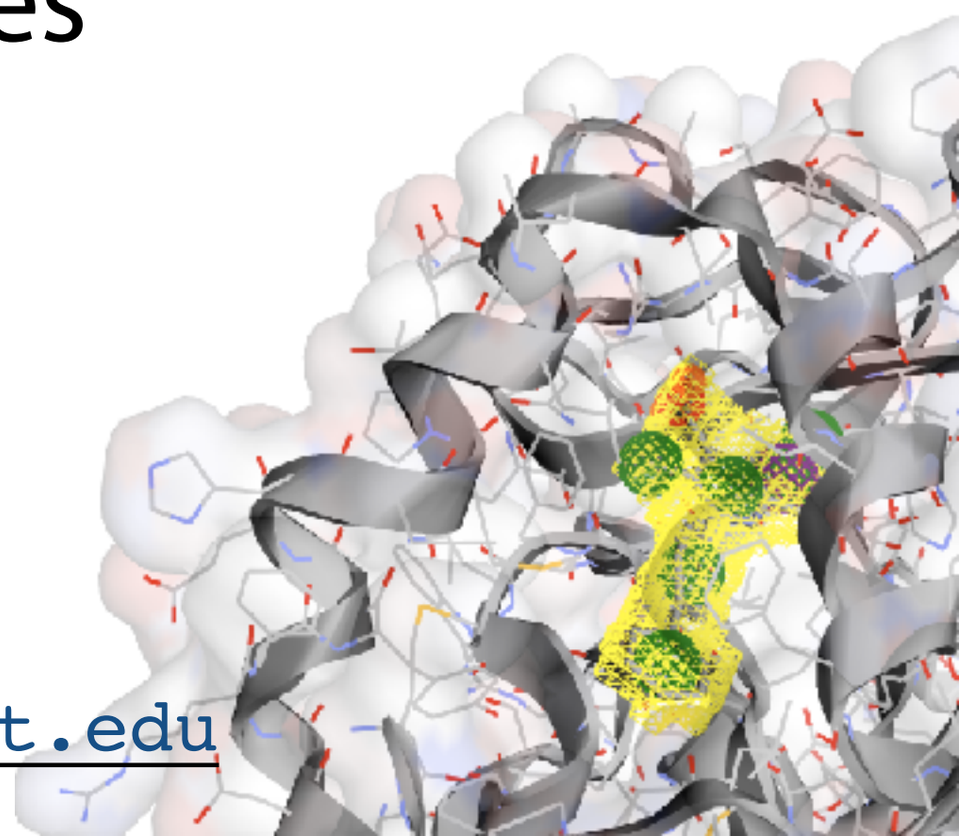
Computational Drug Discovery

David Ryan Koes

4/10/2018



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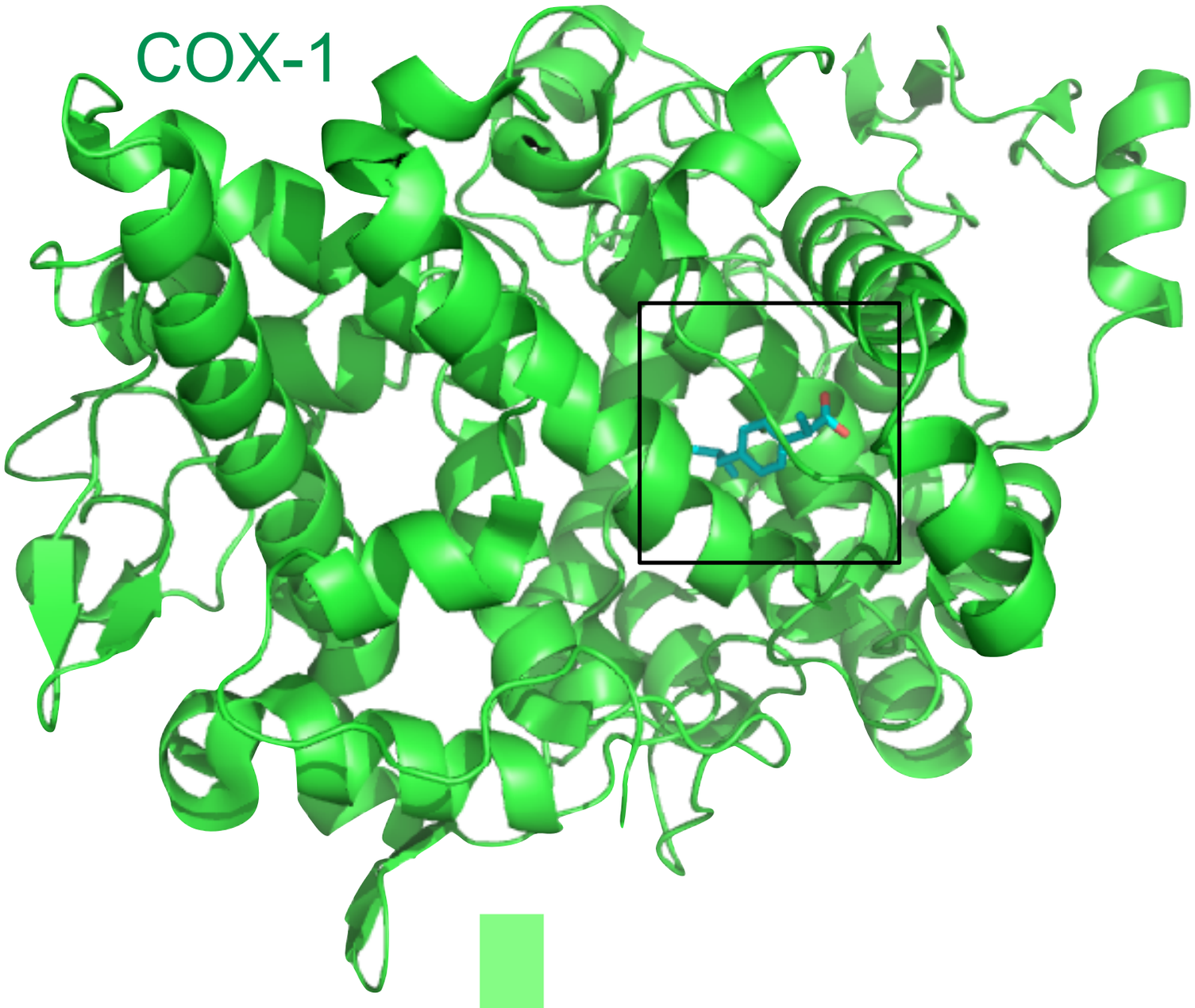
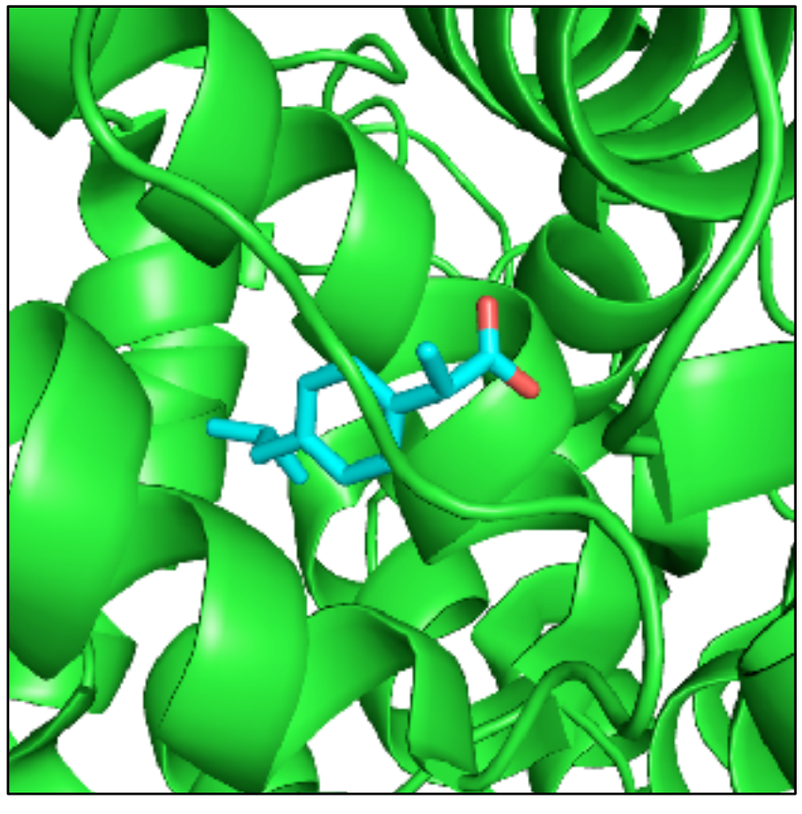
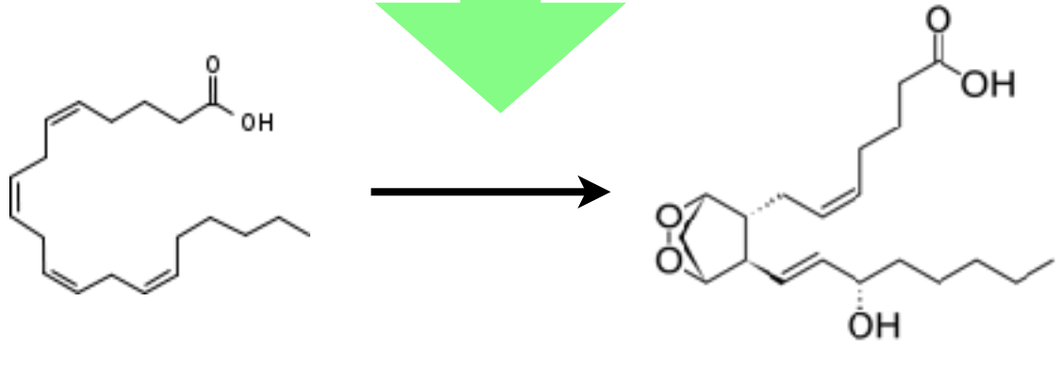
A small molecule intended to affect the structure/function of macromolecules


COX-1




OH
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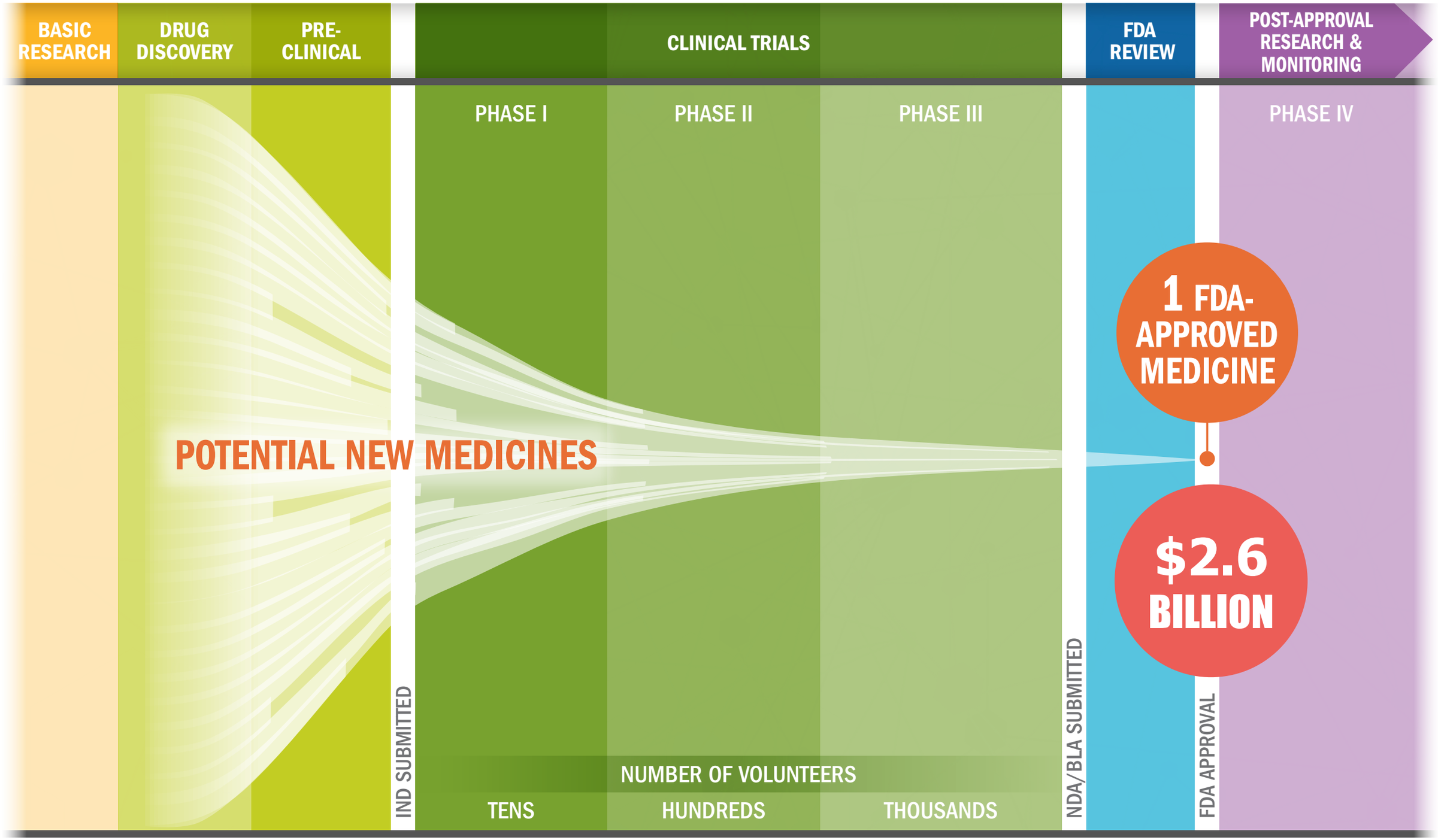
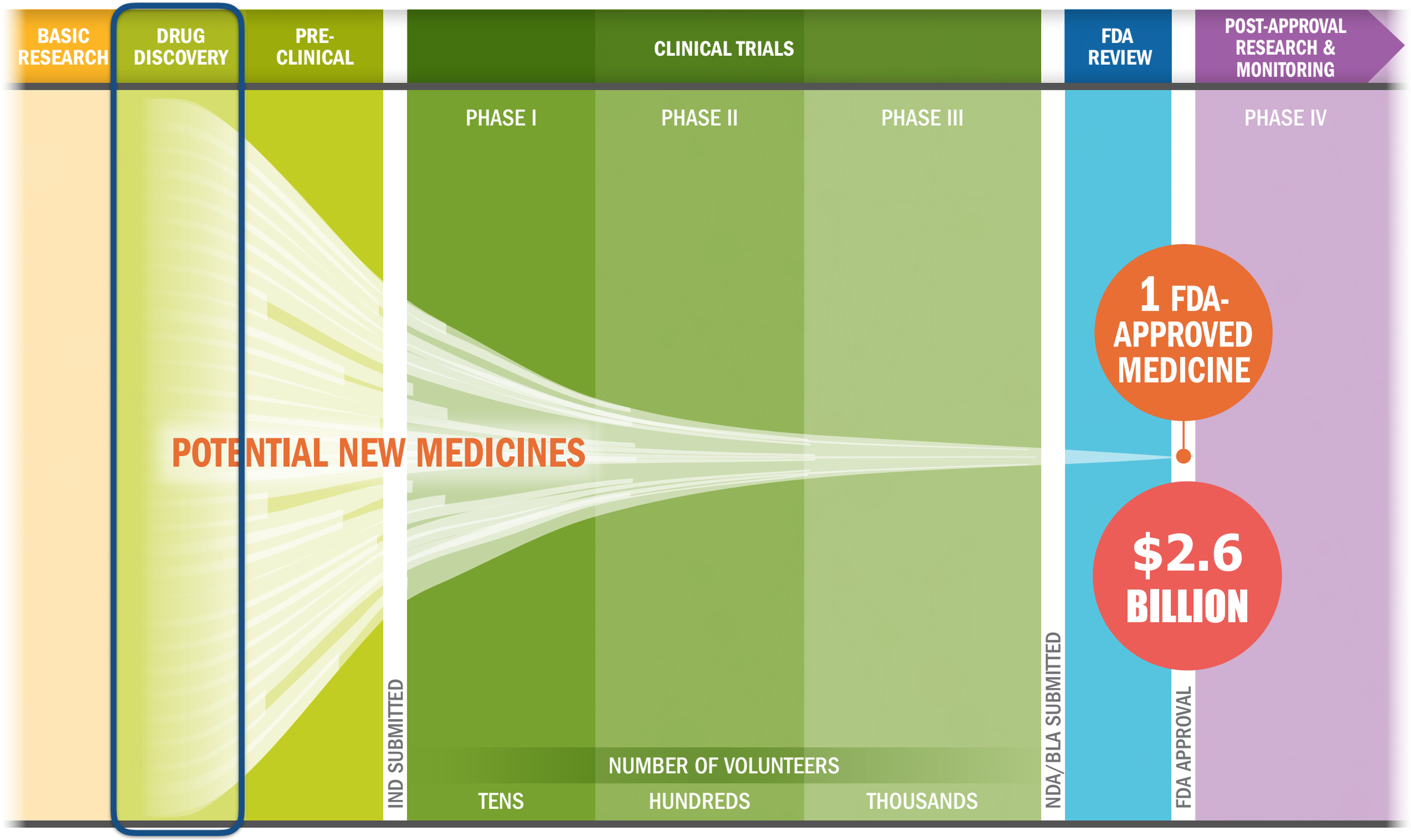
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



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

THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



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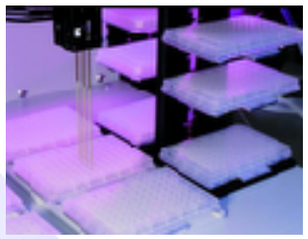
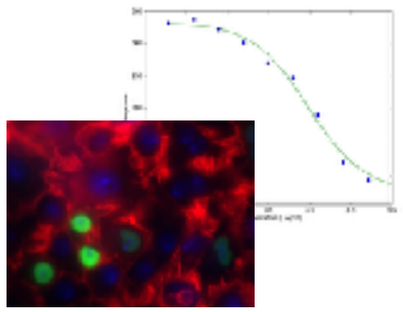
1. Does the compound do what you want it to?
2. Does the compound **not** do what you **don't** want it to?
3. Is what you want it to do the right thing?

Drug Discovery

Target Identification



Screening



Lead Identification

Lead Optimization

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

Cost

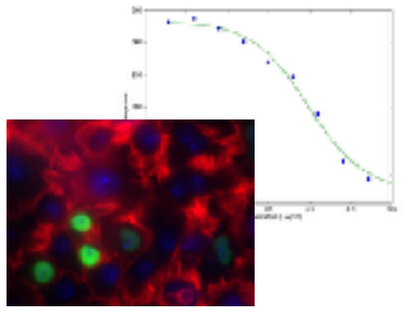
Computational Drug Discovery

Omics

Target Identification

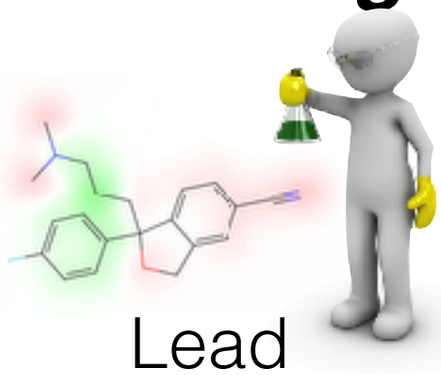
Virtual

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

Kinds of Virtual Screening

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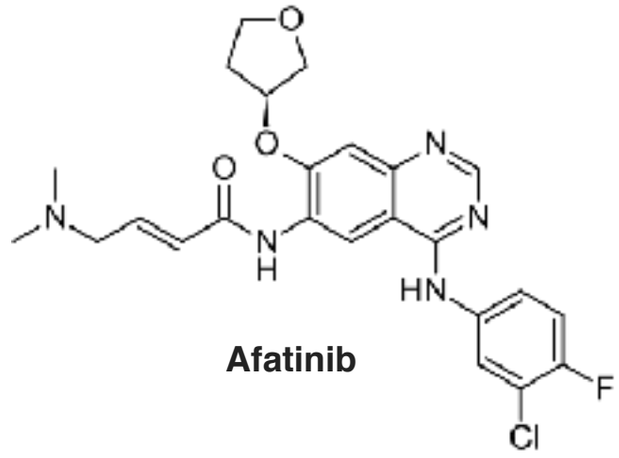
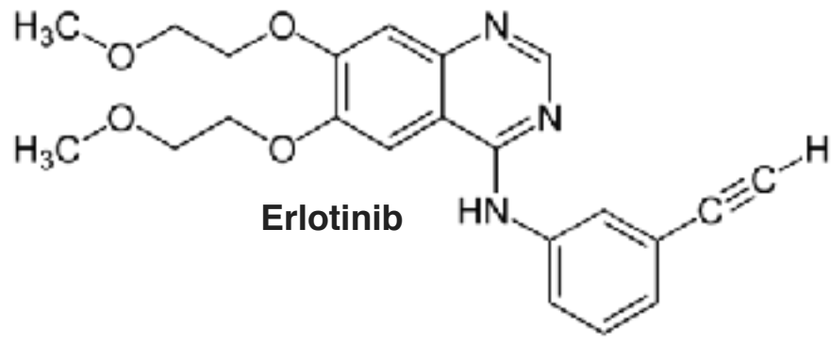
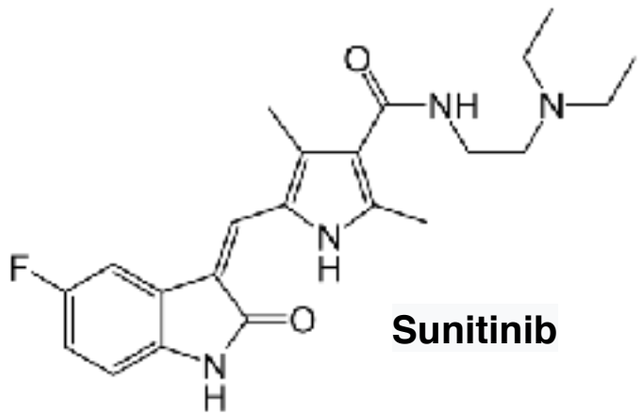


Afatinib



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

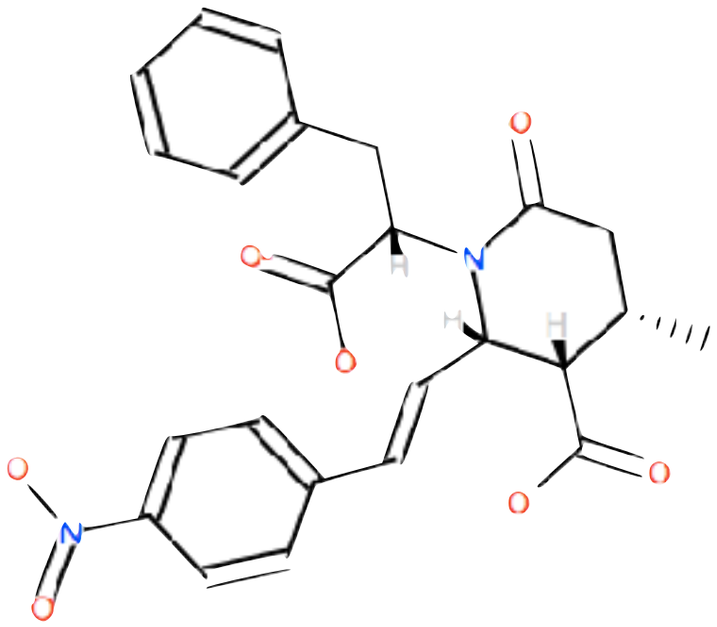
- similarity is “distance” between descriptors
- for bit vectors, Tanimoto distance used

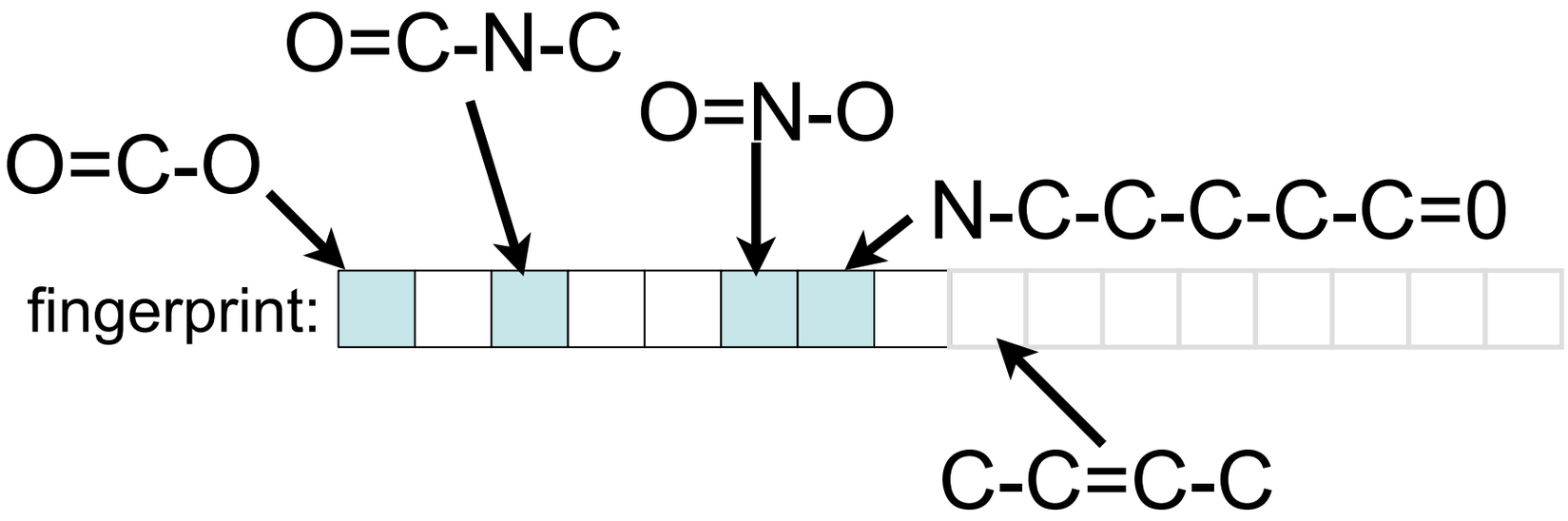
$$T(A,B) = \frac{|A \cap B|}{|A \cup B|}$$

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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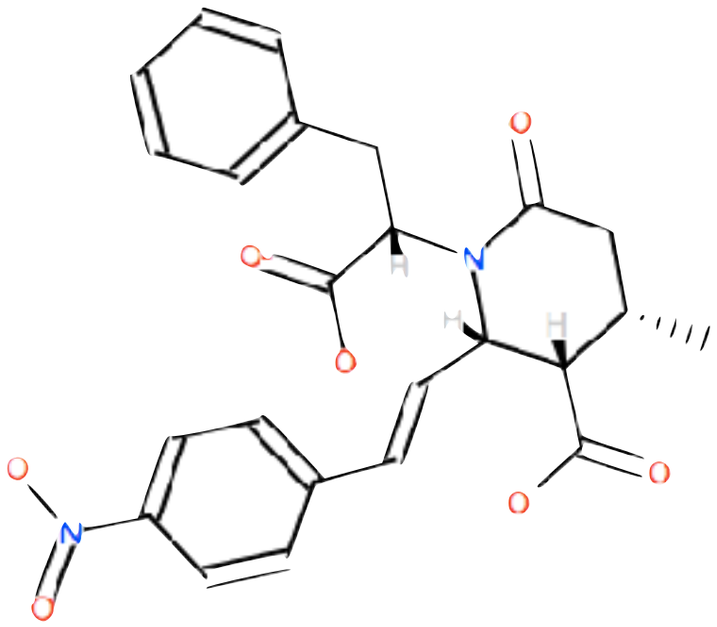
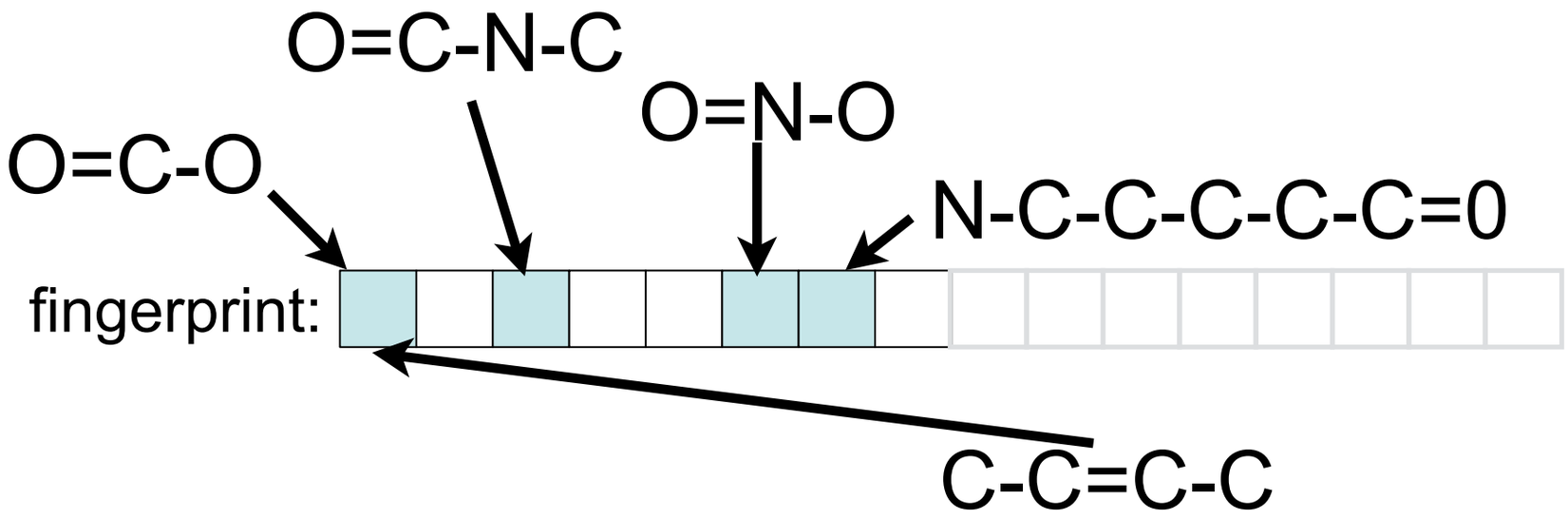
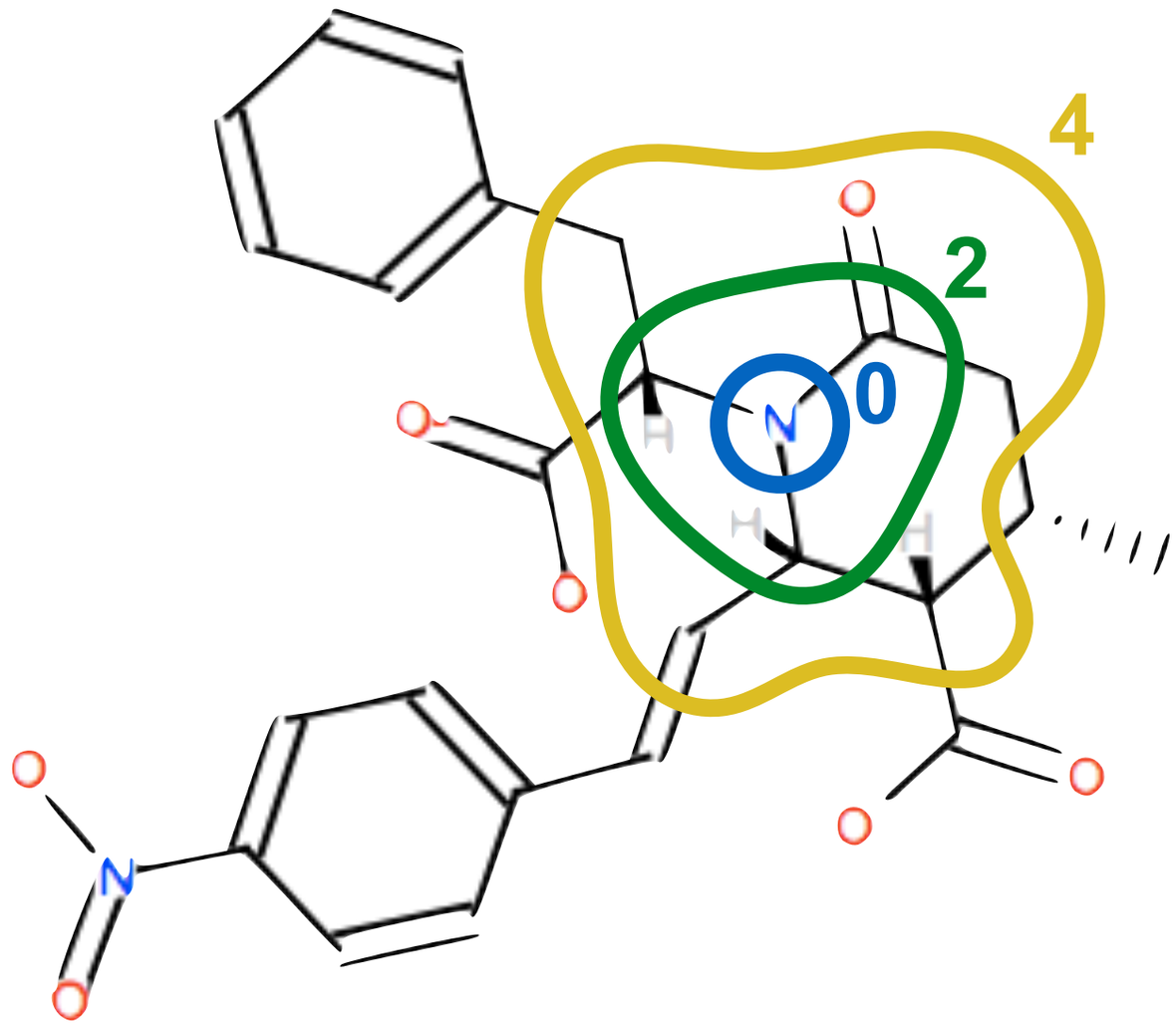




Topological Fingerprints

ECFP4

- all substructures with diameter 4 around every atom

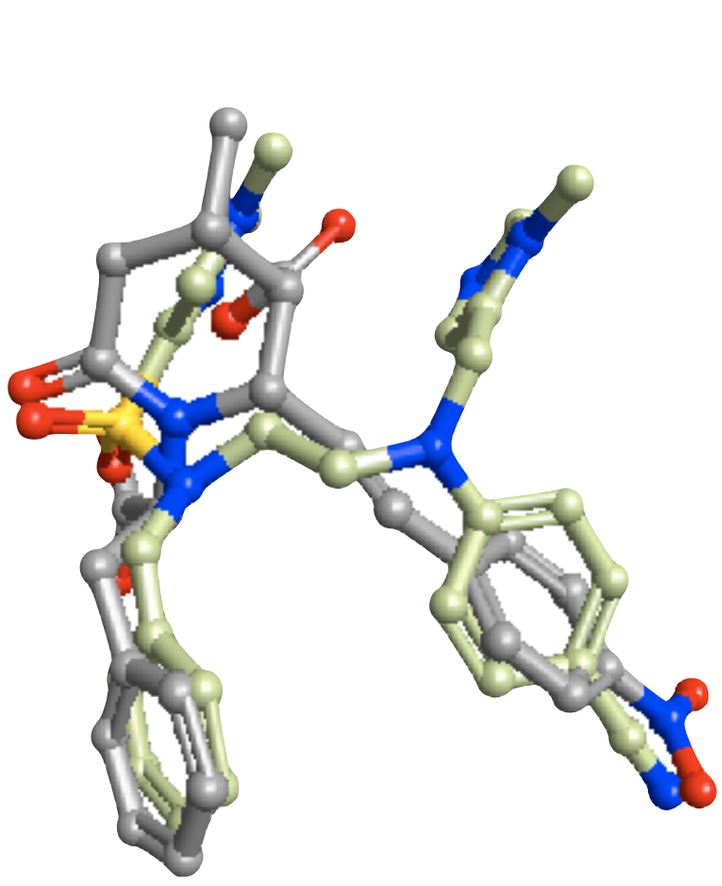


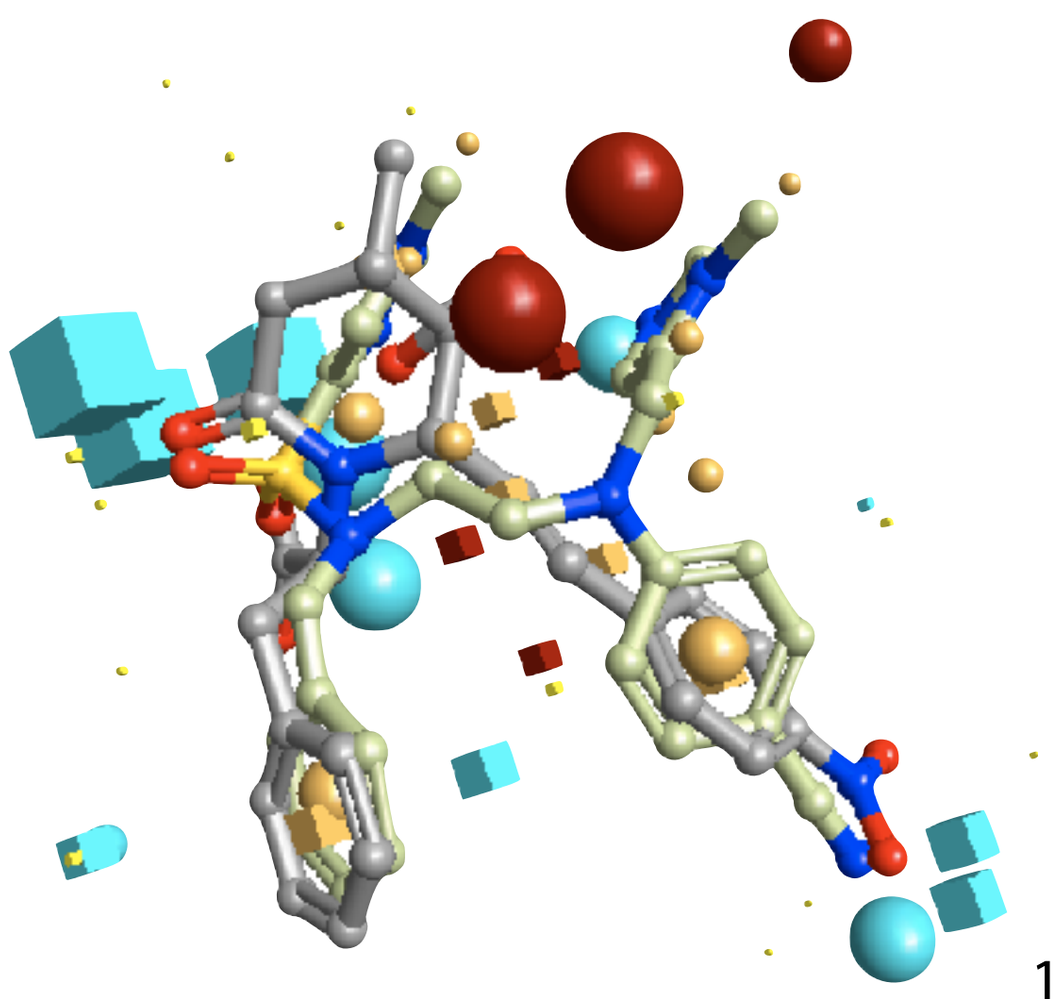
Ligand Based: Similarity

Superposition Methods

- compute "overlap" between molecules

- consider shape, electrostatics, **pharmacophores**





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

Ligand Based: QSAR

Quantitative Structure/Activity Relationships

Properties

Compounds

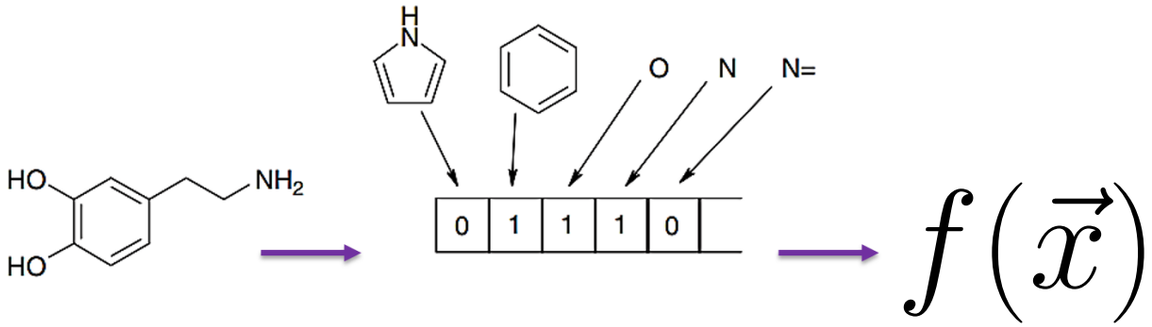
Cmpd Number	Cmpd Name	X	Log EC_{50}	π	Calculated Log EC_{50}	Residual
1	6a	H	1.07	0	0.79	0.28
2	6b	Cl	0.09	0.71	0.21	-0.12
3	6d	NO_2	0.66	-0.28	1.02	-0.36
4	6e	CN	1.42	-0.57	1.26	0.16
5	6f	C_6H_5	-0.62	1.96	-0.81	0.19
6	6g	$N(CH_3)_2$	0.64	0.18	0.65	-0.01
7	6h	I	-0.46	1.12	-0.12	-0.34

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

3D-QSAR: includes geometric/structural properties

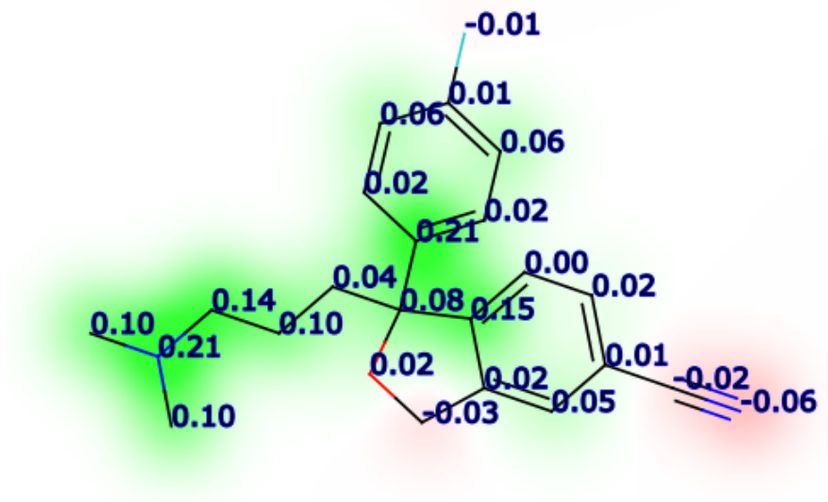
Ligand Based: QSAR

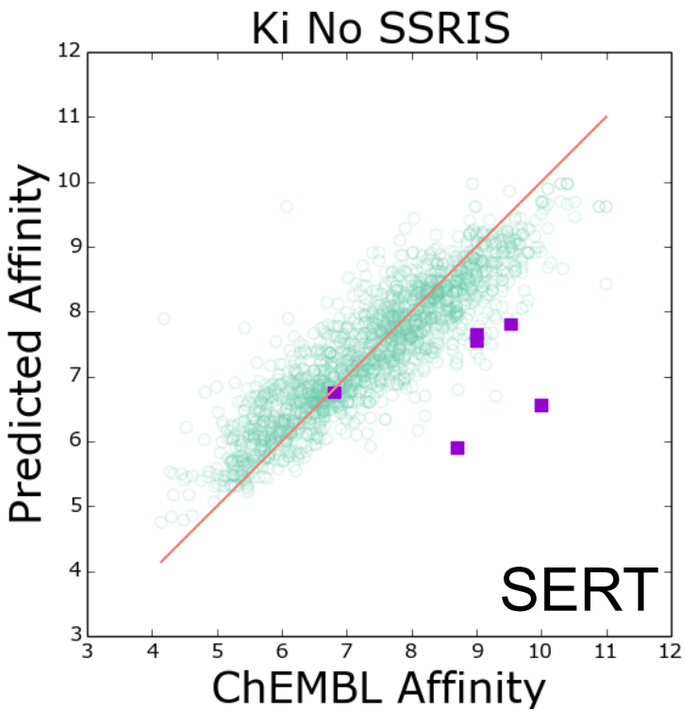
Quantitative Structure/Activity Relationships

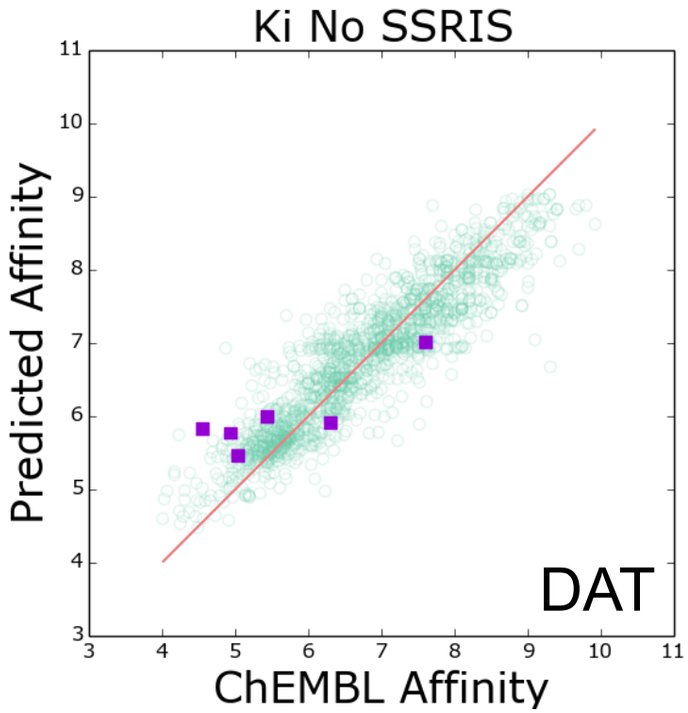


$$f(\vec{x})$$

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





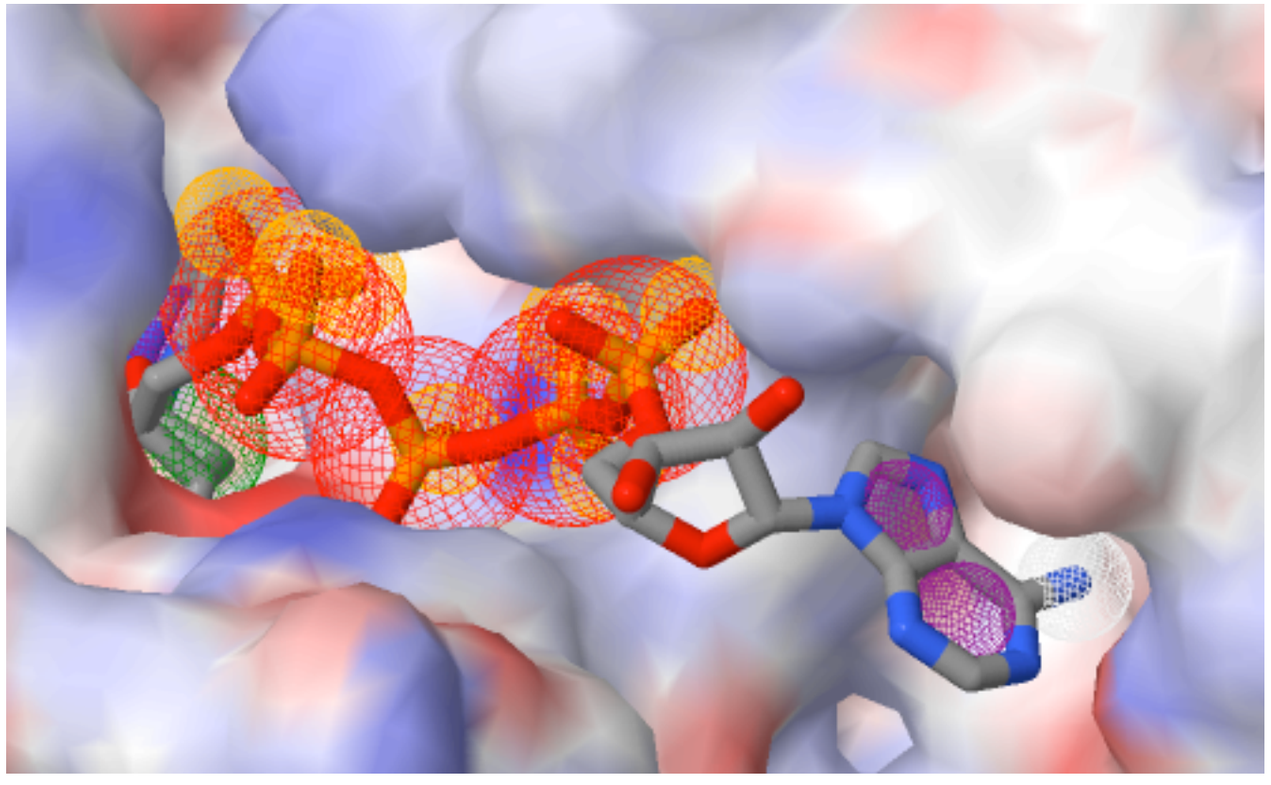


Ligand/Receptor Based: Pharmacophore

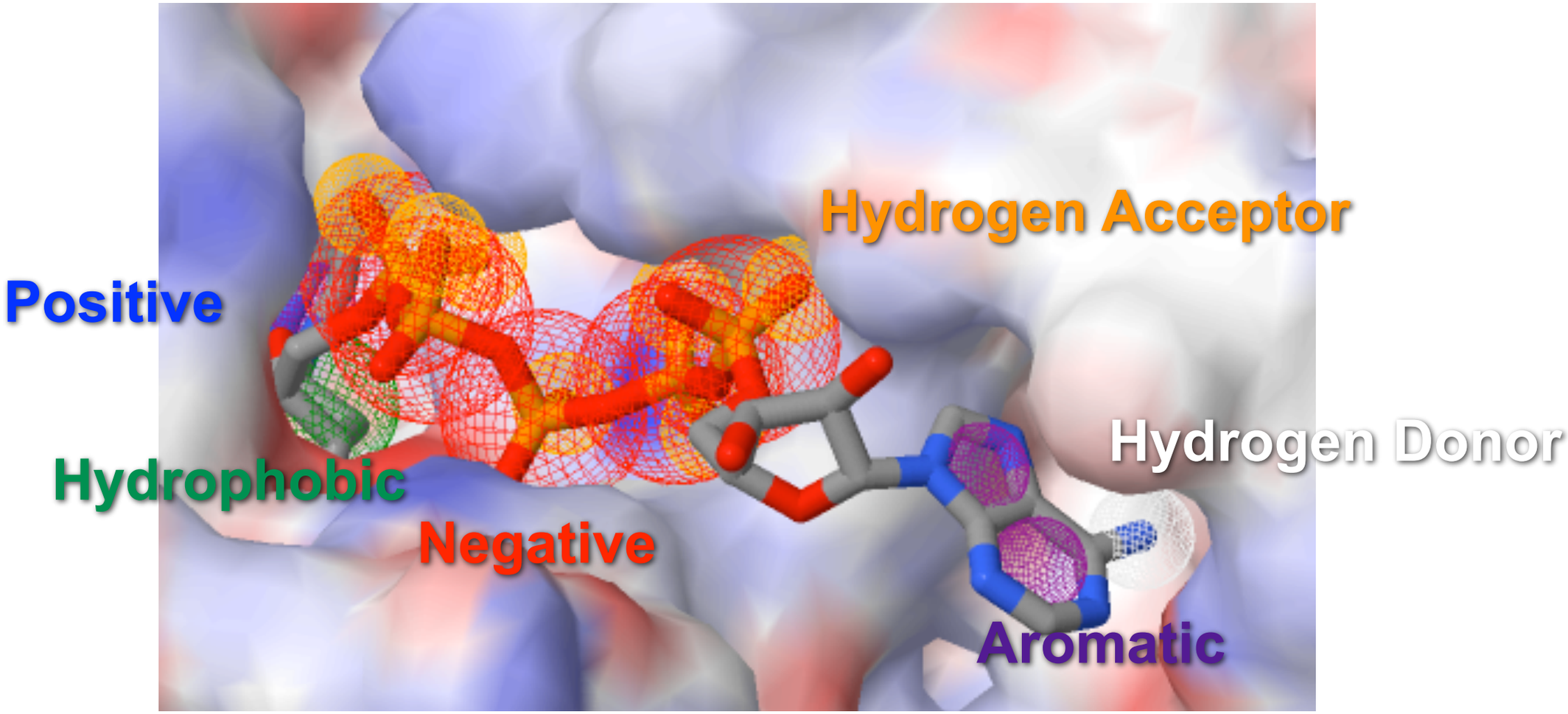
Pharmacophore:

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.

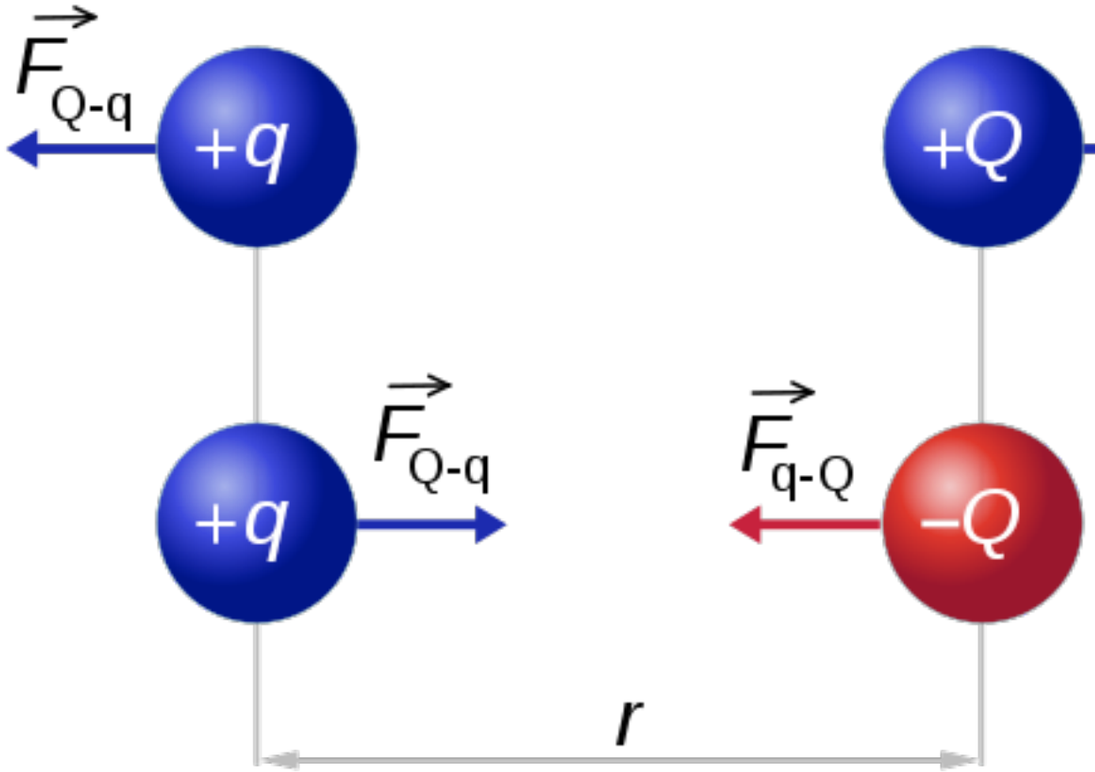
Common Features:
aromatic ring
hydrophobic area
positive ionizable
negative ionizable
hydrogen bond donor
hydrogen bond acceptor



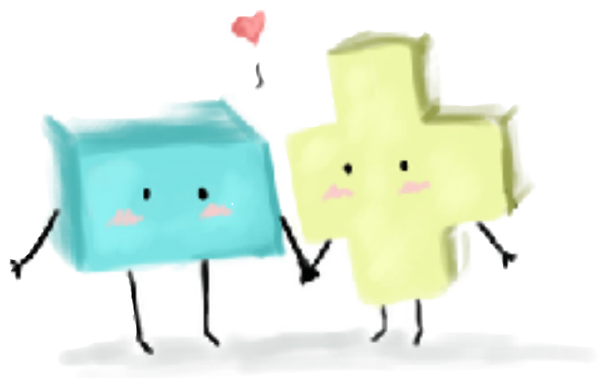
Pharmacophore Features



Charge-Charge



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



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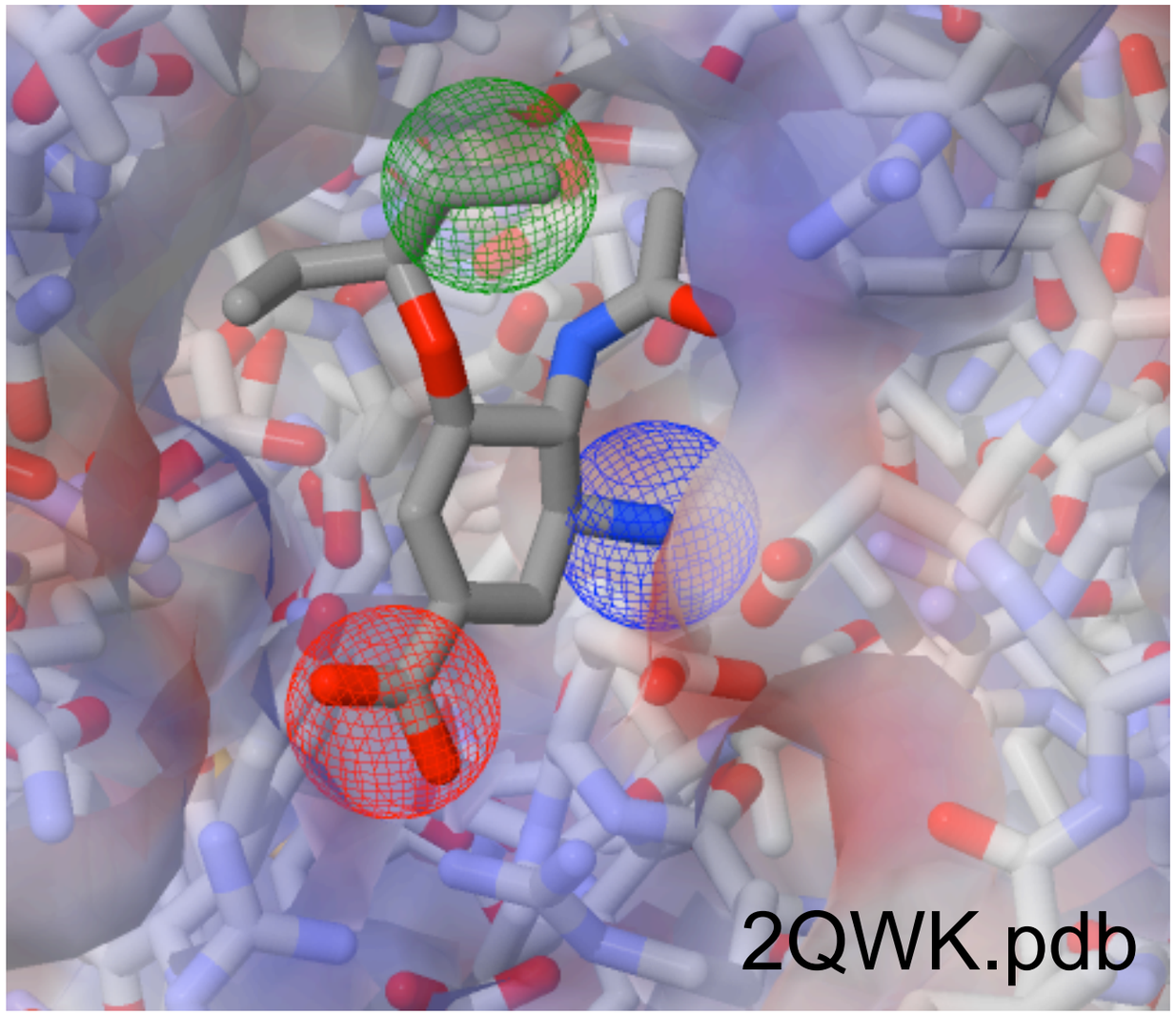
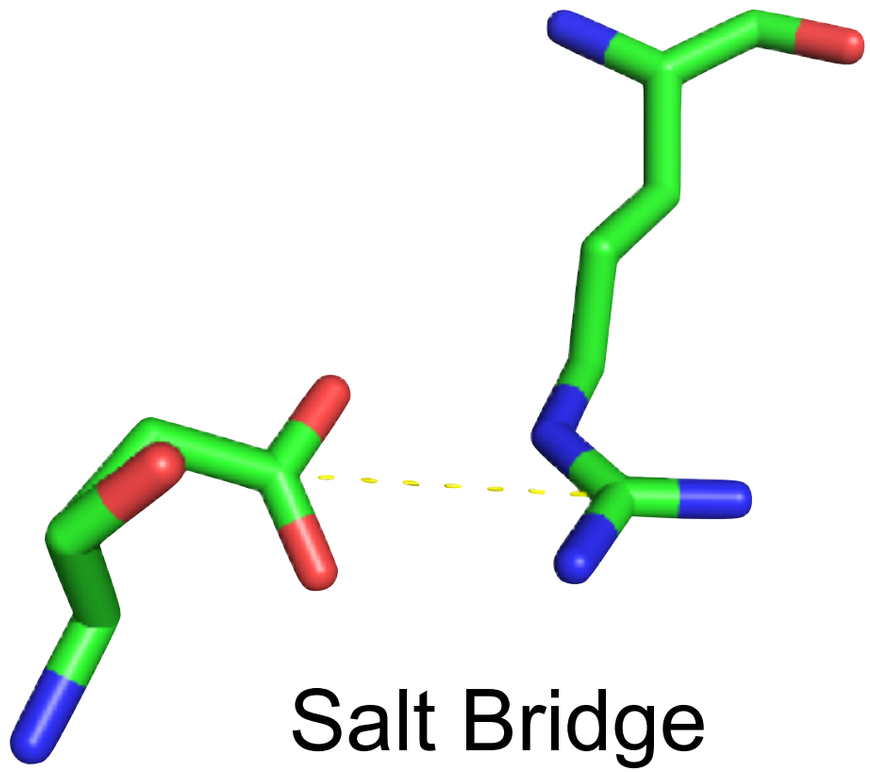
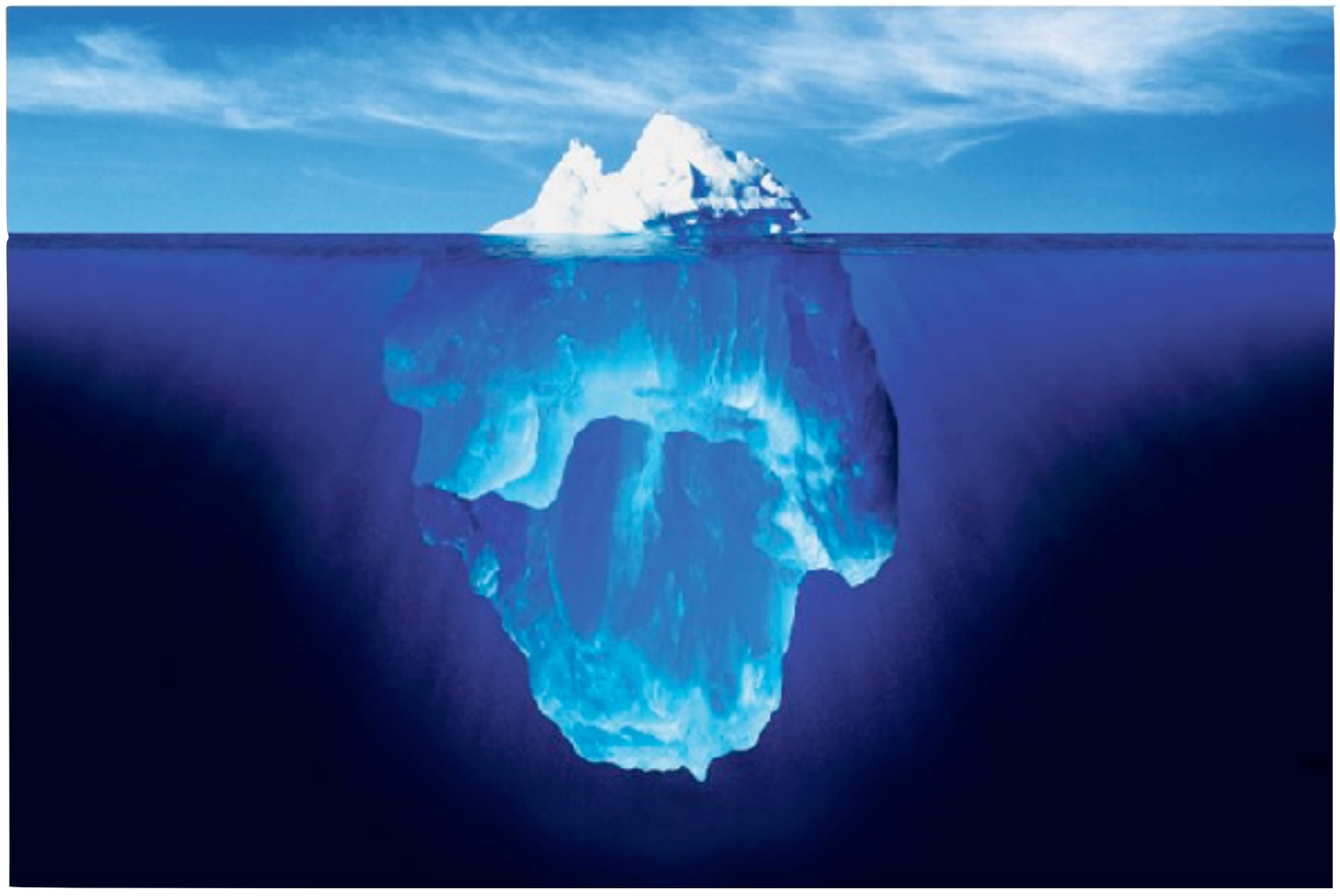


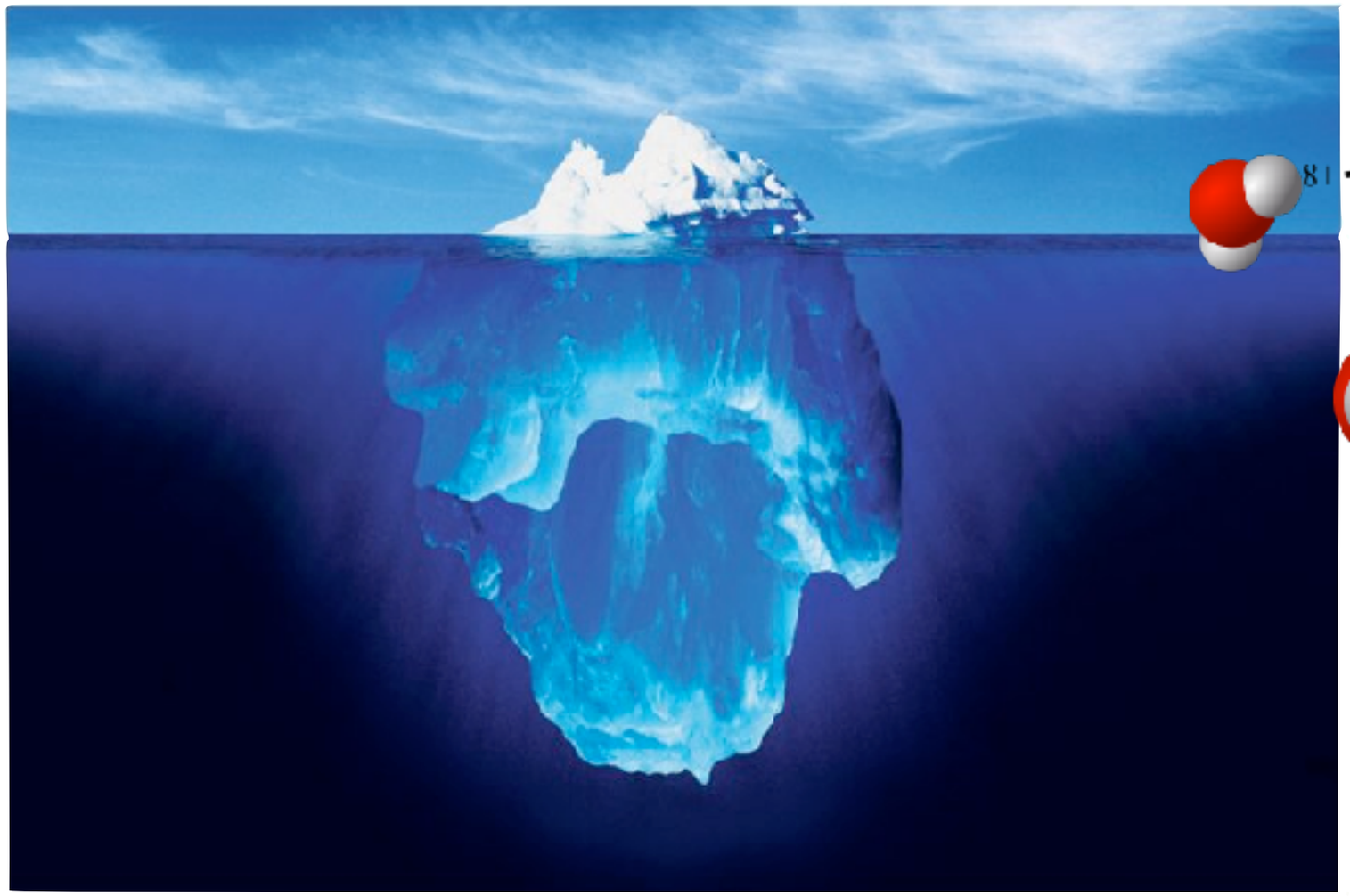


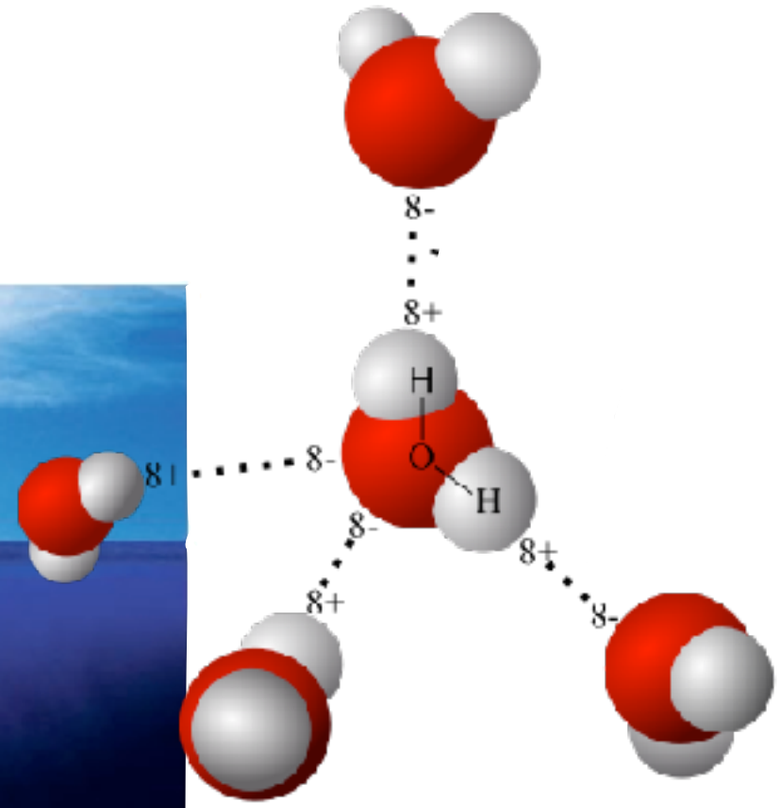
Inhibitor of the influenza virus neuraminidase (antiviral agent)

Hydrogen Bond

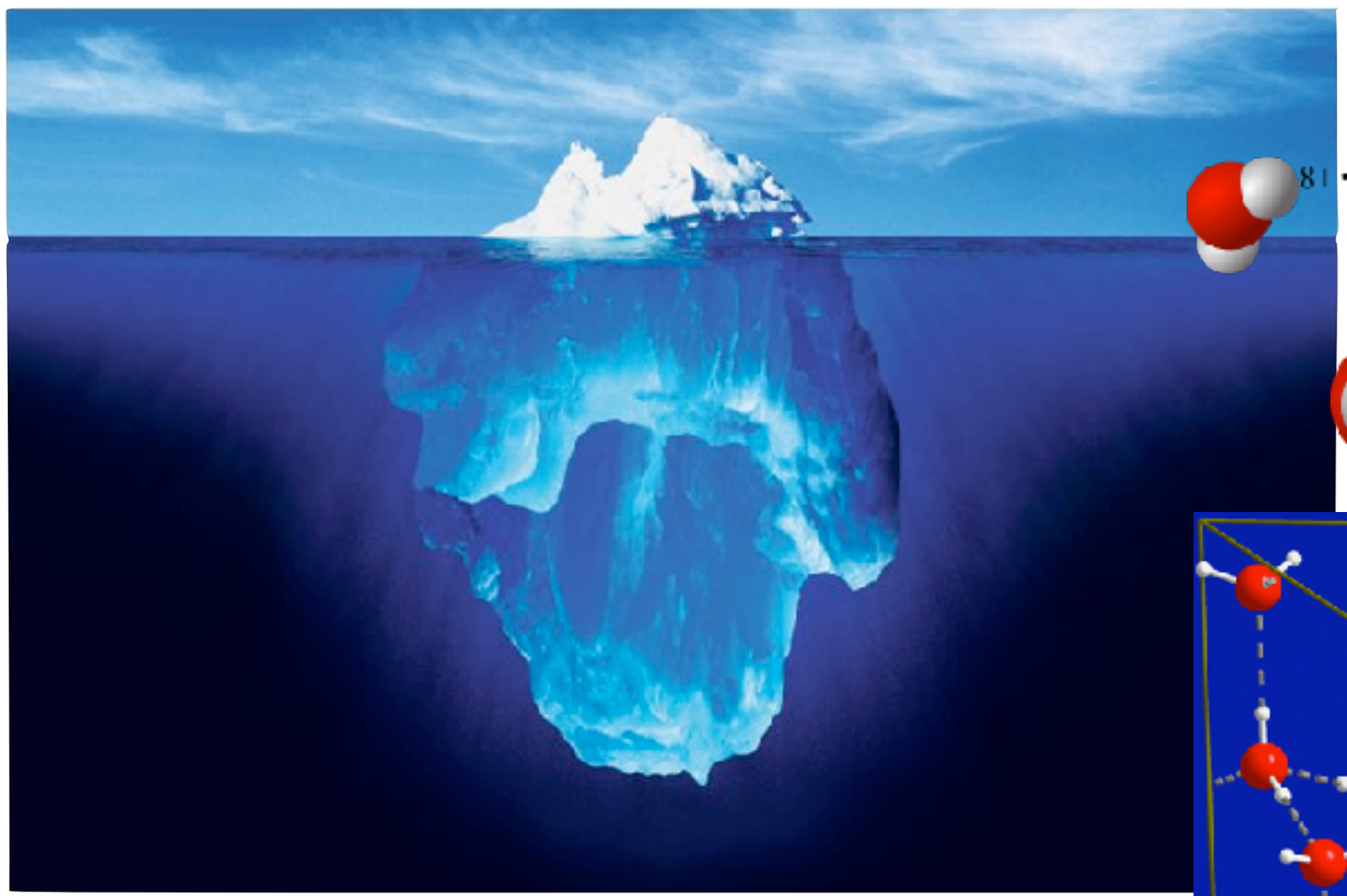


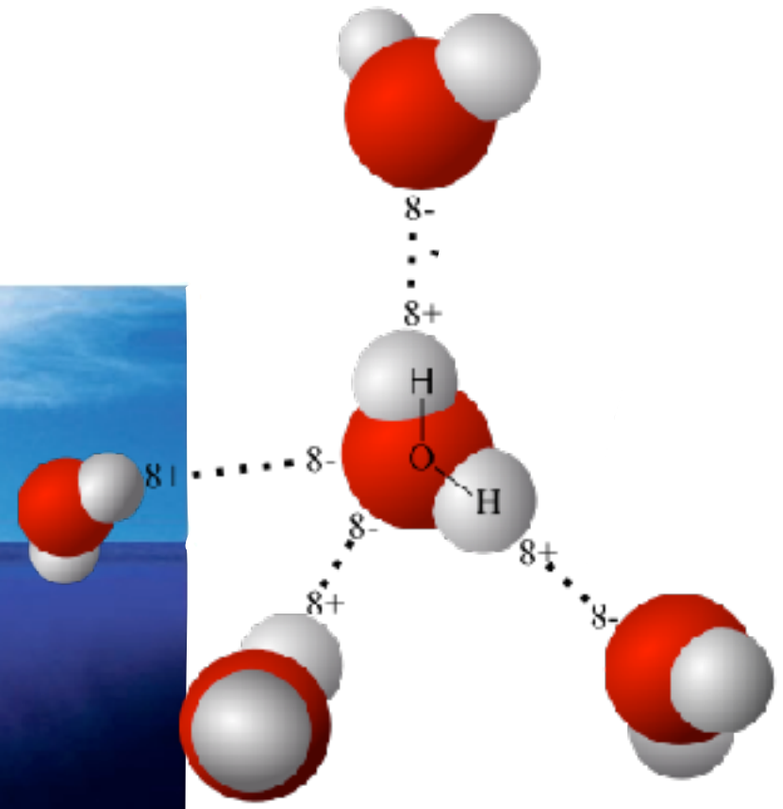
Hydrogen Bond

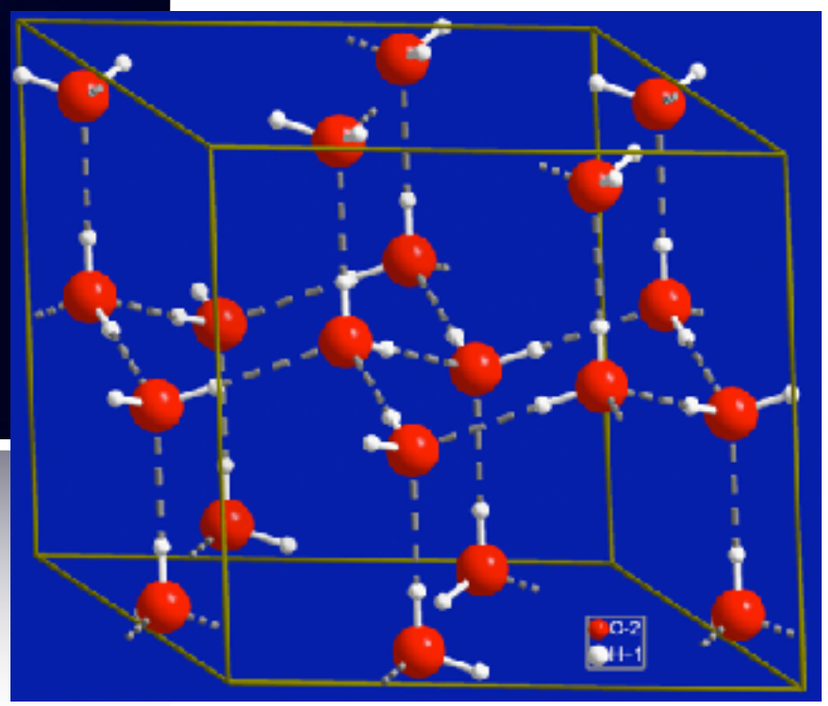




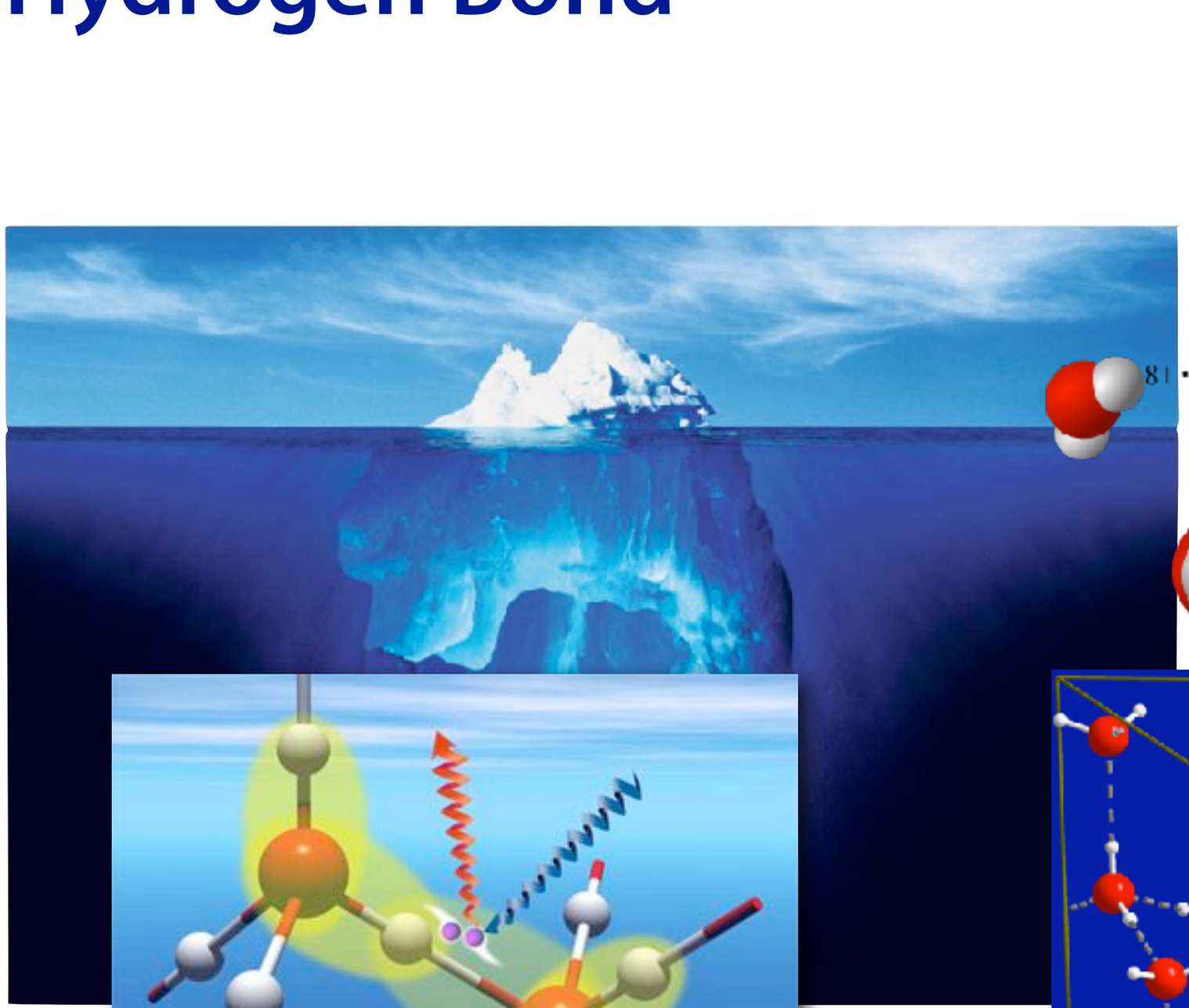
Hydrogen Bond

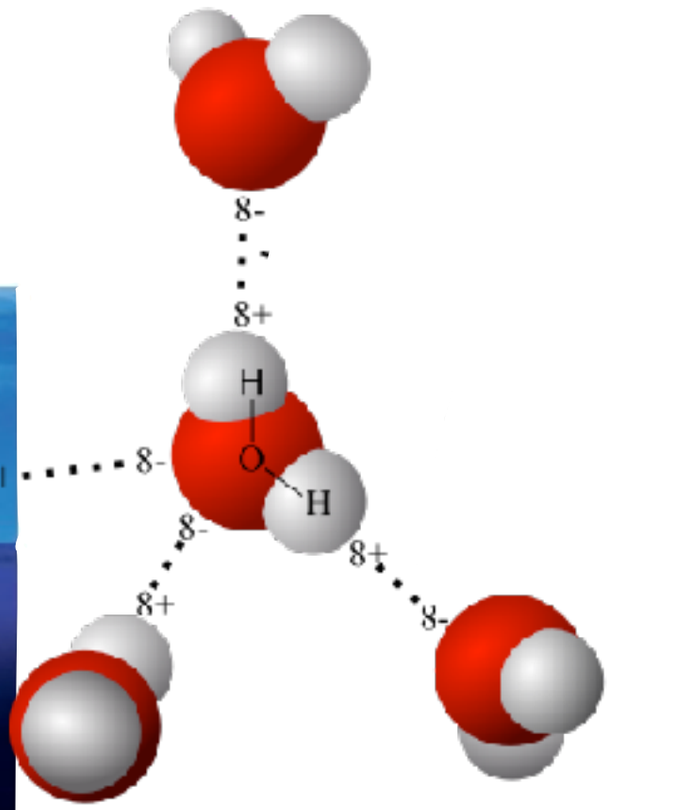


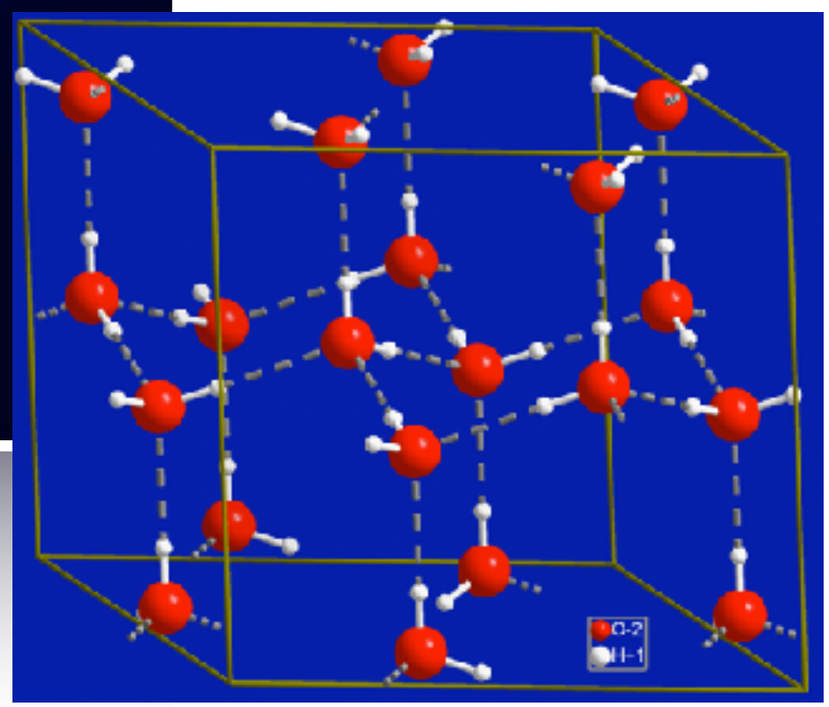




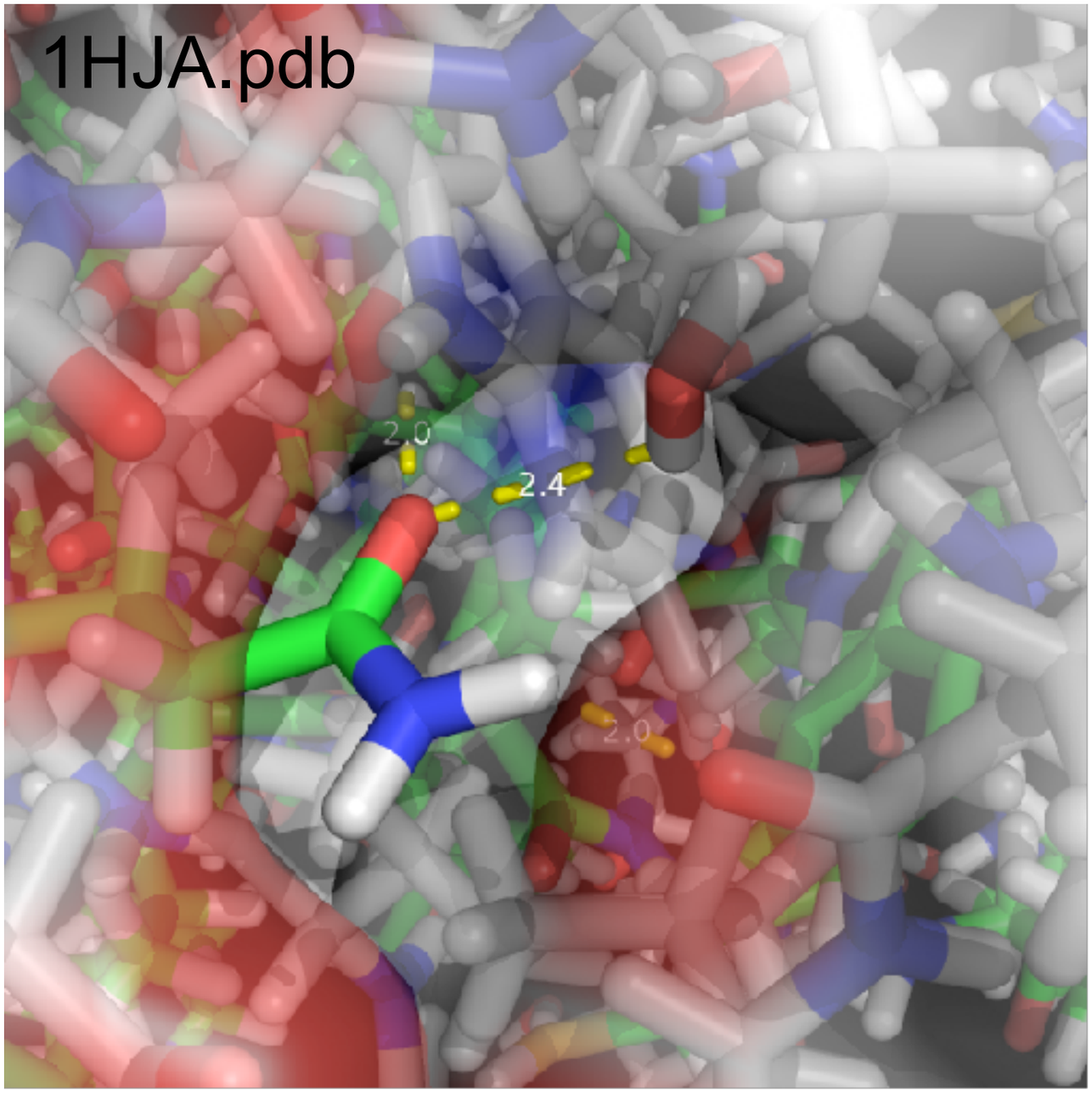
Hydrogen Bond



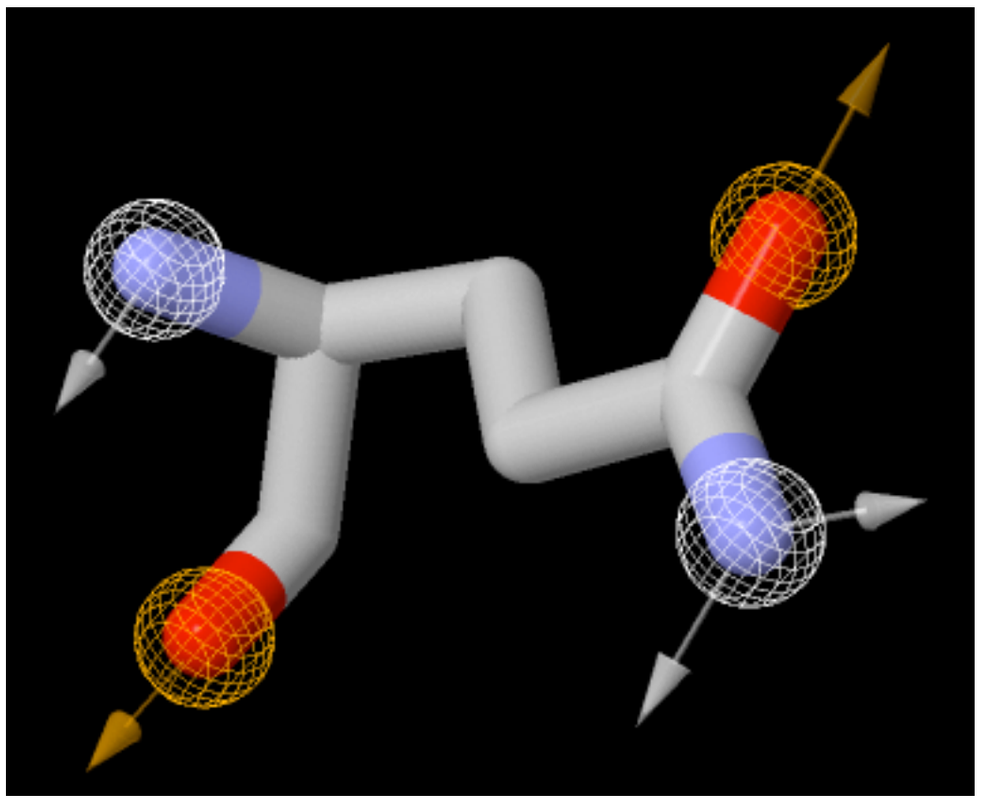




Hydrogen Bond



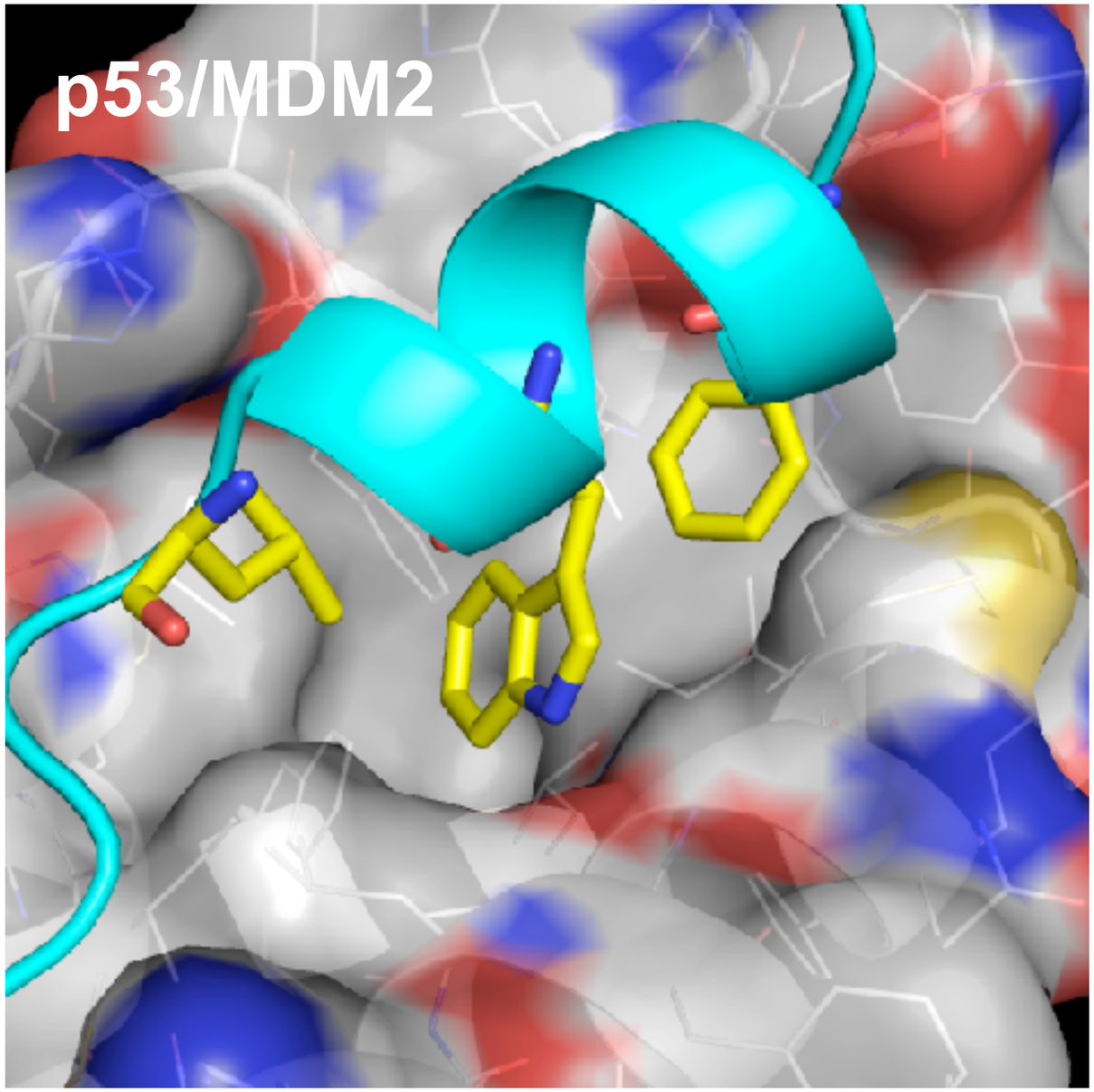
Distance:
D-A: 2.5Å – 3.5Å (4.0Å?)
H-A: 1.5Å – 2.5Å
Angle:
Depends on context



Turkey Ovomucoid Inhibitor

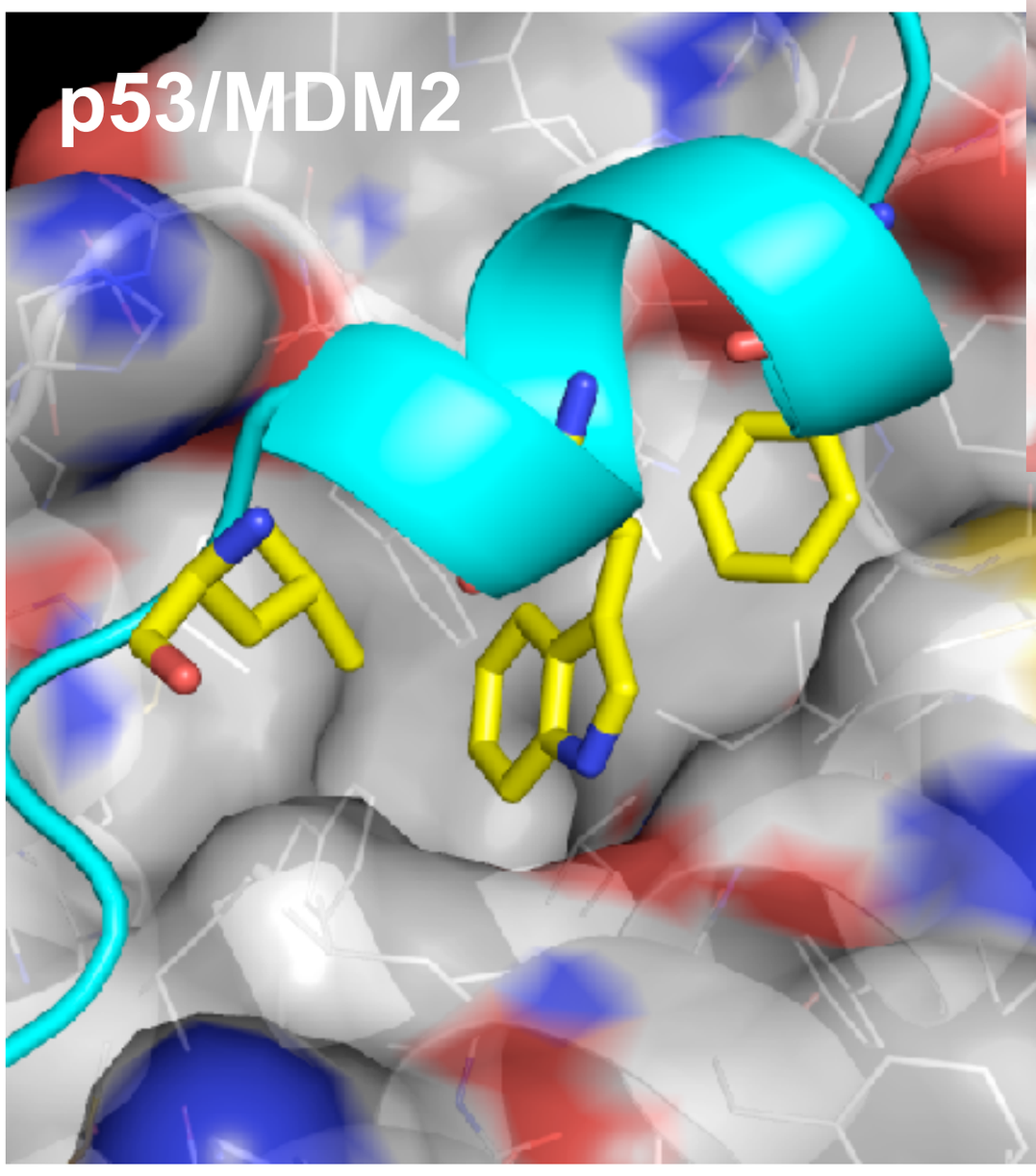
Hydrophobic

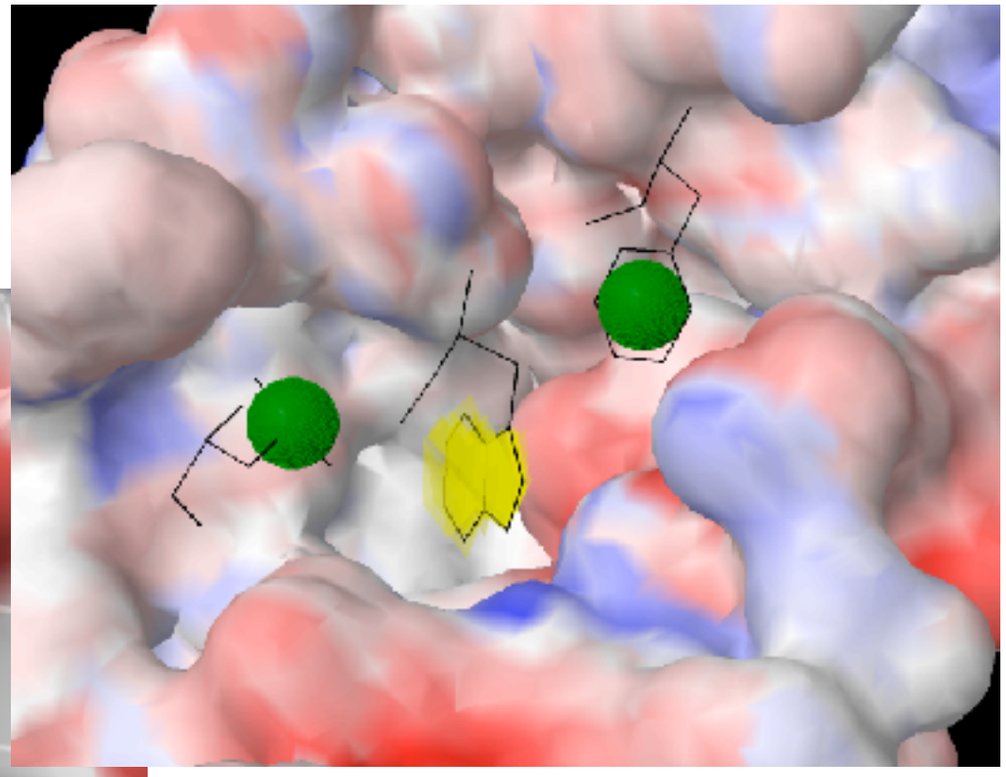
Hydrophobic



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

Hydrophobic





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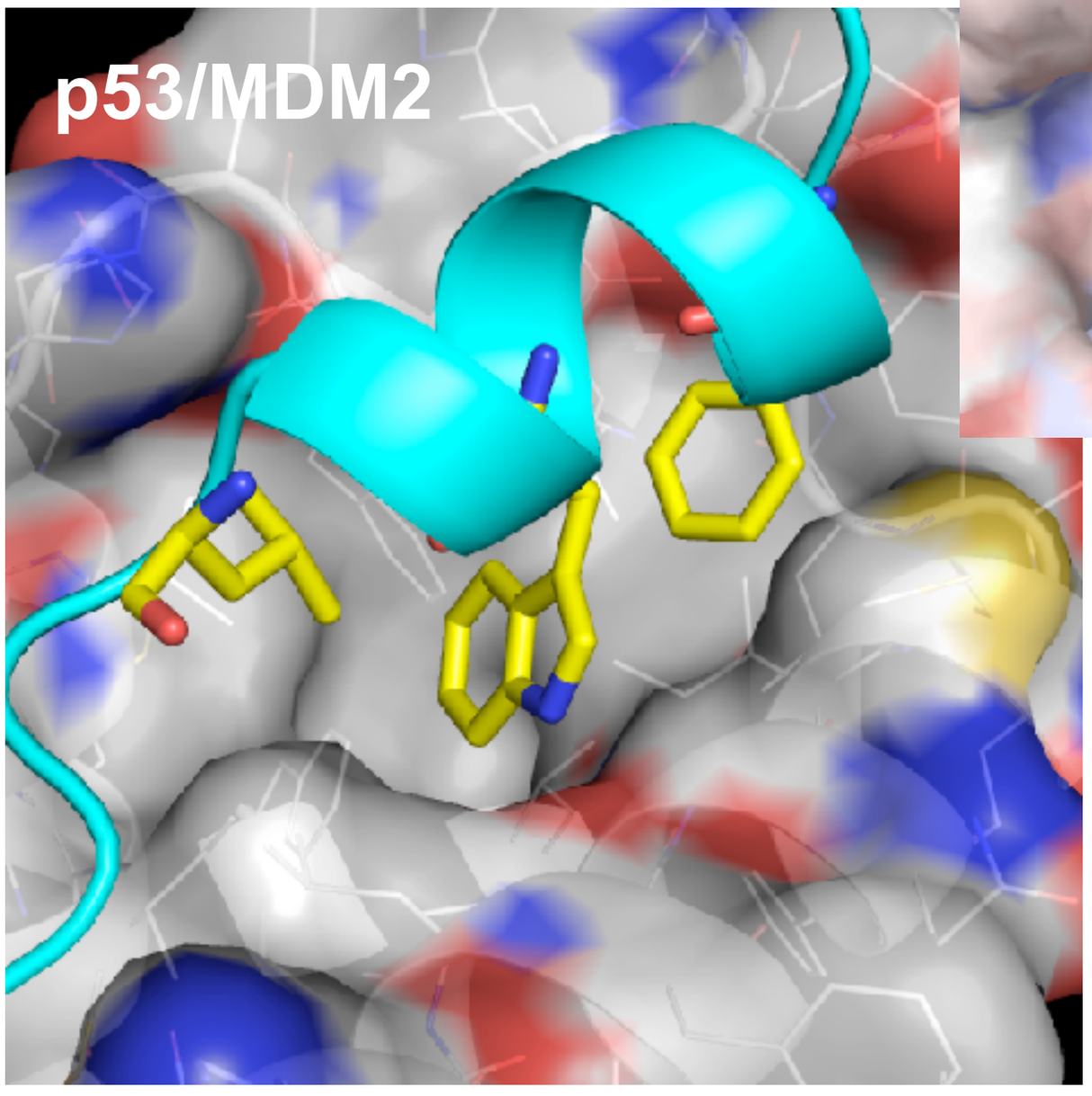

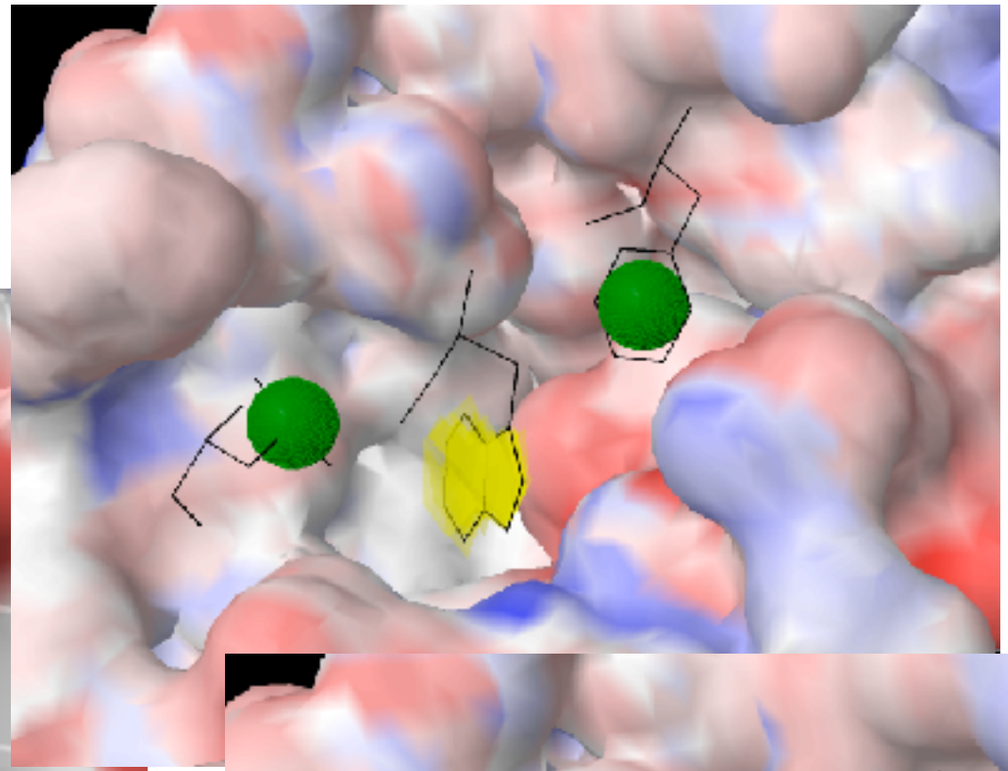

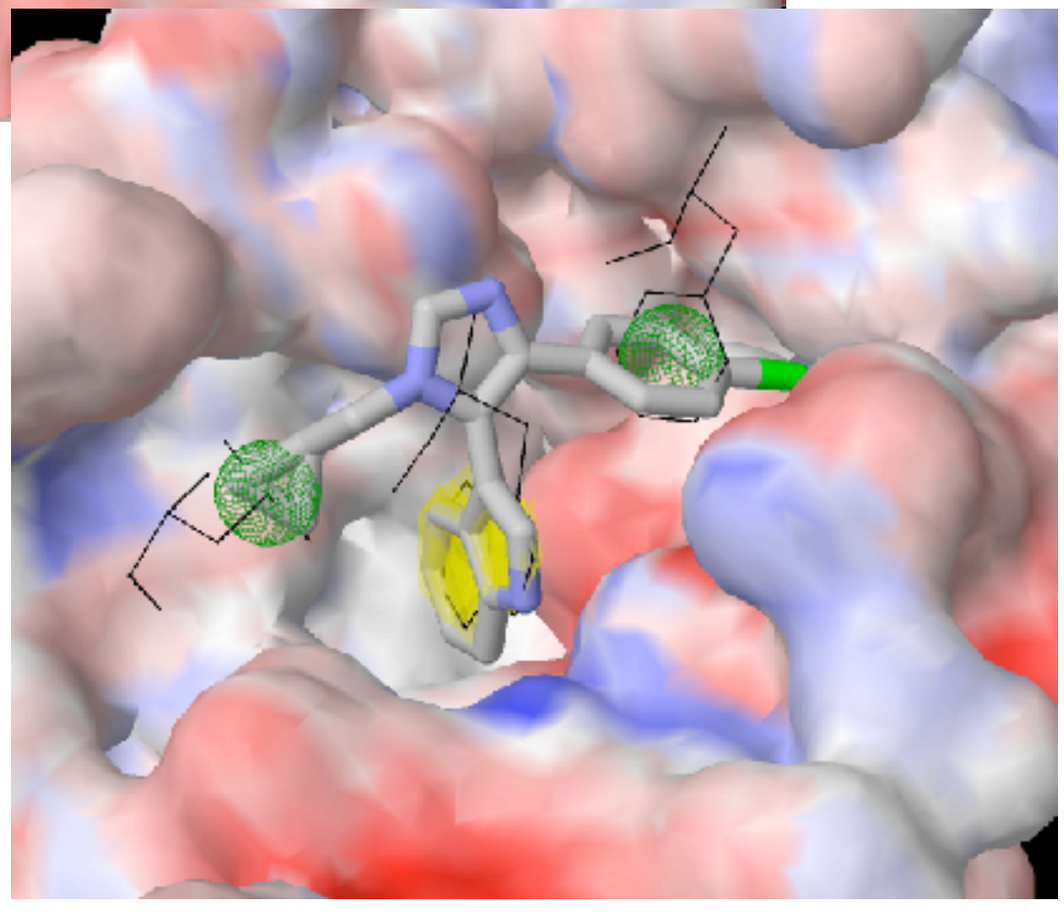

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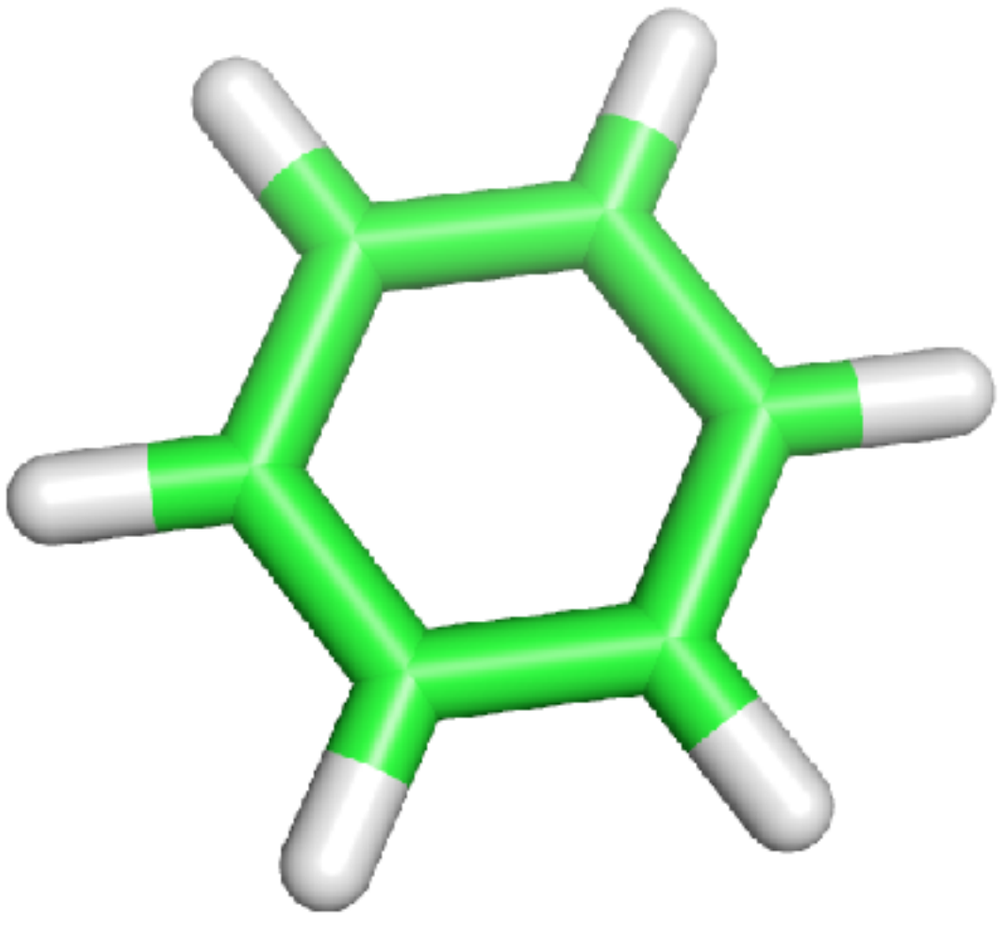
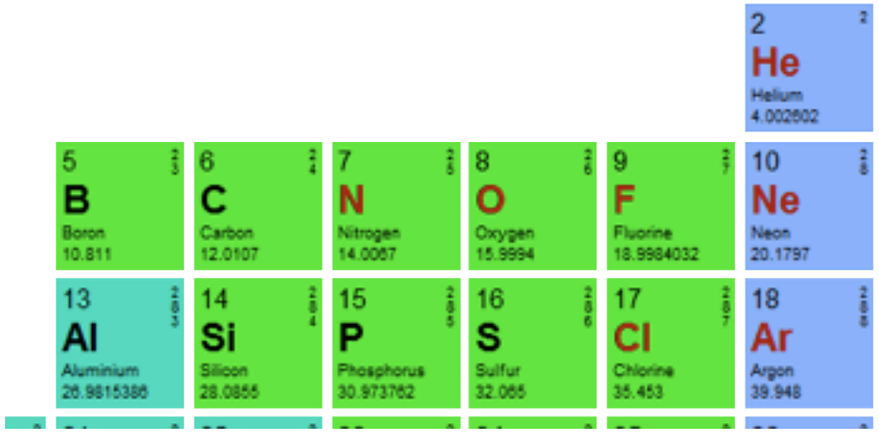
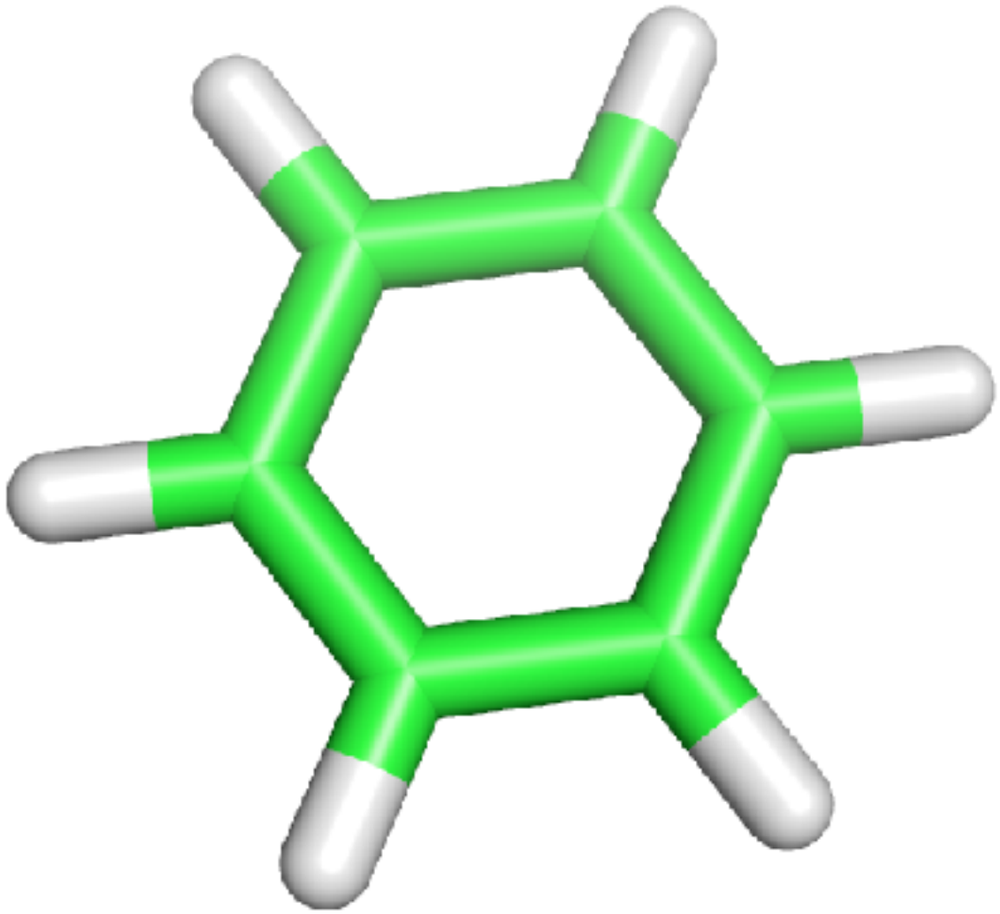
Aromatic

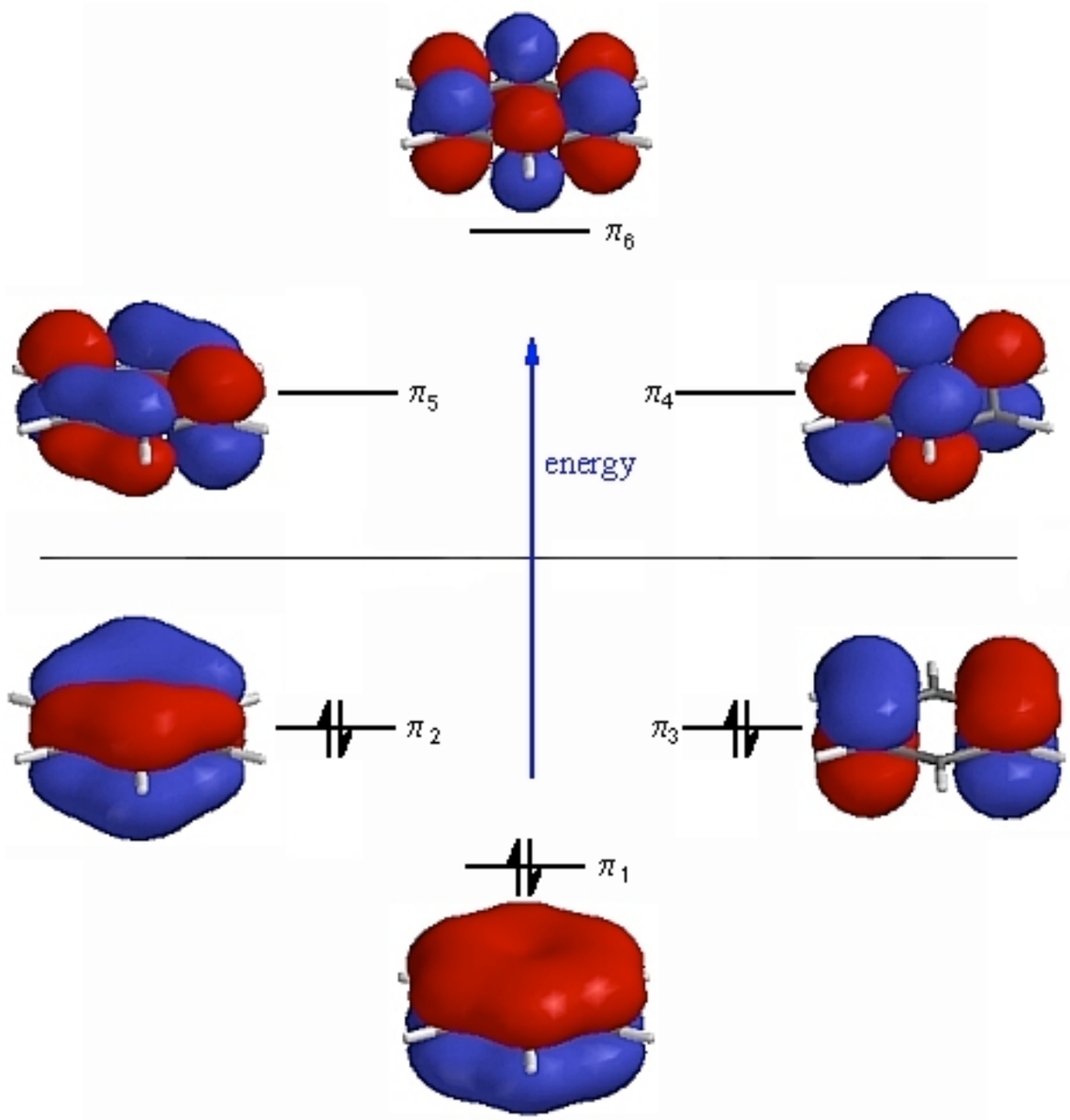




http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch11/benzene-mo.jpg

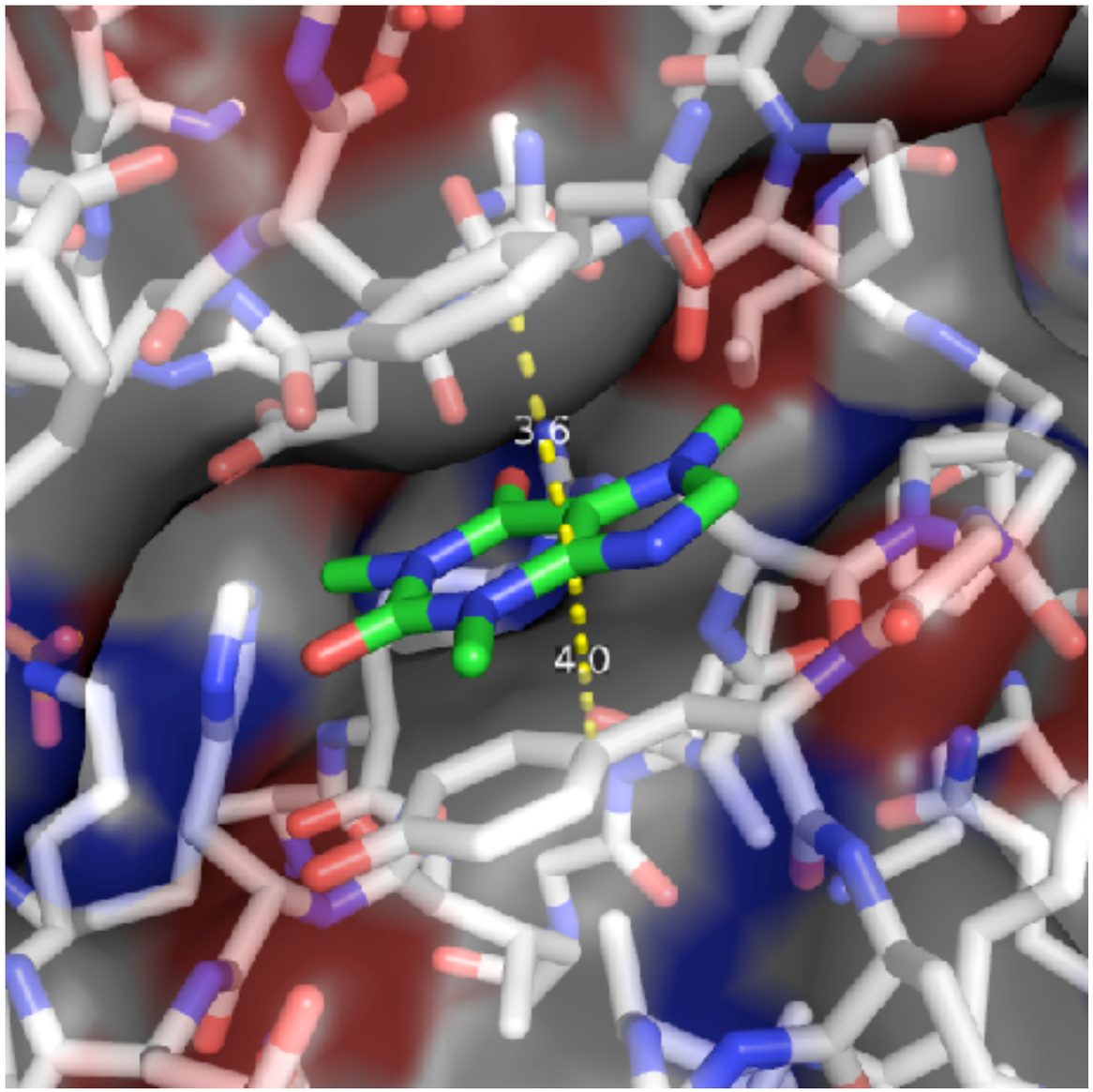
Aromatic



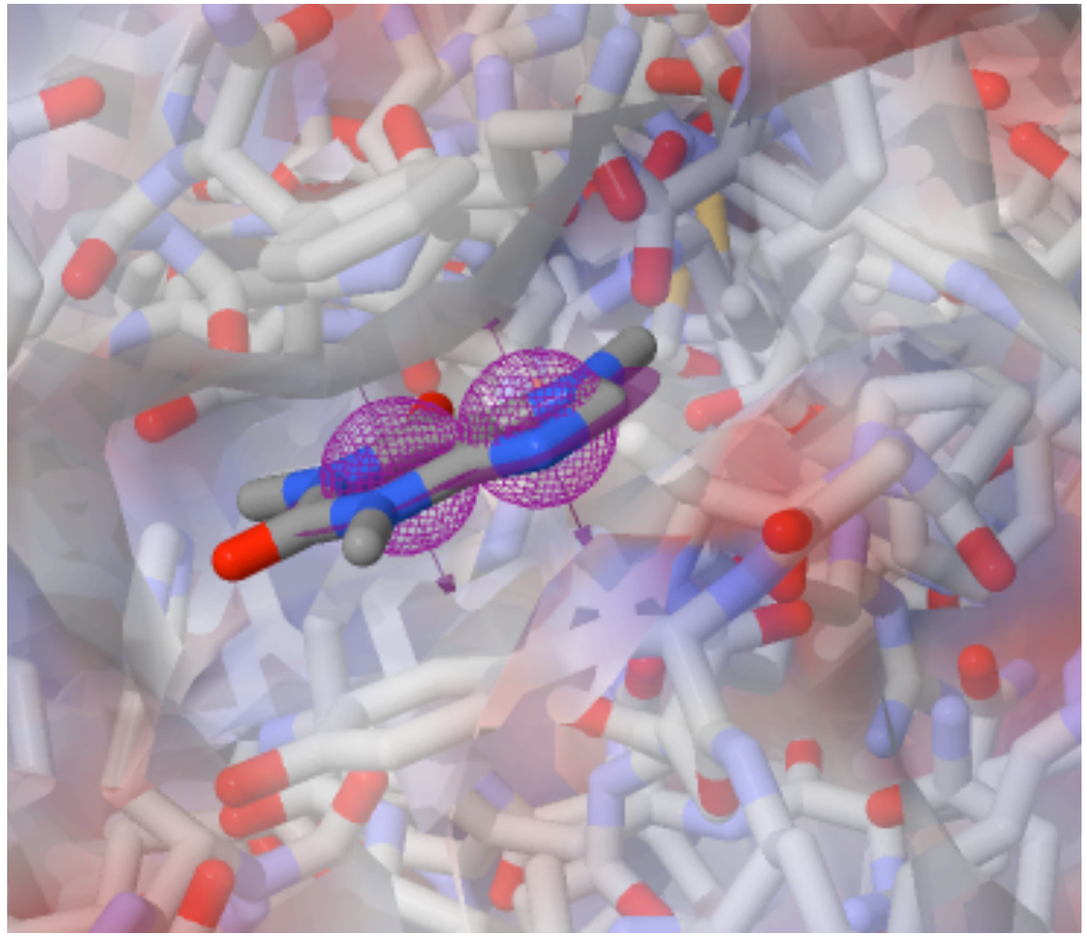


http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch11/benzene-mo.jpg

Aromatic



Rings offset
Interplanar distance: 3.3-3.8Å



Human liver glycogen phosphorylase a complexed with caffeine

pharmit.csb.pitt.edu/search.html

Search PubChem

Pharmacophore Search -> Shape Filter

Load Receptor... Load Features...

Pharmacophore

- ON **Aromatic** (48.19,39.60,-1.00) Radius 1.1
- ON **HydrogenAcceptor** (47.17,41.33,-5.87) Radius 0.5
- ON **HydrogenAcceptor** (49.17,40.46,-6.38) Radius 0.5
- ON **NegativeIon** (48.21,40.61,-5.92) Radius 0.75
- ON **Hydrophobic** (49.4,41.67,-2.93) Radius 1.0
- ON **Hydrophobic** (52.08,44.85,-2.15) Radius 1.0
- ON **Hydrophobic** (48.19,39.88,-1.38) Radius 1.0
- ON **Hydrophobic** (55.14,47.0,-1.04) Radius 1.0
- ON **Hydrophobic** (50.03,43.31,-5.25) Radius 1.0
- ON **Hydrophobic** (46.4,37.97,-1.95) Radius 1.0
- OFF **Aromatic** (49.4,41.67,-2.93) Radius 1.1
- OFF **Aromatic** (52.08,44.85,-2.15) Radius 1.1

Load Session... Save Session...

Pharmacophore Results

Name	RMSD	Mass	RBnds
PubChem-13960682	0.223	392	5
PubChem-23673360	0.223	391	4
PubChem-13960682	0.223	392	5
PubChem-23673360	0.223	391	4
PubChem-13960684	0.243	388	6
PubChem-13960684	0.243	388	6
PubChem-13960684	0.243	388	6
PubChem-13960684	0.250	388	6
PubChem-59810304	0.311	481	8
PubChem-10000399	0.325	389	6
PubChem-10000399	0.327	389	6
PubChem-59081061	0.349	875	15
PubChem-10250942	0.379	387	3
PubChem-23686481	0.379	386	2
PubChem-13960681	0.442	385	7
PubChem-13960681	0.442	385	7
PubChem-13960681	0.444	385	7
PubChem-88181354	0.449	698	10
PubChem-842716	0.462	319	8

Showing 1 to 19 of 38 hits

Previous 1 2 Next

Minimize Save...

Deploy a menu

http://pharmit.csb.pitt.edu

Kinds of Virtual Screening

ADMET

Ligand Based

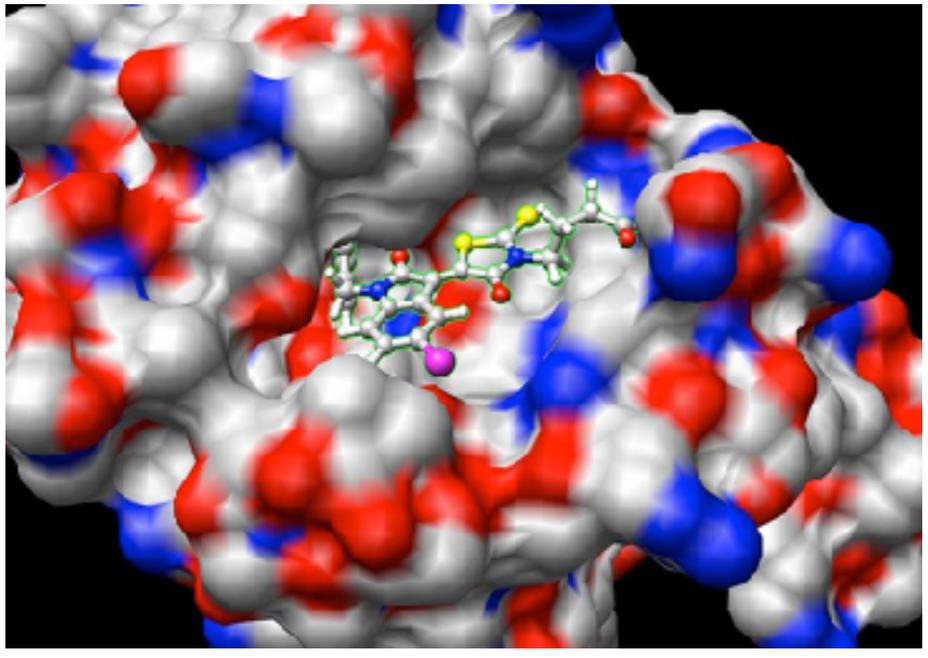
- similarity to known binder

- QSAR

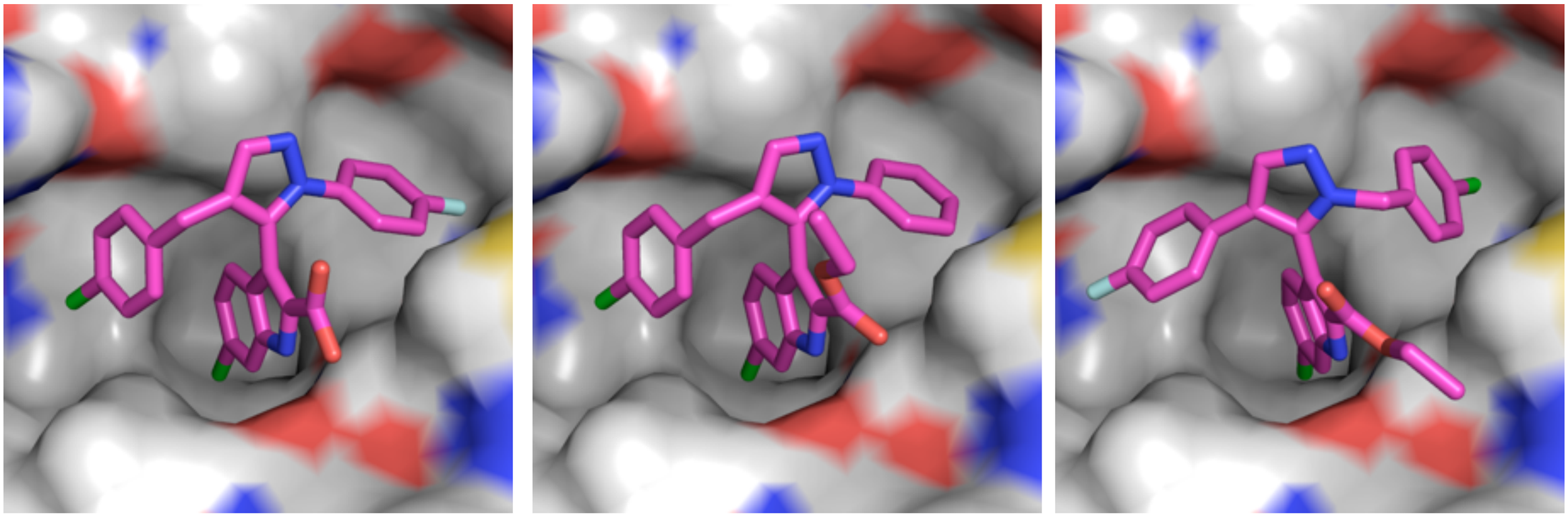
- pharmacophore

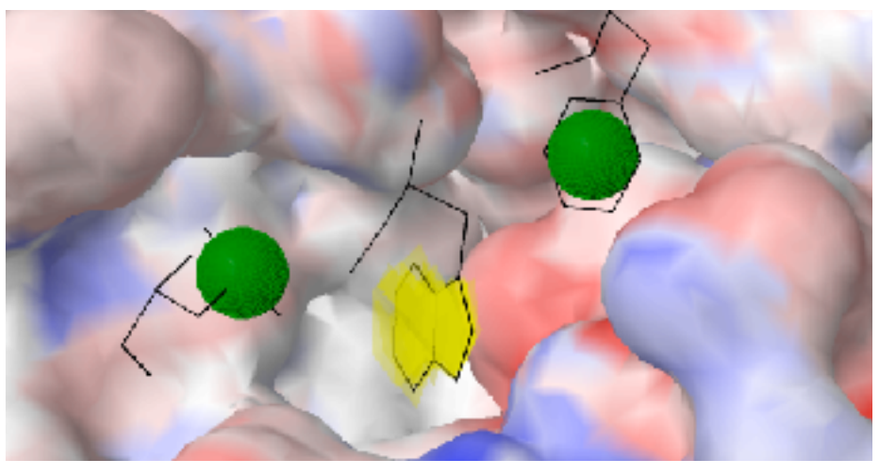
Receptor Based

- dock and score

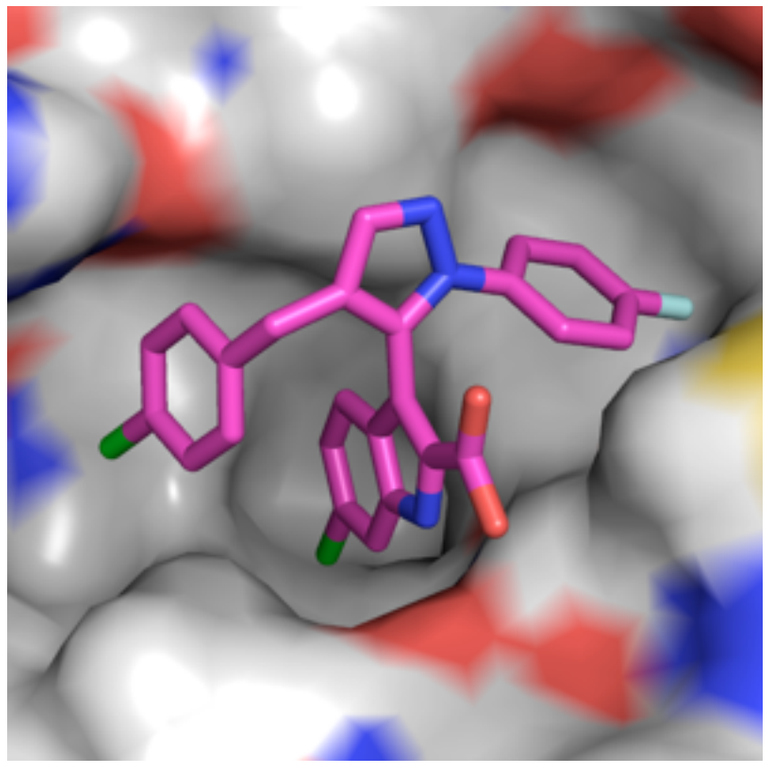


Pharmacophores Aren't Enough

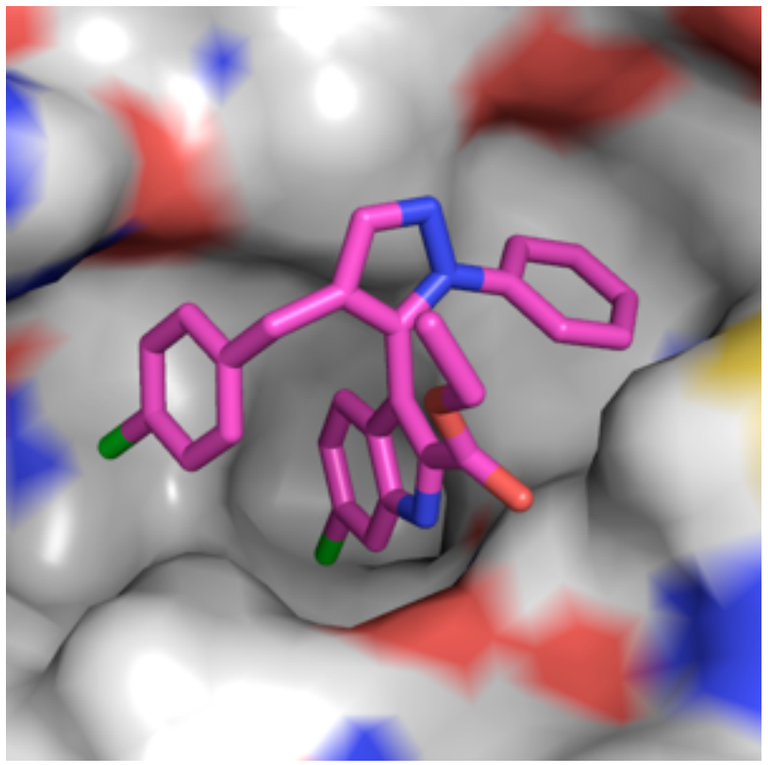




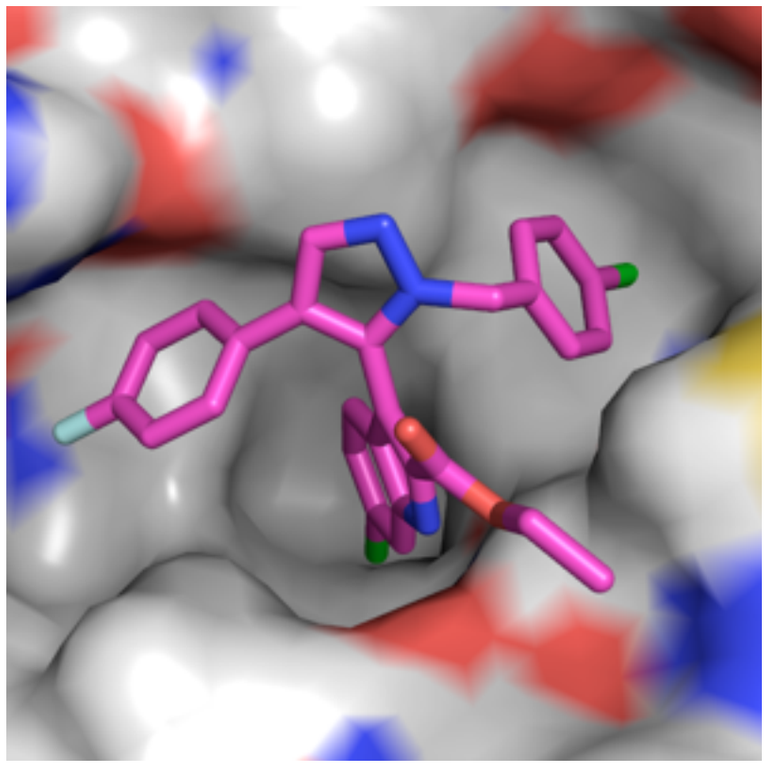
Pharmacophores Aren't Enough



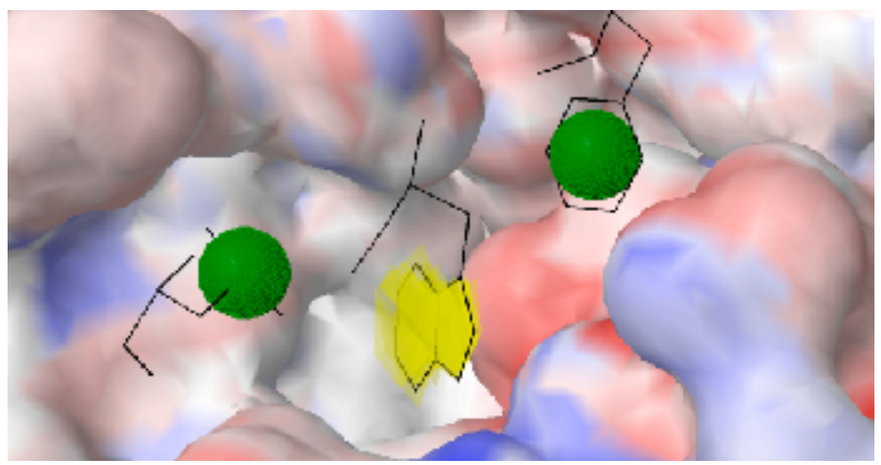
.2μM



50μM



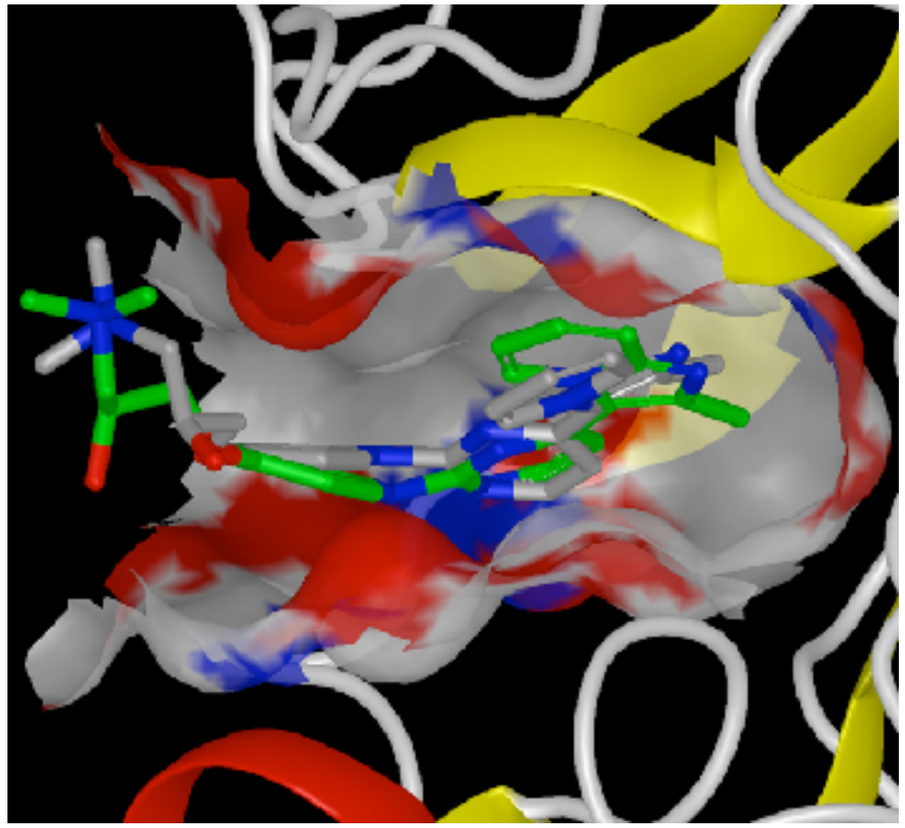
n.i.



Docking

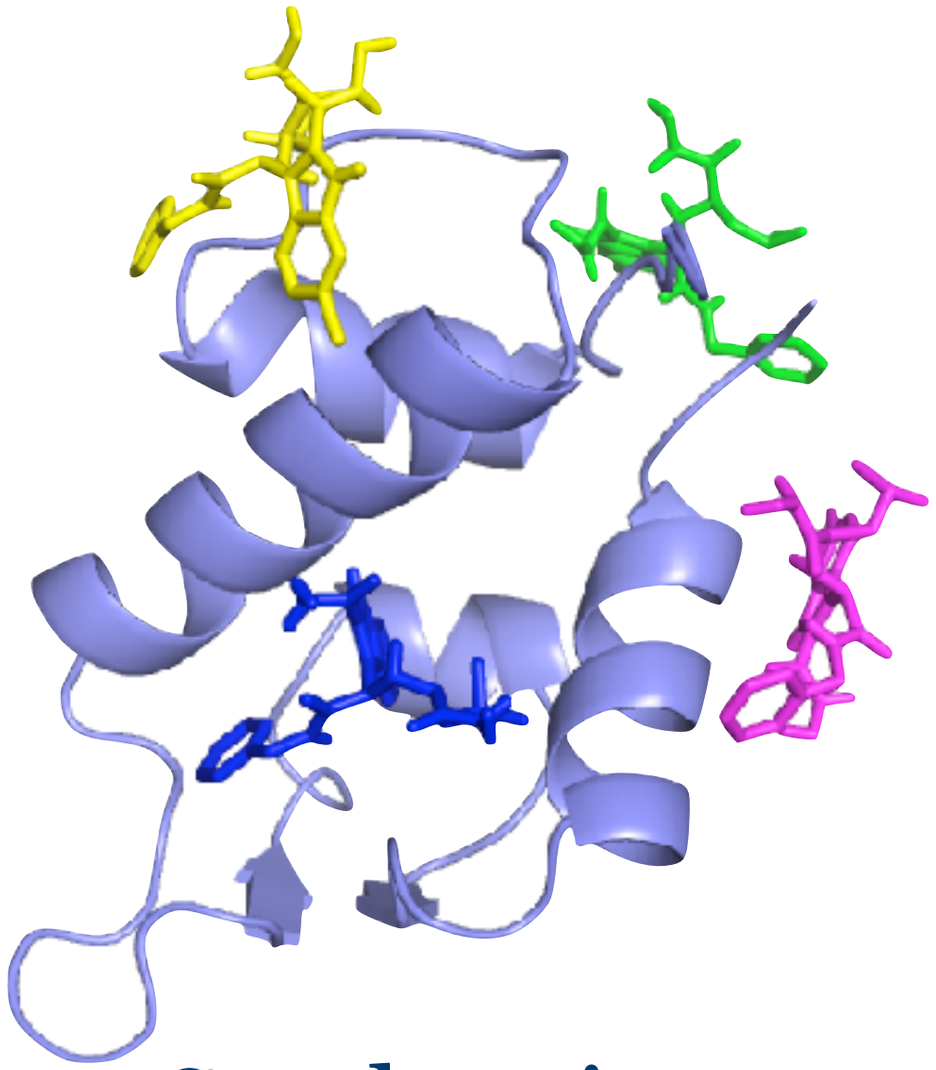
Determine the **conformation** and **pose** of a ligand at a docking site

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



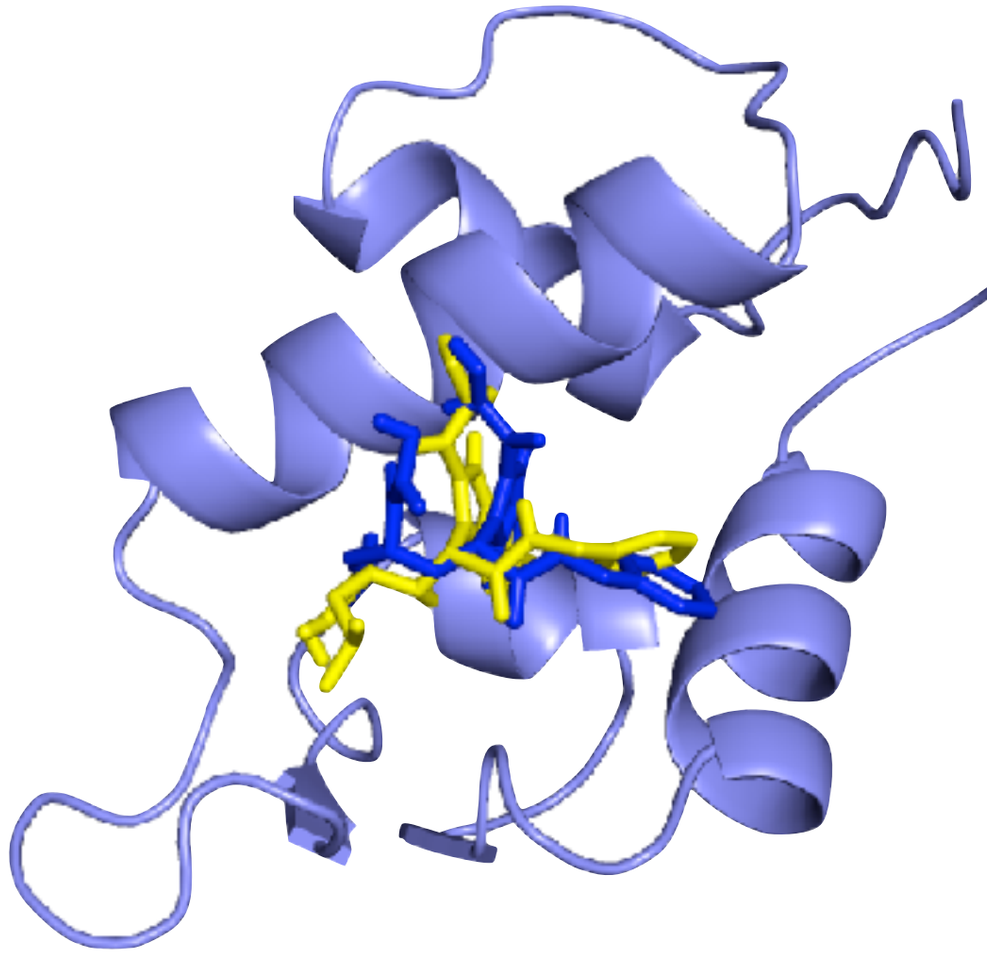
Two Phase Docking

1. Global Pose Estimation



Stochastic

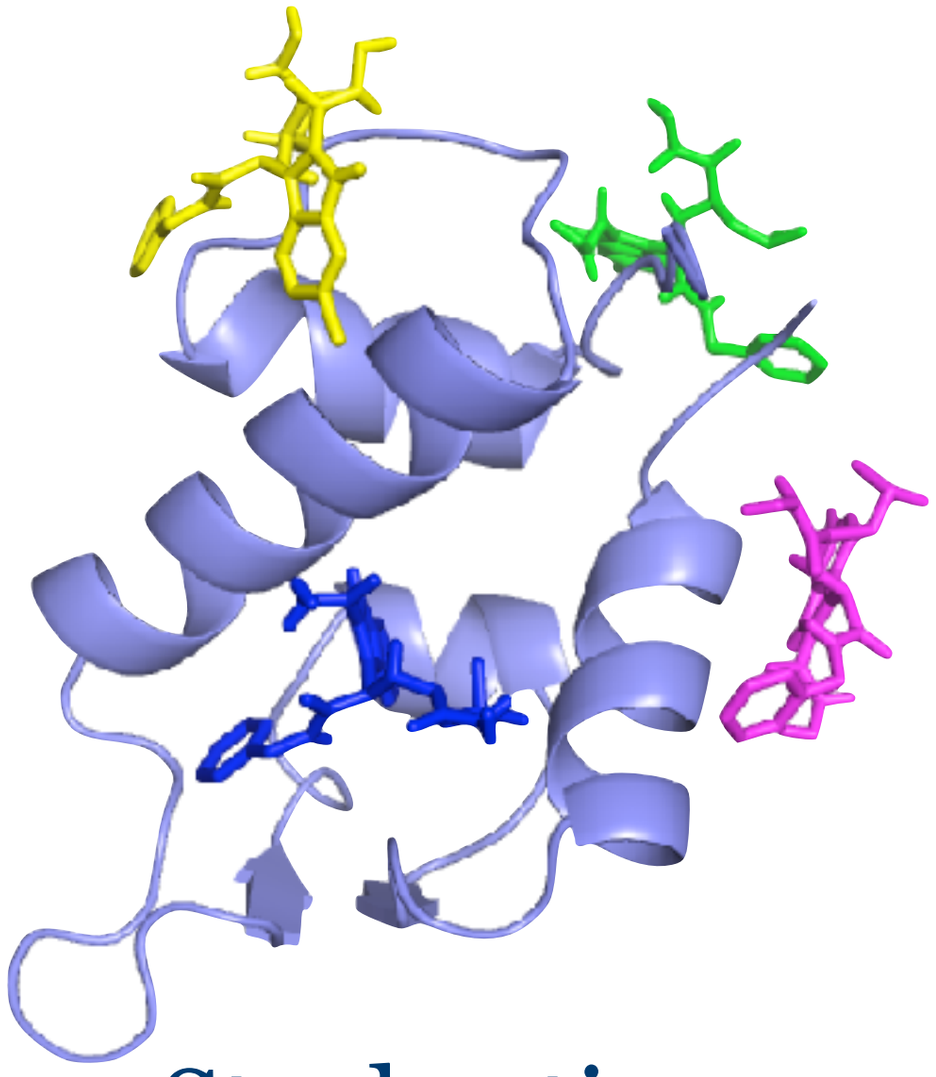
2. Local Refinement



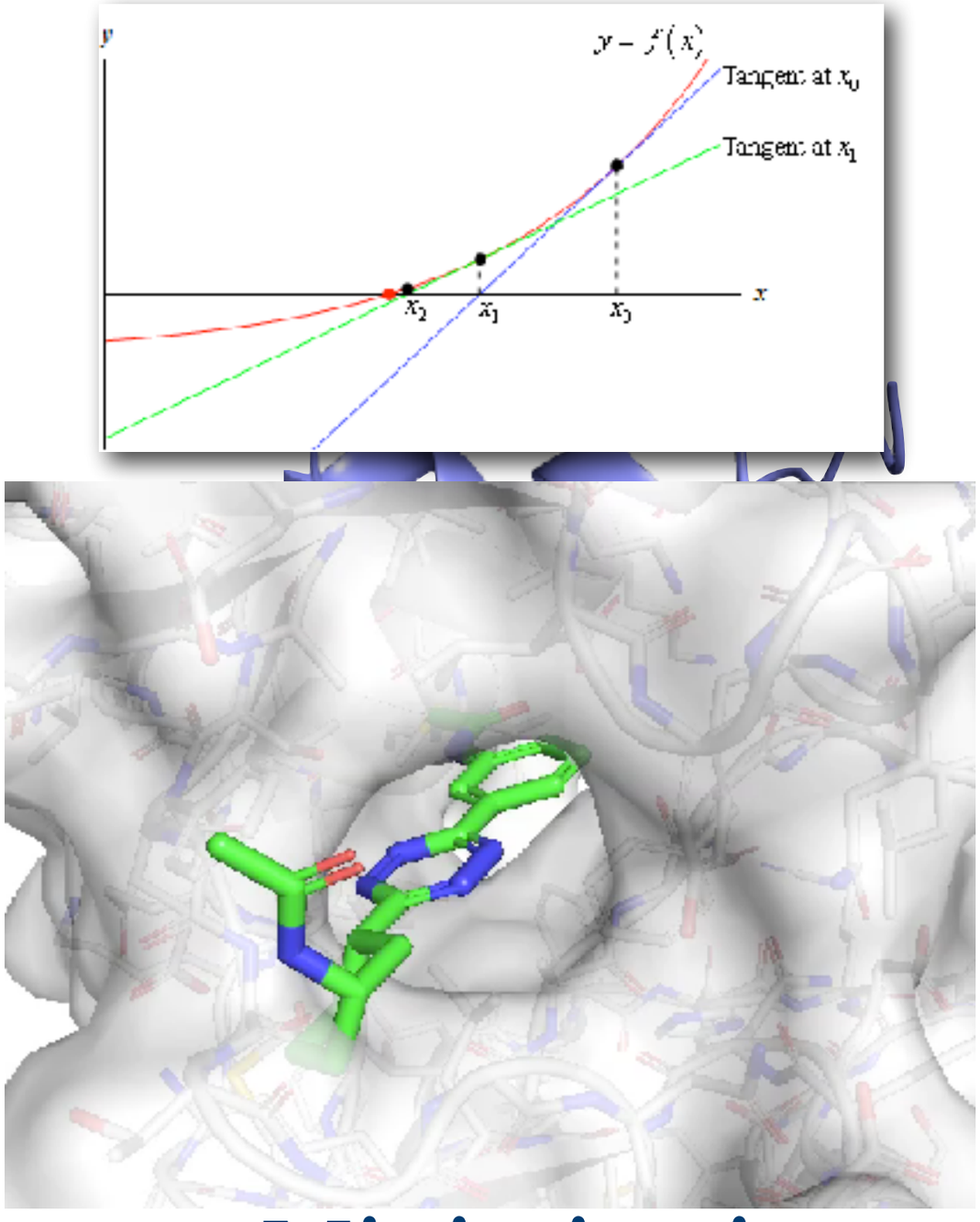
Minimization

Two Phase Docking

1. Global Pose Estimation



Stochastic



Minimization

Scoring Goals

Affinity Prediction

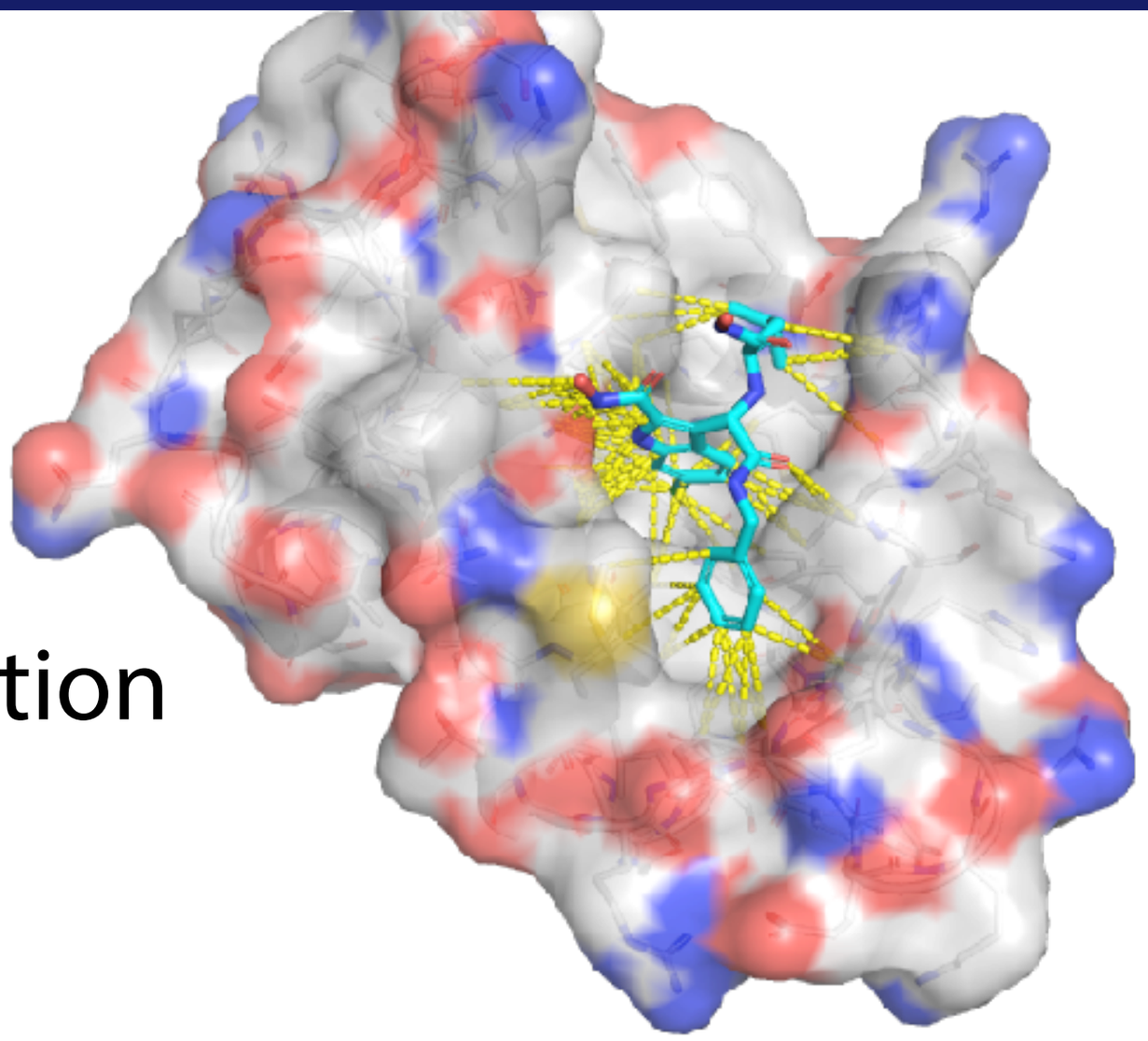
-how well does it bind?

Inactive/Active Discrimination

-does it bind?

Pose Prediction

-how does it bind?



Scoring Goals

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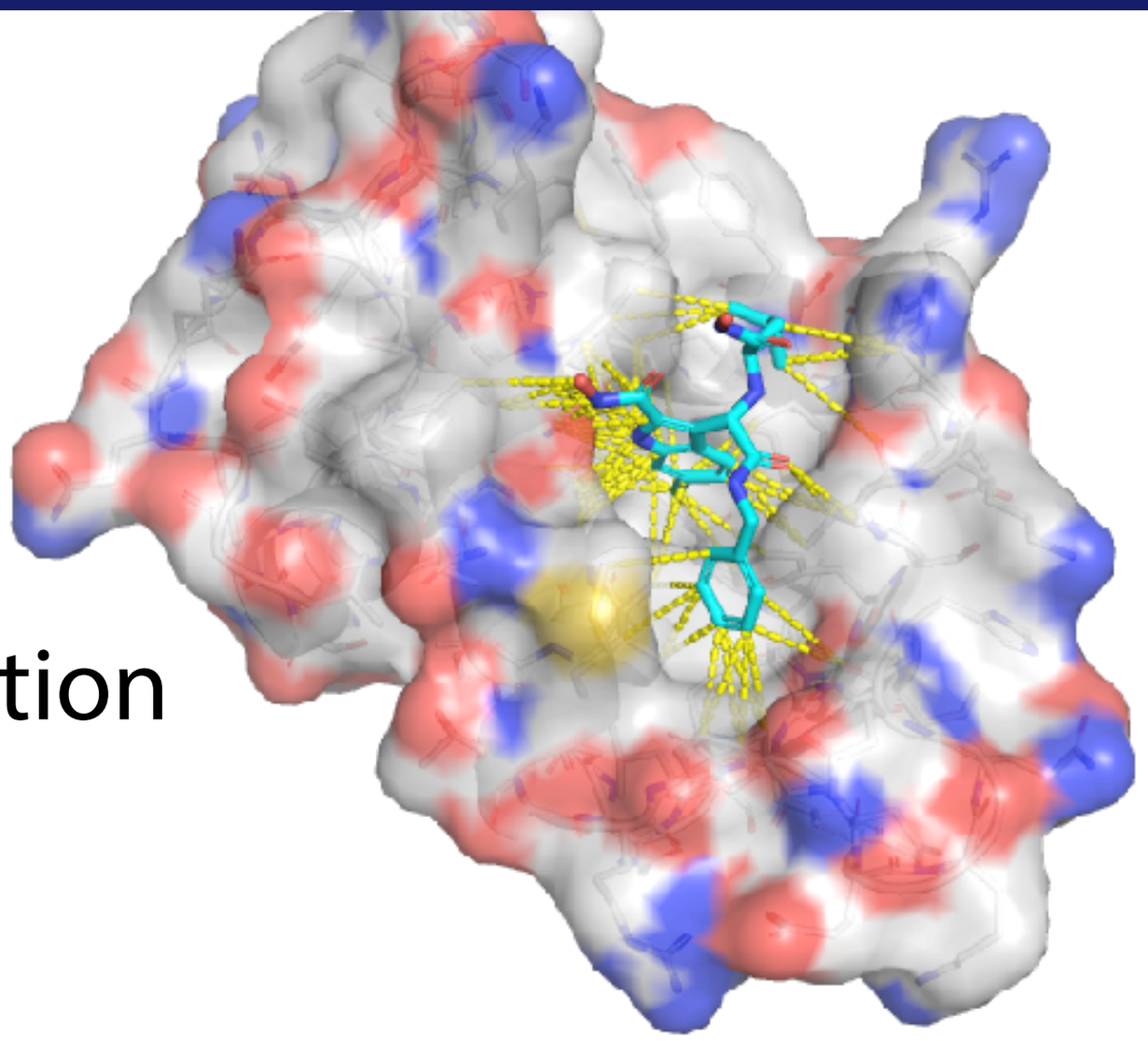
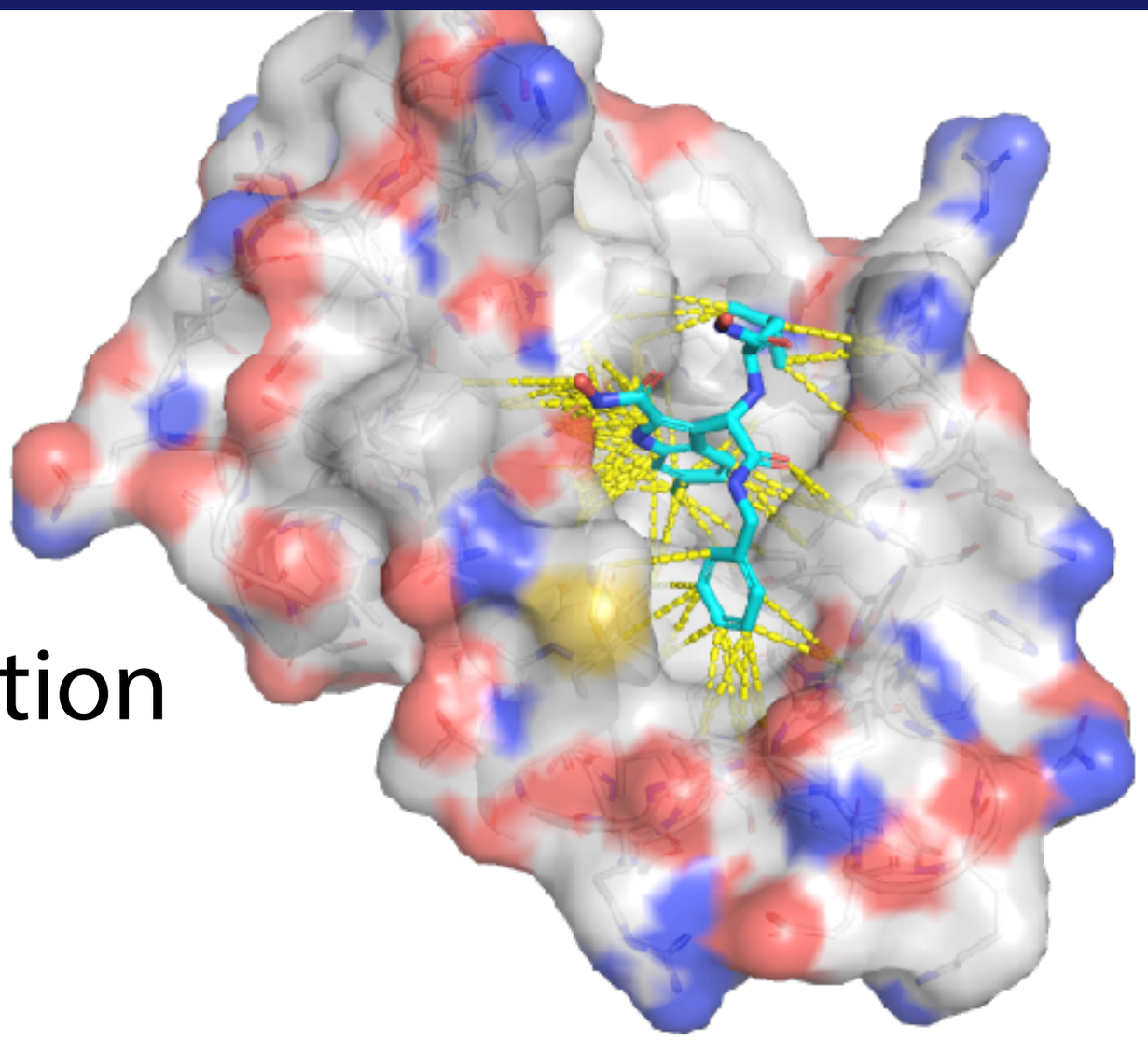


Speed

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 data, not physical principles

Consensus

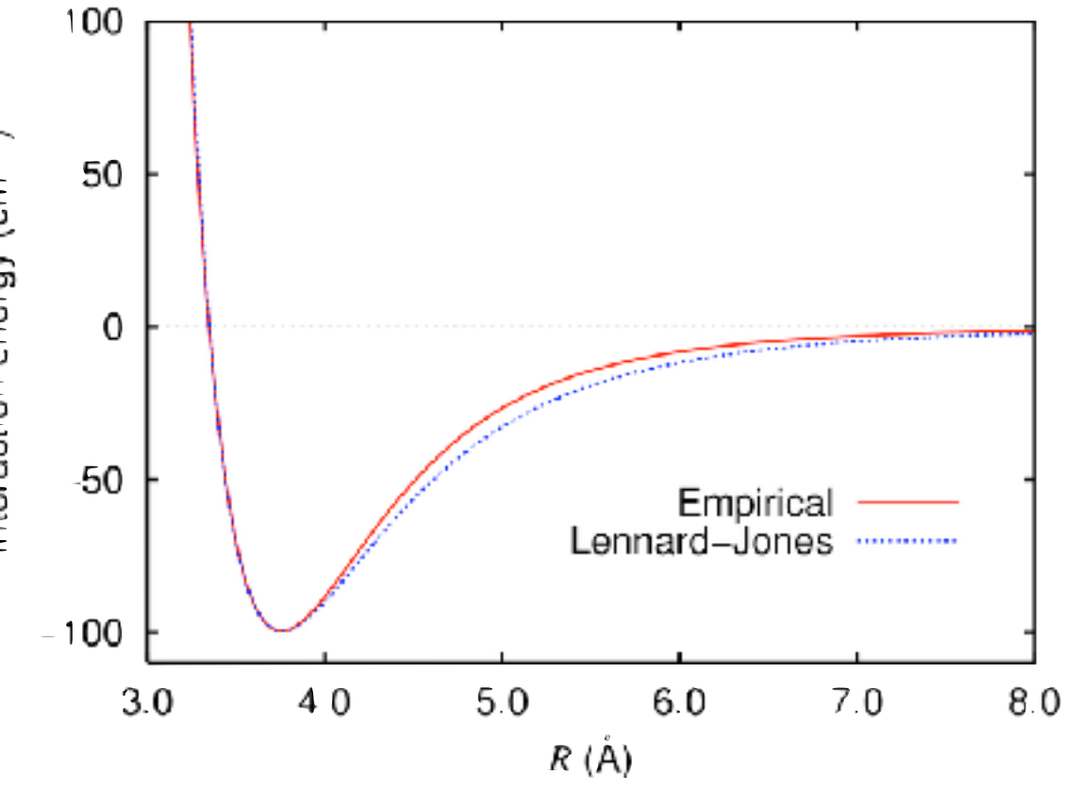
- combine multiple scoring functions

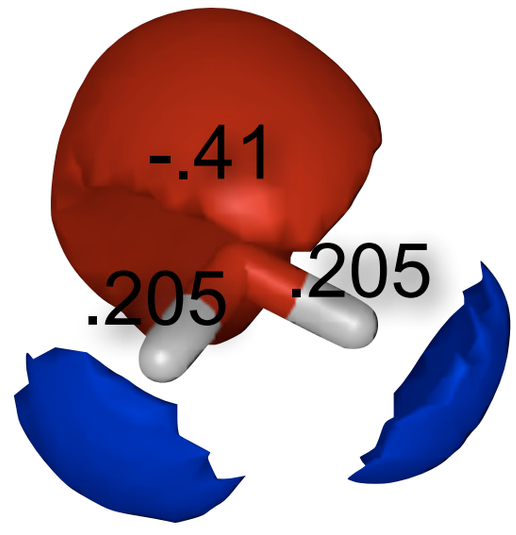
Force Field: Dock 4.0

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

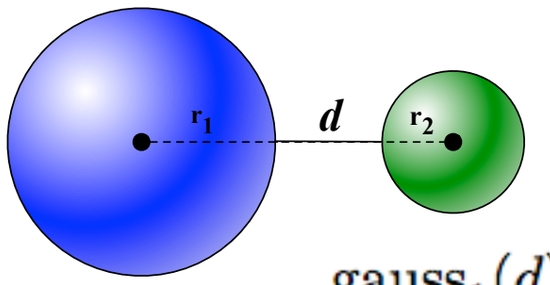
$$E = \sum_{i=1}^{lig} \sum_{j=1}^{rec} \left(\frac{A_{ij}}{r_{ij}^{a}} - \frac{B_{ij}}{r_{ij}^{b}} + 332 \frac{q_i q_j}{D r_{ij}} \right)$$

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





Empirical: AutoDock Vina



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

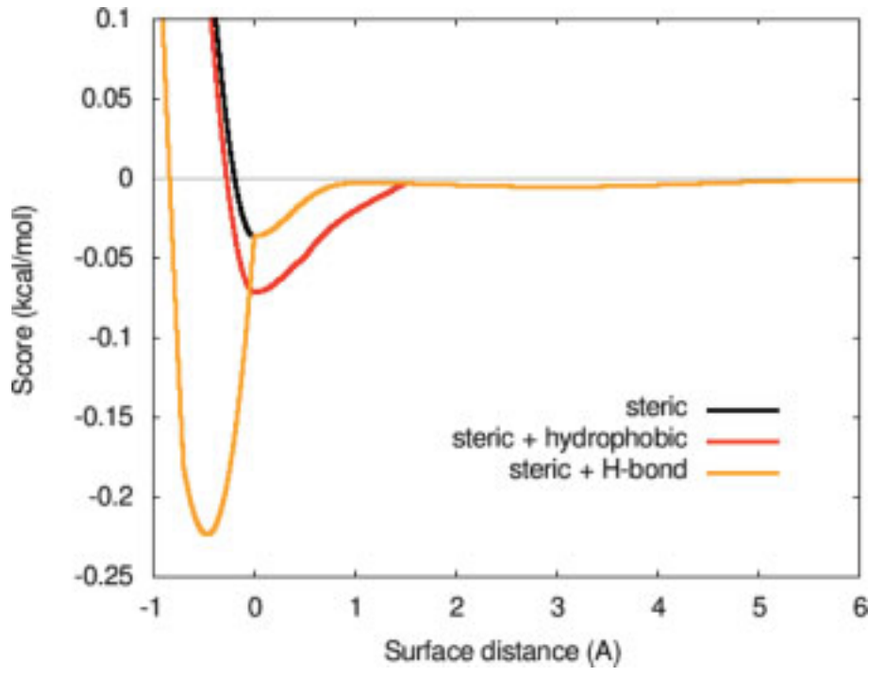
$$\text{gauss}_2(d) = w_{\text{guass}_2} e^{-((d-3)/2)^2}$$

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

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

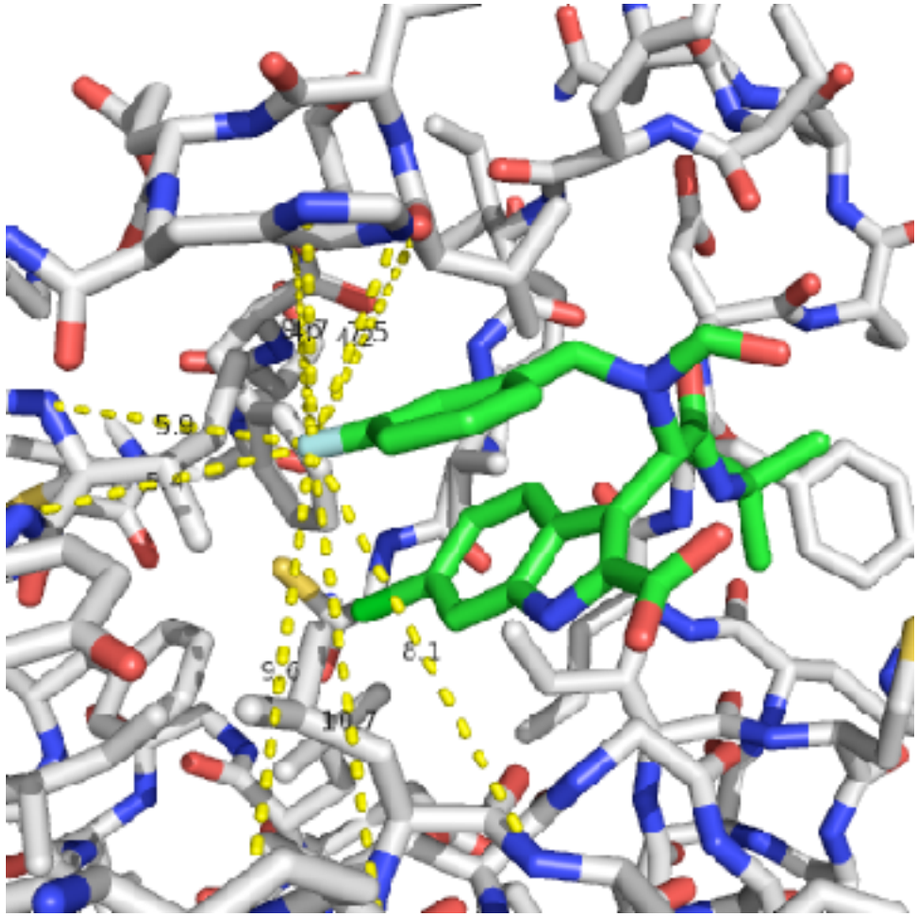
$$\text{hbond}(d) = \begin{cases} w_{\text{hbond}} & d < -0.7 \\ 0 & d > 0 \\ w_{\text{hbond}}(-\frac{10}{7} d) & otherwise \end{cases}$$

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?

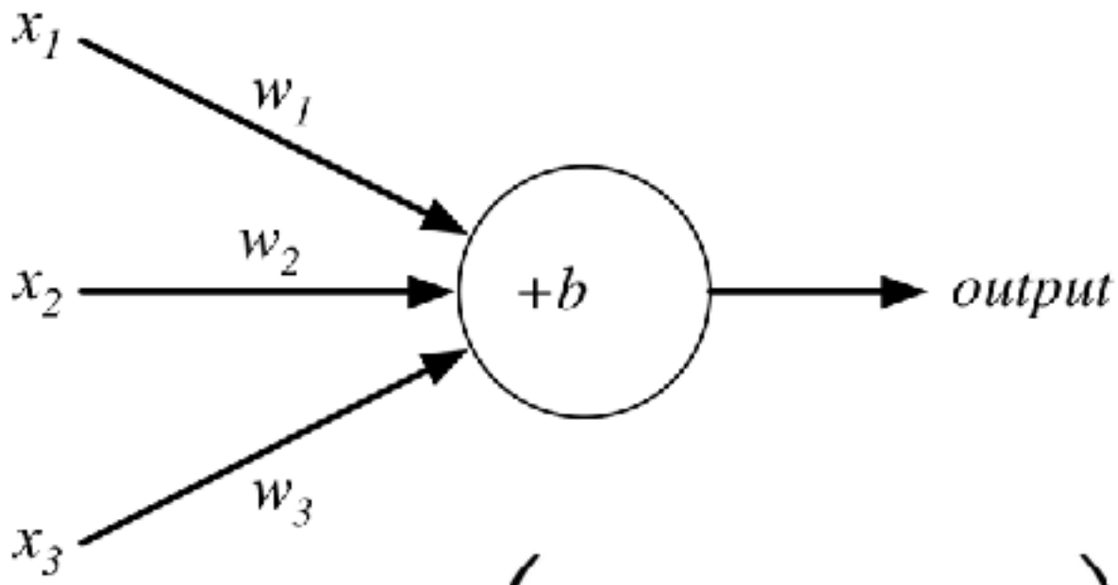
Accurate pose prediction, binding discrimination, **and** affinity prediction without sacrificing performance?

Key Idea: Leverage "big data"

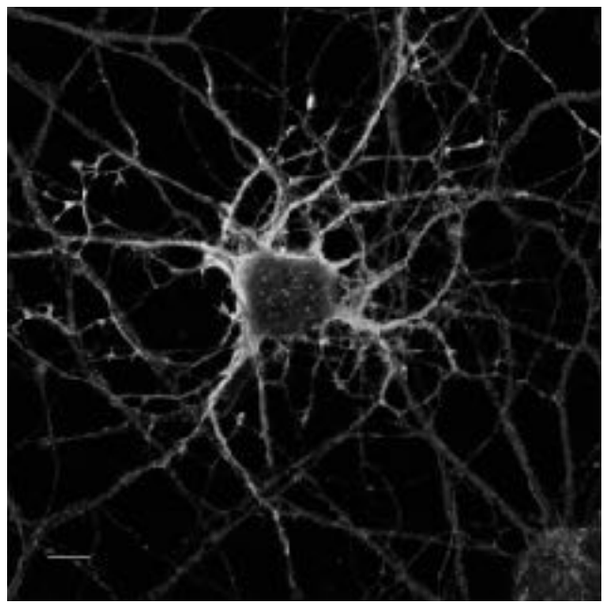
- 231,655,275 bioactivities in PubChem
- 125,526 structures in the PDB
- 16,179 annotated complexes in PDBbind

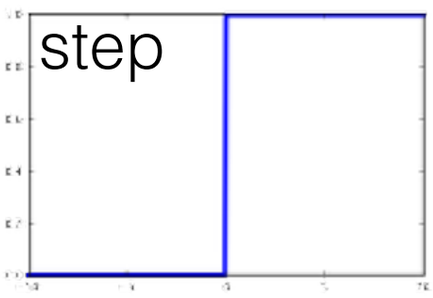
Machine Learning

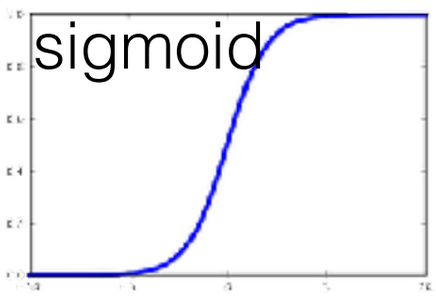
Neural Networks

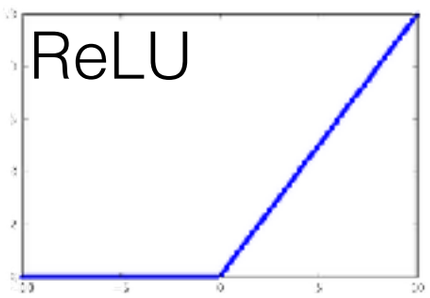


$$output = \sigma\left(\sum_i w_i x_i + b\right)$$

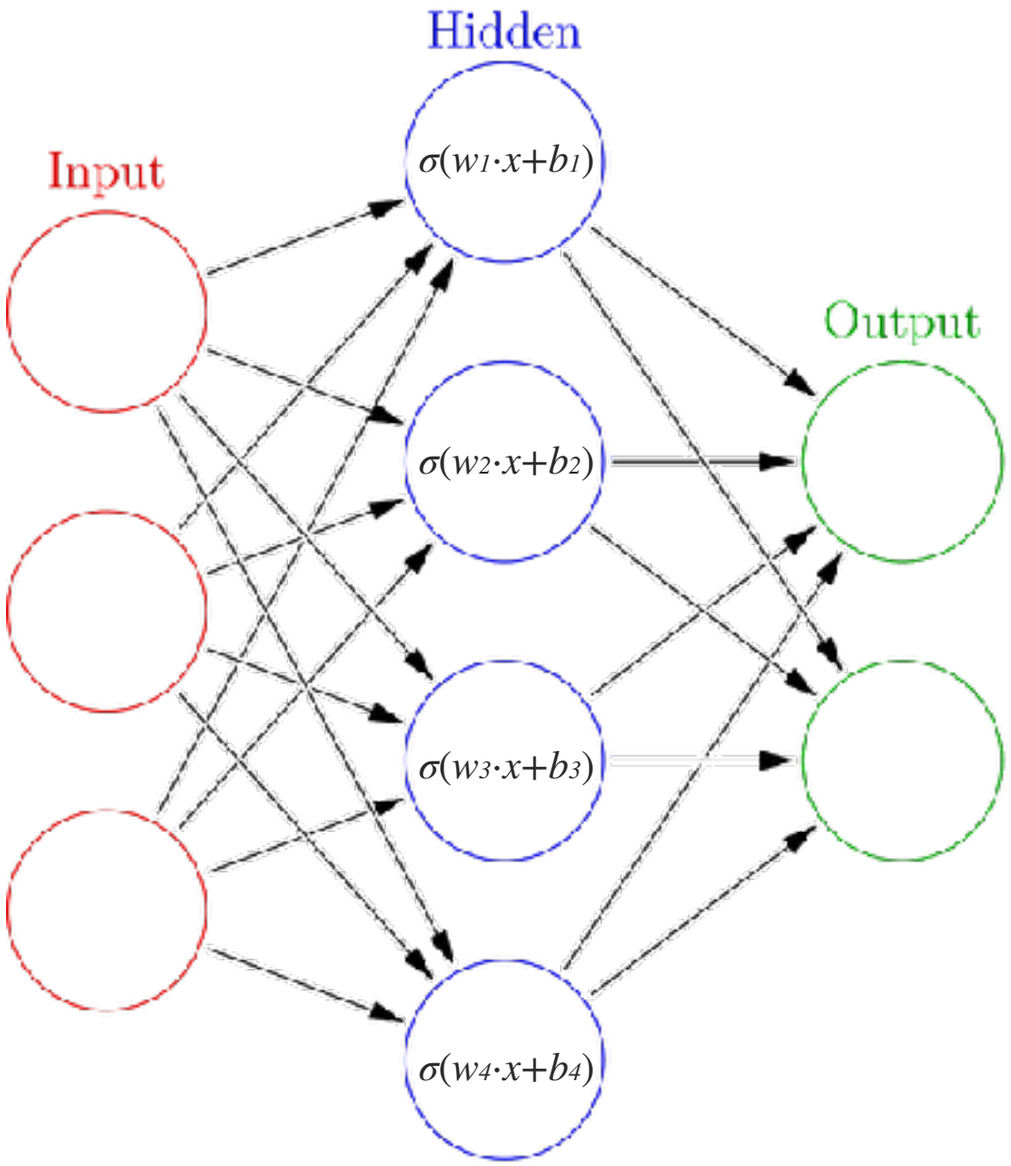


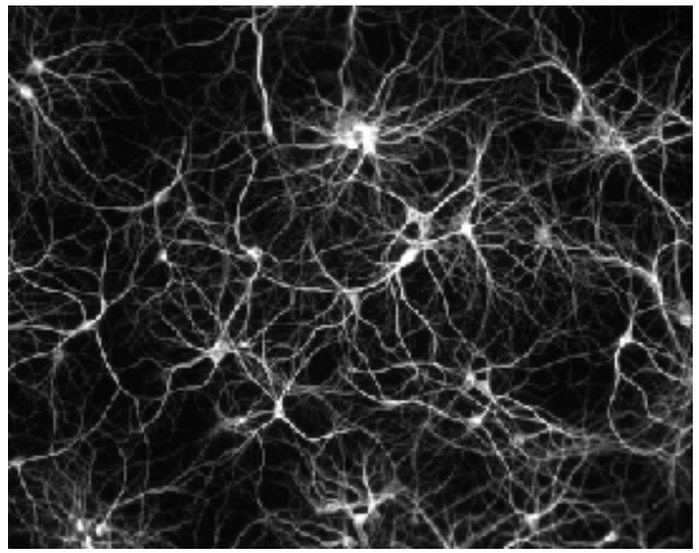






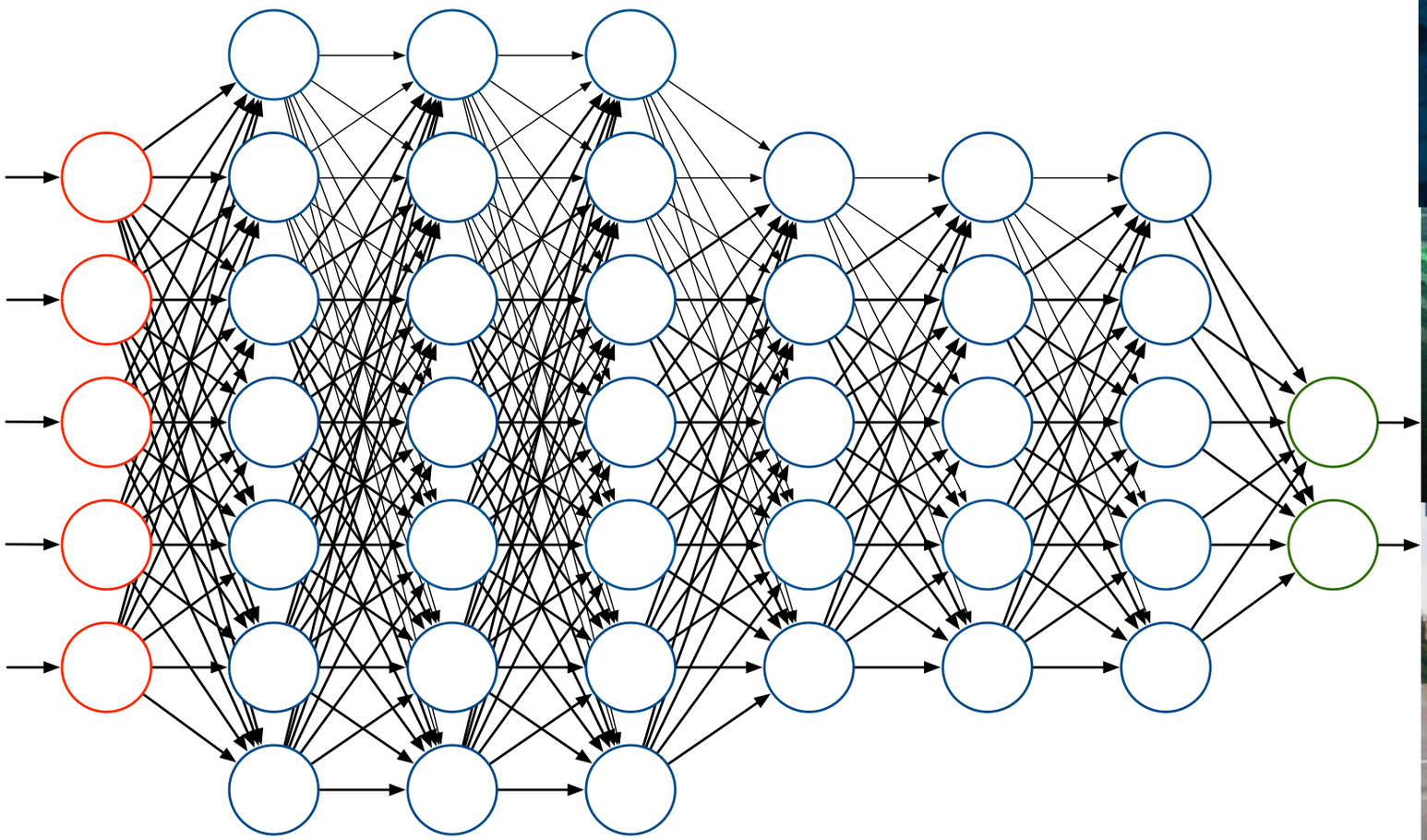
Neural Networks





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

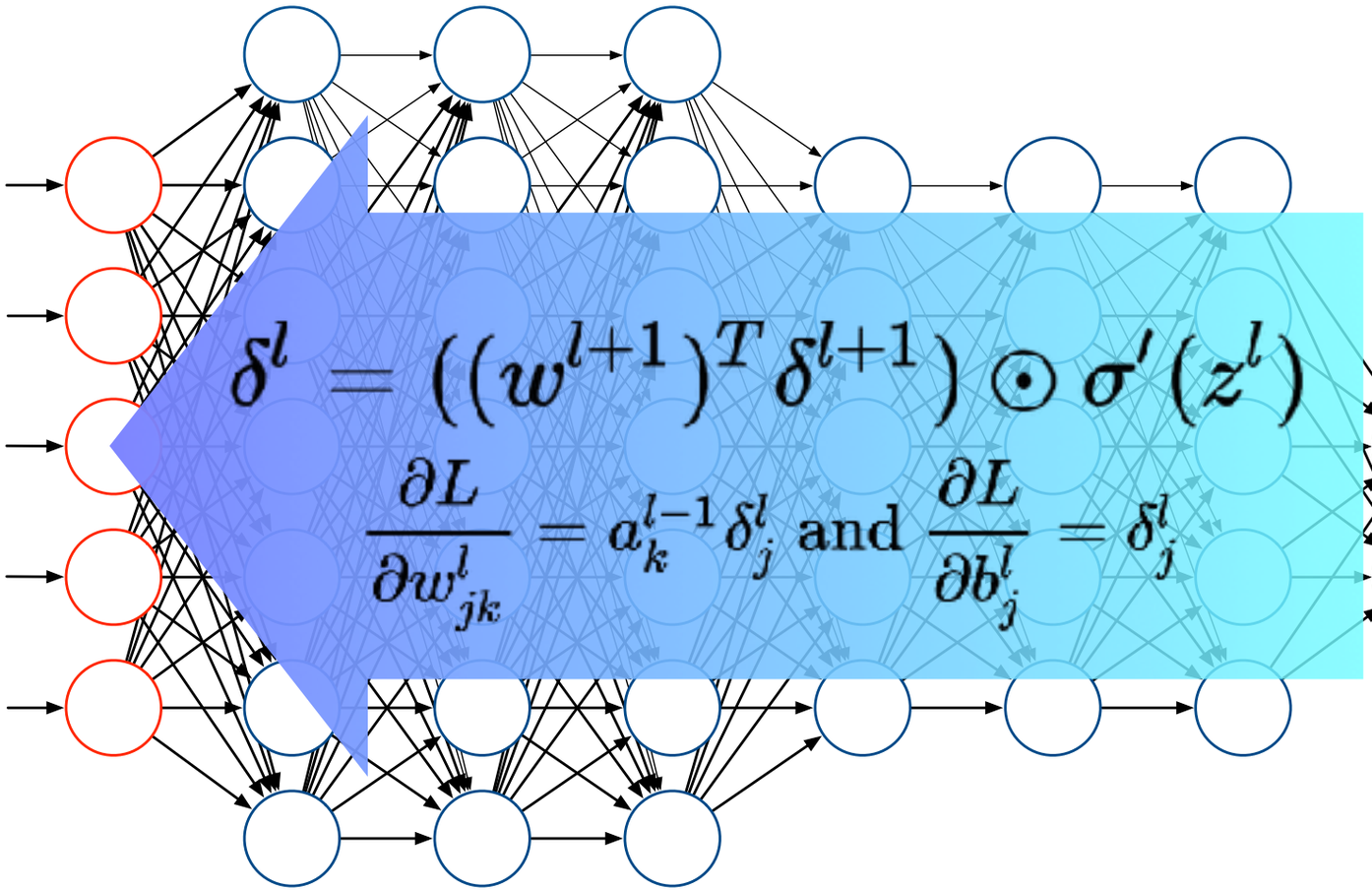
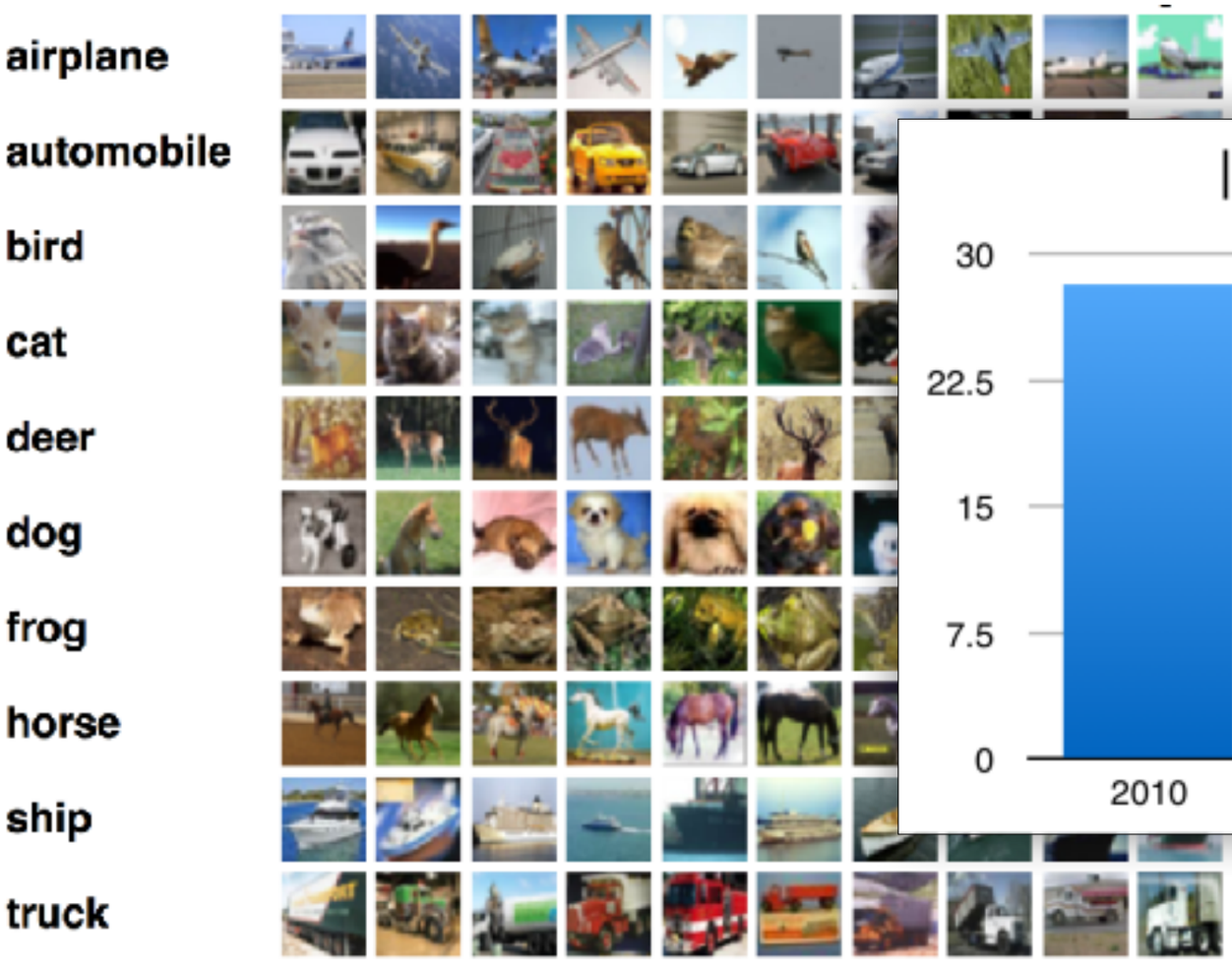
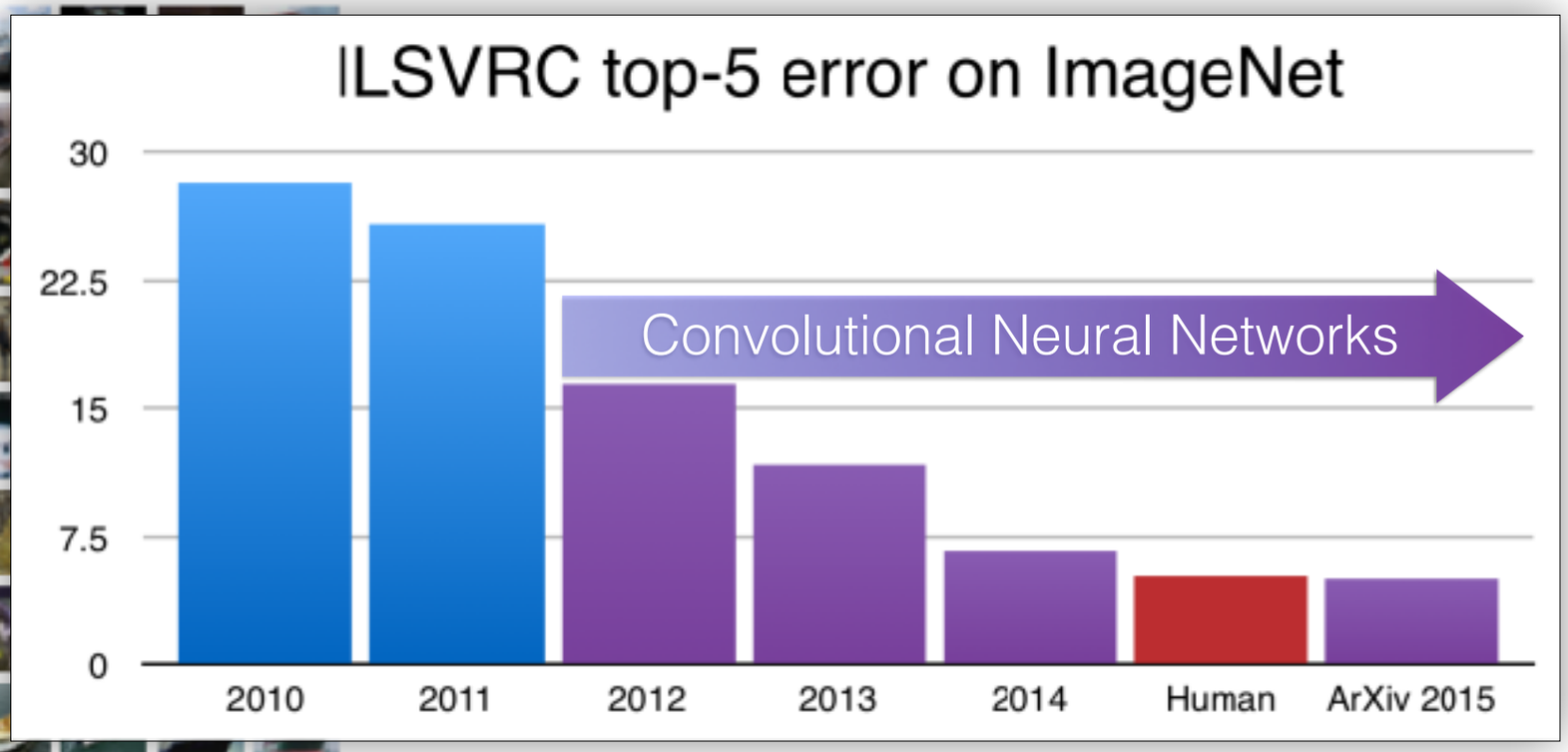


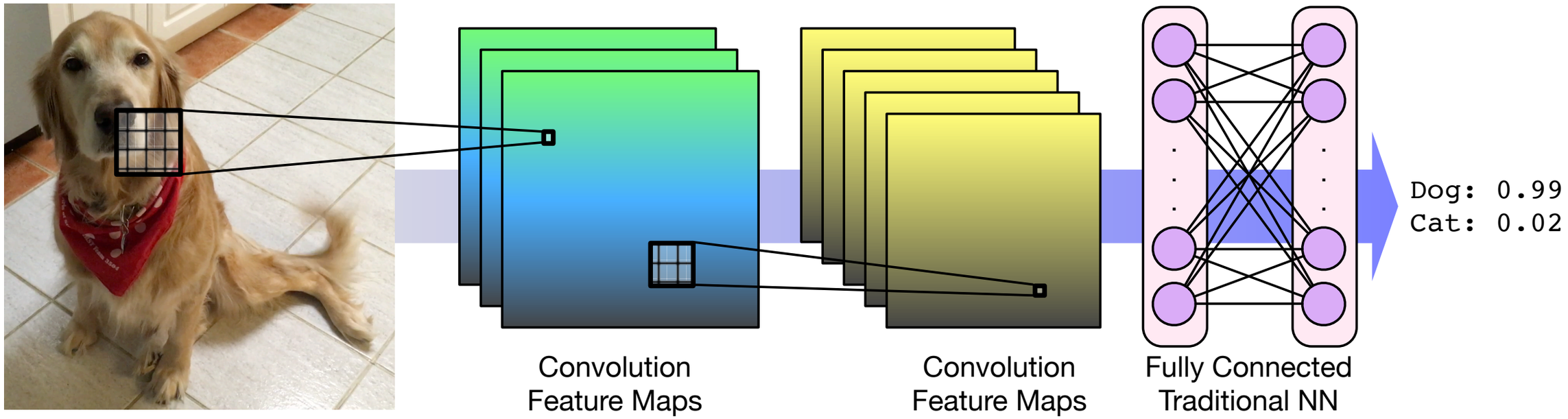
Image Recognition

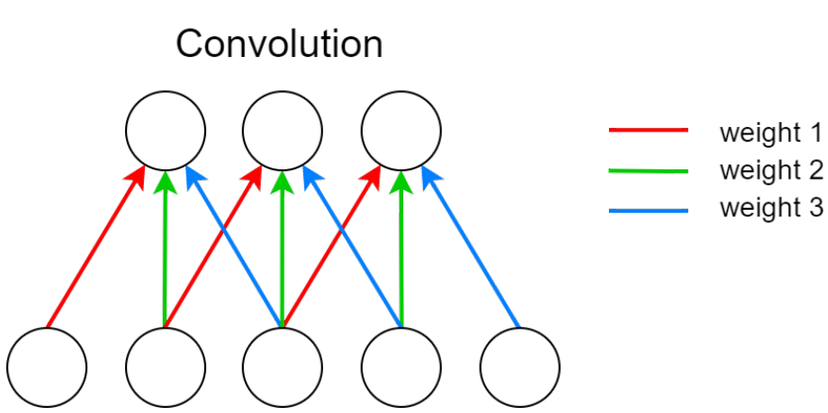


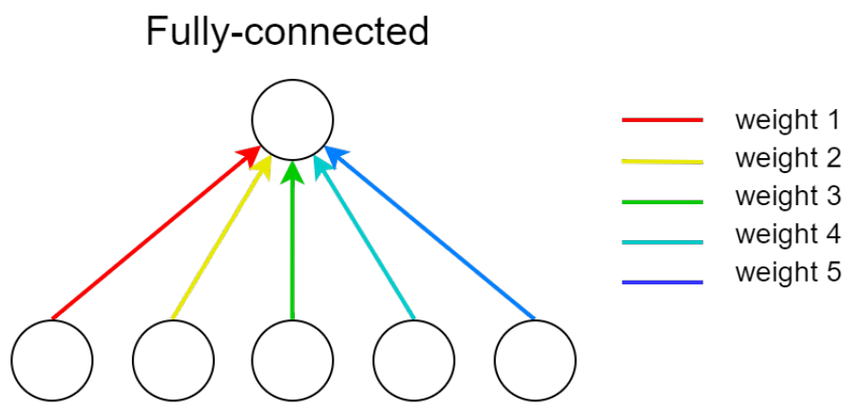


https://devblogs.nvidia.com

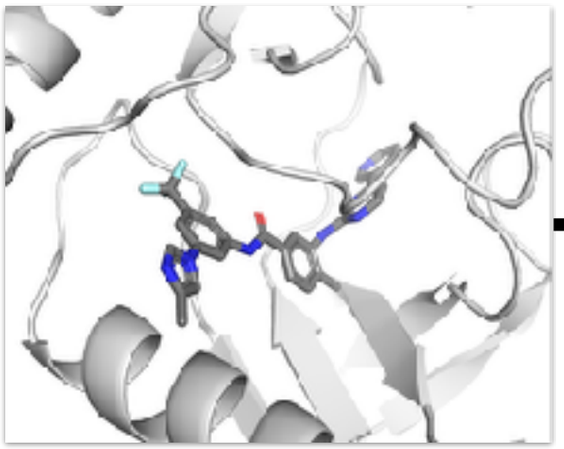
Convolutional Neural Networks







CNNs for Protein-Ligand Scoring



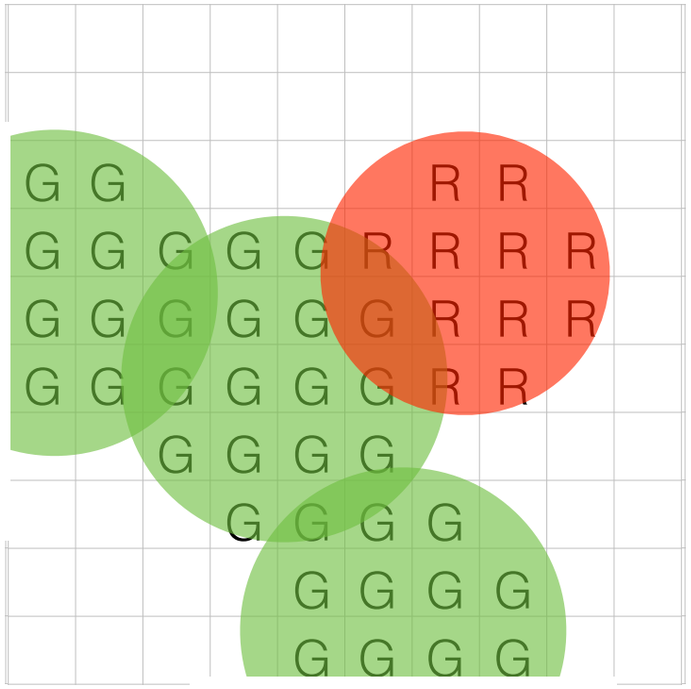
CNN

Pose Prediction

Binding Discrimination

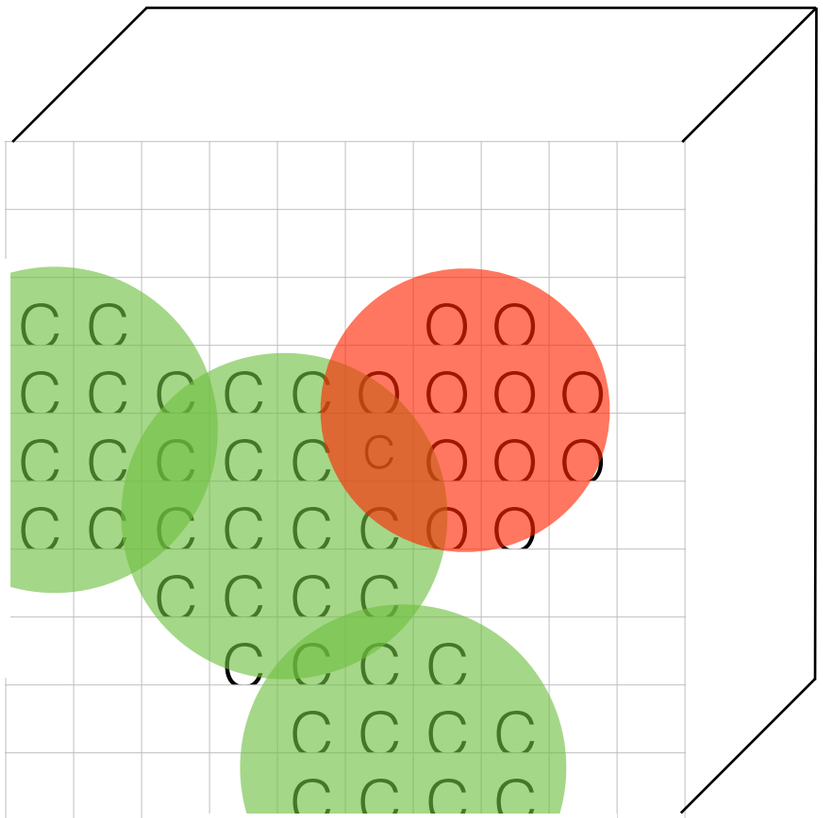
Affinity Prediction

Protein-Ligand Representation



(R,G,B) pixel

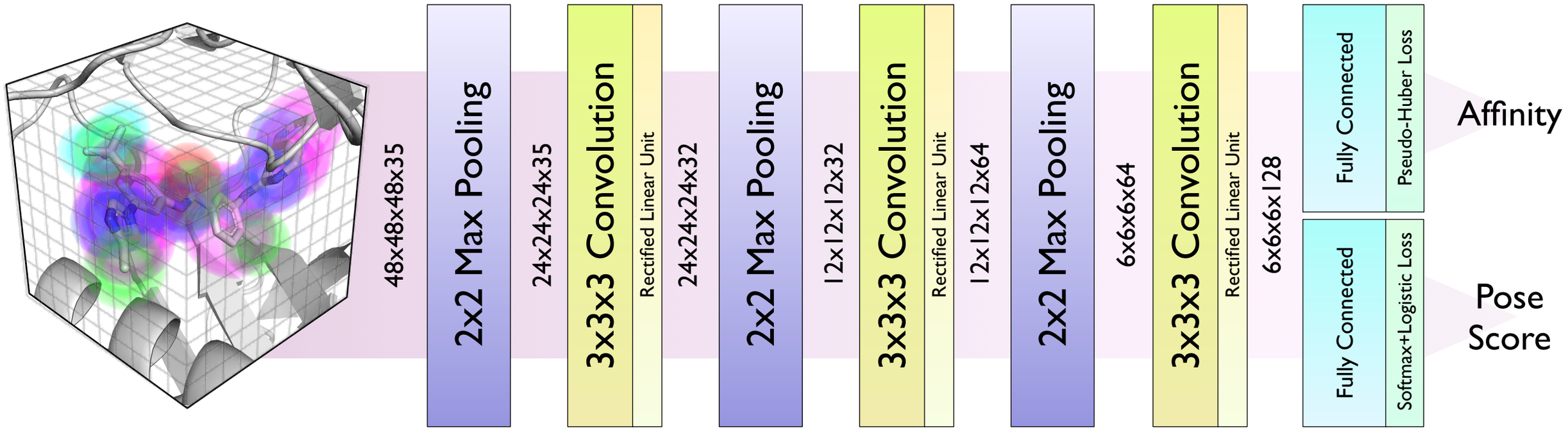
Protein-Ligand Representation



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

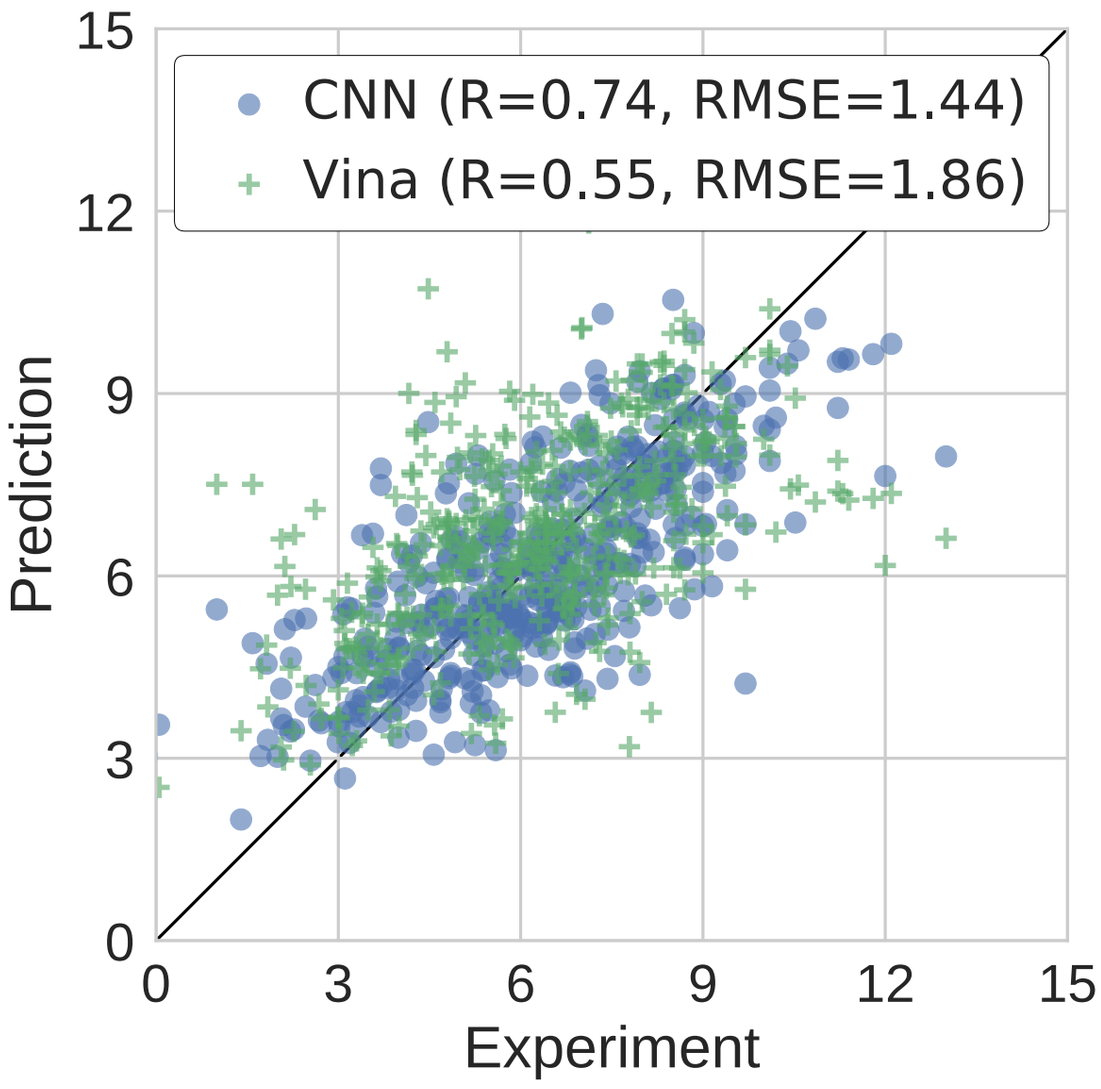
The only parameters for this representation are the choice of **grid resolution**, **atom density**, and **atom types**.

Model

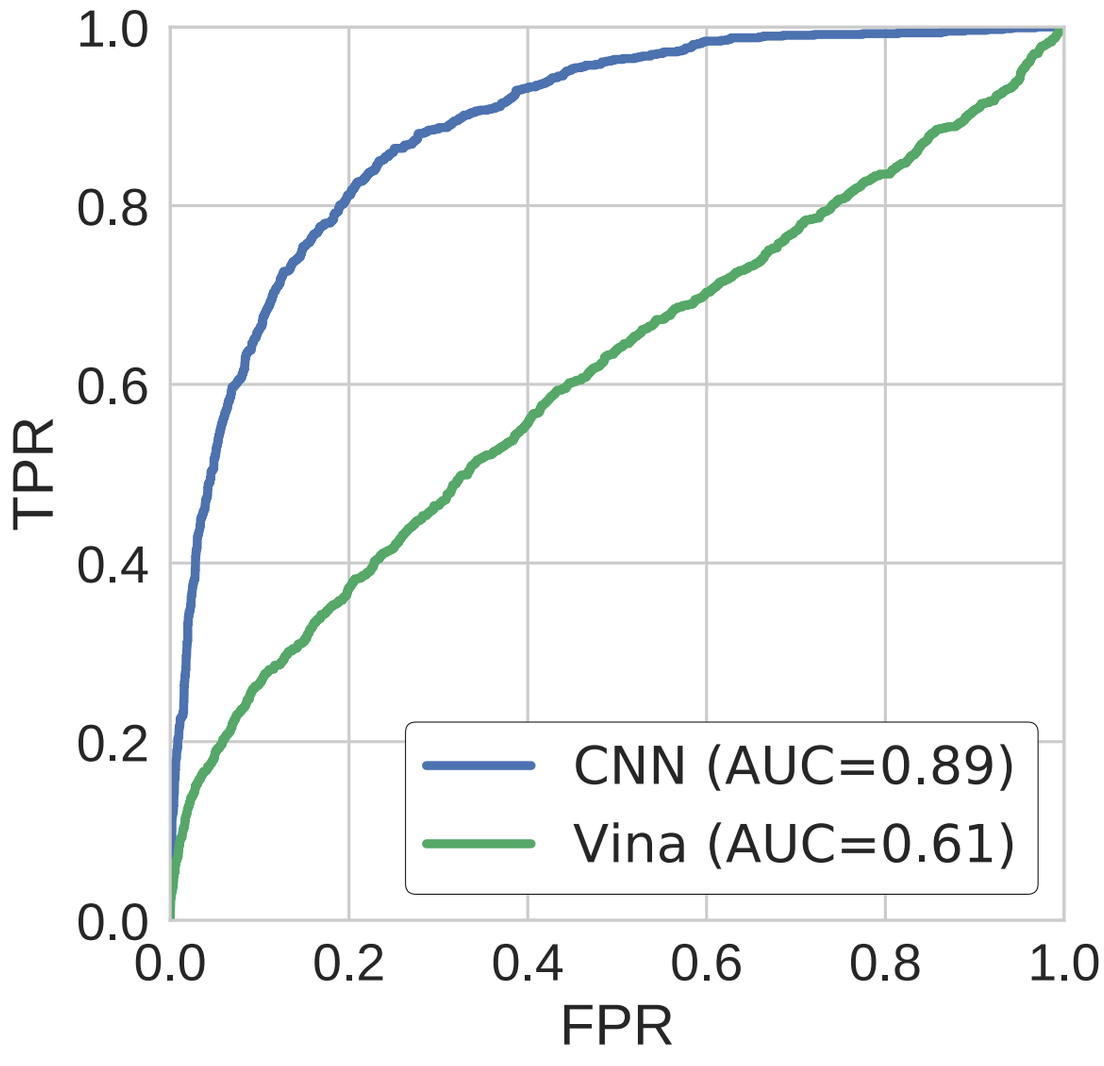

48x48x48x35
2x2 Max Pooling
24x24x24x35
3x3x3 Convolution
Rectified Linear Unit
24x24x24x32
2x2 Max Pooling
12x12x12x32
3x3x3 Convolution
Rectified Linear Unit
12x12x12x64
2x2 Max Pooling
6x6x6x64
3x3x3 Convolution
Rectified Linear Unit
6x6x6x128
Fully Connected
Pseudo-Huber Loss
Affinity
Fully Connected
Softmax+Logistic Loss
Pose Score

Results

Affinity Prediction

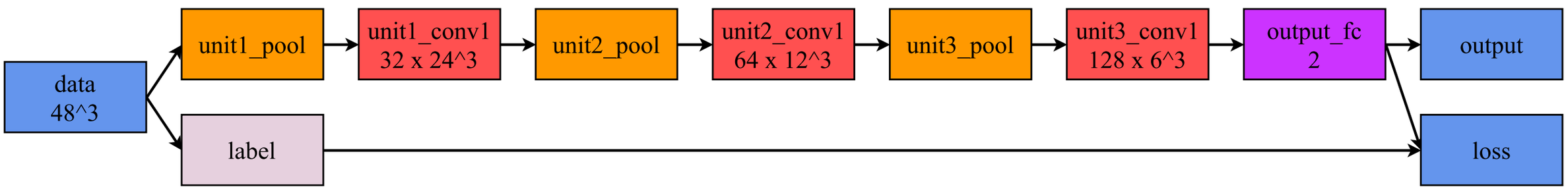


Pose Prediction



Trained on PDBbind refined; tested on CSAR 🤔

Beyond Scoring



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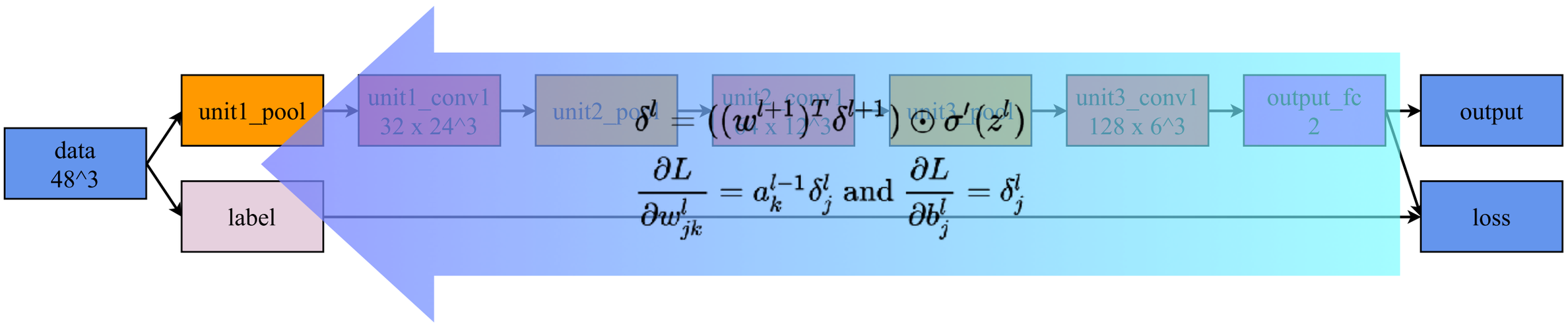

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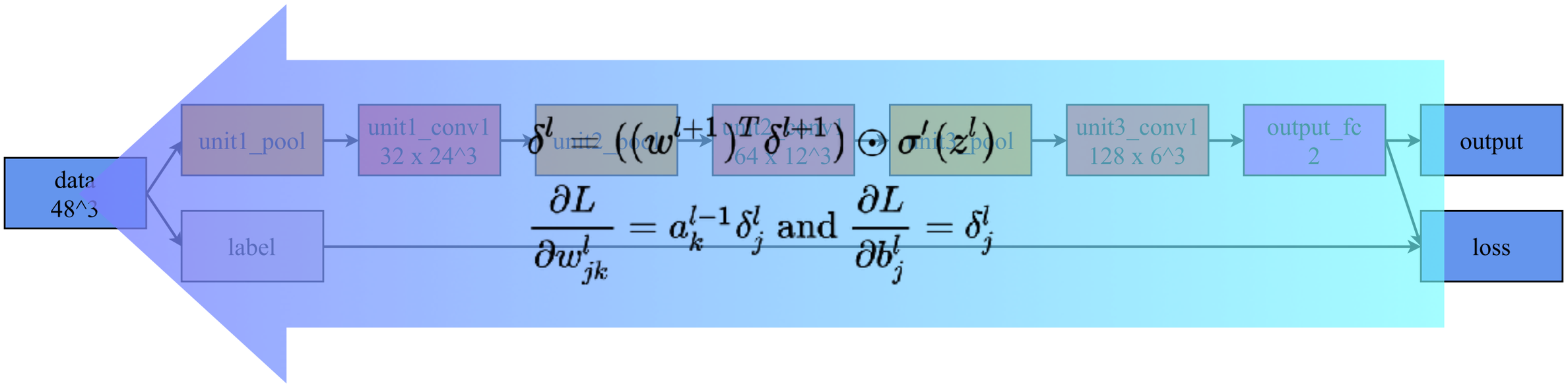

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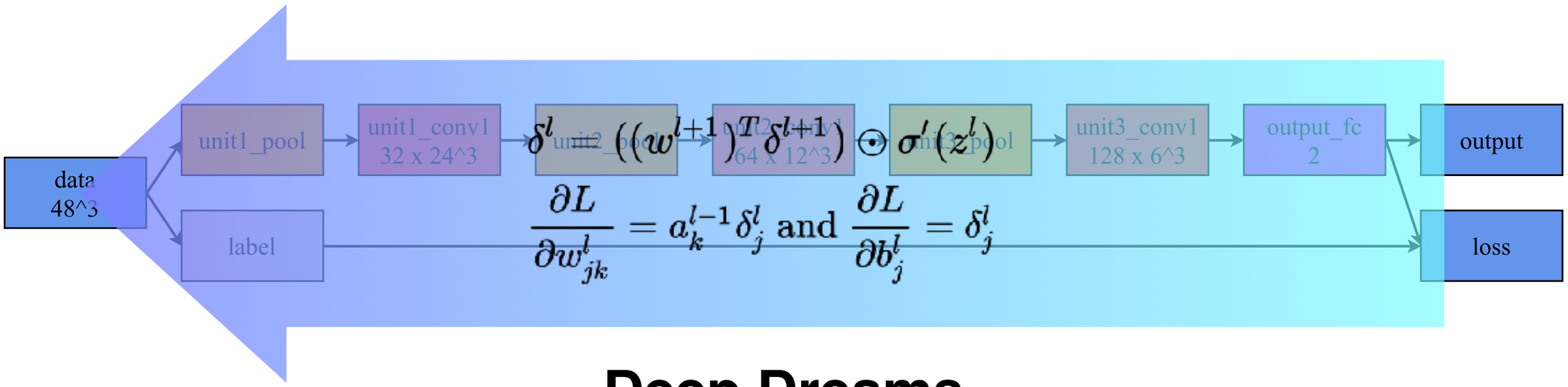
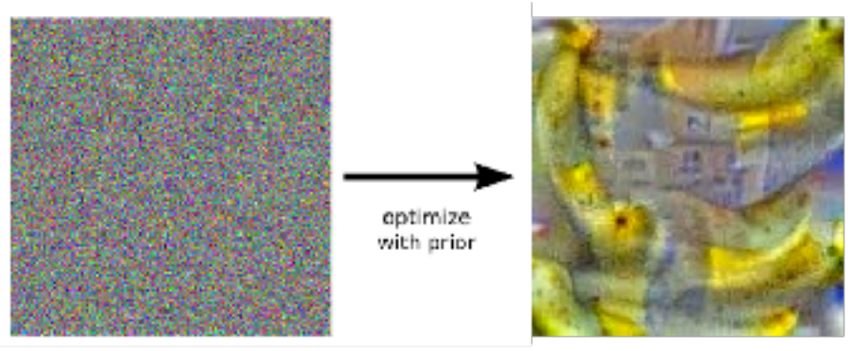
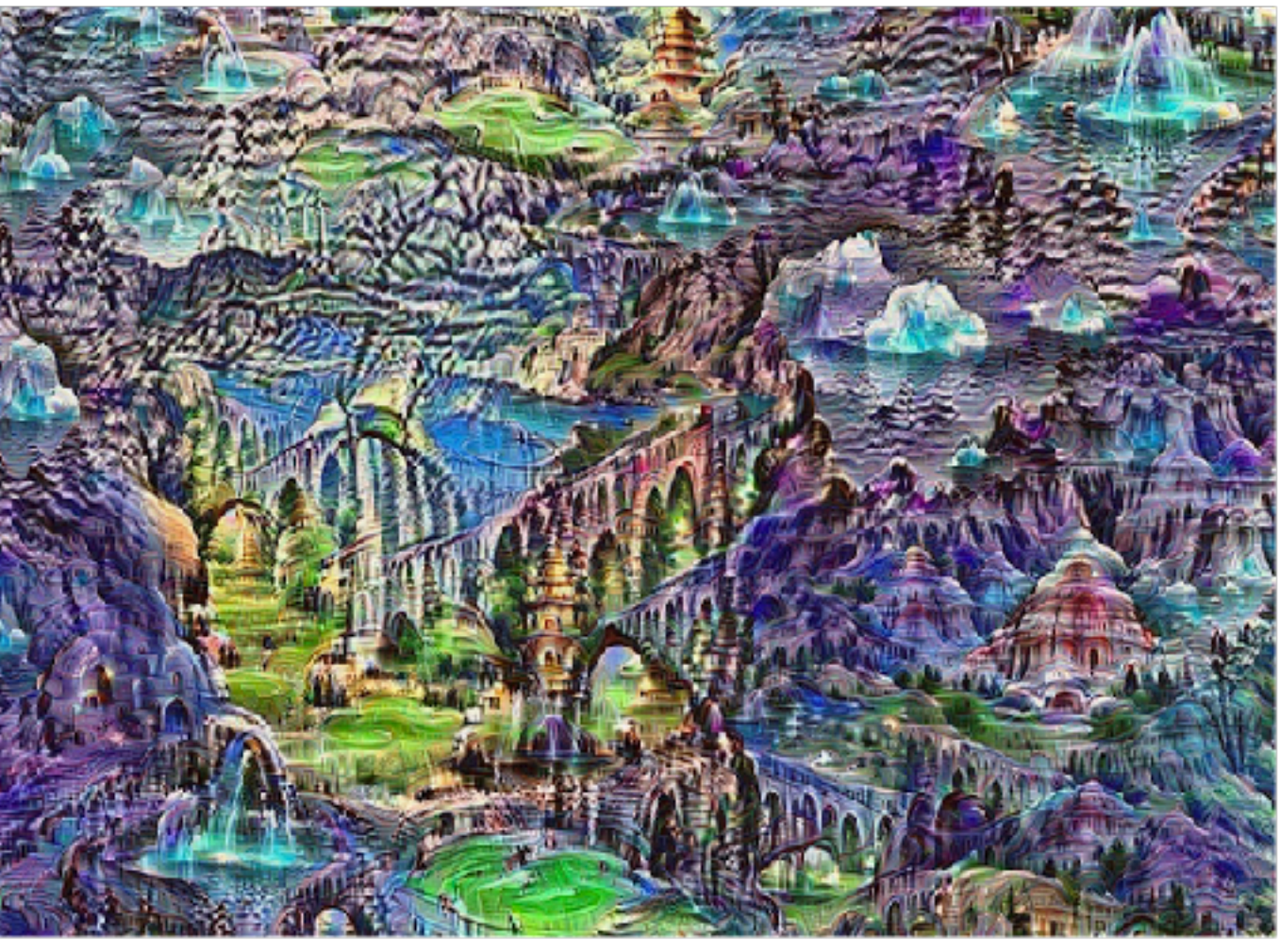
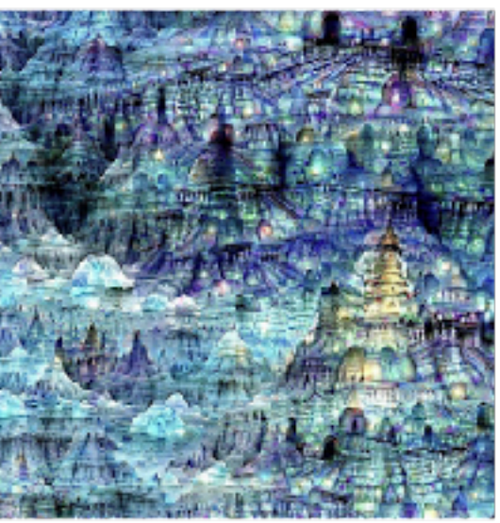


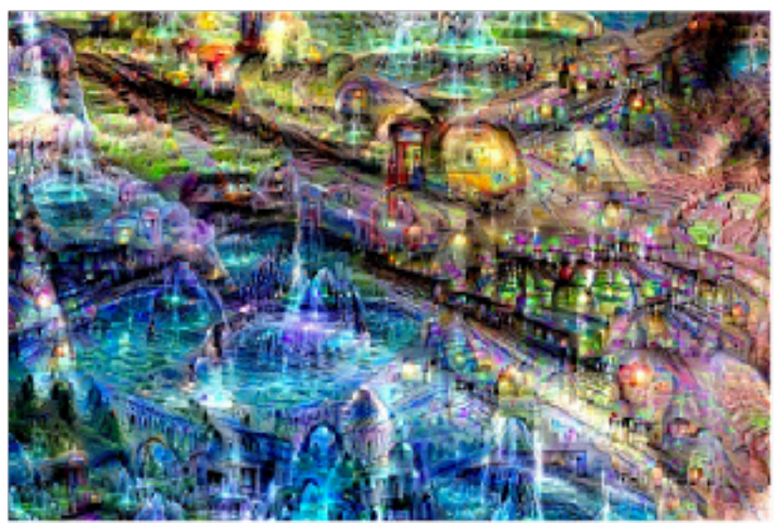
Deep Dreams

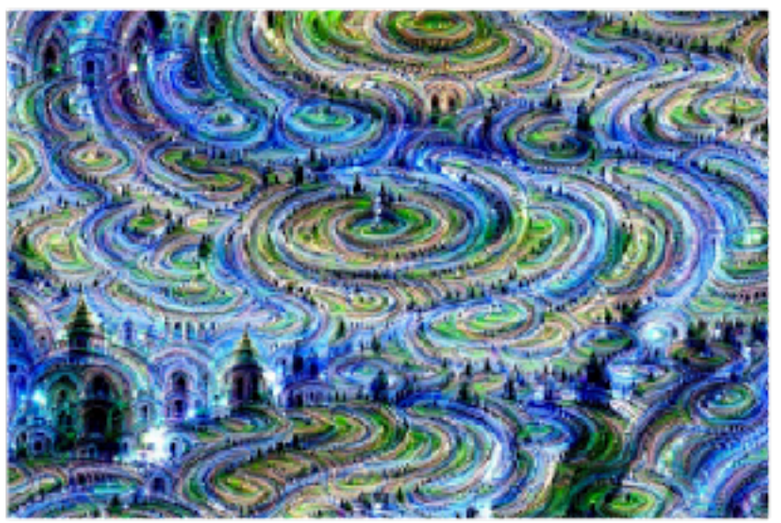


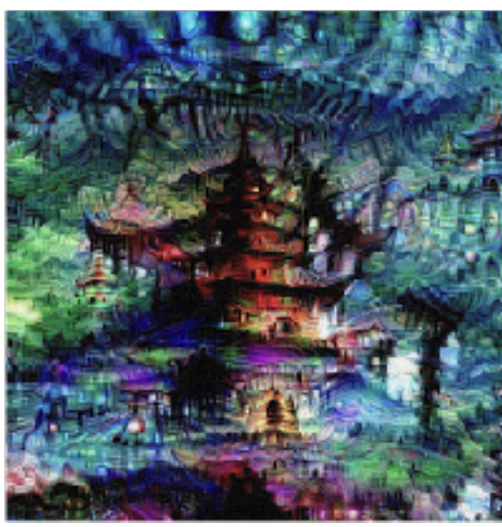
https://research.googleblog.com/2015/06/inceptionism-going-deeper-into-neural.html





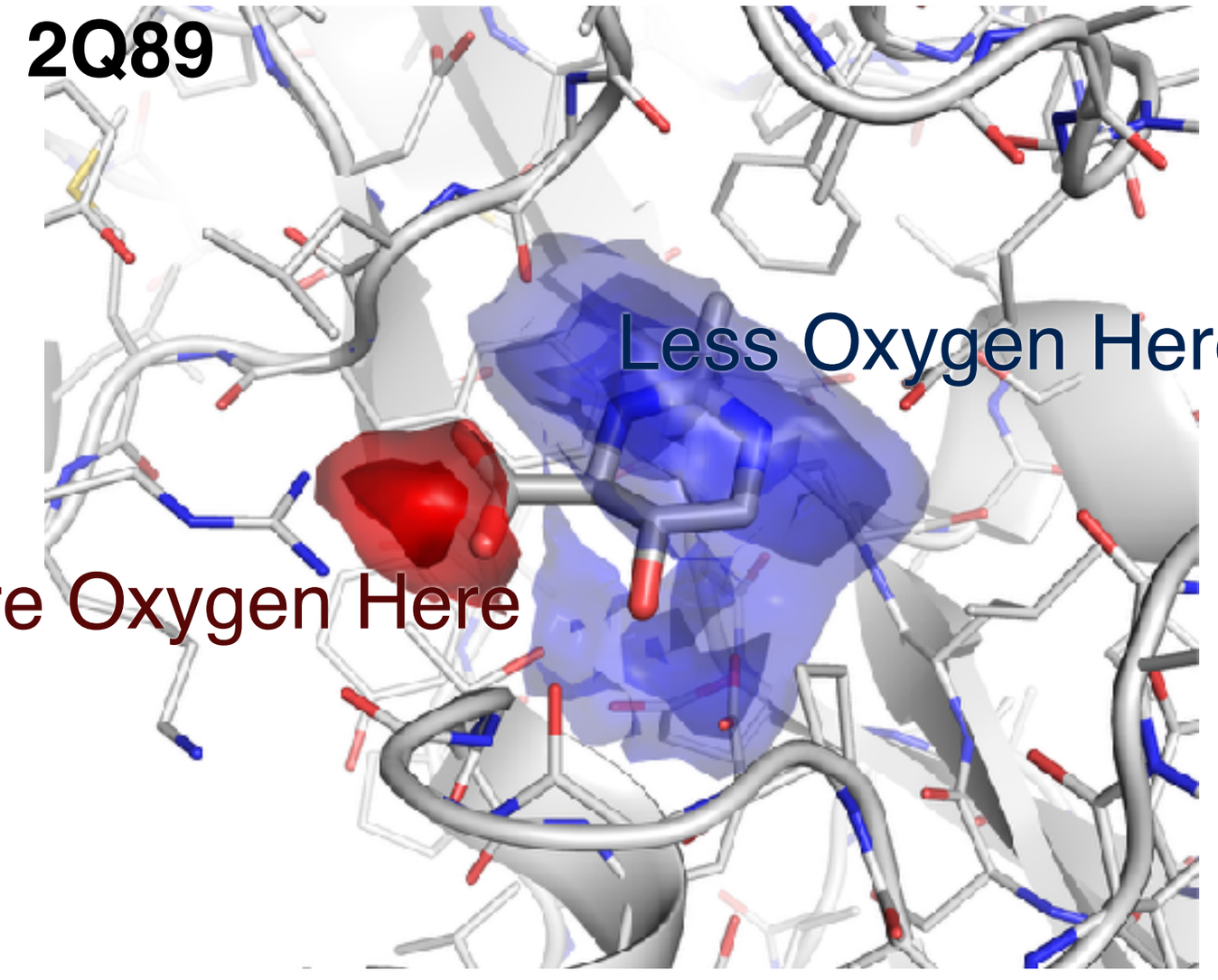






https://deepdreamgenerator.com/#gallery

Beyond Scoring



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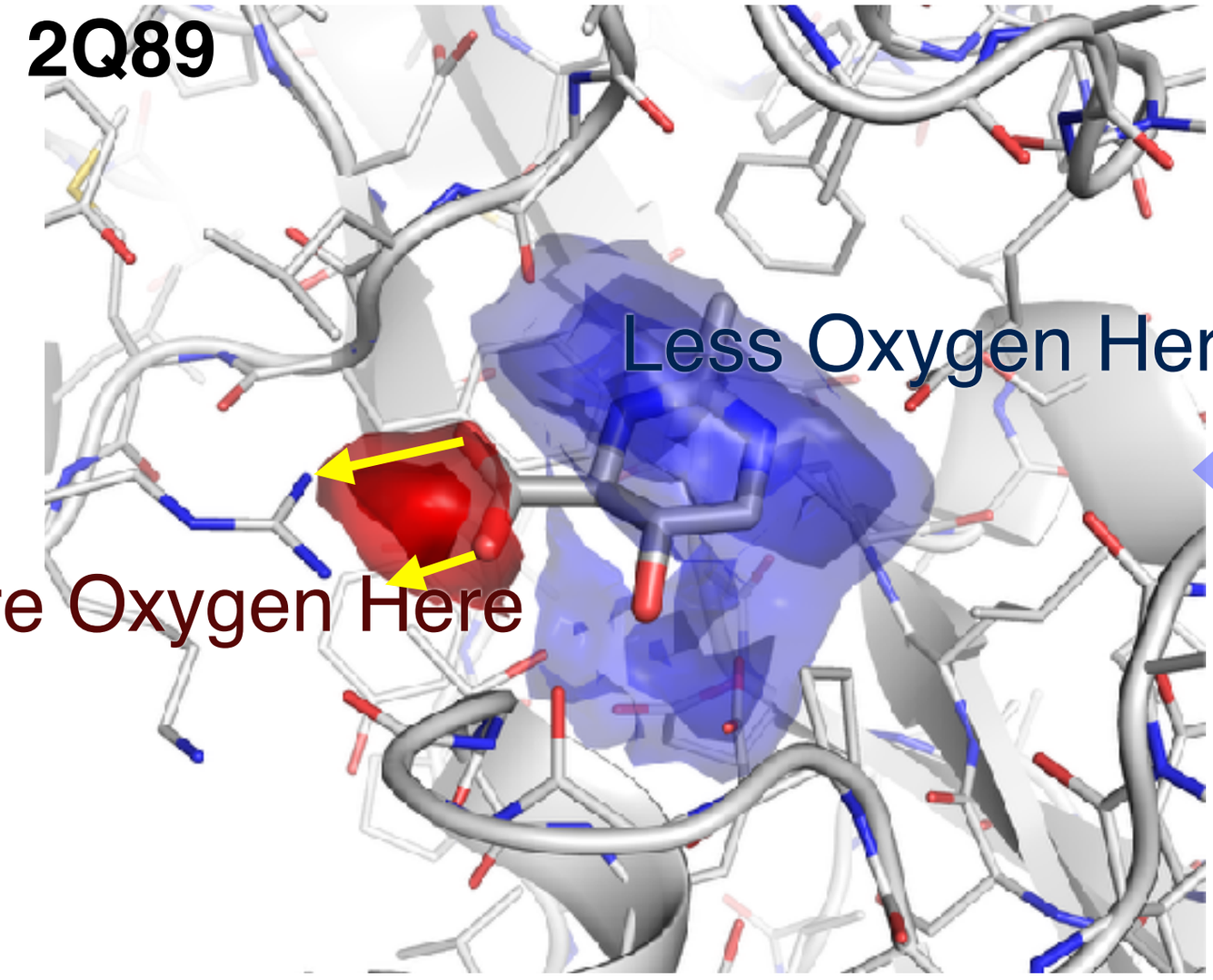
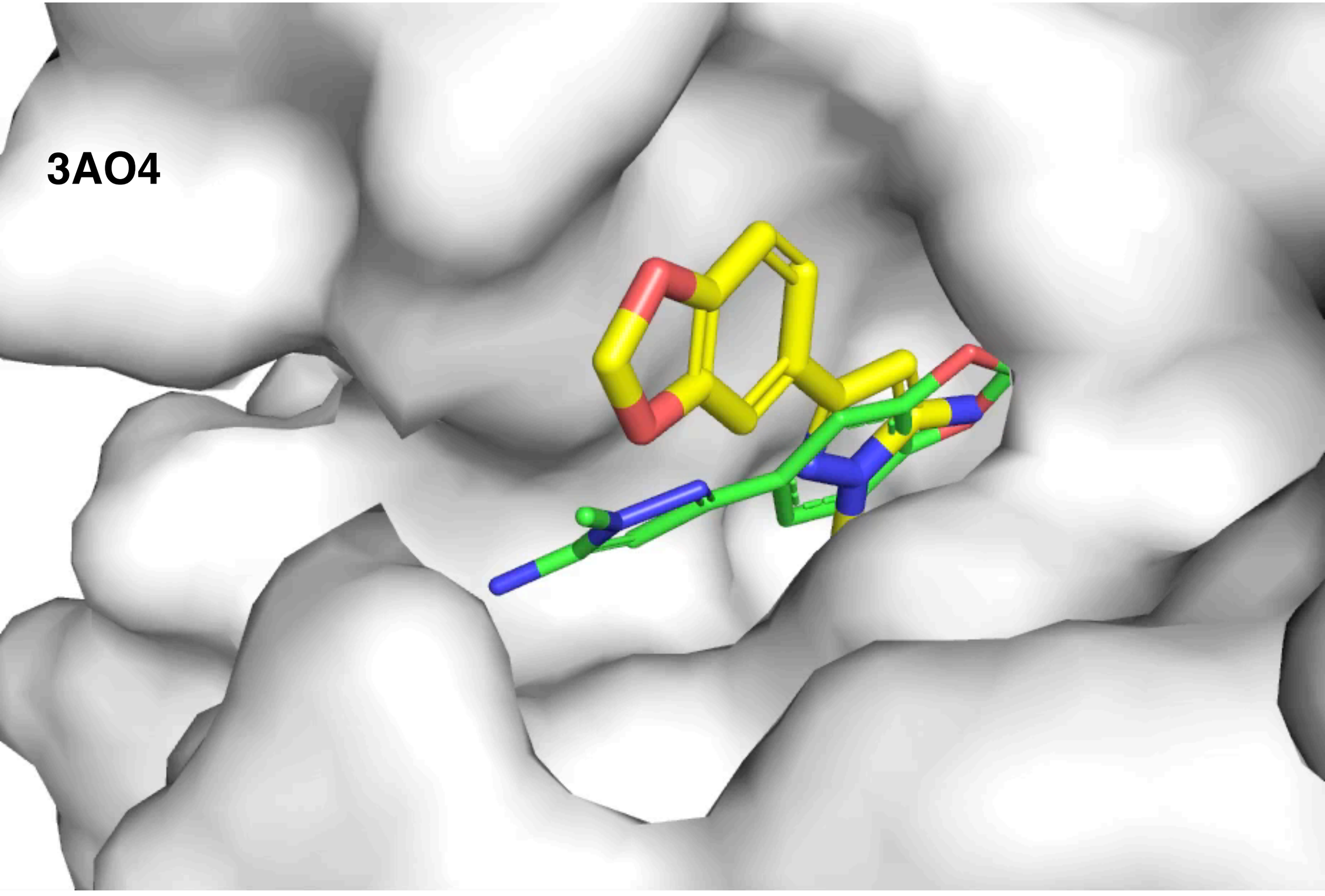
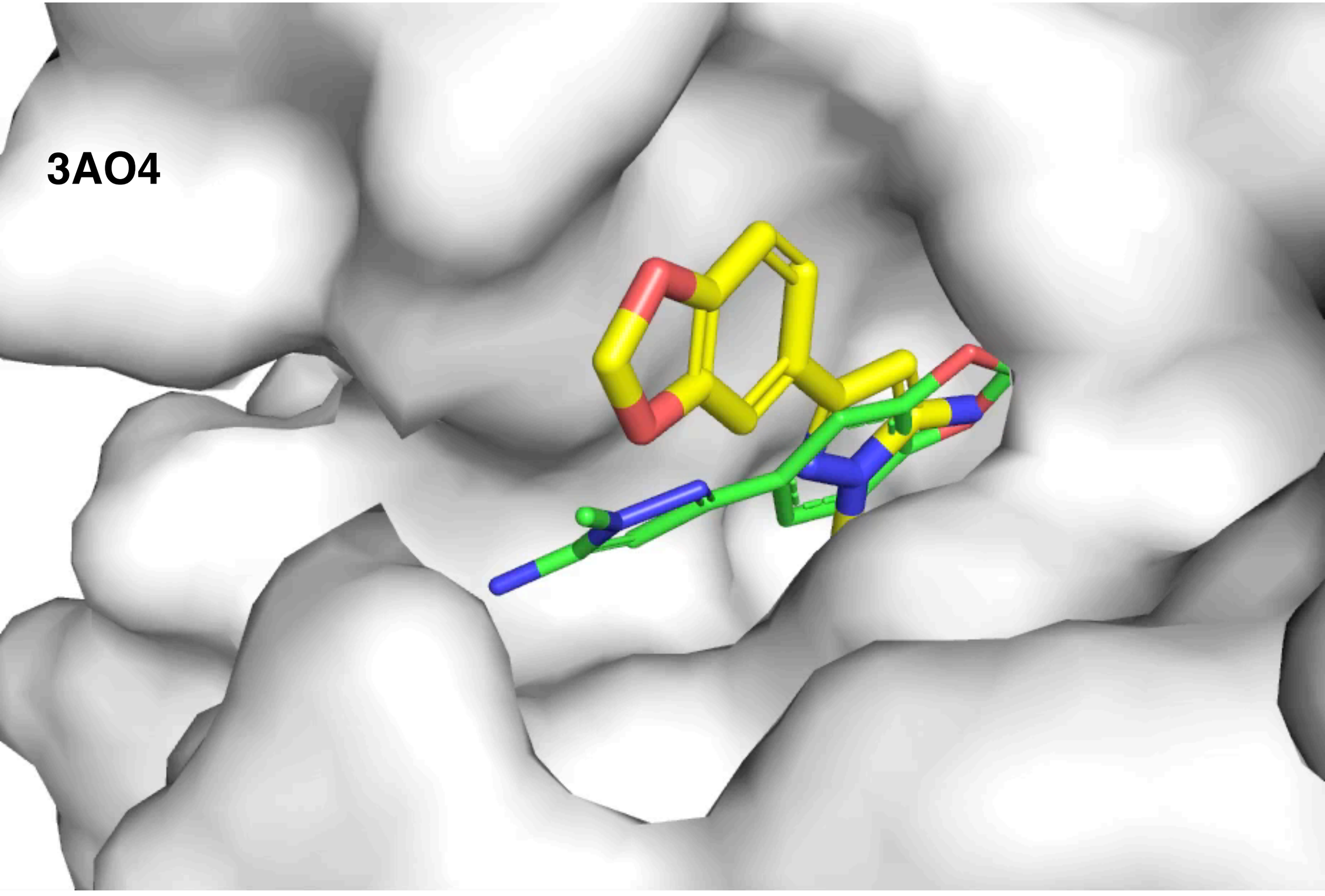


$$\frac{\partial L}{\partial A} = \sum_{i \in G_A} \frac{\partial L}{\partial G_i} \frac{\partial G_i}{\partial D} \frac{\partial D}{\partial A}$$


3AO4


3AO4

Key Concepts

Ligand-Based Virtual Screening

Identifying new active compounds based on similarity to known active compounds; fingerprint is a bit vector representation of a molecule

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

Questions

Developing a new drug costs on the order of
a) 1 million b) 10 million c) 100 million d) 1 billion

What does ADMET stand for?

True or False. If two molecules have the same fingerprint, then they are the same.

True or False. If two molecules are the same, they have the same fingerprint.

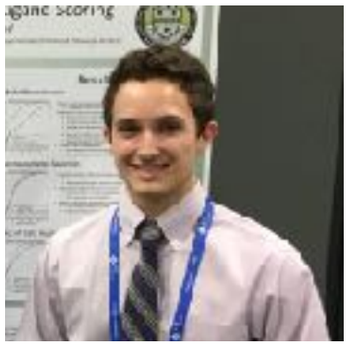
Name three examples of pharmacophore features.

True or False. Similarity search requires a receptor structure.

True or False. Docking requires a receptor structure.

A CNN-based scoring function is
a) physics-based b) empirical c) knowledge-based

Acknowledgements



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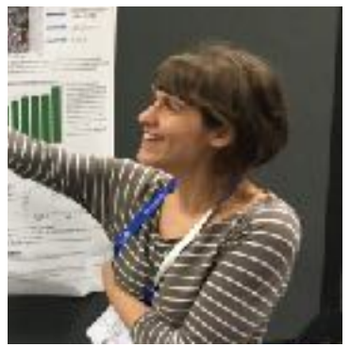

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