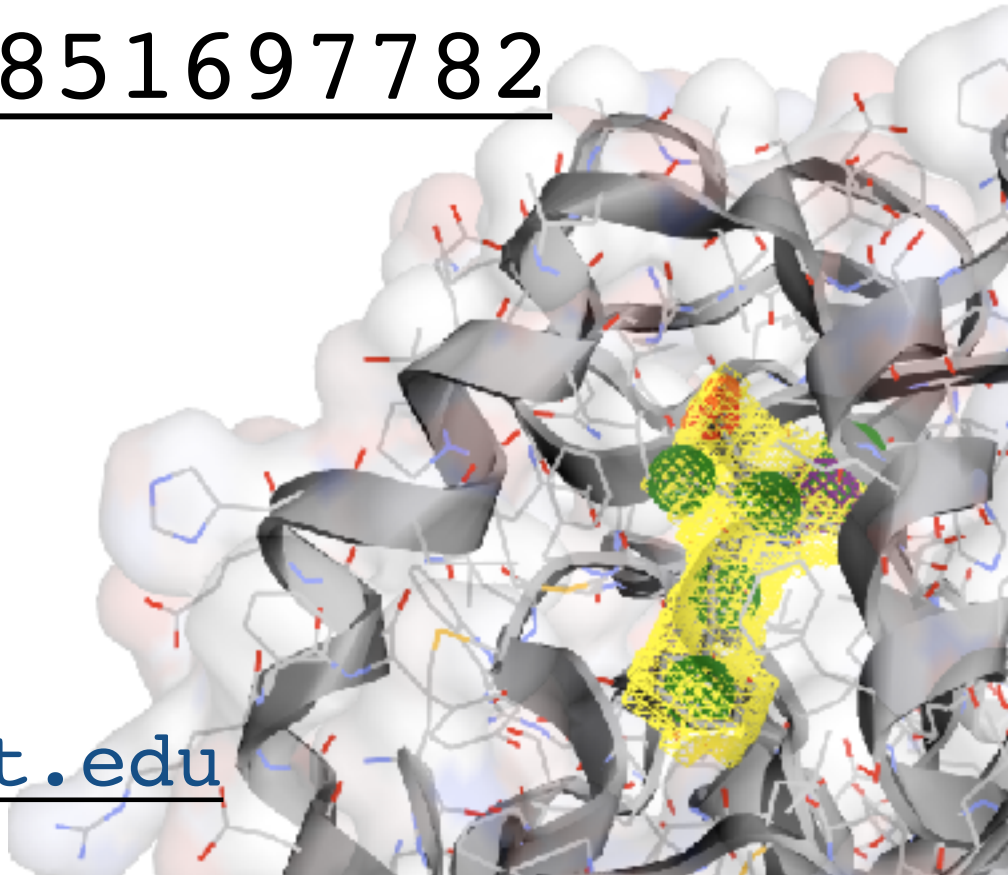
Computational Drug Discovery

David Ryan Koes

4/13/2020

https://zoom.us/j/91851697782



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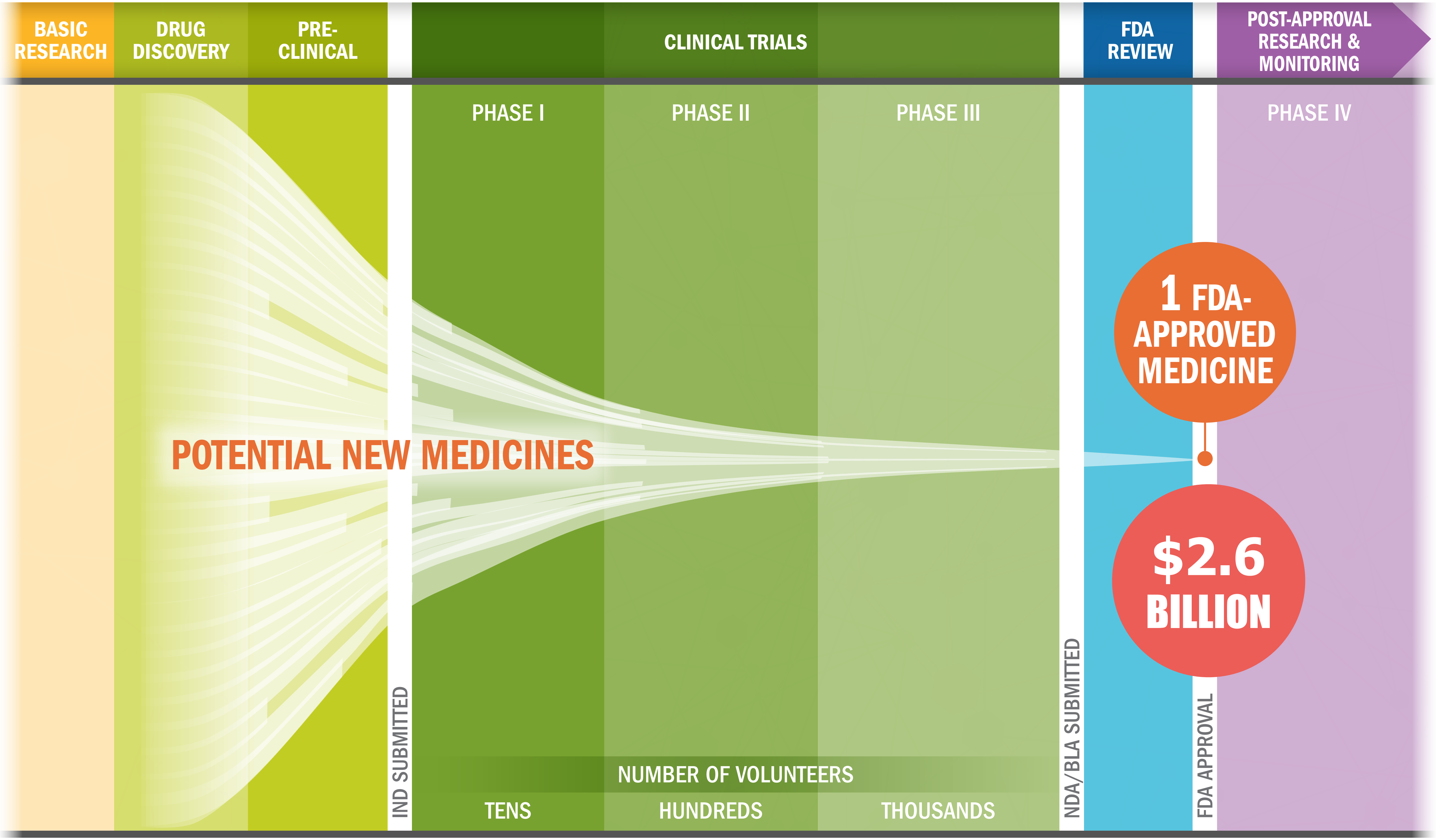
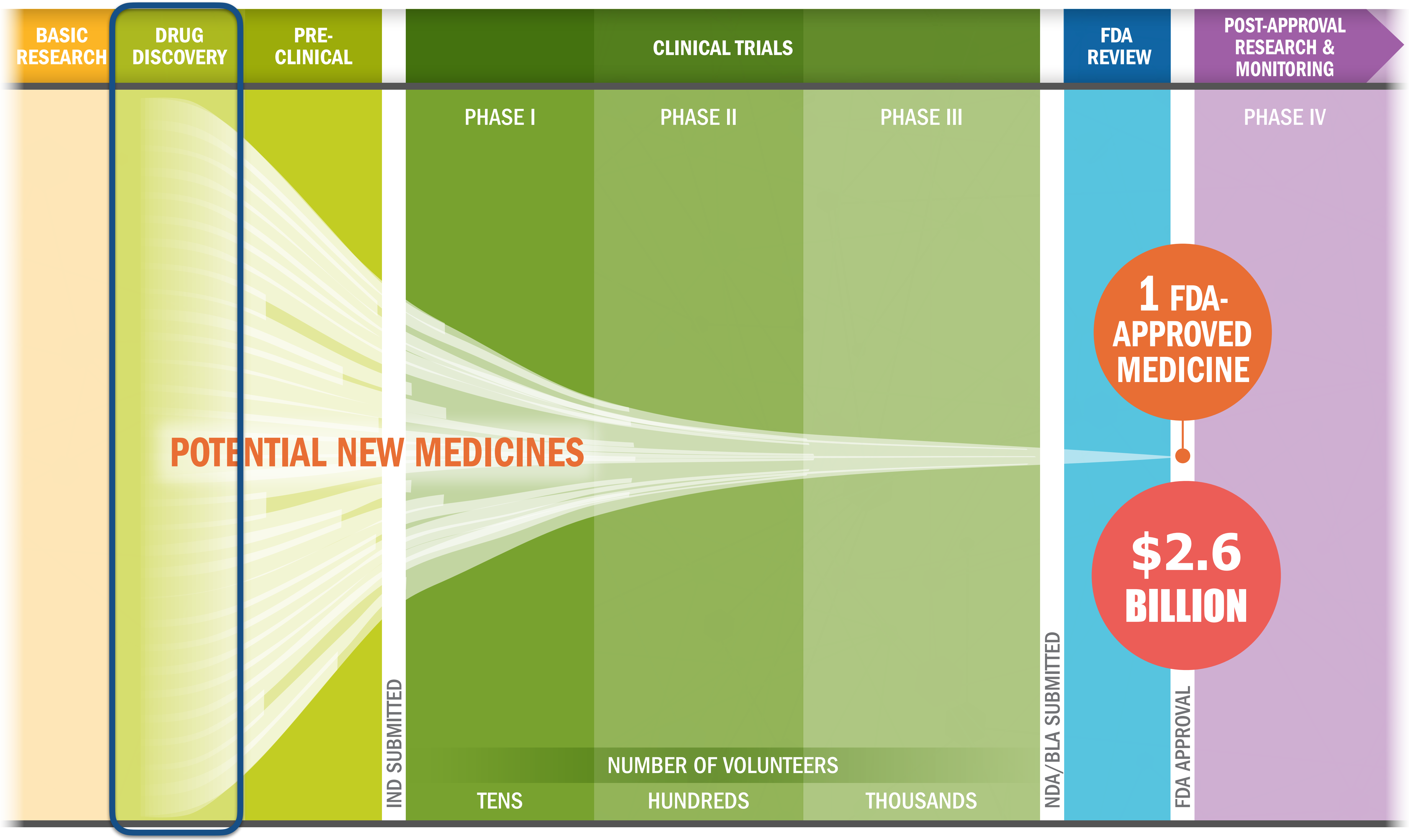
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



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

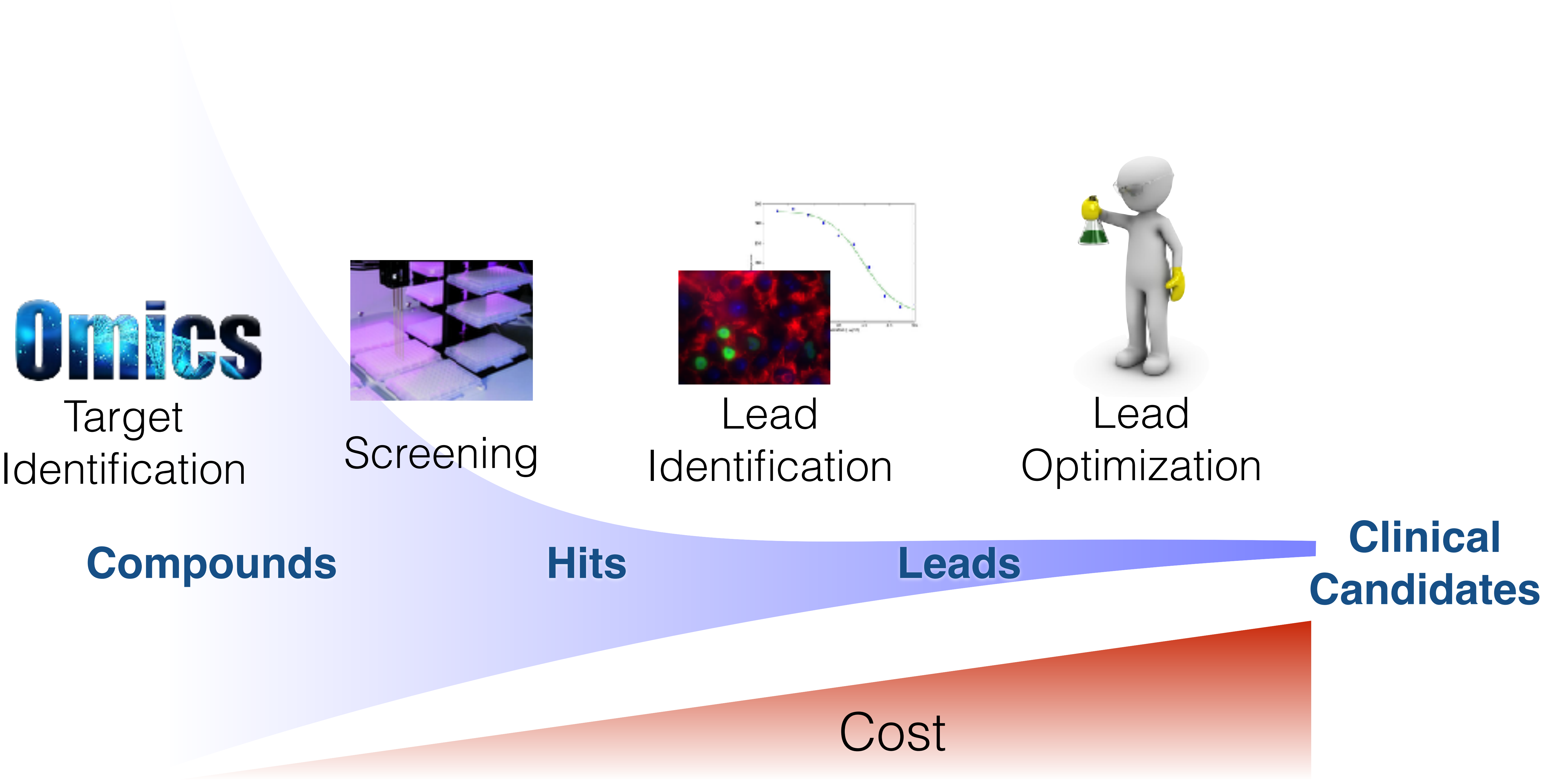
THE BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT PROCESS



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

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

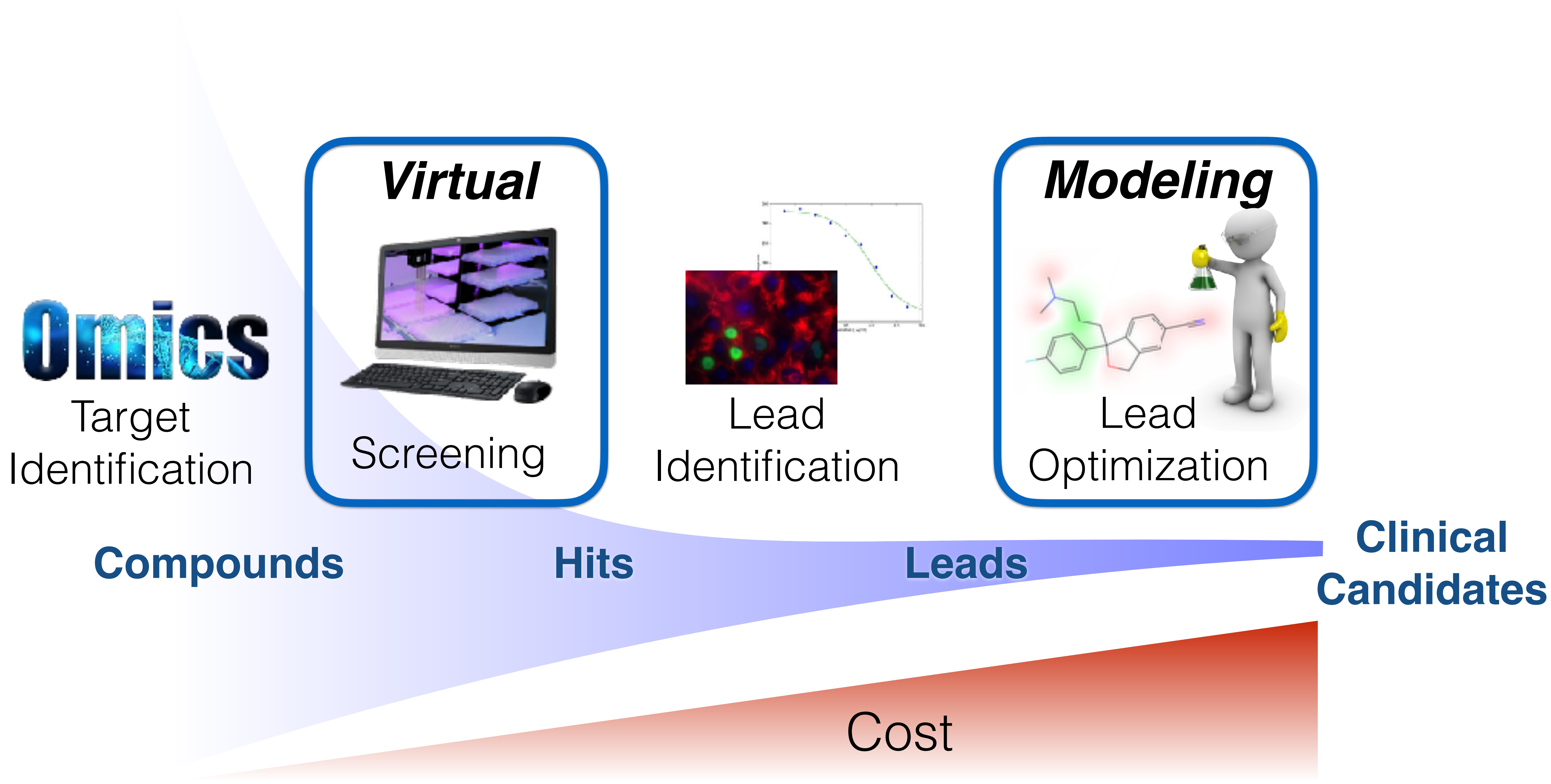
Hits

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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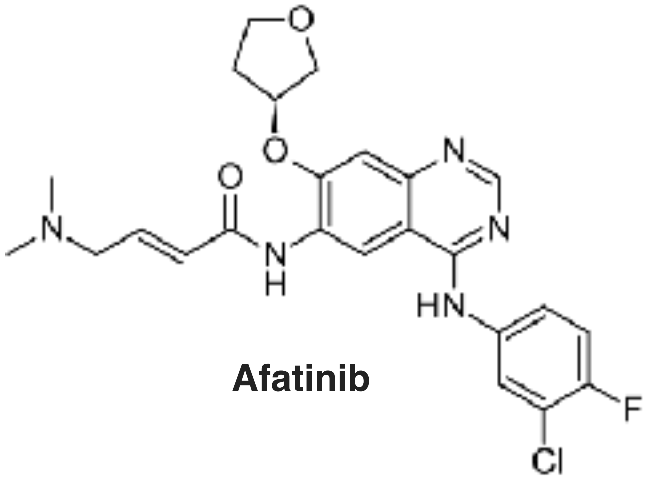
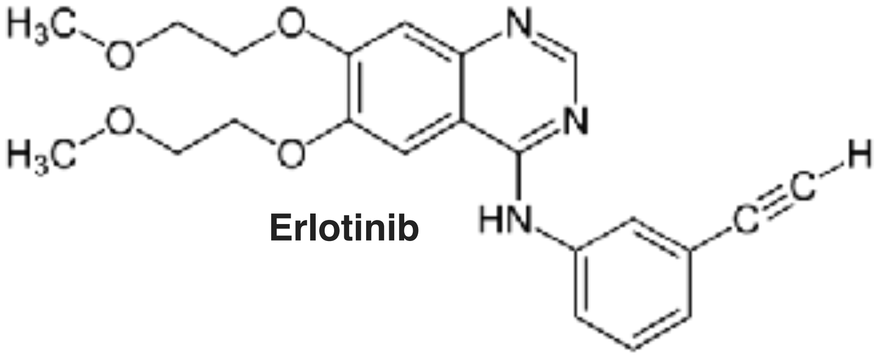
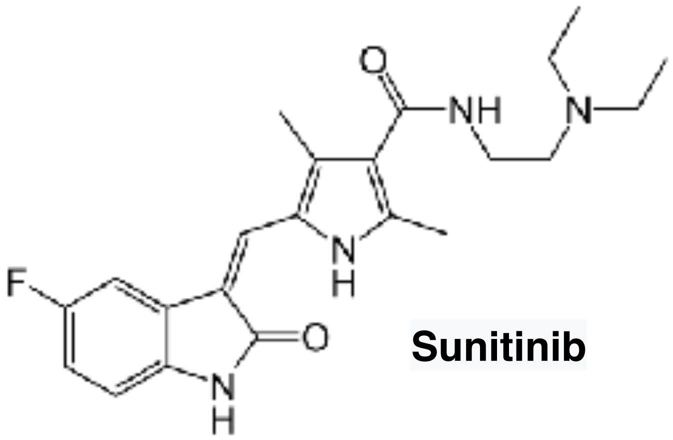
- dock and score



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

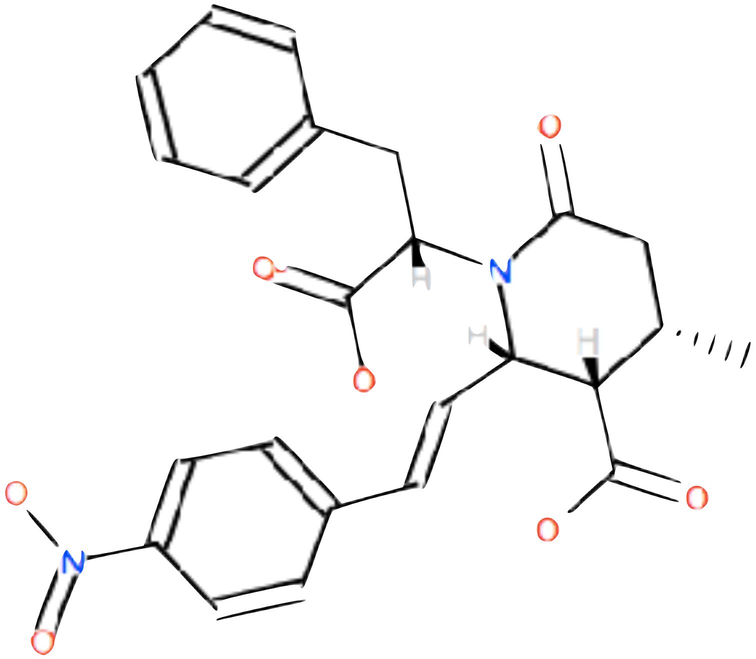
- similarity is “distance” between descriptors
- for bit vectors, Tanimoto distance used

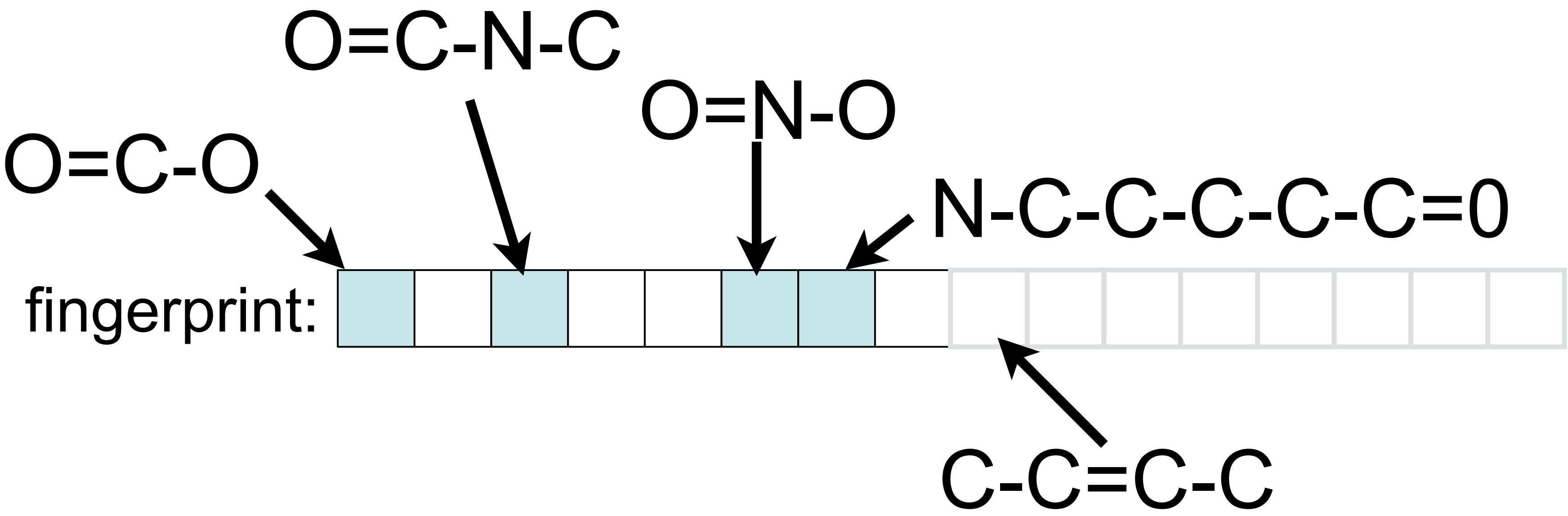
$$T(A,B) = \frac{|A \cap B|}{|A \cup B|}$$

Topological Fingerprints

Daylight/FP2 Fingerprints

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





O=C-N-C

O=N-O

O=C-O

N-C-C-C-C-C=0

fingerprint:

C-C=C-C

Topological Fingerprints

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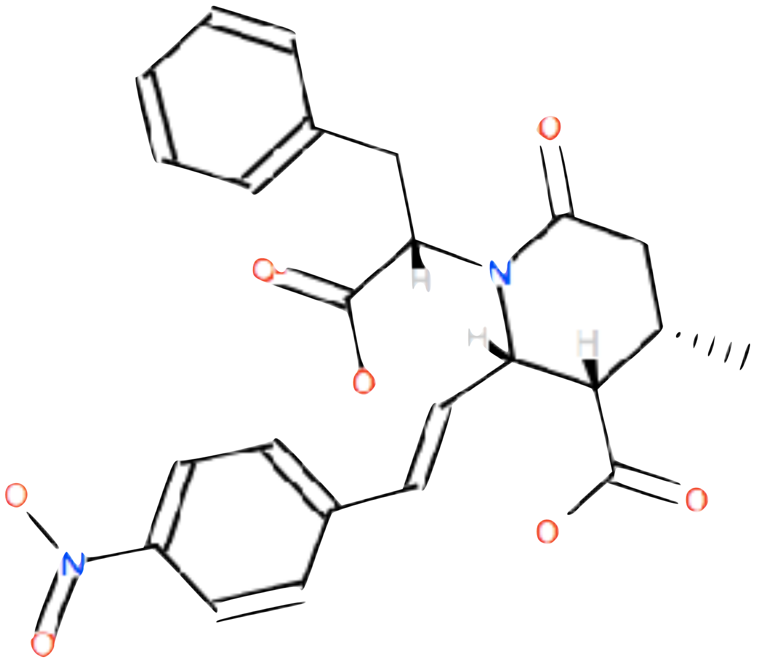
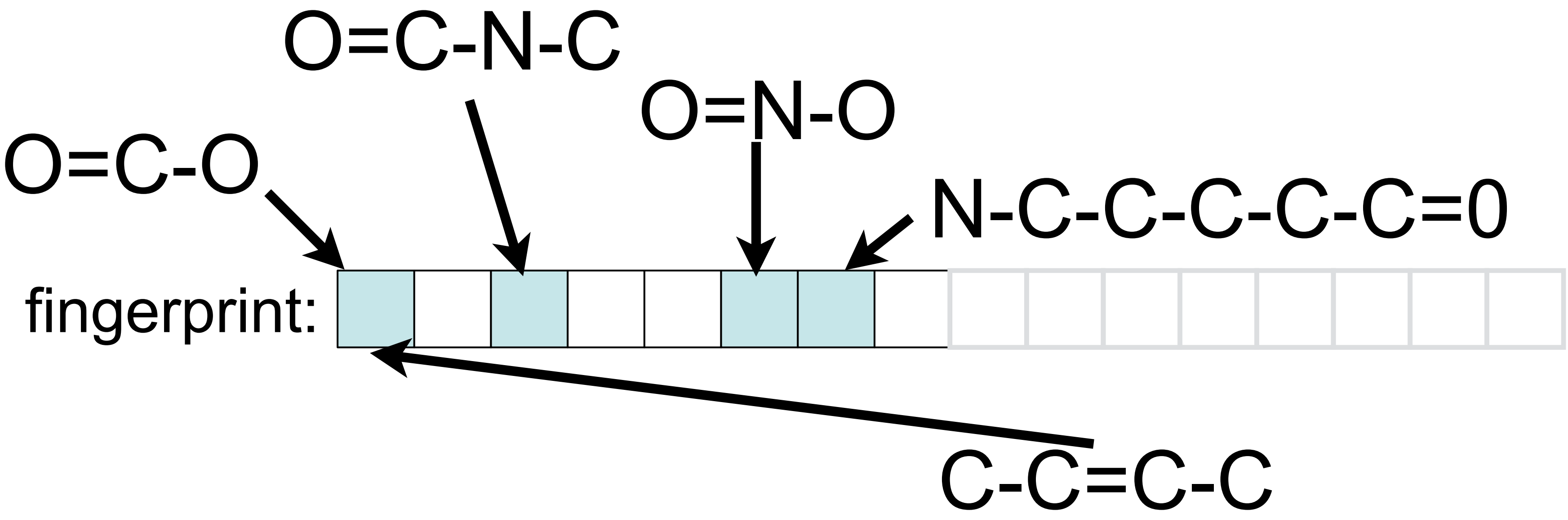




O=C-N-C

O=N-O

O=C-O

N-C-C-C-C-C=0

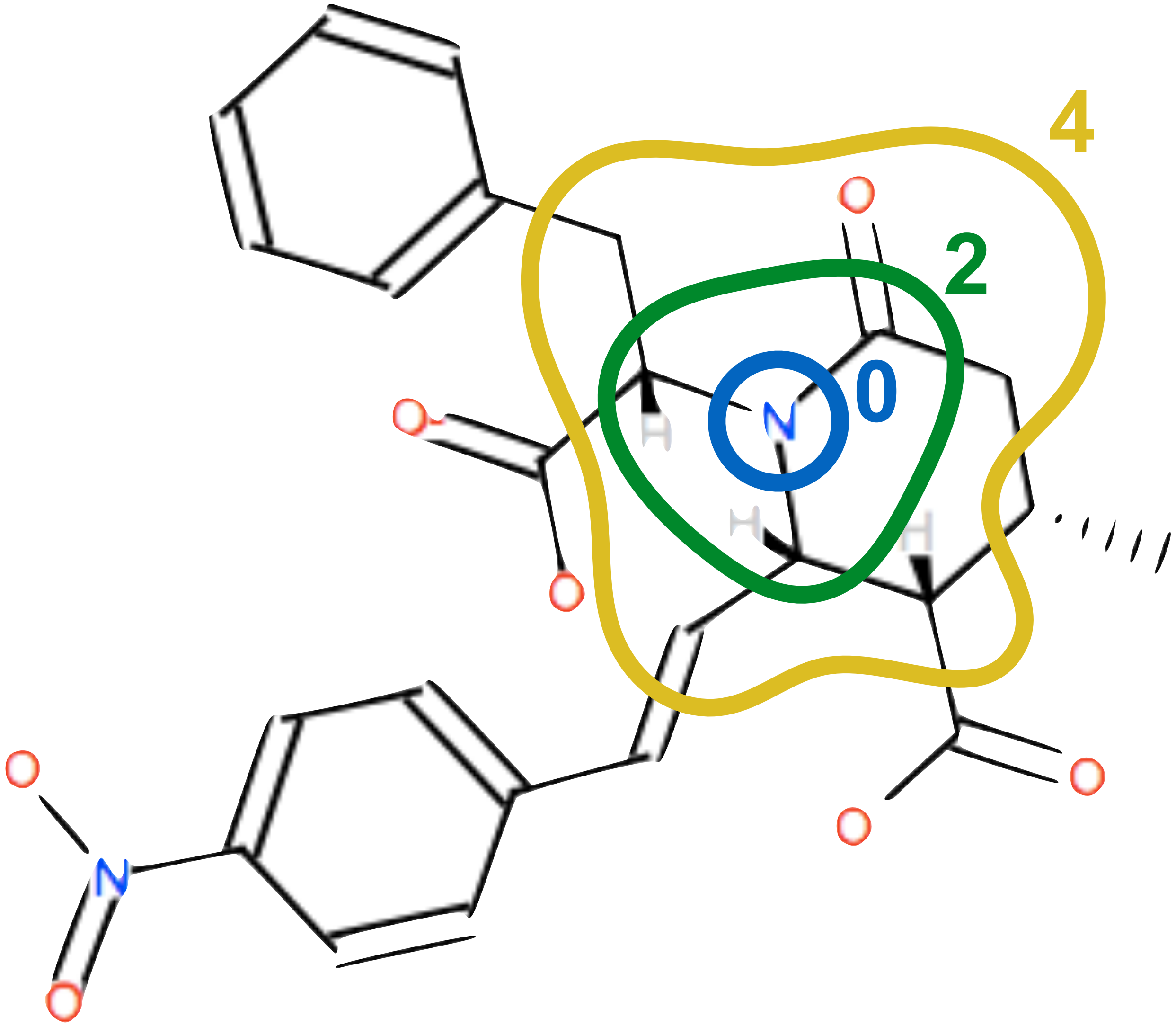
fingerprint:

C-C=C-C

Topological Fingerprints

ECFP4

- all substructures with diameter 4 around every atom



Ligand Based: QSAR

Quantitative Structure/Activity Relationships

Properties

Compounds

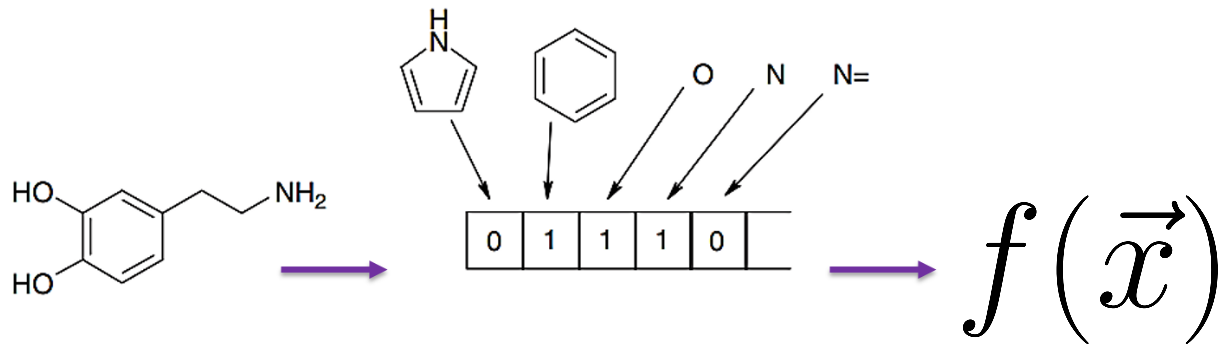
Cmpd Number	Cmpd Name	X	Log EC_{50}	π	Calculated Log EC_{50}	Residual
1	6a	H	1.07	0	0.79	0.28
2	6b	Cl	0.09	0.71	0.21	-0.12
3	6d	NO_2	0.66	-0.28	1.02	-0.36
4	6e	CN	1.42	-0.57	1.26	0.16
5	6f	C_6H_5	-0.62	1.96	-0.81	0.19
6	6g	$N(CH_3)_2$	0.64	0.18	0.65	-0.01
7	6h	I	-0.46	1.12	-0.12	-0.34

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

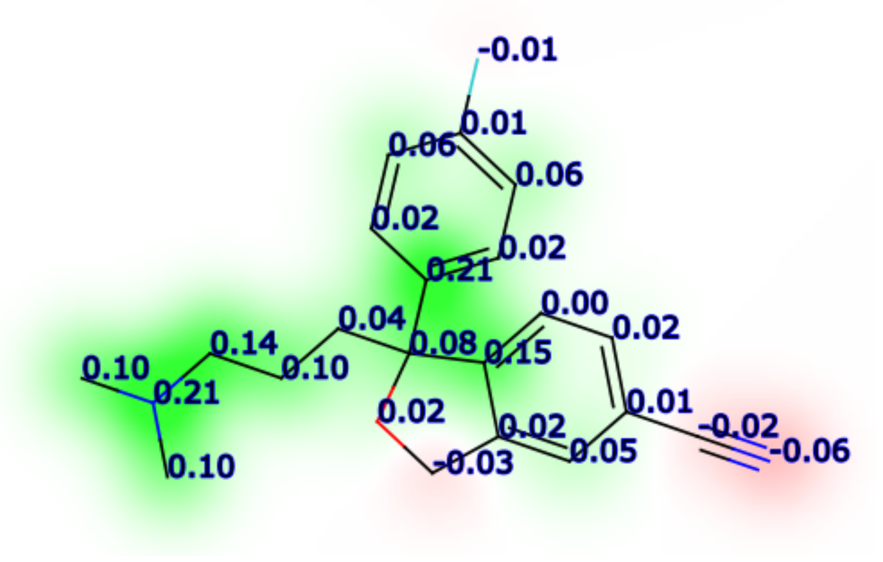
3D-QSAR: includes geometric/structural properties

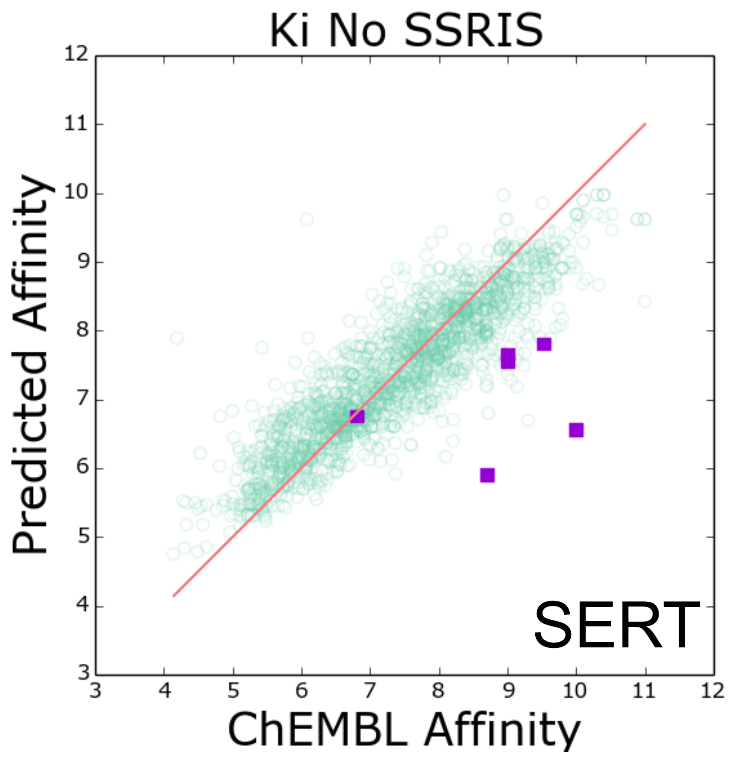
Ligand Based: QSAR

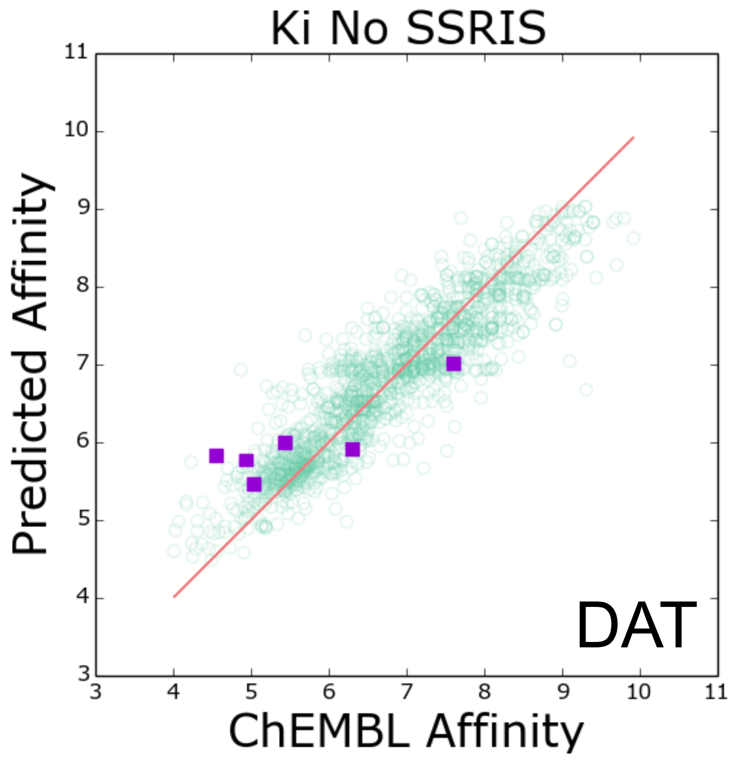
Quantitative Structure/Activity Relationships



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



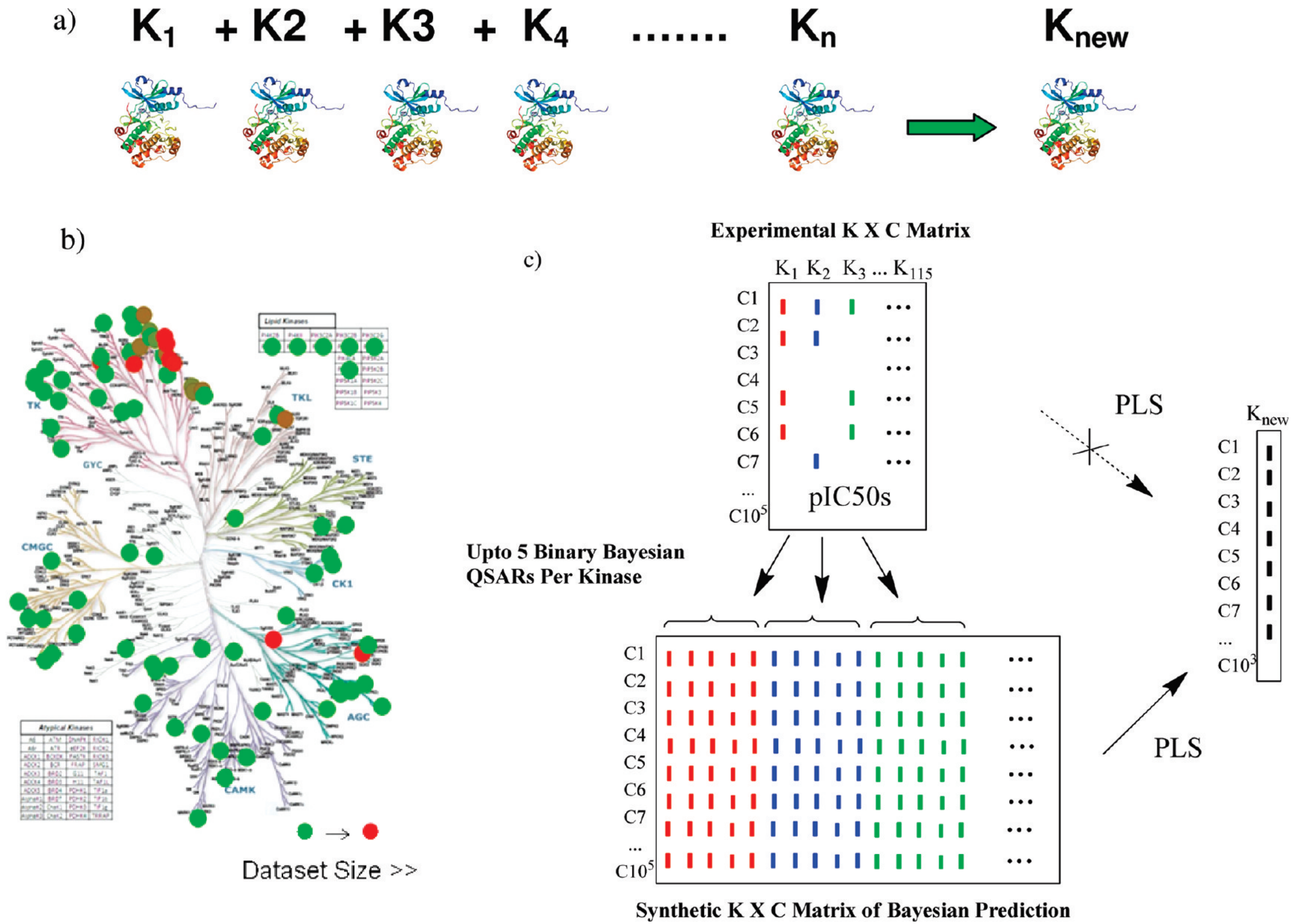




meta-QSAR

Profile-QSAR: A Novel *meta*-QSAR Method that Combines Activities across the Kinase Family To Accurately Predict Affinity, Selectivity, and Cellular Activity

Eric Martin,* Prasenjit Mukherjee, David Sullivan,† and Johanna Jansen



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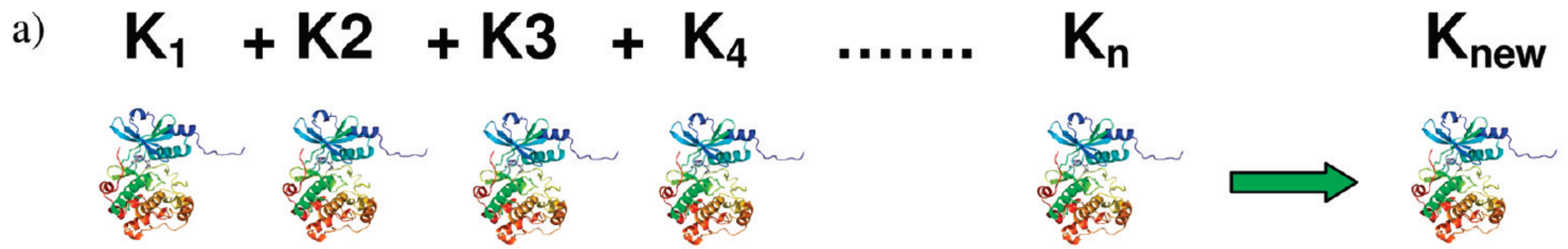
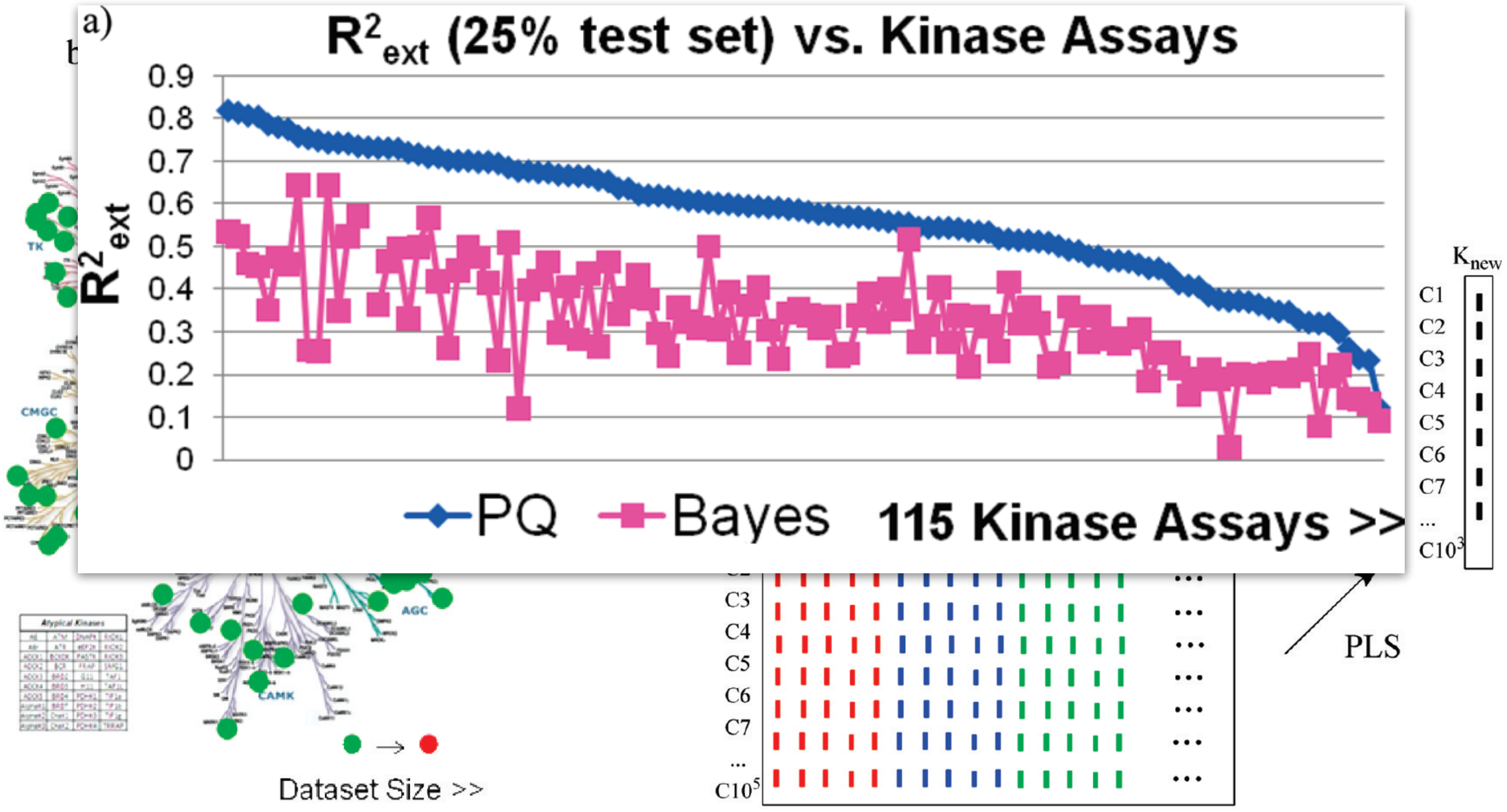


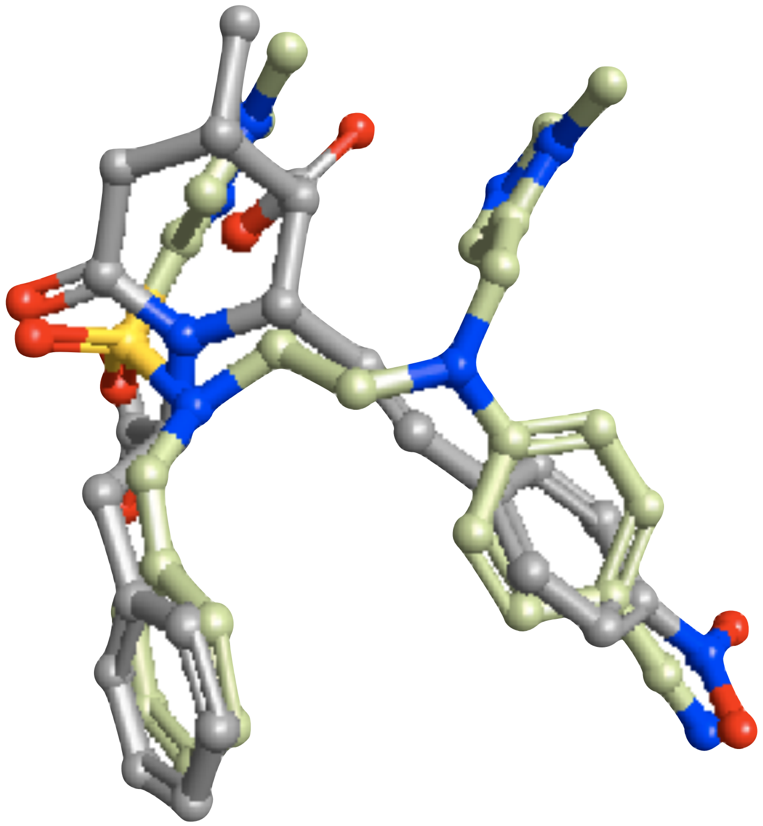


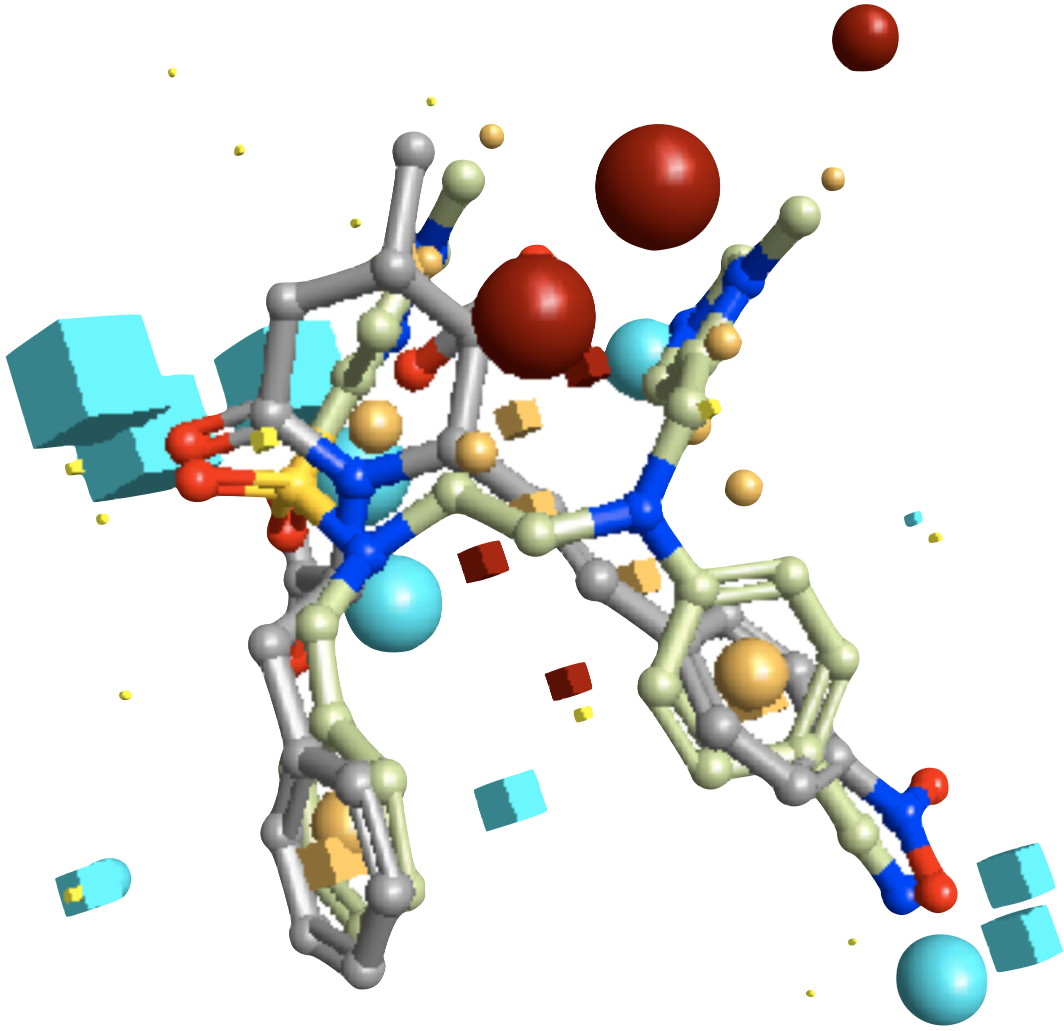
Synthetic K X C Matrix of Bayesian Prediction

Ligand Based: Similarity

Superposition Methods

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





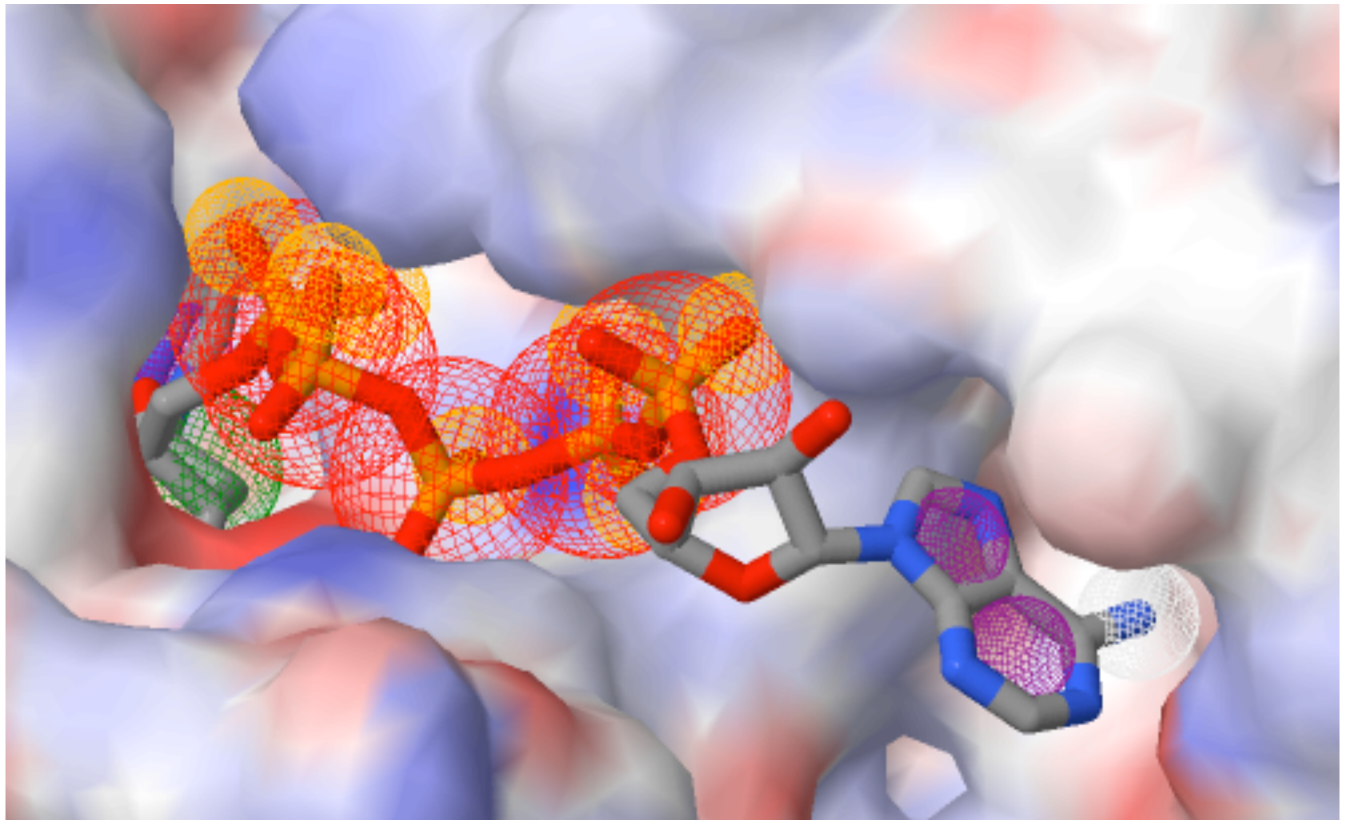
http://www.cresset-group.com/

Ligand/Receptor Based: Pharmacophore

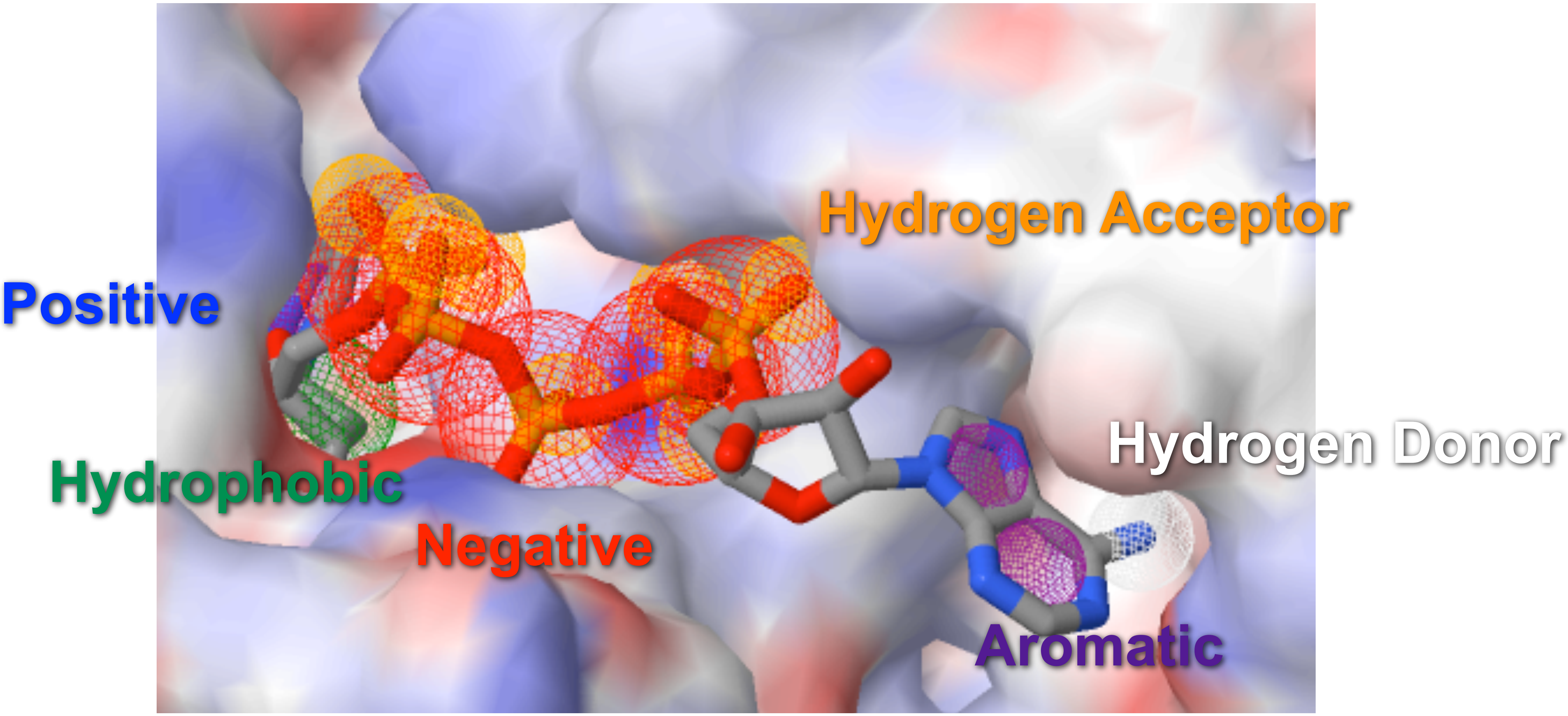
Pharmacophore:

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.

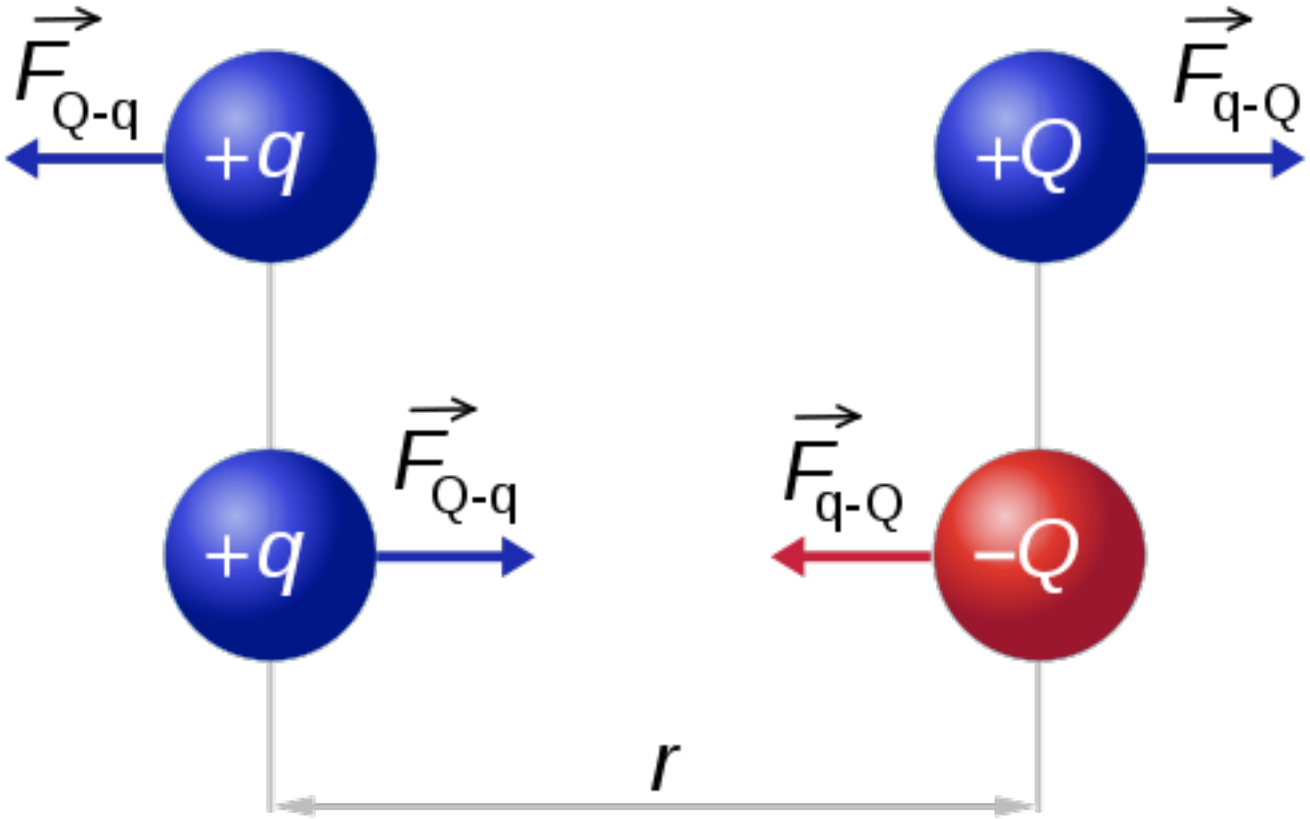
Common Features:
aromatic ring
hydrophobic area
positive ionizable
negative ionizable
hydrogen bond donor
hydrogen bond acceptor



Pharmacophore Features

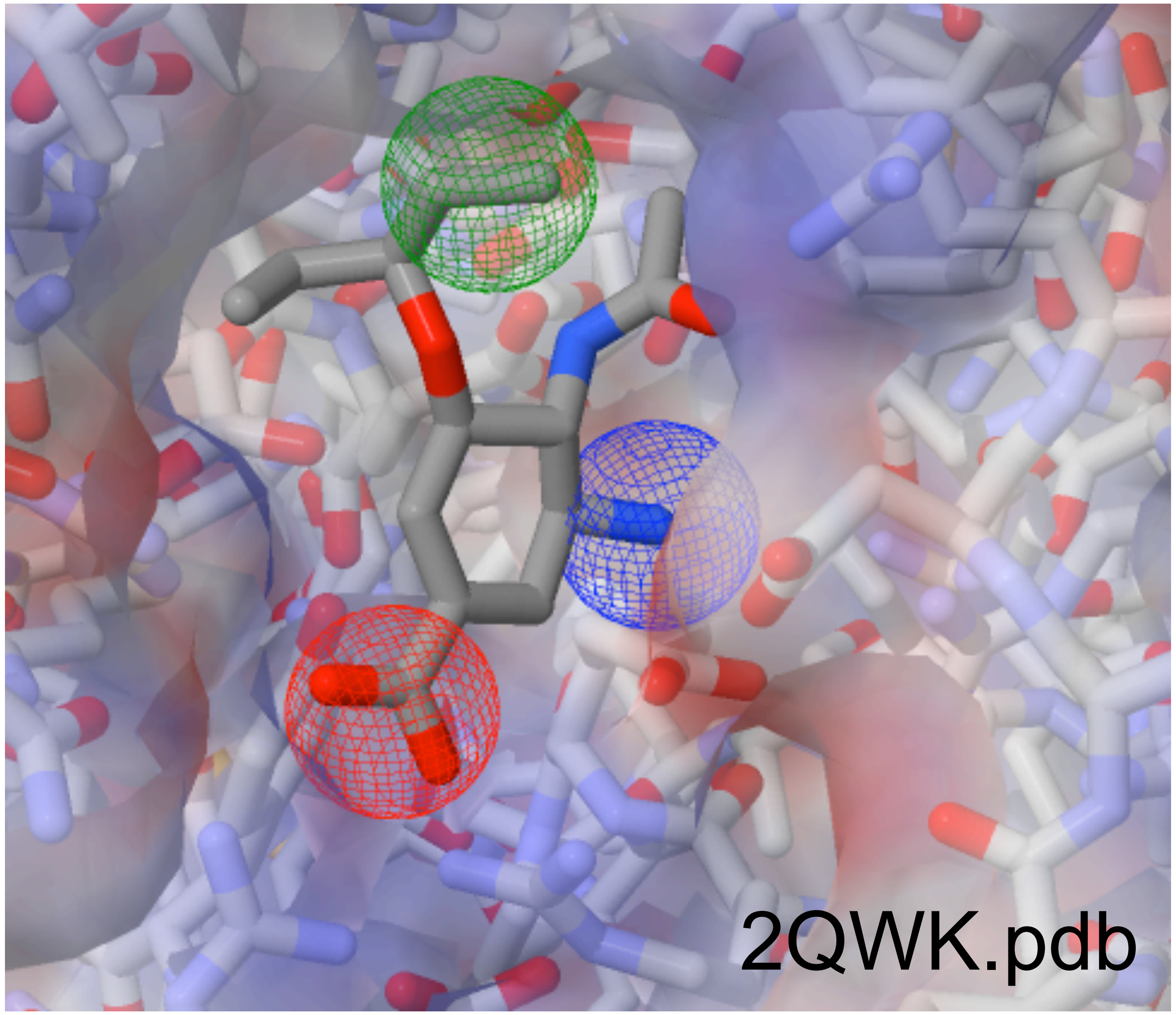


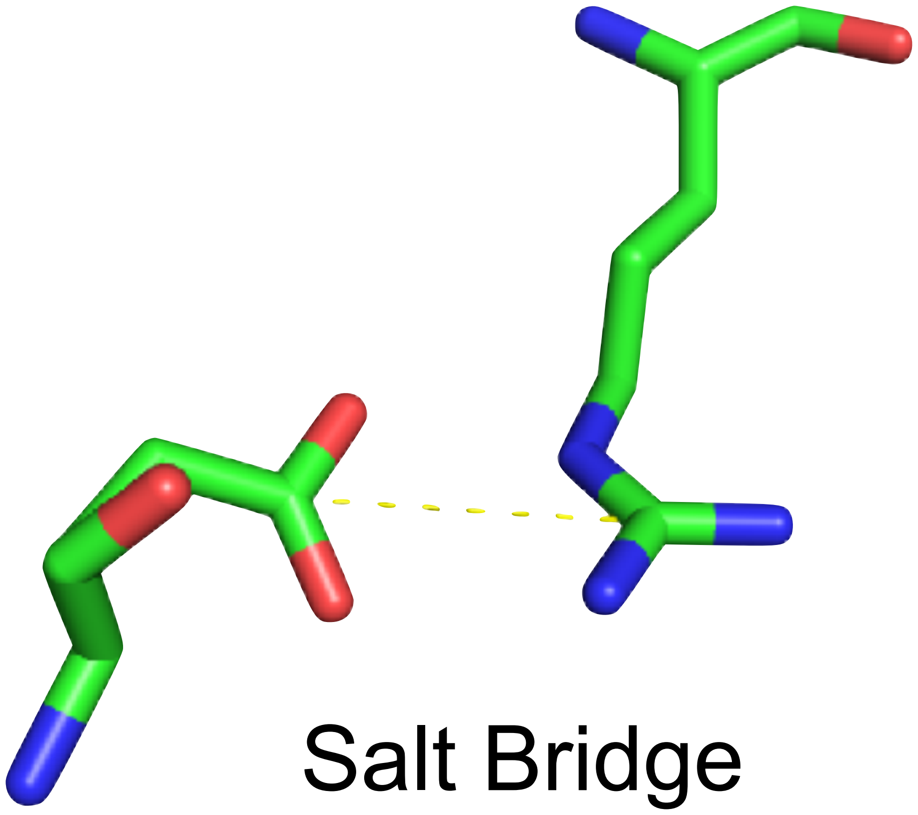
Charge-Charge



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

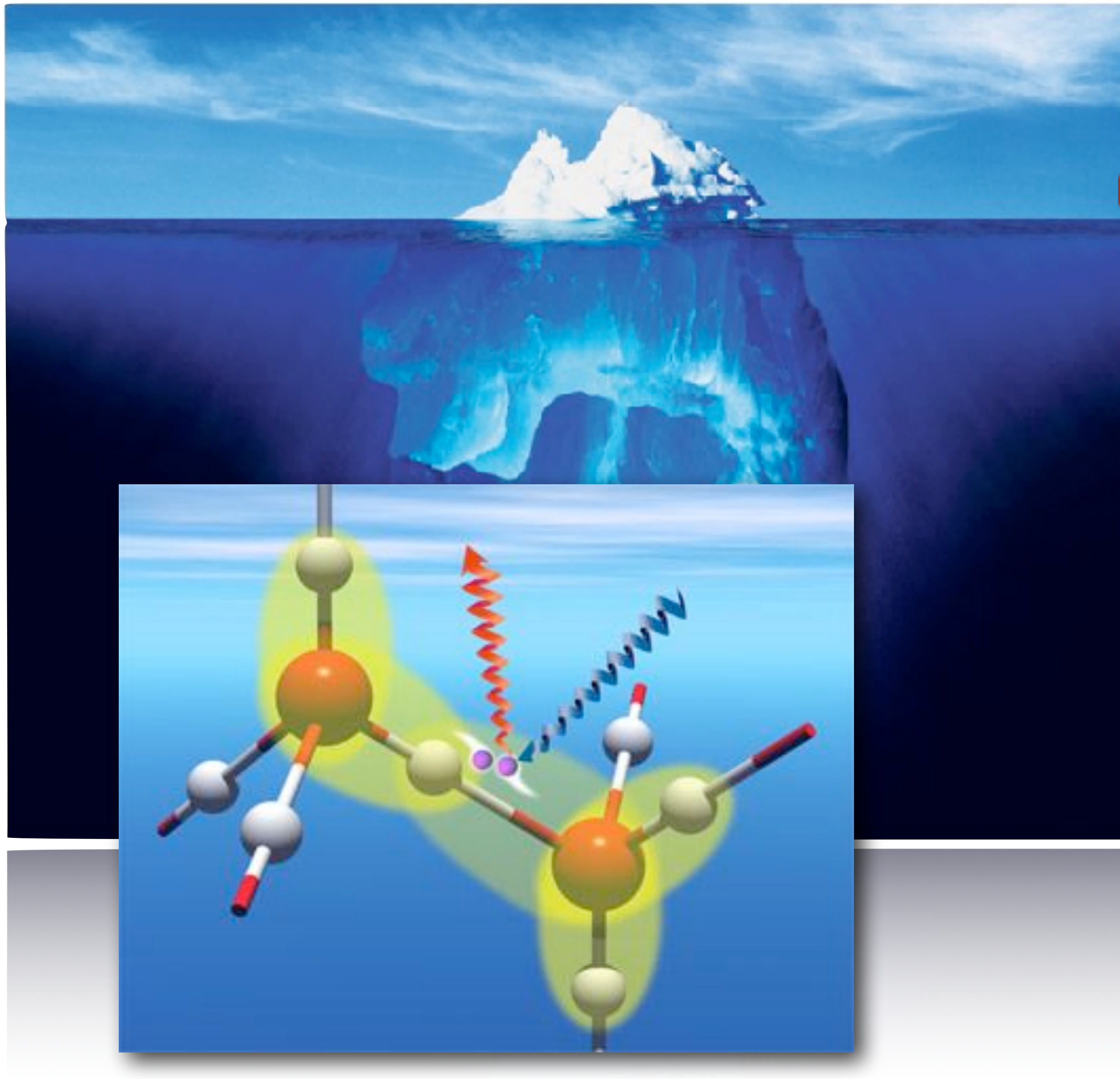
Charge-Charge

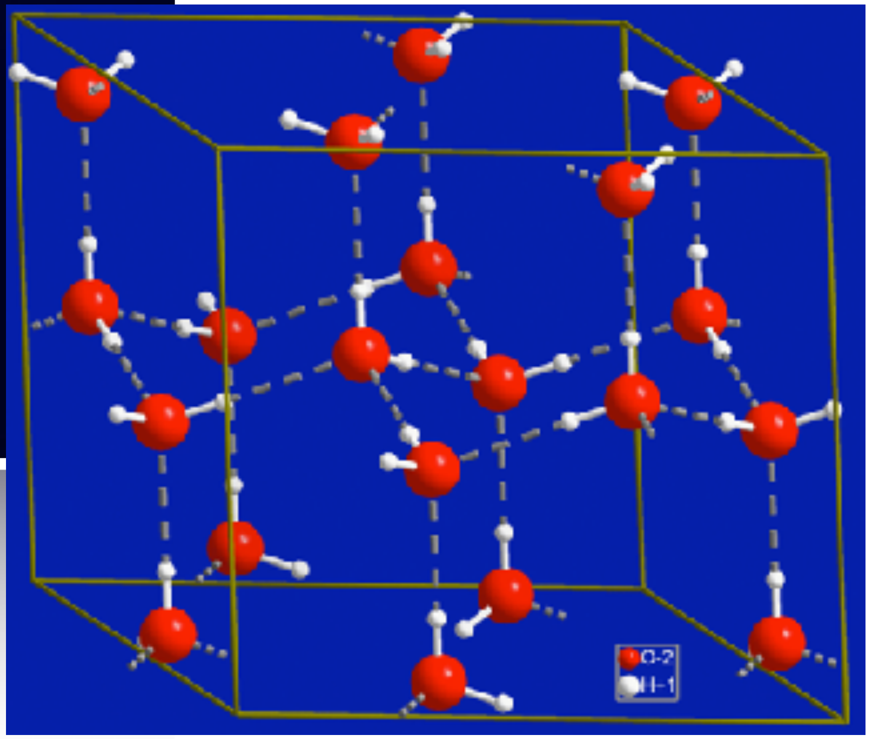




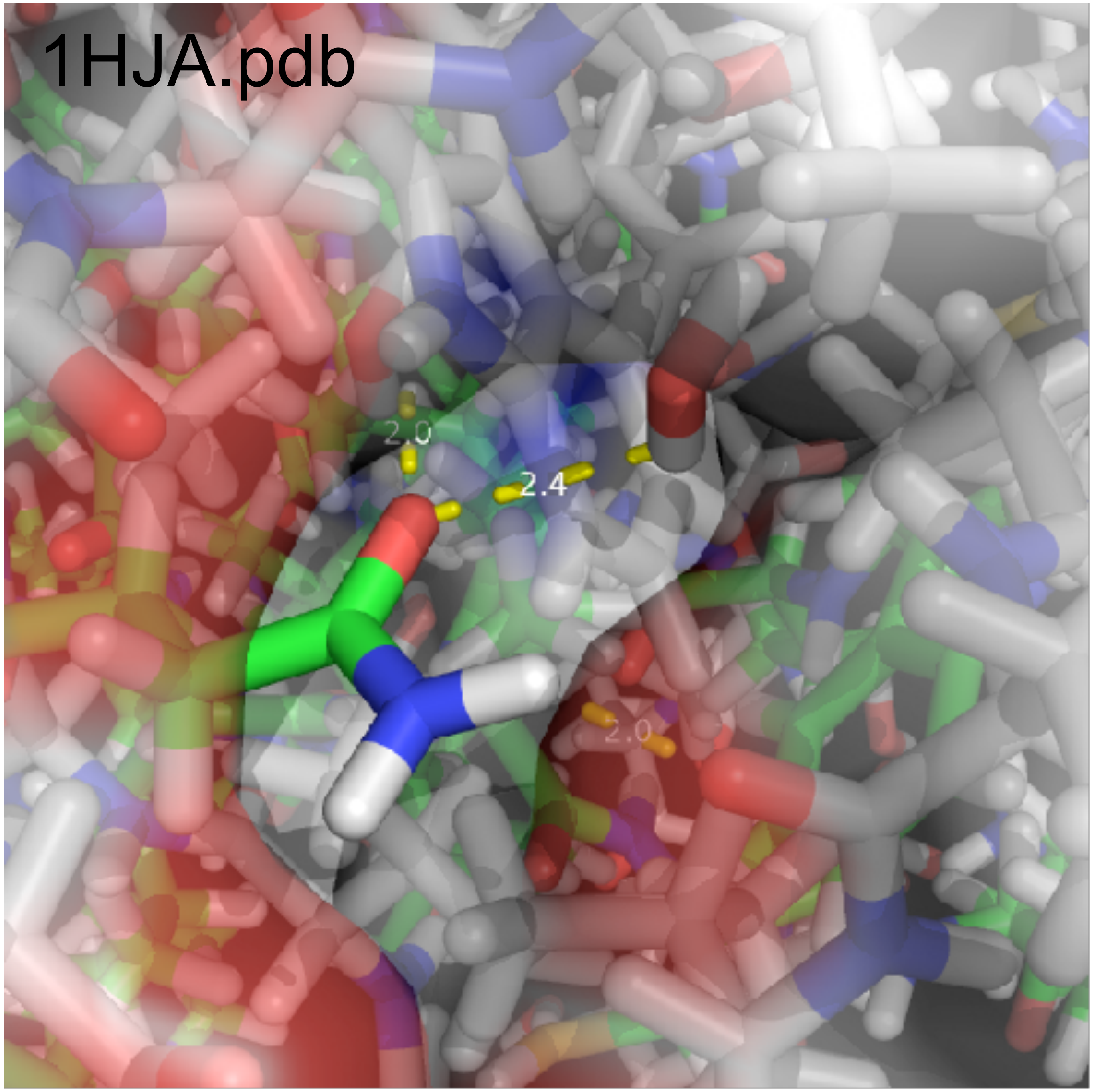
Inhibitor of the influenza virus neuraminidase (antiviral agent)

Hydrogen Bond

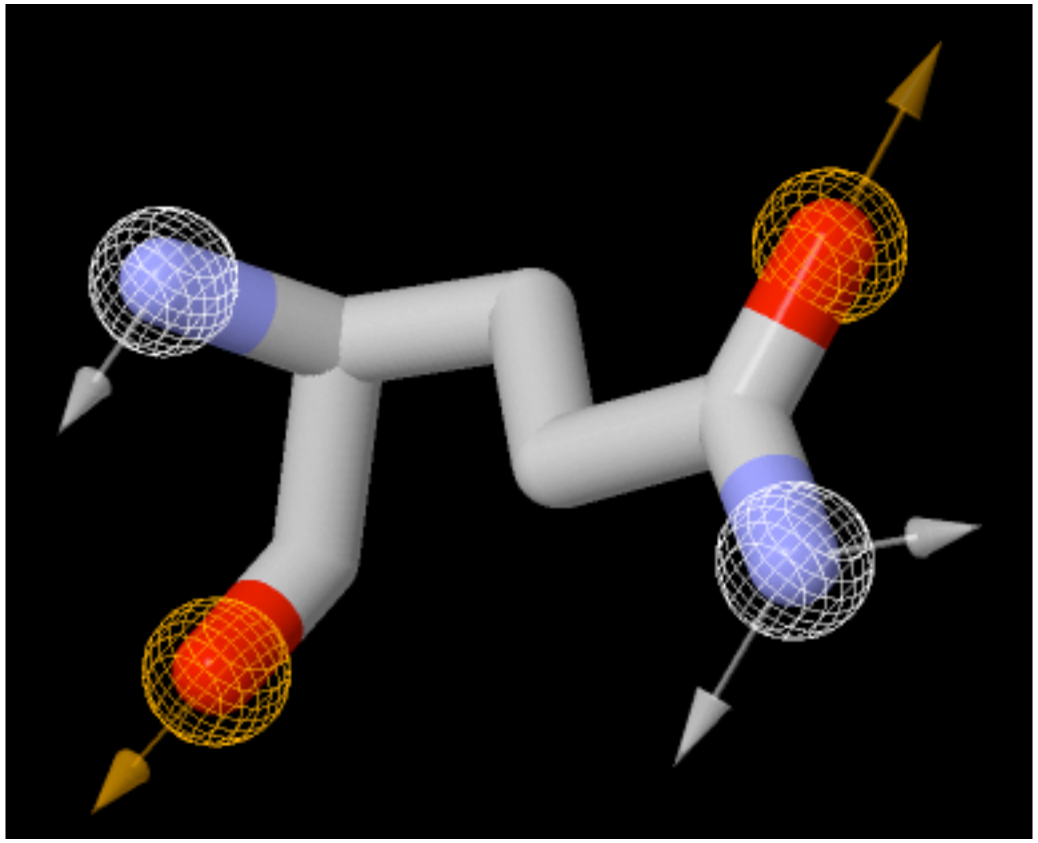




Hydrogen Bond

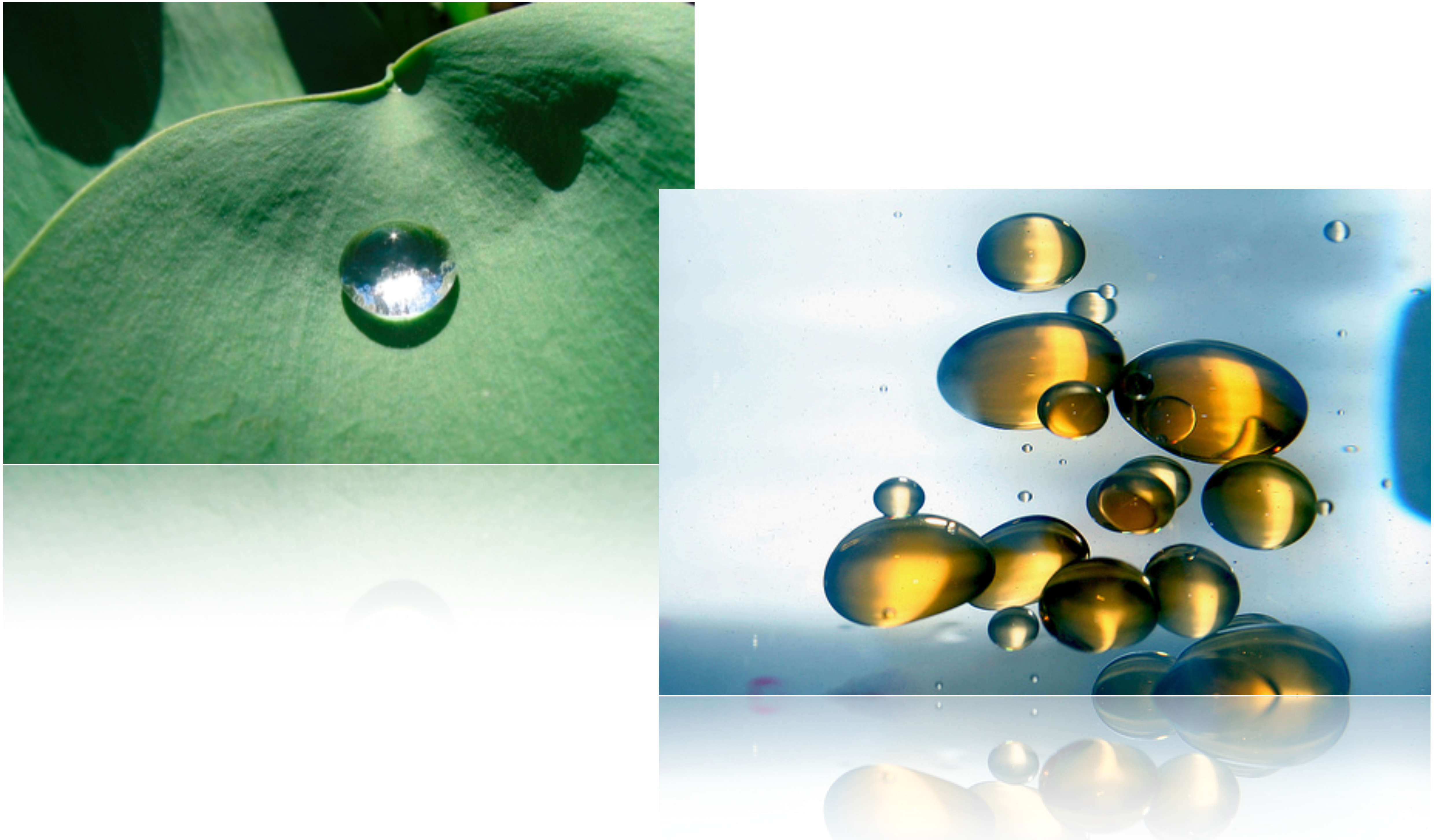


Distance:
D-A: 2.5Å – 3.5Å (4.0Å?)
H-A: 1.5Å – 2.5Å
Angle:
Depends on context

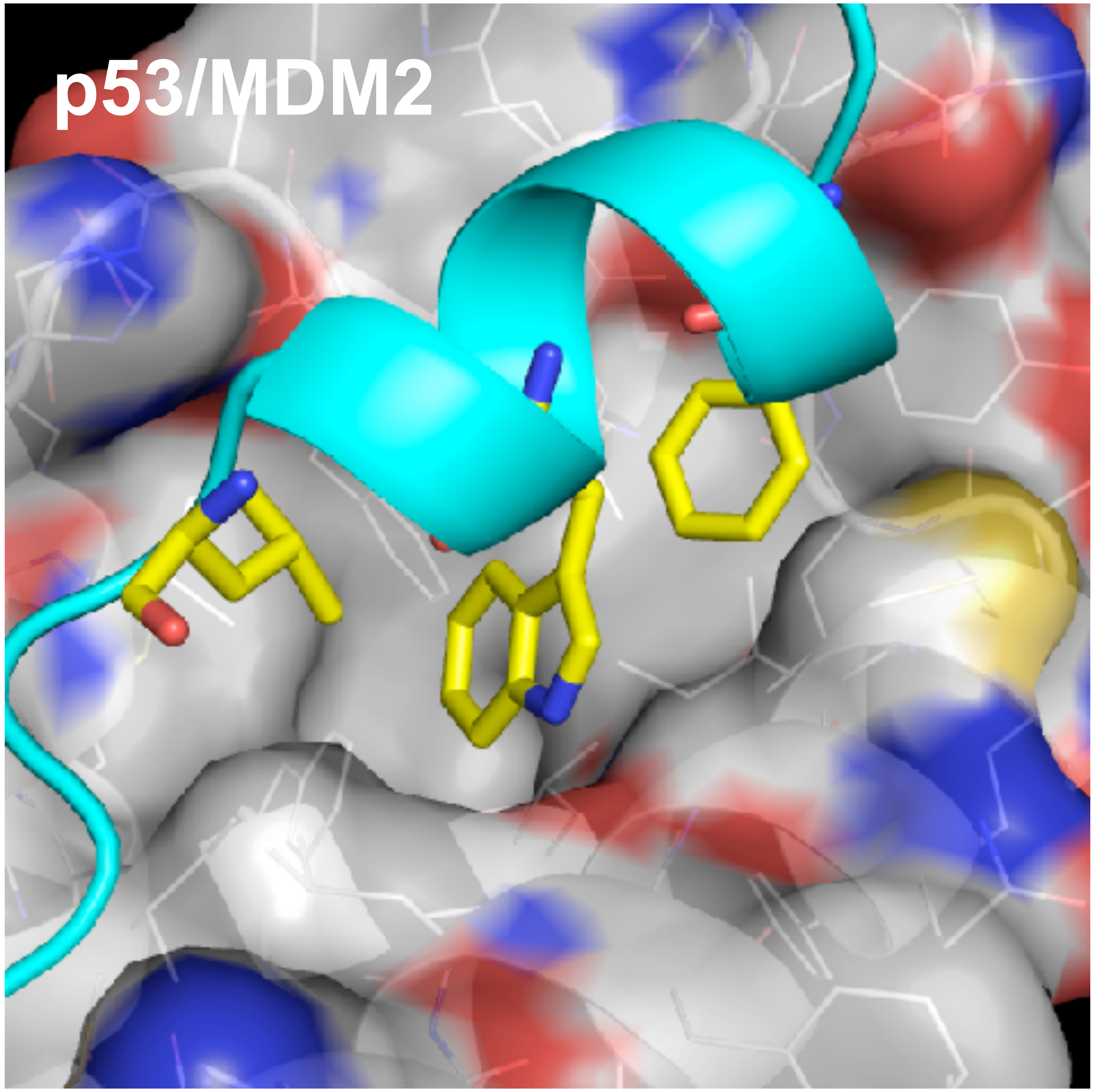


Turkey Ovomucoid Inhibitor

Hydrophobic

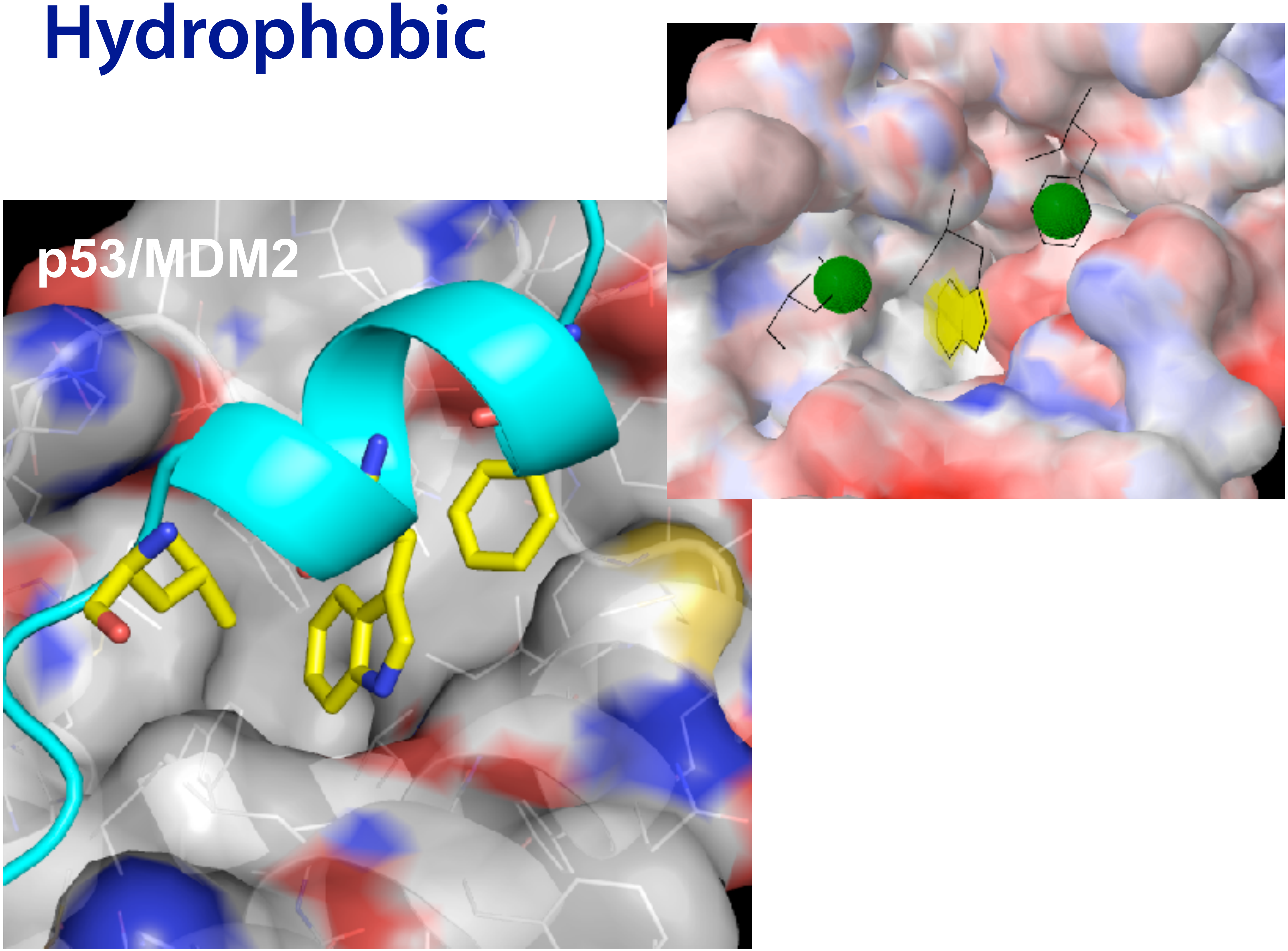


Hydrophobic



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

Hydrophobic



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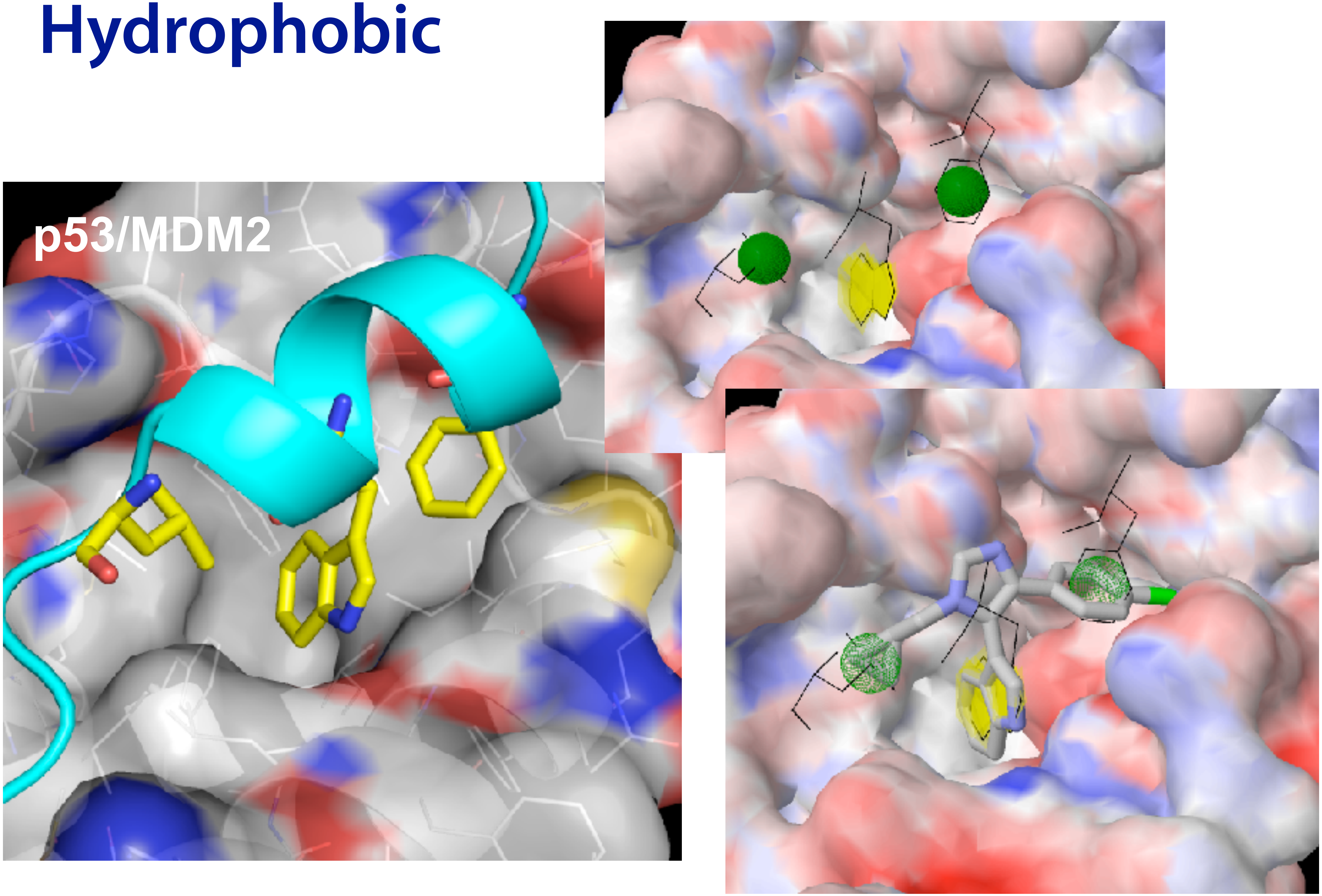
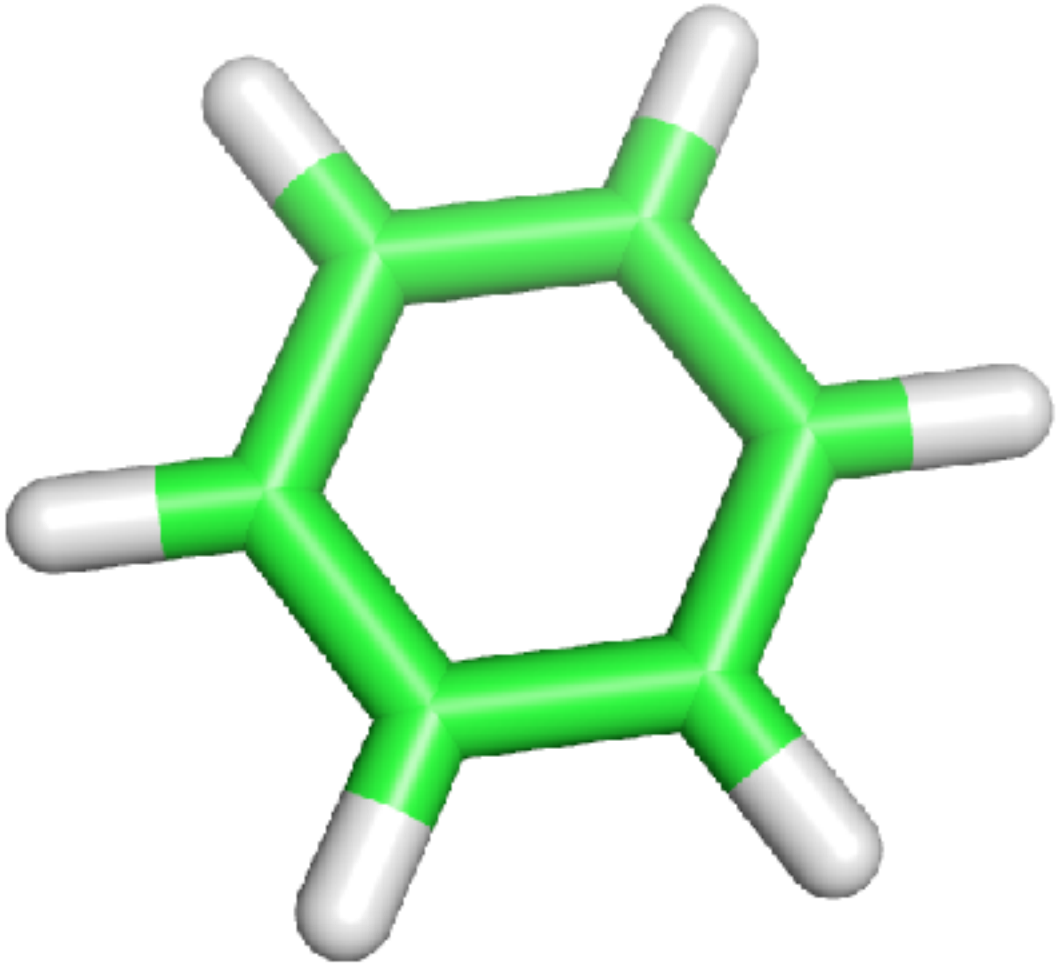
Hydrophobic



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

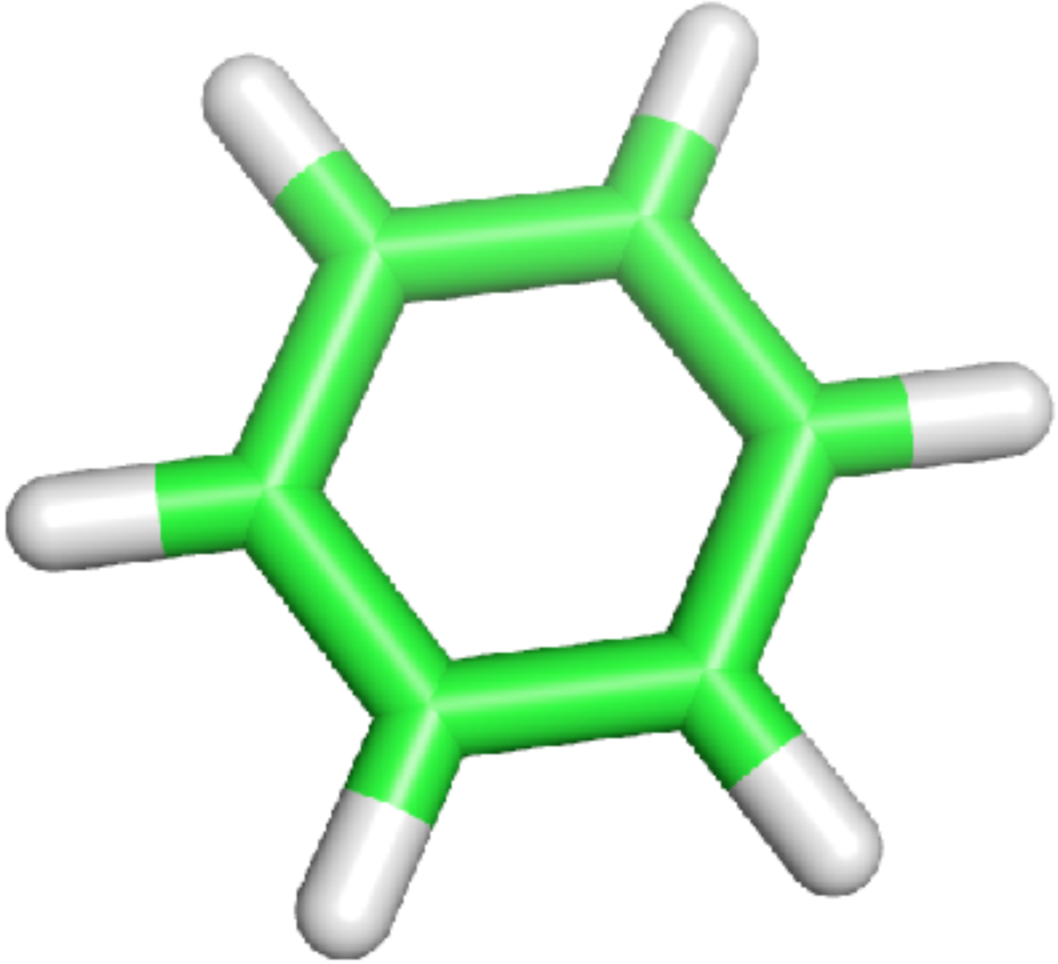
Aromatic



					2 2 **He** Helium 4.002602
5 2 3 **B** Boron 10.811	6 2 4 **C** Carbon 12.0107	7 2 5 **N** Nitrogen 14.0067	8 2 6 **O** Oxygen 15.9994	9 2 7 **F** Fluorine 18.9984032	10 2 8 **Ne** Neon 20.1797
13 2 8 3 **Al** Aluminium 26.9815386	14 2 8 4 **Si** Silicon 28.0855	15 2 8 5 **P** Phosphorus 30.973762	16 2 8 6 **S** Sulfur 32.065	17 2 8 7 **Cl** Chlorine 35.453	18 2 8 8 **Ar** Argon 39.948

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

Aromatic



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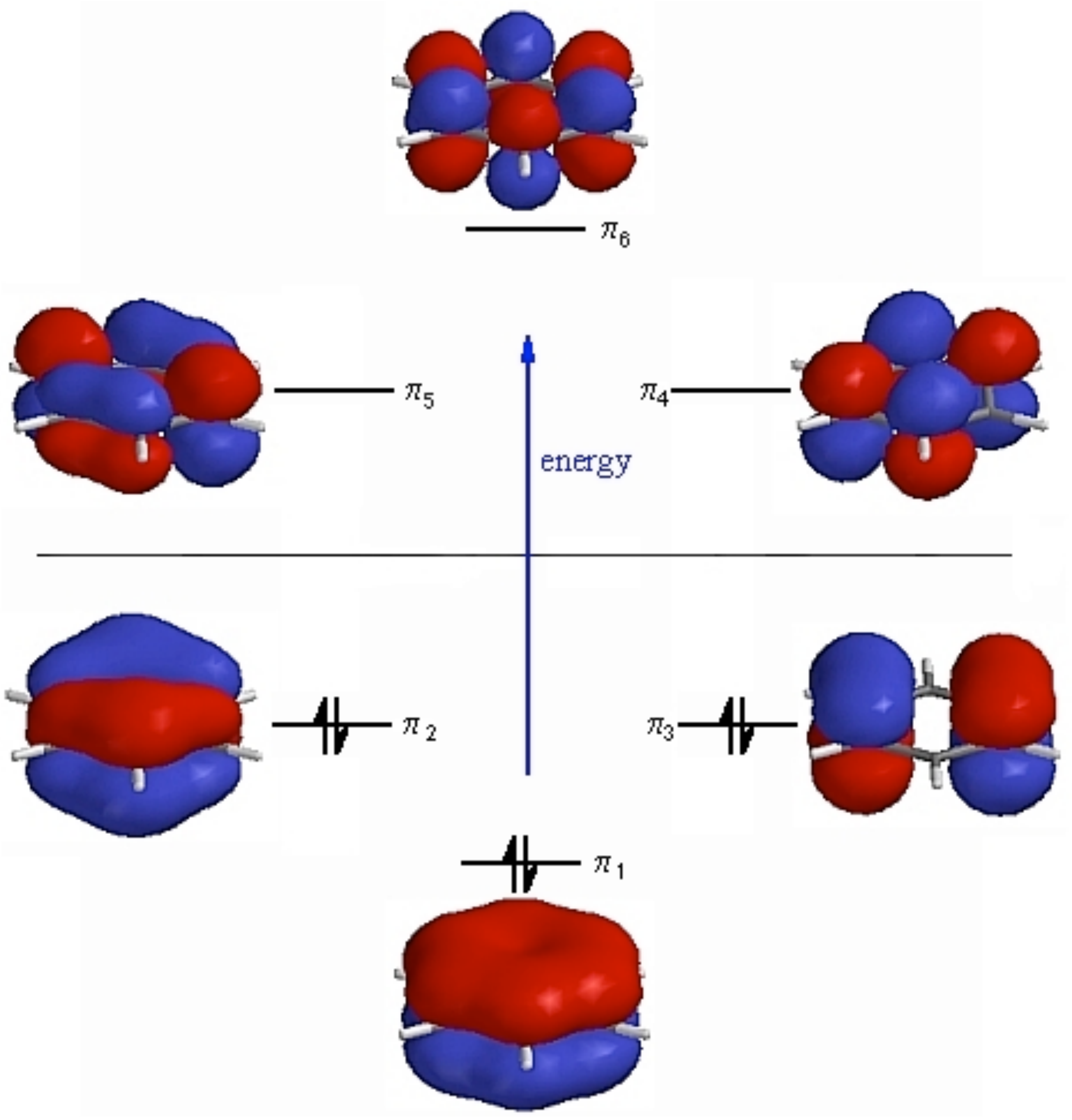
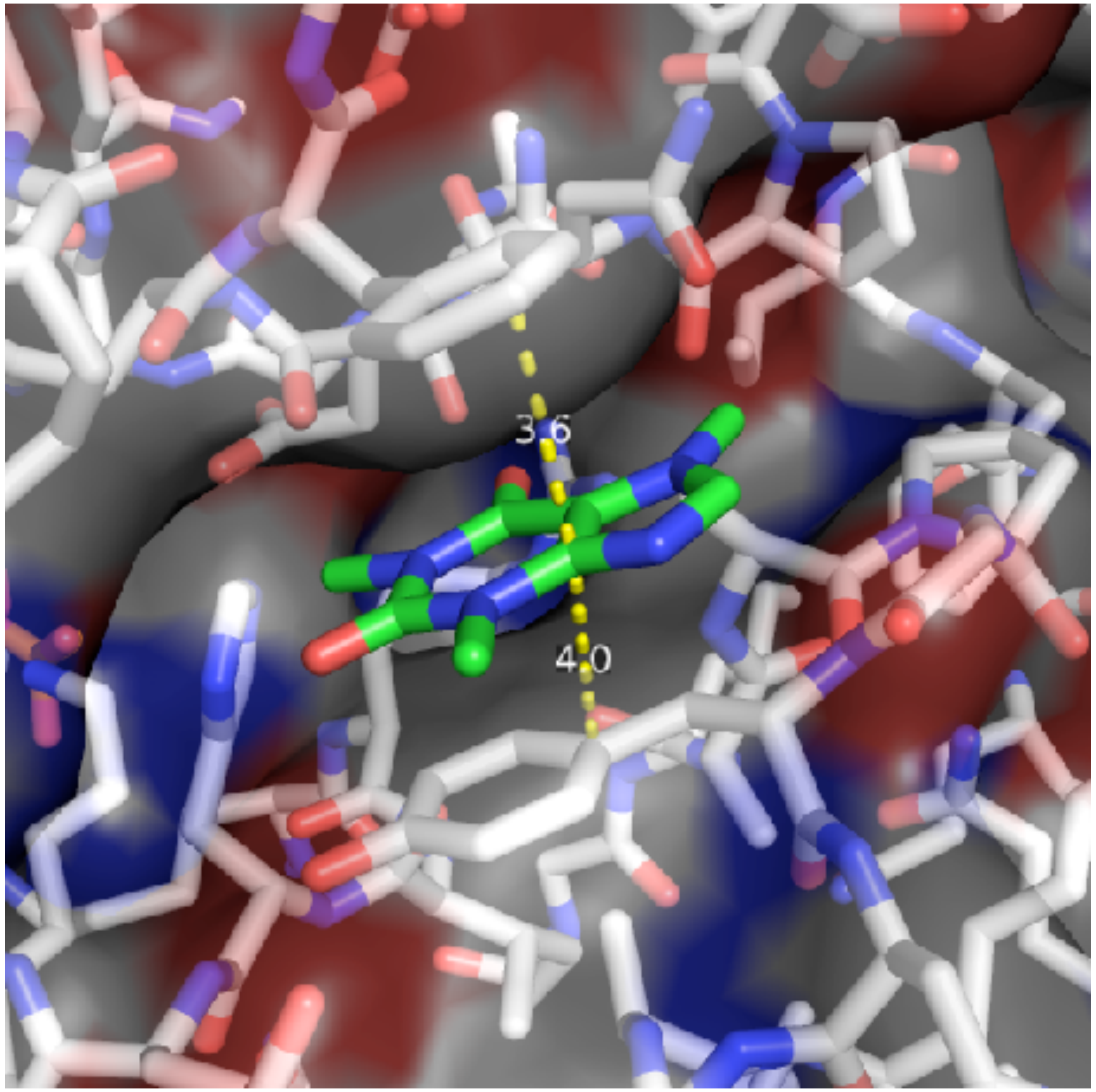
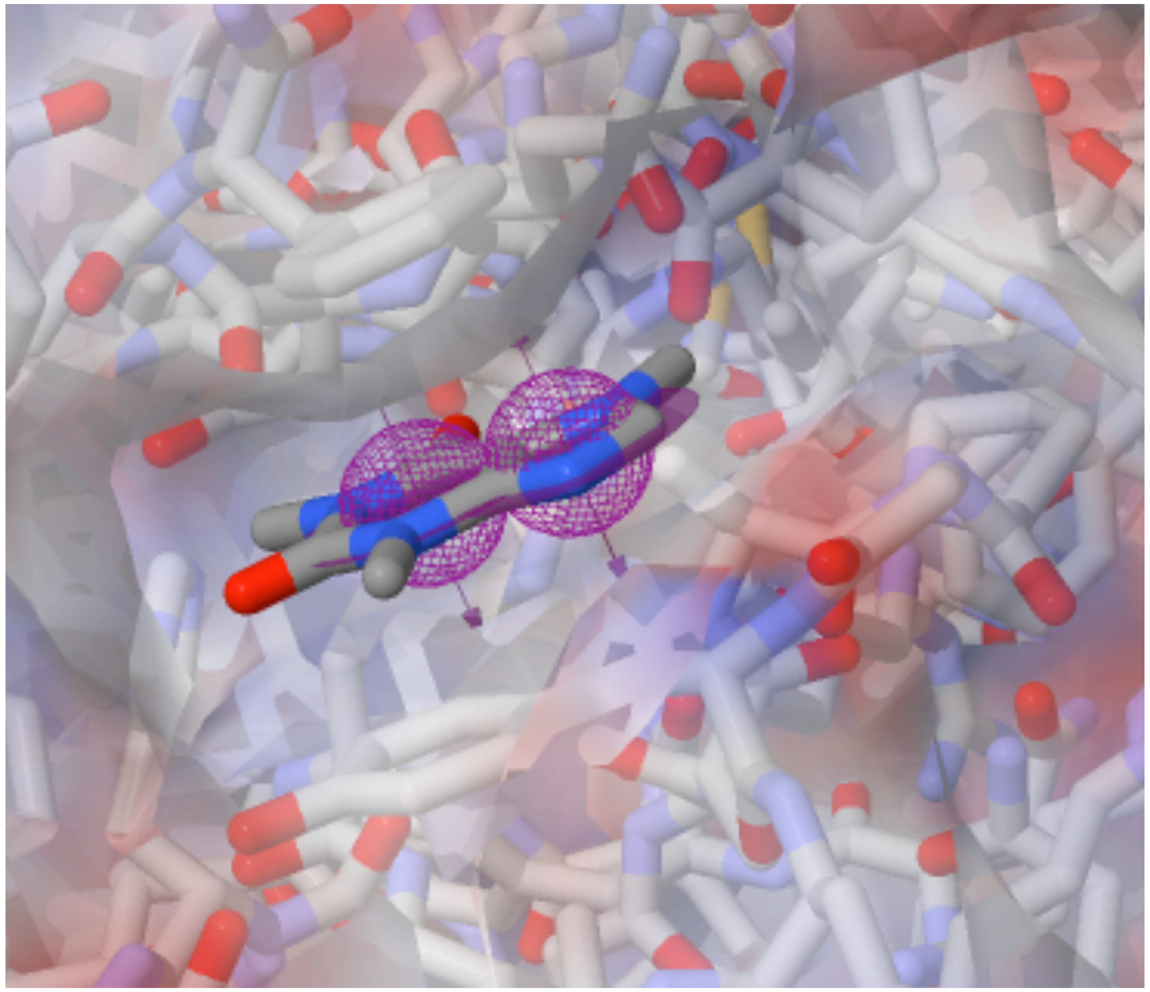


http://www.chem.ucalgary.ca/courses/351/Carey5th/Ch11/benzene-mo.jpg

Aromatic



Rings offset
Interplanar distance: 3.3-3.8Å



Human liver glycogen phosphorylase a complexed with caffeine

Pharmacophore

- ON **Aromatic** (48.19,39.80,-1.30) Radius 1.1
- ON **HydrogenAcceptor** (47.17,41.23,-5.37) 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** (55.14,47.7,-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

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

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http://pharmit.csb.pitt.edu

Kinds of Virtual Screening

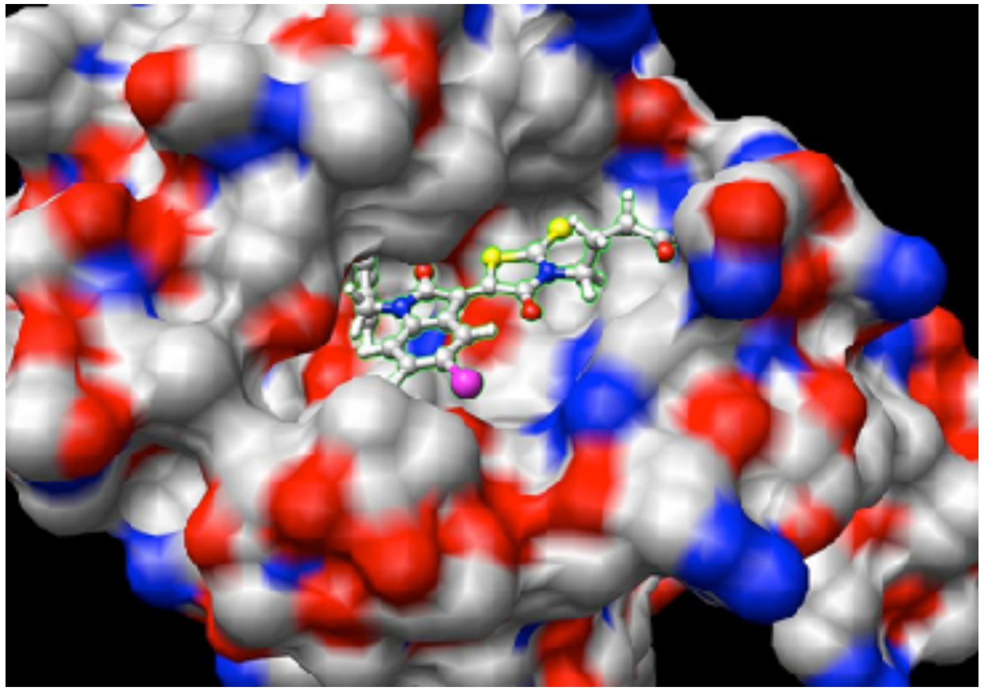
ADMET

Ligand Based

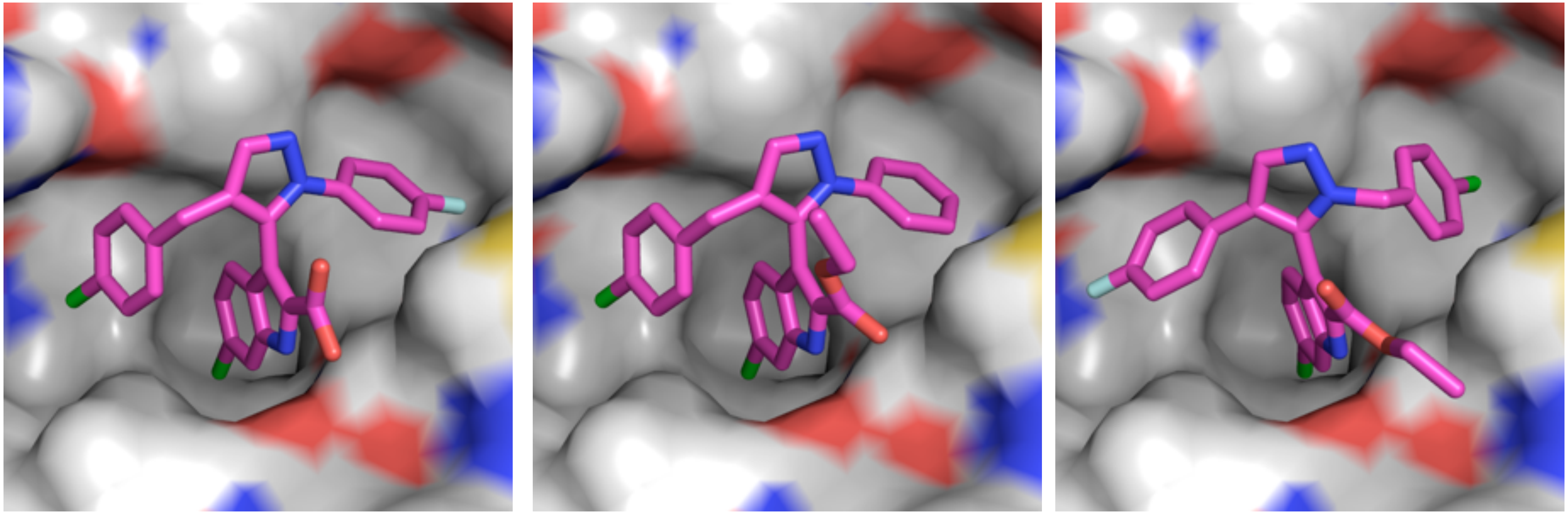
- similarity to known binder
- QSAR
- pharmacophore

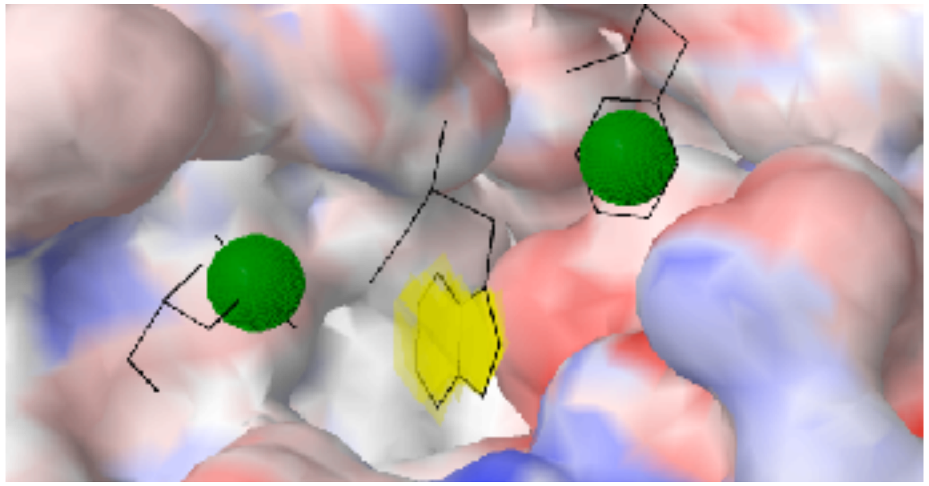
Receptor Based

- **dock and score**



Pharmacophores Aren’t Enough





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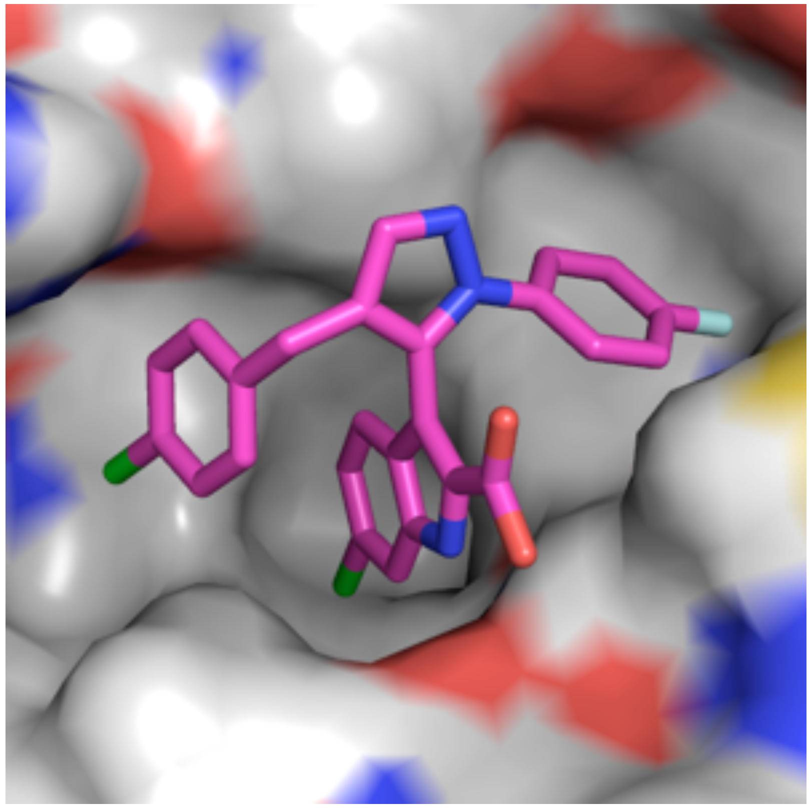
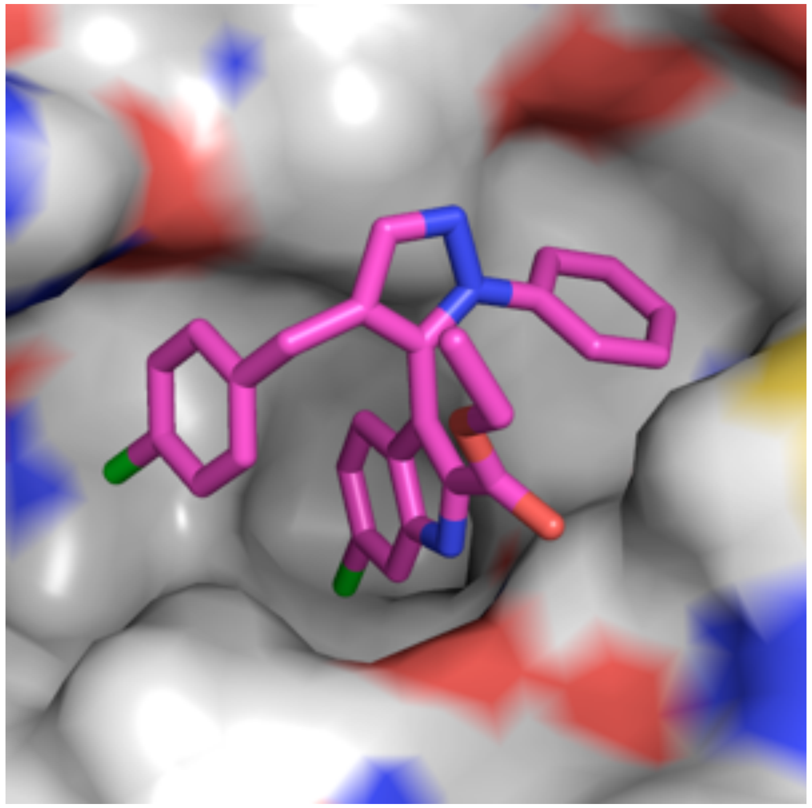
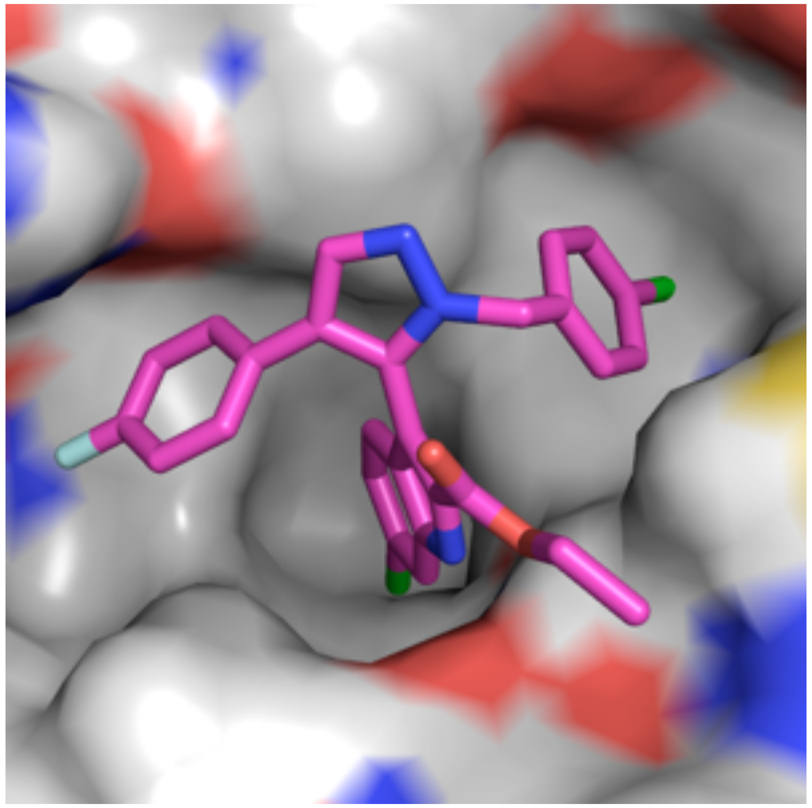


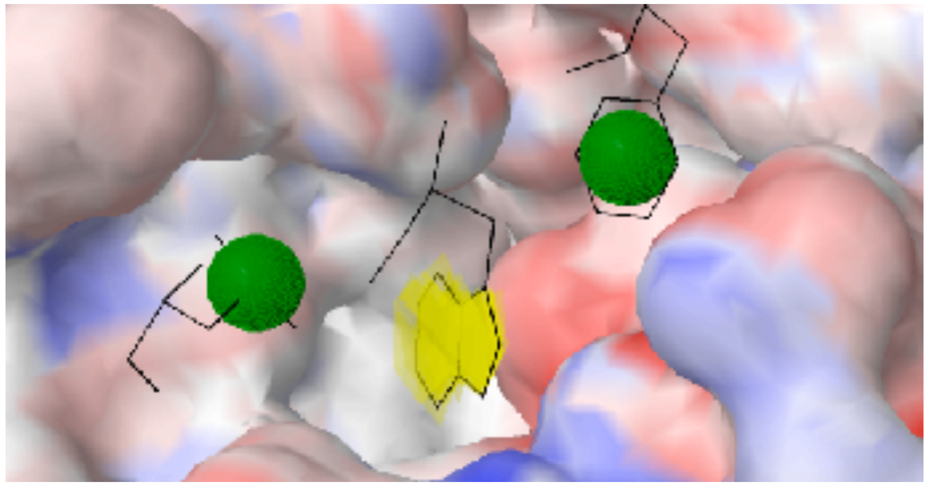
.2μM



50μM



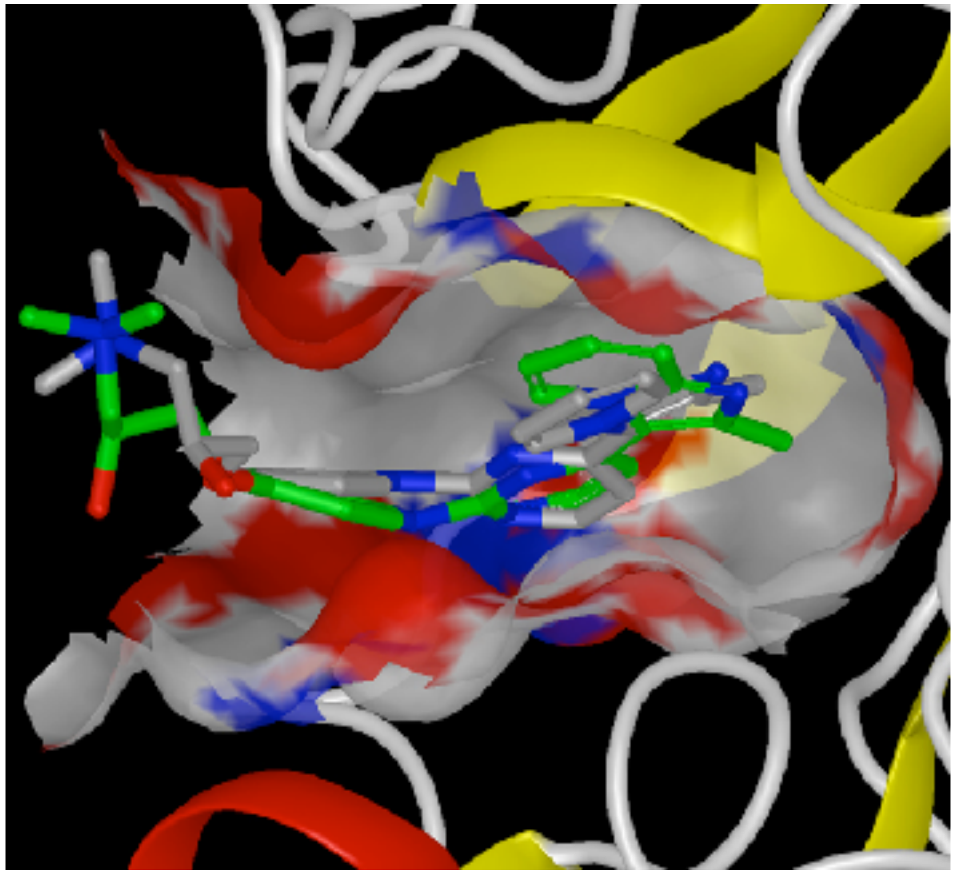
n.i.



Docking

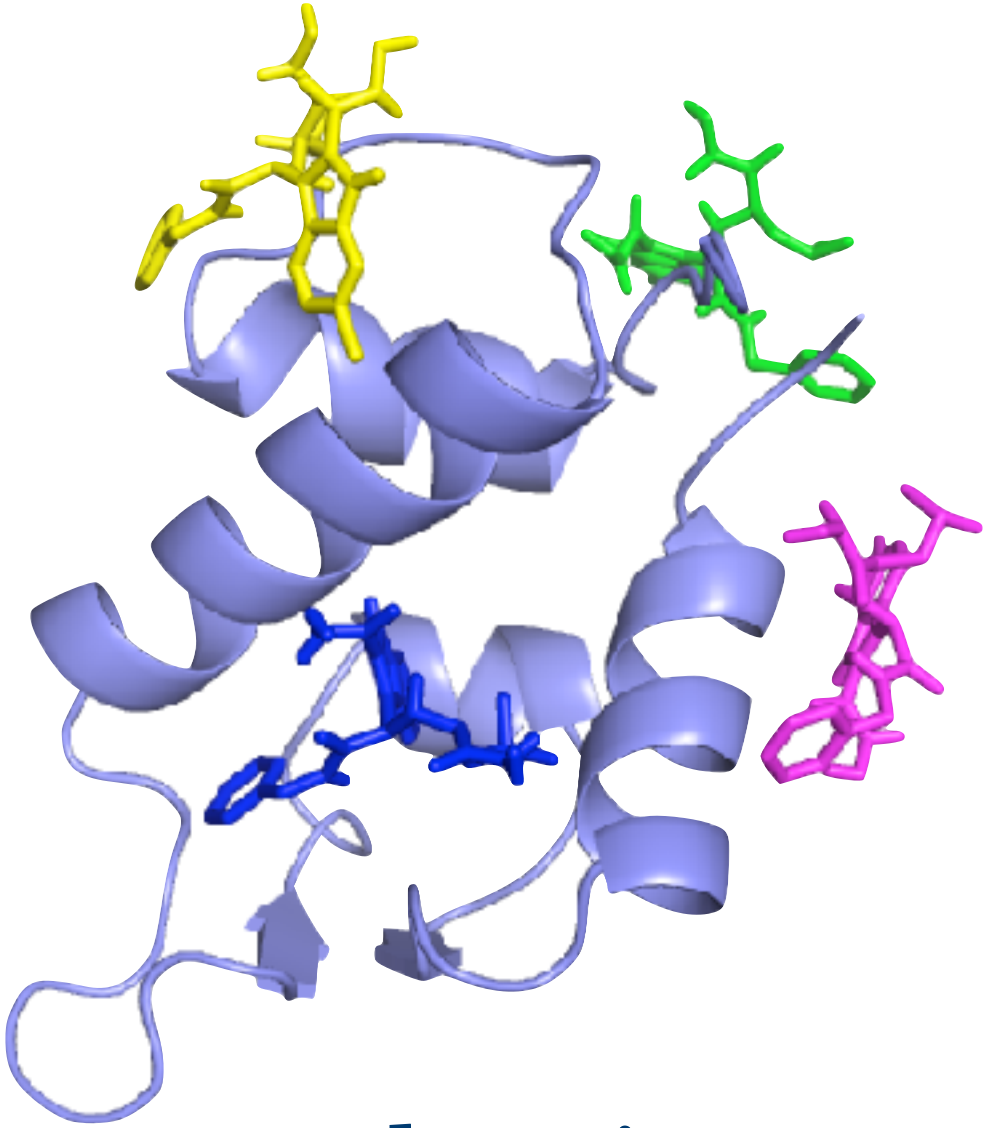
Determine the **conformation** and **pose** of a ligand at a docking site

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



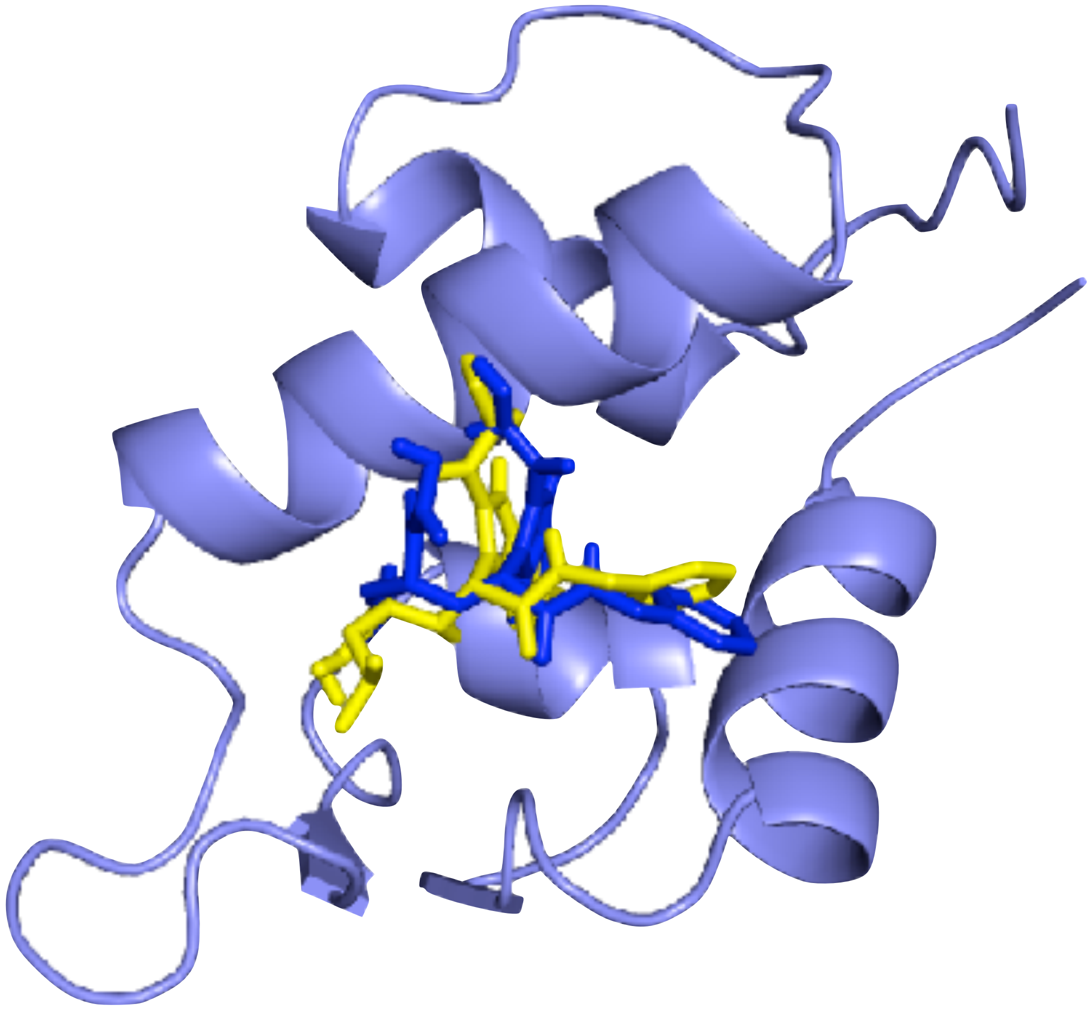
Two Phase Docking

1. Global Pose Estimation



Stochastic

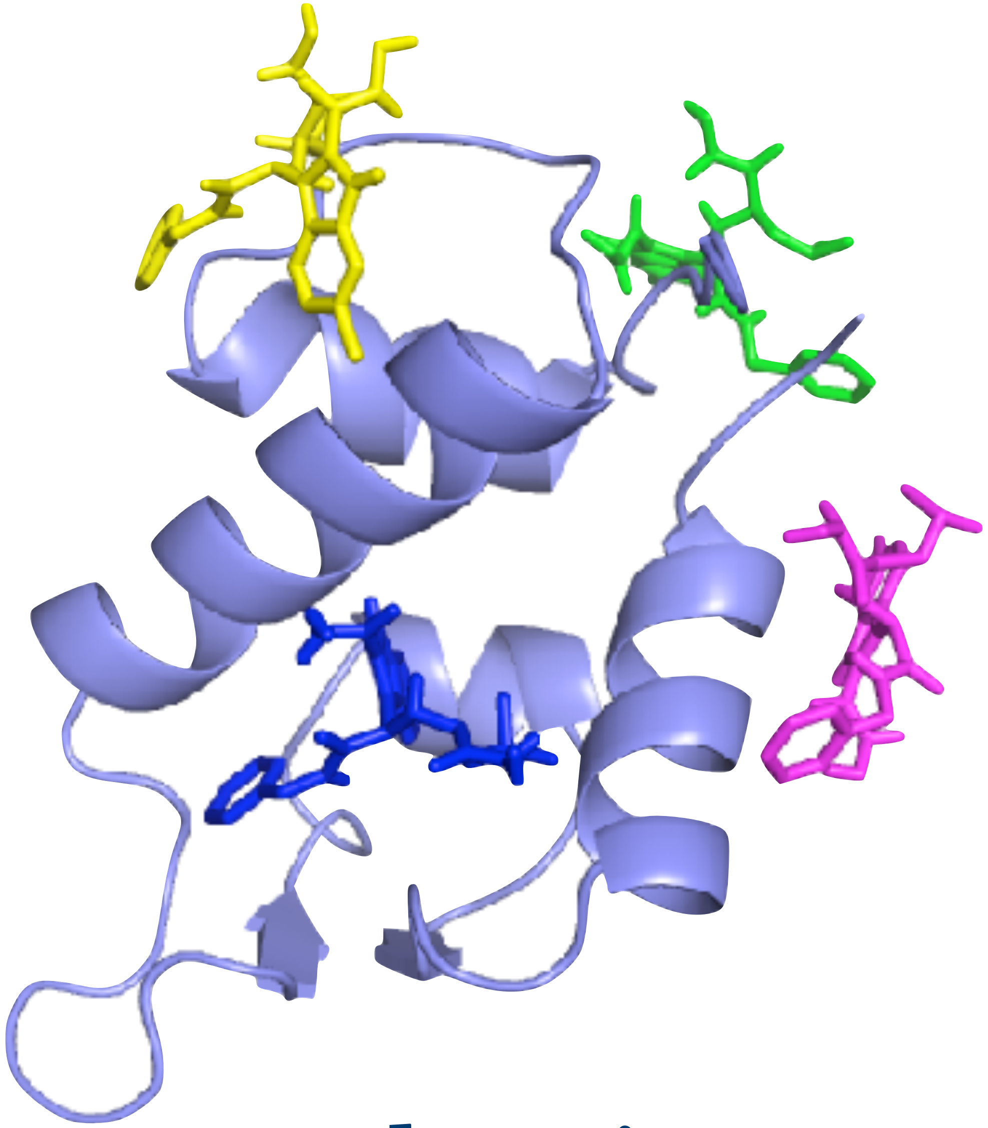
2. Local Refinement



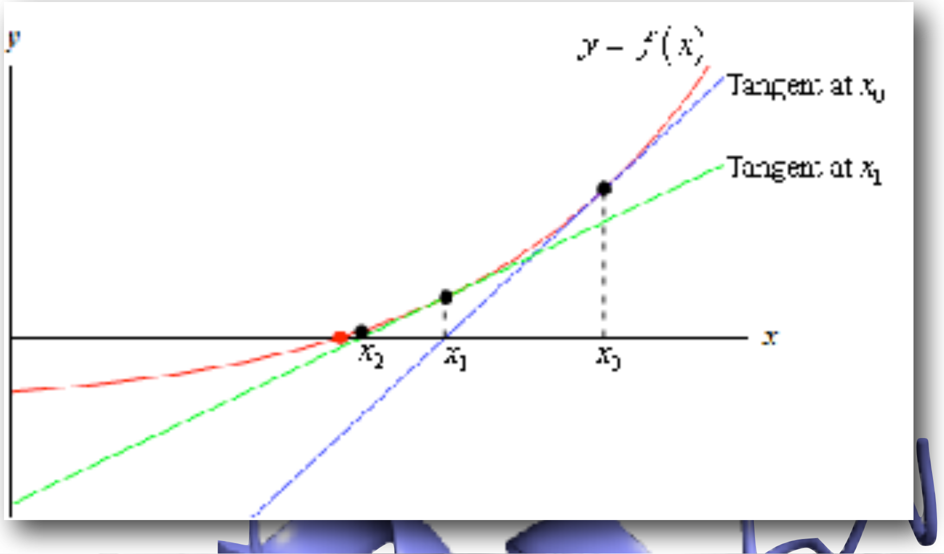
Minimization

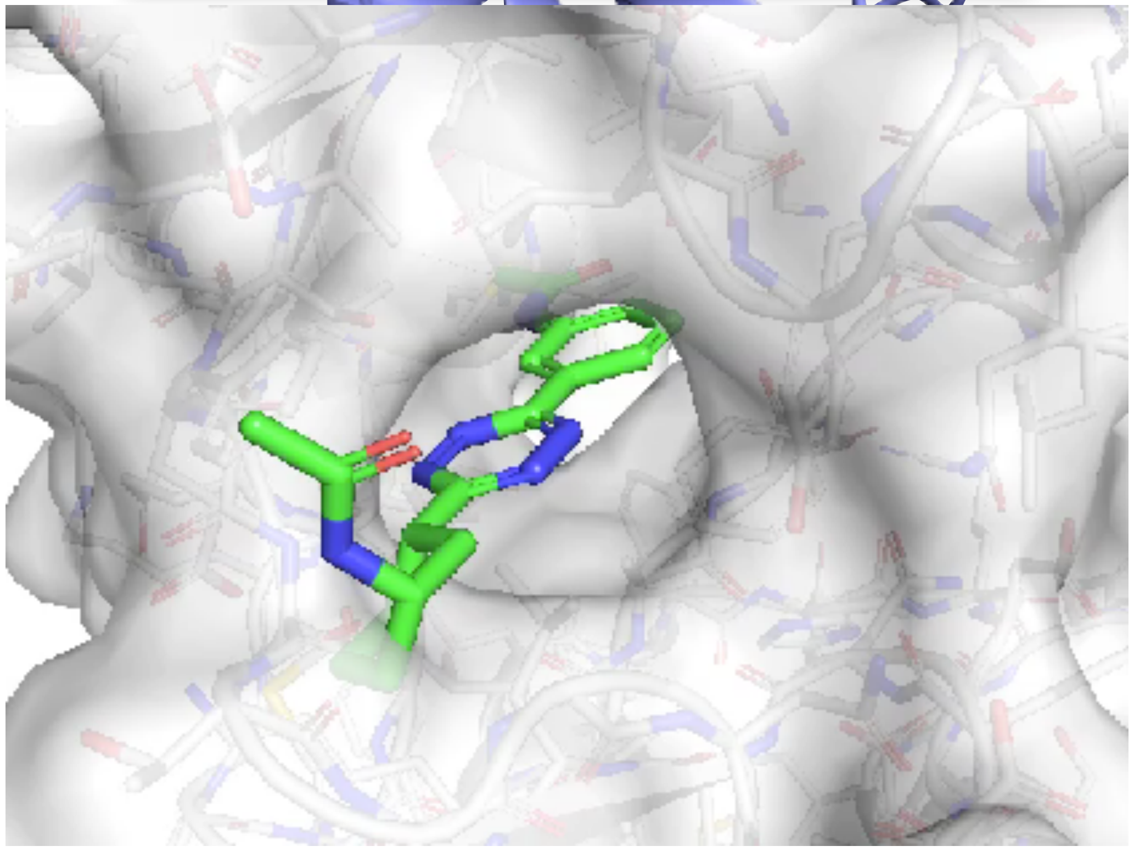
Two Phase Docking

1. Global Pose Estimation



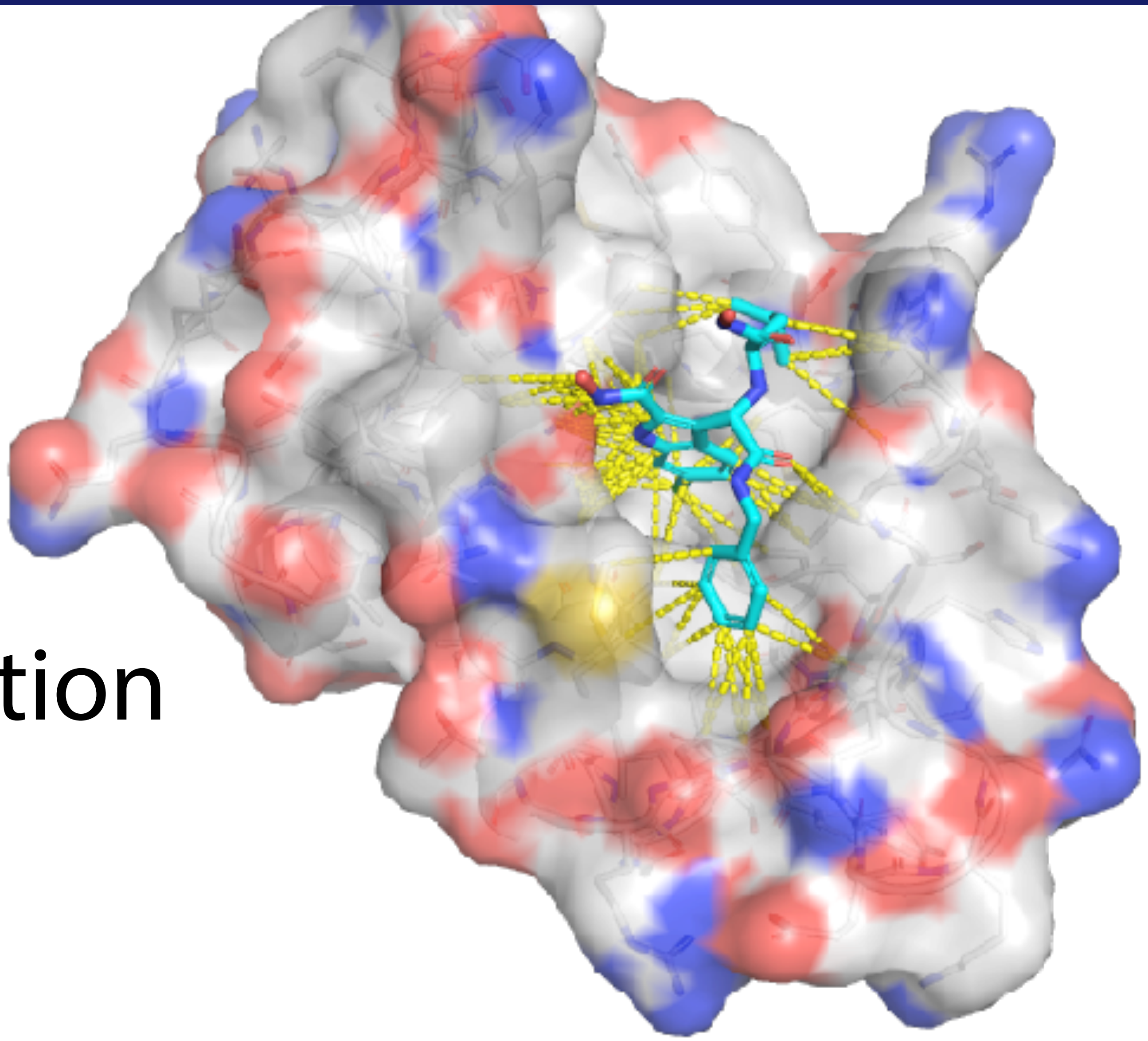
Stochastic





Minimization

Scoring Goals



Affinity Prediction

-how well does it bind?

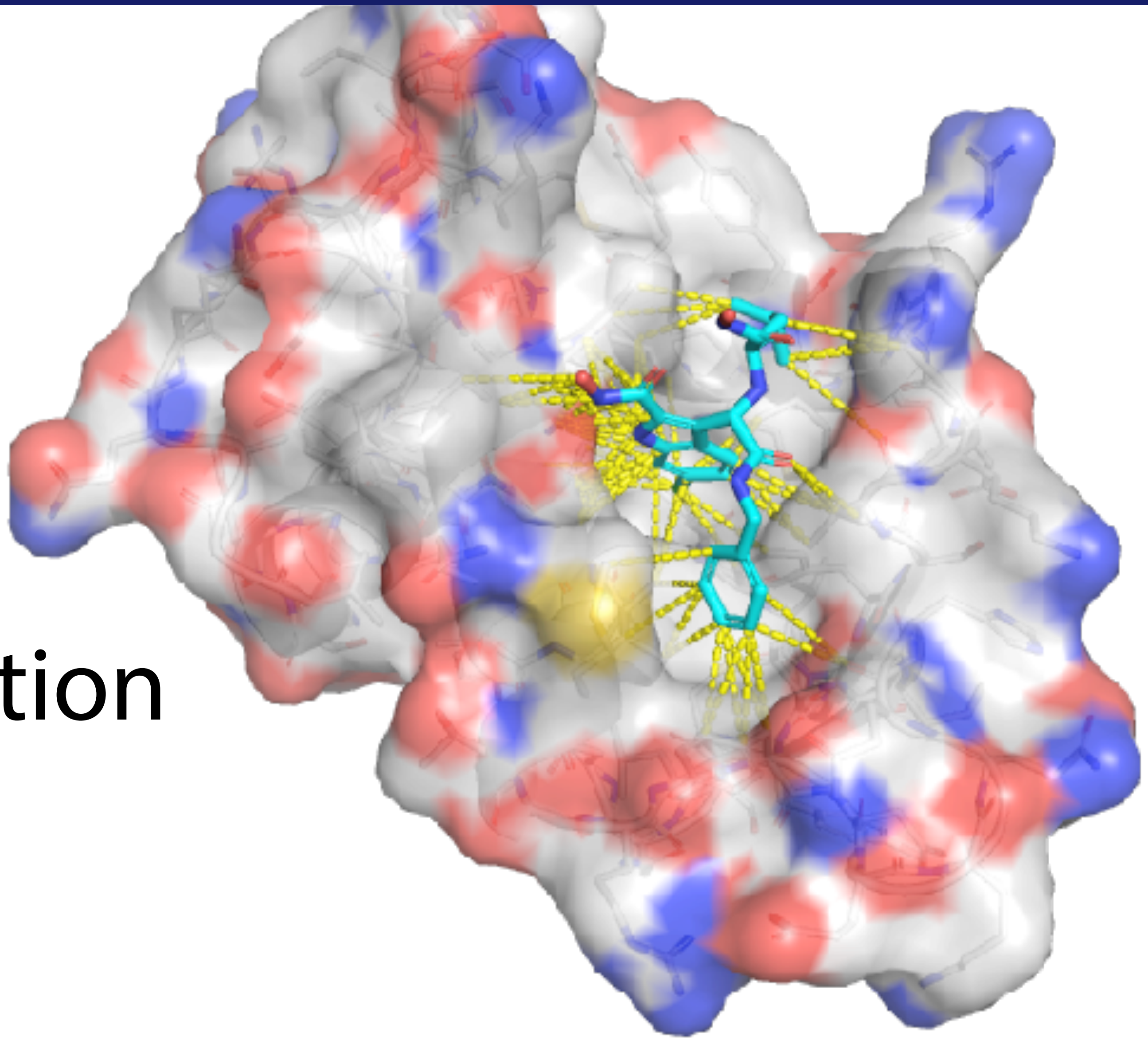
Inactive/Active Discrimination

-does it bind?

Pose Prediction

-how does it bind?

Scoring Goals



Affinity Prediction

-how well does it bind?

Inactive/Active Discrimination

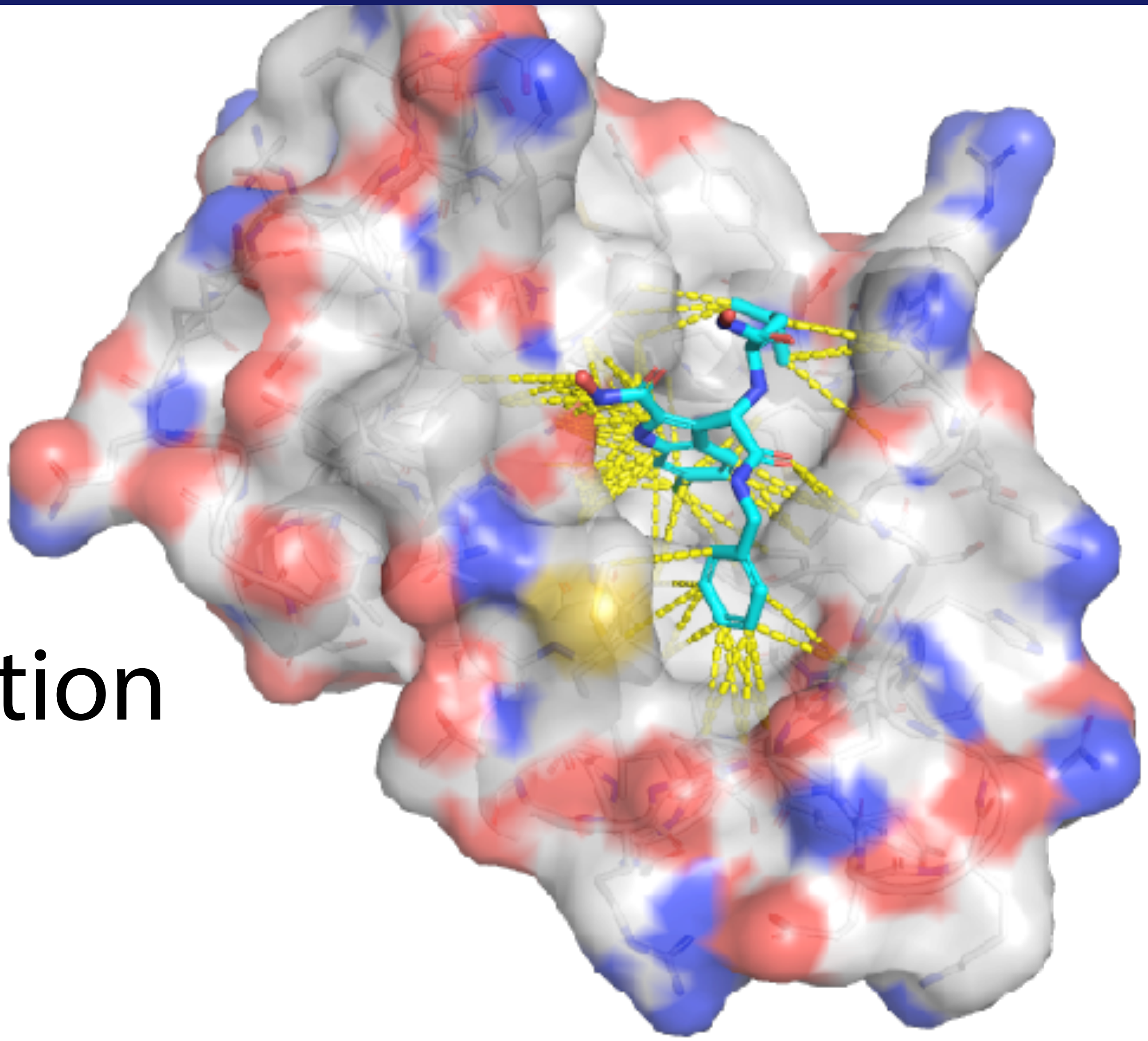
-does it bind?

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

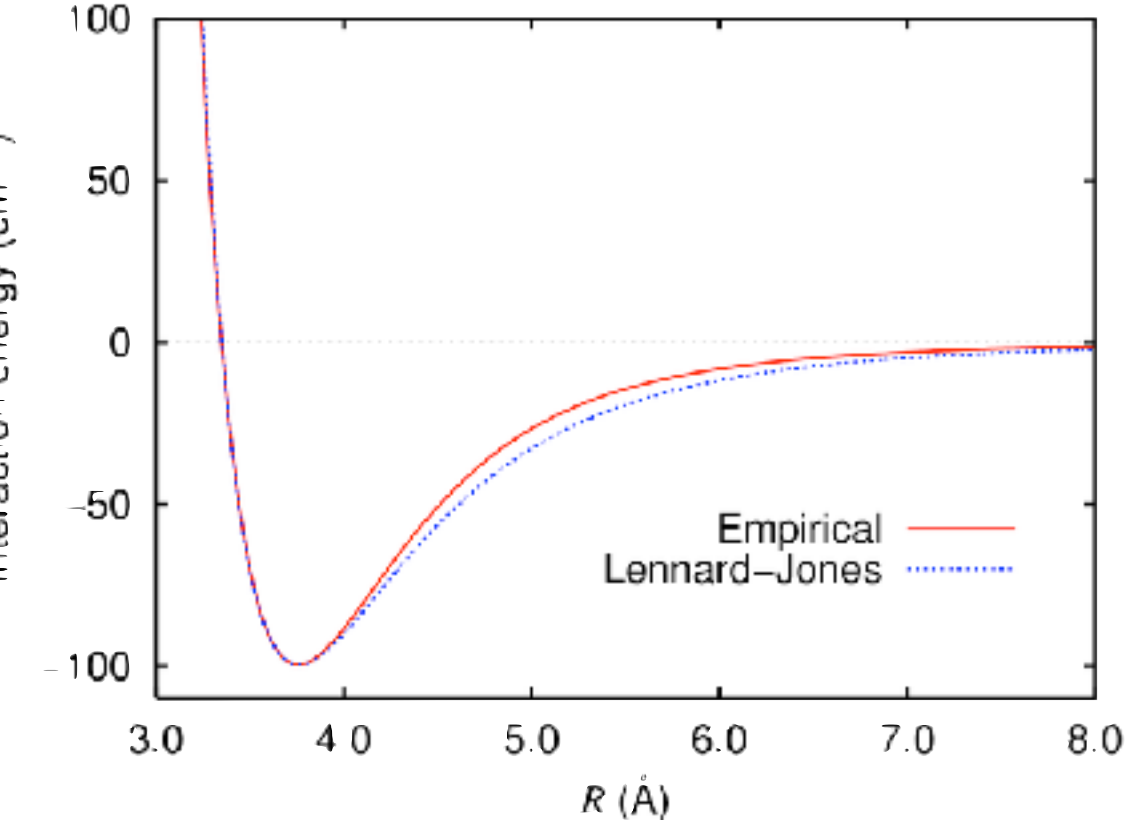
- Force-field based
  - inter- and intra- molecular forces
  - van der Waals, electrostatic, torsional
- Empirical
  - parameterized function is fit to binding energy data
- Knowledge based
  - scoring function based on known structure, not physical principles
- Consensus

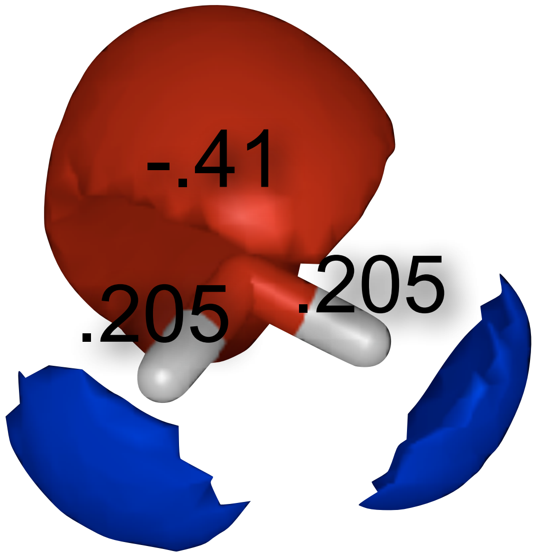
Force Field: Dock 4.0

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

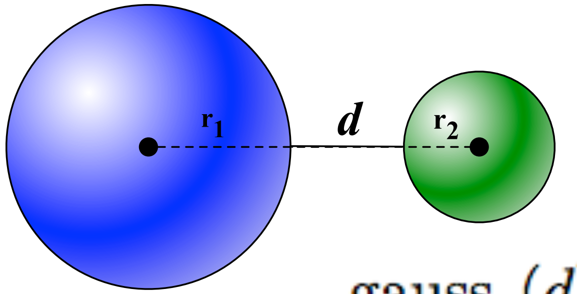
$$E = \sum_{i=1}^{lig} \sum_{j=1}^{rec} \left(\frac{A_{ij}}{r_{ij}^{a}} - \frac{B_{ij}}{r_{ij}^{b}} + 332 \frac{q_i q_j}{D r_{ij}} \right)$$

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





Empirical: AutoDock Vina



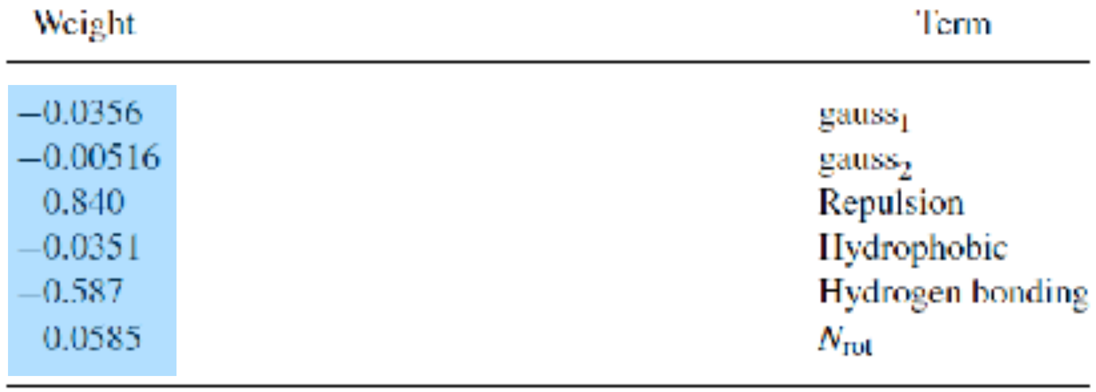
$$\mathrm{gauss}_1(d) = w_{\mathrm{guass}_1} e^{-(d/0.5)^2}$$

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

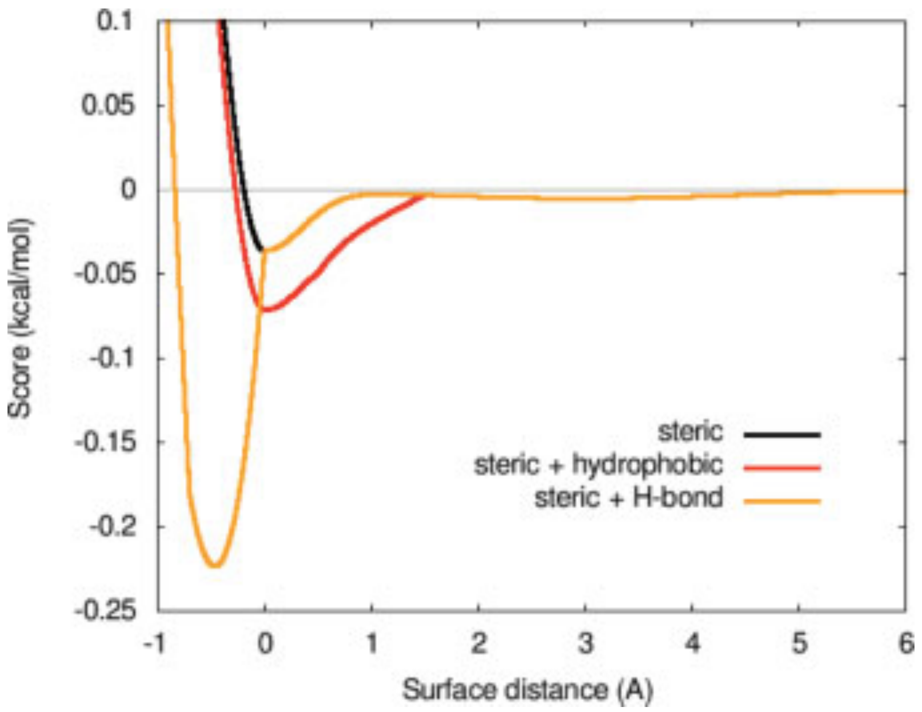
$$\mathrm{repulsion}(d) = \begin{cases} w_{\mathrm{repulsion}} d^2 & d < 0 \\ 0 & d \geq 0 \end{cases}$$

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

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

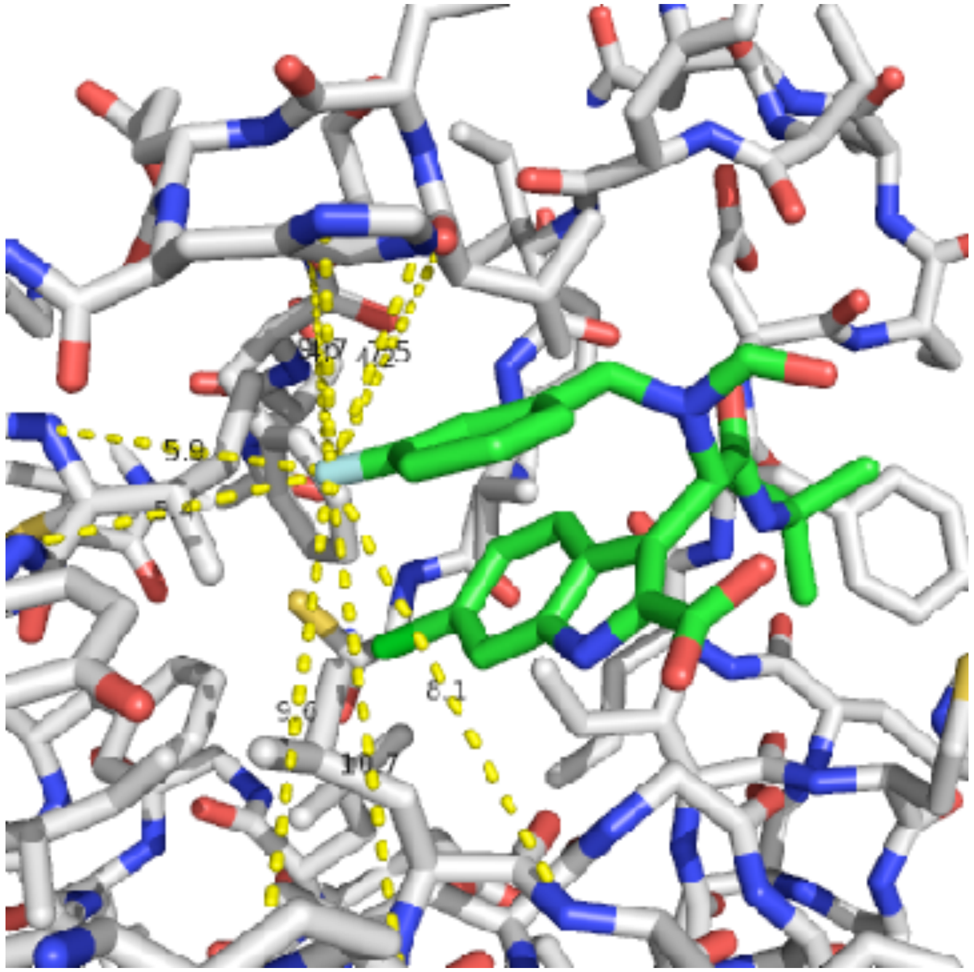


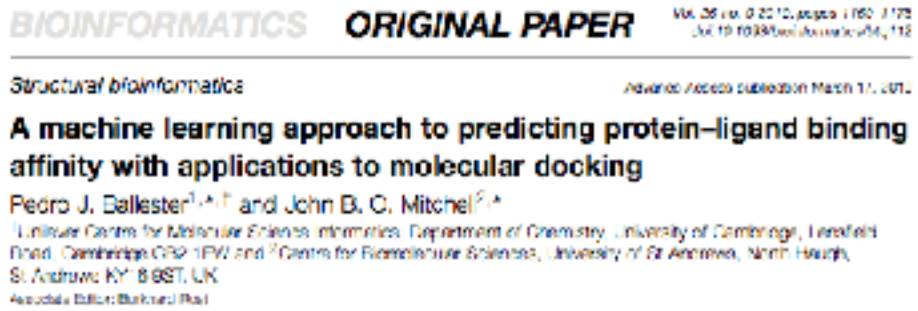
Weight	Term
−0.0356	gauss_1
−0.00516	gauss_2
0.840	Repulsion
−0.0351	Hydrophobic
−0.587	Hydrogen bonding
0.0585	N_{rot}



Knowledge Based: RF-Score

Pairwise Distance Counts (<12Å)





BIOINFORMATICS ***ORIGINAL PAPER***

Structural bioinformatics

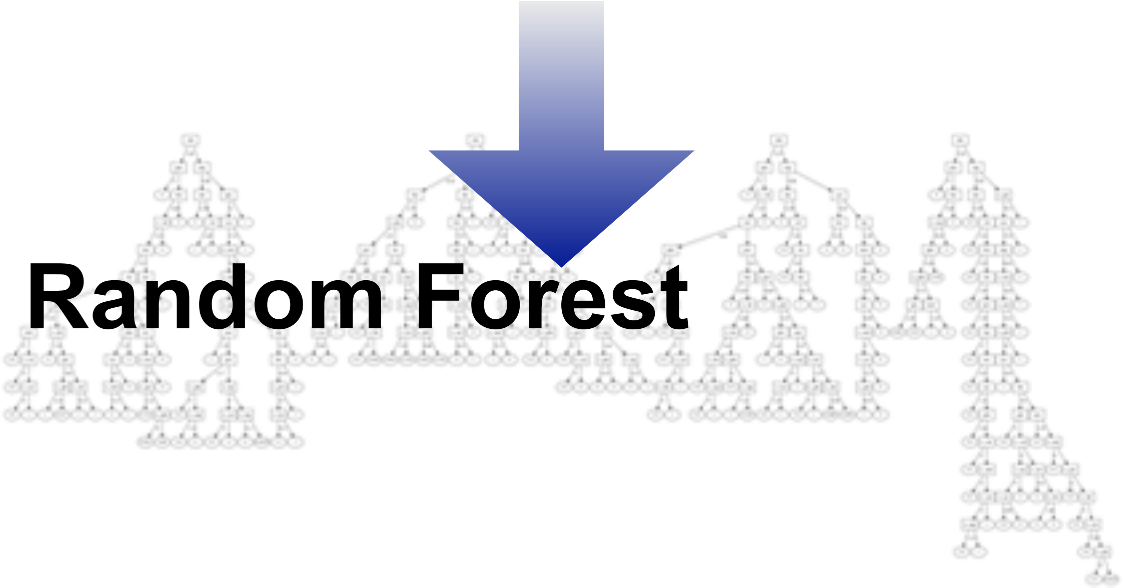
A machine learning approach to predicting protein–ligand binding affinity with applications to molecular docking

Pedro J. Ballester[1,*,†] and John B. O. Mitchel[2,*]

Protein

Ligand

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



Random Forest

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

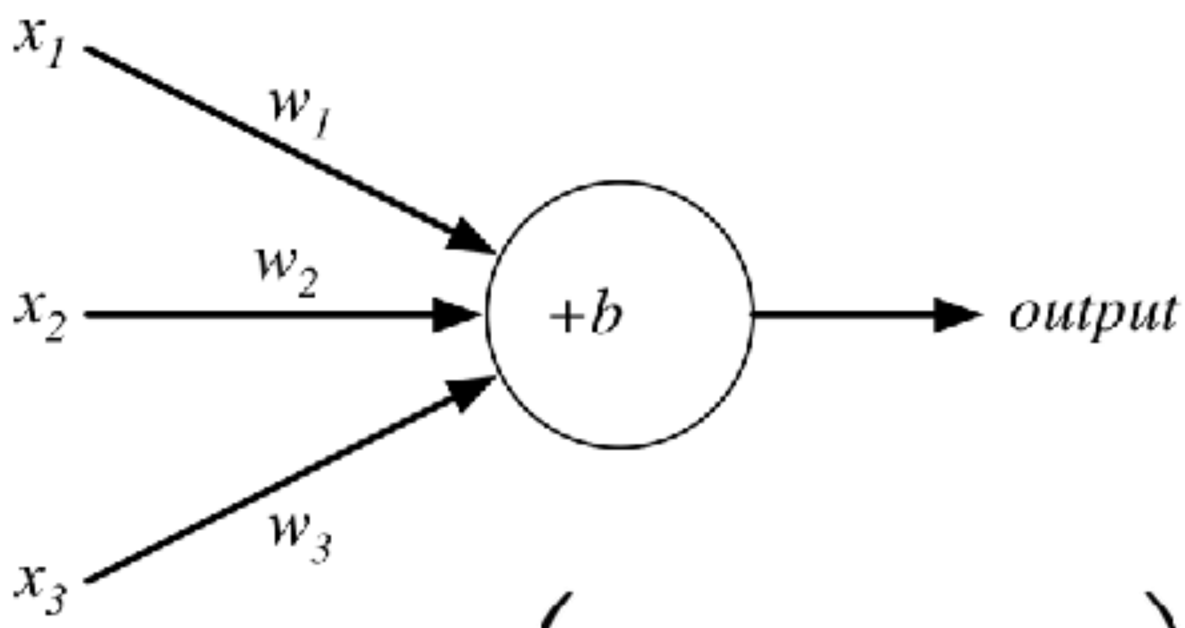
125,526 structures in the PDB

16,179 annotated complexes in PDBbind

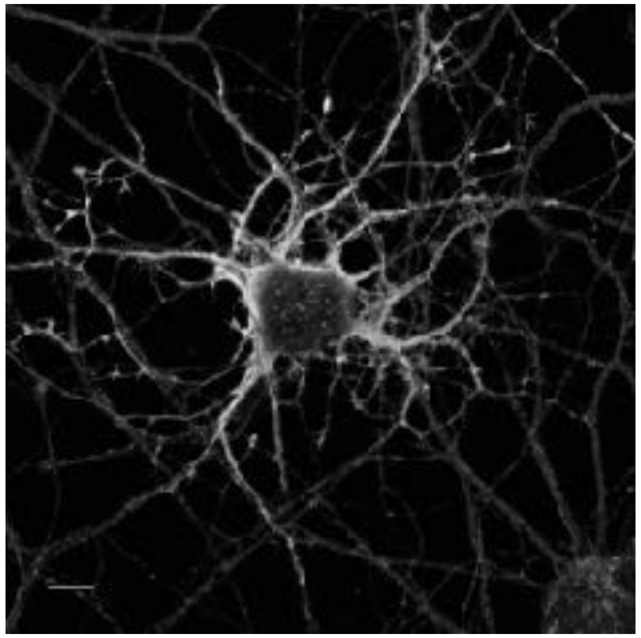
Machine Learning

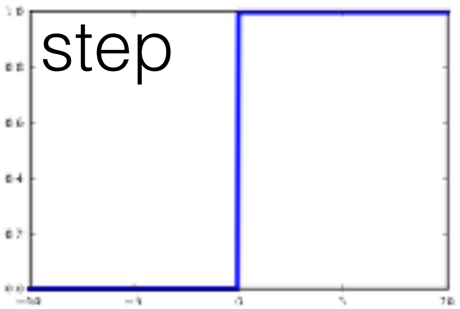
Features $X \rightarrow$ Model $\rightarrow y$ Prediction

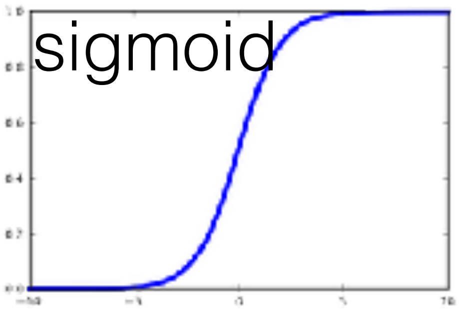
Neural Networks

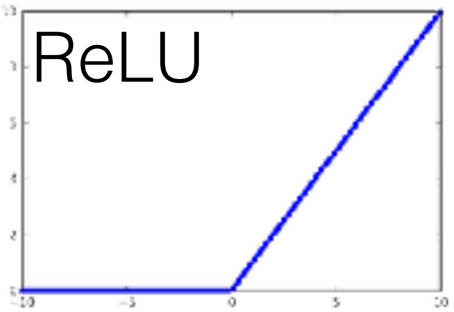


$$output = \sigma\left(\sum_i w_i x_i + b\right)$$

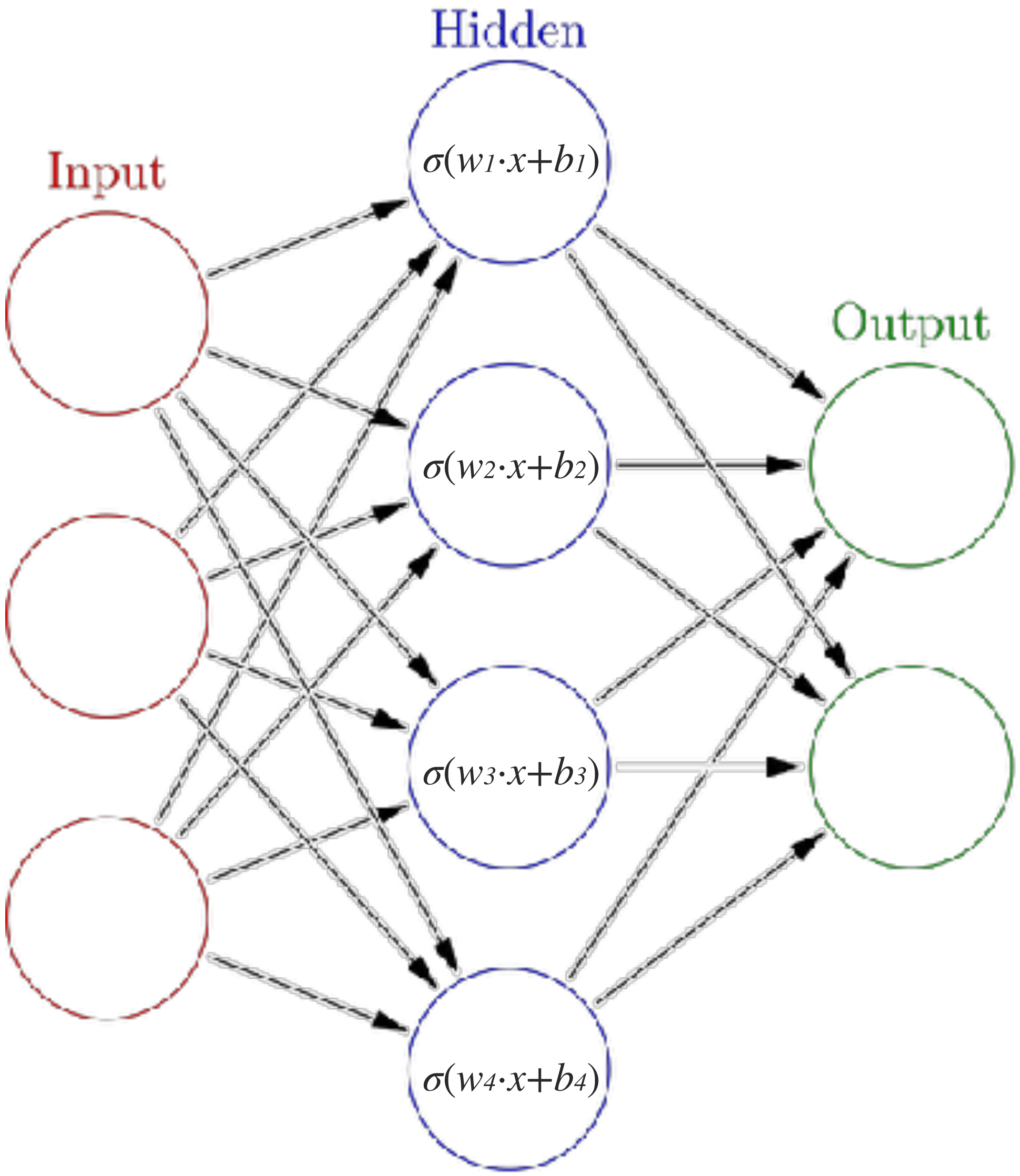


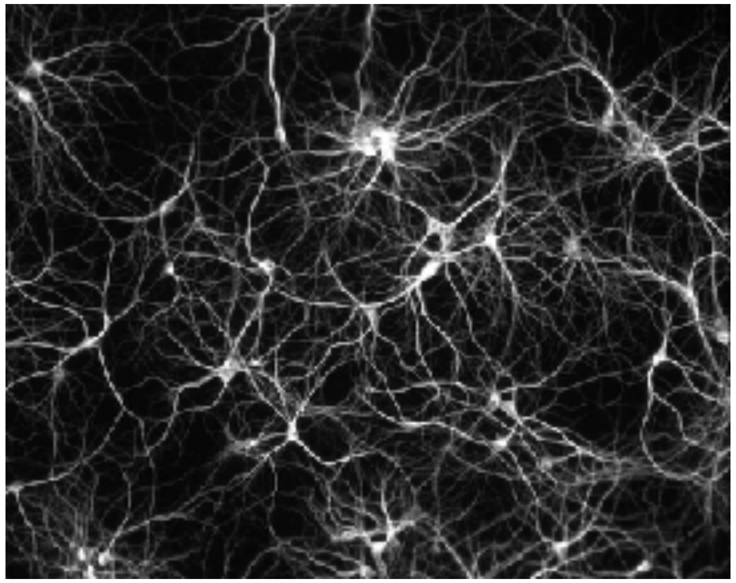






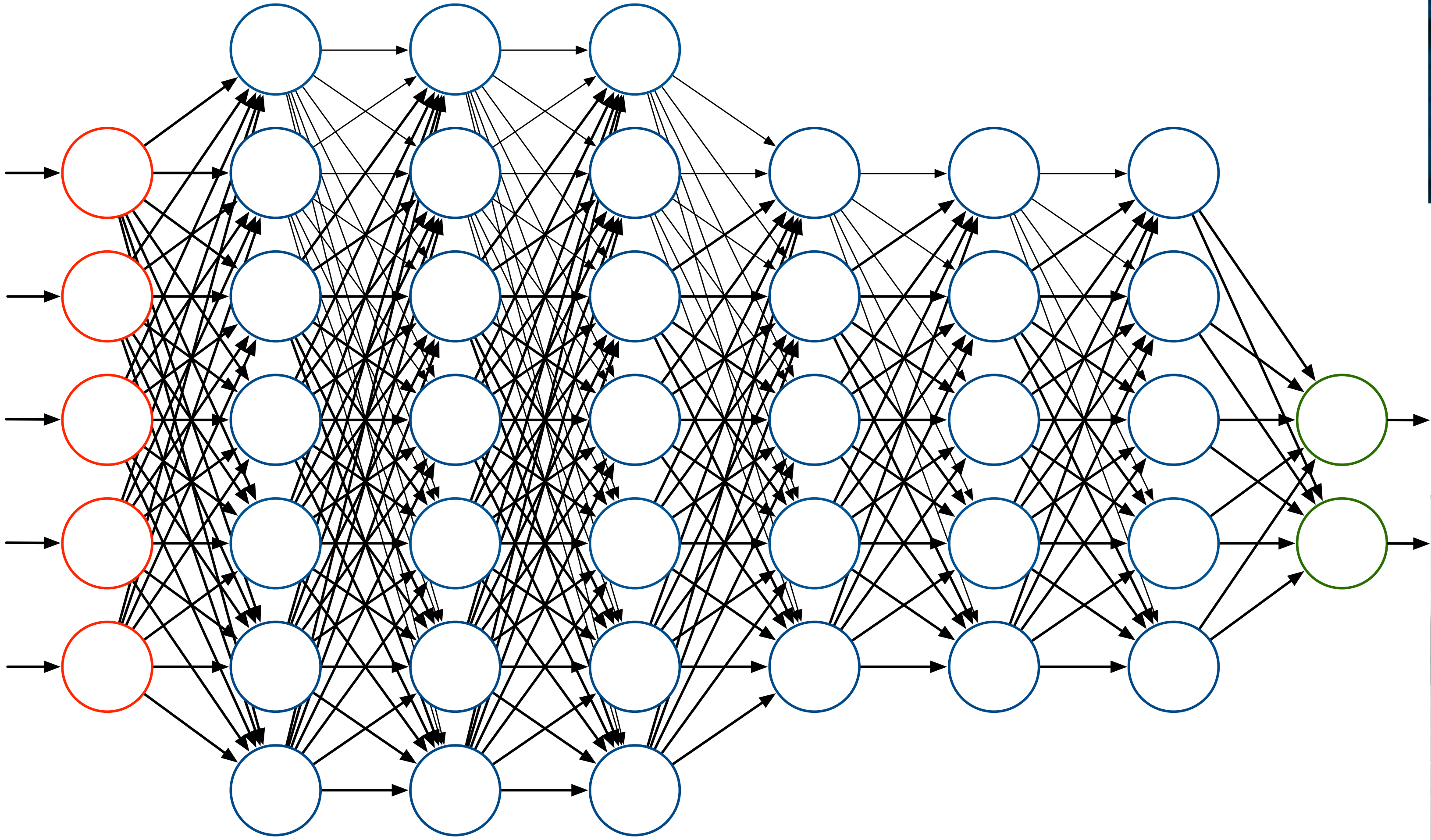
Neural Networks



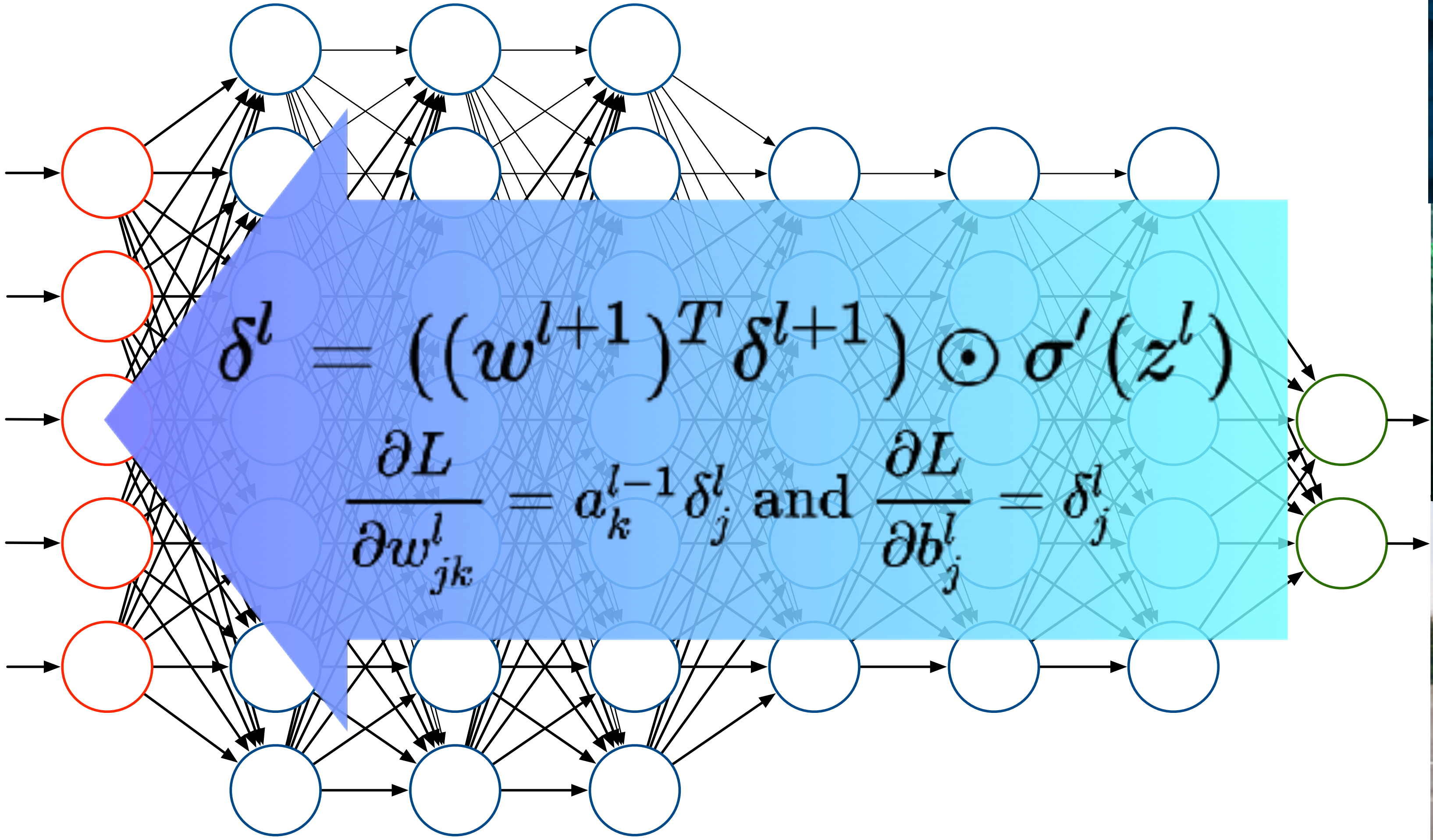


The **universal approximation theorem** states that, under reasonable assumptions, a feedforward **neural network** with a finite number of nodes **can approximate any continuous** function to within a given error over a bounded input domain.

Deep Learning



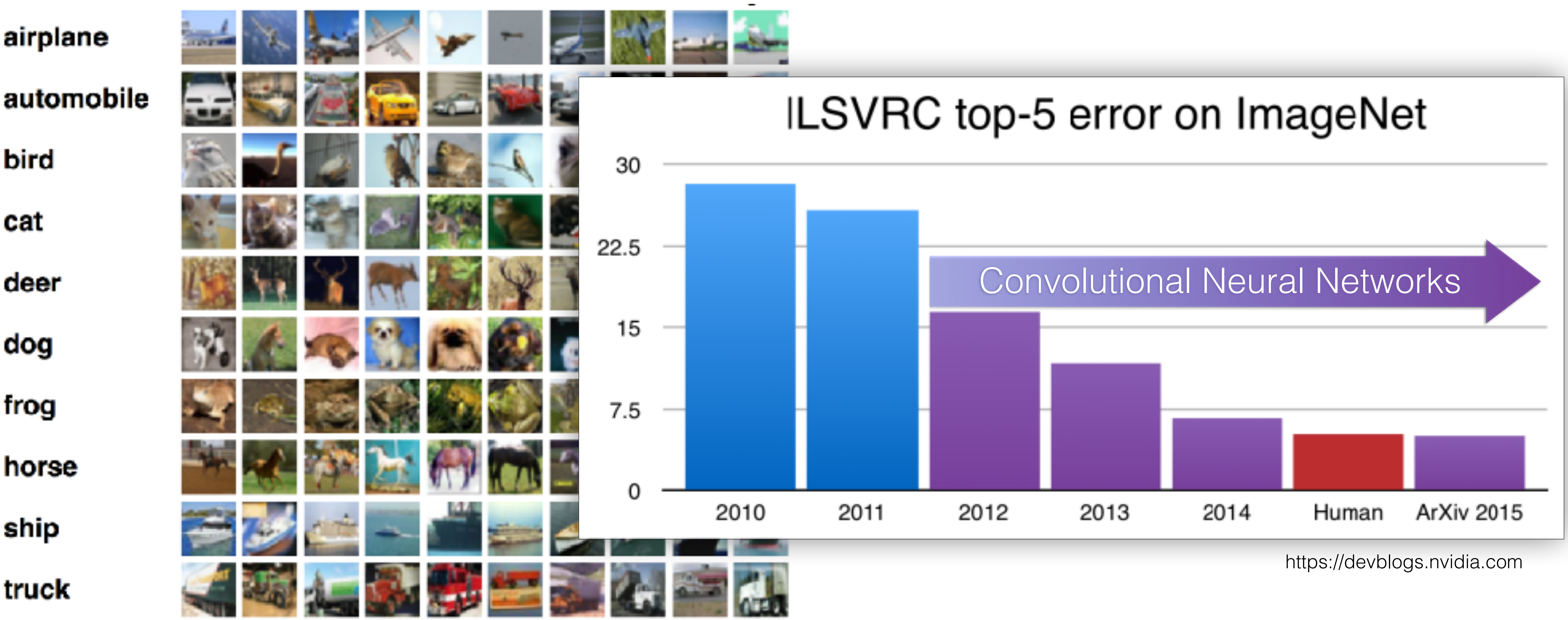
Deep Learning



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

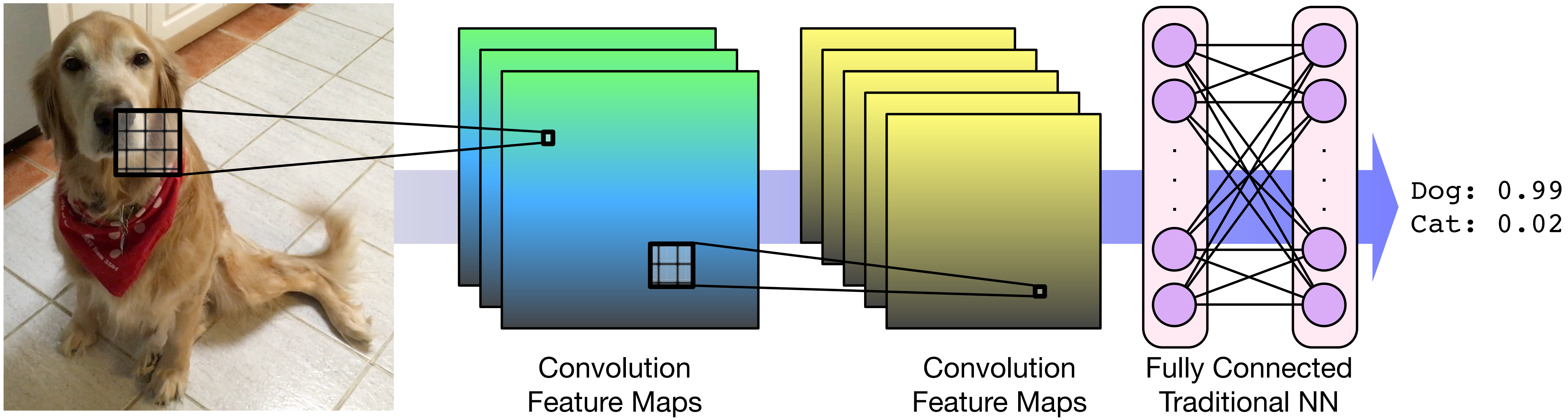
$$\frac{\partial L}{\partial w^l_{jk}} = a^{l-1}_k \delta^l_j \text{ and } \frac{\partial L}{\partial b^l_j} = \delta^l_j$$

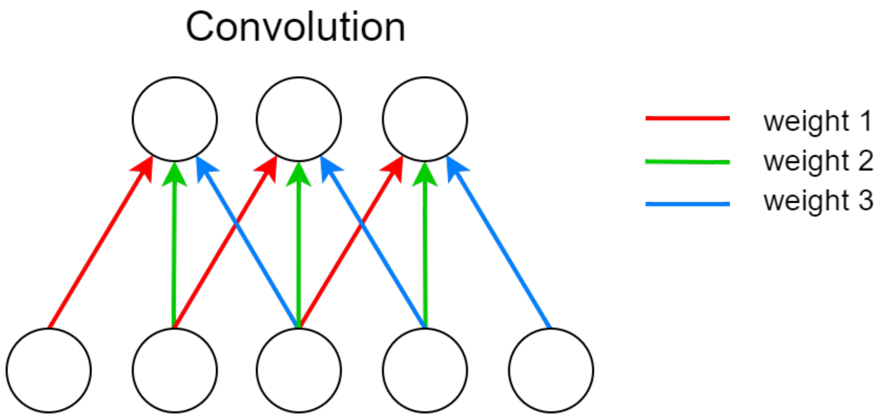
Image Recognition

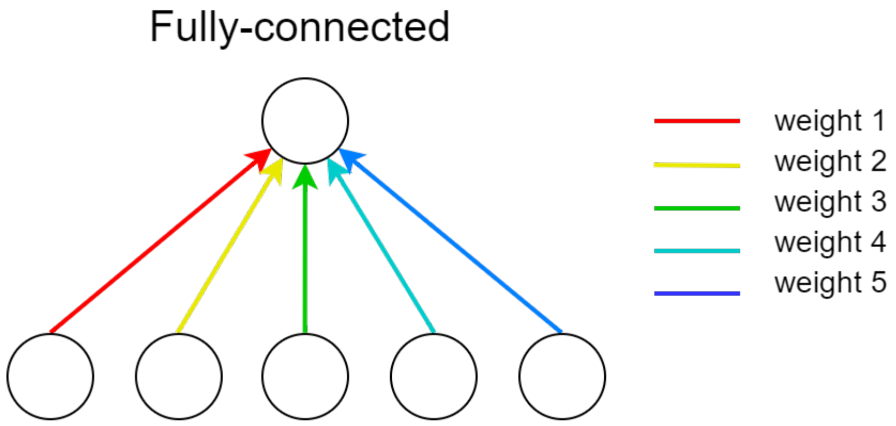


https://devblogs.nvidia.com

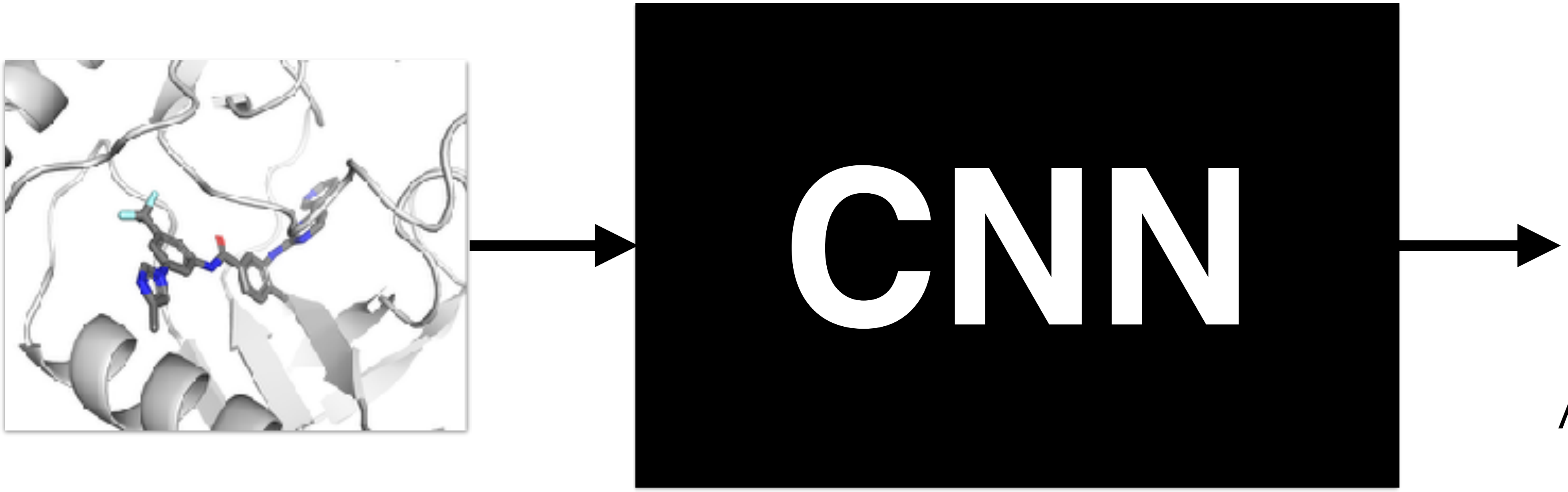
Convolutional Neural Networks







CNNs for Protein-Ligand Scoring



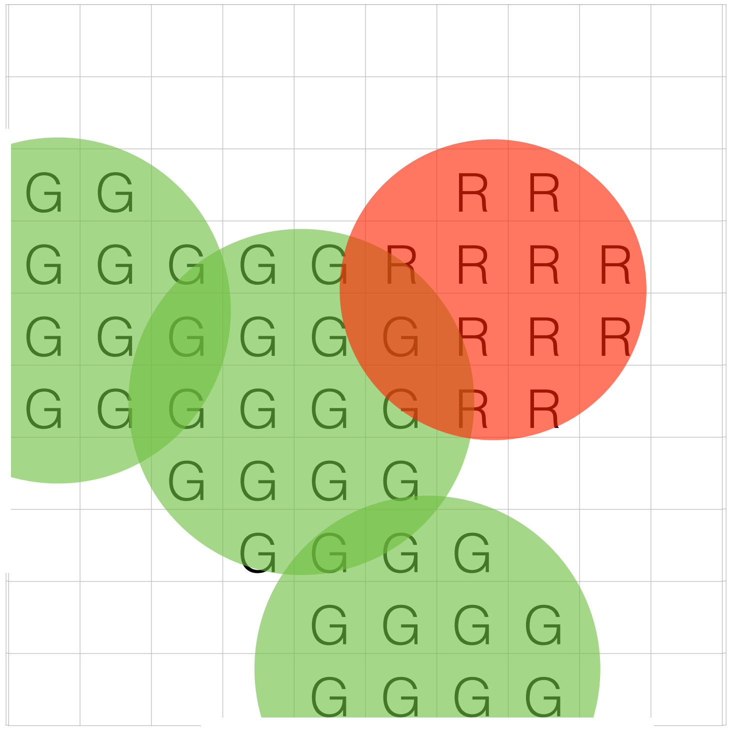
CNN

Pose Prediction

Binding Discrimination

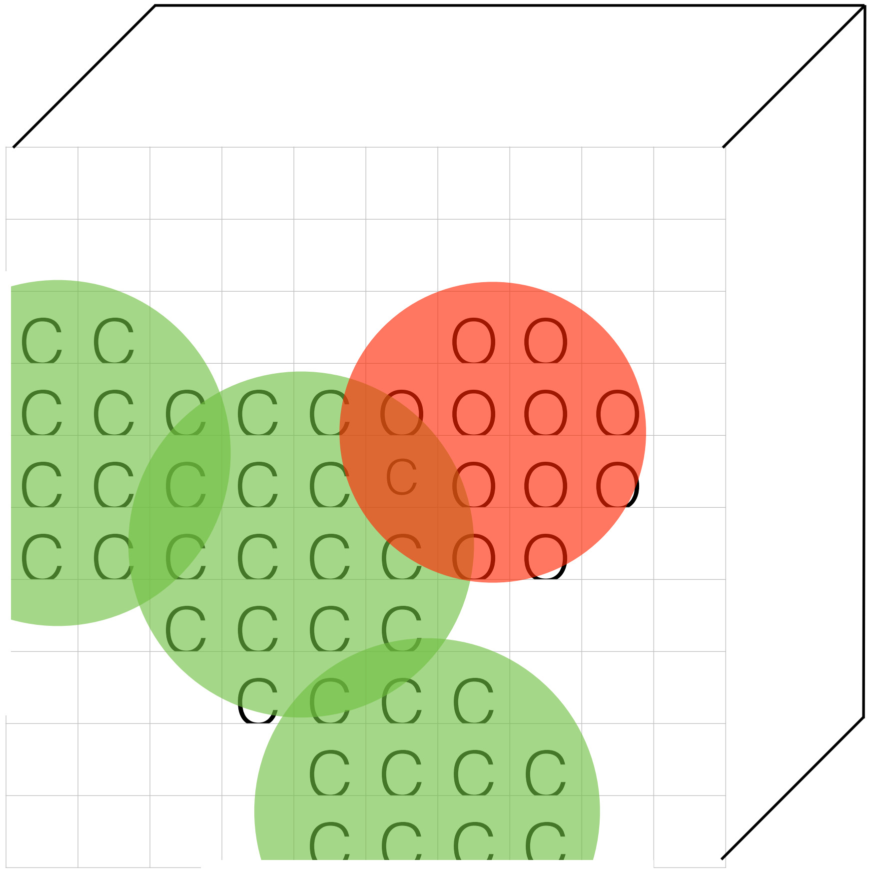
Affinity Prediction

Protein-Ligand Representation



(R,G,B) pixel

Protein-Ligand Representation

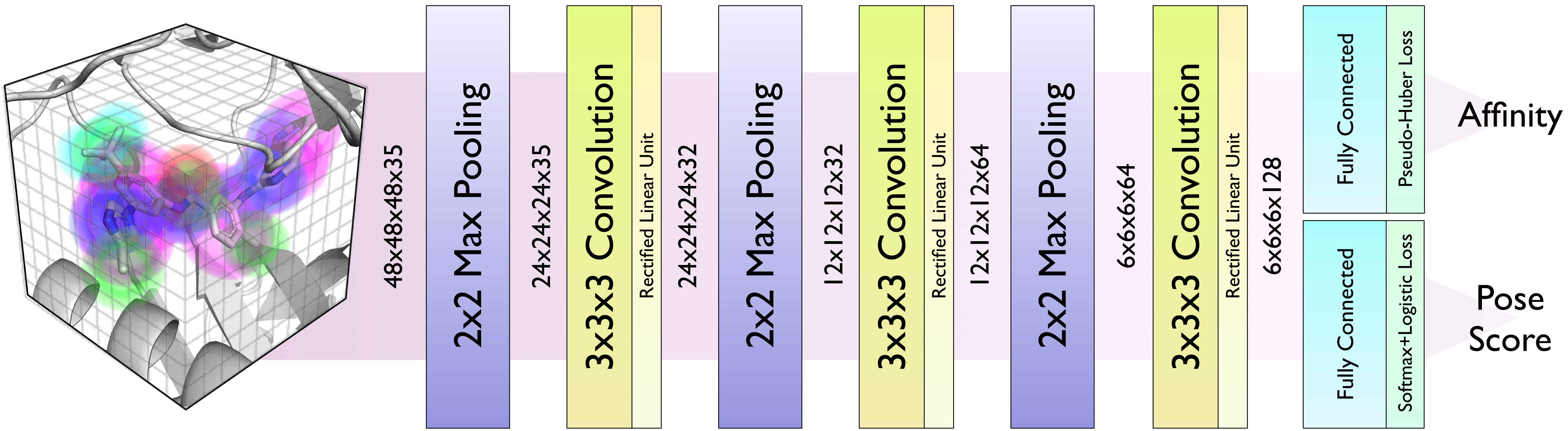


(R,G,B) pixel →

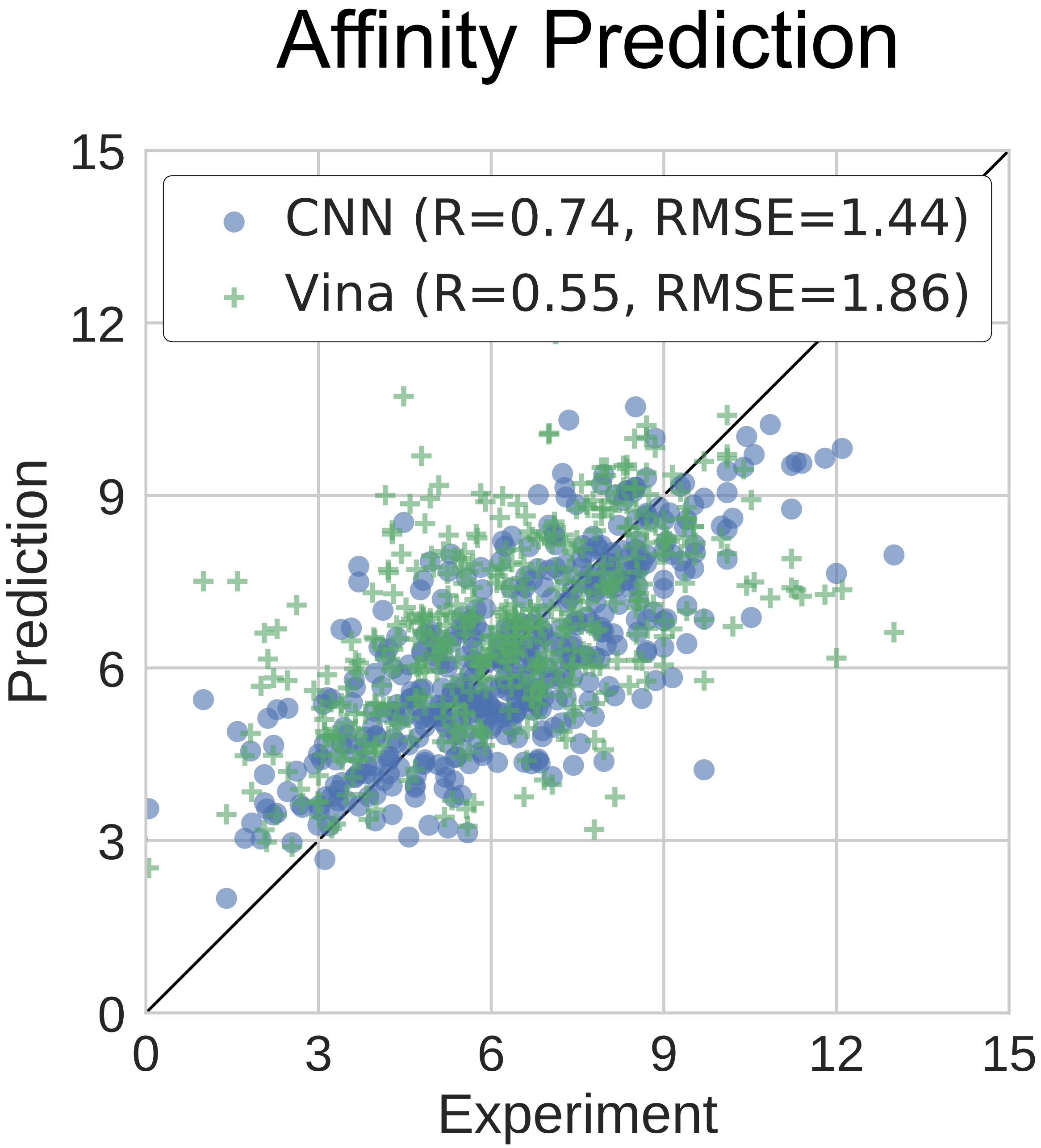
(Carbon, Nitrogen, Oxygen,…) **voxe**

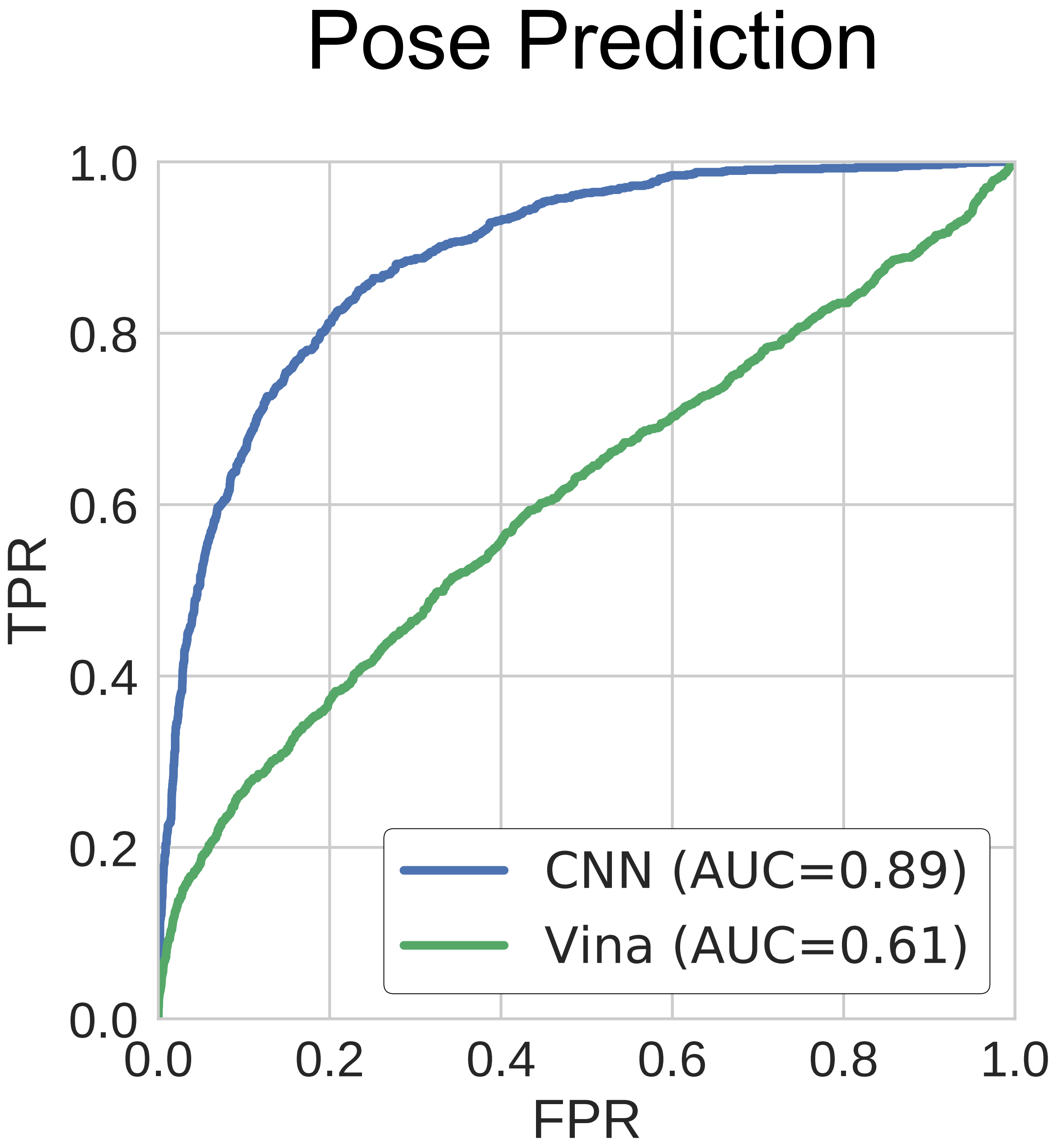
The only parameters for this representation are the choice of **grid resolution**, **atom density**, and **atom types**.

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

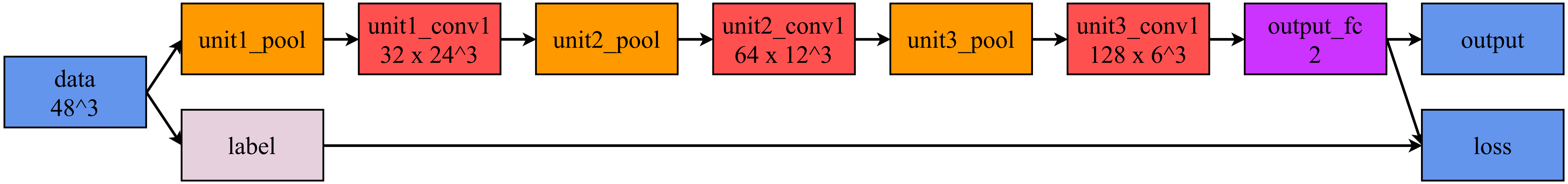
Results



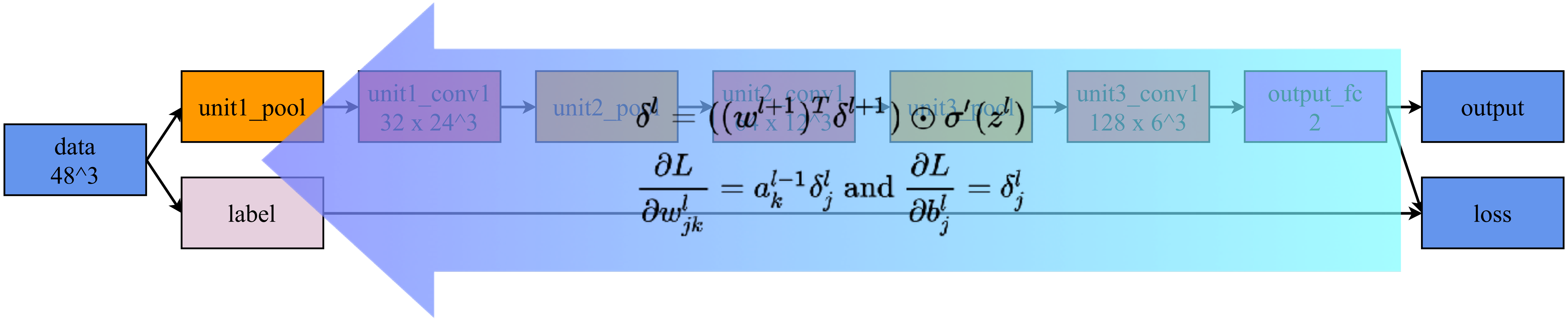


Trained on PDBbind refined; tested on CSAR 🤔

Beyond Scoring



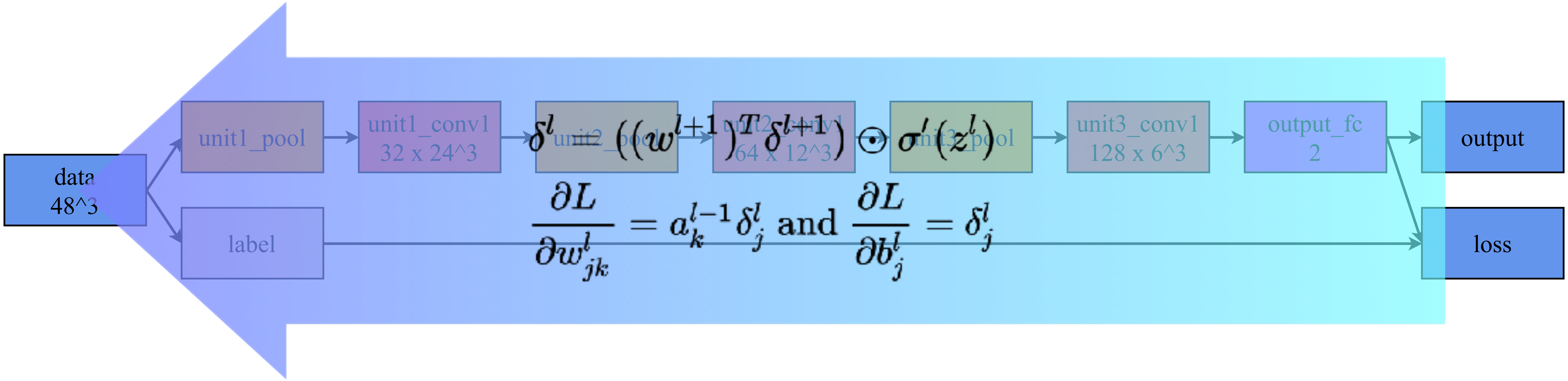
Beyond Scoring



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

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

Beyond Scoring



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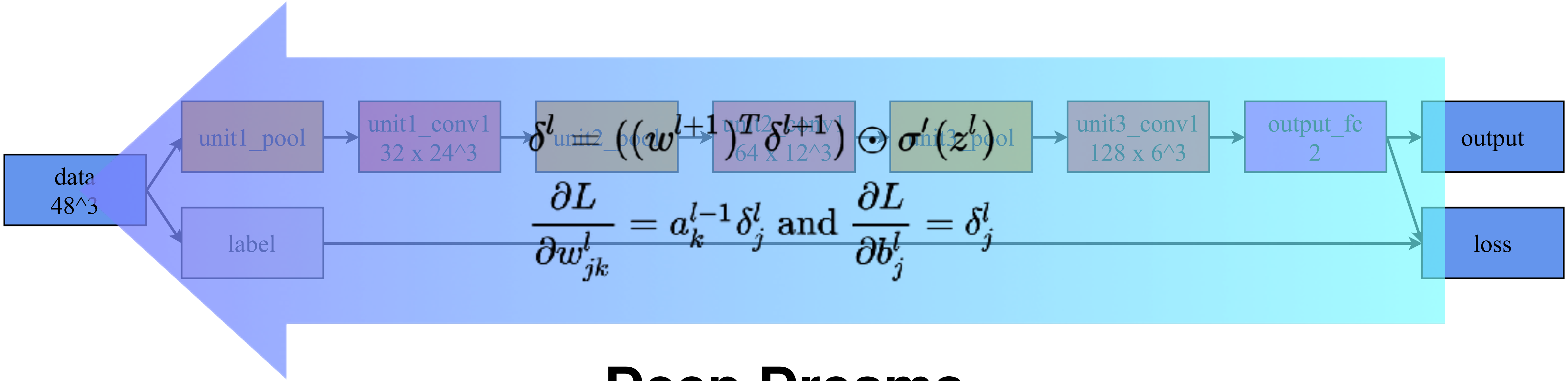
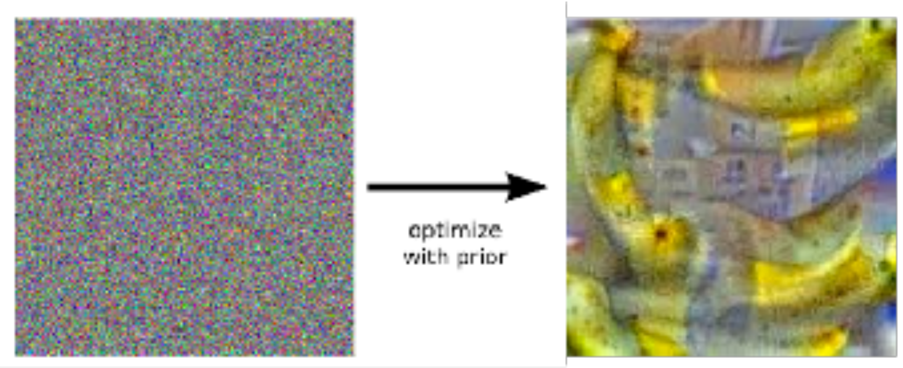
Beyond Scoring



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

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

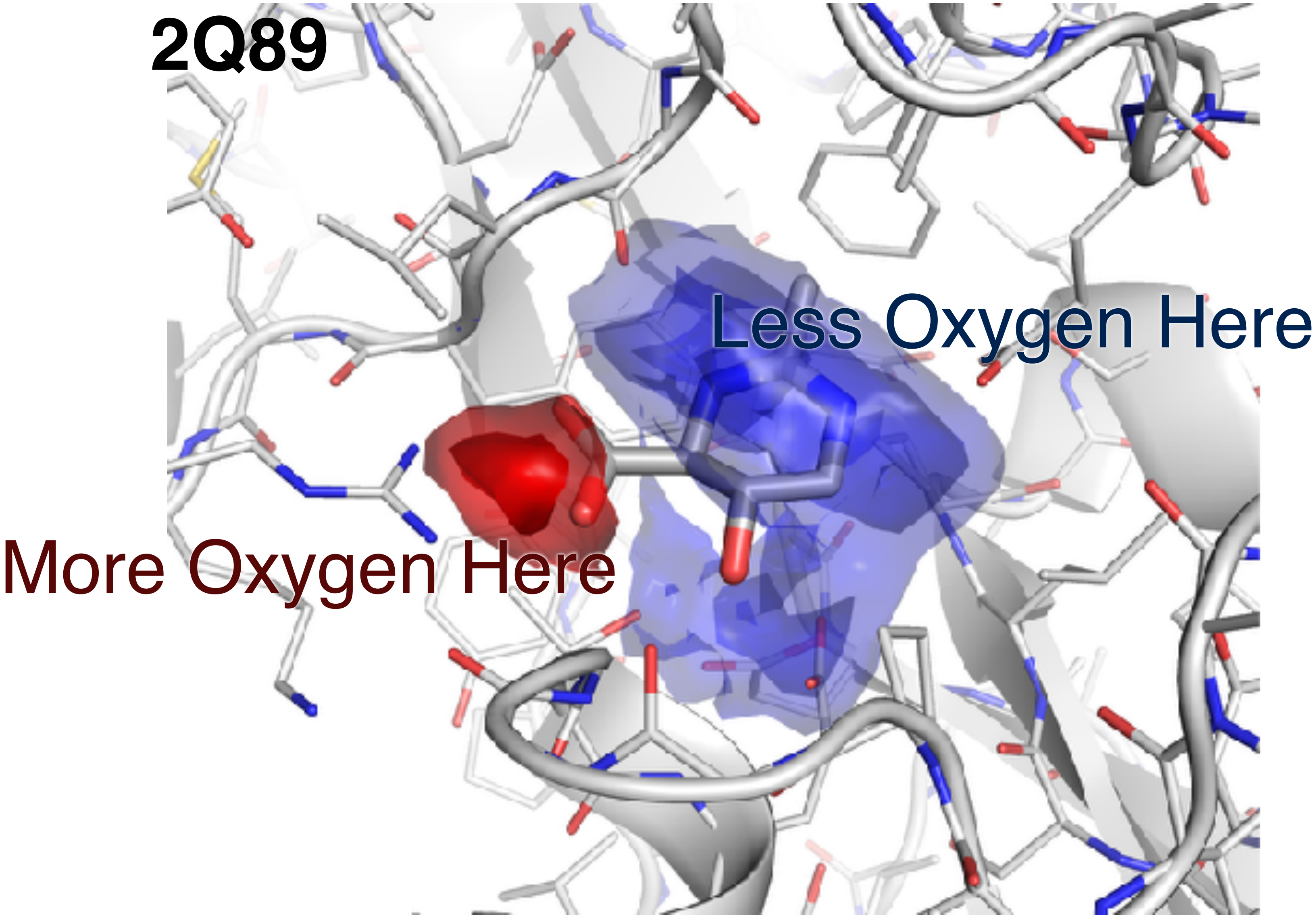
Deep Dreams



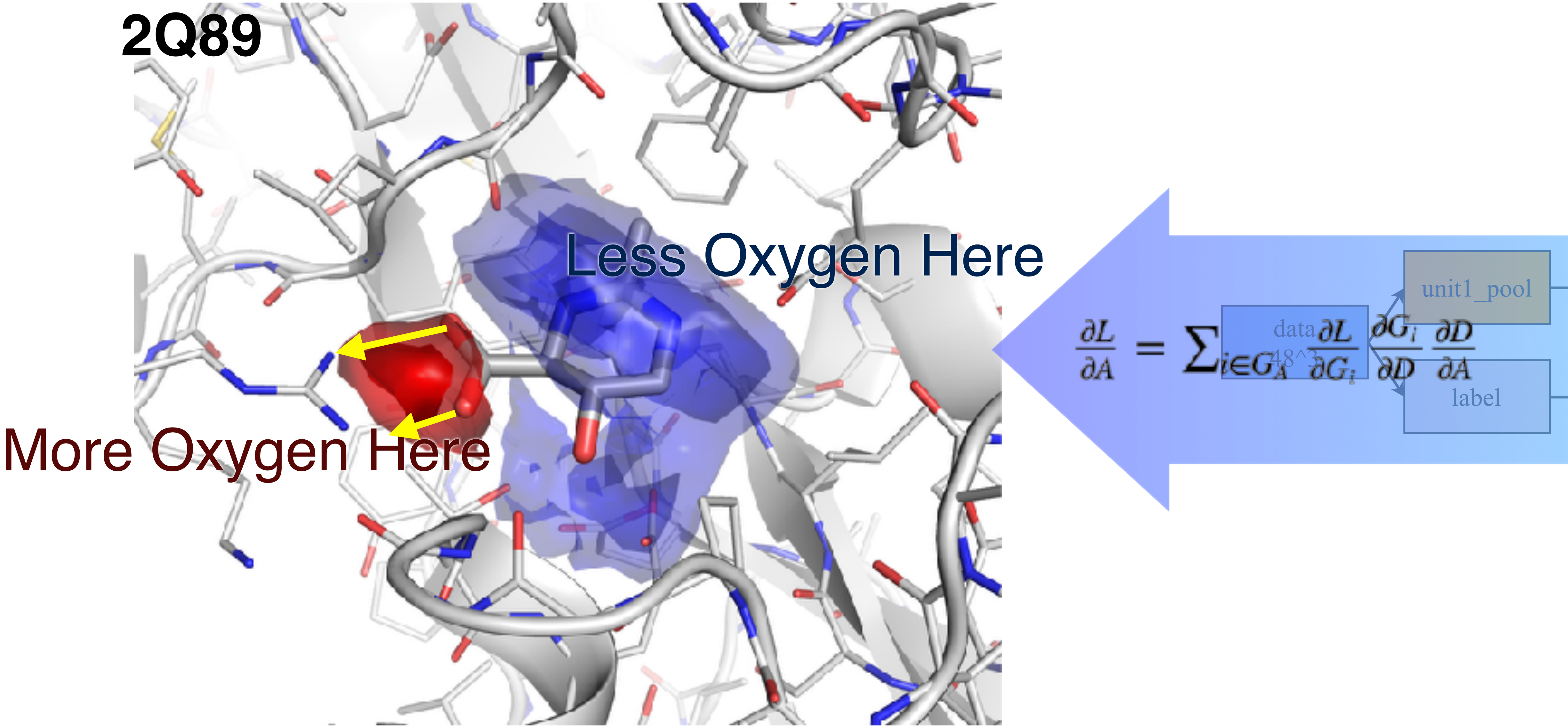
https://research.googleblog.com/2015/06/inceptionism-going-deeper-into-neural.html

https://deepdreamgenerator.com/#gallery

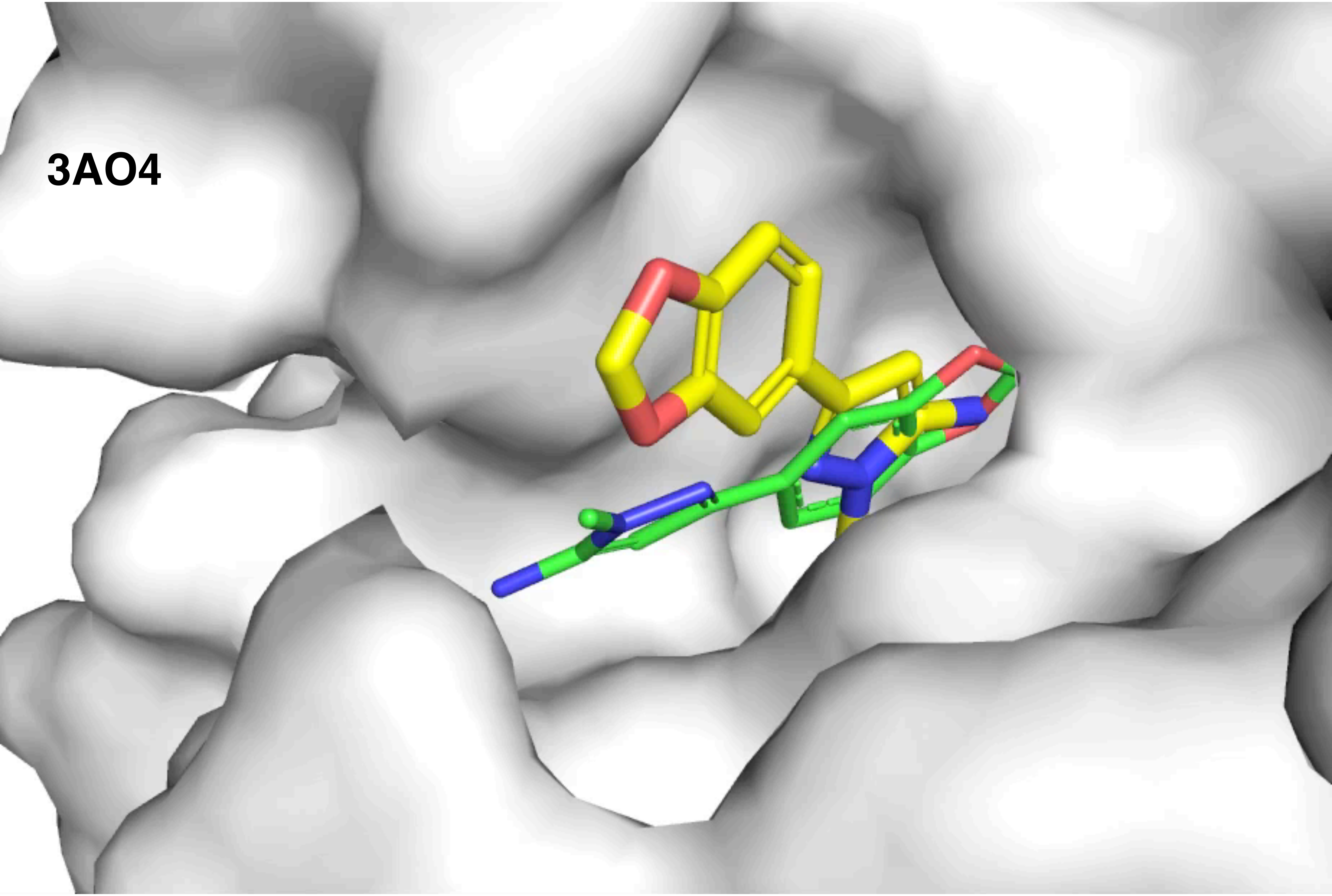
Beyond Scoring



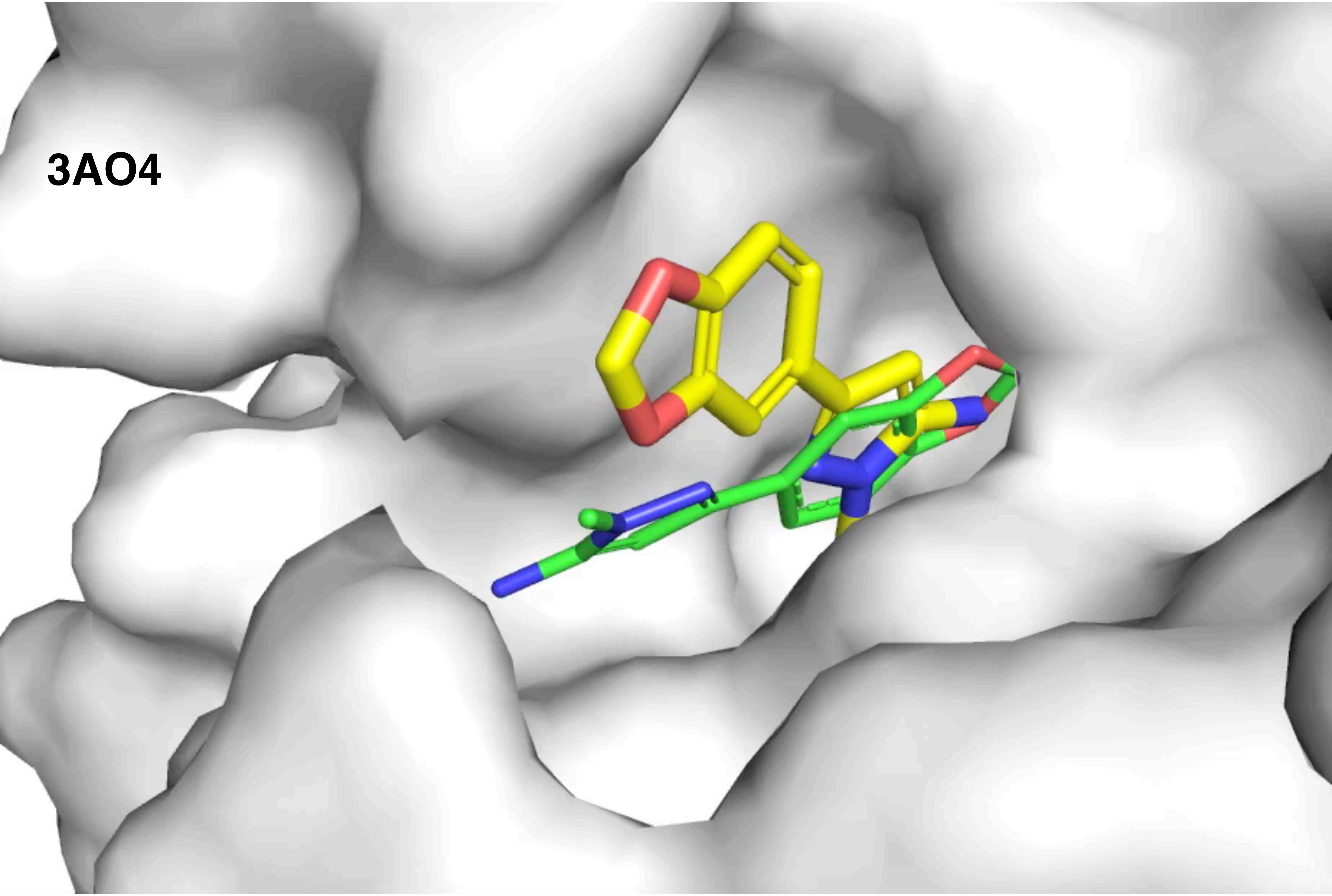
Beyond Scoring



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



3AO4


3AO4

Related Work

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

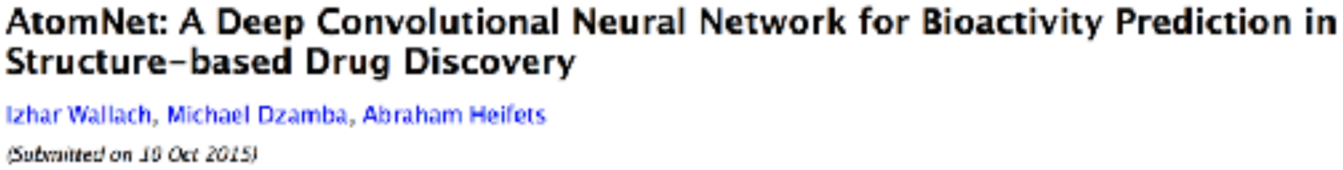
Kristof T. Schütt, Pieter-Jan Kindermans, Huziel E. Sauceda, Stefan Chmiela, Alexandre Tkatchenko, Klaus-Robert Müller

(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

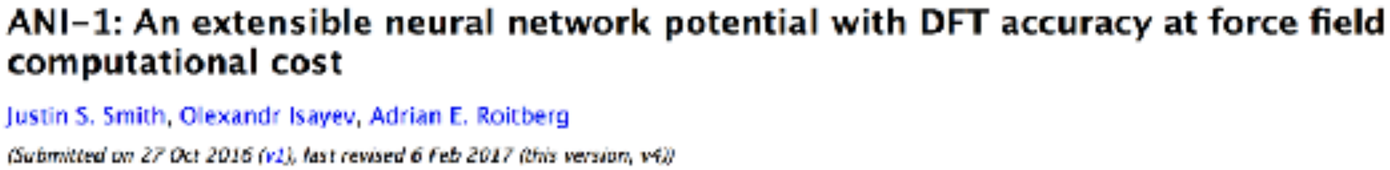
(Submitted on 7 Oct 2016 (v1), last revised 6 Jan 2017 (this version, v2))



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

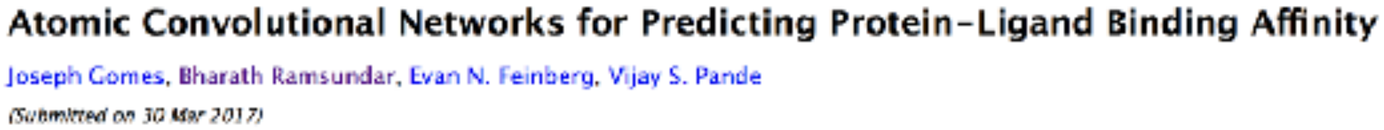
Justin S. Smith, Olexandr Isayev, Adrian E. Roitberg

(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

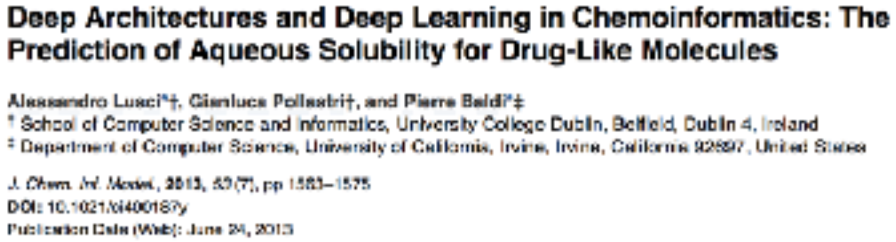
(Submitted on 30 Sep 2015 (v1), last revised 3 Nov 2015 (this version, v2))



Atomic Convolutional Networks for Predicting Protein-Ligand Binding Affinity

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

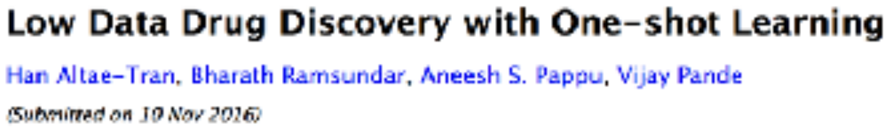
(Submitted on 30 Mar 2017)



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
‡ Department of Computer Science, University of California, Irvine, Irvine, California 92697, United States

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

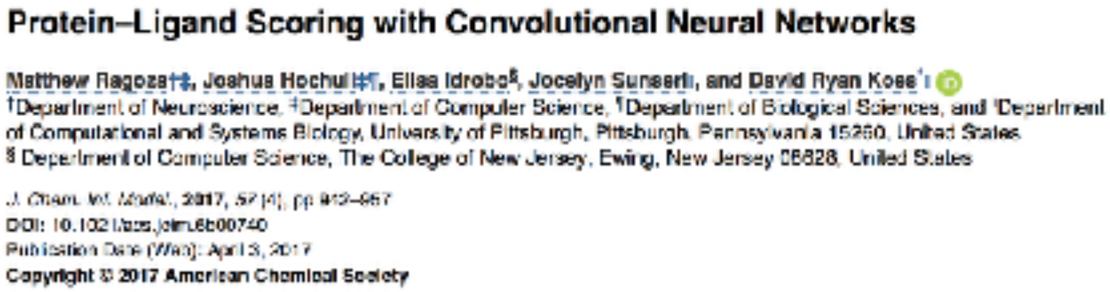
Han Altae-Tran, Bharath Ramsundar, Aneesh S. Pappu, Vijay Pande

(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¶
†Department of Neuroscience, ‡Department of Computer Science, ¶Department of Biological Sciences, and ¶Department of Computational and Systems Biology, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States
§ Department of Computer Science, The College of New Jersey, Ewing, New Jersey 08628, United States

J. Chem. Inf. Model., 2017, 57 (4), pp 942–957
DOI: 10.1021/acs.jcim.6b00740
Publication Date (Web): April 3, 2017
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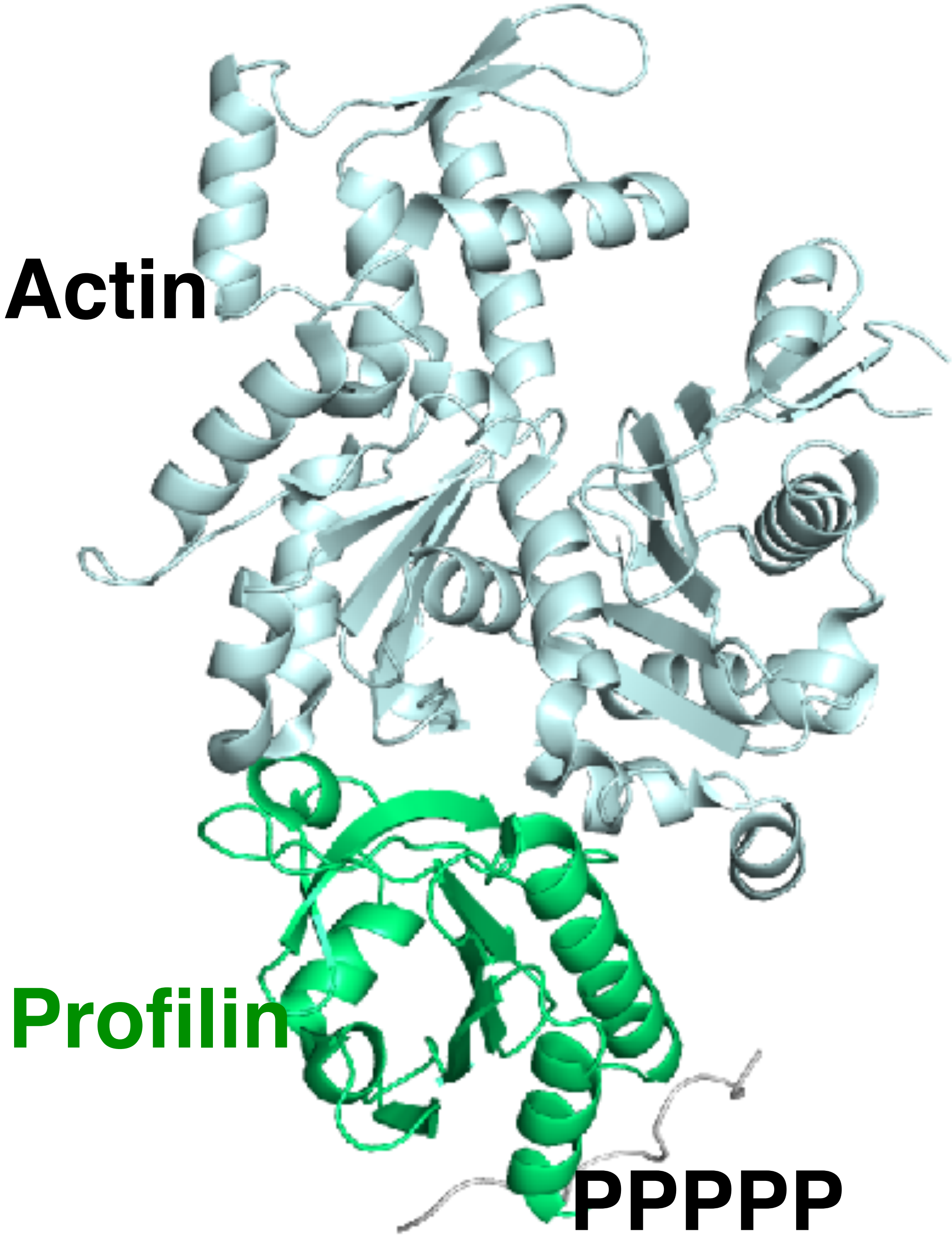
Case Study: Profilin-Actin

Profilin

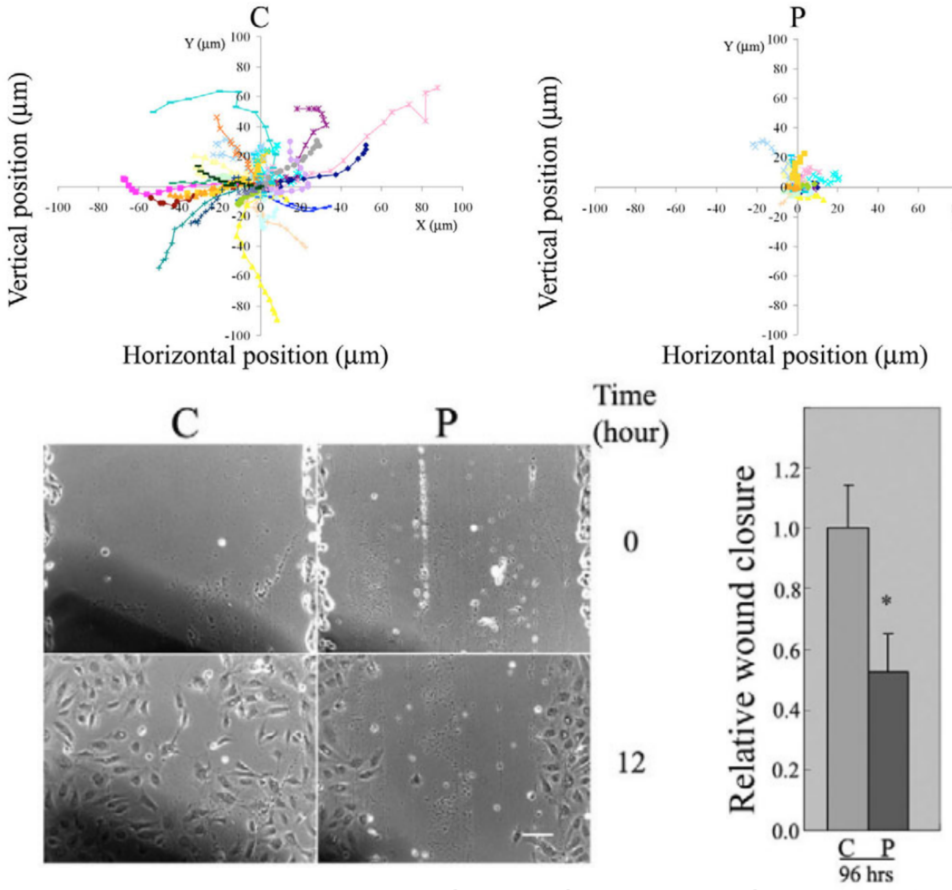


- Actin-binding protein
- Accelerates actin polymerization in presence of proline-rich proteins (e.g. formin, WASP, VASP)
- Sequesters actin otherwise

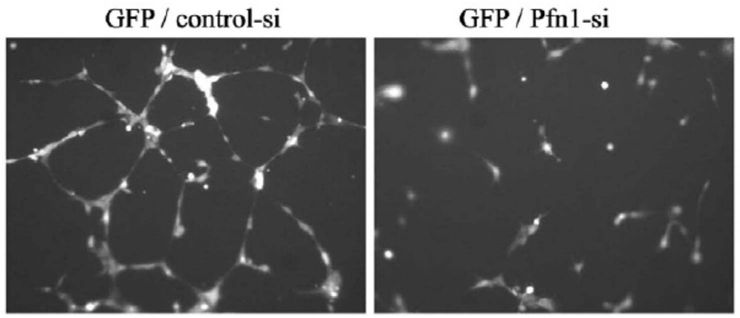

Dave Gau


Partha Roy

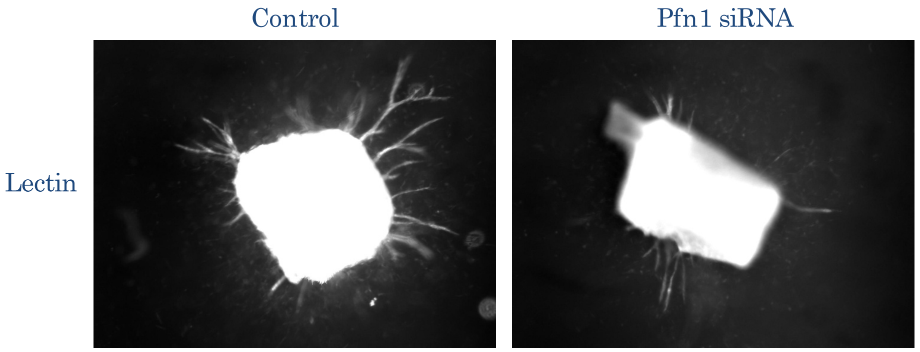
Profilin is important for angiogenesis



Endothelial Cell Single-Cell Migration and Wound Closure



2D Cord Morphogenesis Assay

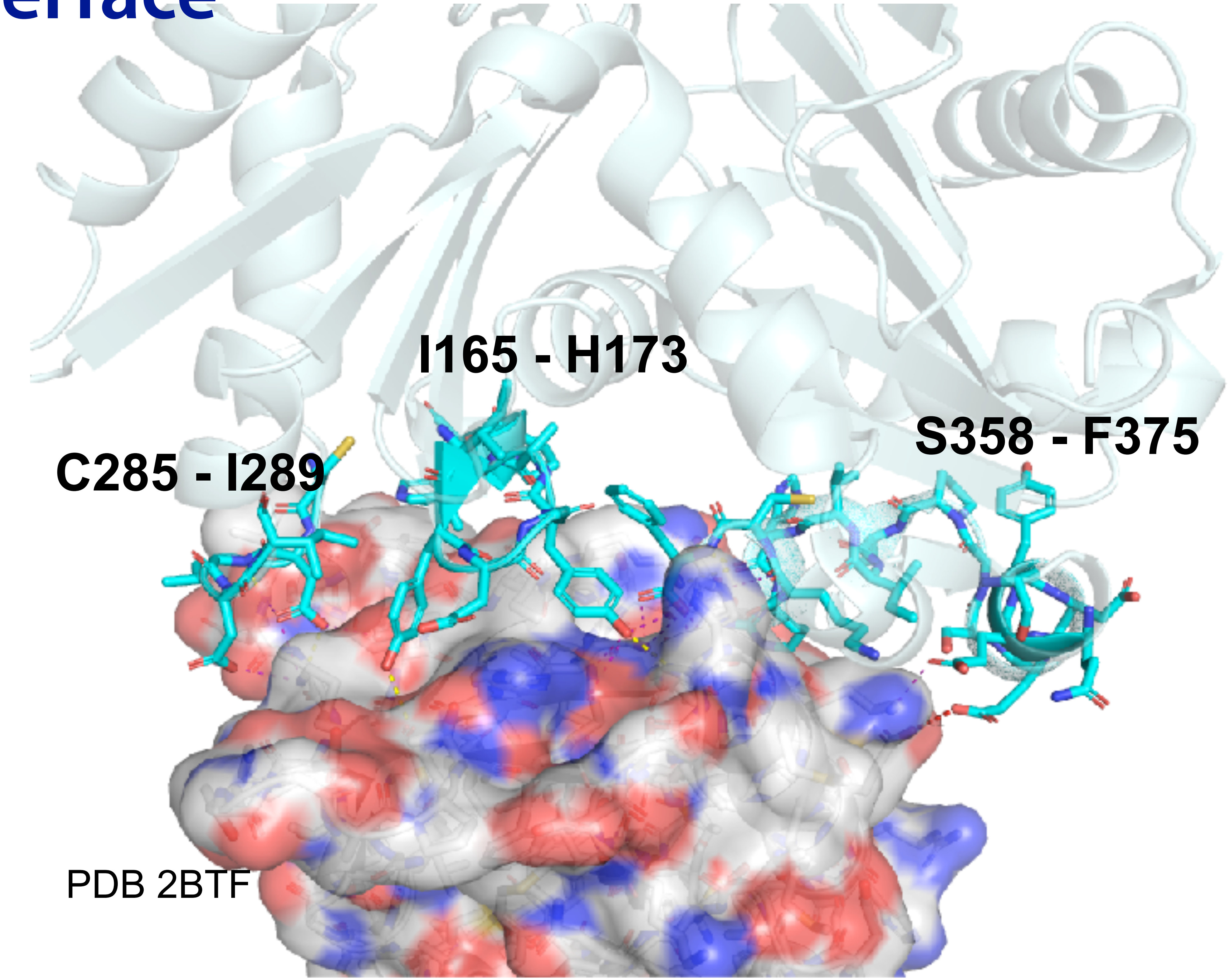


Sprouting of Explanted Aortic Rings

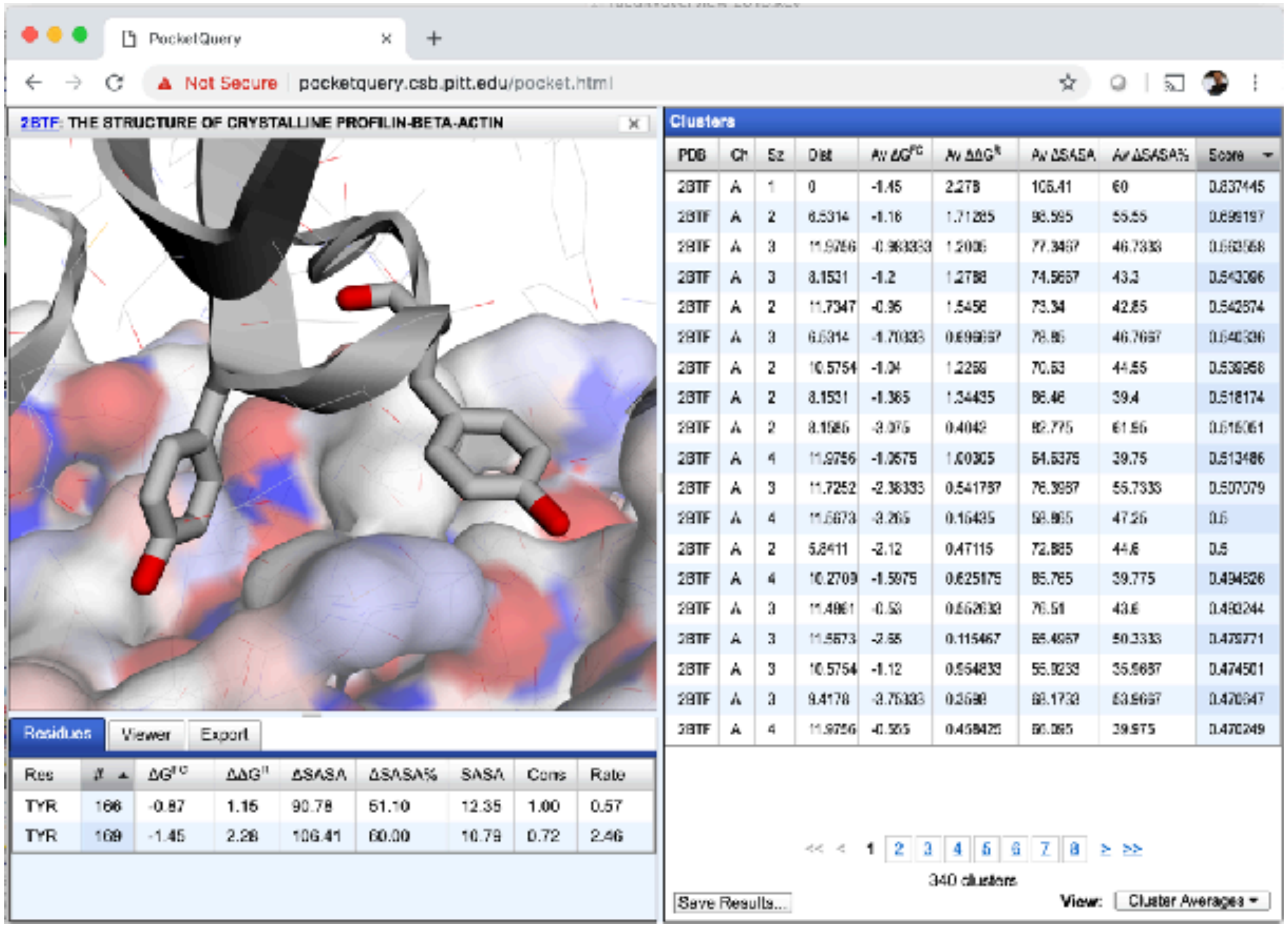
Ding, Z., Lambrechts, A., Parepally, M., and **Roy, P.**, 2006, "Silencing profilin-1 inhibits endothelial cell proliferation, migration and cord morphogenesis.," Journal of cell science, vol.119, no.Pt 19, pp. 4127-37, 16968742.

Ding, Z., **Gau, D.**, Deasy, B., Wells, A., and **Roy, P.**, 2009, "Both actin and polyproline interactions of profilin-1 are required for migration, invasion and capillary morphogenesis of vascular endothelial cells.," Experimental cell research, vol.315, no.17, pp. 2963-73, 19607826.

Interface



Interface Analysis



Not Secure pocketquery.csb.pitt.edu/pocket.html

2BTF: THE STRUCTURE OF CRYSTALLINE PROFILIN-BETA-ACTIN

Clusters

PDB	Ch	Sz	Dist	Av ΔG^{FC}	Av $\Delta\Delta G^{R}$	Av ΔSASA	Av ΔSASA%	Score
2BTF	A	1	0	-1.45	2.278	106.41	60	0.837445
2BTF	A	2	6.5314	-1.16	1.71285	98.595	55.55	0.699197
2BTF	A	3	11.9756	-0.983333	1.2006	77.3467	46.7333	0.563558
2BTF	A	3	8.1531	-1.2	1.2788	74.5667	43.2	0.543096
2BTF	A	2	11.7347	-0.95	1.5458	73.34	42.85	0.542574
2BTF	A	3	6.5314	-1.70333	0.696667	78.86	46.7667	0.540336
2BTF	A	2	10.5754	-1.04	1.2268	70.63	44.55	0.539958
2BTF	A	2	8.1531	-1.365	1.34435	86.46	39.4	0.518174
2BTF	A	2	8.1586	-3.075	0.4049	92.775	61.56	0.516061
2BTF	A	4	11.9756	-1.0675	1.00305	64.6375	39.75	0.513486
2BTF	A	3	11.7252	-2.38333	0.541767	76.3967	55.7333	0.507079
2BTF	A	4	11.5673	-3.265	0.16435	98.865	47.26	0.5
2BTF	A	2	5.8411	-2.12	0.47115	72.885	44.6	0.5
2BTF	A	4	10.2709	-1.5975	0.625175	85.765	39.775	0.494526
2BTF	A	3	11.4861	-0.53	0.662639	76.51	43.6	0.493244
2BTF	A	3	11.5673	-2.65	0.115467	85.4667	50.3333	0.479771
2BTF	A	3	10.5754	-1.12	0.554839	55.9233	35.9667	0.474501
2BTF	A	3	9.4178	-3.75333	0.2698	89.1733	53.9667	0.470347
2BTF	A	4	11.9756	-0.565	0.458425	90.065	39.975	0.470249

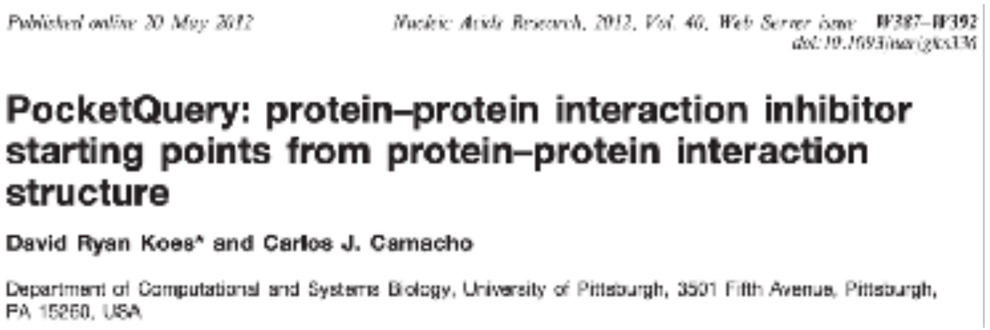
<< < 1 2 3 4 5 6 7 8 > >>

340 clusters

Save Results...

View: Cluster Averages

Res	#	ΔG^{FC}	$\Delta\Delta G^{R}$	ΔSASA	ΔSASA%	SASA	Cons	Rate
TYR	166	-0.87	1.15	90.78	51.10	12.35	1.00	0.57
TYR	169	-1.45	2.28	106.41	60.00	10.79	0.72	2.46

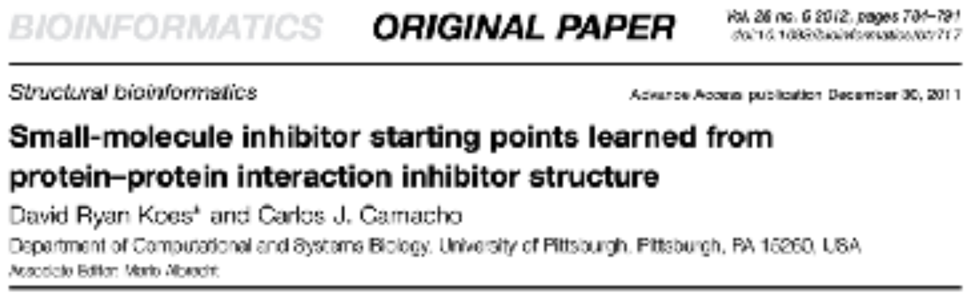


Published online 20 May 2012 Nucleic Acids Research, 2012, Vol. 40, Web Server issue W387–W392
doi:10.1093/nar/gks336

PocketQuery: protein–protein interaction inhibitor starting points from protein–protein interaction structure

David Ryan Koes* and Carlos J. Camacho

Department of Computational and Systems Biology, University of Pittsburgh, 3501 Fifth Avenue, Pittsburgh, PA 15260, USA



BIOINFORMATICS **ORIGINAL PAPER** Vol. 28 no. 6 2012, pages 784–791

Structural bioinformatics Advance Access publication December 30, 2011

Small-molecule inhibitor starting points learned from protein–protein interaction inhibitor structure

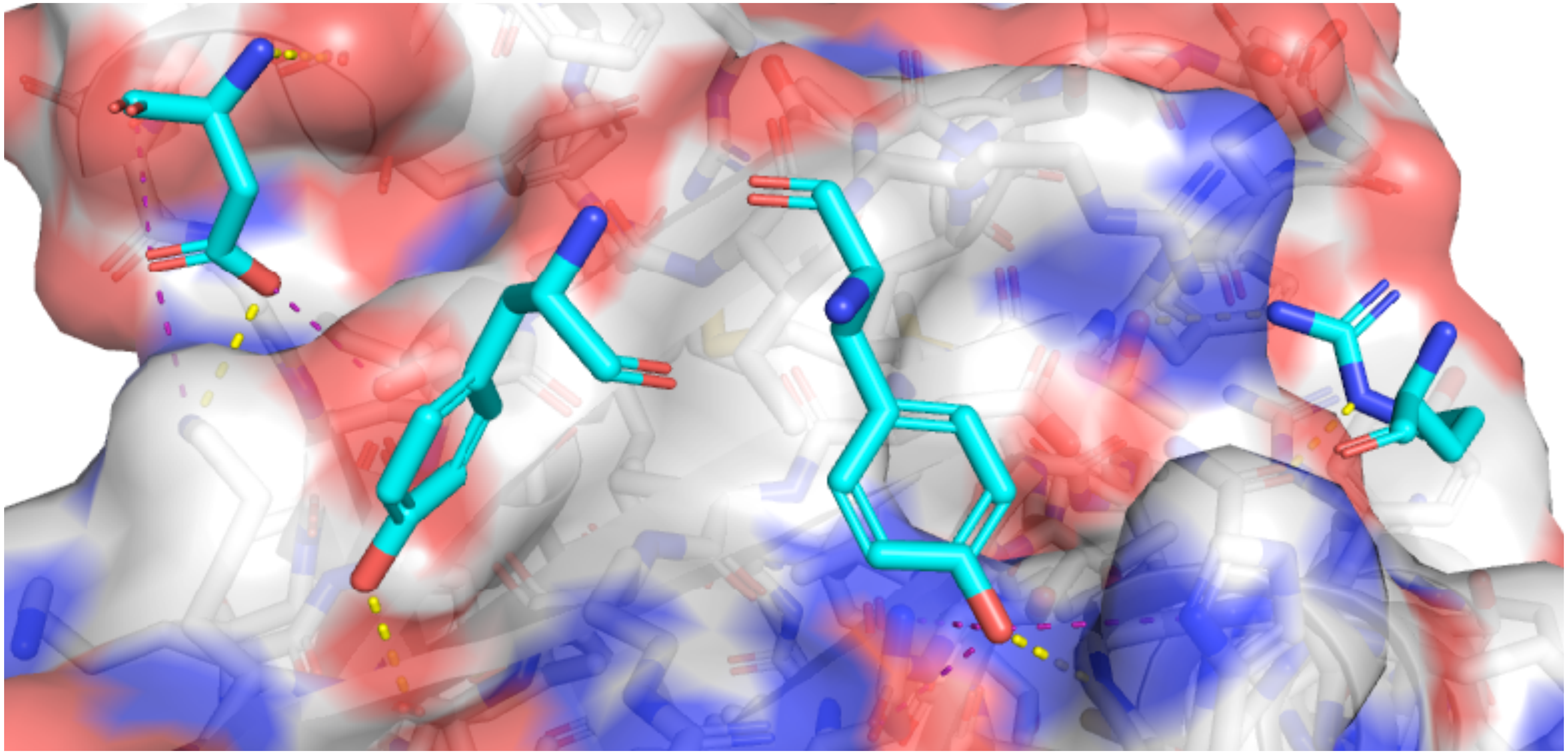
David Ryan Koes* and Carlos J. Camacho

Department of Computational and Systems Biology, University of Pittsburgh, Pittsburgh, PA 15260, USA

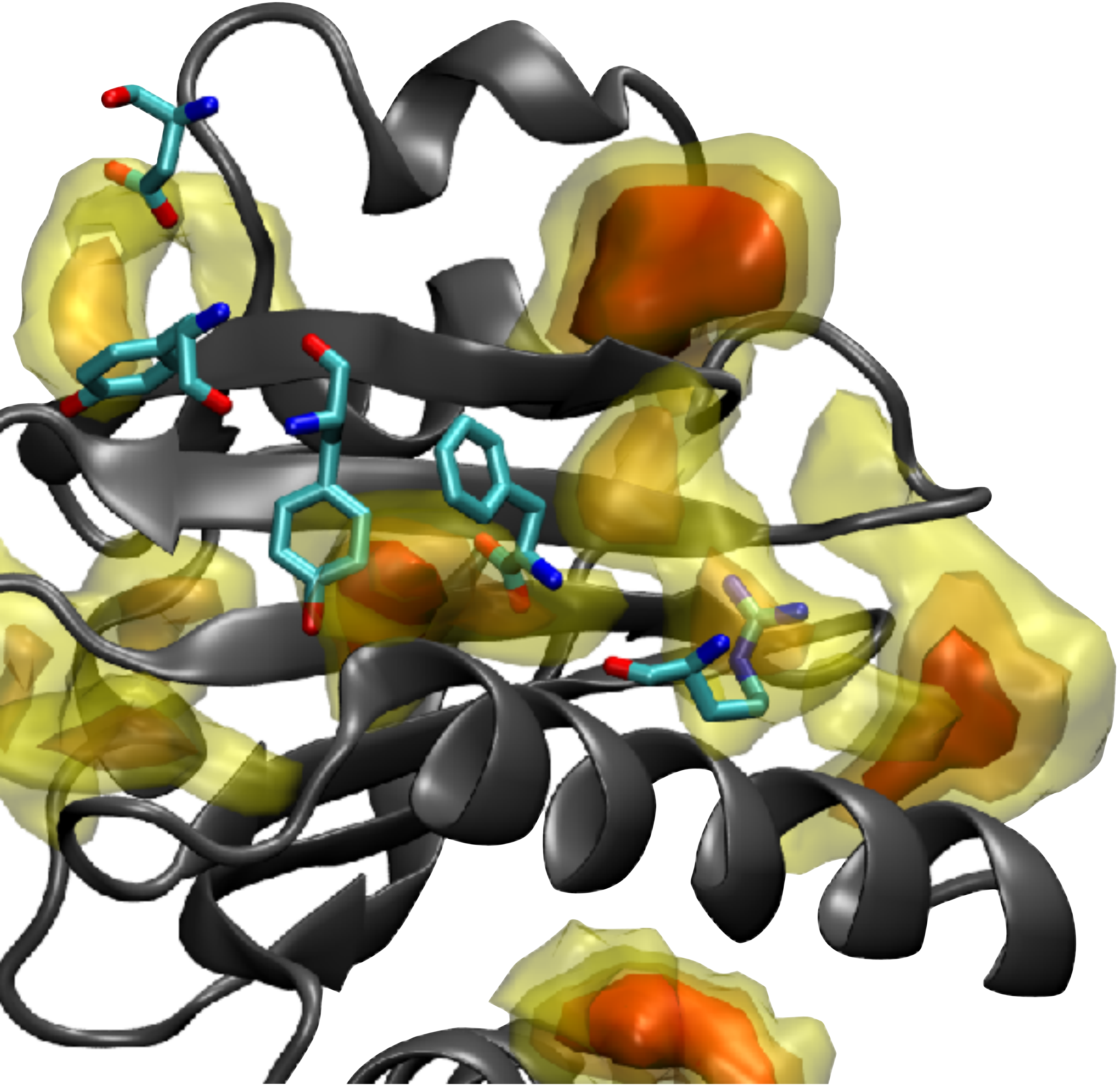
Associate Editor: Mario Albrecht

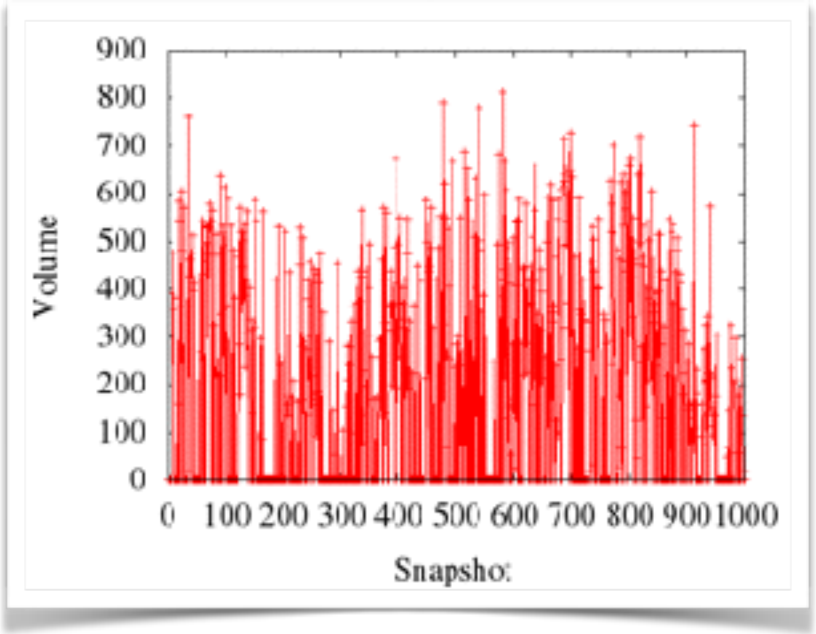
Key Contacts

D286	**Y166**	**Y169**	**R372**
-5.3 ΔG	-0.9 ΔG	-1.5 ΔG	-2.6 ΔG
73% ΔSASA%	51% ΔSASA%	60% ΔSASA%	72% ΔSASA%



Pocket Hunting

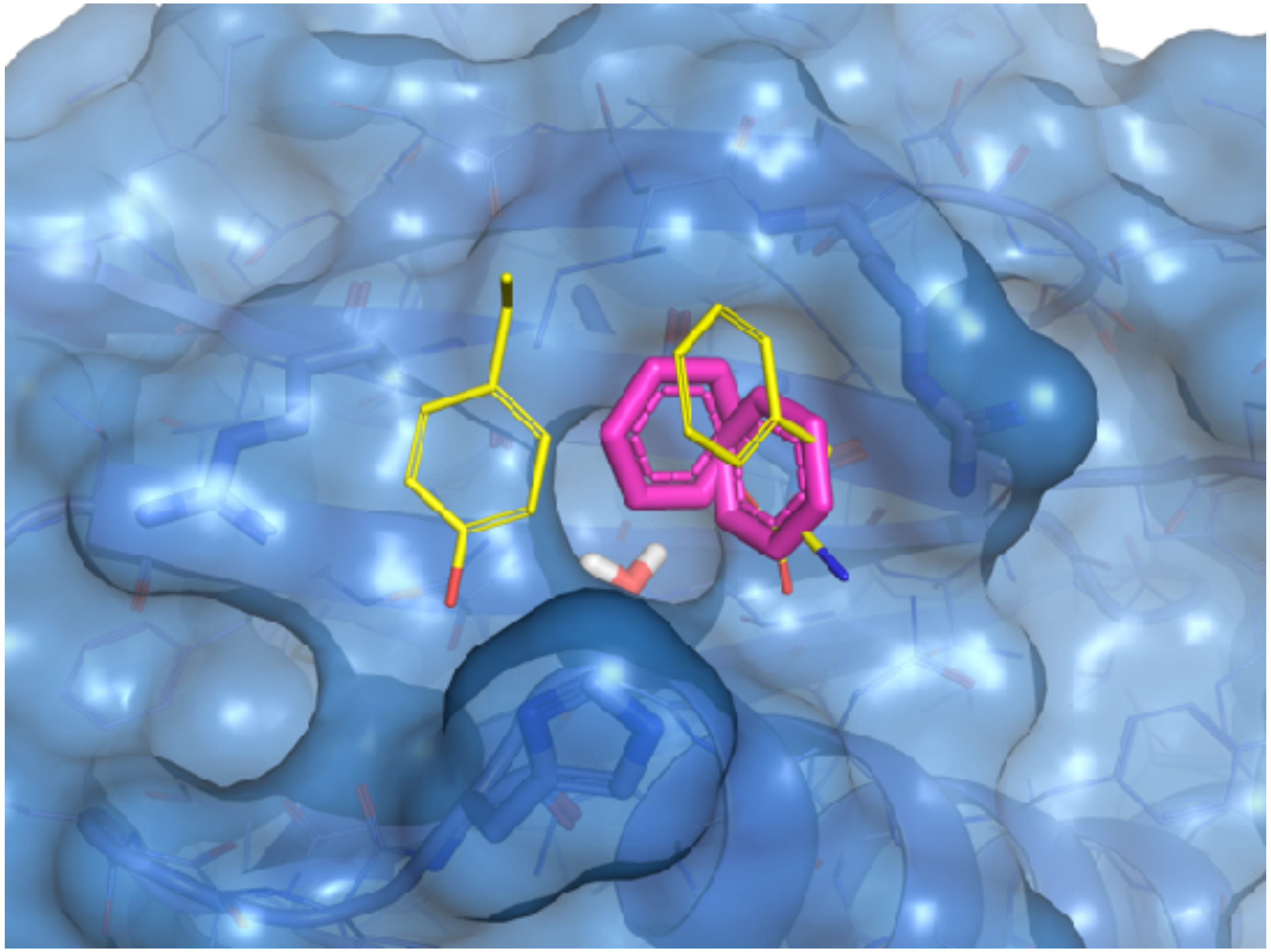




fpocket

AMBER

Fragment Docking



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Scoring and Minimization with AutoDock Vina

Status: Beta

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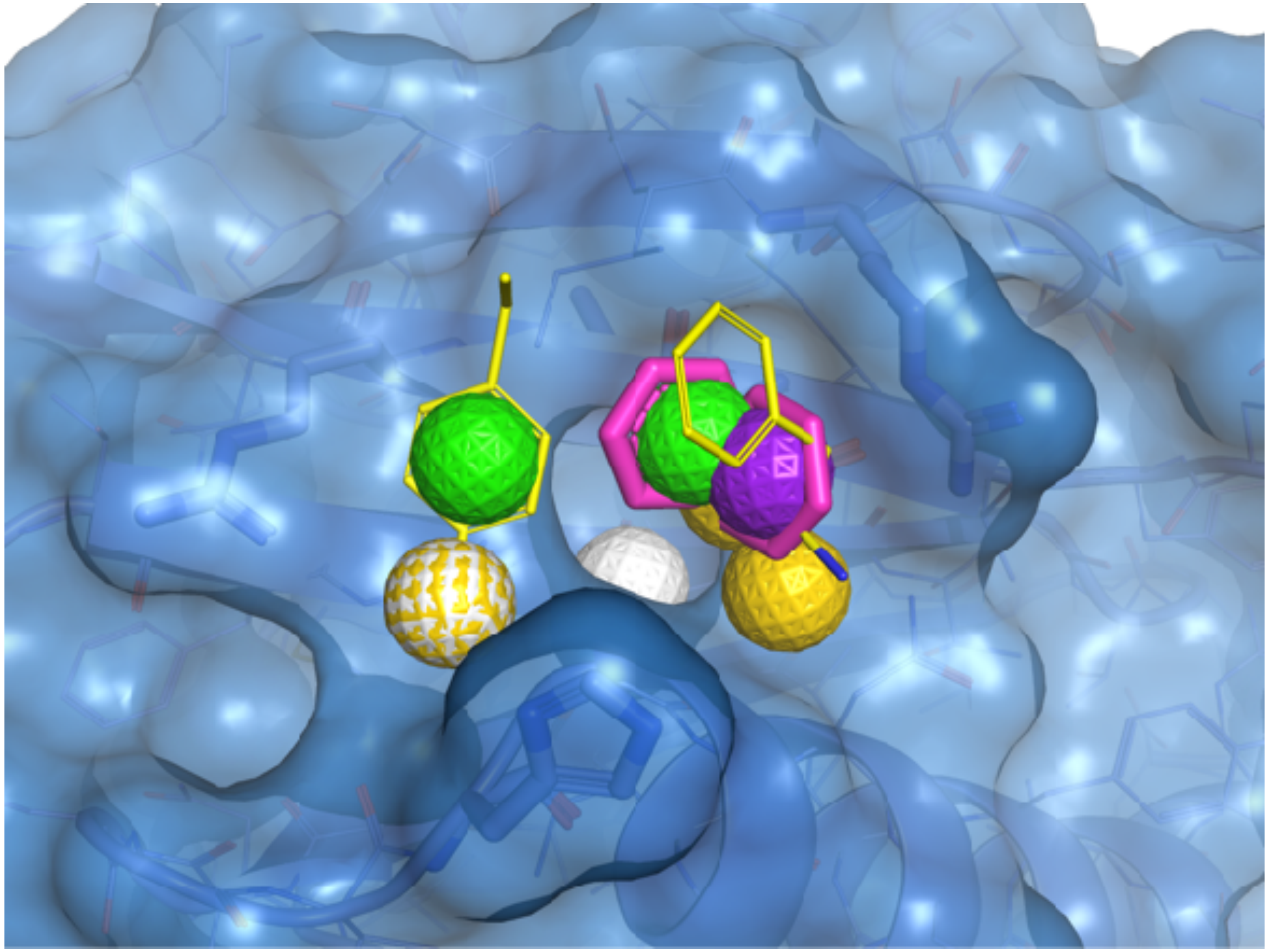
★★★★★ 4 Reviews

Downloads: 41 This Week

Dock **benzene** and **water** to structures extracted from molecular dynamics simulation

Pharmacophores

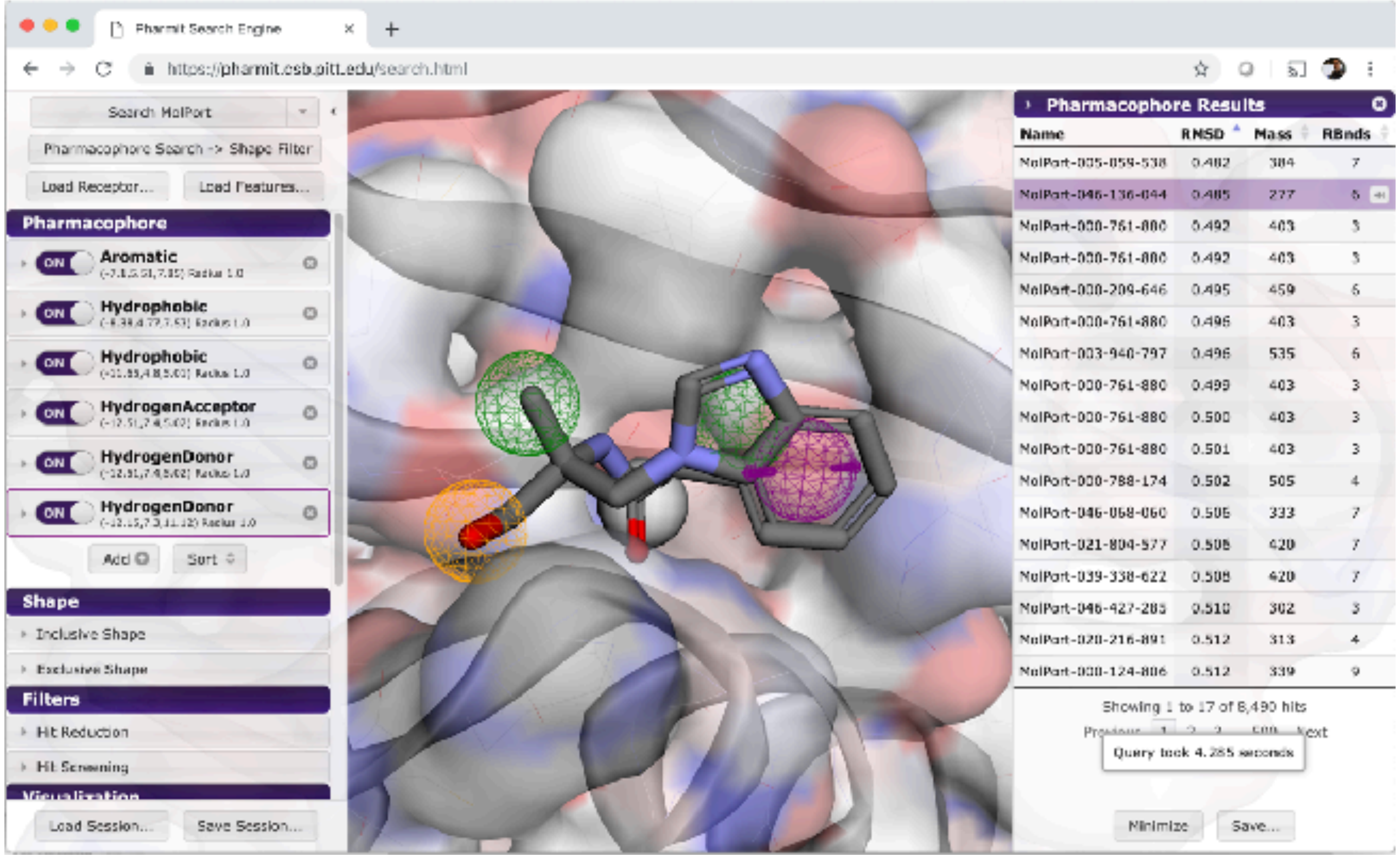


10 pharmacophores

hydrophobic core + $\binom{5}{3}$ hbond features

Pharmacophore Search

http://pharmit.csb.pitt.edu/

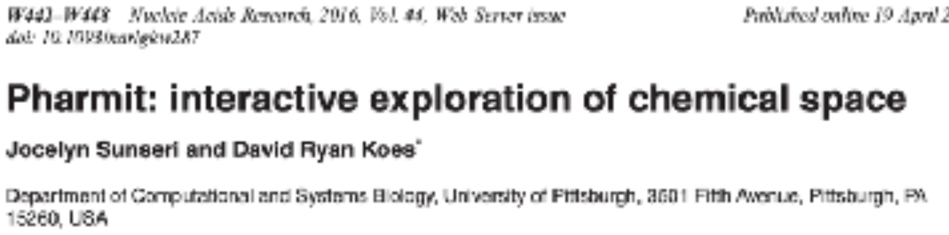


Pharmacophore Results

Name	RMSD	Mass	RBnds
MolPort-035-058-538	0.482	384	7
MolPort-046-136-044	0.485	277	5
MolPort-030-761-880	0.492	403	3
MolPort-030-761-880	0.492	403	3
MolPort-030-209-646	0.495	459	6
MolPort-030-761-880	0.496	403	3
MolPort-003-940-797	0.496	535	6
MolPort-030-761-880	0.499	403	3
MolPort-030-761-880	0.500	403	3
MolPort-030-761-880	0.501	403	3
MolPort-030-788-174	0.502	505	4
MolPort-046-068-060	0.506	333	7
MolPort-021-804-577	0.508	420	7
MolPort-039-338-622	0.508	420	7
MolPort-046-427-285	0.510	302	3
MolPort-020-216-891	0.512	313	4
MolPort-030-124-806	0.512	339	9

Showing 1 to 17 of 8,490 hits

Query took 4.285 seconds



W441–W448 Nucleic Acids Research, 2016, Vol. 44, Web Server issue Published online 19 April 2
doi: 10.1093/nar/gkw287

Pharmit: interactive exploration of chemical space

Jocelyn Sunseri and David Ryan Koes*

Department of Computational and Systems Biology, University of Pittsburgh, 3501 Fifth Avenue, Pittsburgh, PA 15260, USA

Pharmer: Efficient and Exact Pharmacophore Search

David Ryan Koes*† and Carlos J. Camacho†
Department of Computational and Systems Biology, University of Pittsburgh, Pittsburgh, Pennsylvania, United States

J. Chem. Inf. Model., **2011**, *51* (6), pp 1307–1314
DOI: 10.1021/ci200097m
Publication Date (Web): May 23, 2011
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E-mail: dkoes@pitt.edu.

Cite this: *J. Chem. Inf. Model.* 2011, 51, 6, 1307-1314

Journal of COMPUTATIONAL CHEMISTRY

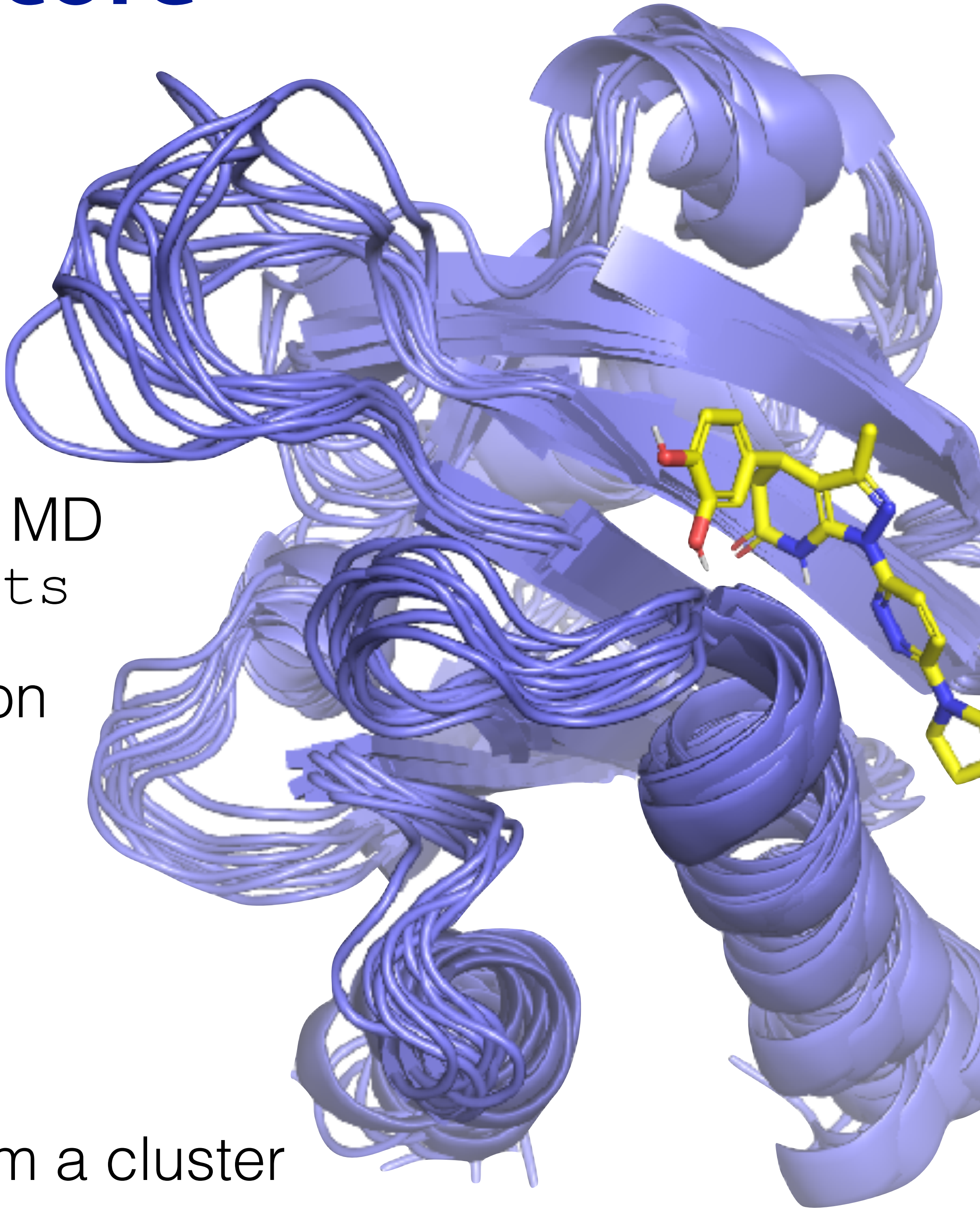
Full Paper

Shape-based virtual screening with volumetric aligned molecular shapes

David Ryan Koes, Carlos J. Camacho

First published: 22 July 2014 | https://doi.org/10.1002/jcc.23690 | Cited by: 5

Refine and Consensus Score



Select 10 representative conformations from MD
`https://github.com/dkoes/md-scripts`

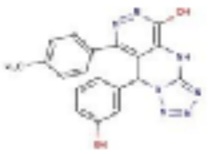
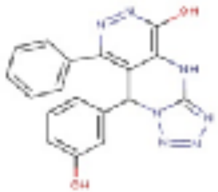
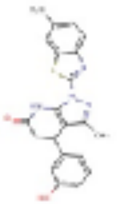
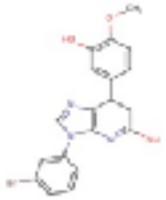
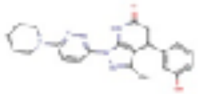
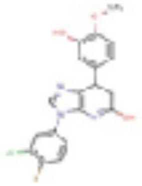
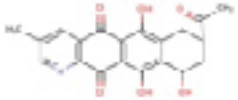
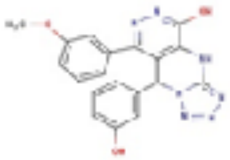
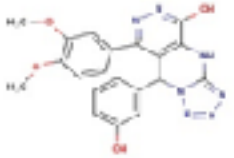
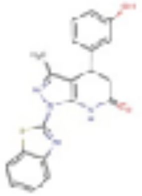
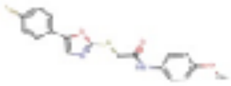
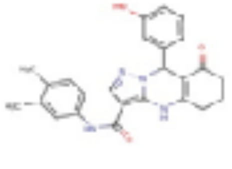
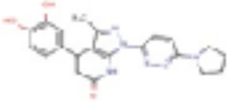
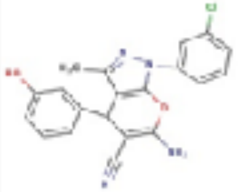
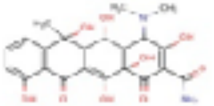
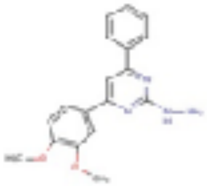
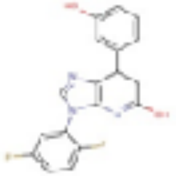
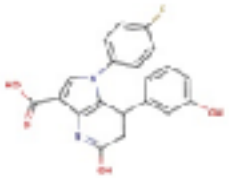
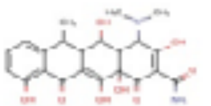
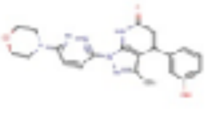
Minimize with smina and Vina scoring function

Consensus score

Cluster using OpenBabel FP2 fingerprints
`https://pymolwiki.org/index.php/Cluster_mols`

Select top ranked compounds, at most 2 from a cluster

20 Compounds Ordered

Compound	MolPort#	Structure
C1	MolPort-000-139-035	
C2	MolPort-000-139-027	
C3	MolPort-010-655-167	
C4	MolPort-008-332-724	
C20	MolPort-016-589-024	
C5	MolPort-008-334-836	
C6	MolPort-002-806-727	
C7	MolPort-010-757-363	
C8	MolPort-010-757-388	
C9	MolPort-007-694-167	
C10	MolPort-010-765-977	
C11	MolPort-010-765-659	
C12	MolPort-016-588-786	
C13	MolPort-001-827-841	
C14	MolPort-002-323-861	
C15	MolPort-002-166-888	
C16	MolPort-008-334-341	
C17	MolPort-008-332-636	
C18	MolPort-002-964-477	
C19	MolPort-016-588-896	

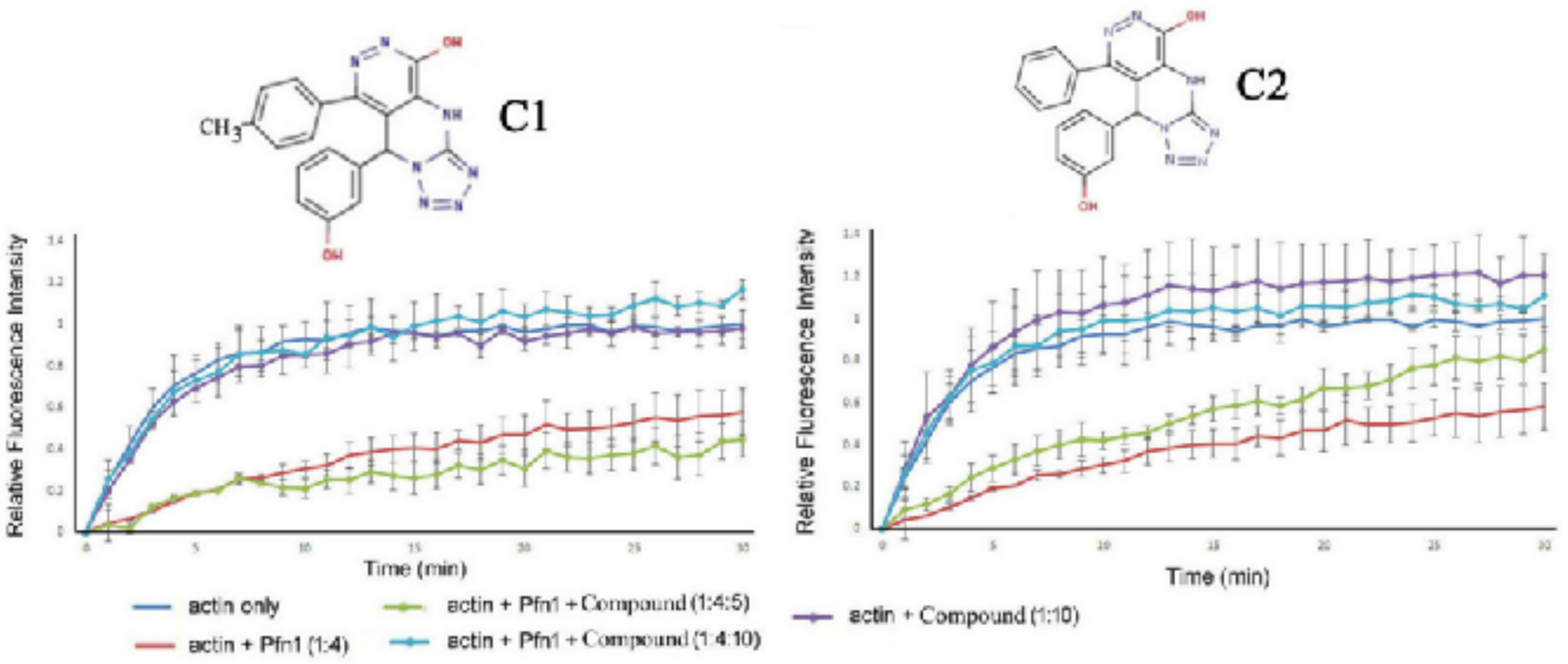
20 Compounds Ordered

Compound	MolPort#	Structure
C1	MolPort-000-139-035	
C2	MolPort-000-139-027	
C3	MolPort-010-655-167	✗
C4	MolPort-008-332-724	✗
C20	MolPort-016-589-024	✗
C5	MolPort-008-334-836	✗
C6	MolPort-002-806-727	✗
C7	MolPort-010-757-363	✗
C8	MolPort-010-757-388	✗
C9	MolPort-007-694-167	✗
C10	MolPort-010-765-977	✗
C11	MolPort-010-765-659	✗
C12	MolPort-016-588-786	✗
C13	MolPort-001-827-841	✗
C14	MolPort-002-323-861	✗
C15	MolPort-002-166-888	✗
C16	MolPort-008-334-341	✗
C17	MolPort-008-332-636	✗
C18	MolPort-002-964-477	✗
C19	MolPort-016-588-896	✗

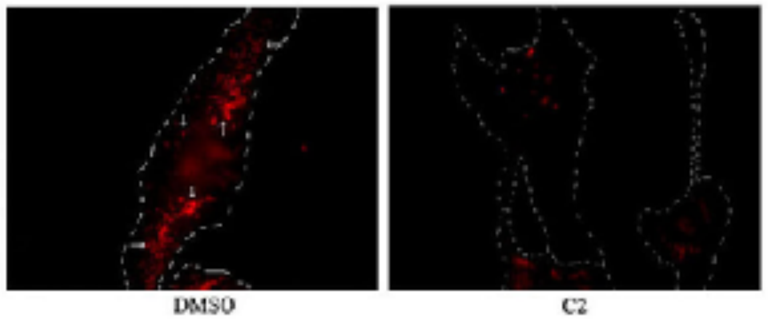
Structure-based virtual screening identifies a small-molecule inhibitor of the profilin 1–actin interaction

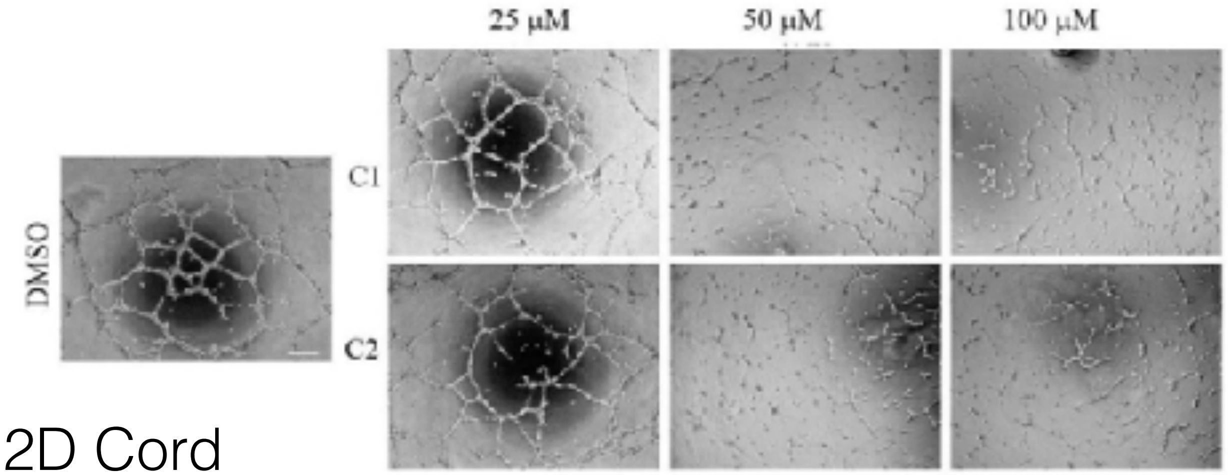
Received for publication, July 27, 2017, and in revised form, December 6, 2017 Published, Papers in Press, December 27, 2017, DOI 10.1074/jbc.M117.809137

David Gau[‡1], Taber Lewis[§], Lee McDermott[¶], Peter Wipf[§‖], David Koes[¶], and Partha Roy[‡‖**2]
From the Departments of [‡]Bioengineering, [§]Chemistry, [¶]Computational and Systems Biology, [‖]Cell Biology, and [**]Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania 15219



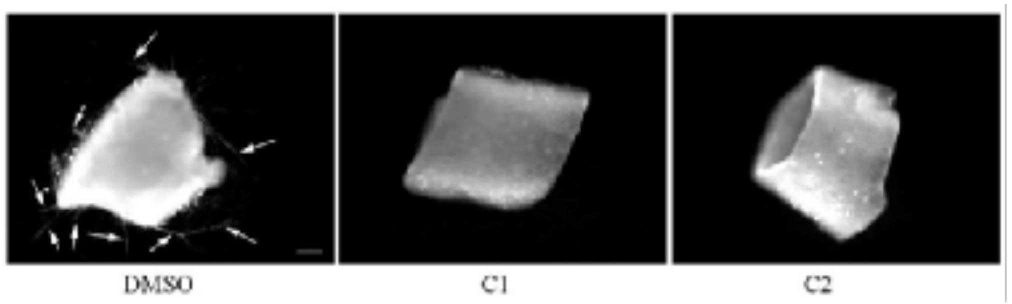
Proximity ligation assay



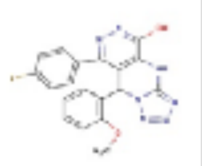
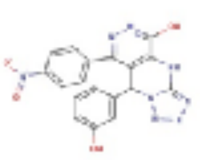
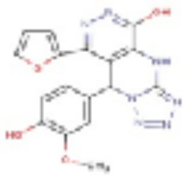
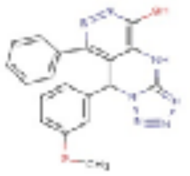
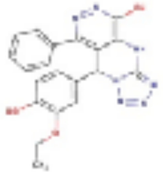
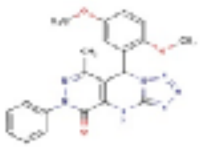
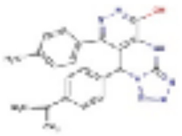
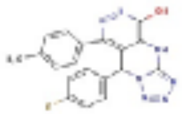
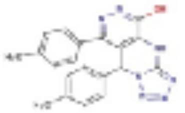
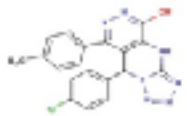
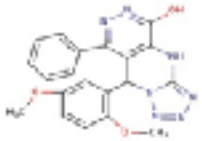
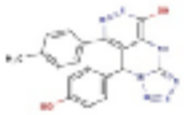
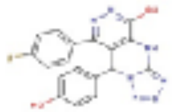
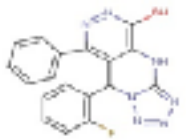
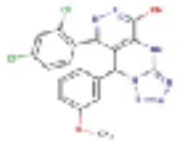
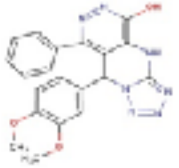
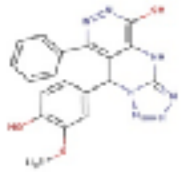
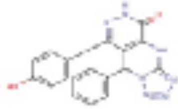
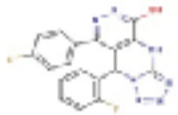
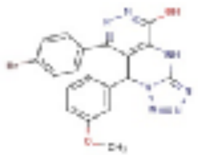
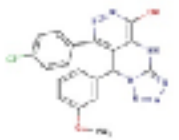
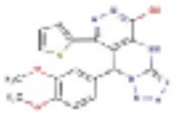


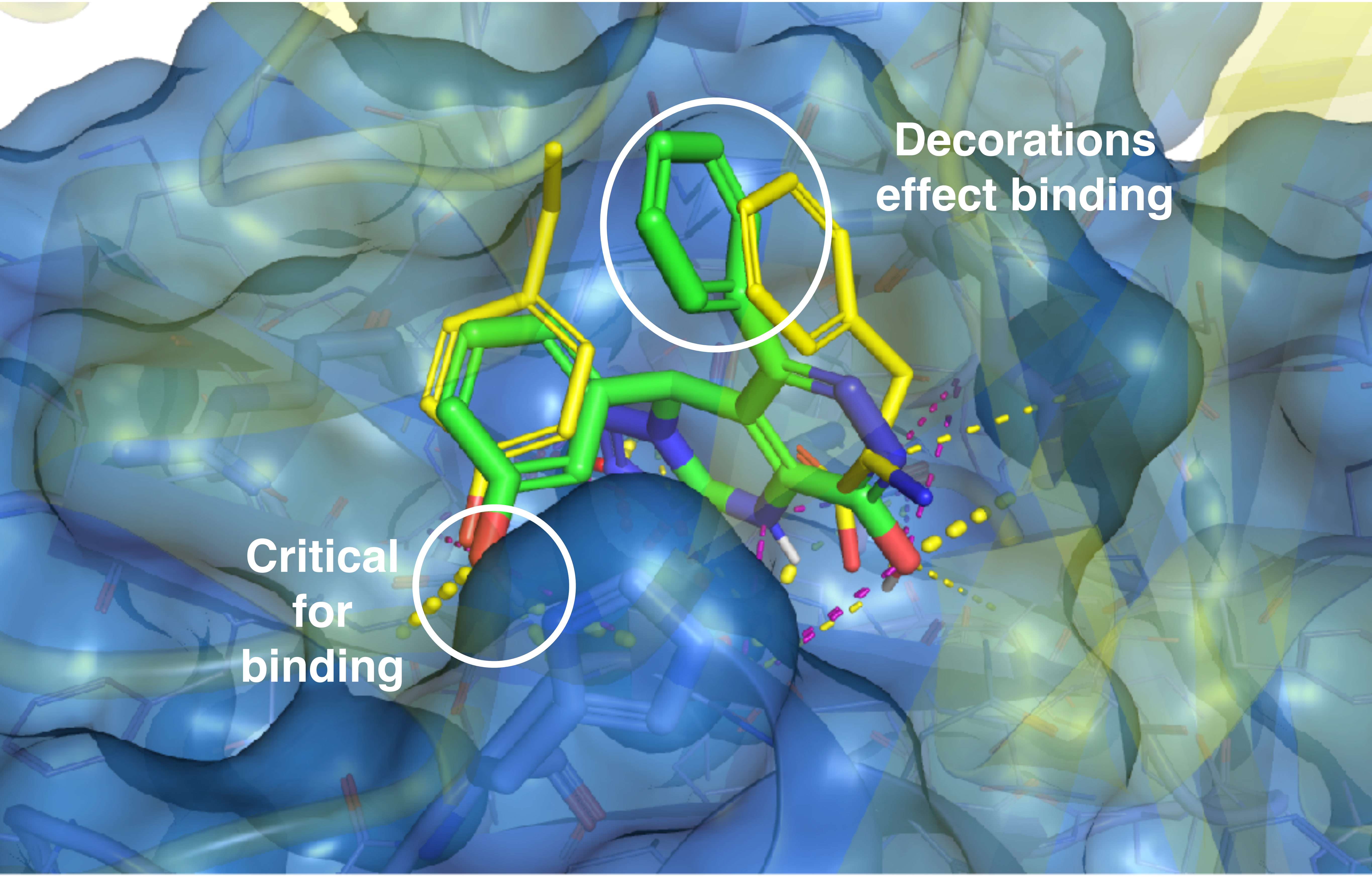
2D Cord Morphogenesis

Sprouting of Explanted Aortic Rings



But wait! There's more...

Compound	MolPort#	Structure
C21	MolPort-007-689-835	
C22	MolPort-010-757-336	
C23	MolPort-010-757-402	
C24	MolPort-002-029-687	
C25	MolPort-002-791-144	
C26	MolPort-015-162-387	
C27	MolPort-010-755-324	
C28	MolPort-000-139-032	
C29	MolPort-010-755-317	
C30	MolPort-010-755-318	
C31	MolPort-010-755-315	
C32	MolPort-000-139-036	
C33	MolPort-010-755-333	
C34	MolPort-000-139-025	
C35	MolPort-010-757-408	
C36	MolPort-002-791-228	
C37	MolPort-002-791-281	
C38	MolPort-002-748-586	
C39	MolPort-007-689-839	
C40	MolPort-010-755-336	
C41	MolPort-000-139-041	
C42	MolPort-015-162-430	



Decorations effect binding

Critical for binding

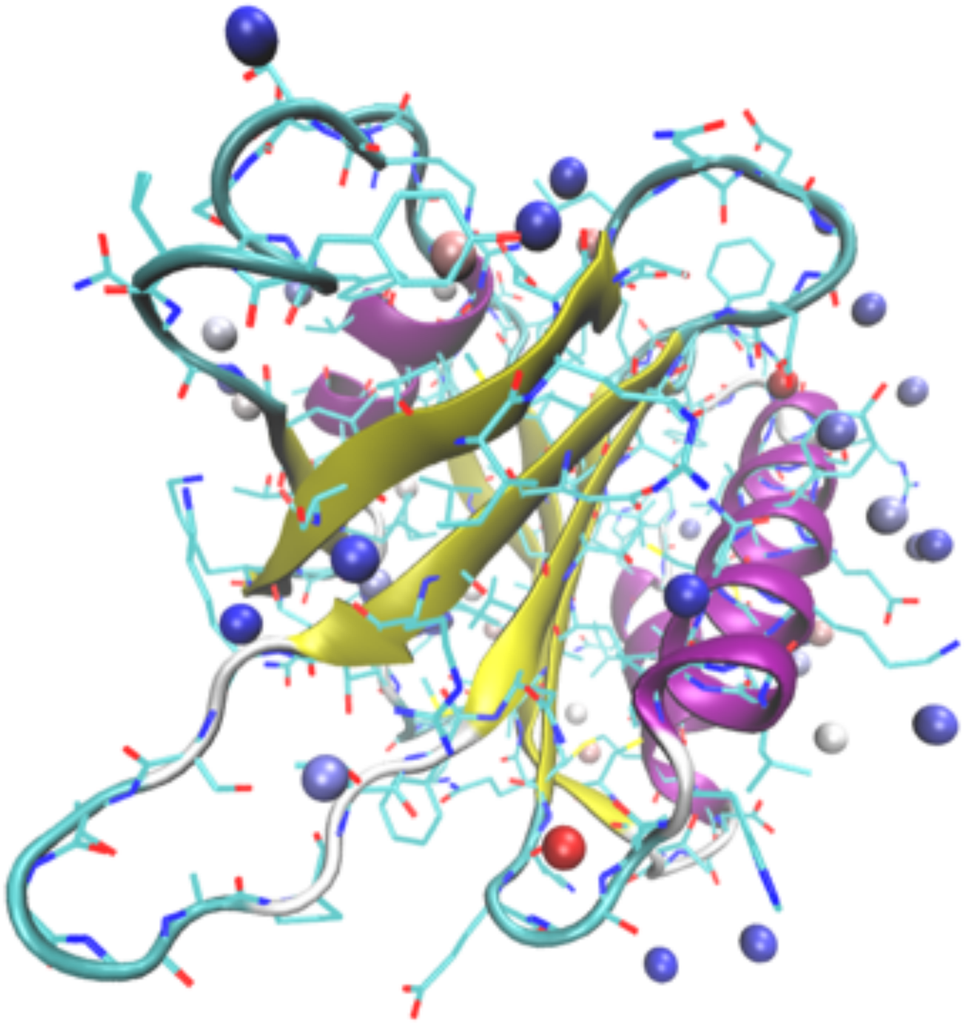
Investigating Alternative Binding Modes

NAMD simulations via DrugGUI

http://prody.csb.pitt.edu/drugui/

Default settings & all possible grids

NO DRUGGABLE SITES



Investigating Alternative Binding Modes

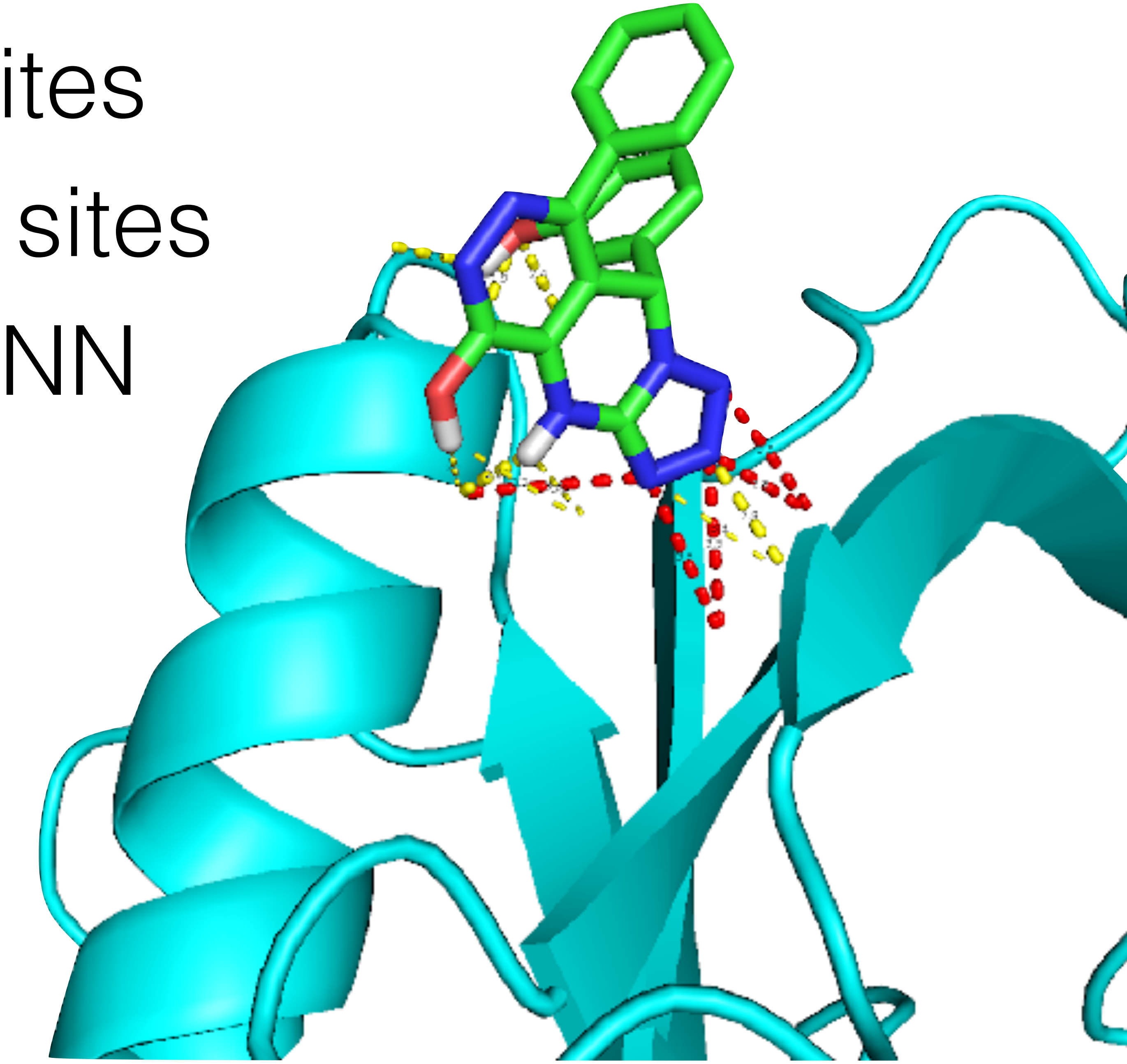
Whole protein docking of C2

Identified 5 alternative sites

Screened against these sites

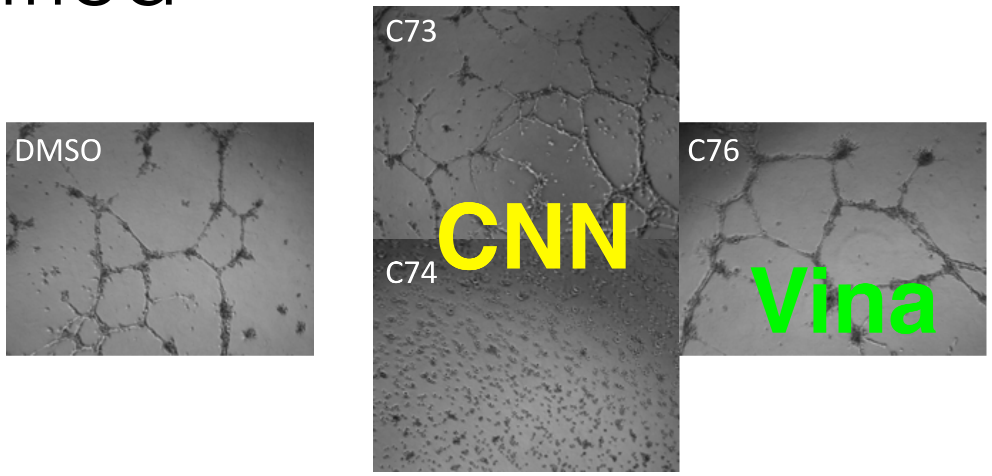
Ranked with Vina and CNN

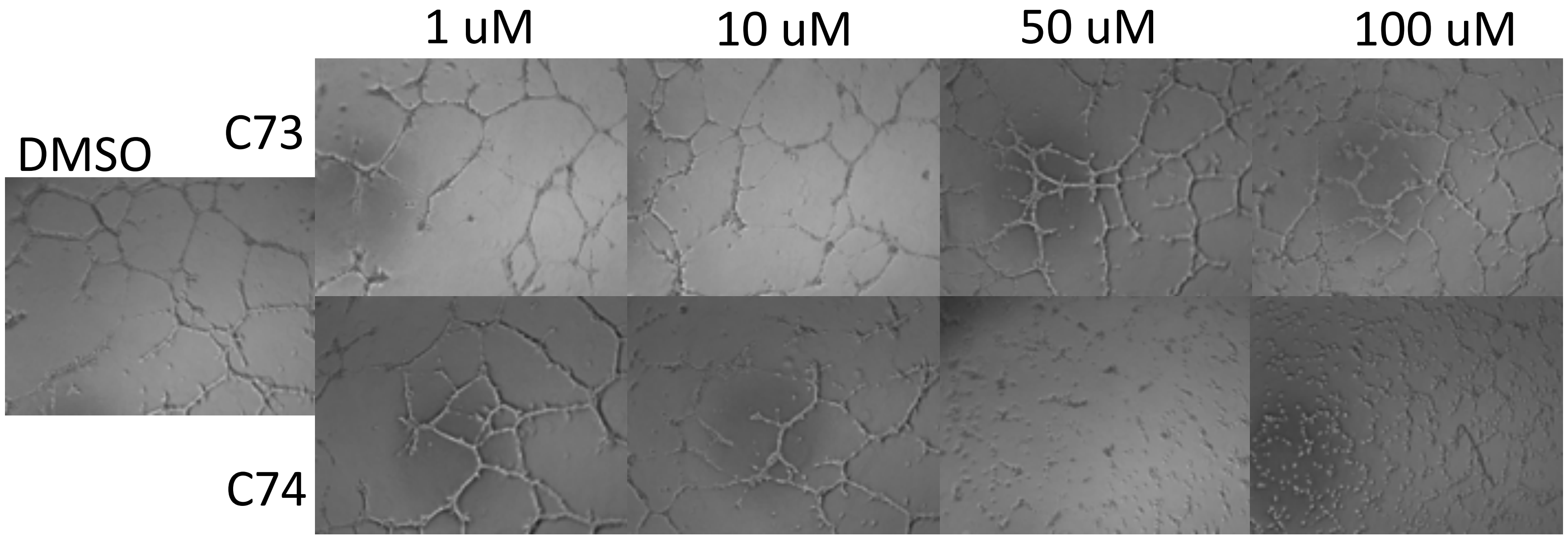
https://github.com/gnina



Alternative Binding Site Results

57 compounds tested, **3 actives** identified

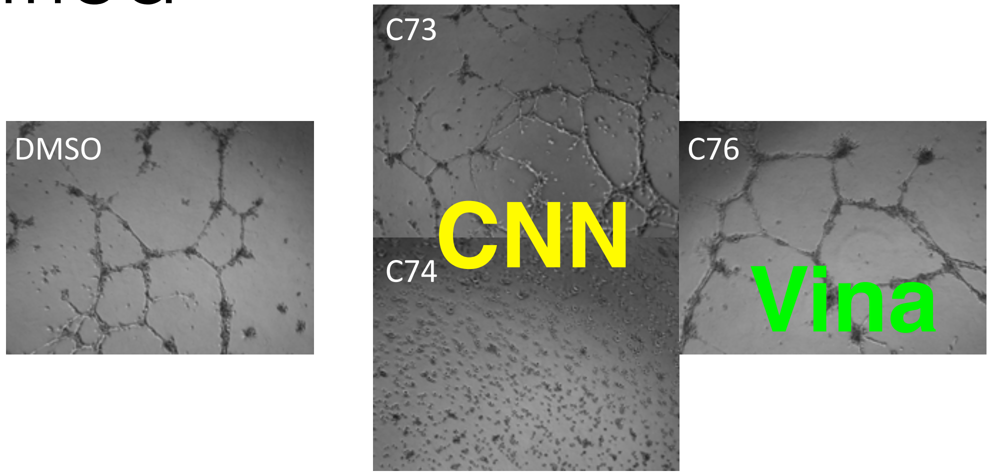


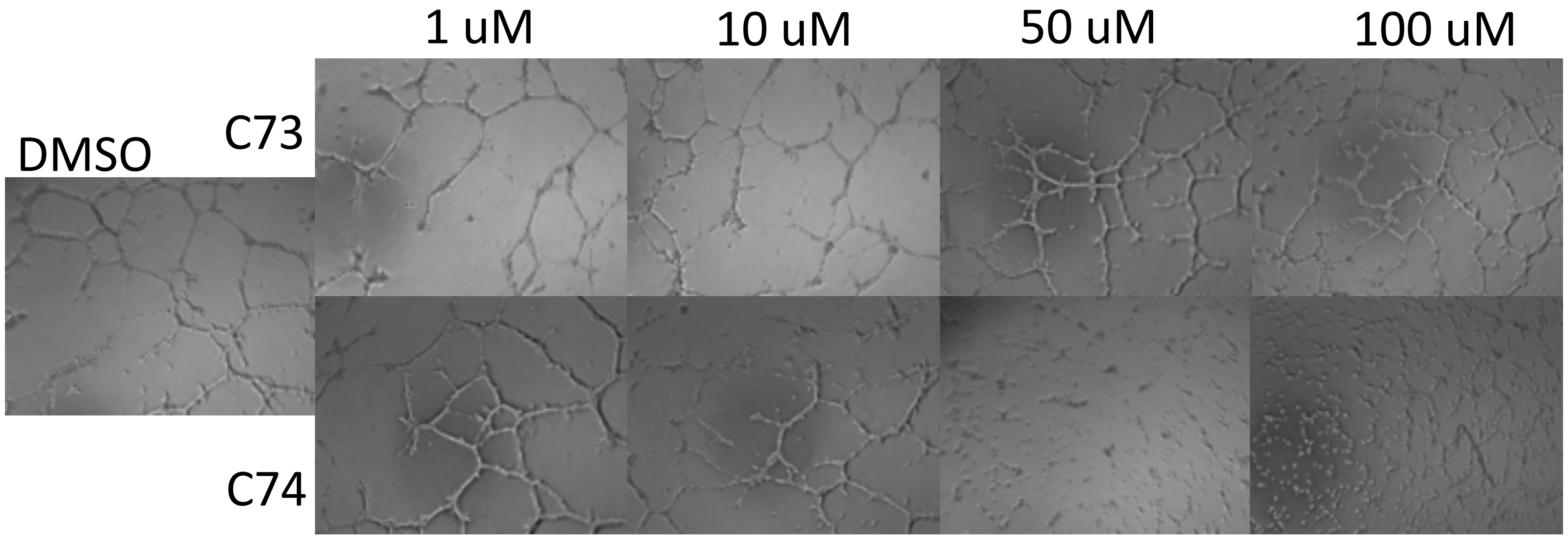


Alternative Binding Site Results

57 compounds tested, **3 actives** identified

1 didn't work in cells



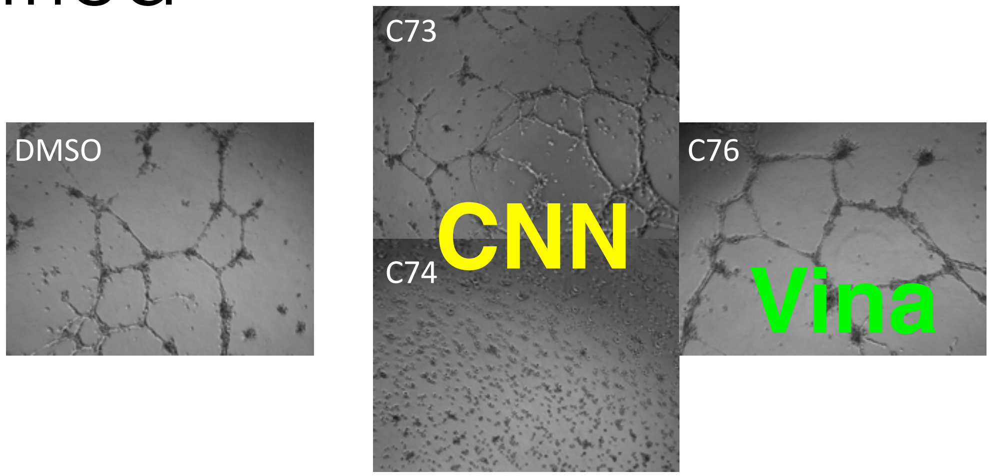


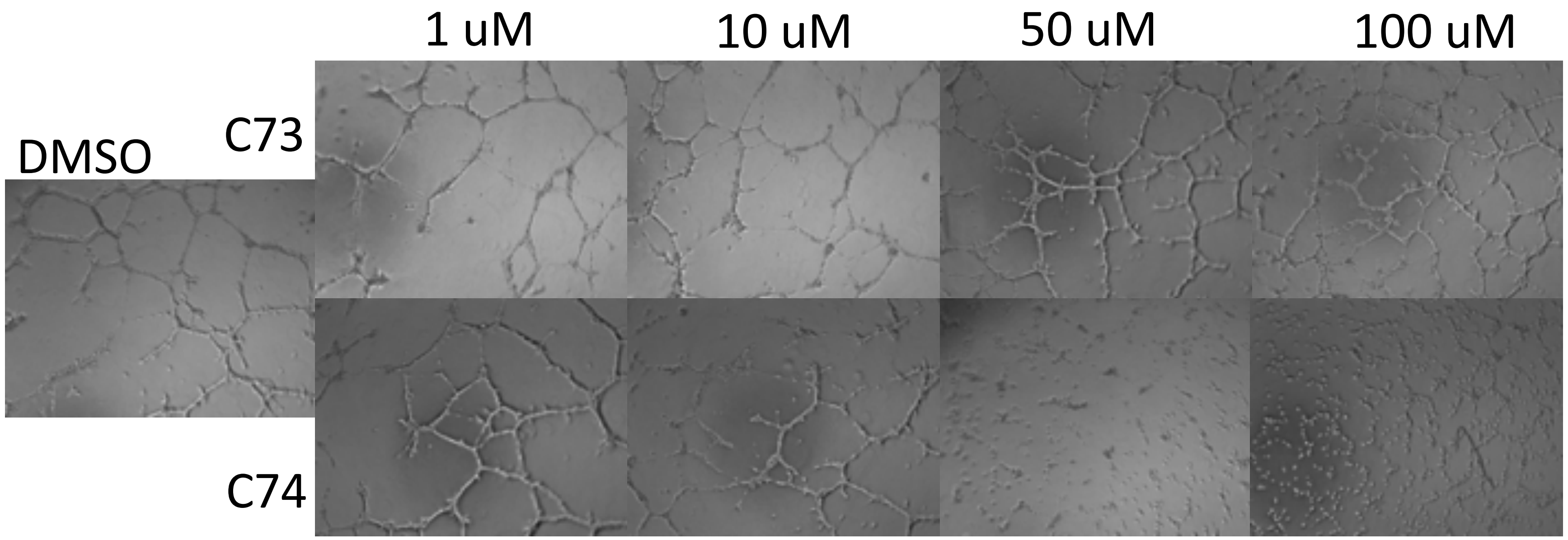
Alternative Binding Site Results

57 compounds tested, **3 actives** identified

1 didn't work in cells

All predicted to bind to different sites





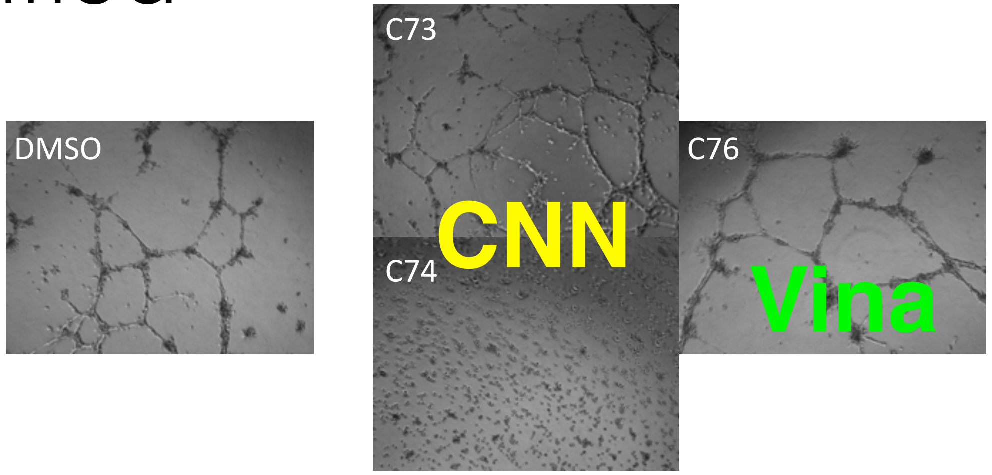
Alternative Binding Site Results

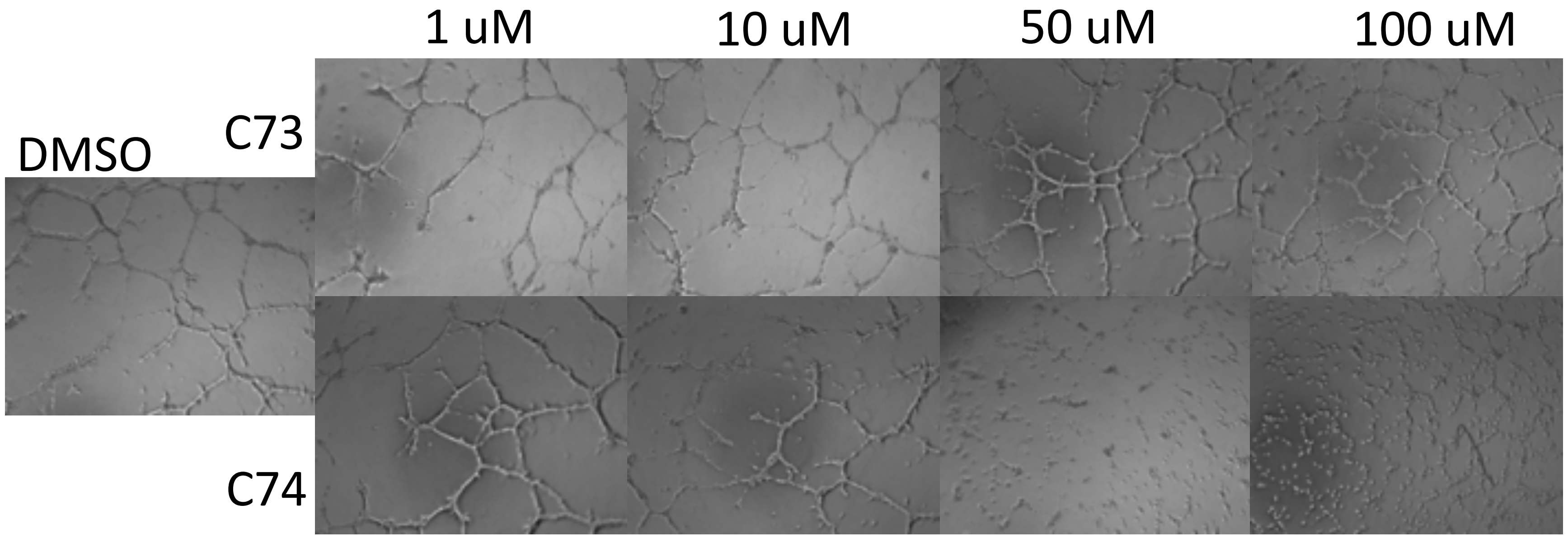
57 compounds tested, **3 actives** identified

1 didn't work in cells

All predicted to bind to different sites

But not original site





So...

Not sure of binding mode

Not 100% sure on target (could be hitting actin)

But...

- works in biochemical assay w/purified proteins
- works in cells
- work ex vivo
- works in vivo (oxygen-induced retinopathy mouse model)

@david_koes

github.com/gnina

http://bits.csb.pitt.edu