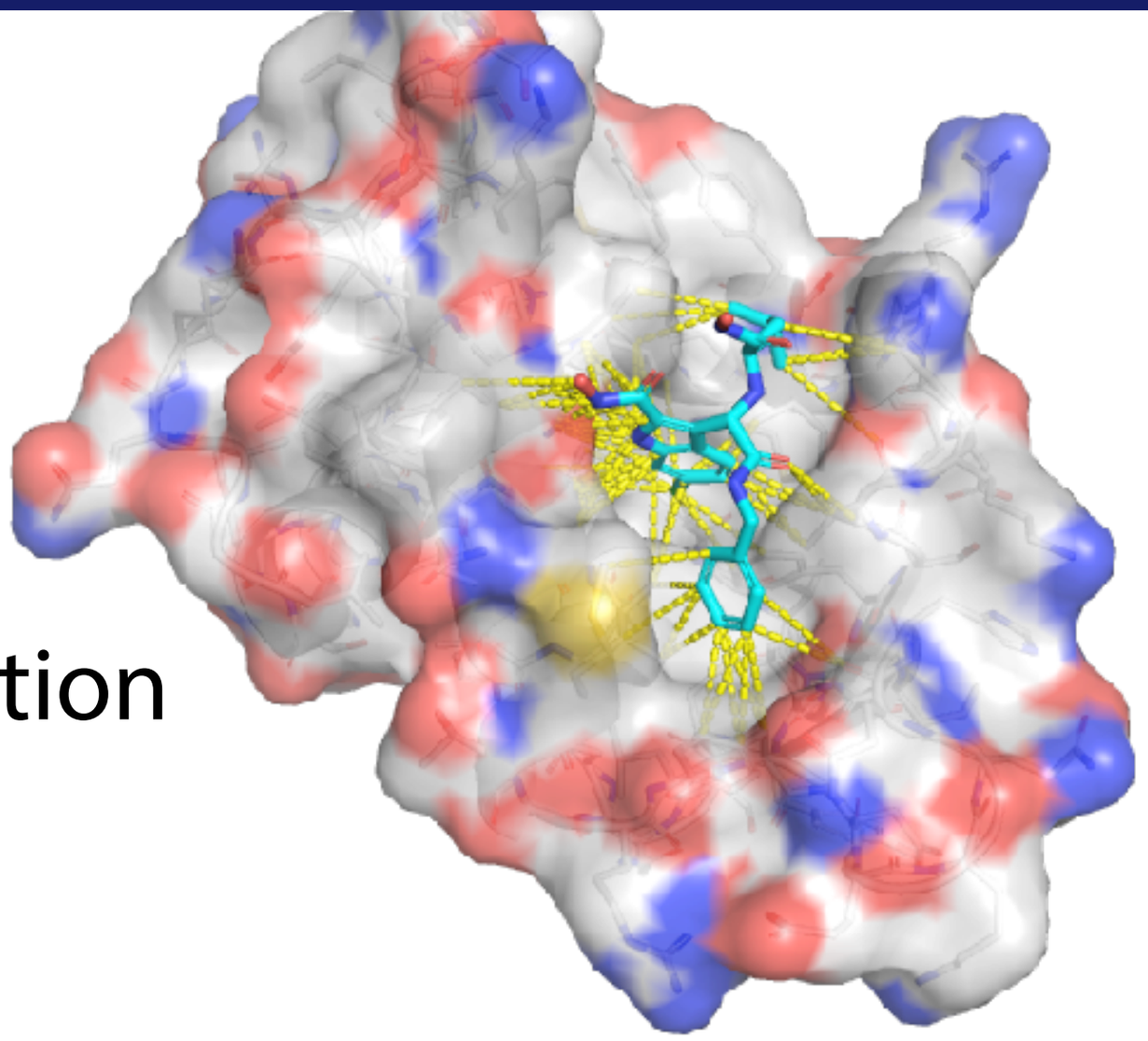
-how well does it bind?

Inactive/Active Discrimination

-does it bind?

Pose Prediction

-how does it bind?



Scoring Goals

Affinity Prediction

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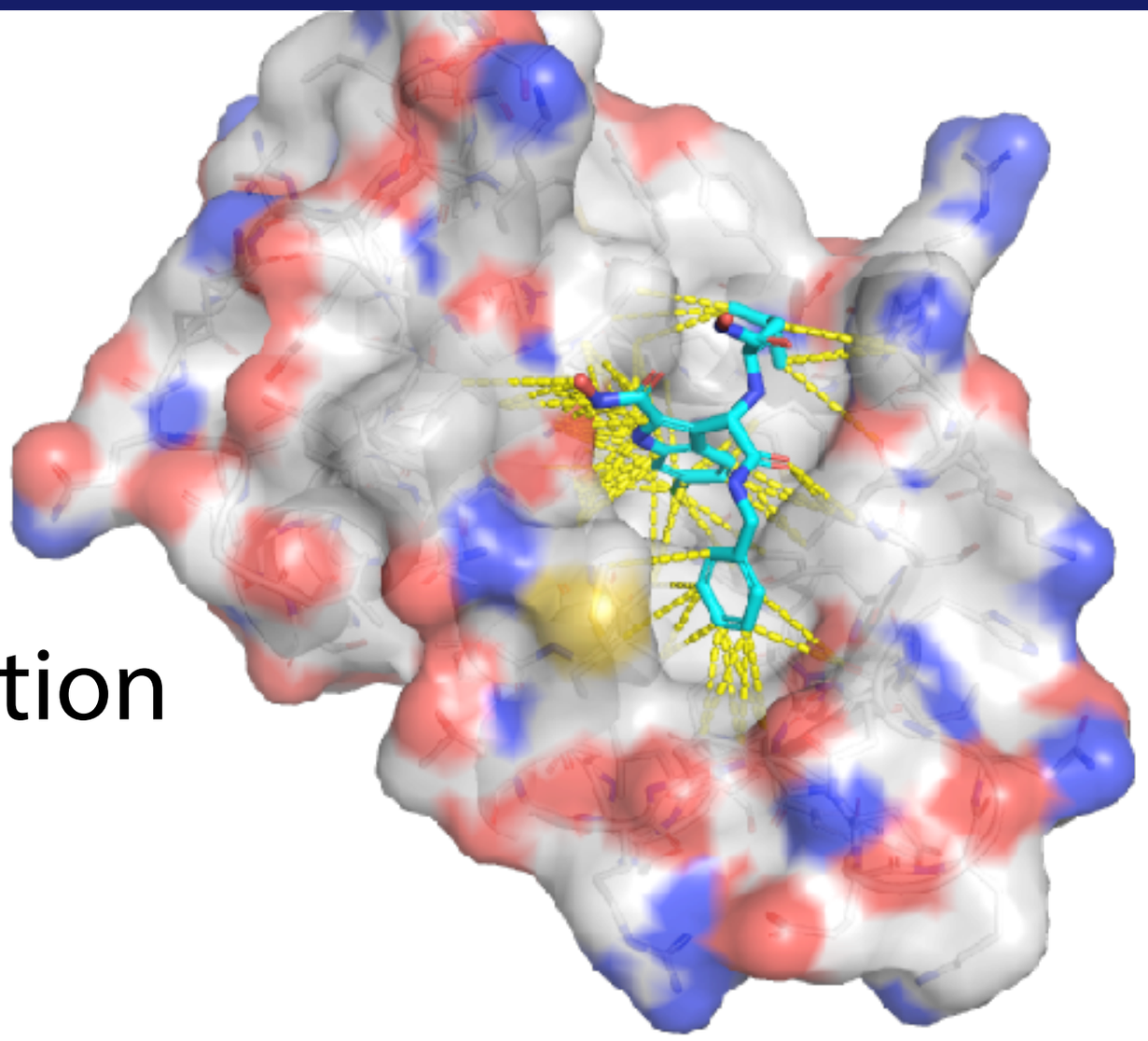
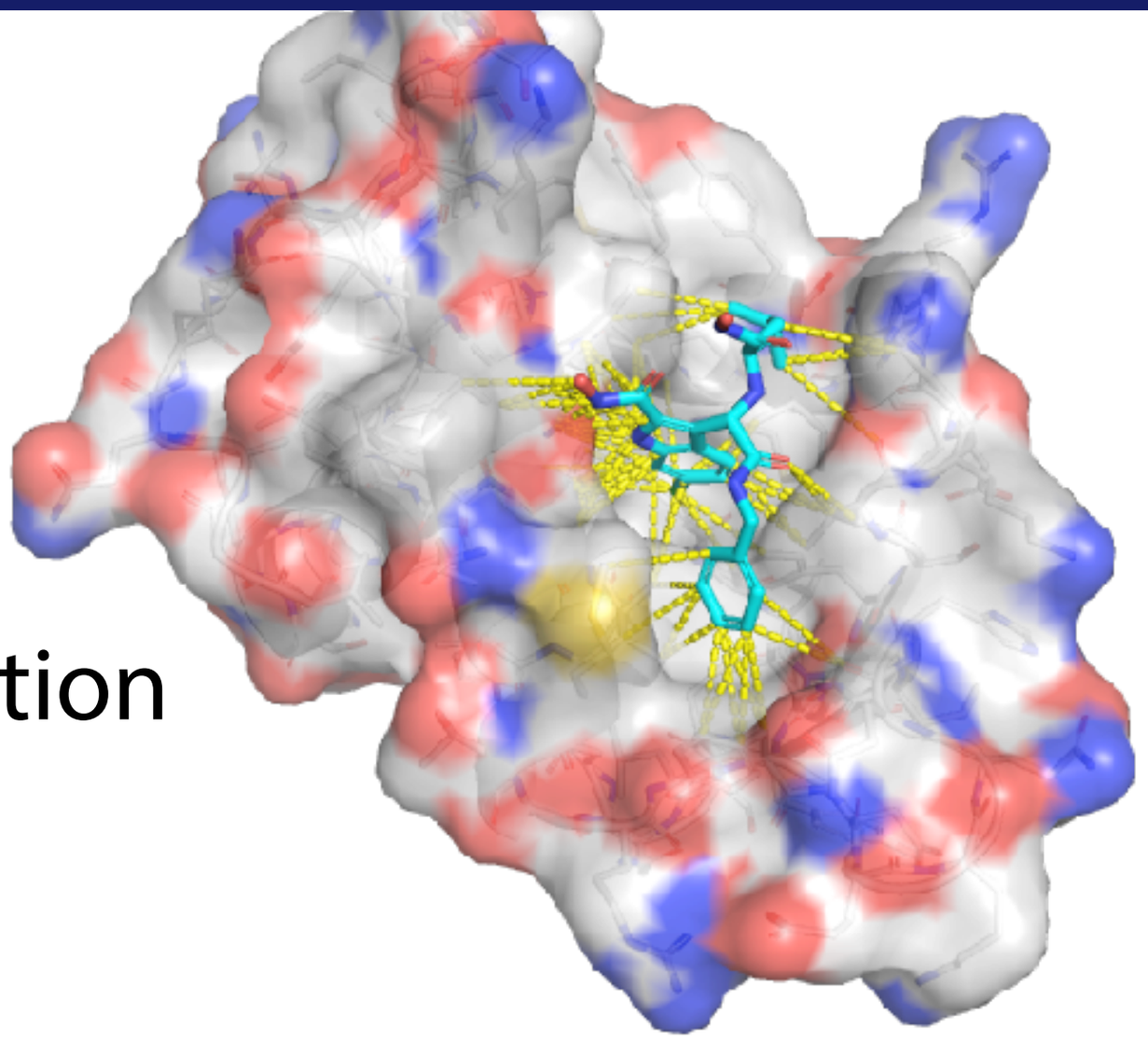


Speed

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

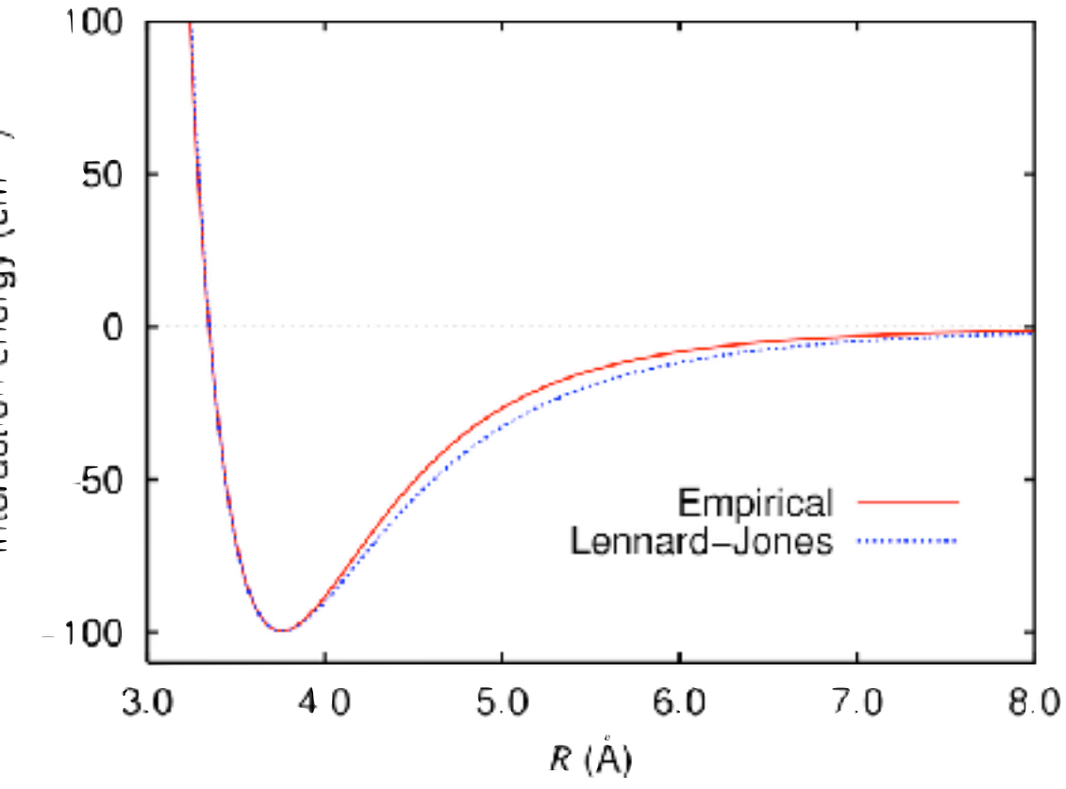
Consensus

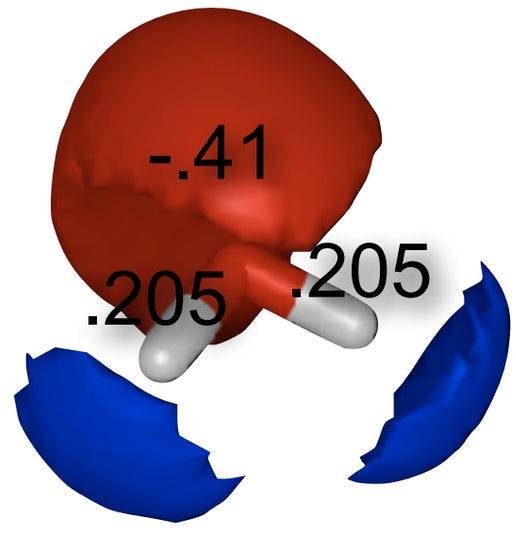
Force Field: Dock 4.0

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

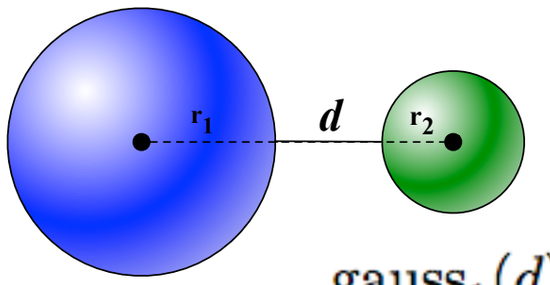
$$E = \sum_{i=1}^{lig} \sum_{j=1}^{rec} \left(\frac{A_{ij}}{r_{ij}^{a}} - \frac{B_{ij}}{r_{ij}^{b}} + 332 \frac{q_i q_j}{D r_{ij}} \right)$$

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





Empirical: AutoDock Vina



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

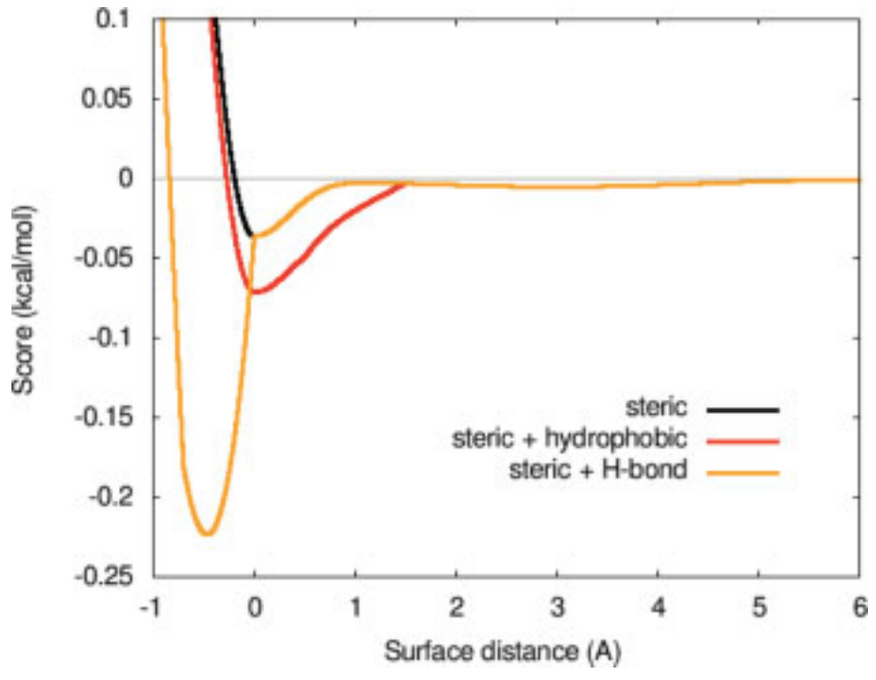
$$\text{gauss}_2(d) = w_{\text{guass}_2} e^{-((d-3)/2)^2}$$

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

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

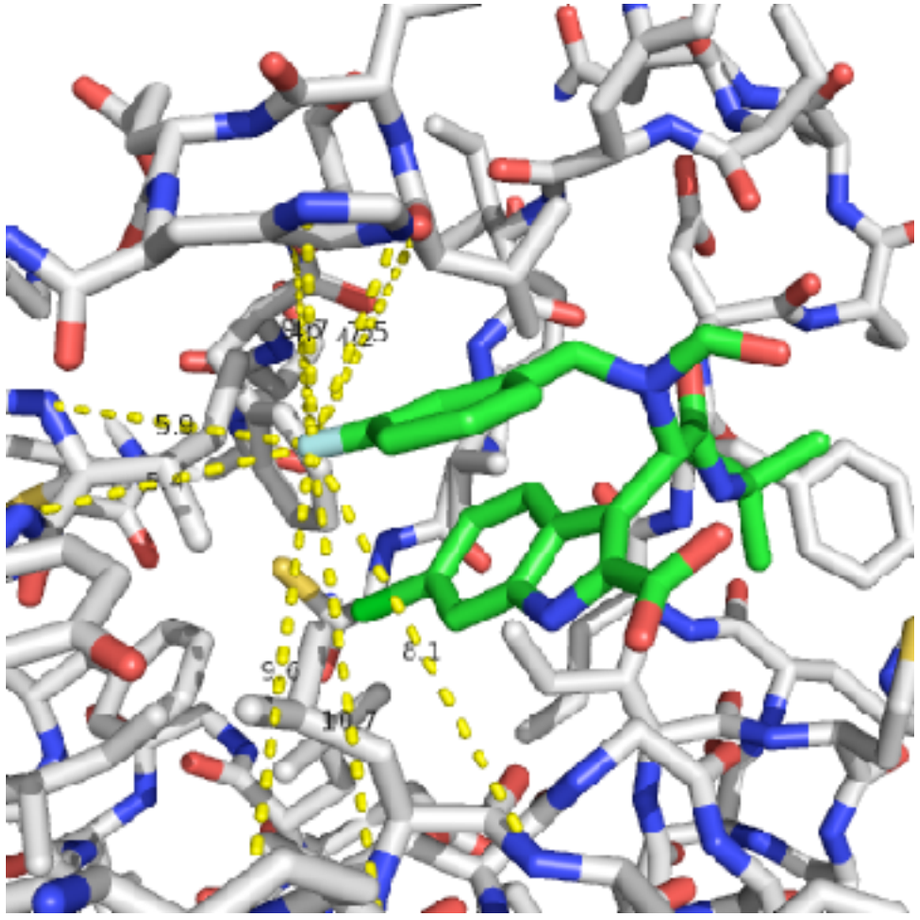
$$\text{hbond}(d) = \begin{cases} w_{\text{hbond}} & d < -0.7 \\ 0 & d > 0 \\ w_{\text{hbond}}(-\frac{10}{7} d) & otherwise \end{cases}$$

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: RF-Score

Pairwise Distance Counts (<12Å)



Protein

Ligand

	C	N	O	S
C				
N				
O				
S				
P				
F		9		
Cl				
Br				
I				

Random Forest

BIOINFORMATICS **ORIGINAL PAPER**

Structural bioinformatics

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

Pedro J. Ballester and John B. O. Mitchell

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"

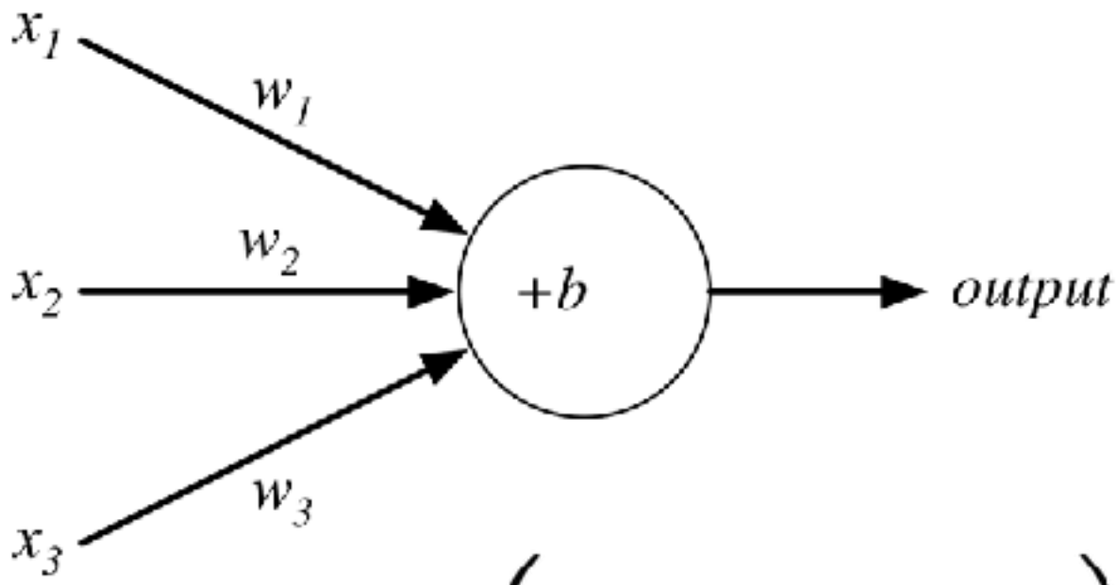
231,655,275 bioactivities in PubCher

125,526 structures in the PDB

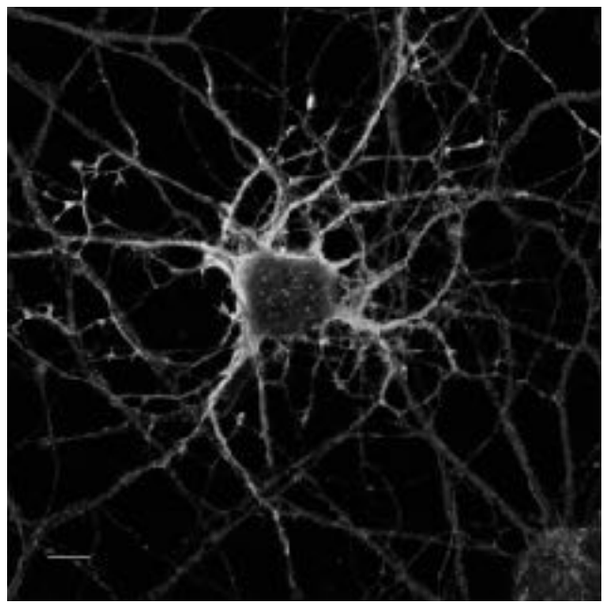
16,179 annotated complexes in PDBbind

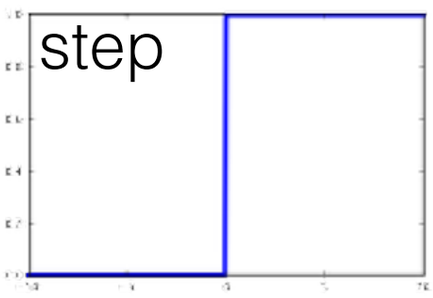
Machine Learning

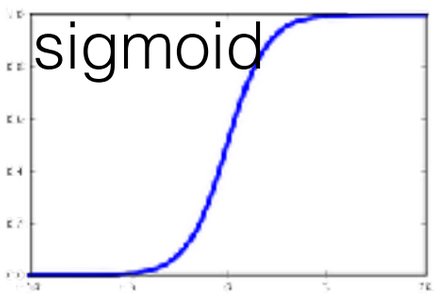
Neural Networks

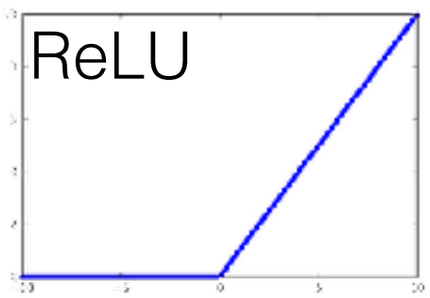


$$output = \sigma\left(\sum_i w_i x_i + b\right)$$

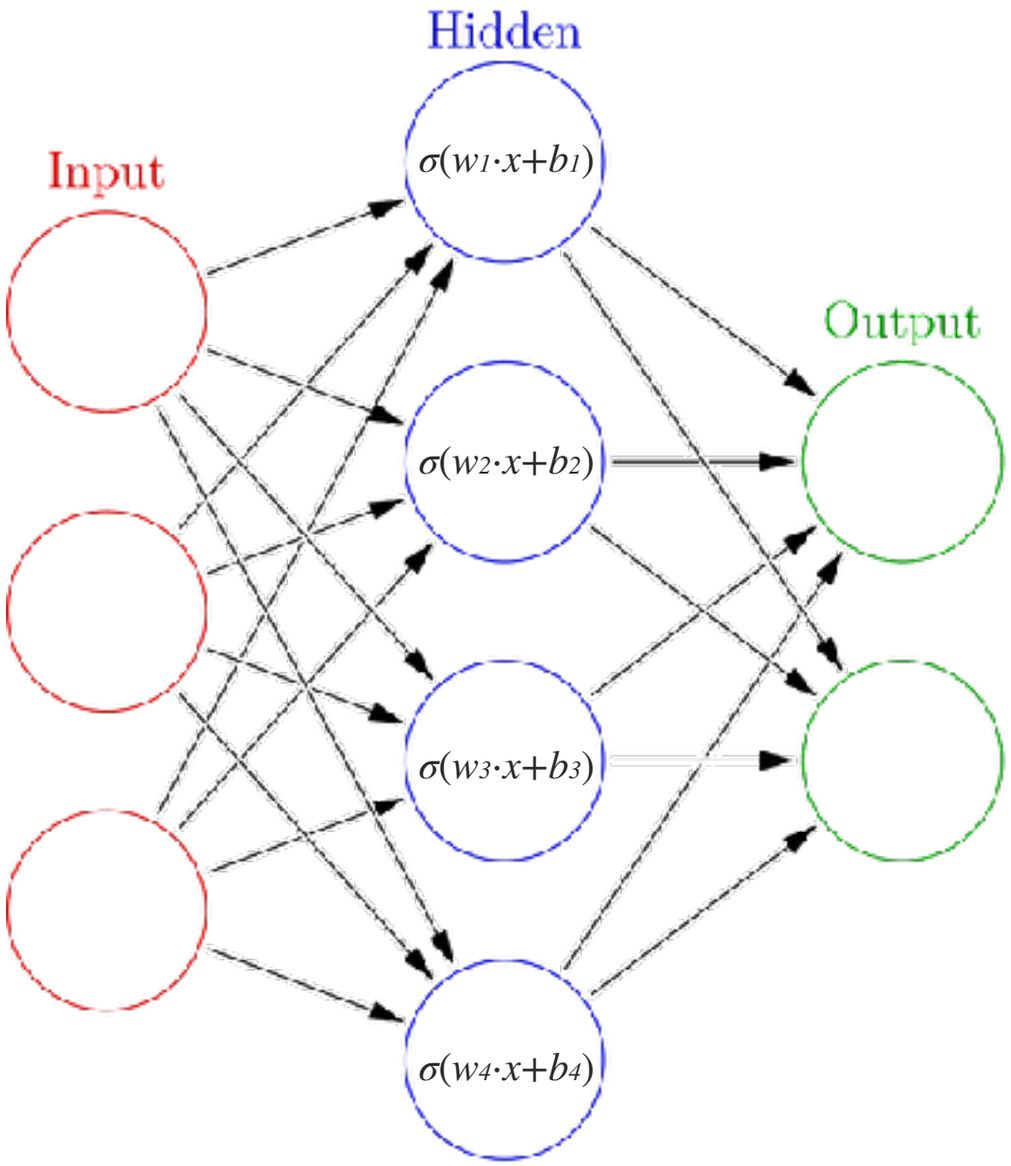


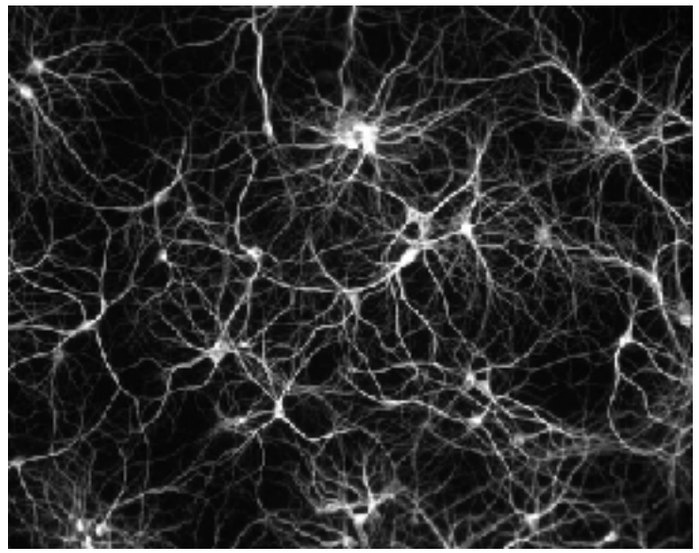






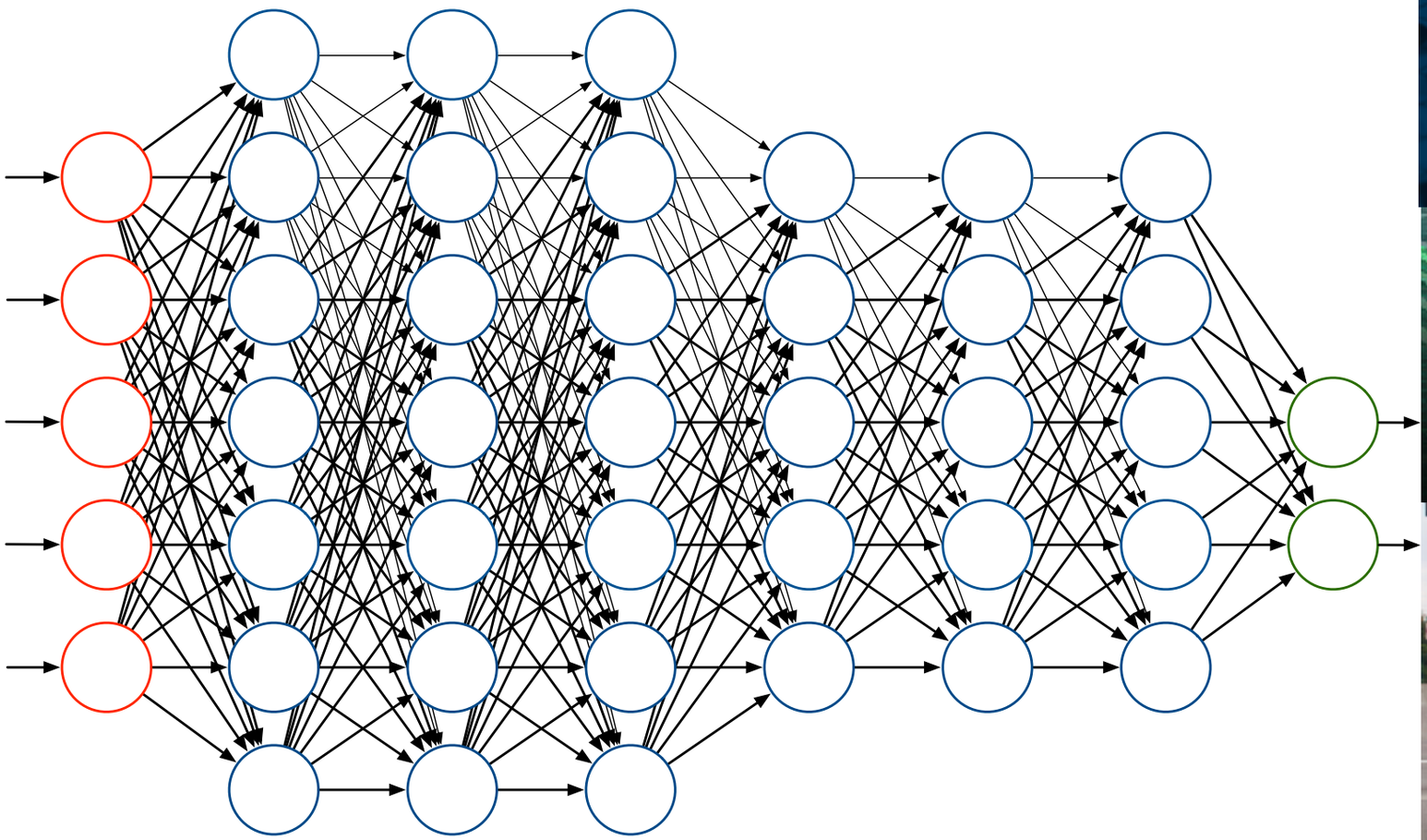
Neural Networks





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

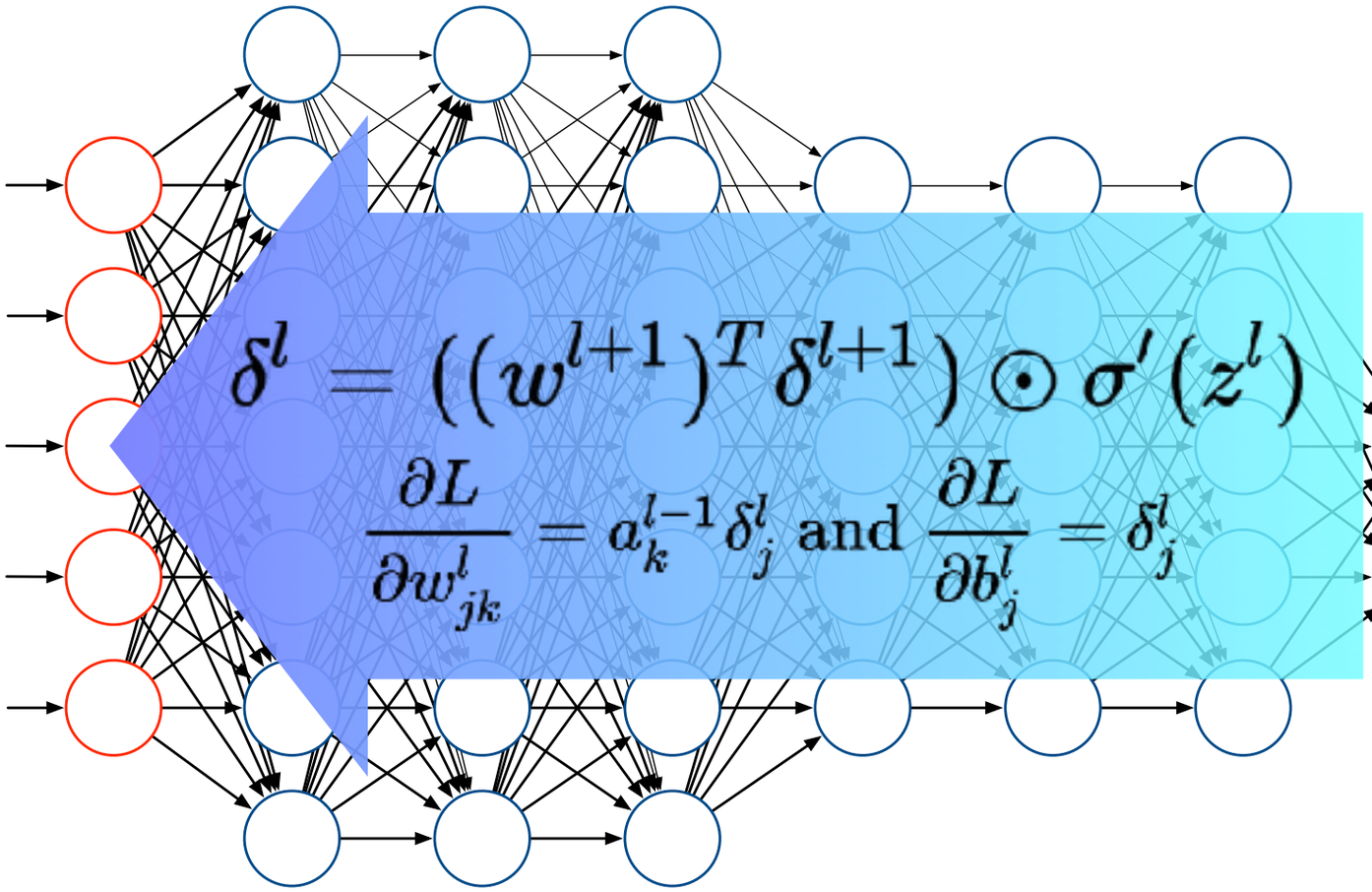
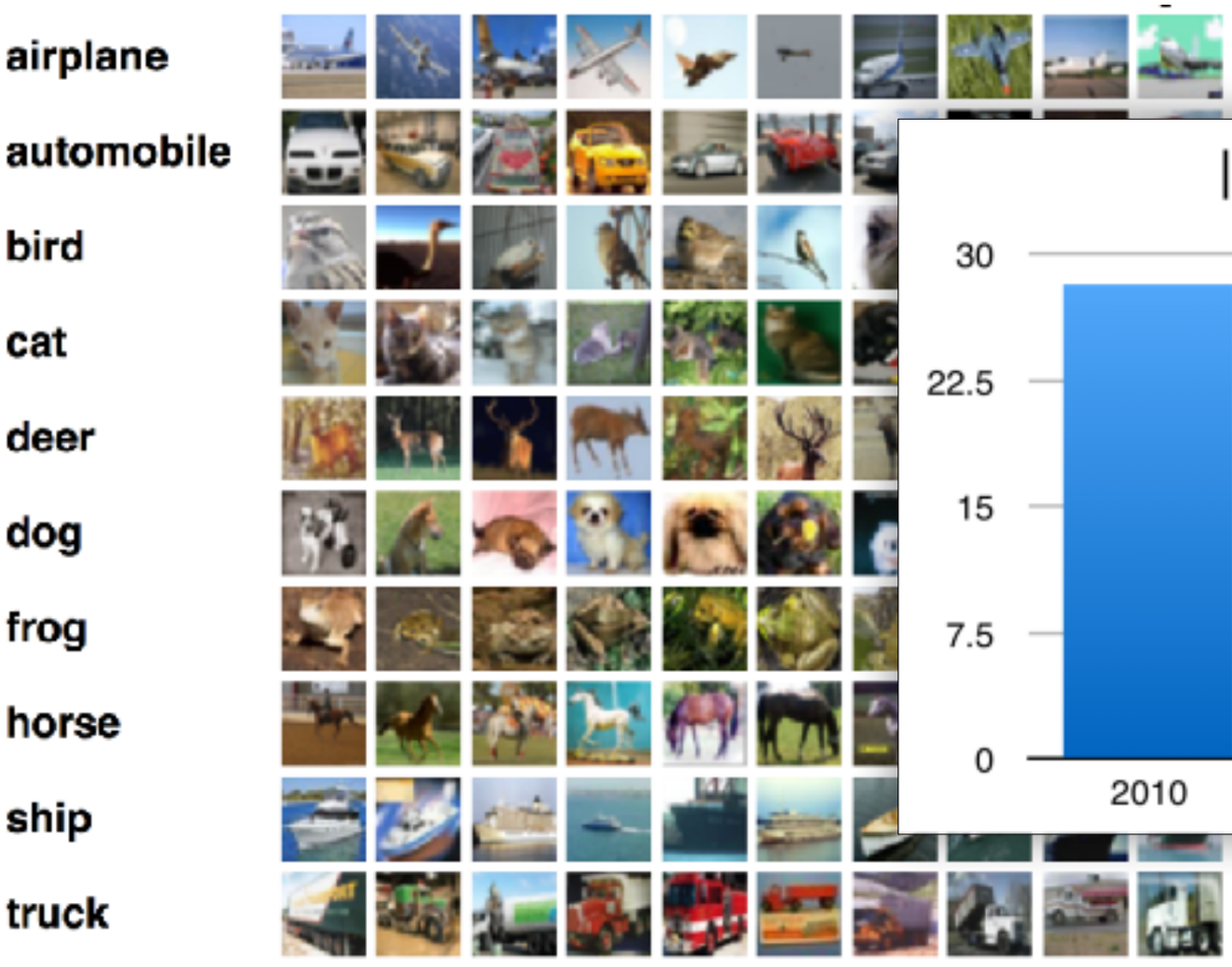
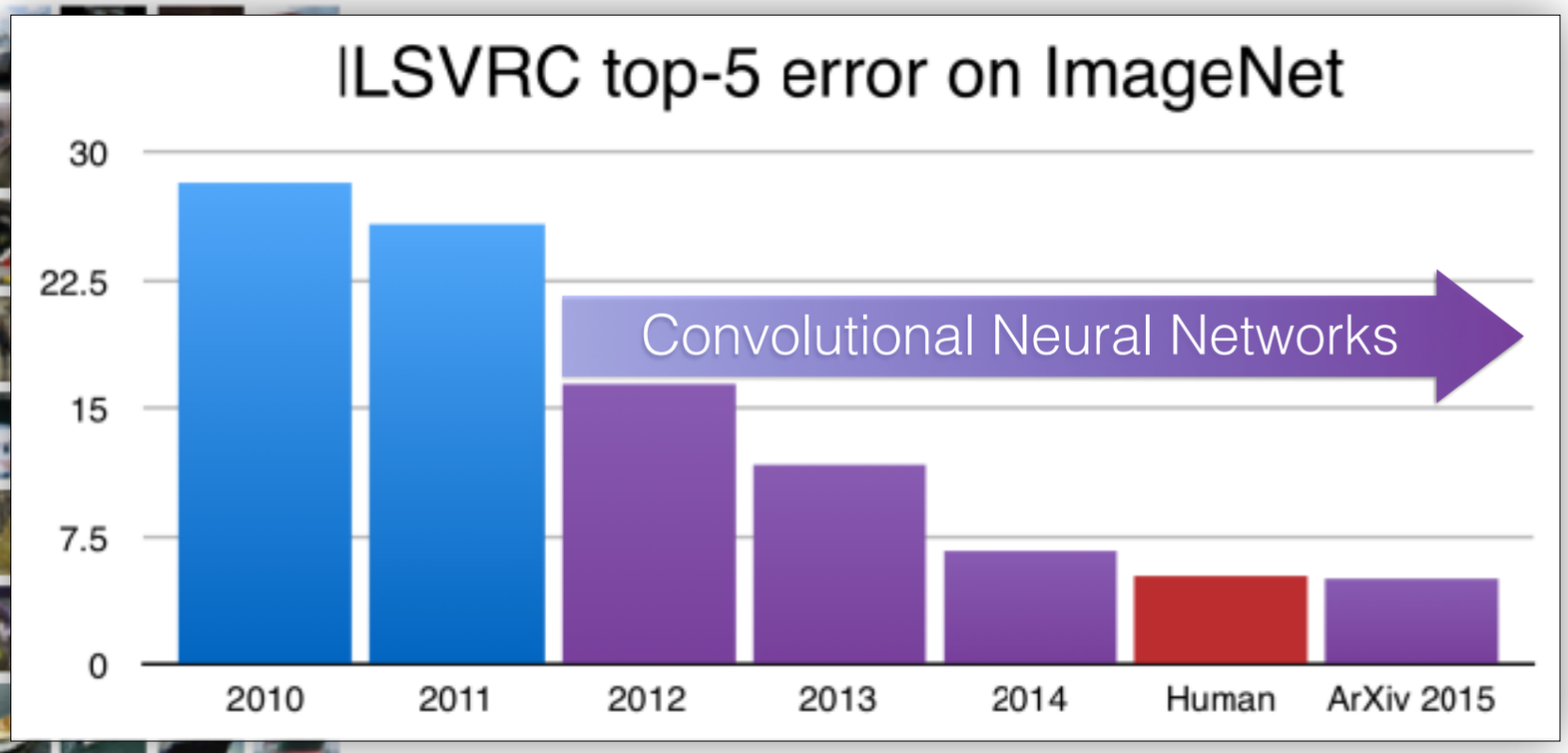


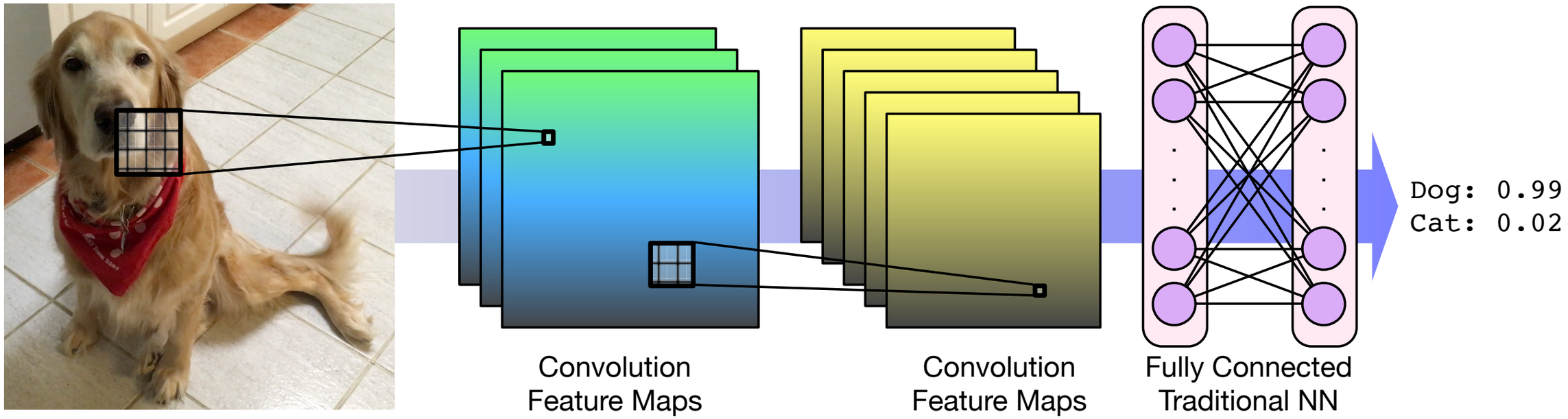
Image Recognition

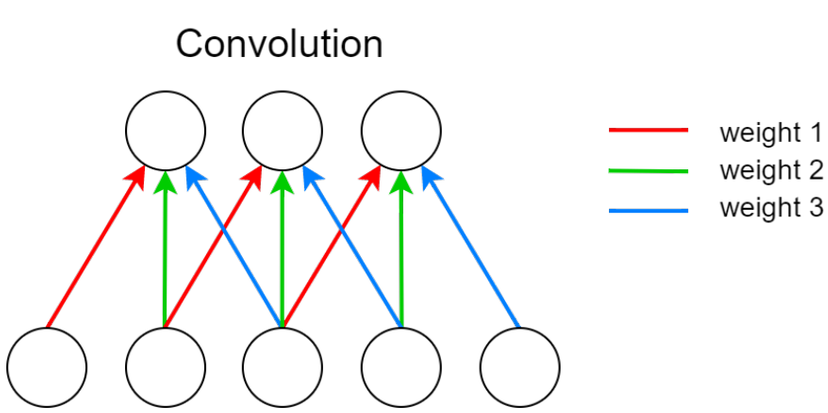


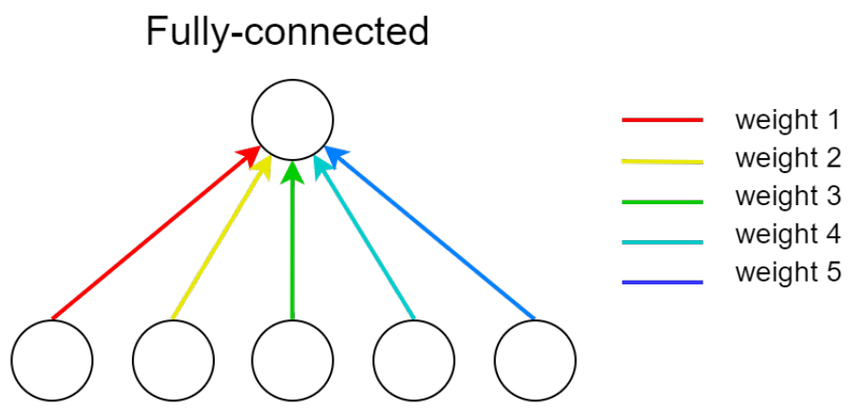


https://devblogs.nvidia.com

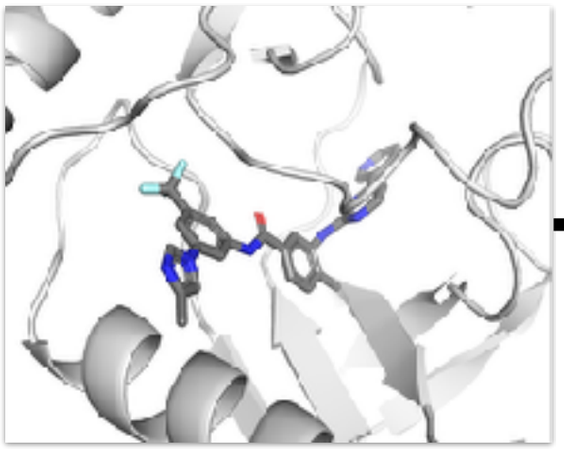
Convolutional Neural Networks







CNNs for Protein-Ligand Scoring



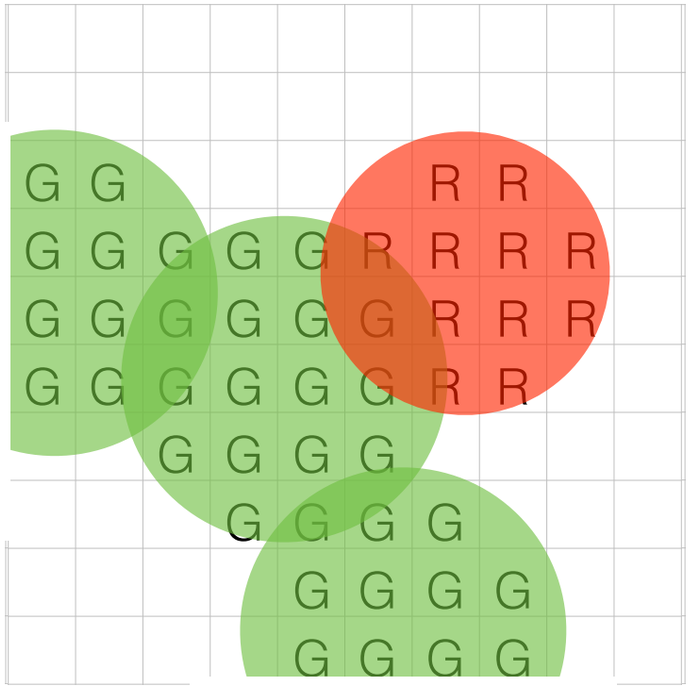
CNN

Pose Prediction

Binding Discrimination

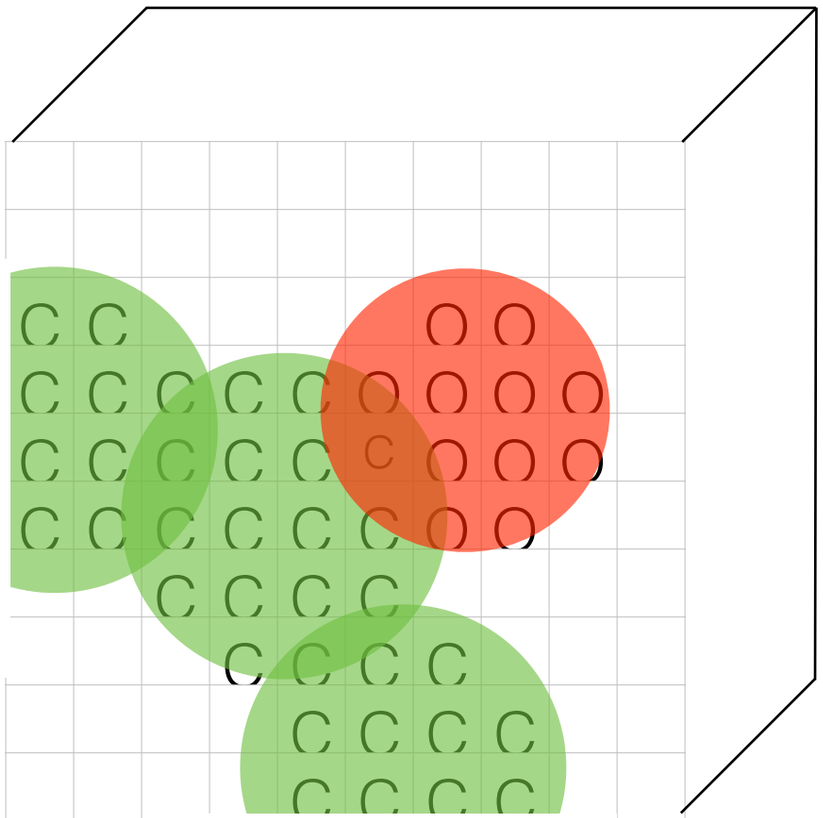
Affinity Prediction

Protein-Ligand Representation



(R,G,B) pixel

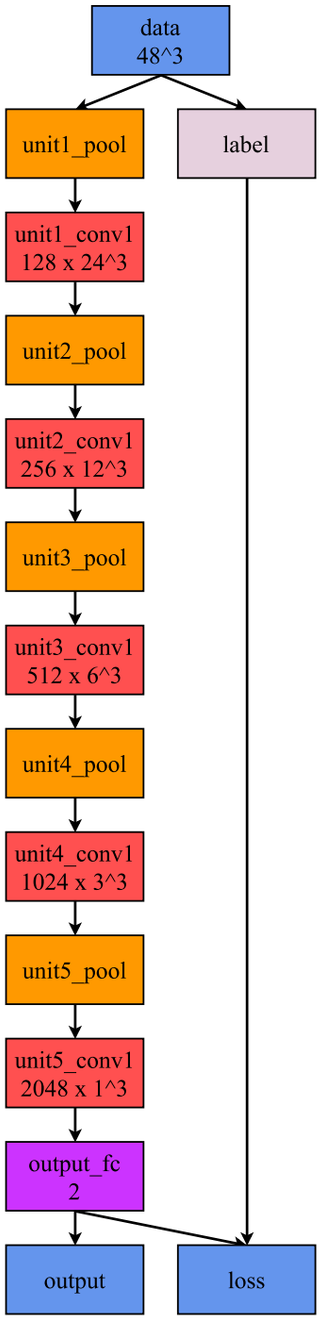
Protein-Ligand Representation



(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**.

Model Optimization



Atom Types
- Vina (34)
- element-only (18)
- ligand-protein (2)

Atom Density Type
- Boolean
- Gaussian

Radius Multiple

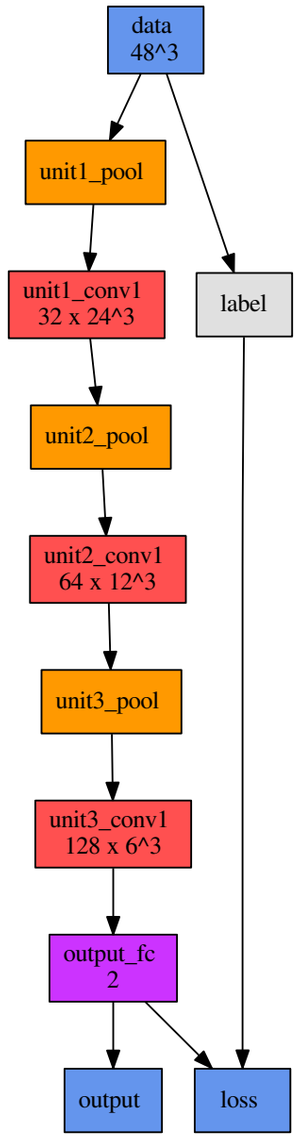
Resolution

Pooling

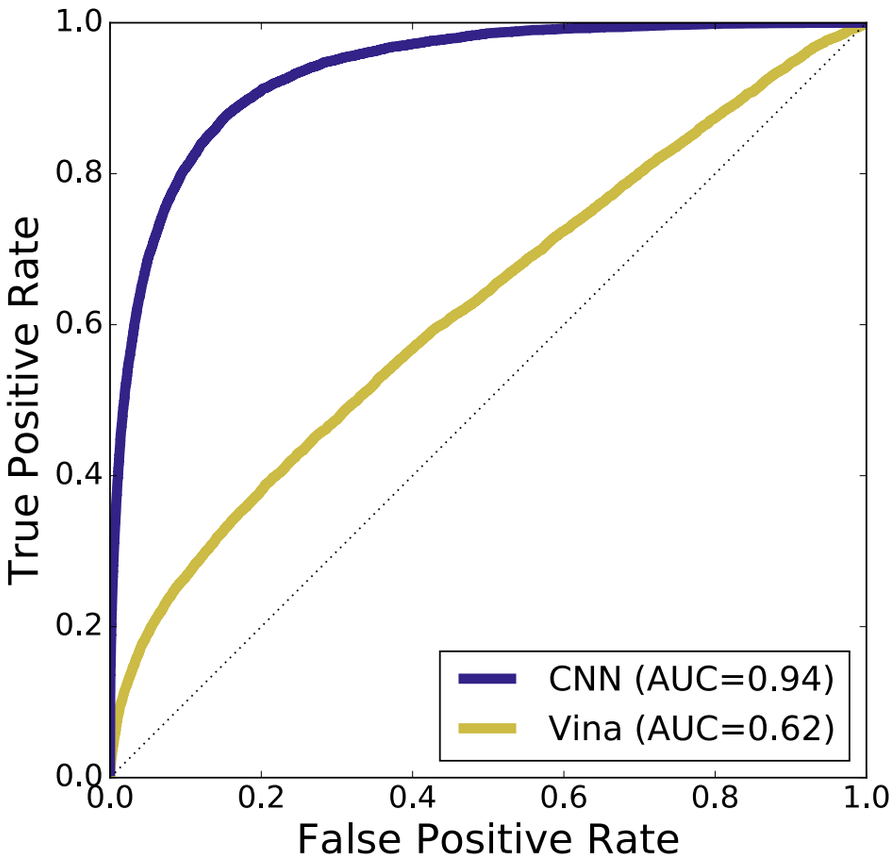
Depth

Width

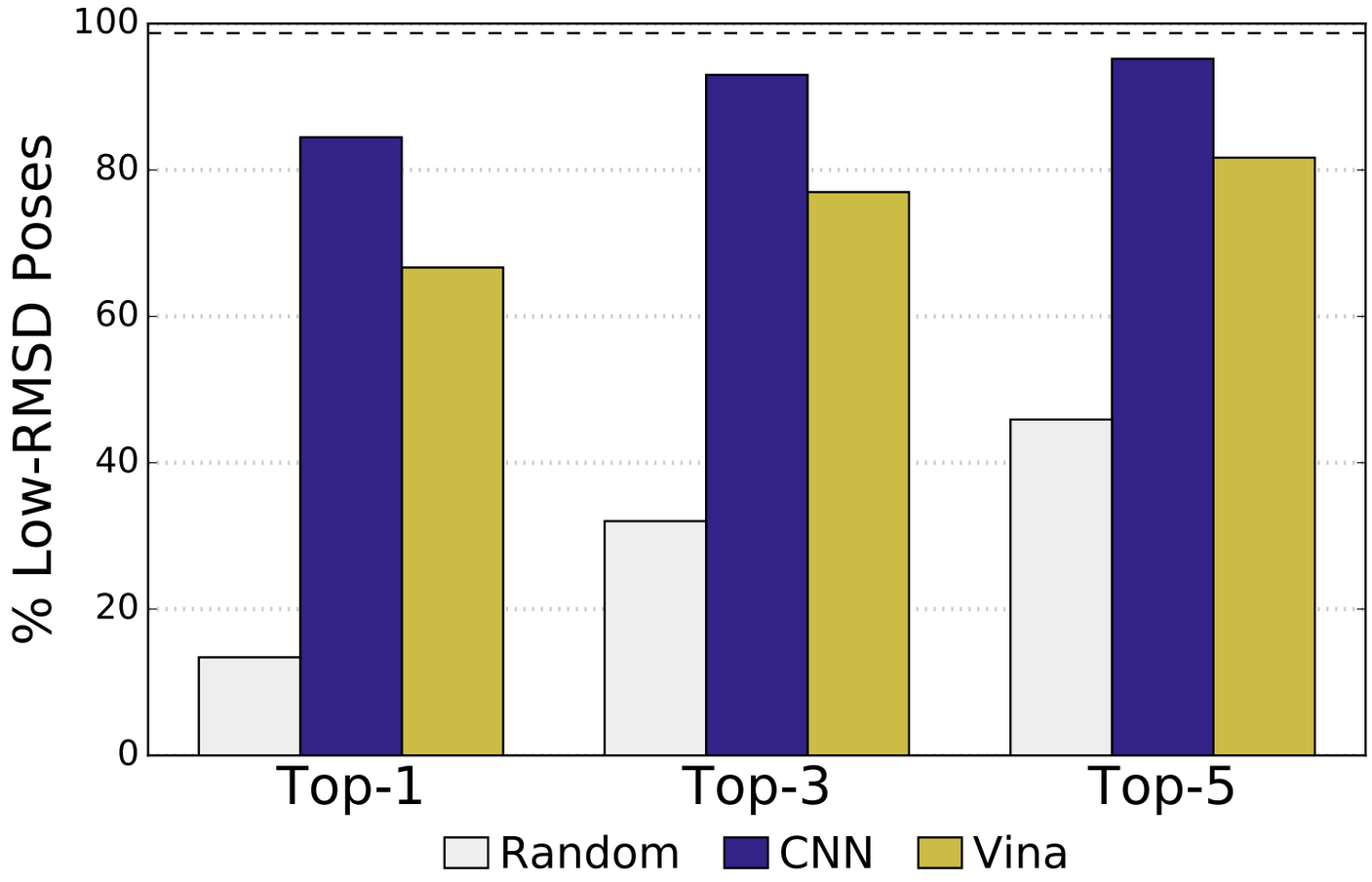
Fully Connected Layers



Pose Prediction (PDBbind)

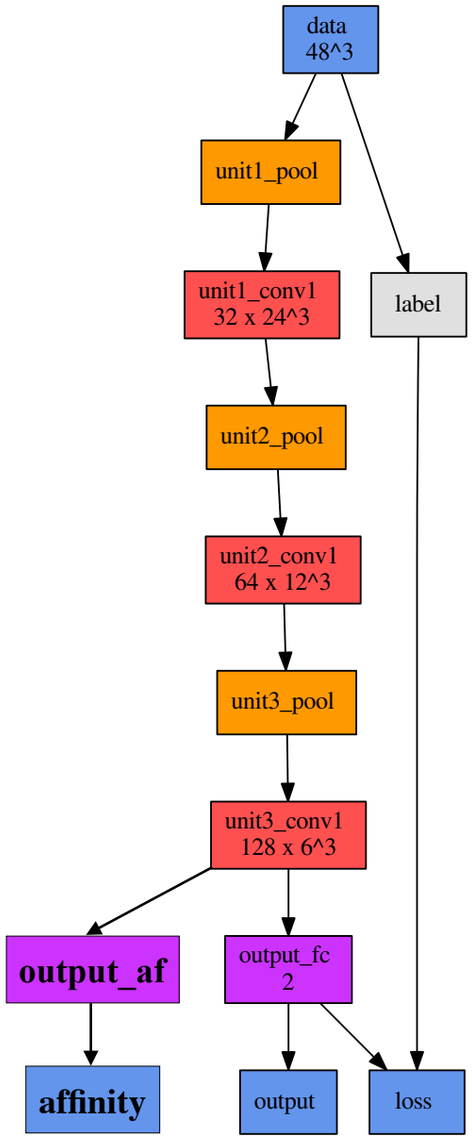


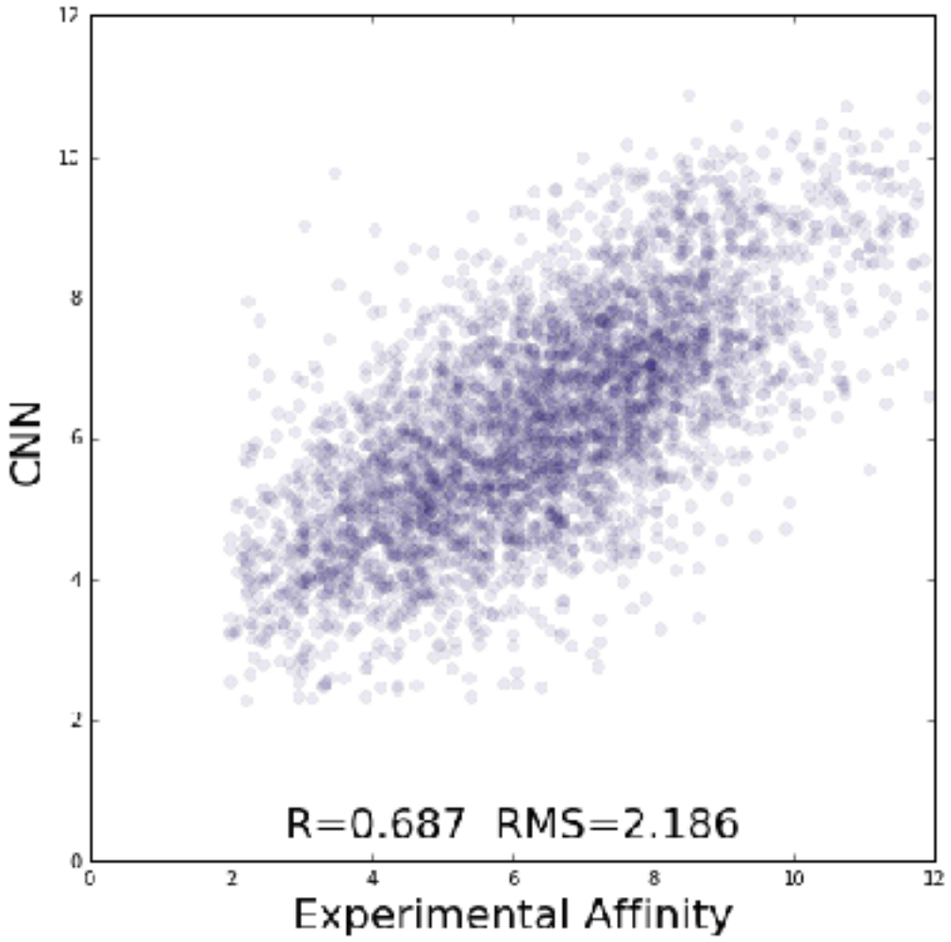
inter-target ranking

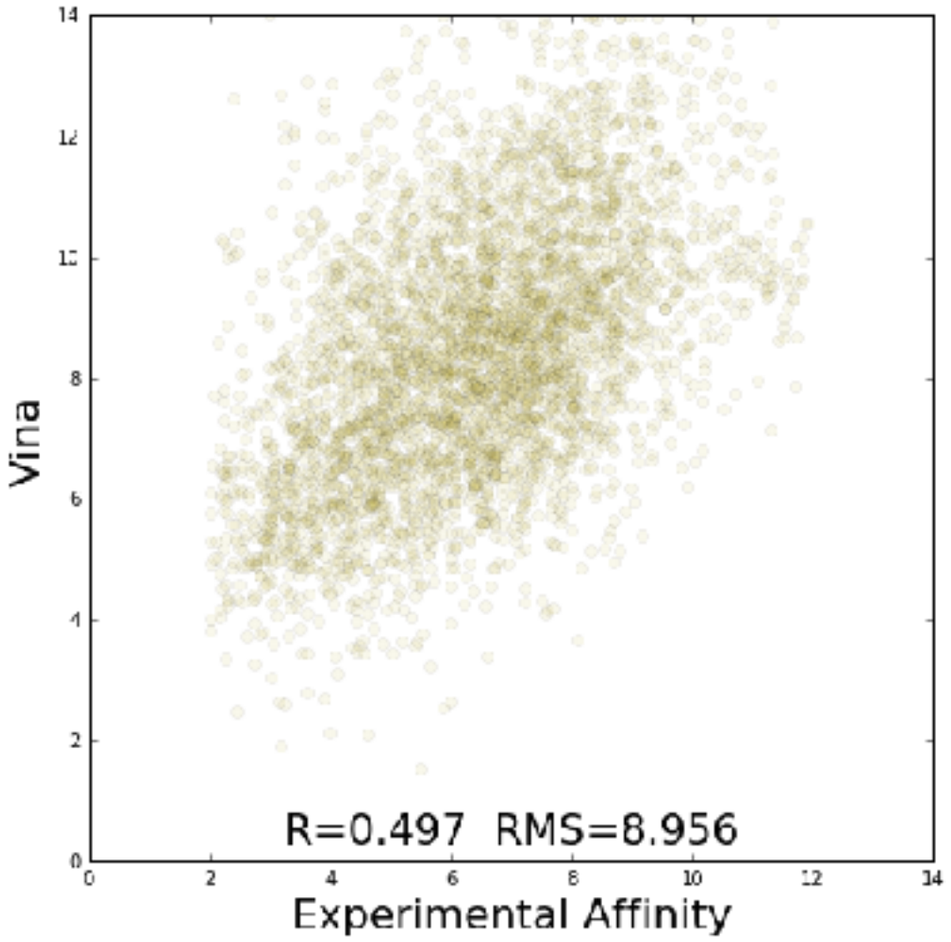


intra-target ranking

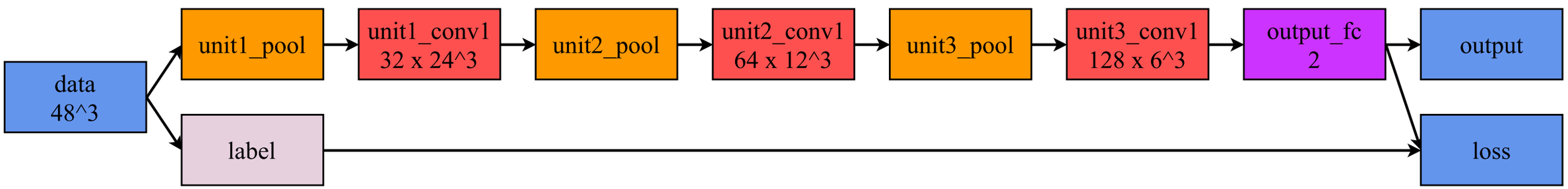
Affinity Prediction







Beyond Scoring



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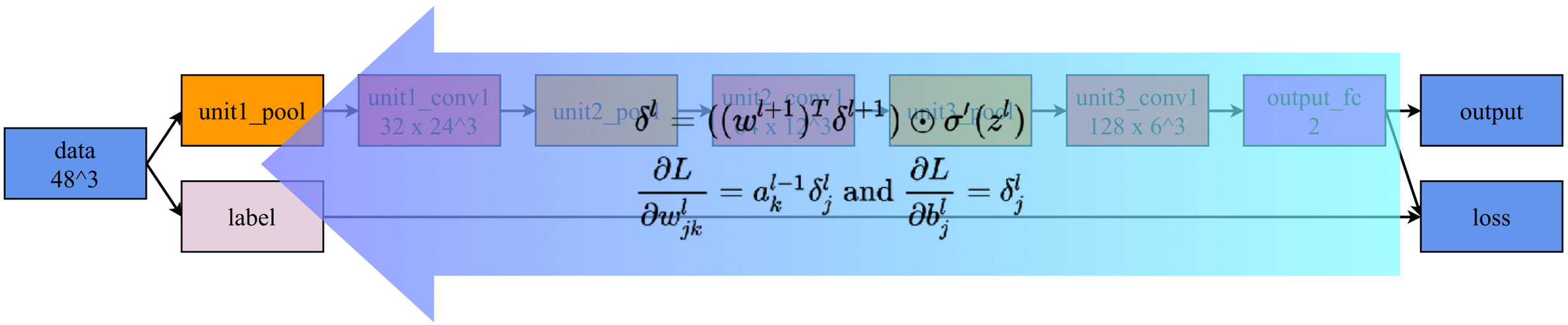

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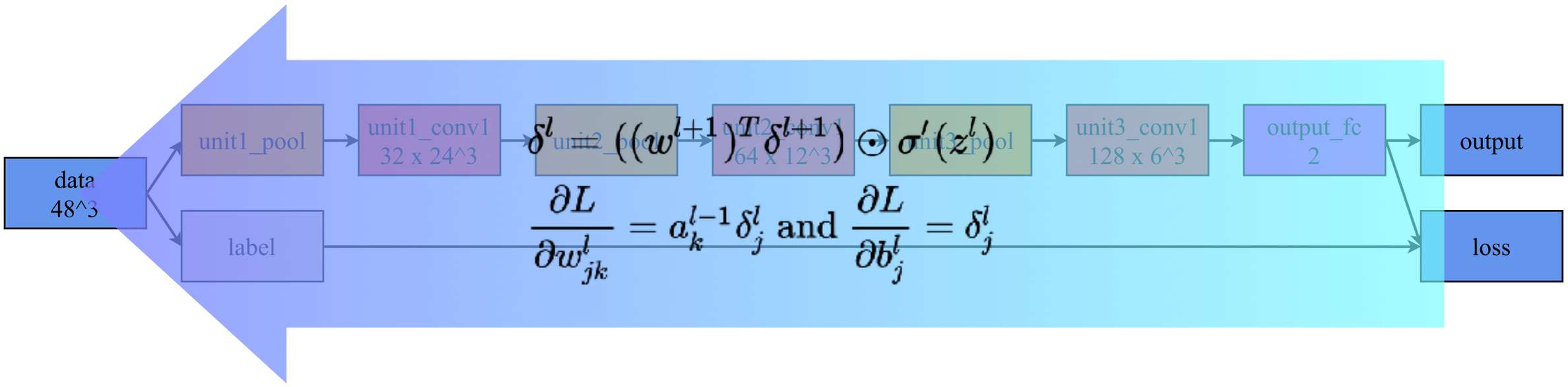

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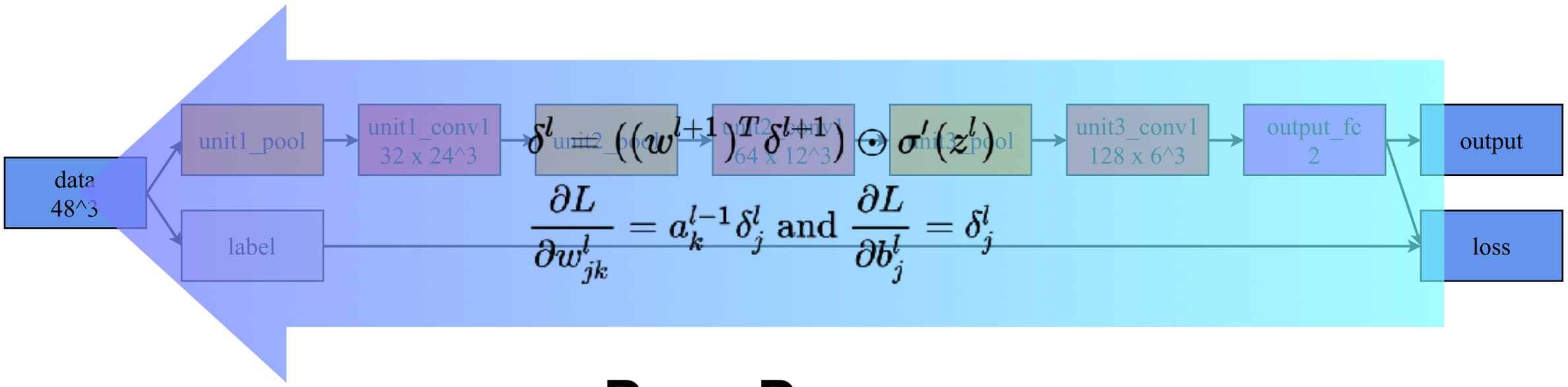
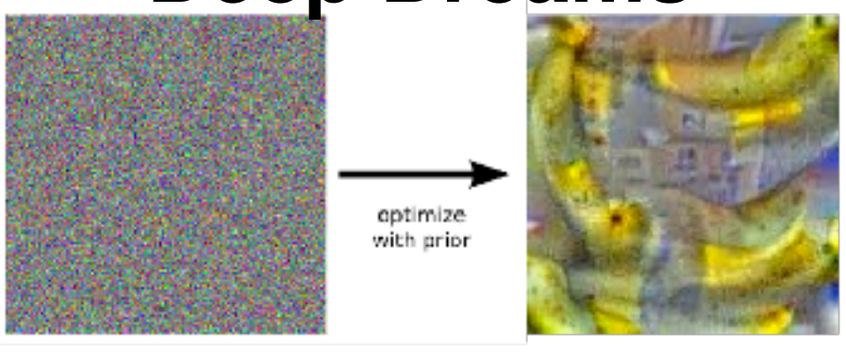
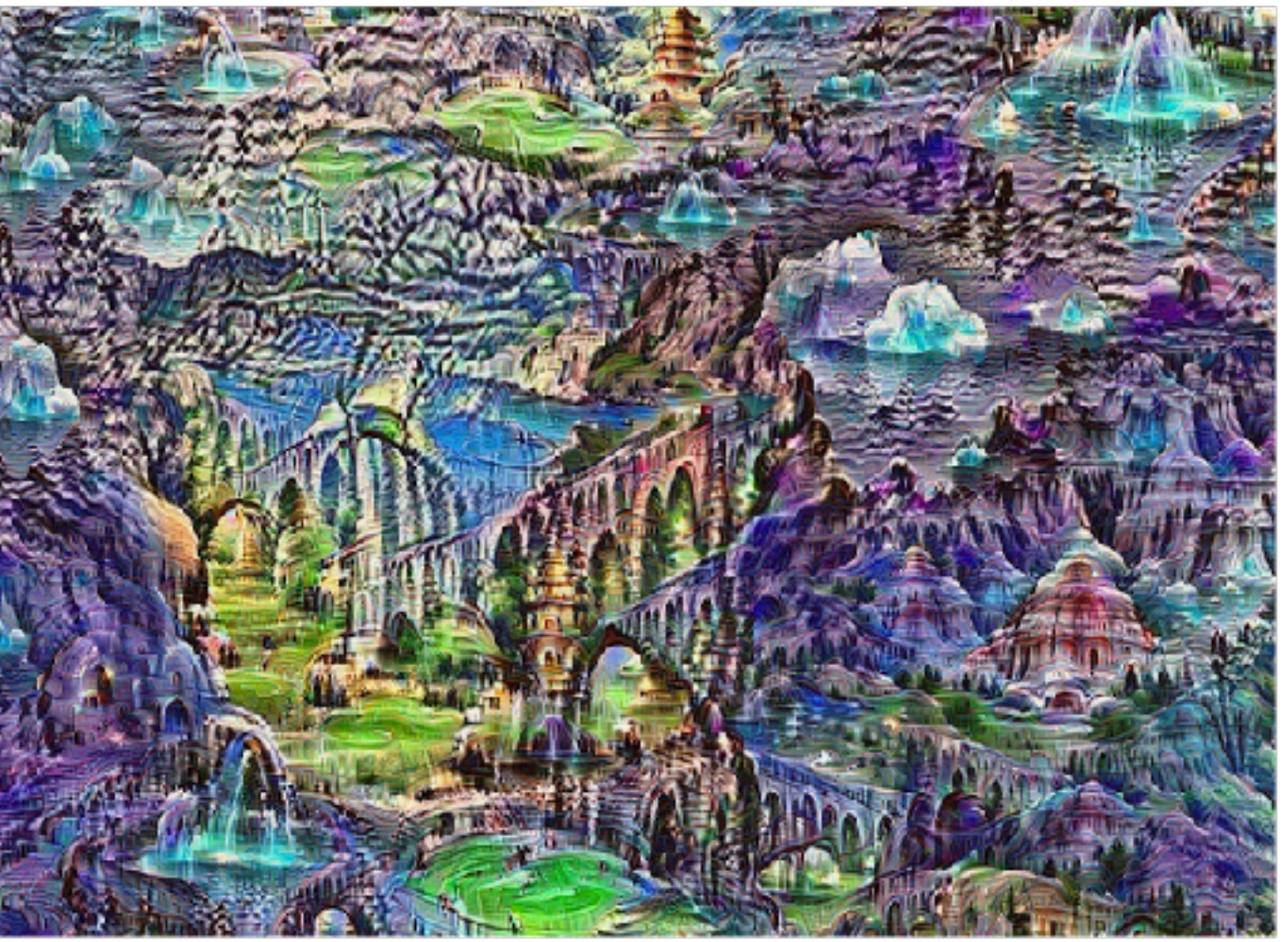
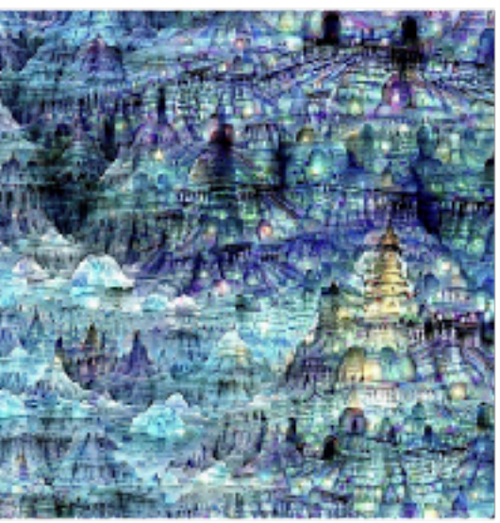


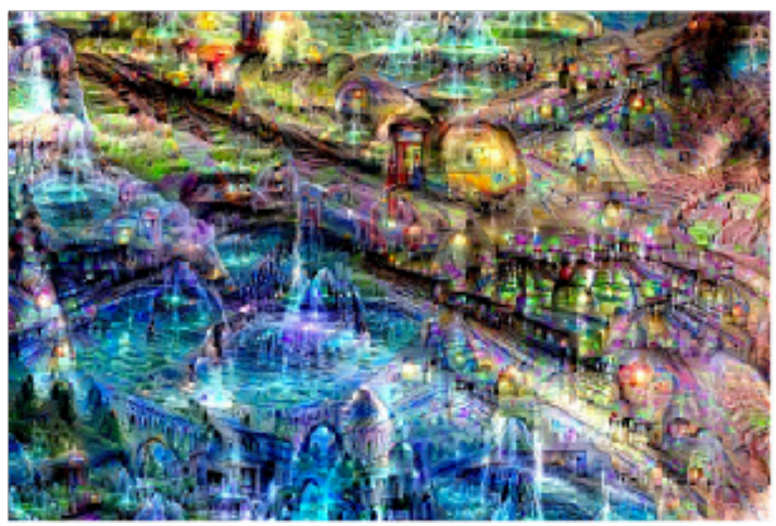
Deep Dreams

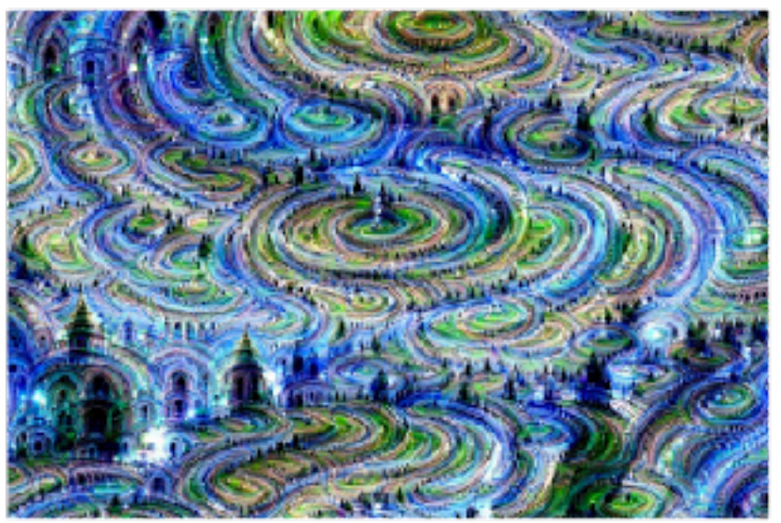


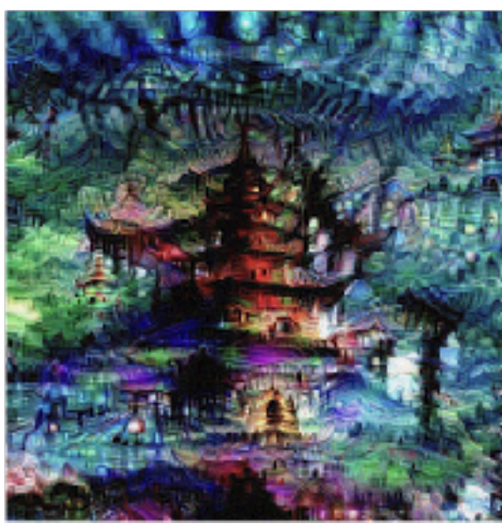
https://research.googleblog.com/2015/06/inceptionism-going-deeper-into-neural.html





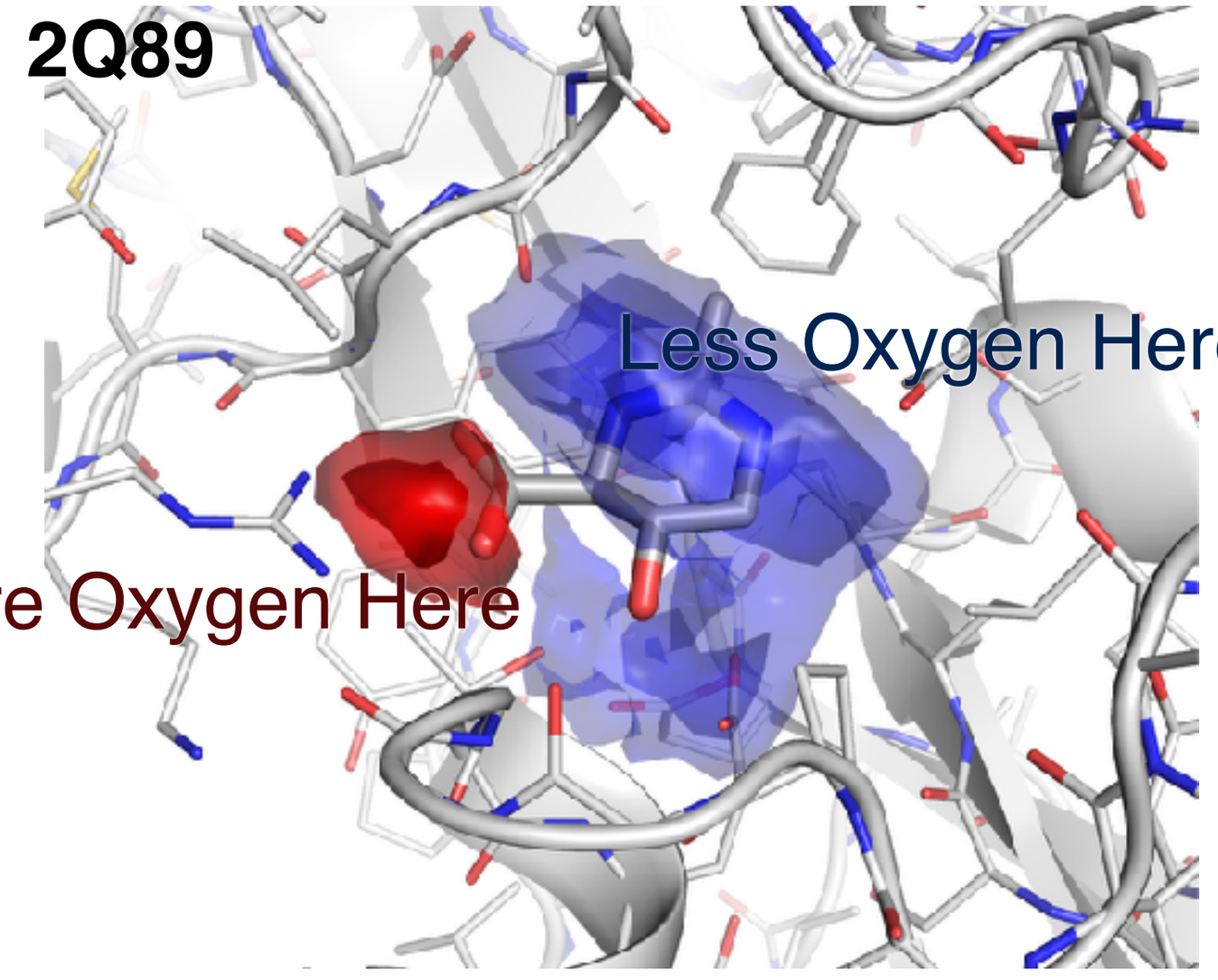






https://deepdreamgenerator.com/#gallery

Beyond Scoring



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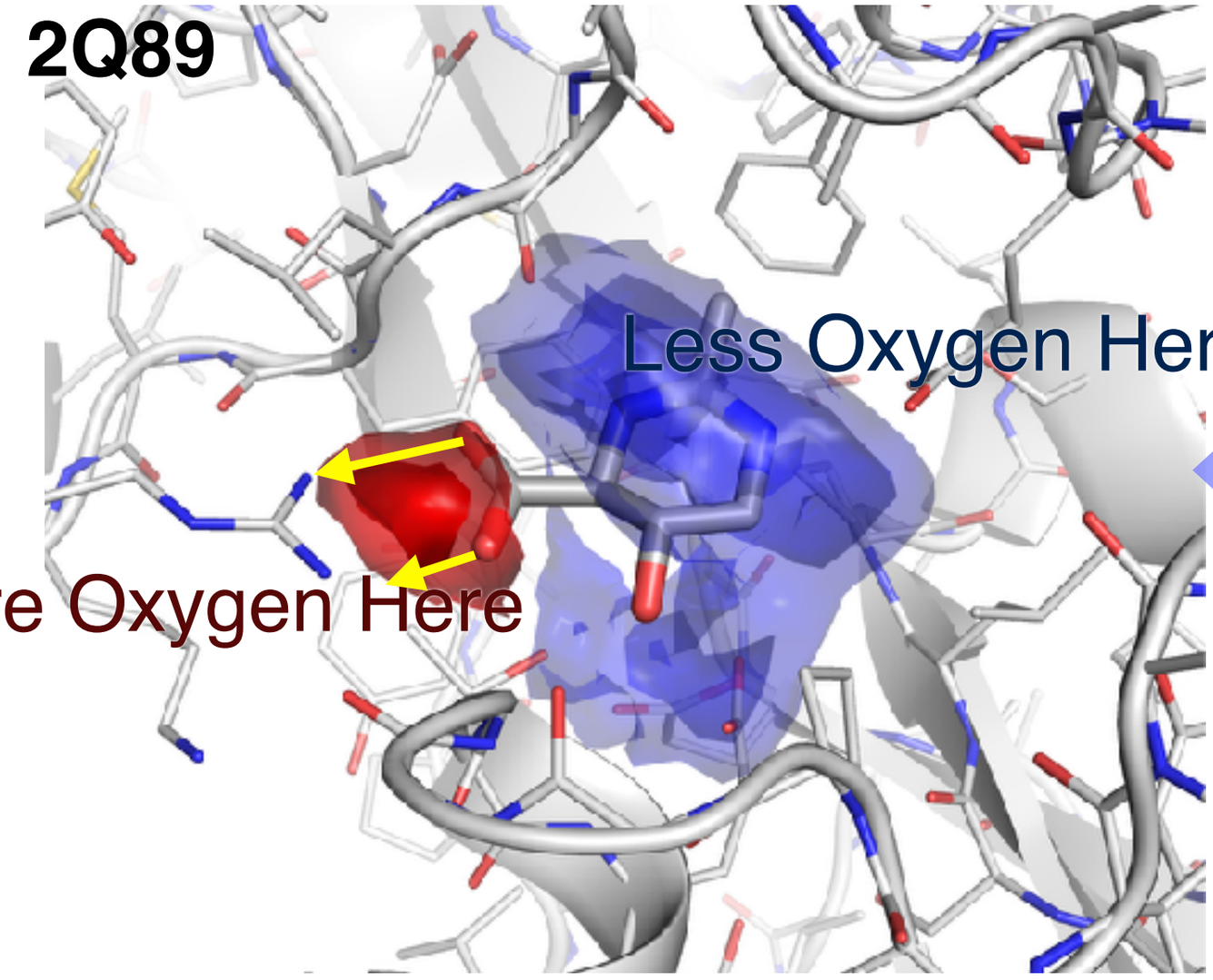
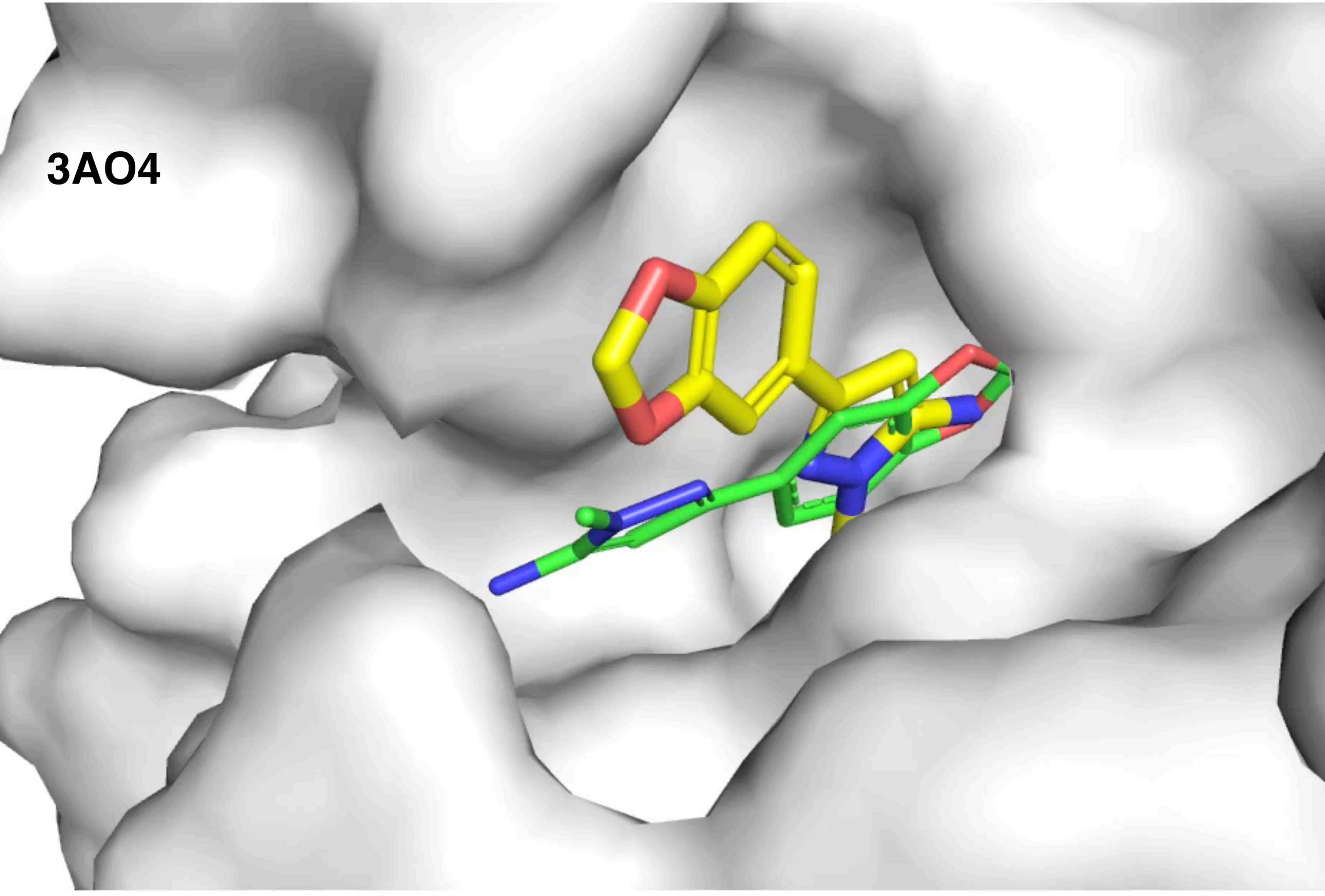
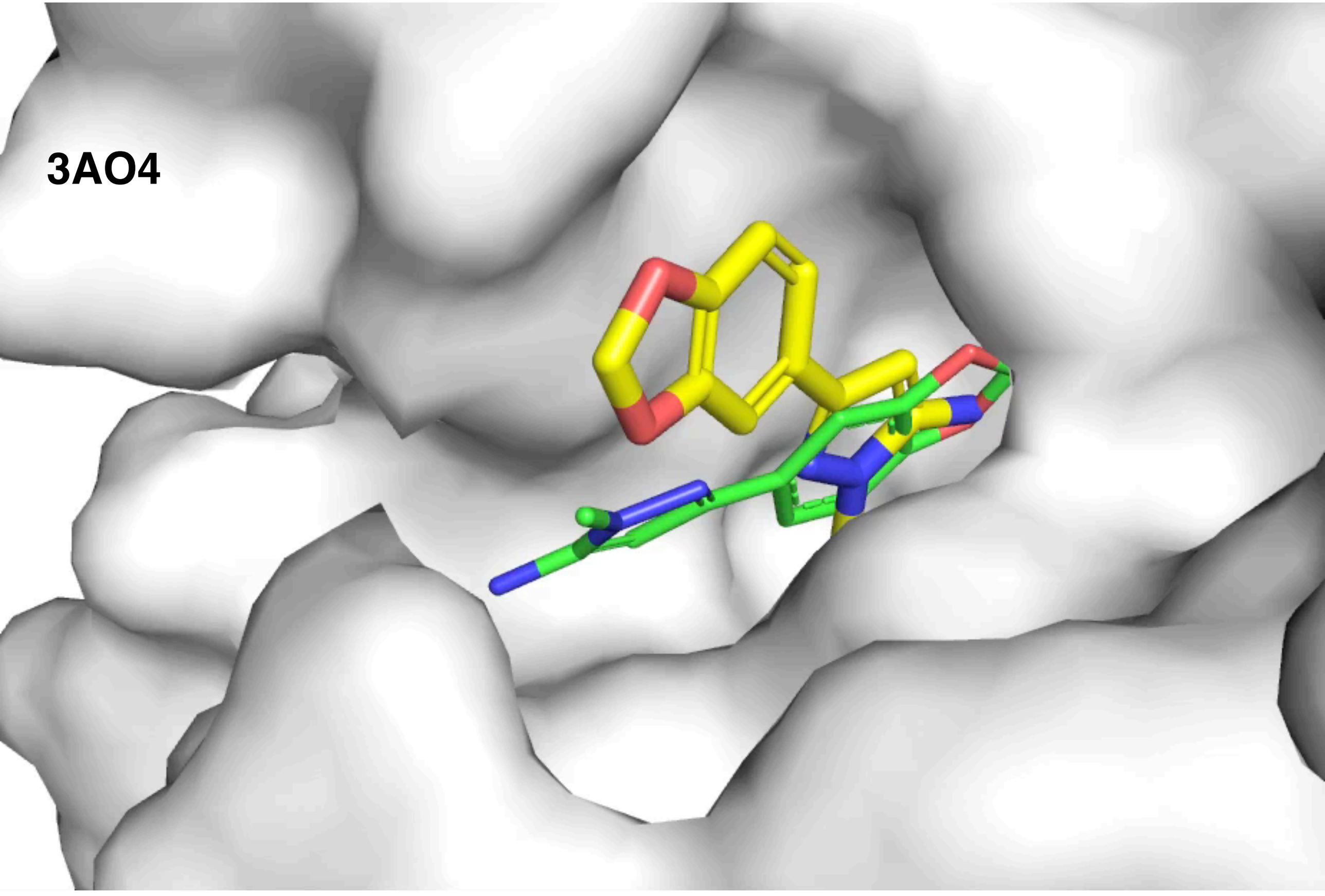


$$\frac{\partial L}{\partial A} = \sum_{i \in G_A} \frac{\partial L}{\partial G_i} \frac{\partial G_i}{\partial D} \frac{\partial D}{\partial A}$$


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

(Submitted on 27 Oct 2016 (v1), last revised 6 Feb 2017 (this version, v4))

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

(Submitted on 30 Sep 2015 (v1), last revised 3 Nov 2015 (this version, v2))

Atomic Convolutional Networks for Predicting Protein-Ligand Binding Affinity

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

(Submitted on 30 Mar 2017)

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

Alessandro Lusci*†, Gianluca Pollastri†, and Pierre Baldi*‡
† School of Computer Science and Informatics, University College Dublin, Belfield, Dublin 4, Ireland
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J. Chem. Inf. Model., 2013, 53 (7), pp 1563–1575
DOI: 10.1021/ci400187y
Publication Date (Web): June 24, 2013

Low Data Drug Discovery with One-shot Learning

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

(Submitted on 10 Nov 2016)

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

Matthew Ragoza†‡, Joshua Hochuli‡¶, Elisa Idrobo§, Jocelyn Sunseri‖, and David Ryan Koes*‡
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J. Chem. Inf. Model., 2017, 57 (4), pp 942–957
DOI: 10.1021/acs.jcim.6b00740
Publication Date (Web): April 3, 2017

Key Concepts

Ligand-Based Virtual Screening

Identifying new active compounds based on similarity to known active compounds

Pharmacophore

A spatial arrangement of molecular features essential for biological activity - hydrogen bonding, hydrophobic, charged, etc.

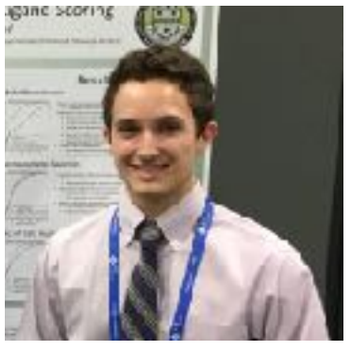
Docking

Predict the position, pose and affinity of a molecule using the receptor structure

Scoring

force field … empirical … knowledge based

Acknowledgements



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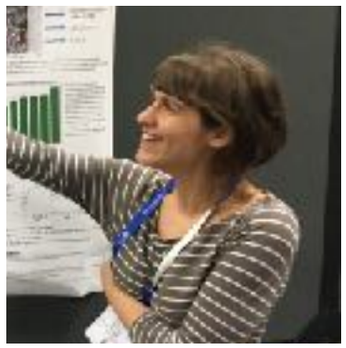
Josh Hochuli

Elisa Idrobo



Jocelyn Sunseri

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