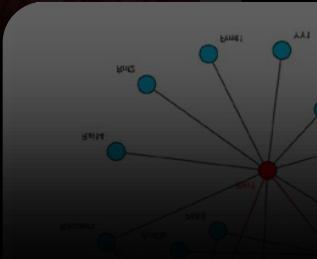
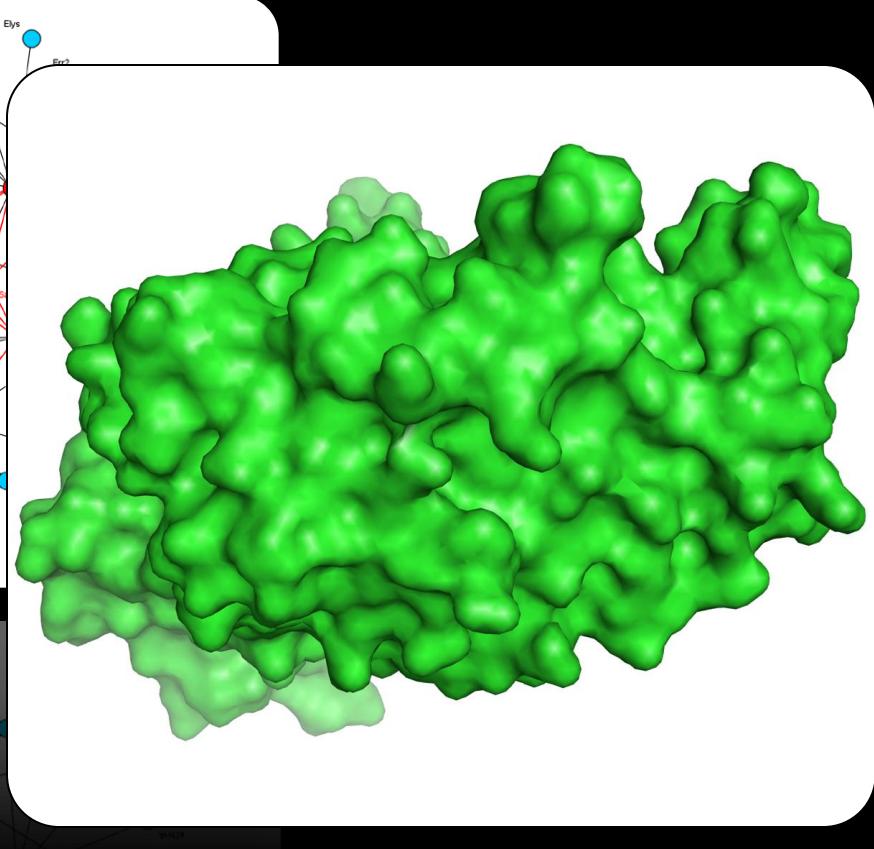
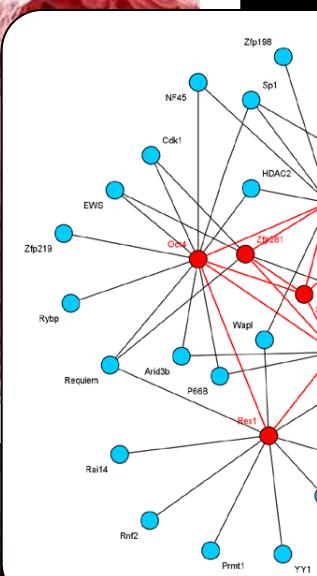
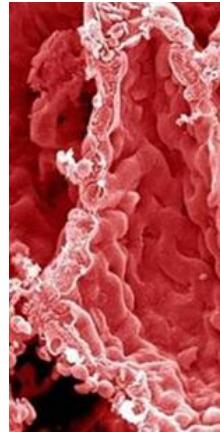


Structural Bioinformatics

Structural Bioinformatics

All biological systems are nested and interacting machines



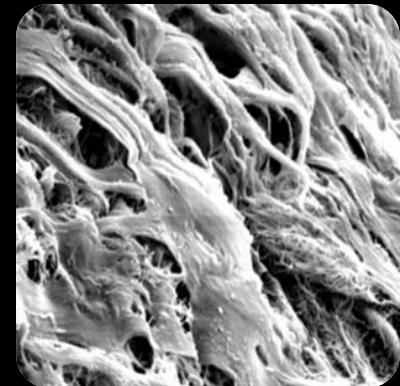
Drug Design



Biofuels



Biomaterials



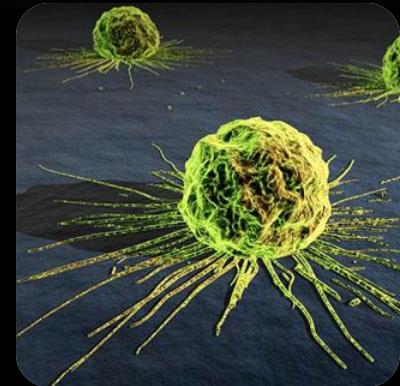
The leading edge of technology



Medical Diagnostics



Agriculture



Cancer

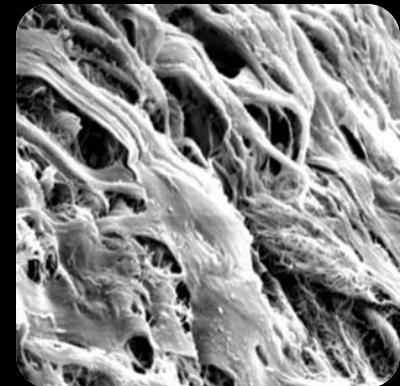
Drug Design



Biofuels



Biomaterials



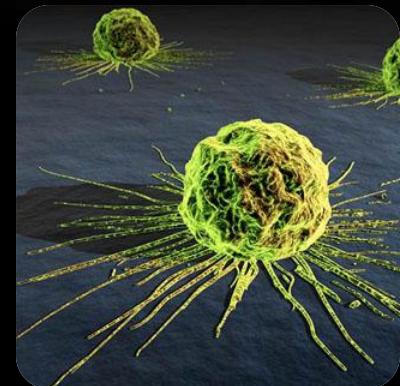
How do these biological systems work?



Medical Diagnostics

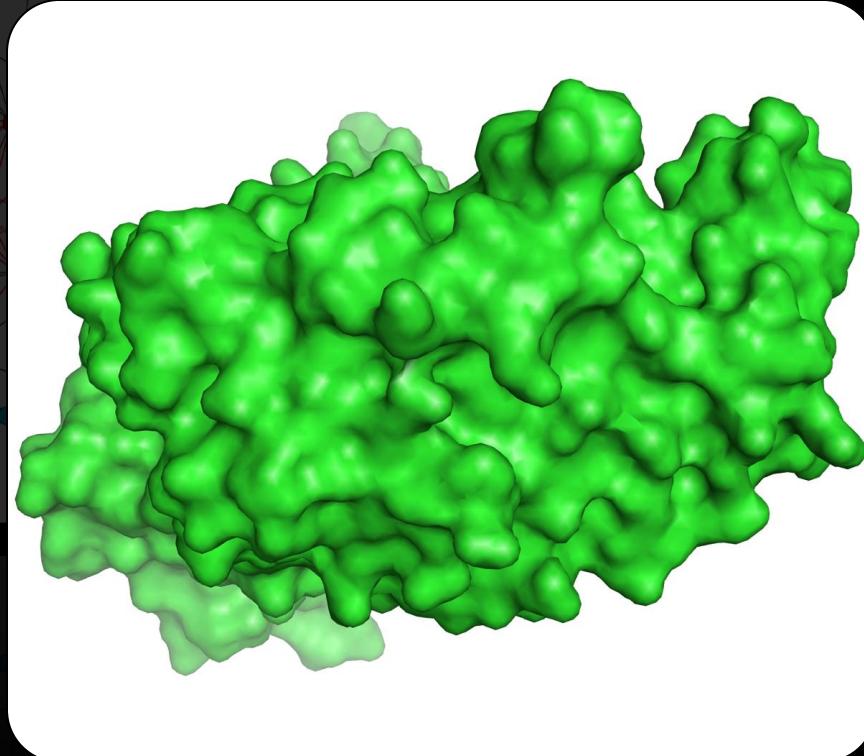
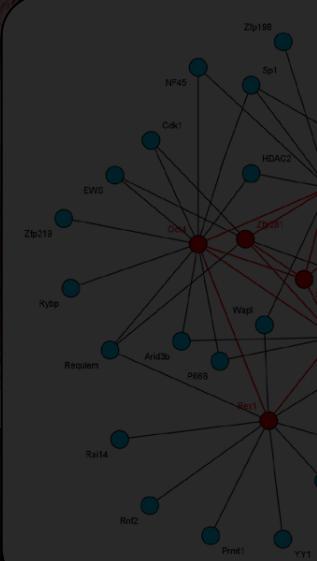
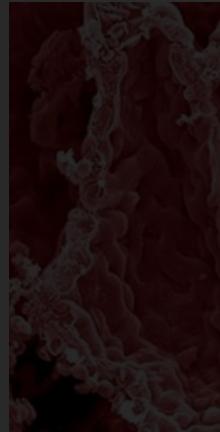
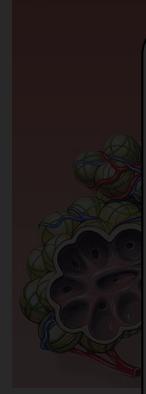
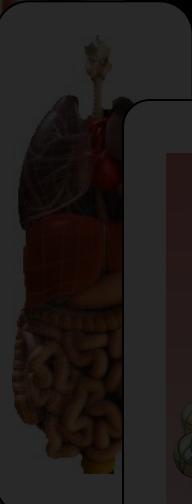
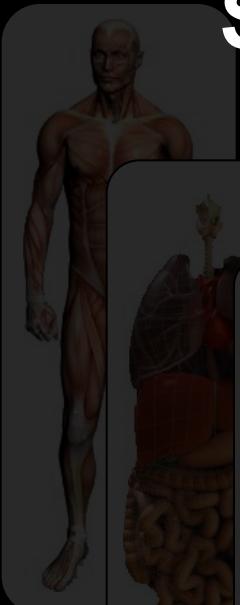


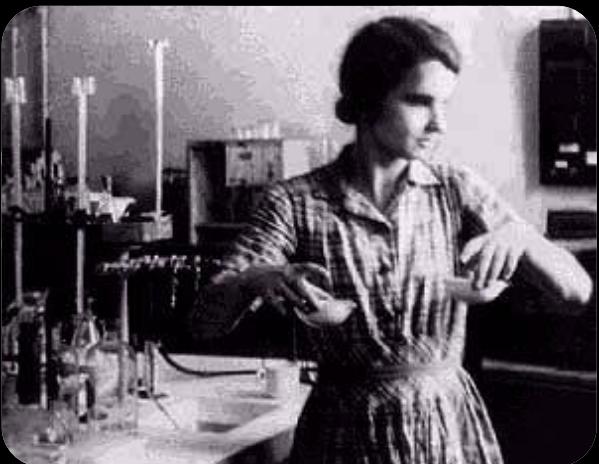
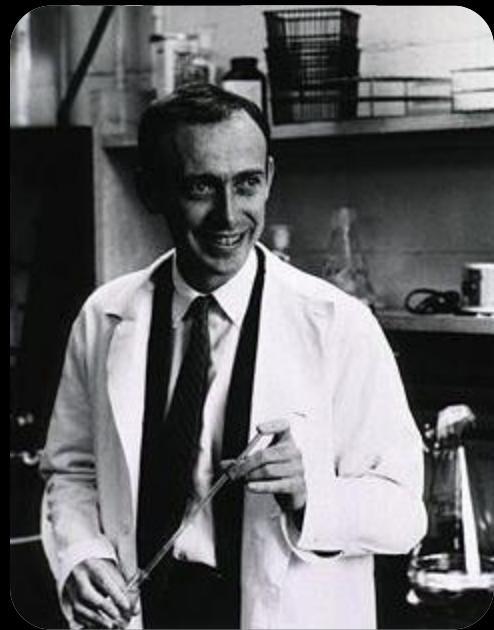
Agriculture



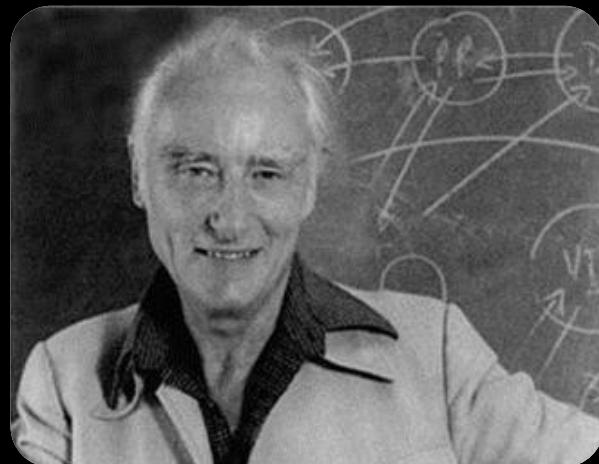
Cancer

Structural Biology can help understand the foundations of these systems



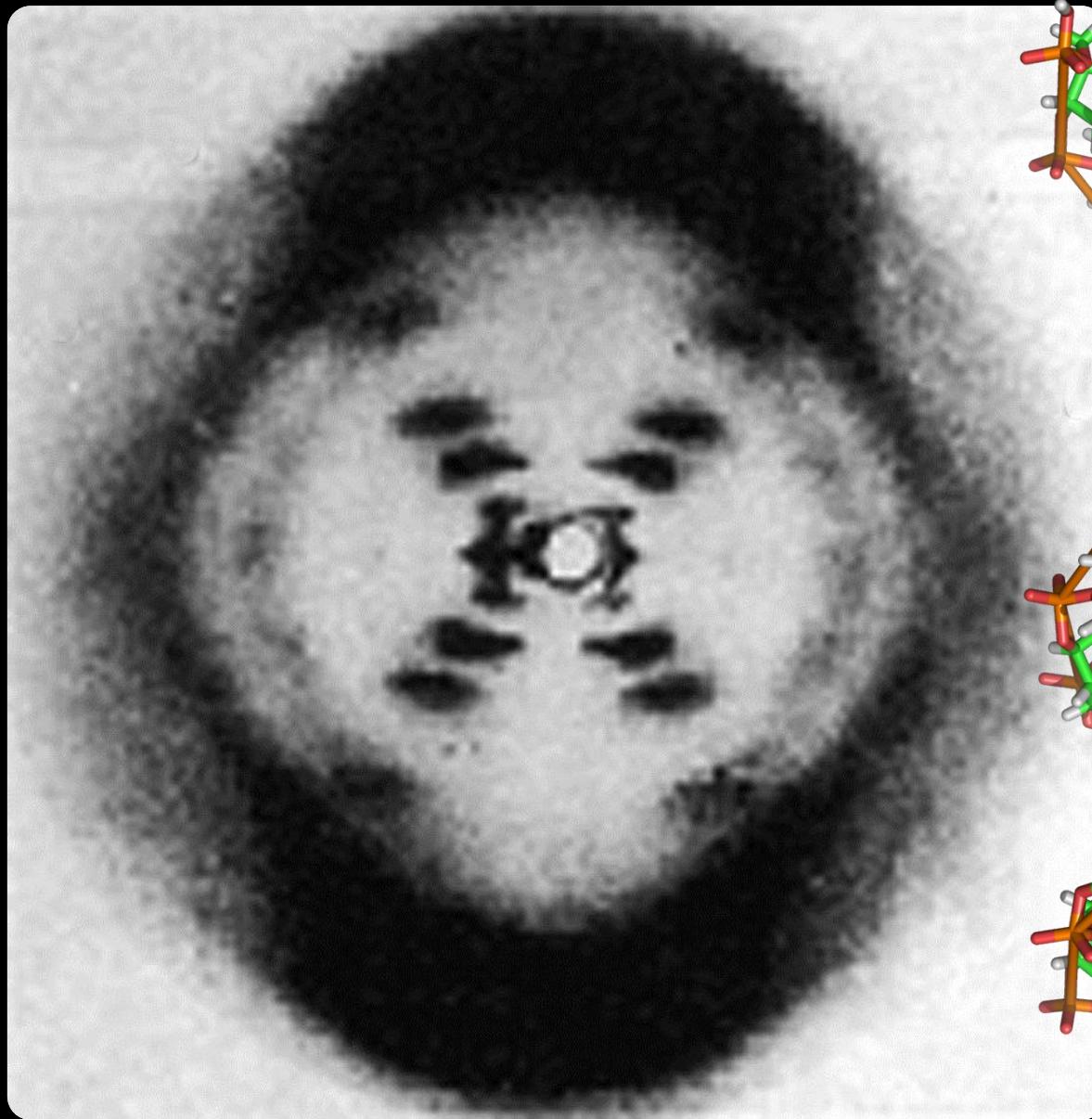


Rosalind Franklin



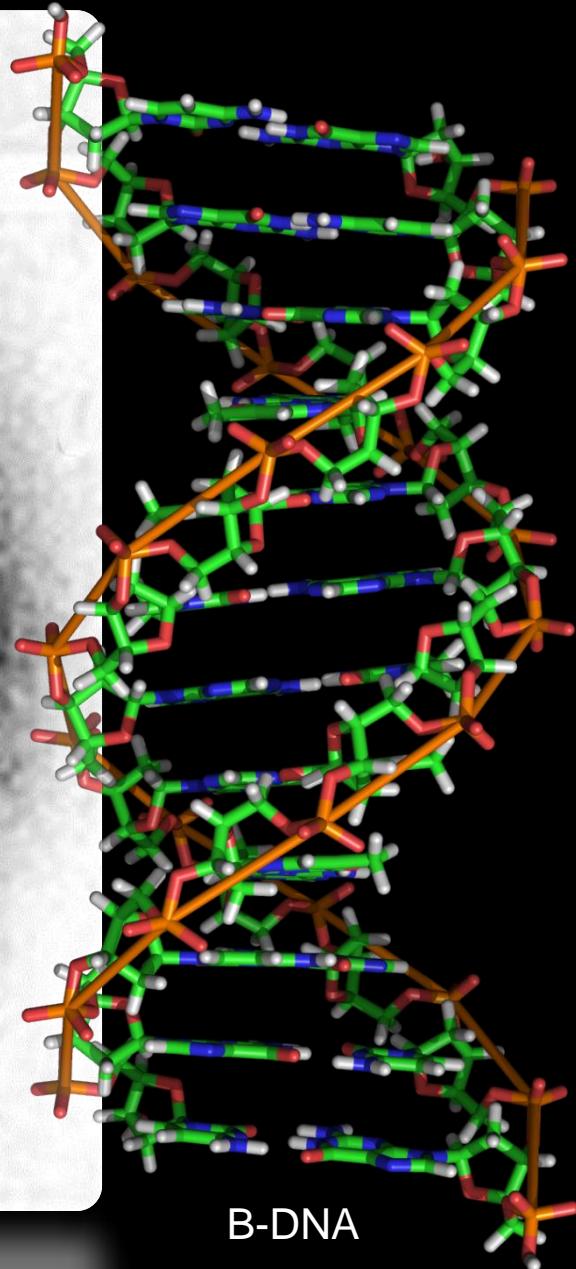
Francis Crick

Source: pbs.org



X-ray diffraction pattern of B-DNA, by R. Franklin

Source: cmgm.stanford.edu, wikimediacommons.org



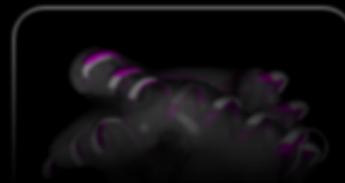
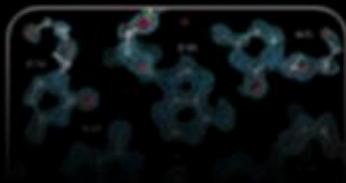
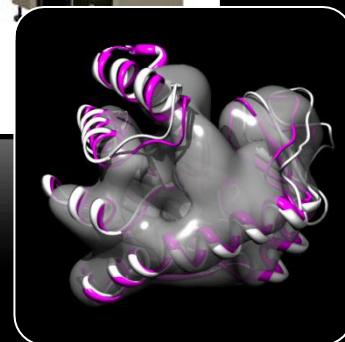
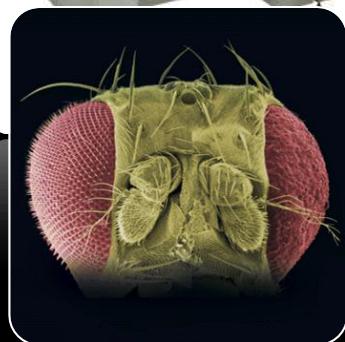
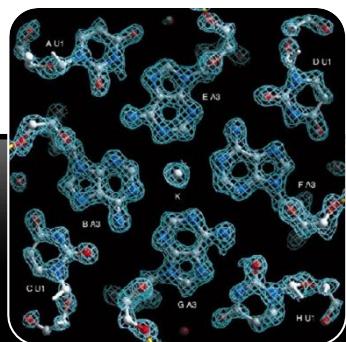
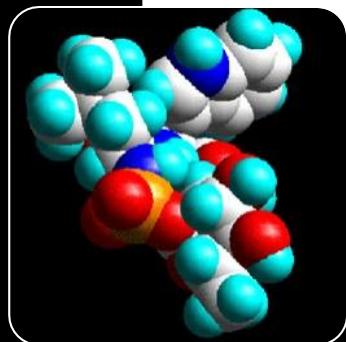
B-DNA

Source: cmgm.stanford.edu, wikimediacommons.org

SOLEIL beamline diagram, Paris

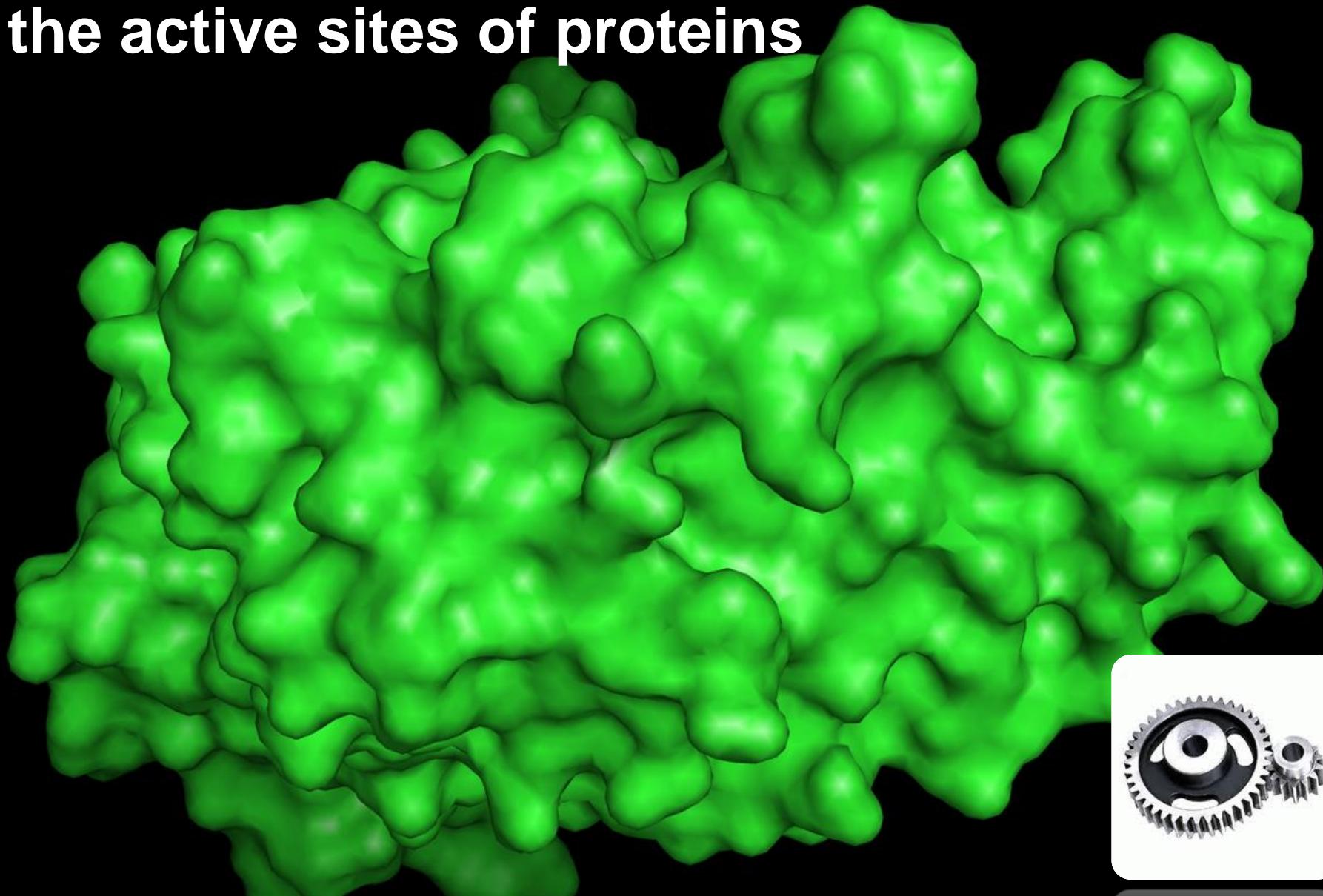


Jeol Electron Microscope

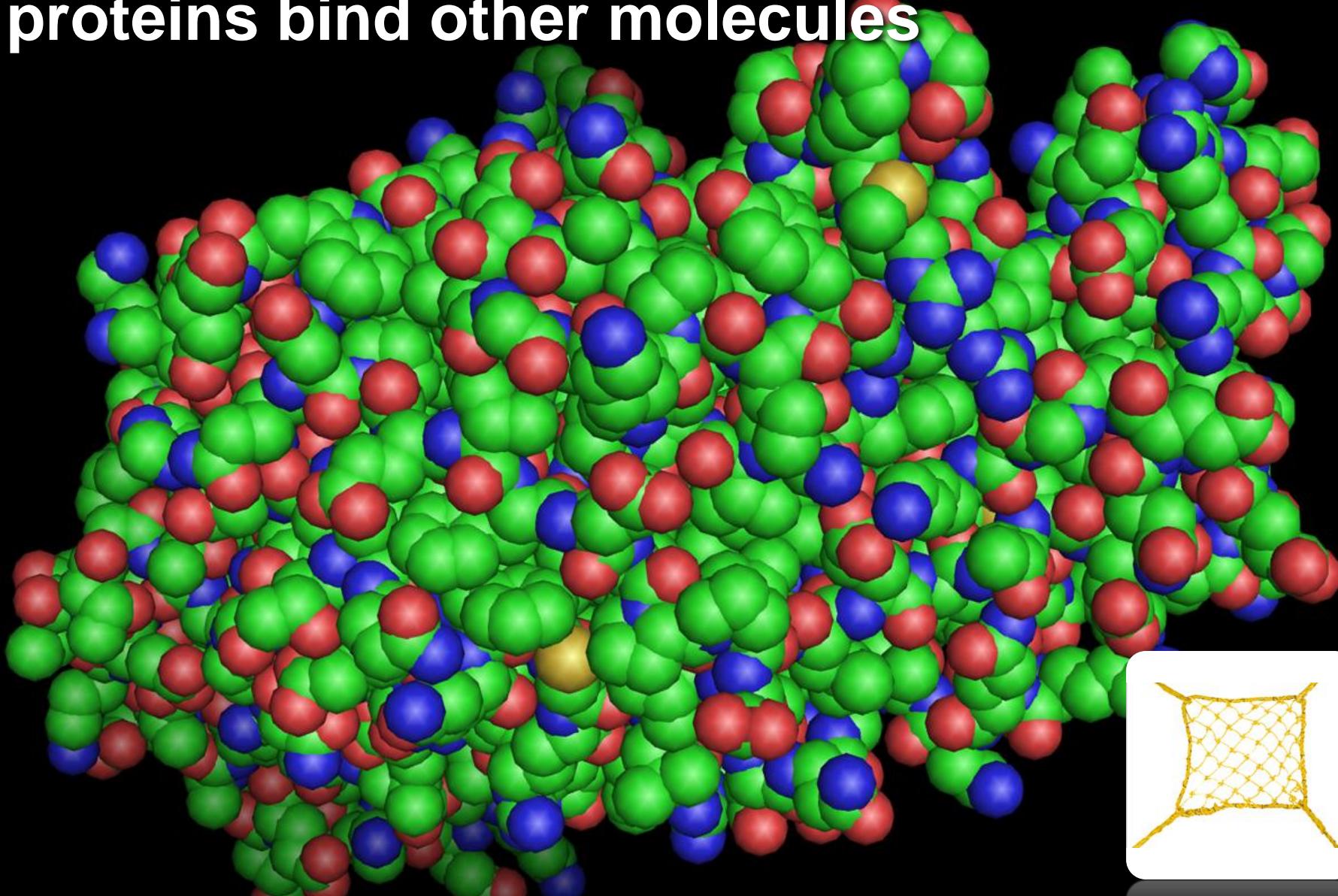


Source: synchrotron-soleil.fr, Jeol.com, cnx.org, esrf.eu, jbc.org, salilab.org.

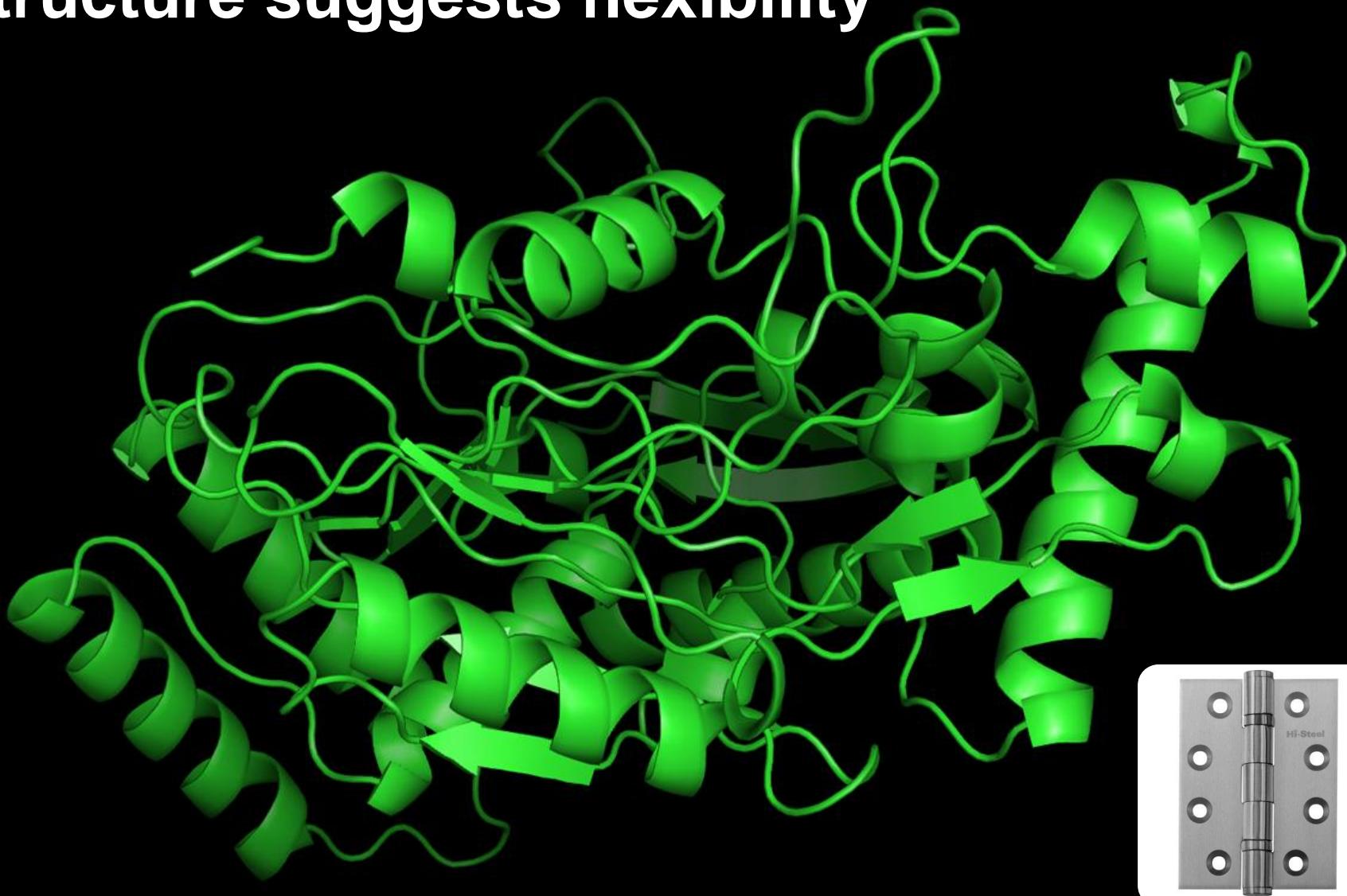
Molecular surfaces can reveal the active sites of proteins



Atomic coordinates can show how proteins bind other molecules



Protein topology and secondary structure suggests flexibility



Structural biology has made significant contributions

- Timeline of Nobel Prizes in Structural Biology
- 1946: Sumner
 - 1962: Crick, Watson, Wilkins
 - 1962: Perutz, Kendrew
 - 1964: Hodgkin
 - 1972: Anfinsen
 - 1982: Klug
 - 1988: Deisenhofer, Huber, Michel
 - 1991: Ernst
 - 1997: Walker
 - 2002: Wuthrich
 - 2003: MacKinnon
 - 2006: Kornberg
 - 2009: Steitz, Yonath
 - Ramakrishnan,

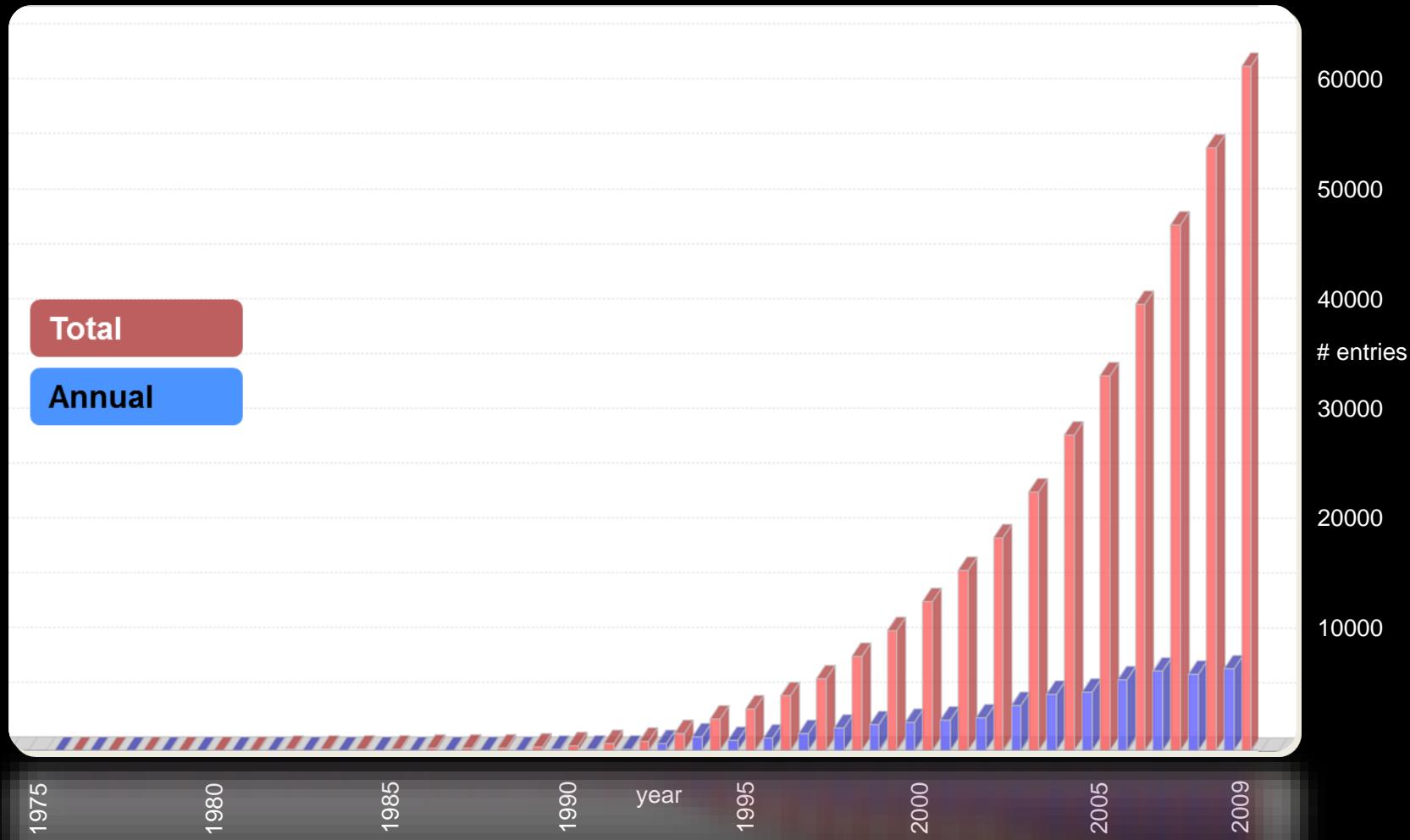


2009 Nobel Prize Ceremony

Source: nobelprize.org

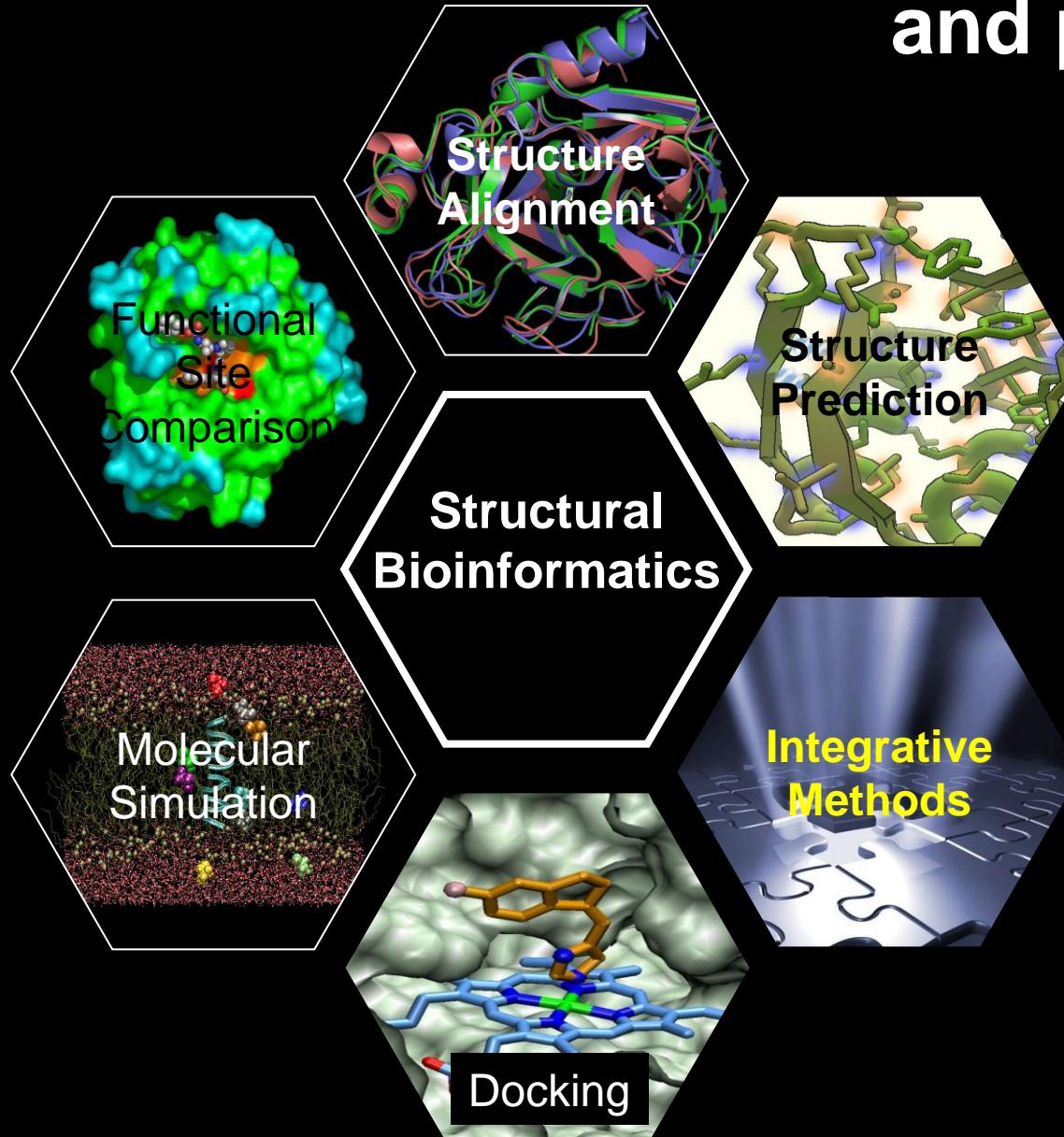
Structural biology has become data rich

Number of Entries in the Protein Data Bank

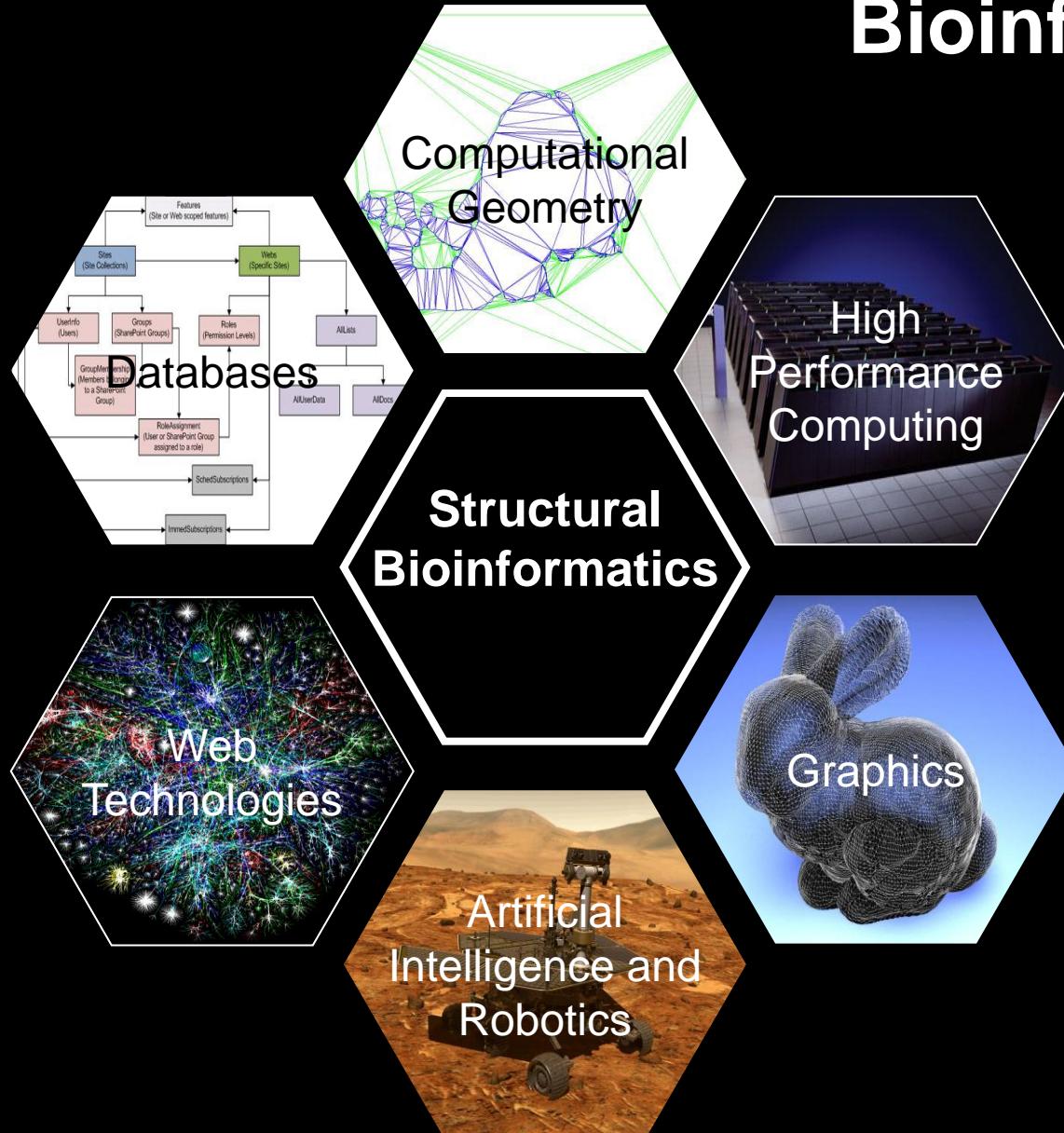


Source: www.pdb.org

Structural bioinformatics adds scale and precision



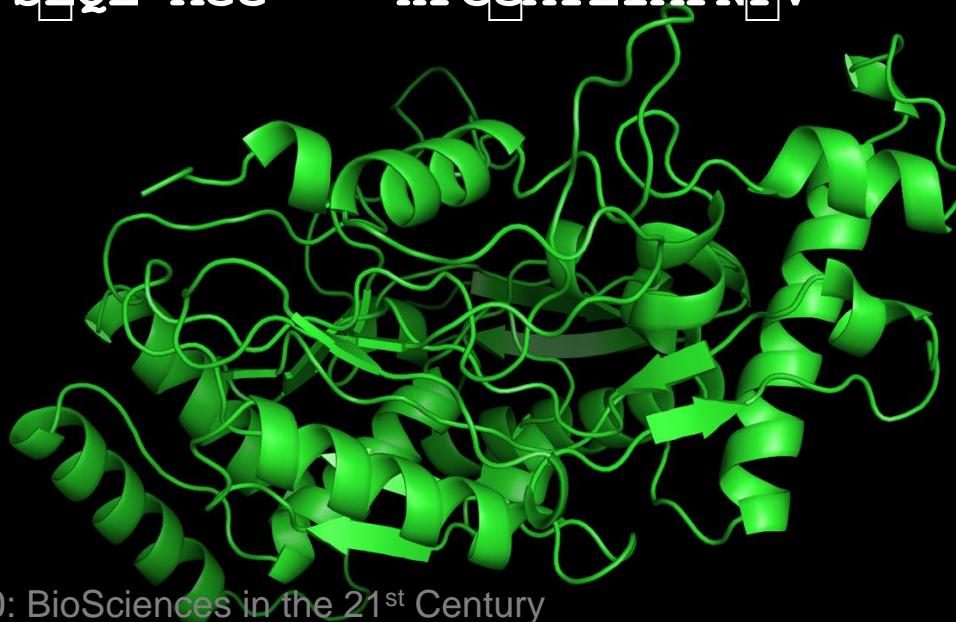
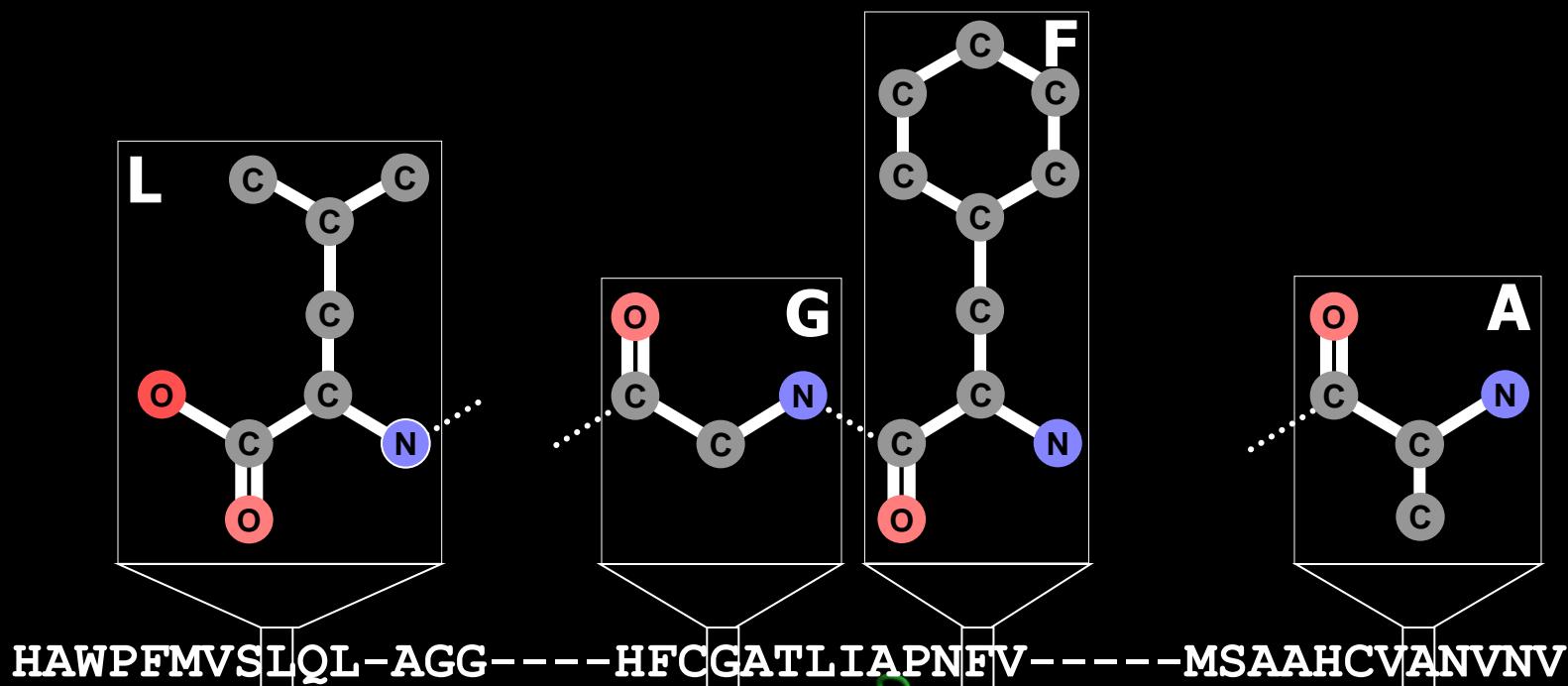
Many computational fields support Structural Bioinformatics



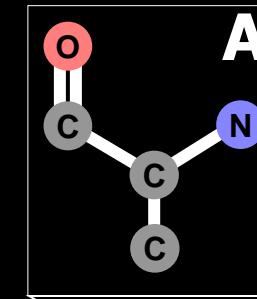
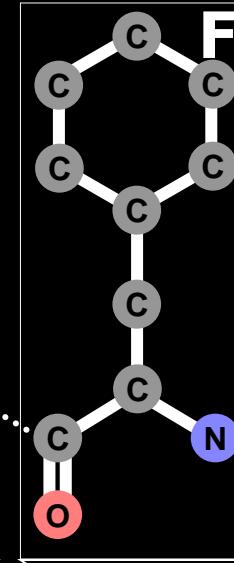
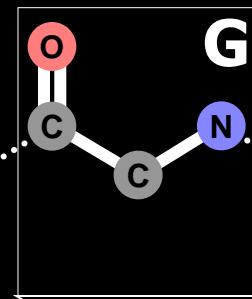
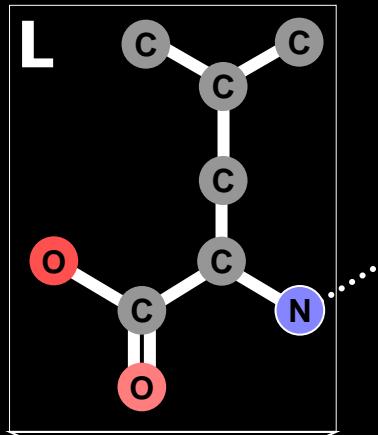
The Task:

Gather, analyze, and integrate data that can indicate biological function

The Data: Chains of amino acids in 3-D



Similar sequences imply similar function

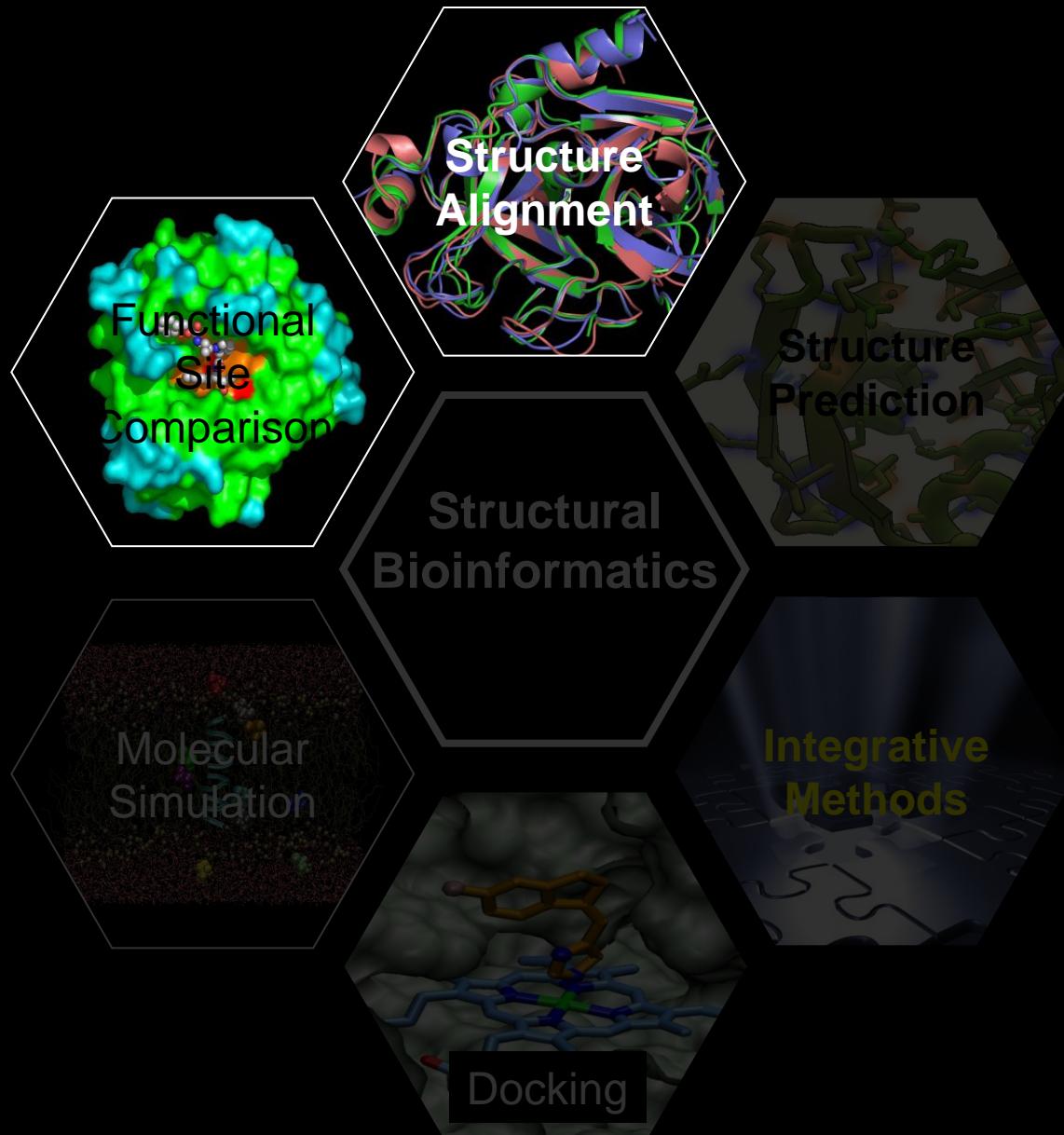


HAWPFMVS**L**QL-**A**GG-----HFCGATLIAPNFVMSAAHC**V**ANVN
HAWPFMVS**L**QL-**R**GG-----HFCGATLIAPNFVMSAAHC**V**ANVK-
HSWPW**Q**I**S**LQY-**S**KNDAWG**H**T**C**GGTLIASNYVL**T**AAHC**I**SNAKT
HSRPY**M**VSL**Q**V-**Q**---G-N**H**FCGGTLIHP**Q**FVMTAAHC**I**D**K**INP
LA-**P**YIASLQRN**R**GG-----HFCGGTLI**H**QQFVMTAAHC**I**NSRN**V**

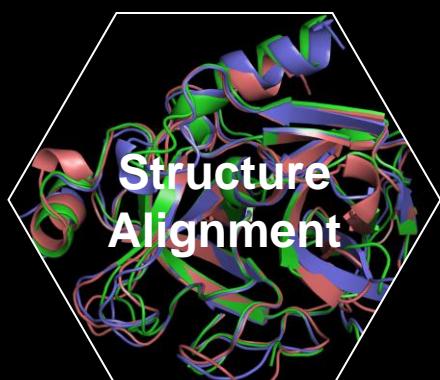
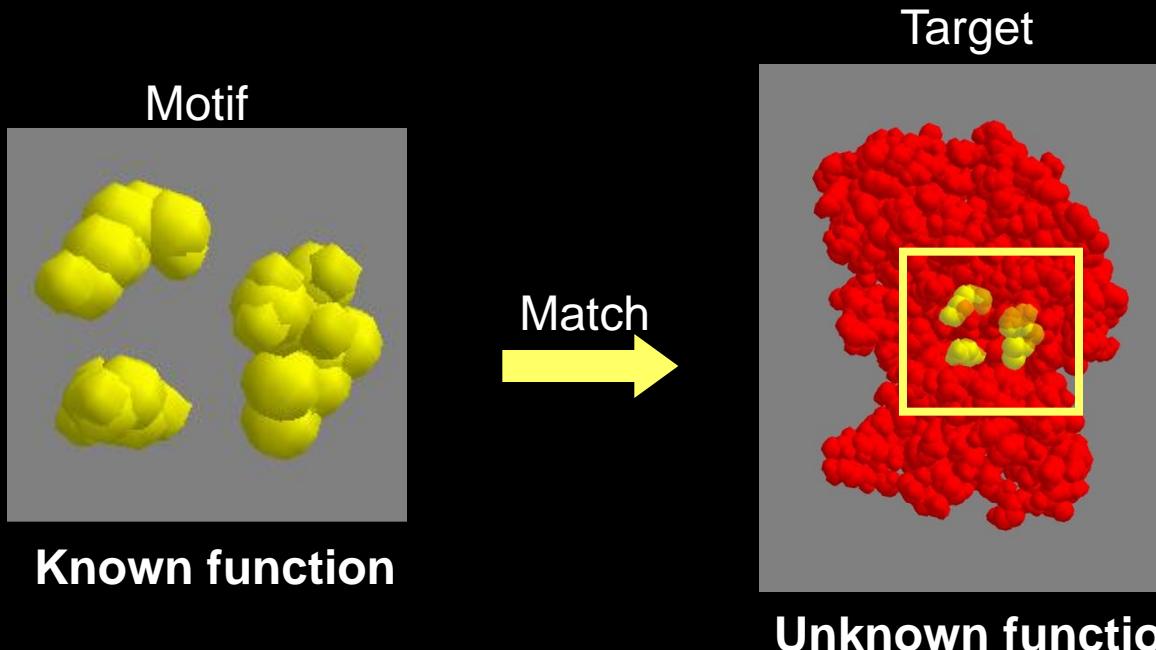
Software

ConSurf	Glaser, et al. <i>Bioinformatics</i> , 2003.
Evolutionary Trace	Mihalek, et al. <i>Proteins</i> , 2006.
HMAP	Tang, et al. <i>J. Mol. Biol.</i> 2003.
FASTA	Mackey, et al. <i>Mol. Cell. Prot.</i> 2002.
CLUSTALW	Larkin et al. <i>Bioinformatics</i> , 2007.
BLAST	Altschul et al. <i>Nuc. Acid. Res.</i> 1997.

Two fields of Structural Bioinformatics



Similar active sites imply similar function



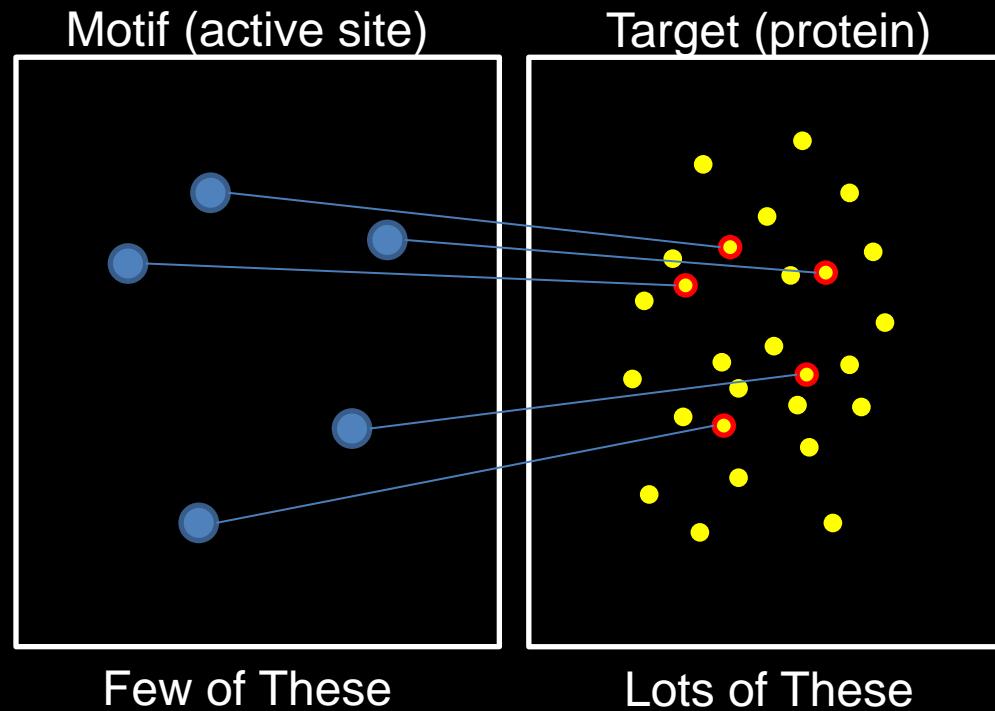
Software

MASH
Combinatorial Extension
Geometric Hashing
pevoSOAR
Ska
Geometric Sieving
PINTS
JESS
Dali

Chen et al, *J. Comput. Biol.*, 2007
Jia et al, *J. Comput. Biol.*, 2004
Nussinov et al, *Proteins*, 2001
Tseng et al, *J. Mol. Biol.*, 2009
Petrey et al, *Methods Enzymol.* 2003.
Chen et al, *J. Bioinf. Comput. Biol.*, 2007
Stark et al, *Nucleic Acids Res.*, 2003.
Barker et al, *Bioinformatics*, 2003.
Holm et al, *Bioinformatics*, 2008.

Geometric software matches active sites

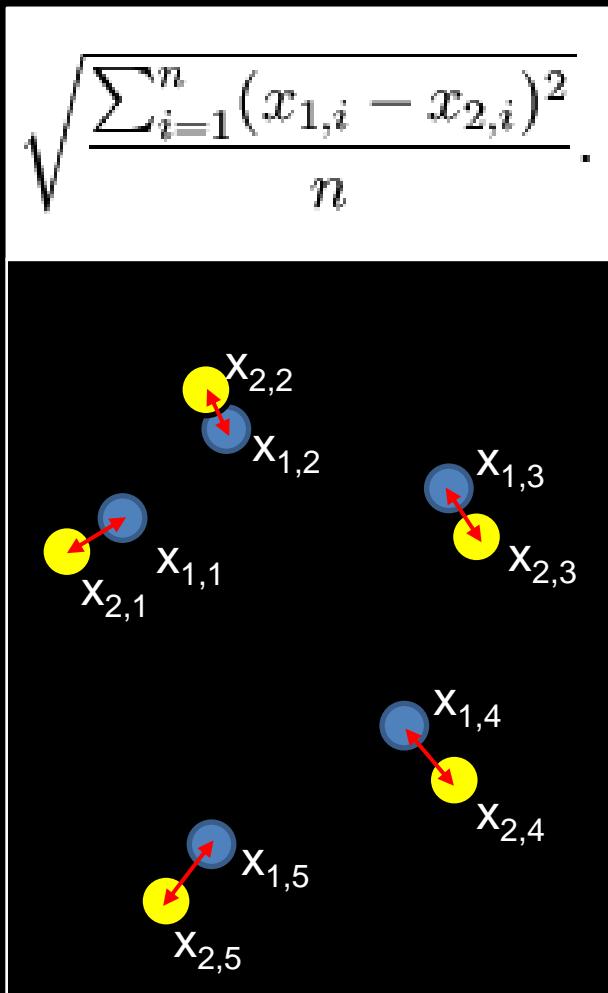
- Input: a Motif and Target protein
- Output: Target atoms corresponding to motif atoms with lowest RMSD (e.g. most geometric similarity)
- Corresponding atoms must be chemically equivalent



Approximate number
Of matches to test:
$$\binom{250}{5}$$

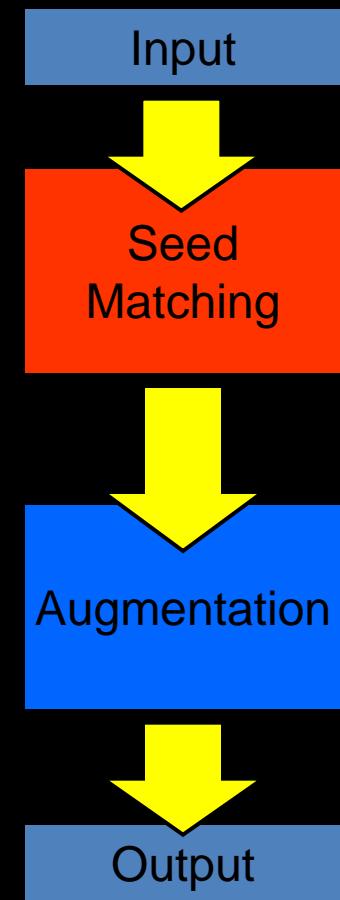
7,817,031,300
combinations

RMSD is an average of interpoint distance



An example of motif matching software

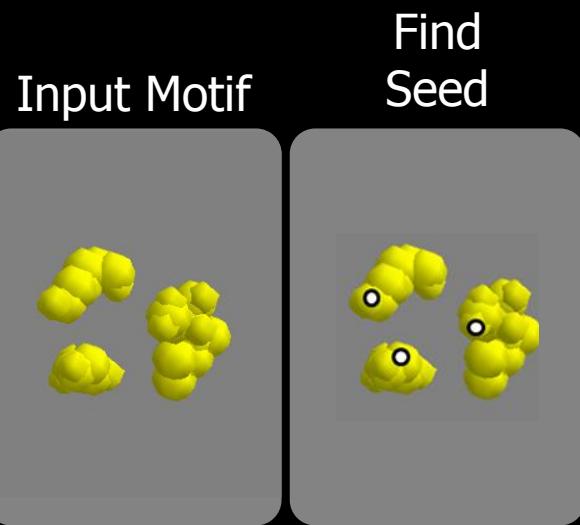
- Seed Matching
 - Matching for highest ranked 3 motif points
 - Distance hashing technique makes this efficient
 - Produces preliminary Seed Matches
- Augmentation
 - Extends Seed Matches to include remaining points
 - Hierarchical depth first search



Algorithms for Structural Comparison and Statistical Analysis of 3D Protein Motifs. Brian Y. Chen*, Viacheslav Y. Fofanov*, David M. Kristensen, Marek Kimmel, Olivier Lichtarge, Lydia E. Kavraki. Proc. Pac. Symp. Biocomput. pp. 334-345, 2005.

Seed Matching

- Isolate Seed: Three highest-ranking motif atoms

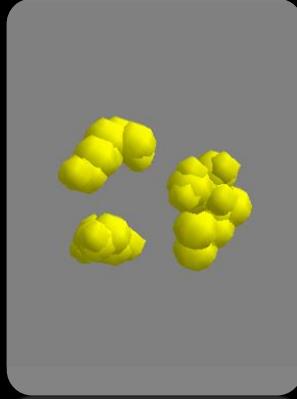


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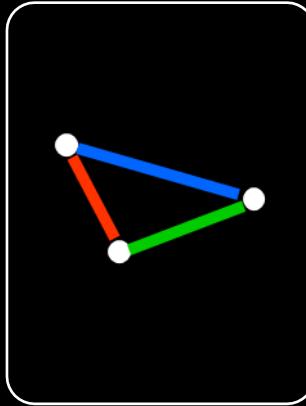
Seed Matching

- Isolate Seed: Three highest-ranking motif atoms
- Record inter-point distances as red, blue, green

Input Motif



Record Distances

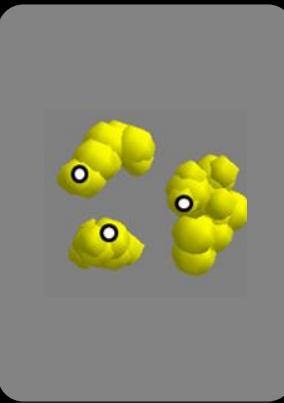
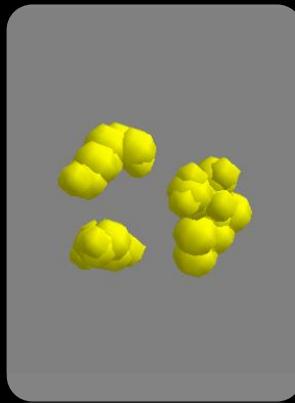


Algorithms for Structural Comparison and Statistical Analysis of 3D Protein Motifs. Brian Y. Chen*, Viacheslav Y. Fofanov*, David M. Kristensen, Marek Kimmel, Olivier Lichtarge, Lydia E. Kavraki. *Proc. Pac. Symp. Biocomput.* pp. 334-345, 2005.

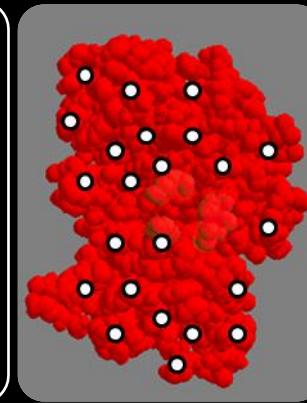
Seed Matching

- Isolate Seed: Three highest-ranking motif atoms
- Record inter-point distances as red, blue, green
- Find compatible target points at similar distances

Input Motif



Find
Target Points

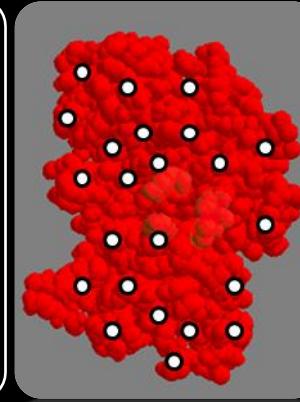
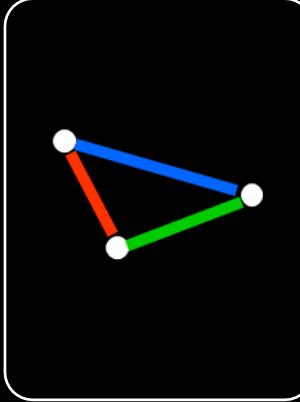
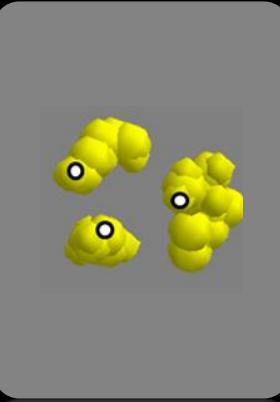
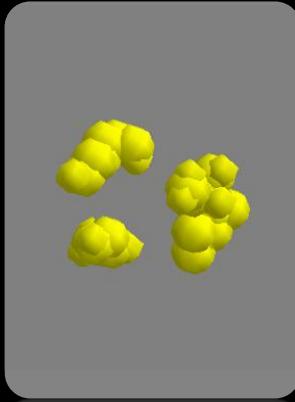


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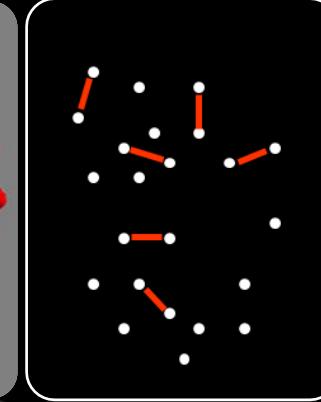
Seed Matching

- Isolate Seed: Three highest-ranking motif atoms
- Record inter-point distances as red, blue, green
- Find compatible target points at similar distances
- Search resulting graph for 3-color triangles

Input Motif



Find
Red Edges

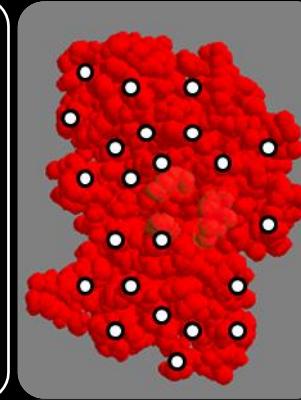
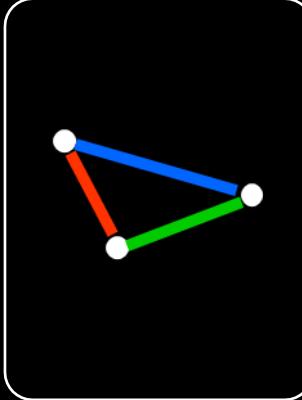
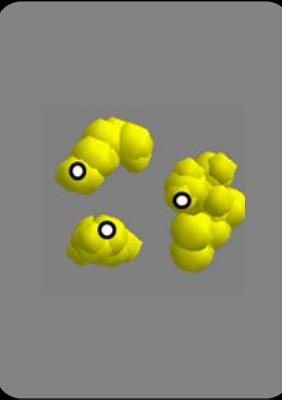
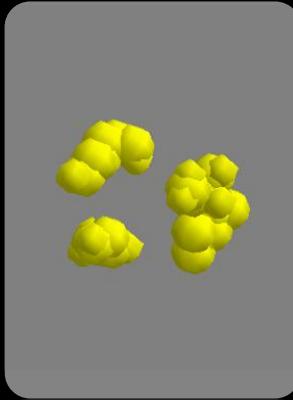


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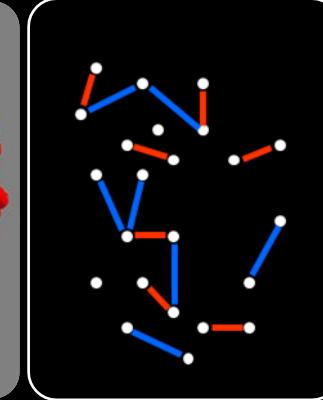
Seed Matching

- Isolate Seed: Three highest-ranking motif atoms
- Record inter-point distances as red, blue, green
- Find compatible target points at similar distances
- Search resulting graph for 3-color triangles

Input Motif



Find
Blue Edges

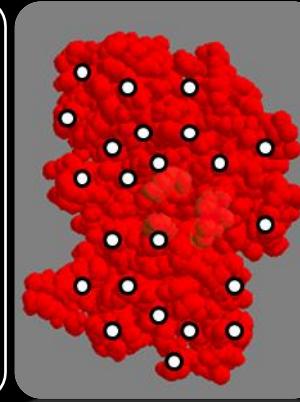
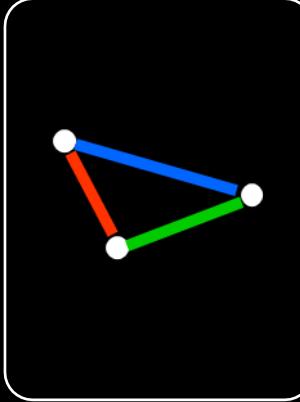
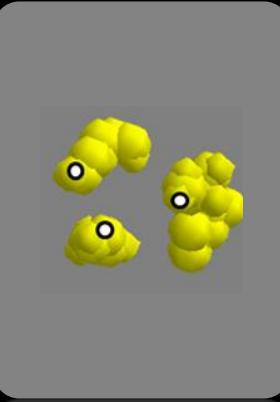
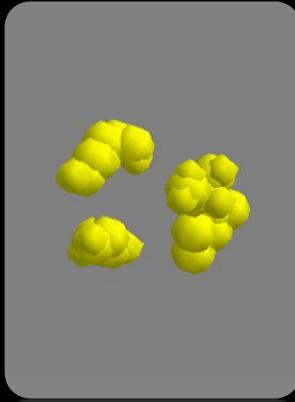


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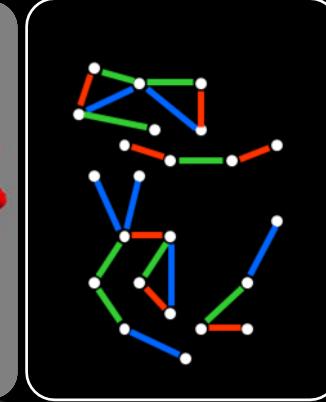
Seed Matching

- Isolate Seed: Three highest-ranking motif atoms
- Record inter-point distances as red, blue, green
- Find compatible target points at similar distances
- Search resulting graph for 3-color triangles

Input Motif



Find
Green Edges

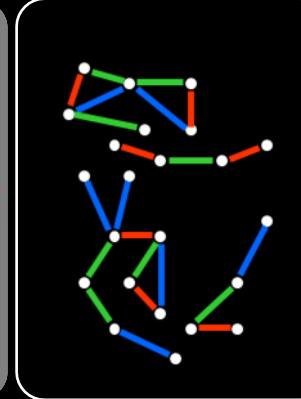
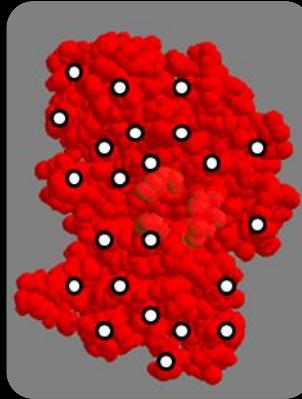
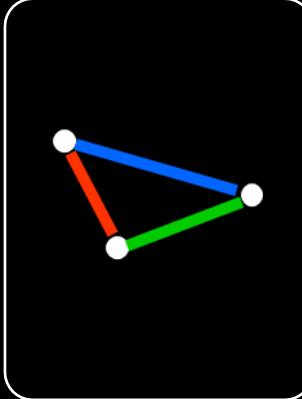
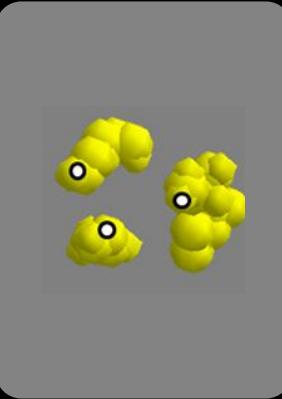
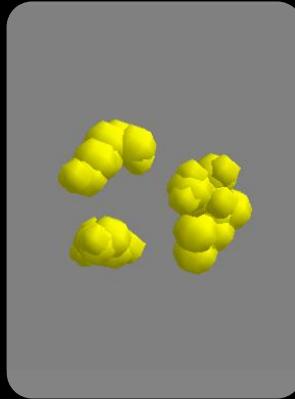


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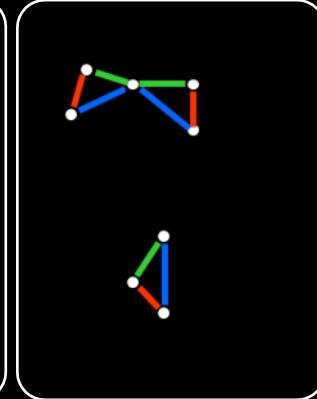
Seed Matching

- Isolate Seed: Three highest-ranking motif atoms
- Record inter-point distances as red, blue, green
- Find compatible target points at similar distances
- Search resulting graph for 3-color triangles
- Align all Seed Matches by LRMSD, and store in a stack
- Output match stack

Input Motif



Output
Triangles



Algorithms for Structural Comparison and Statistical Analysis of 3D Protein Motifs. Brian Y. Chen*, Viacheslav Y. Fofanov*, David M. Kristensen, Marek Kimmel, Olivier Lichtarge, Lydia E. Kavraki. Proc. Pac. Symp. Biocomput. pp. 334-345, 2005.

Augmentation

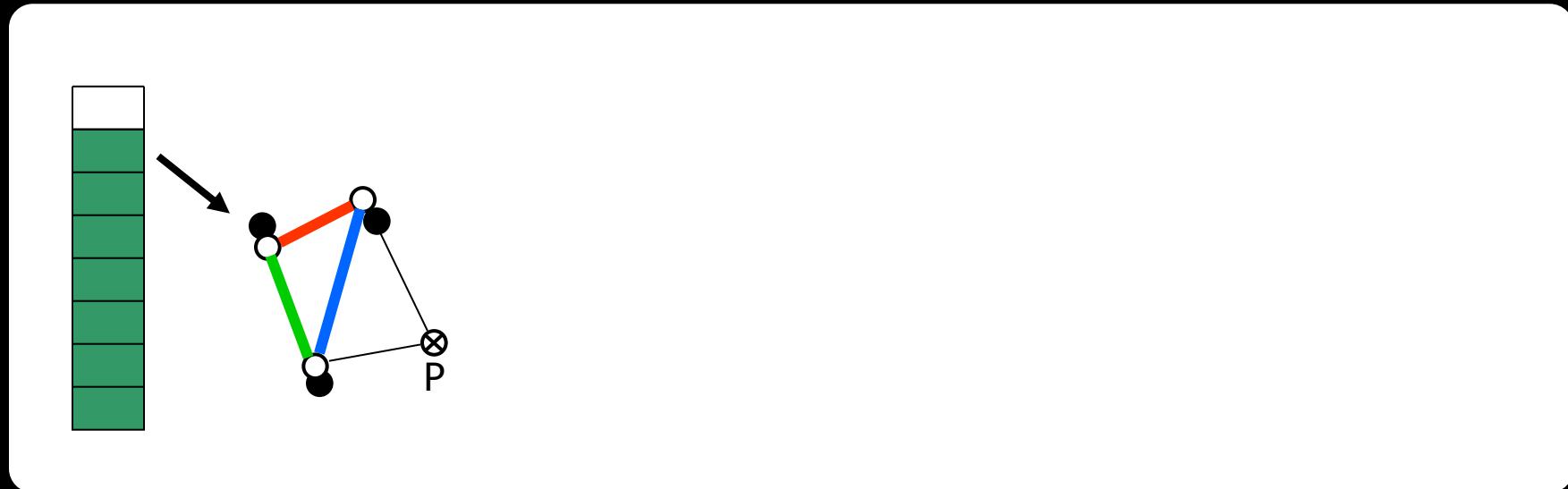
- Input: Stack populated with Seed Matches.



Algorithms for Structural Comparison and Statistical Analysis of 3D Protein Motifs. Brian Y. Chen*, Viacheslav Y. Fofanov*, David M. Kristensen, Marek Kimmel, Olivier Lichtarge, Lydia E. Kavraki. *Proc. Pac. Symp. Biocomput.* pp. 334-345, 2005.

Augmentation

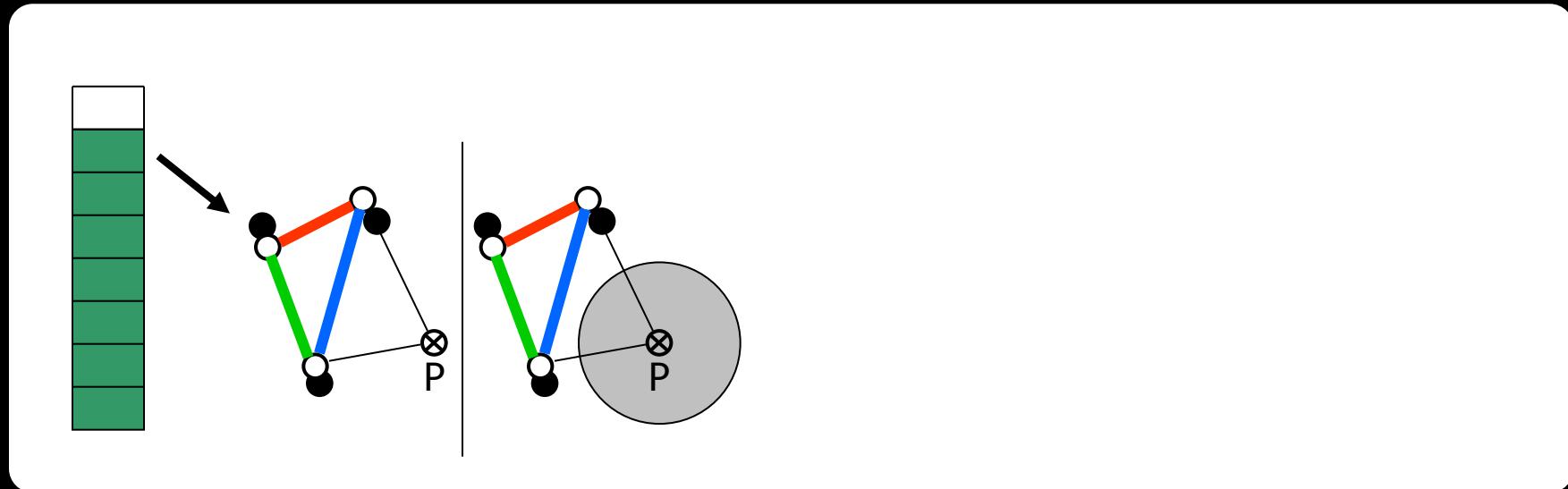
- Input: Stack populated with Seed Matches.
- Pop off a match, get highest ranked unmatched atom P



Algorithms for Structural Comparison and Statistical Analysis of 3D Protein Motifs. Brian Y. Chen*, Viacheslav Y. Fofanov*, David M. Kristensen, Marek Kimmel, Olivier Lichtarge, Lydia E. Kavraki. Proc. Pac. Symp. Biocomput. pp. 334-345, 2005.

Augmentation

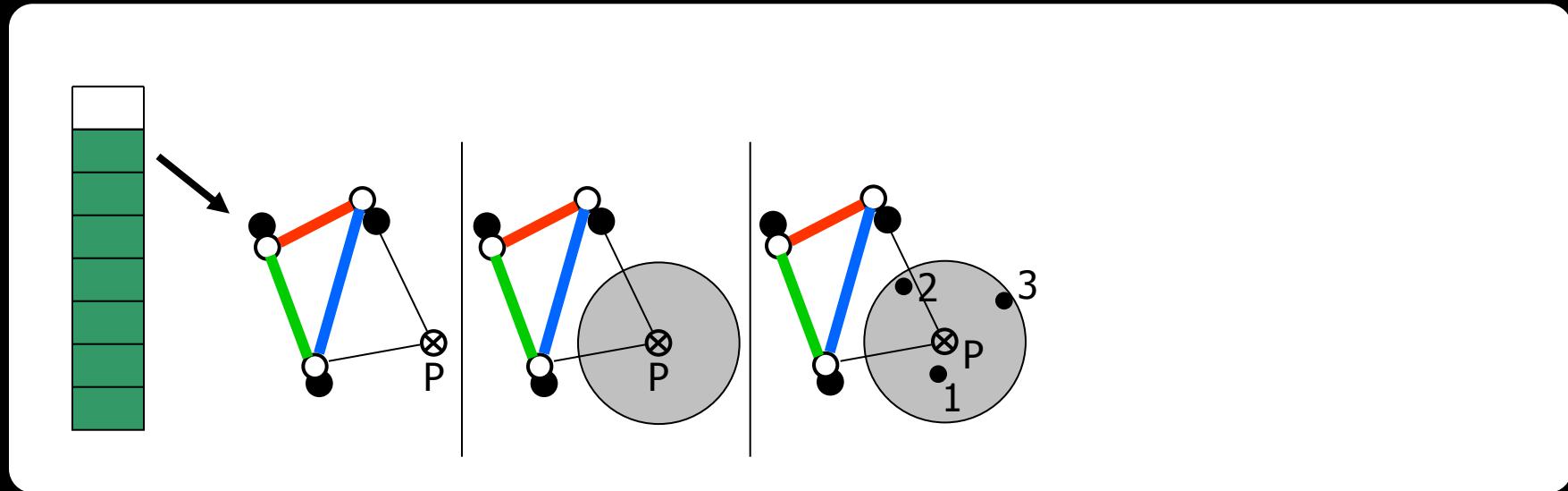
- Input: Stack populated with Seed Matches.
- Pop off a match, get highest ranked unmatched atom P
- Find compatible target atoms in the vicinity of P



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Augmentation

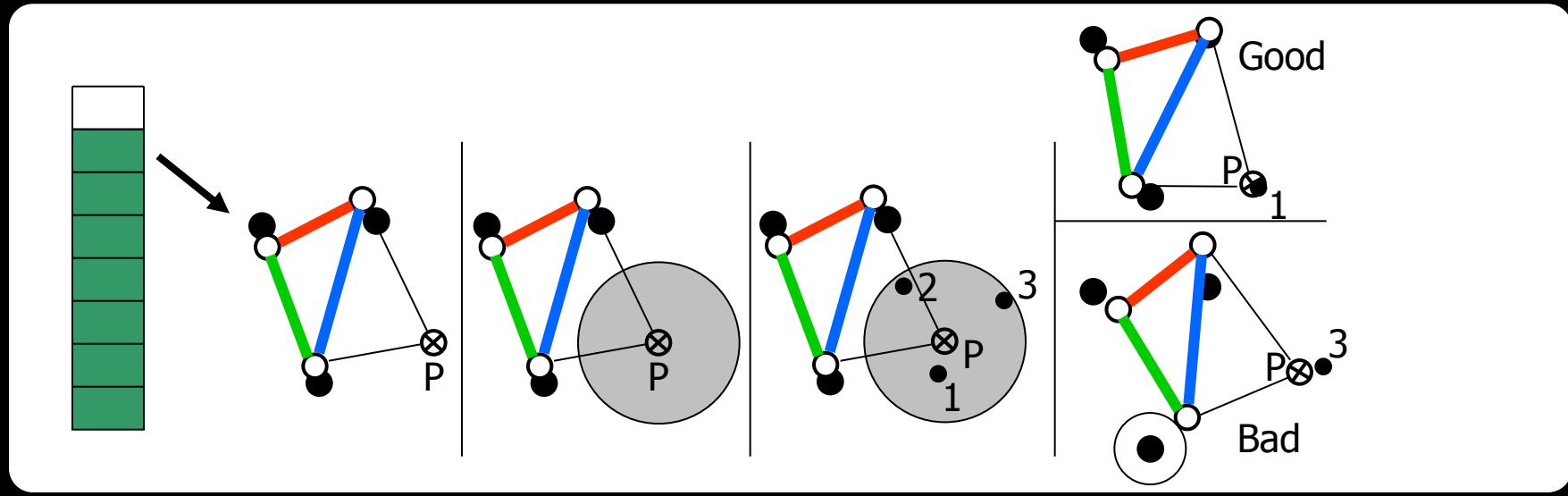
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- Find compatible target atoms in the vicinity of P



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Augmentation

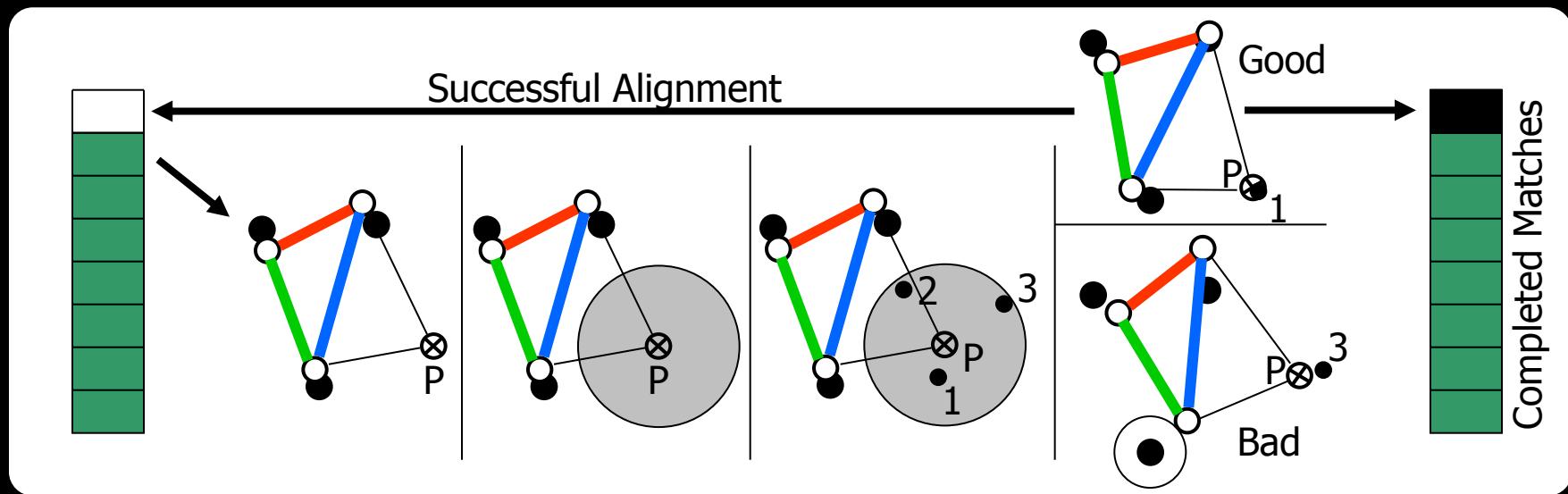
- Input: Stack populated with Seed Matches.
- Pop off a match, get highest ranked unmatched atom P
- Find compatible target atoms in the vicinity of P
- Test alignments with each atom compatible with P



Algorithms for Structural Comparison and Statistical Analysis of 3D Protein Motifs. Brian Y. Chen*, Viacheslav Y. Fofanov*, David M. Kristensen, Marek Kimmel, Olivier Lichtarge, Lydia E. Kavraki. Proc. Pac. Symp. Biocomput. pp. 334-345, 2005.

Augmentation

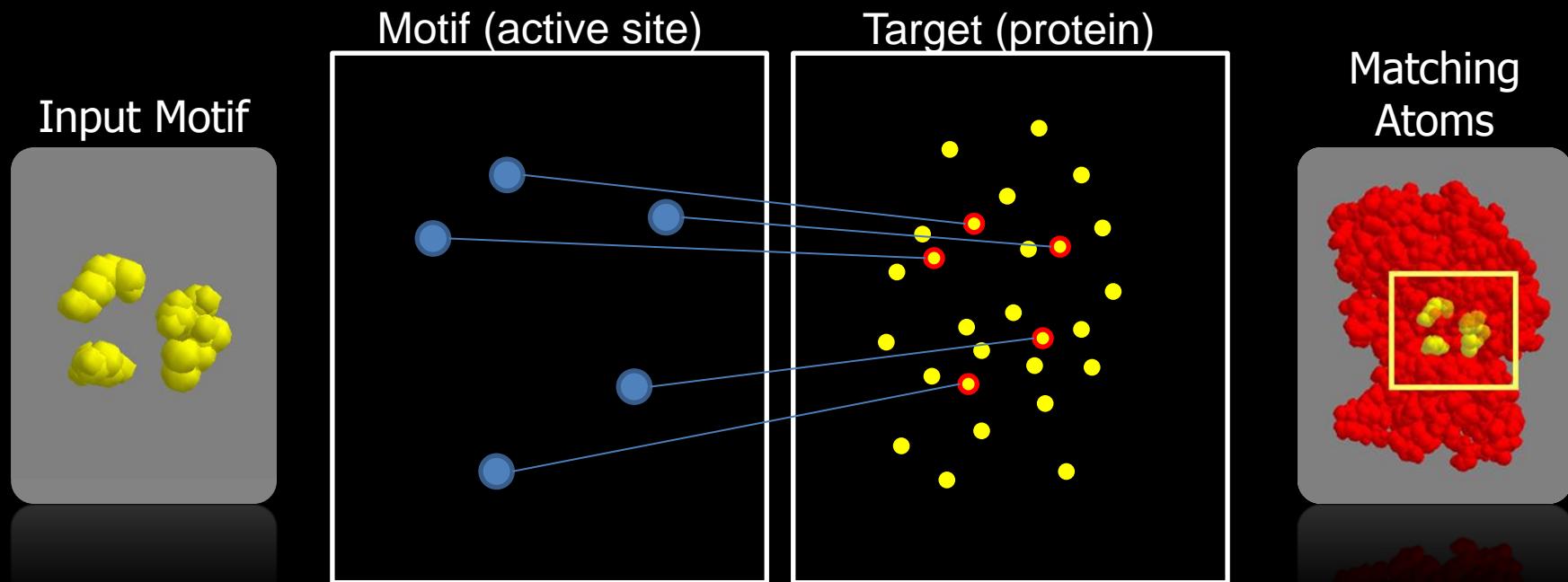
- Input: Stack populated with Seed Matches.
- Pop off a match, get highest ranked unmatched atom P
- Find compatible target atoms in the vicinity of P
- Test alignments with each atom compatible with P
- Put successful alignments back on stack, or store completed matches



Algorithms for Structural Comparison and Statistical Analysis of 3D Protein Motifs. Brian Y. Chen*, Viacheslav Y. Fofanov*, David M. Kristensen, Marek Kimmel, Olivier Lichtarge, Lydia E. Kavraki. Proc. Pac. Symp. Biocomput. pp. 334-345, 2005.

Matching Output

- Matching atoms with greatest geometric similarity
- Corresponding atoms with similar chemical properties

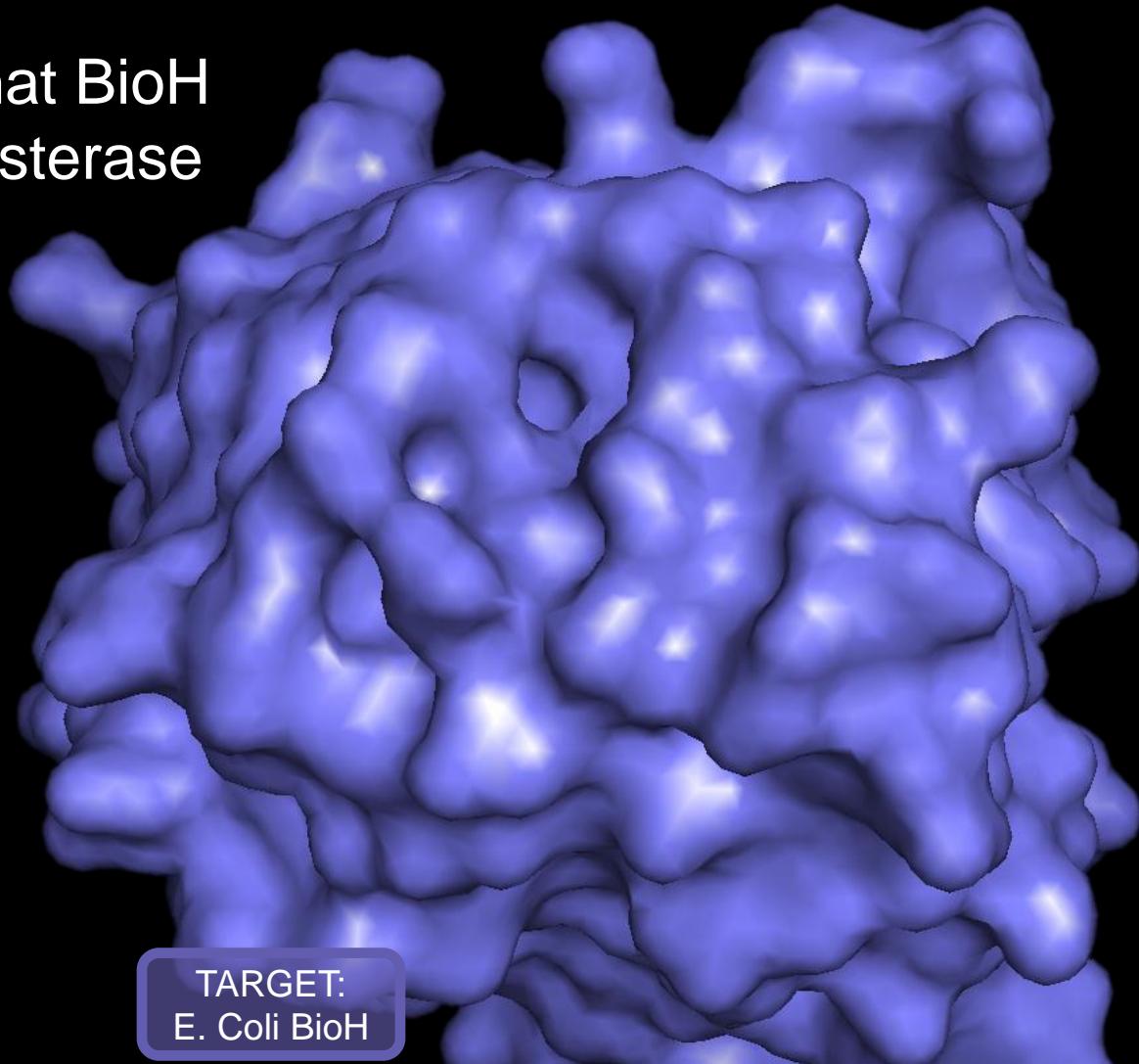
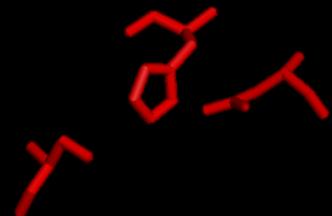


Algorithms for Structural Comparison and Statistical Analysis of 3D Protein Motifs. Brian Y. Chen*, Viacheslav Y. Fofanov*, David M. Kristensen, Marek Kimmel, Olivier Lichtarge, Lydia E. Kavraki. Proc. Pac. Symp. Biocomput. pp. 334-345, 2005.

Matching can suggest unknown function

- Matching suggests that BioH performs a carboxylesterase function

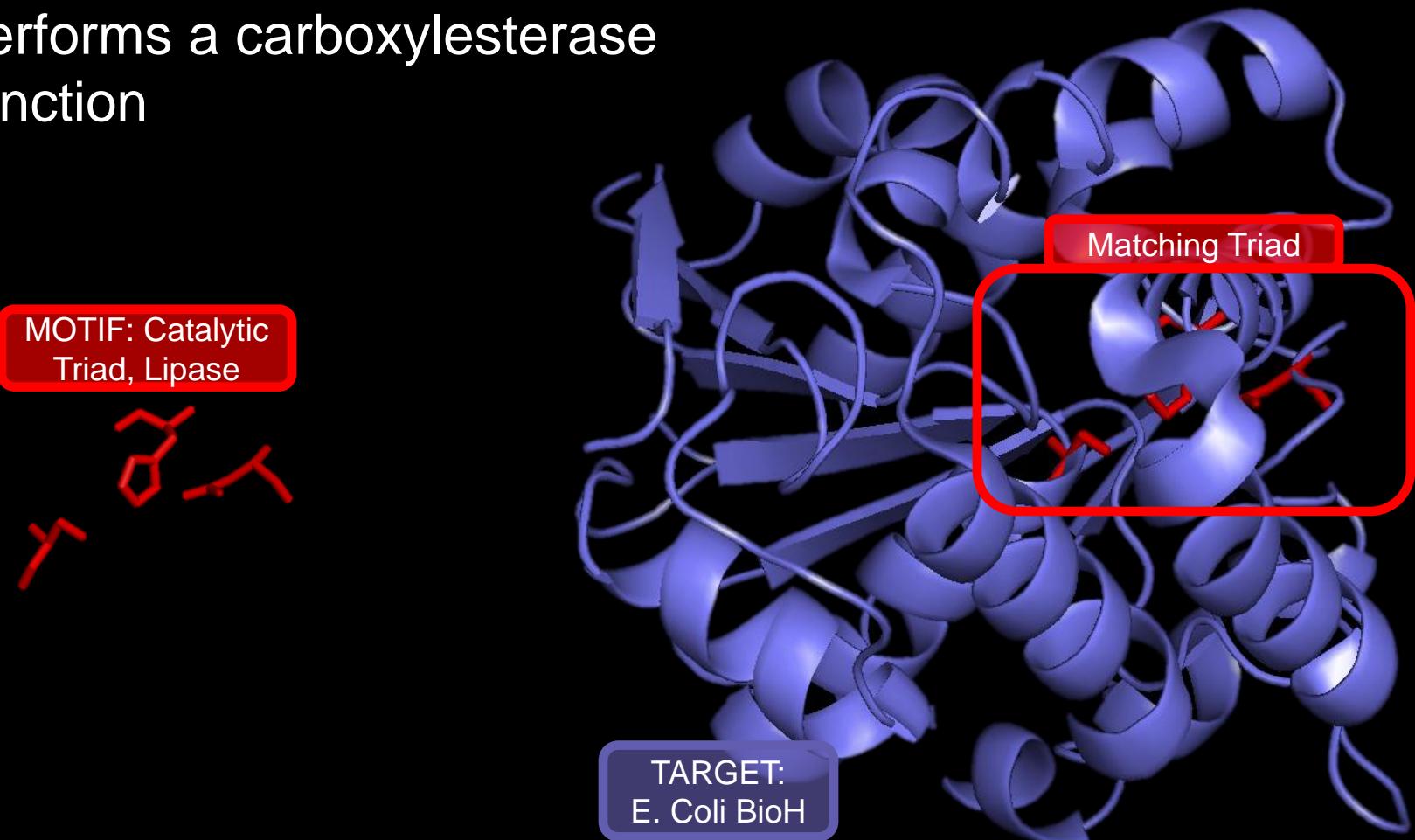
MOTIF: Catalytic Triad, Lipase



Integrating structure, bioinformatics, and enzymology to discover function:
BioH, a new carboxylesterase from *Escherichia coli*.
Sanishvili R, et al. *J. Biol. Chem.* 278(28):26039-45, 2003.

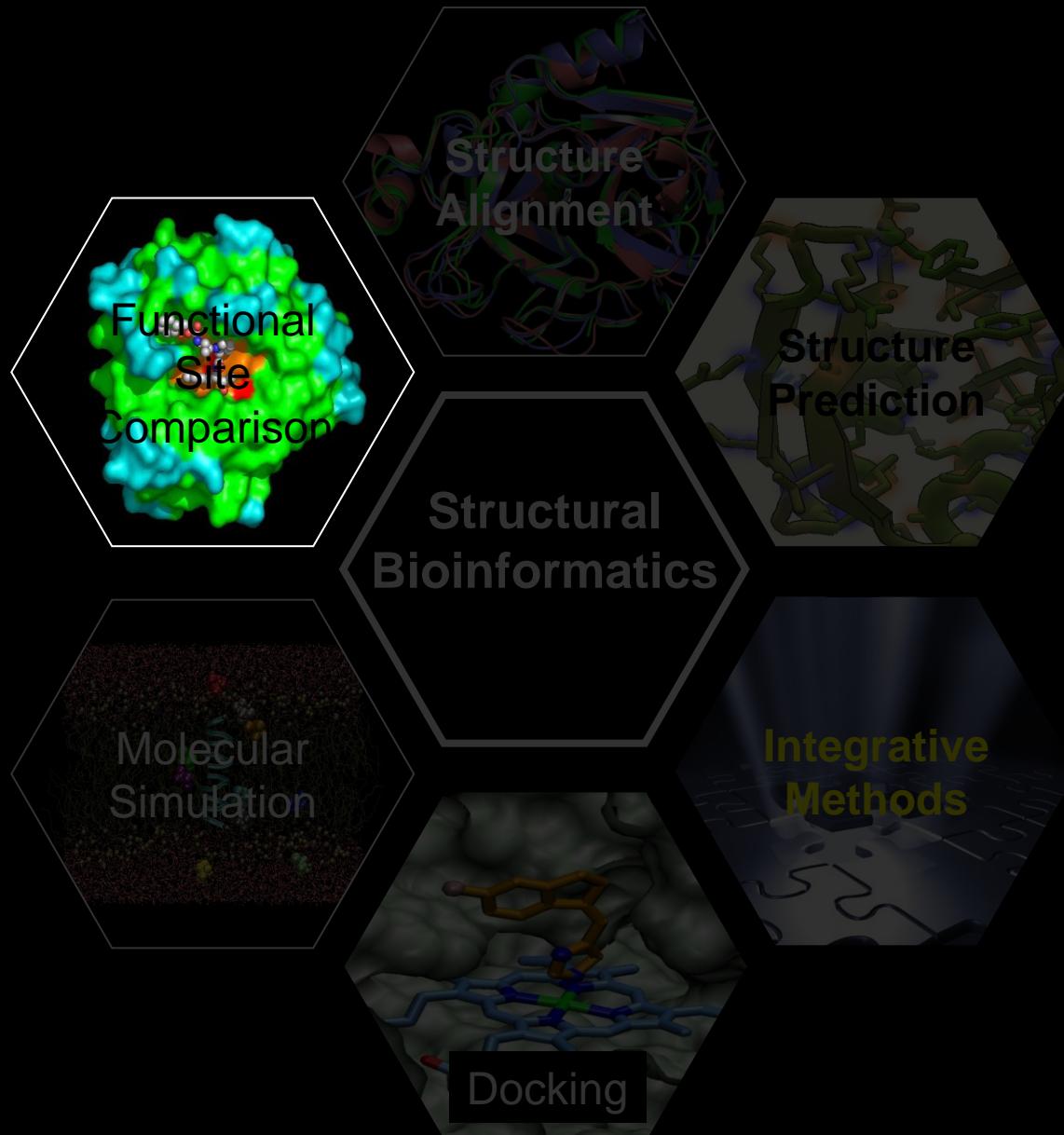
Matching can suggest unknown function

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Integrating structure, bioinformatics, and enzymology to discover function:
BioH, a new carboxylesterase from Escherichia coli.
Sanishvili R, et al. *J. Biol. Chem.* 278(28):26039-45, 2003.

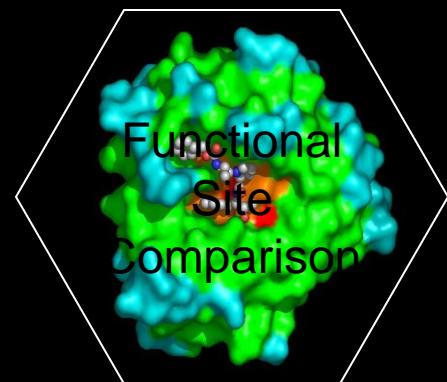
Two fields of Structural Bioinformatics



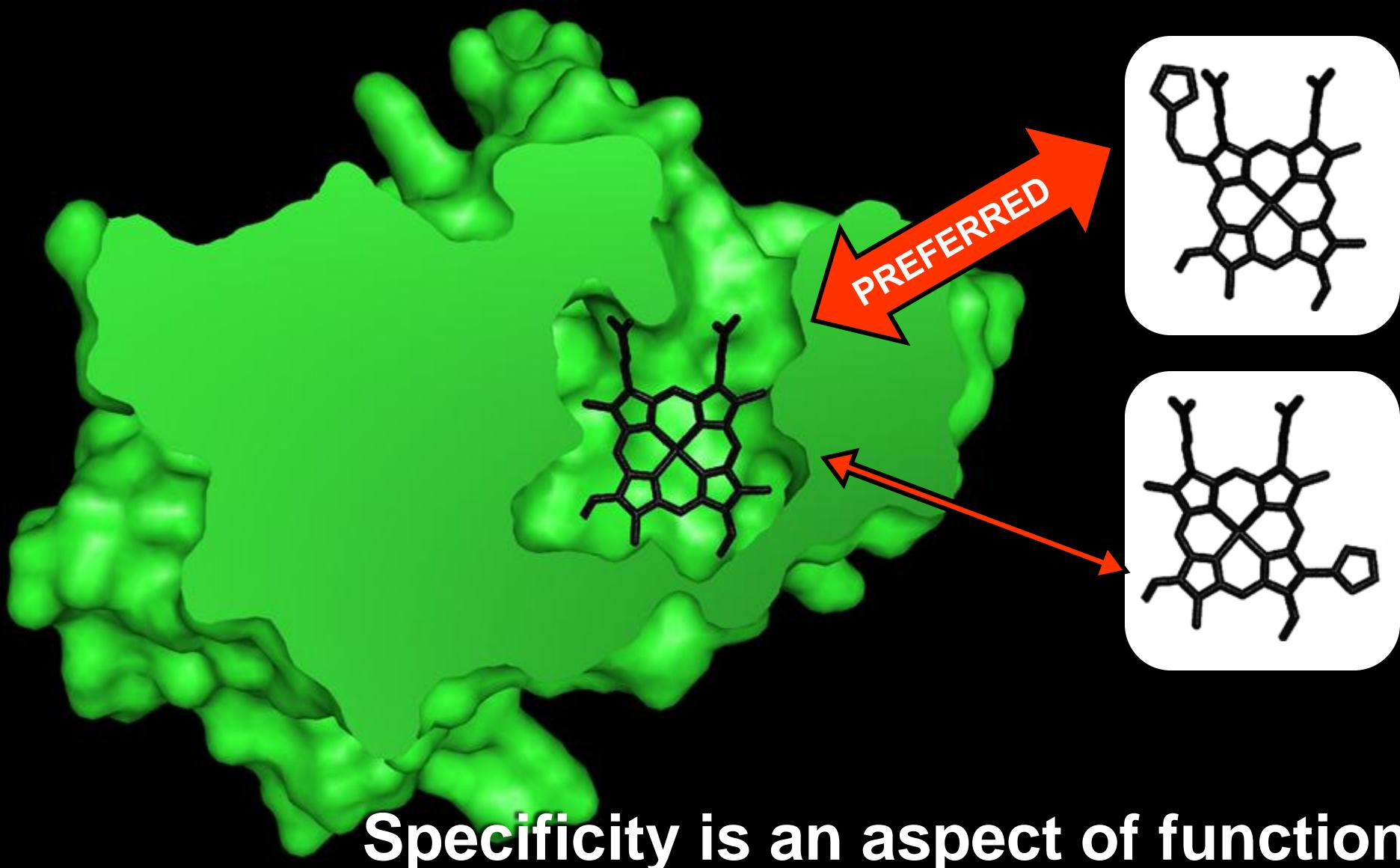
Matching doesn't tell us everything

How does this protein fit in the system?

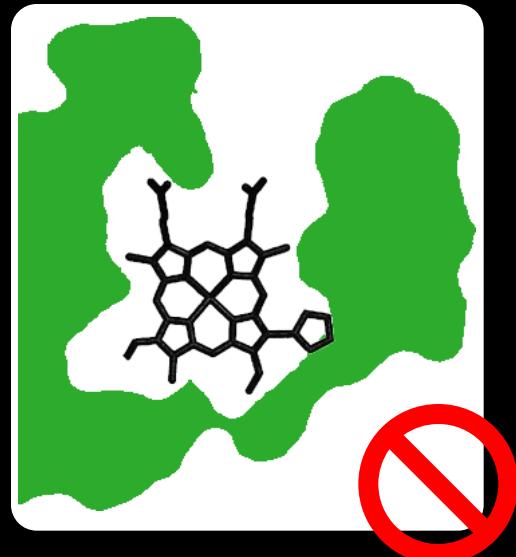
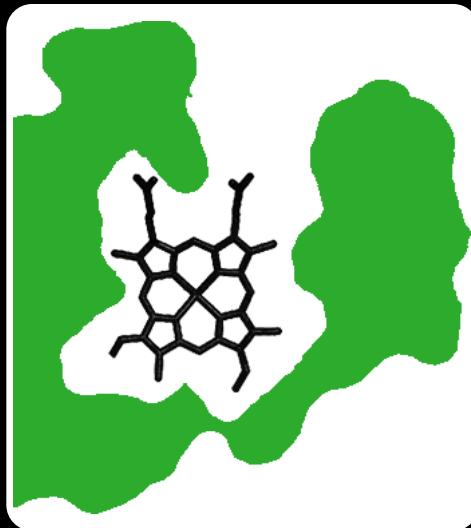
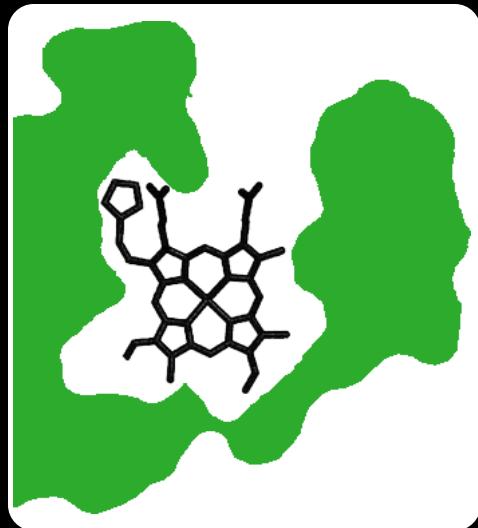
What parts of the protein make it work?



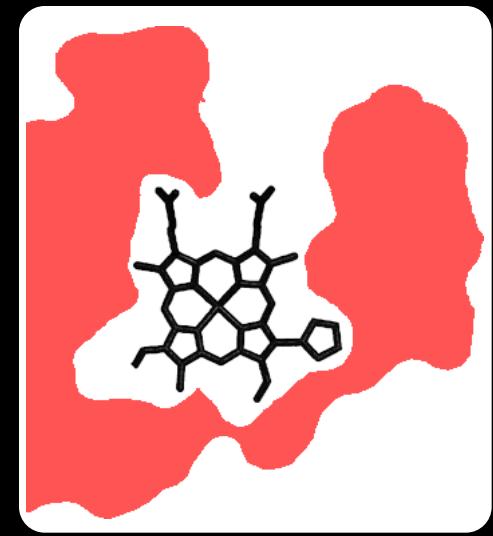
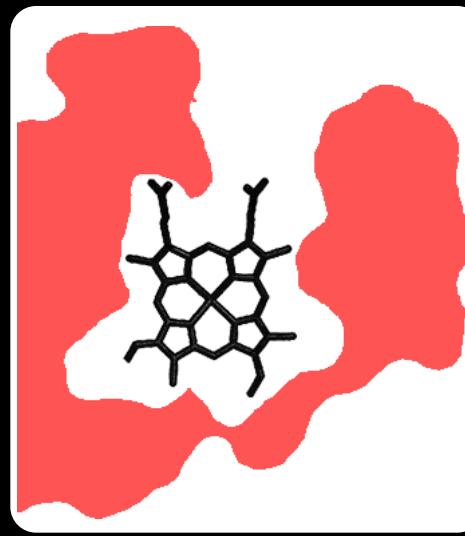
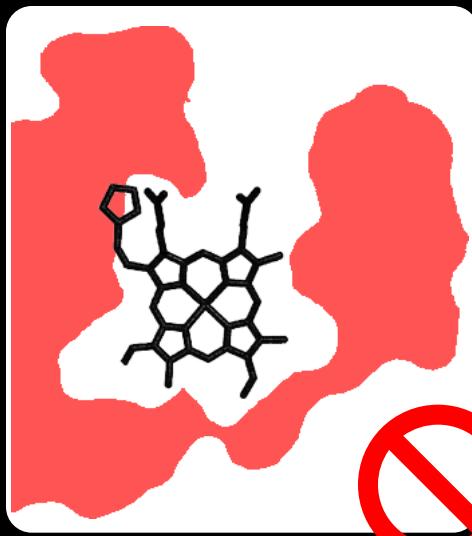
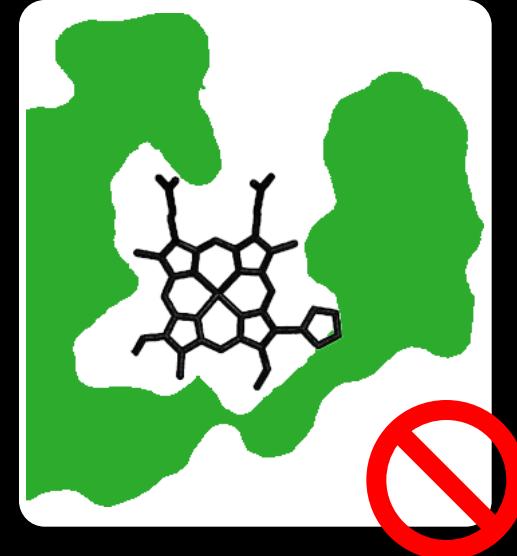
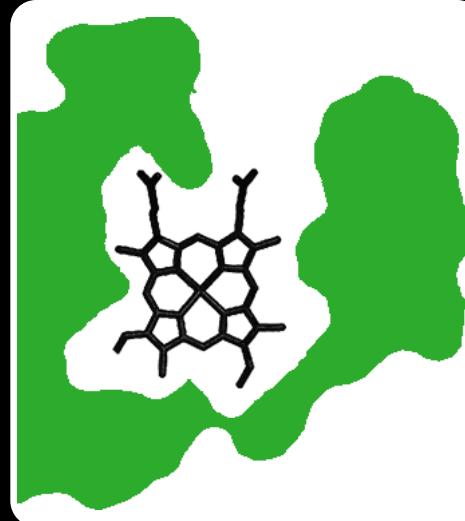
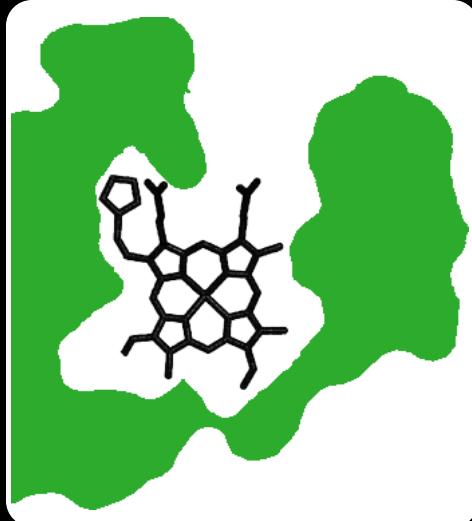
Specificity is preferential binding



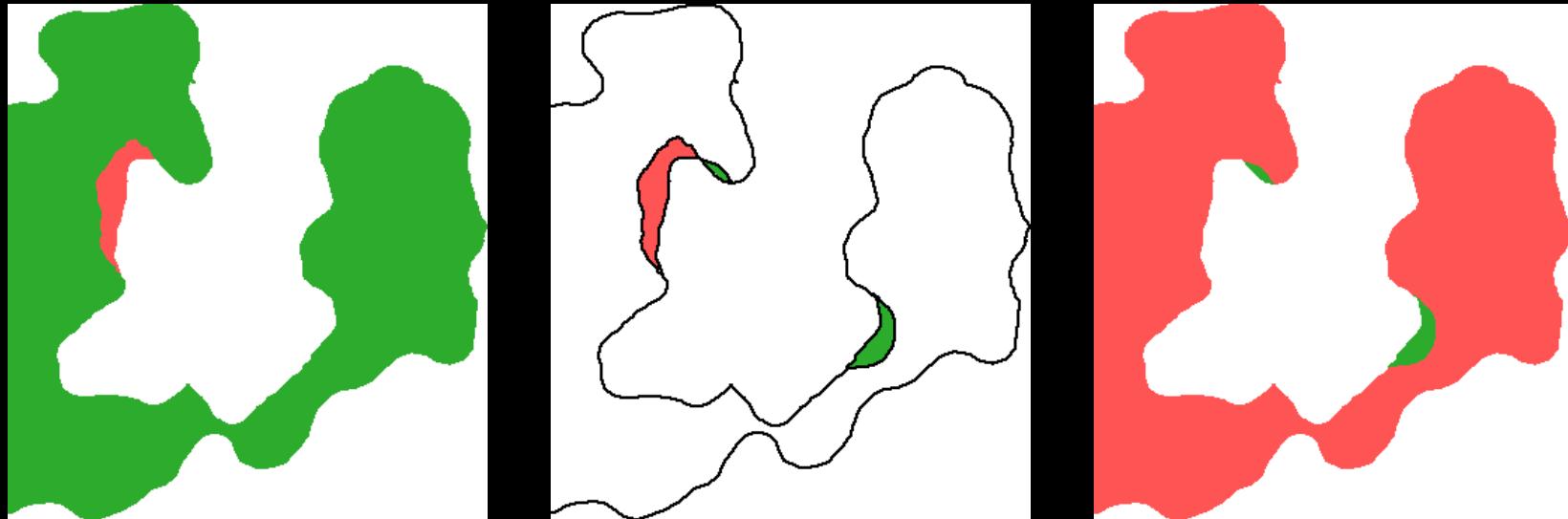
Cavity shape influences specificity



Proteins with the same function can have different specificity



VASP isolates differences in cavity shape to find influences on specificity



VASP: Volumetric Analysis of the Surfaces of Proteins

- Identify amino acids that alter cavity shape
- Identify subcavities that alter cavity shape

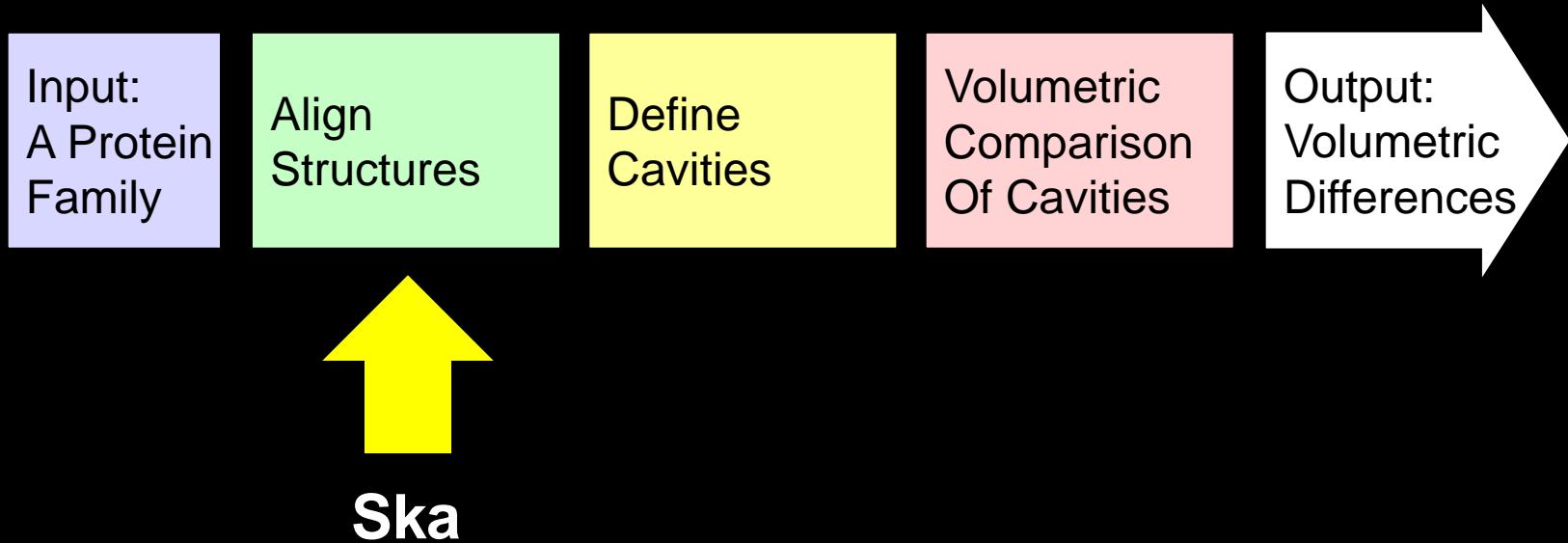
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

The VASP procedure



VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

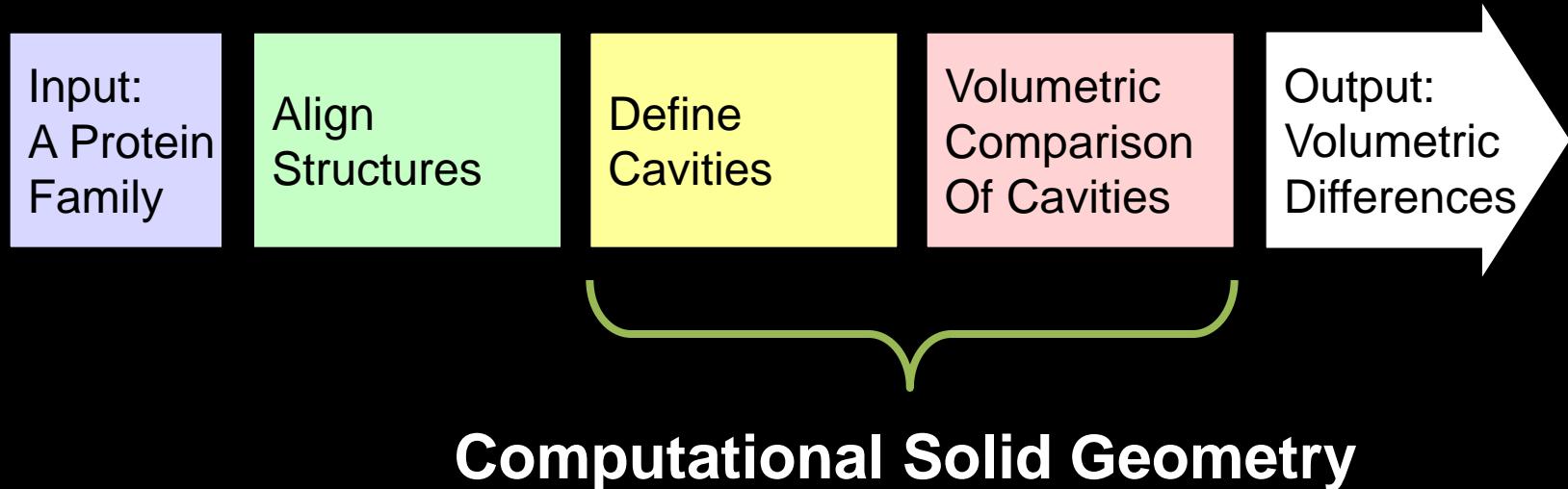
The VASP procedure



Petrey D, Honig B. GRASP2: visualization, surface properties, and electrostatics of macromolecular structures and sequences. *Methods Enzymol.* 374:492-509. 2003.

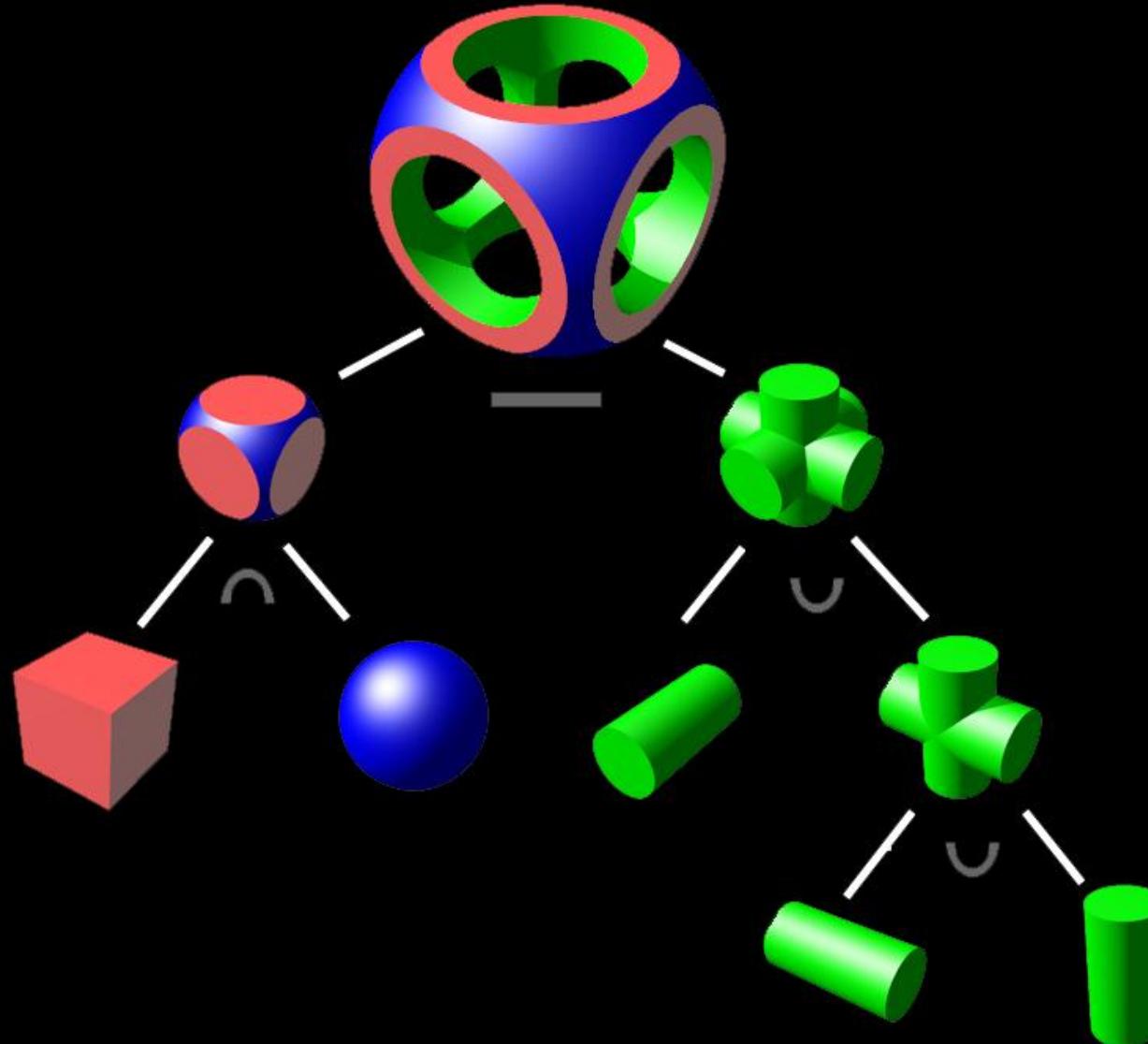
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The VASP procedure



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Computational Solid Geometry (CSG)



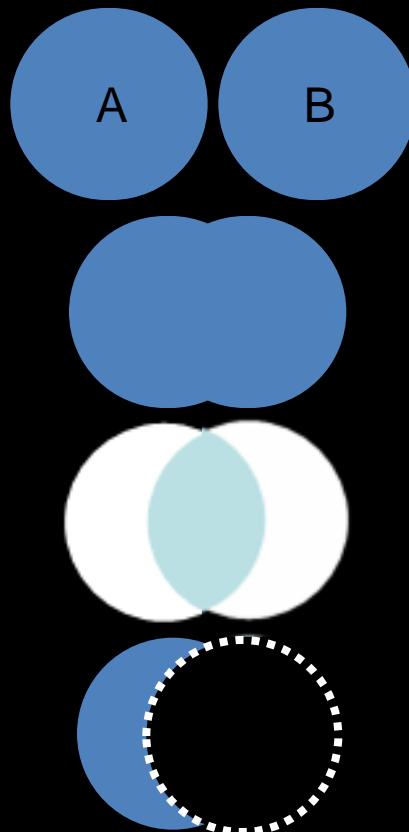
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

CSG was originally for modeling parts



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Computational Solid Geometry (CSG)



Boolean Set Operations

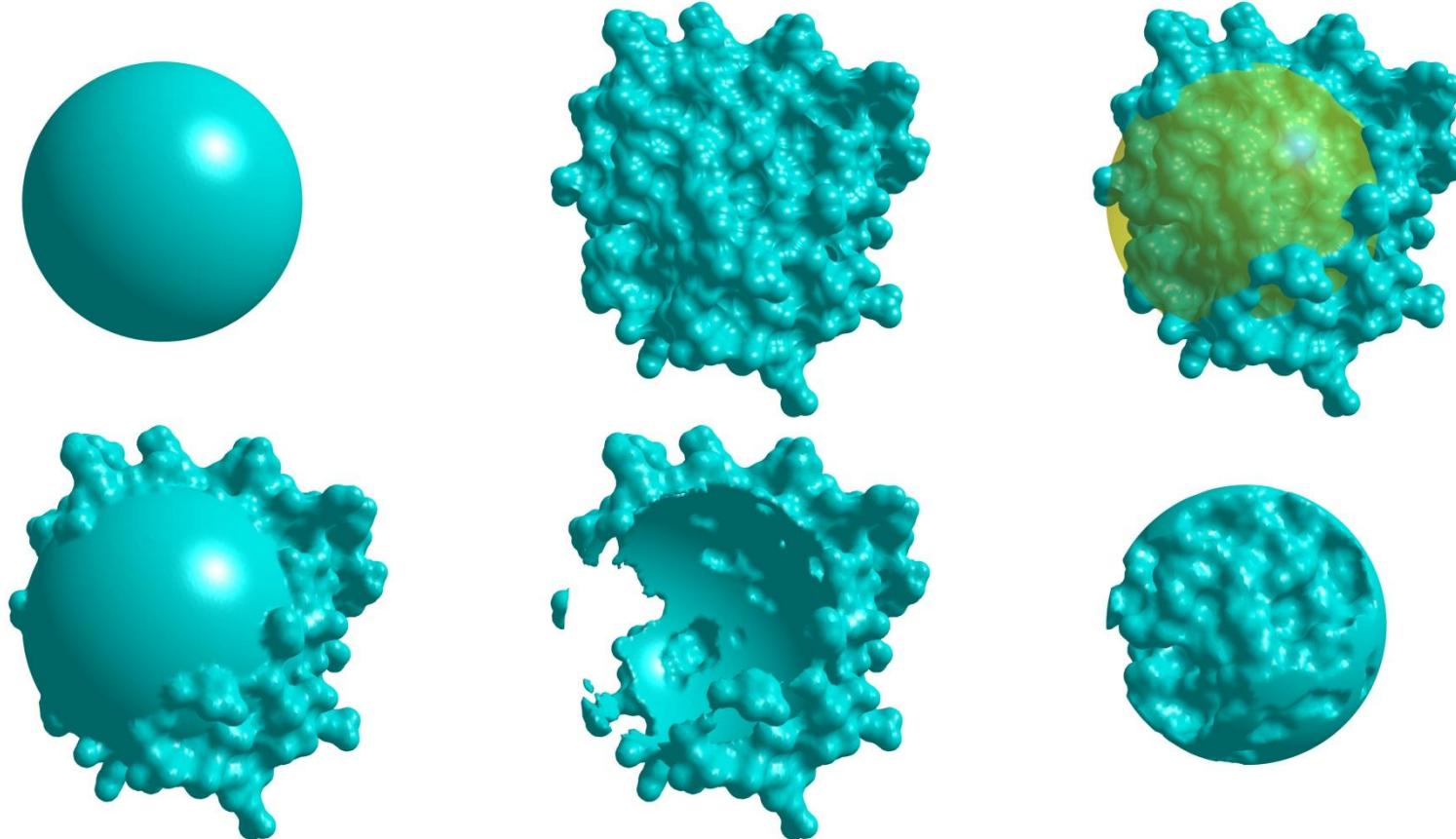
Union

Intersection

Difference

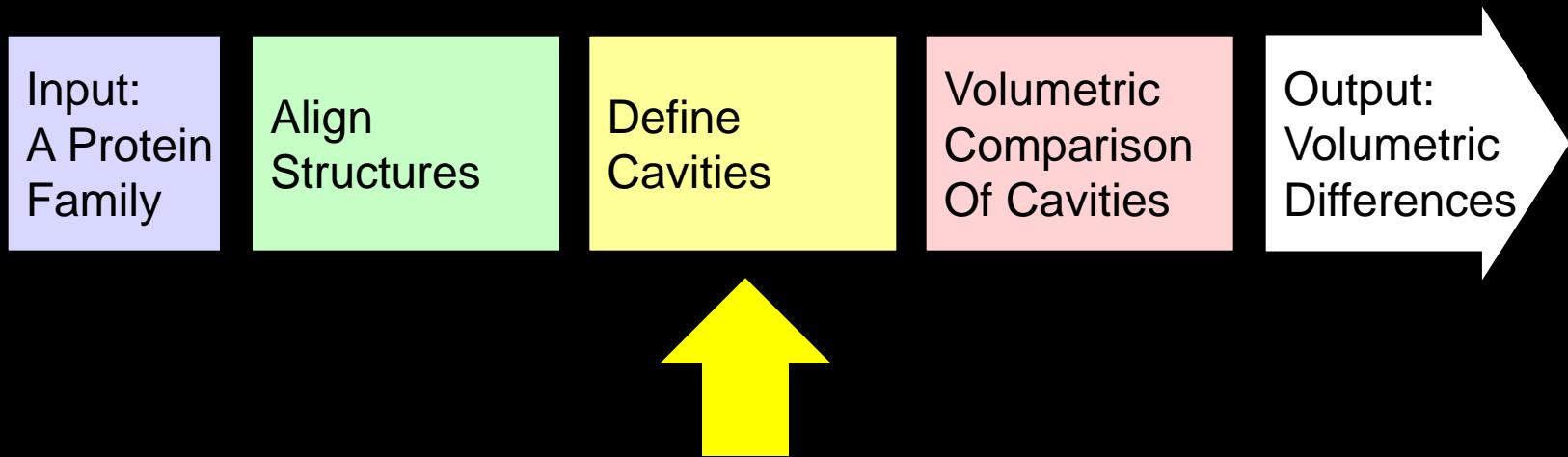
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

Using CSG with protein structures



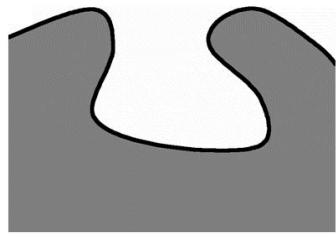
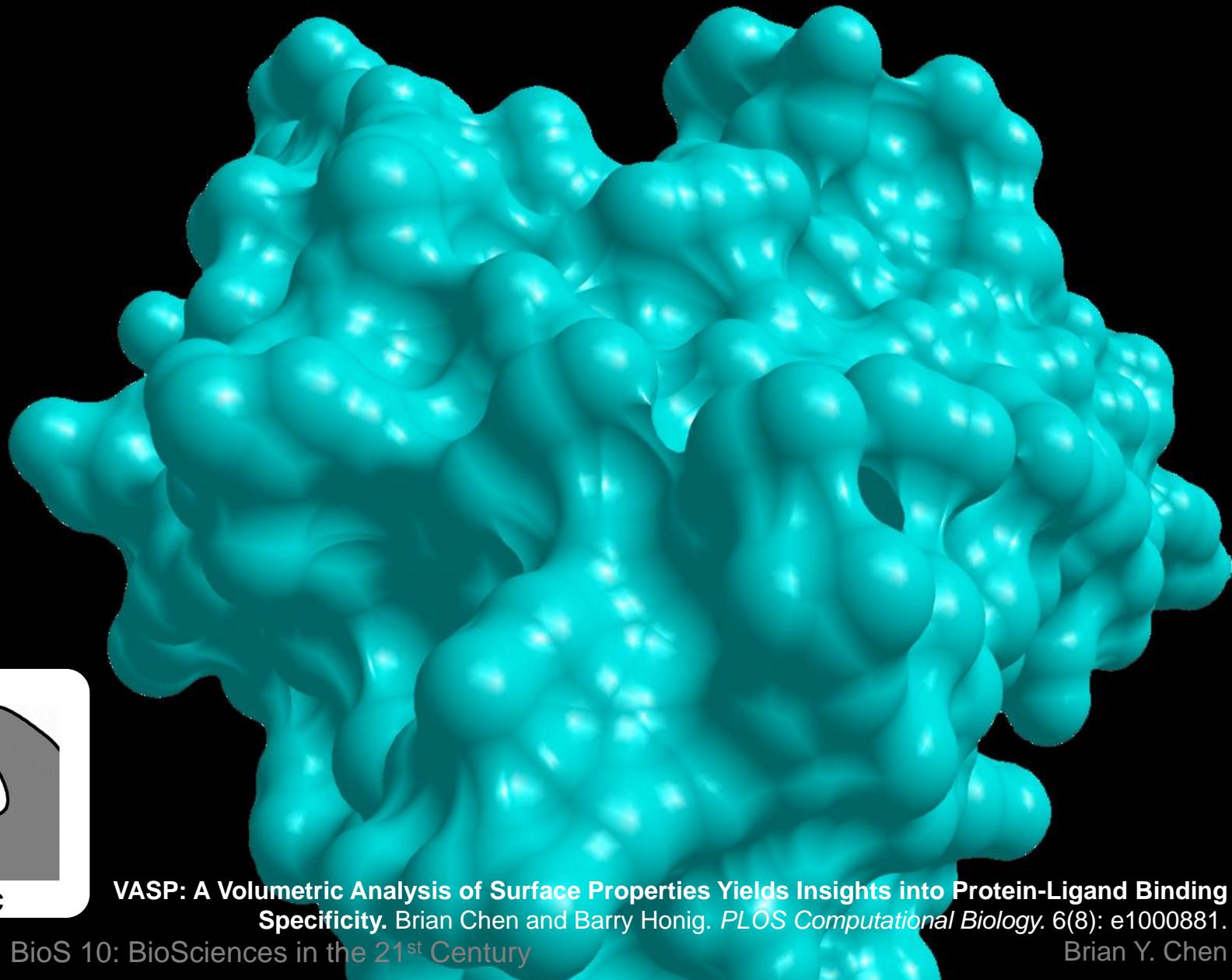
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The VASP procedure



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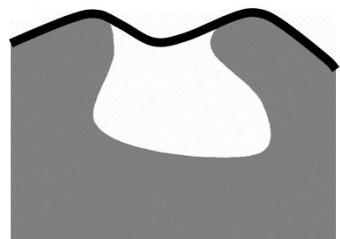
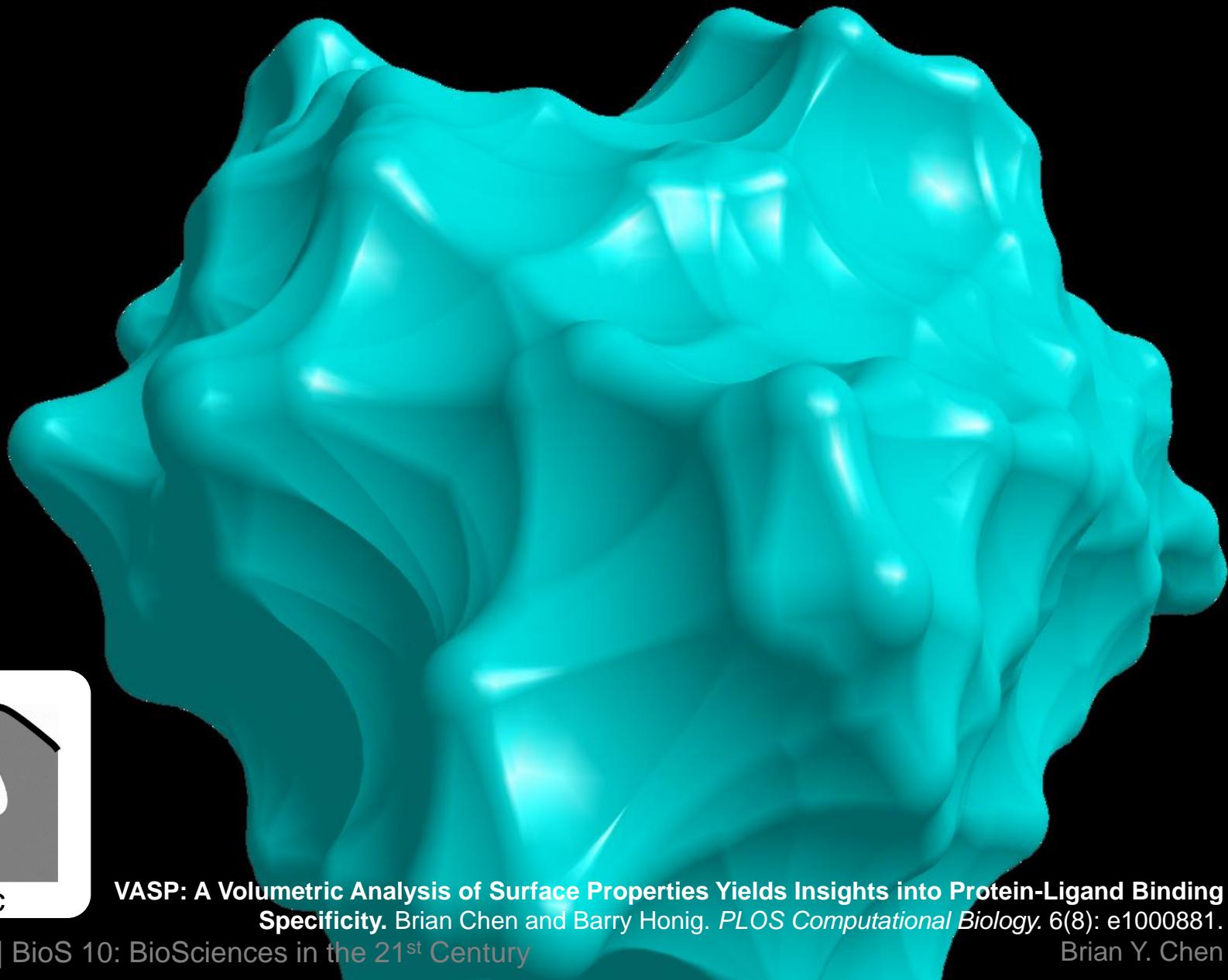
Begin with the molecular surface



Schematic

VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

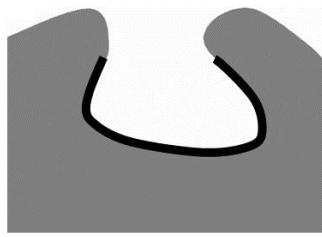
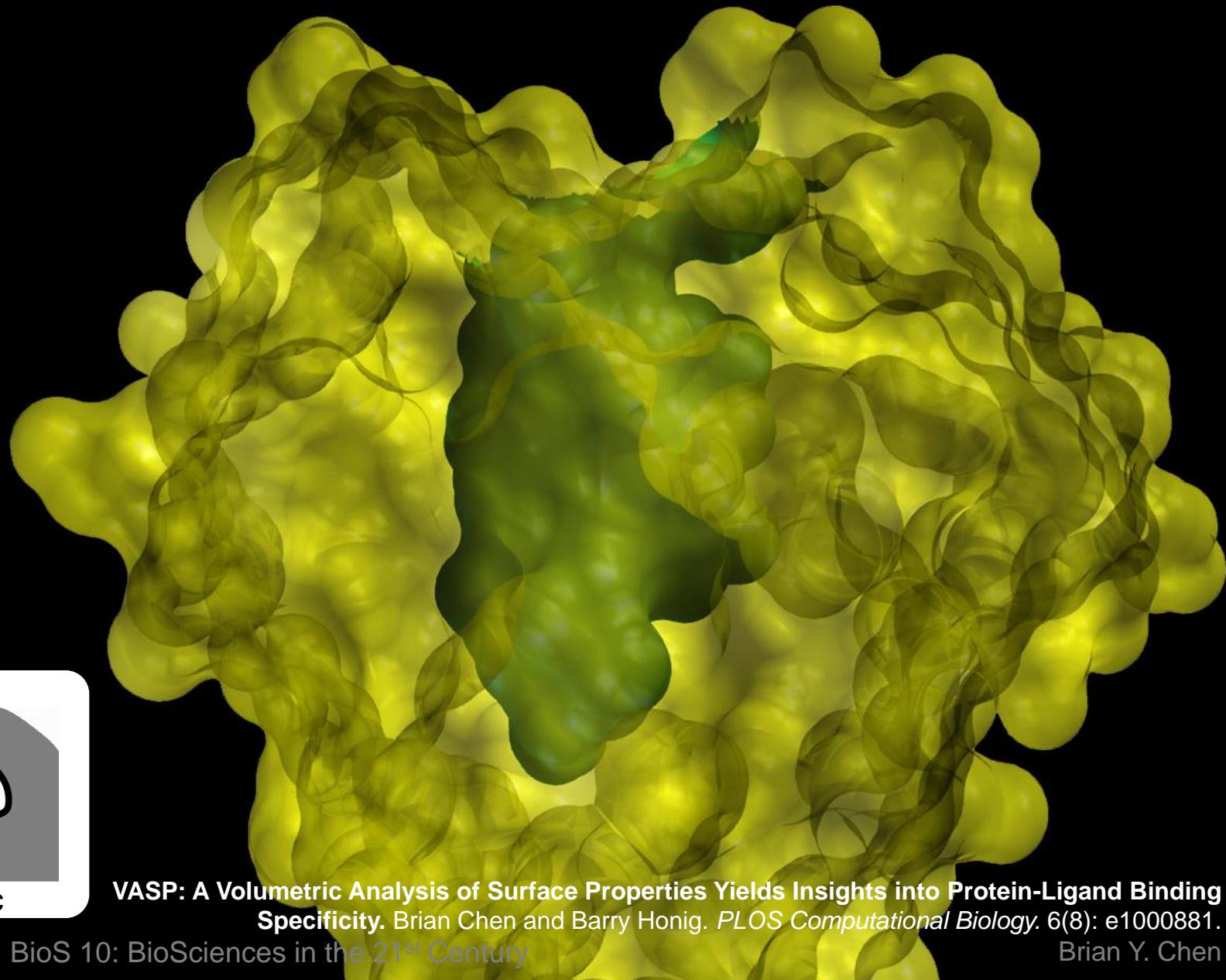
Compute an envelope surface



Schematic

VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

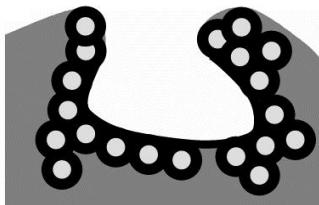
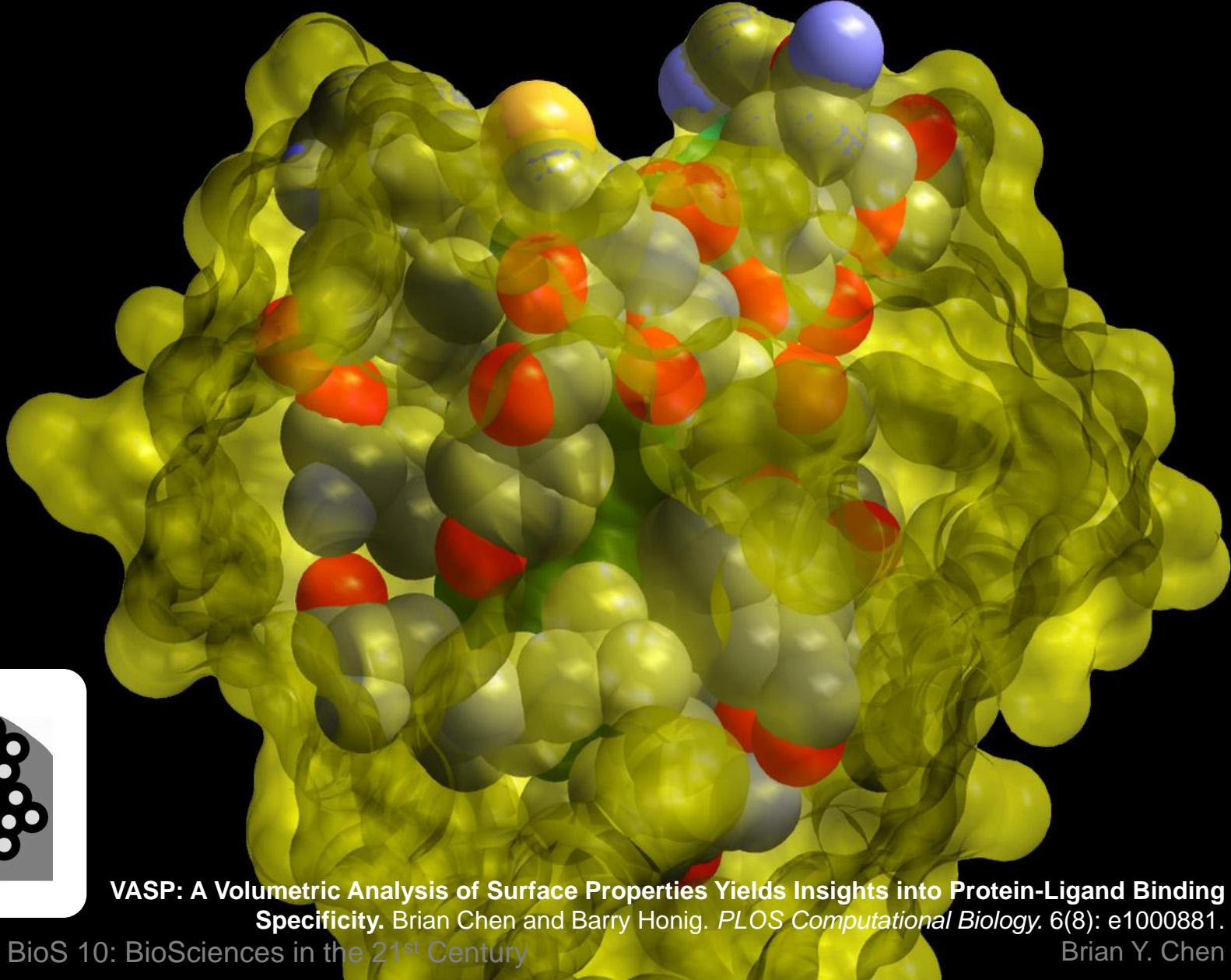
Find the interior surface



Schematic

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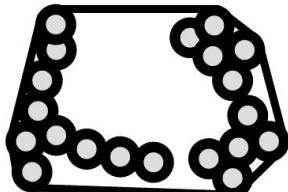
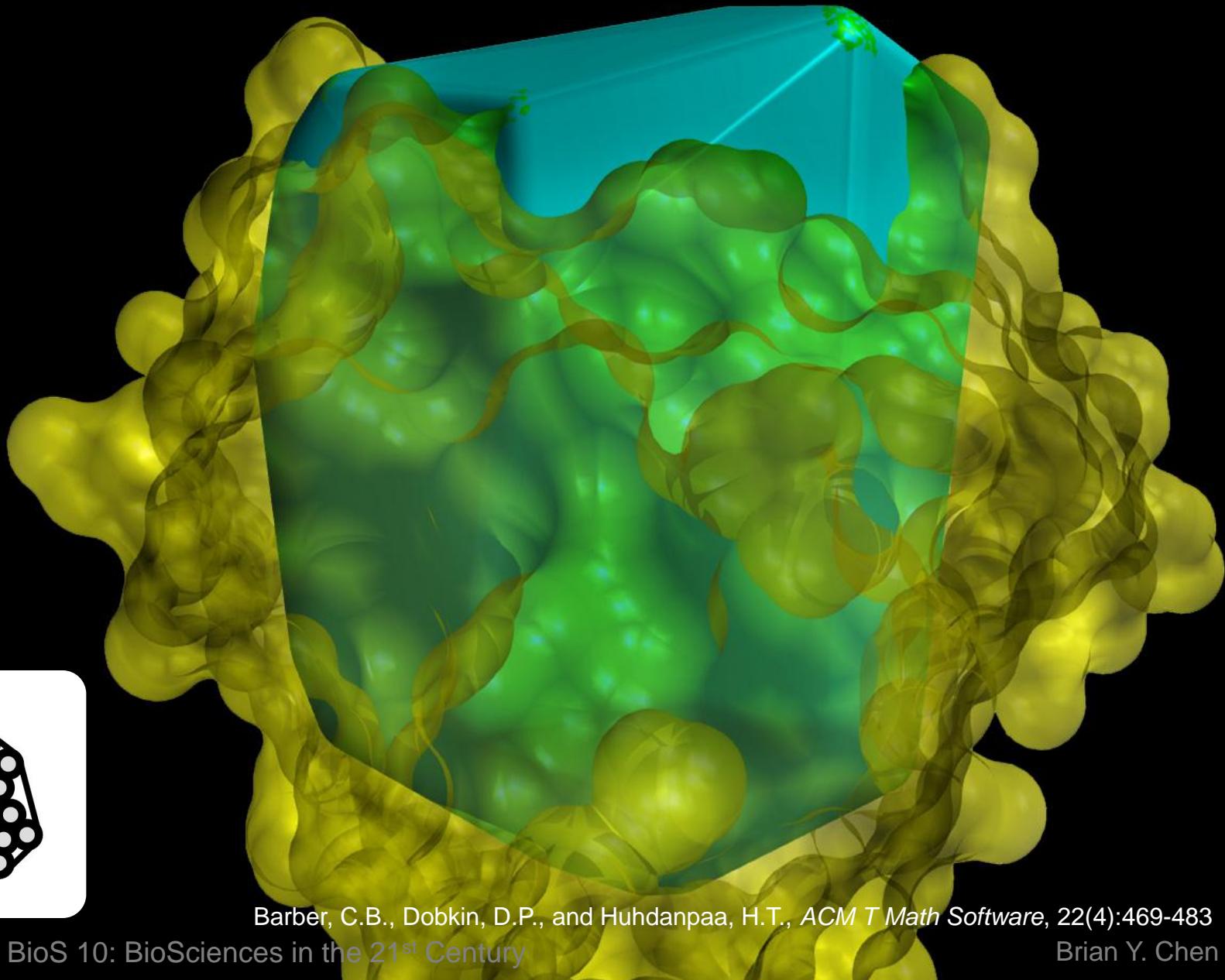
Identify nearby amino acids



Schematic

VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

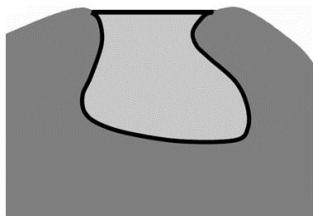
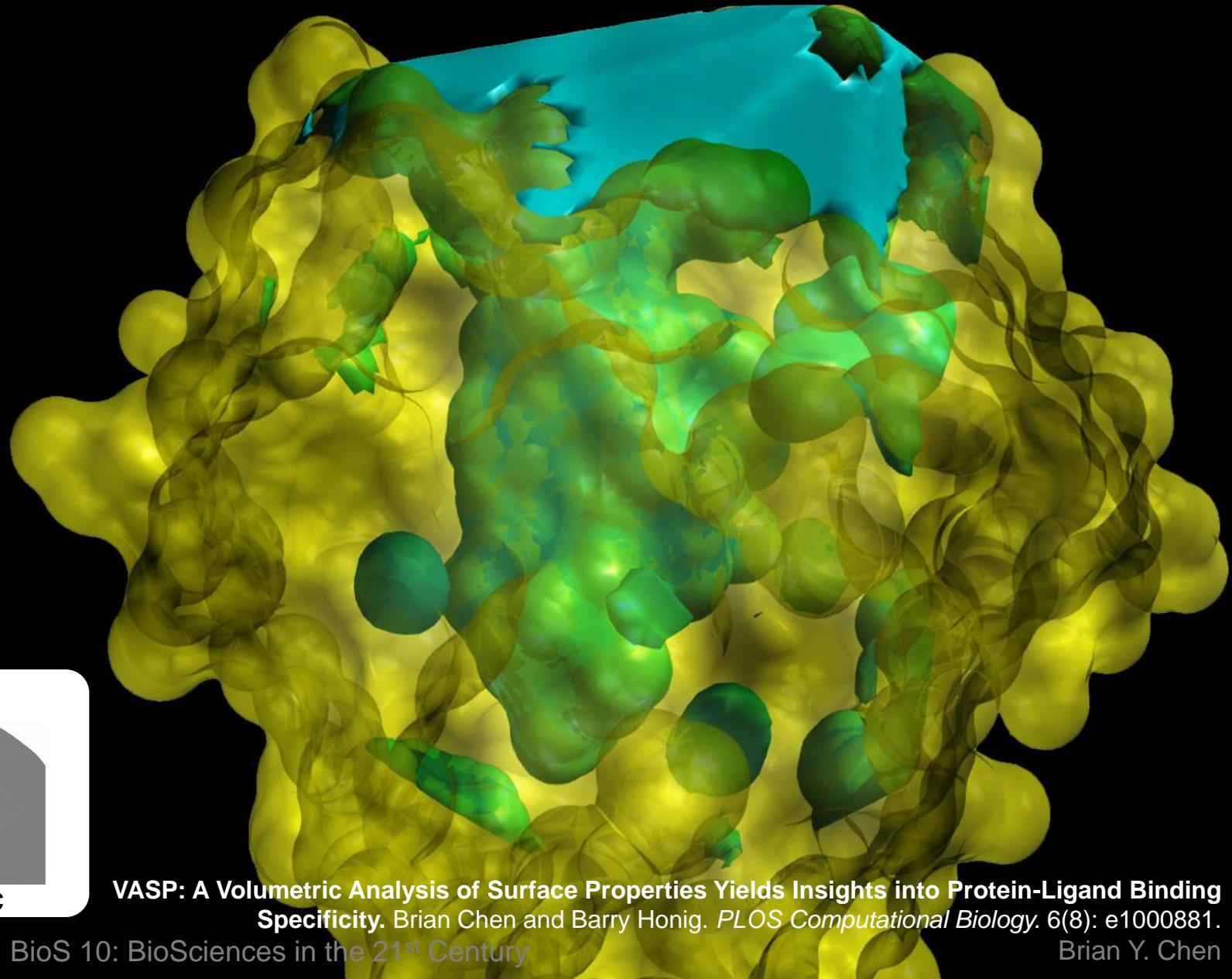
Compute the convex hull



Schematic

Barber, C.B., Dobkin, D.P., and Huhdanpaa, H.T., *ACM T Math Software*, 22(4):469-483

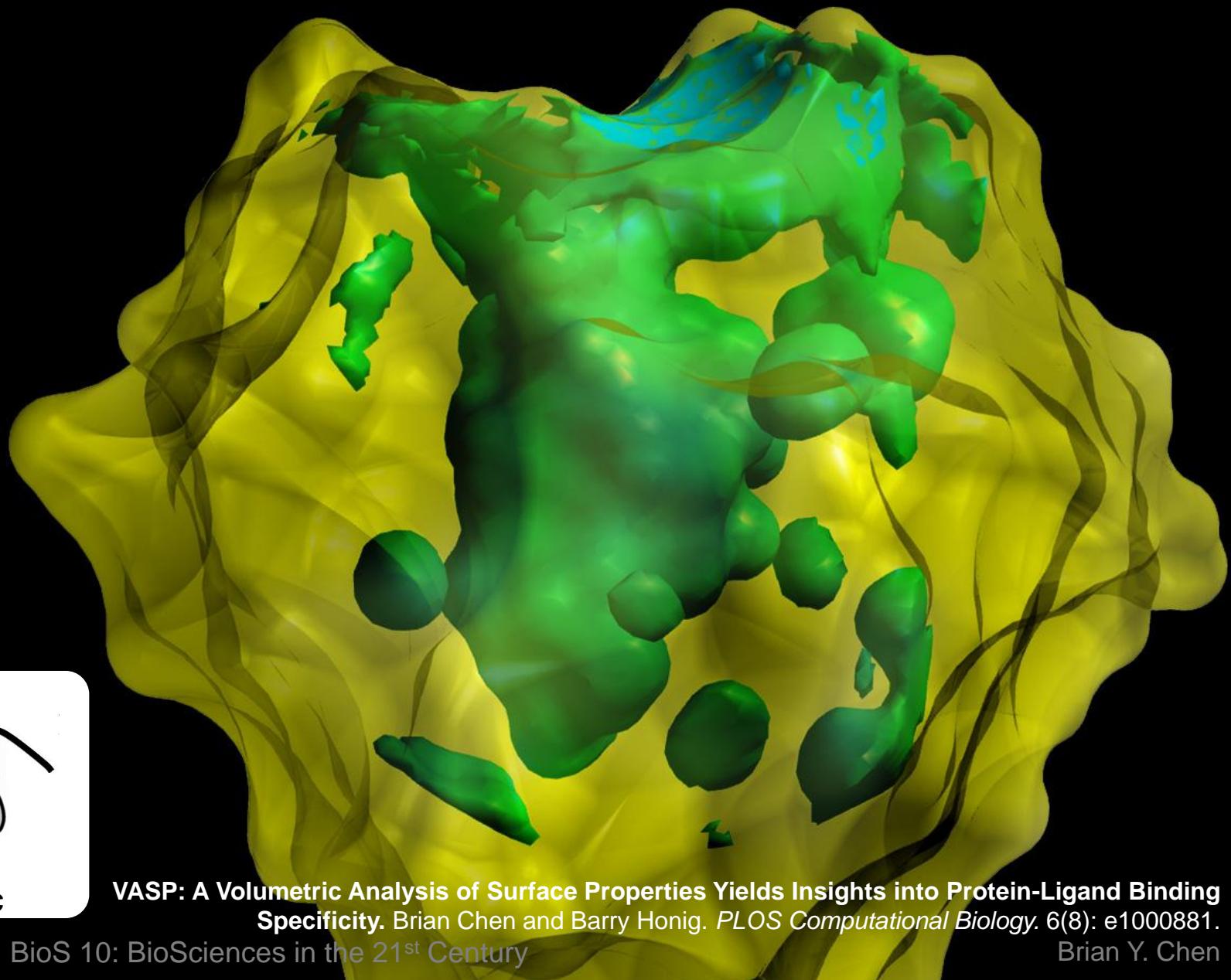
CSG hull minus molecular surface



Schematic

VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

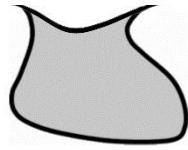
CSG intersection with the envelope surface



Schematic

VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

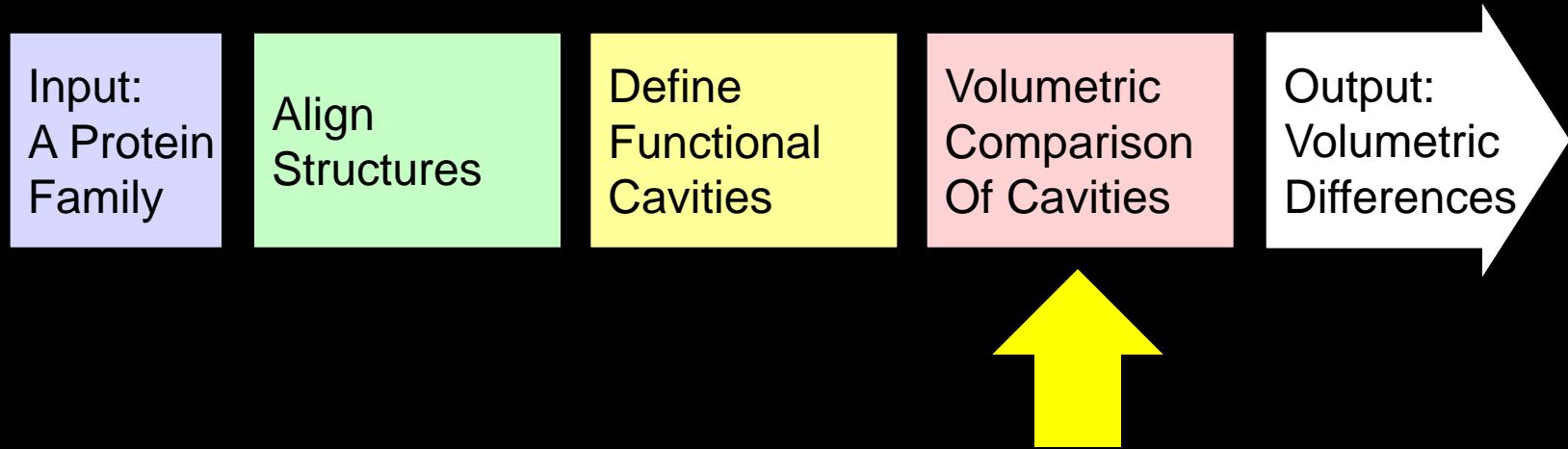
Remove disconnected pieces



Schematic

VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

The VASP procedure



- Amino Acids affecting cavity shape
- Subcavities affecting cavity shape

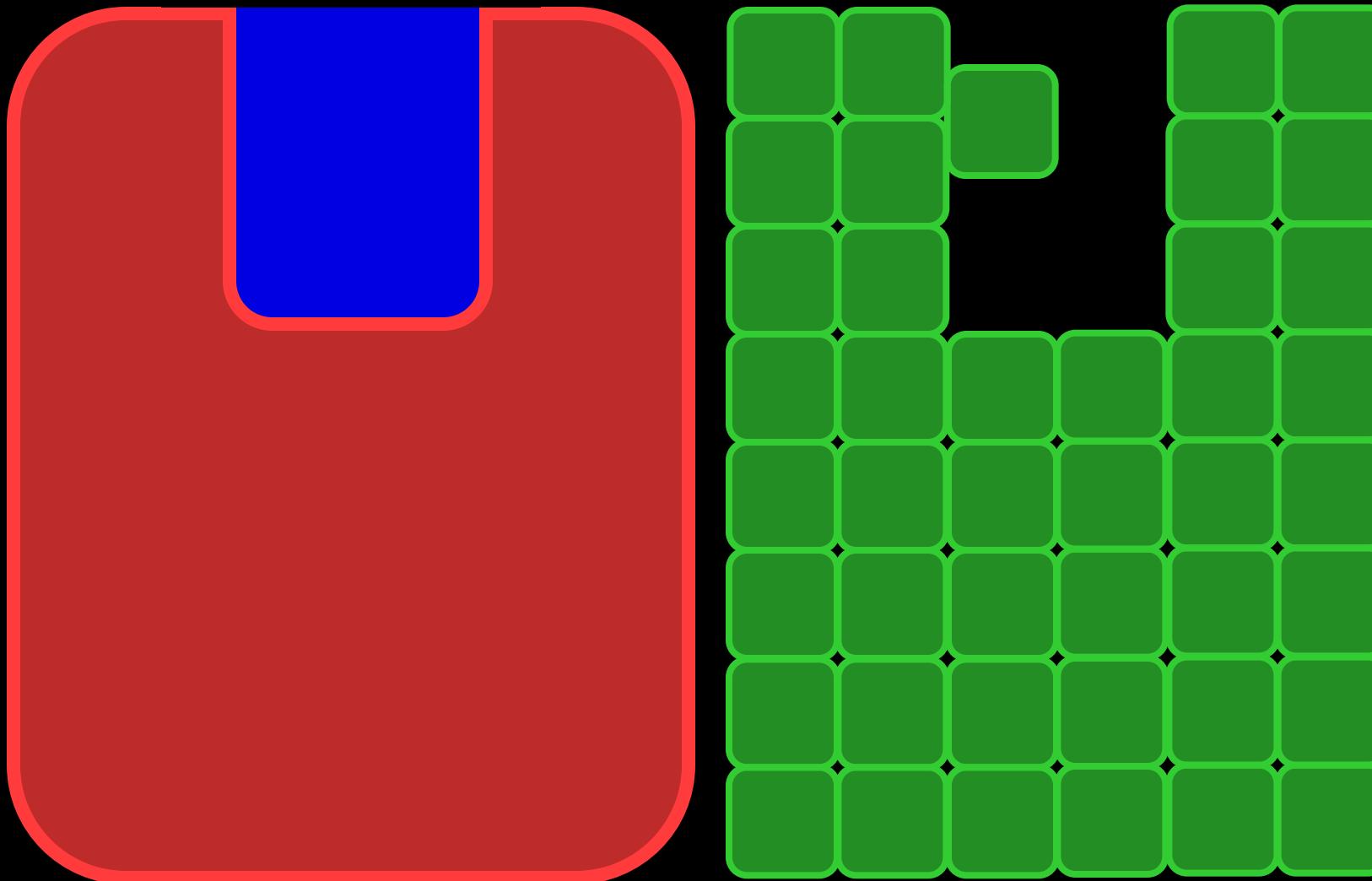
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

Finding amino acids that affect cavity shape



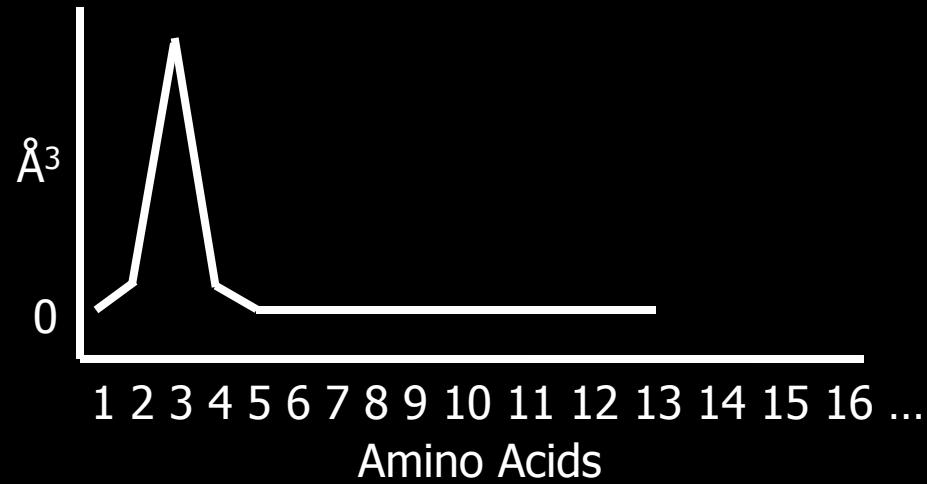
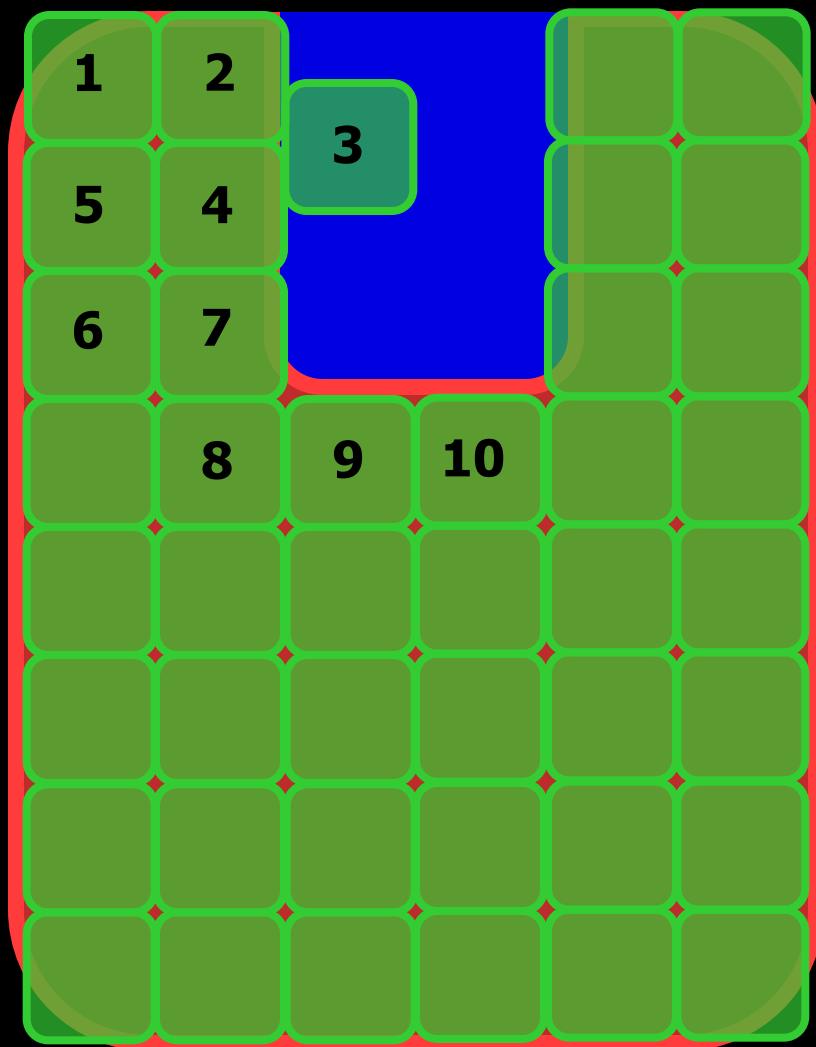
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Finding amino acids that affect cavity shape



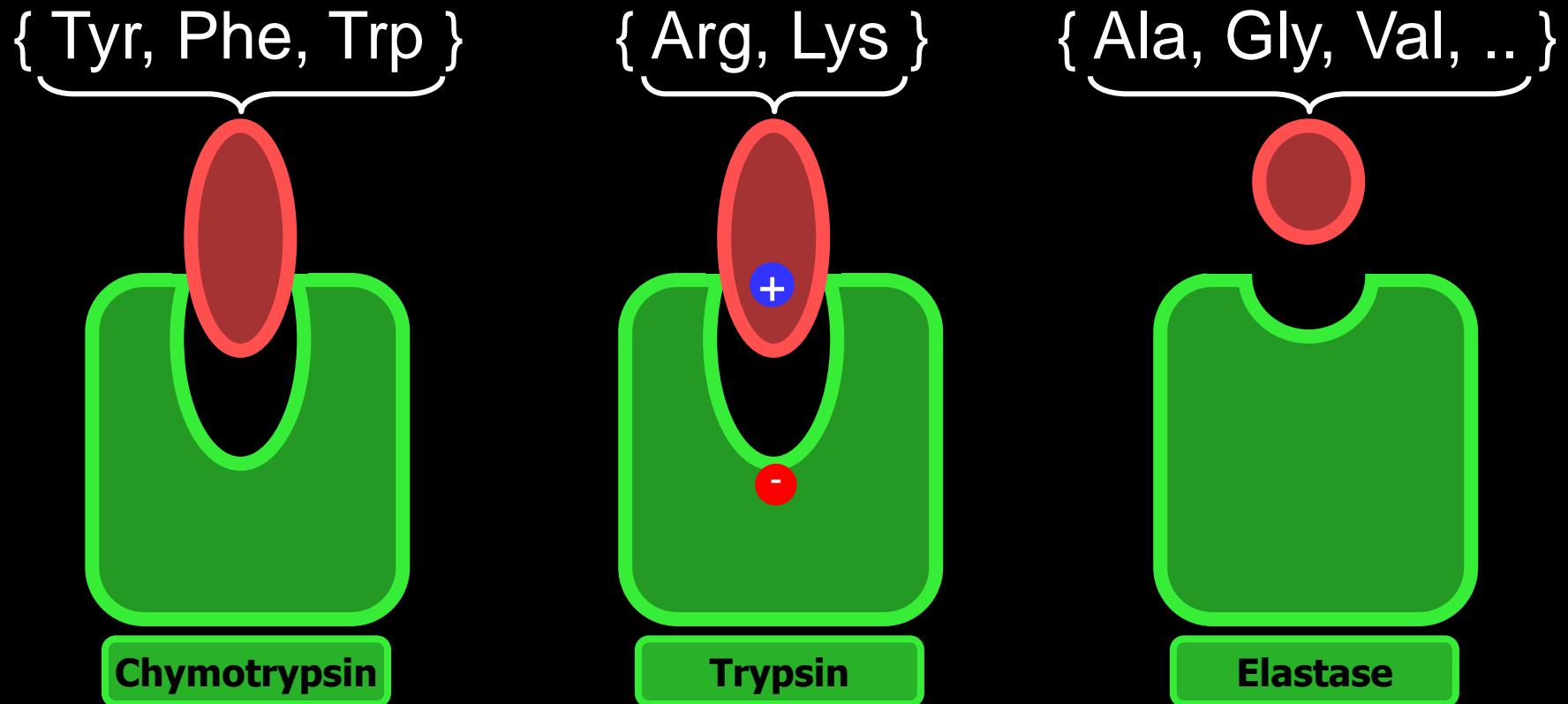
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

Finding amino acids that affect cavity shape



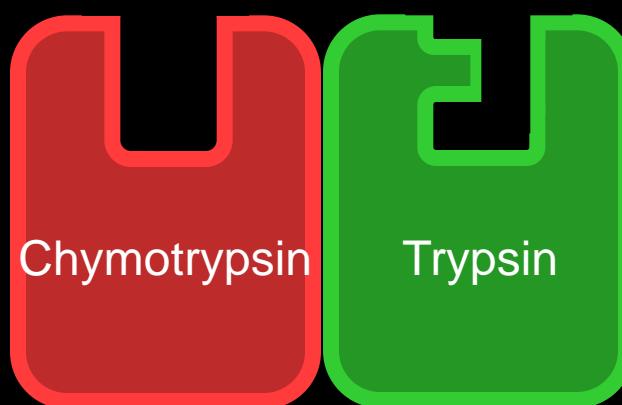
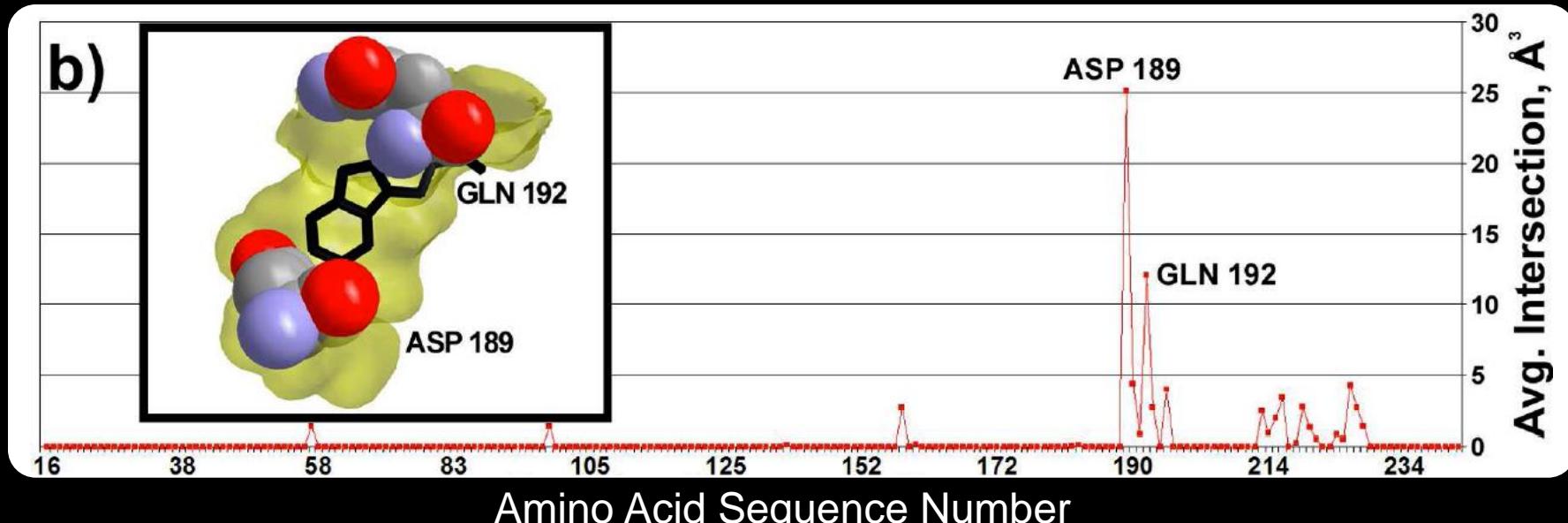
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

Three proteins with different preferences



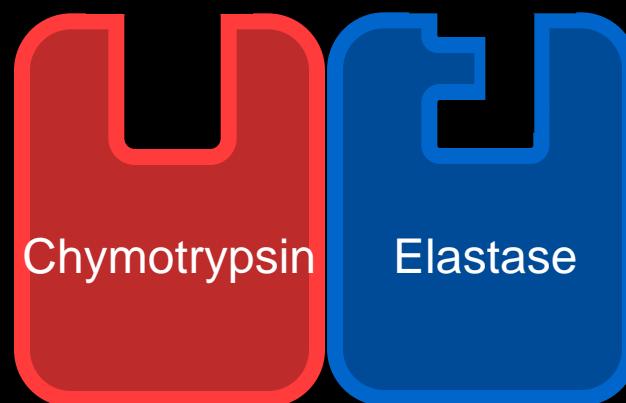
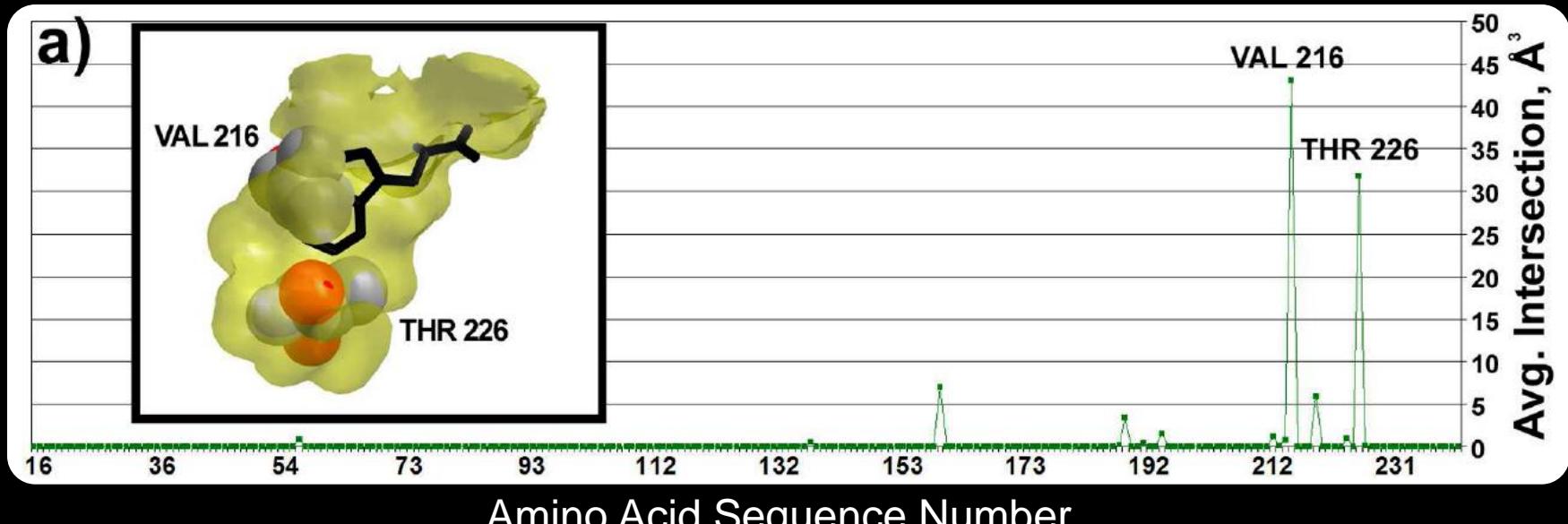
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

VASP finds amino acids in trypsins that influence specificity



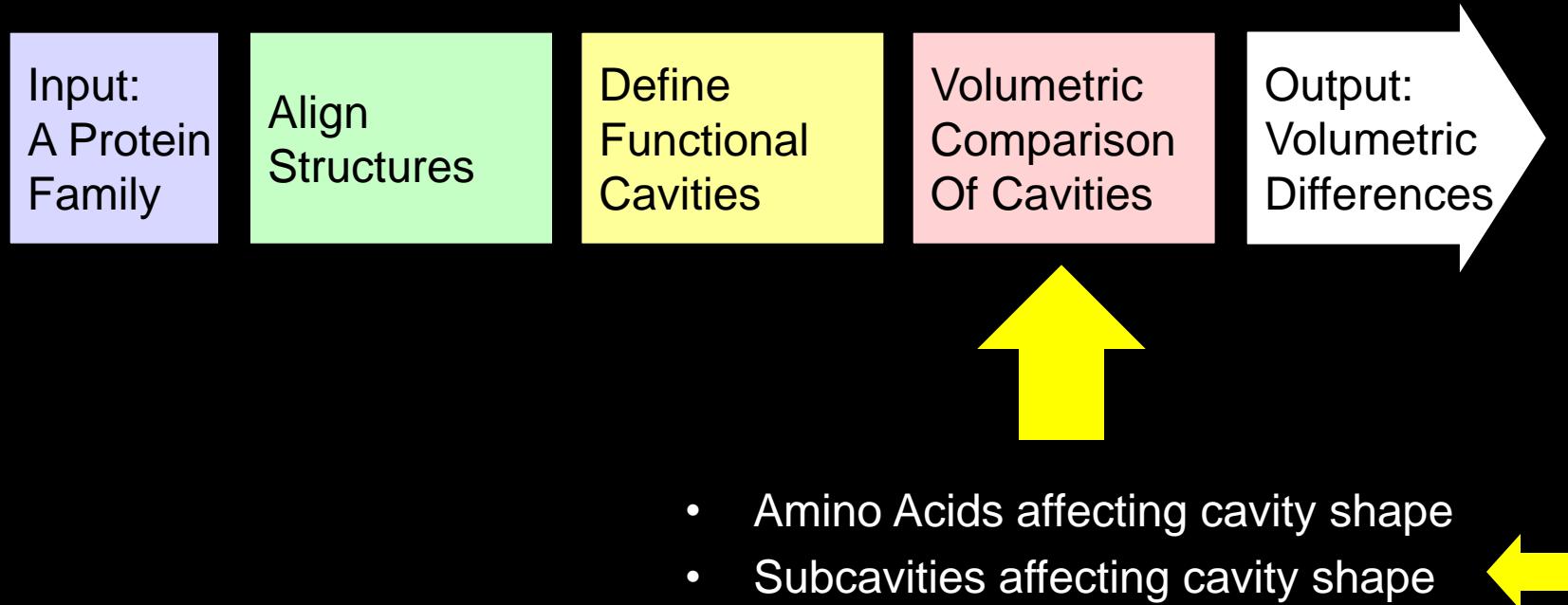
Steitz T.A., Henderson R., Blow D.M. Structure of crystalline alpha-chymotrypsin. 3. Crystallographic studies of substrates and inhibitors bound to the active site of alpha-chymotrypsin. *J. Mol. Biol.* **46**(2): 337-348. 1969.

VASP finds amino acids in elastase that influence specificity



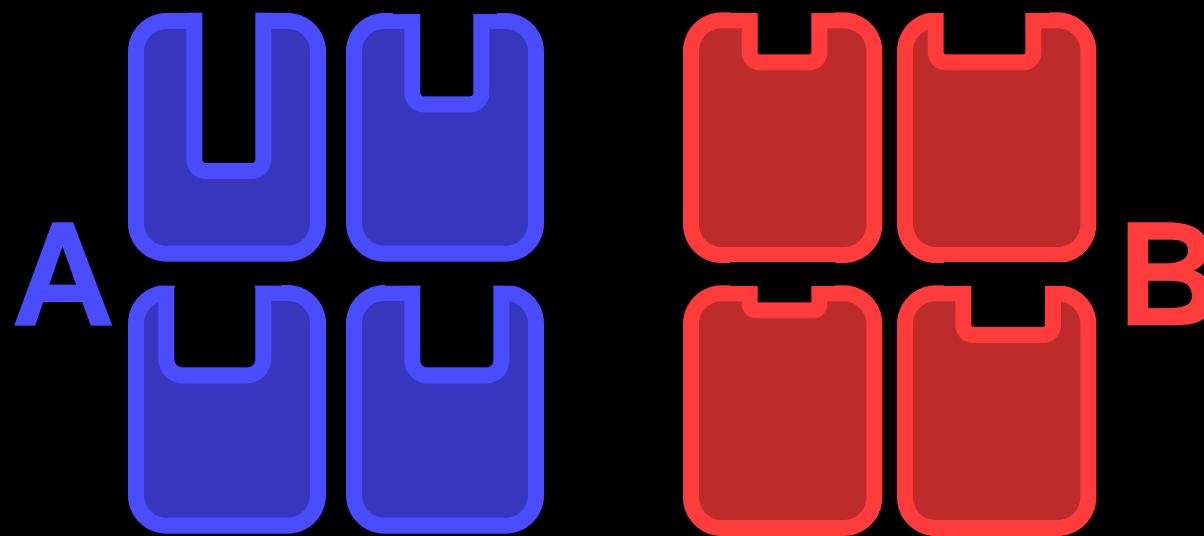
Shotton D.M., Watson H.C. Three-dimensional structure of tosyl-elastase.
Nature **225**(5235): 811-816. 1970.

The VASP procedure



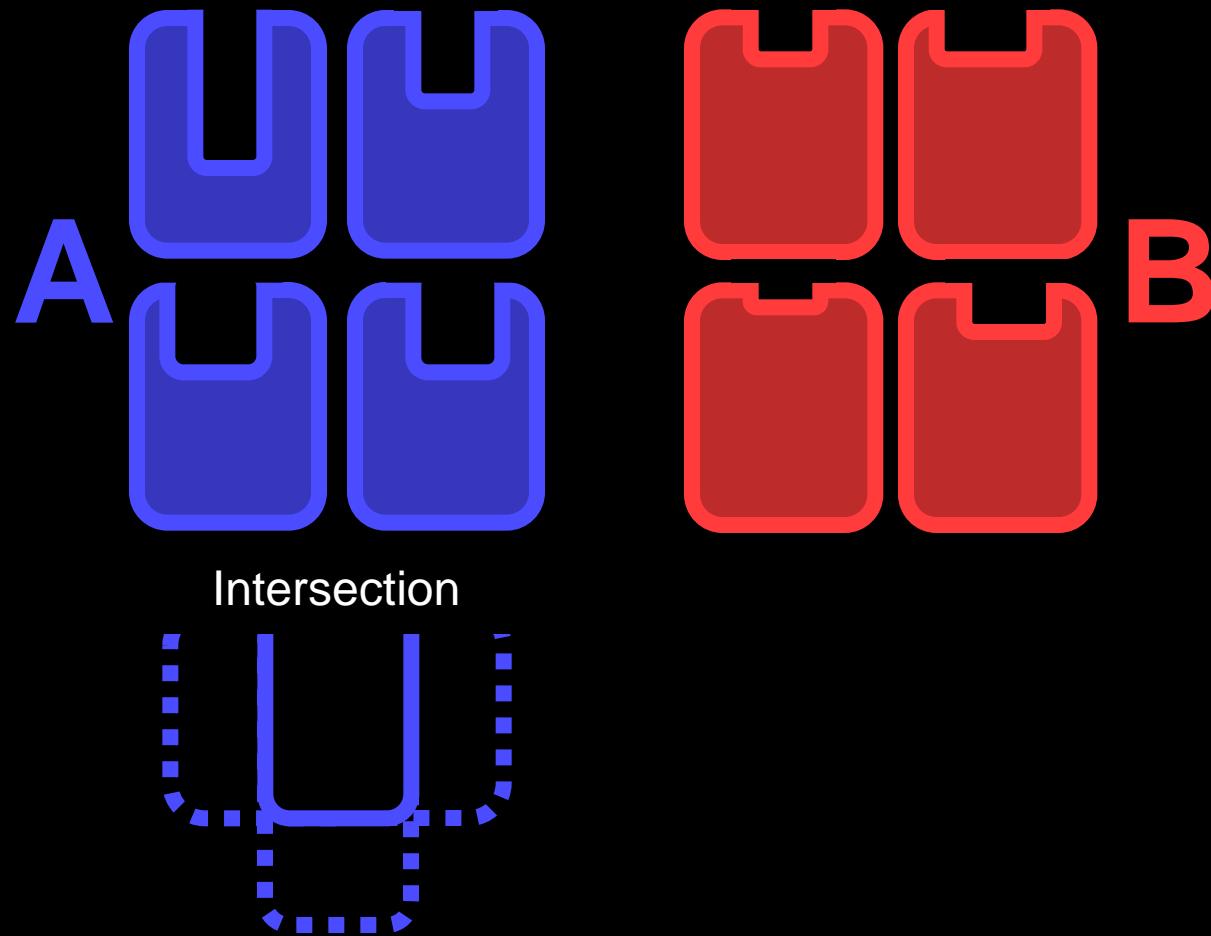
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

What makes A cavities different from B?



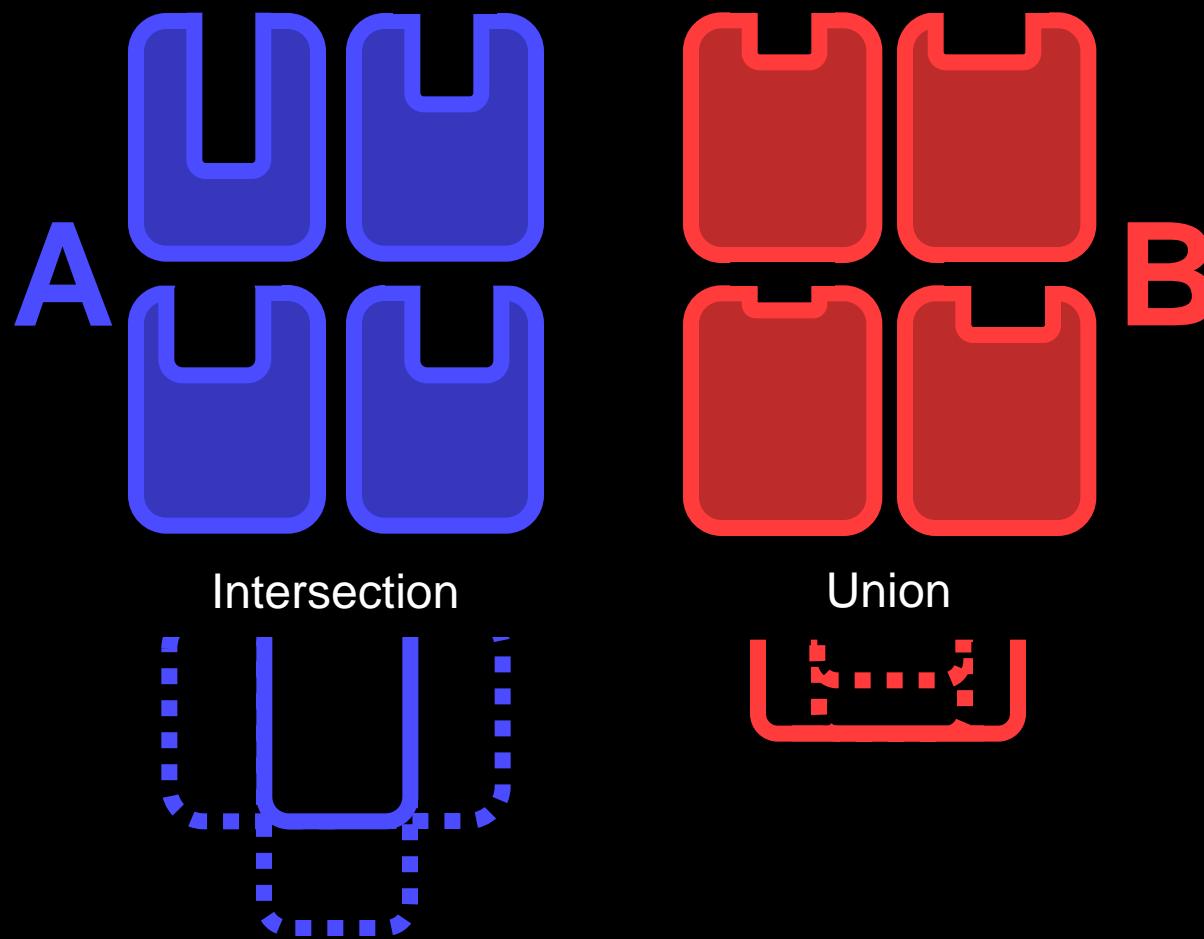
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

What is common in A?



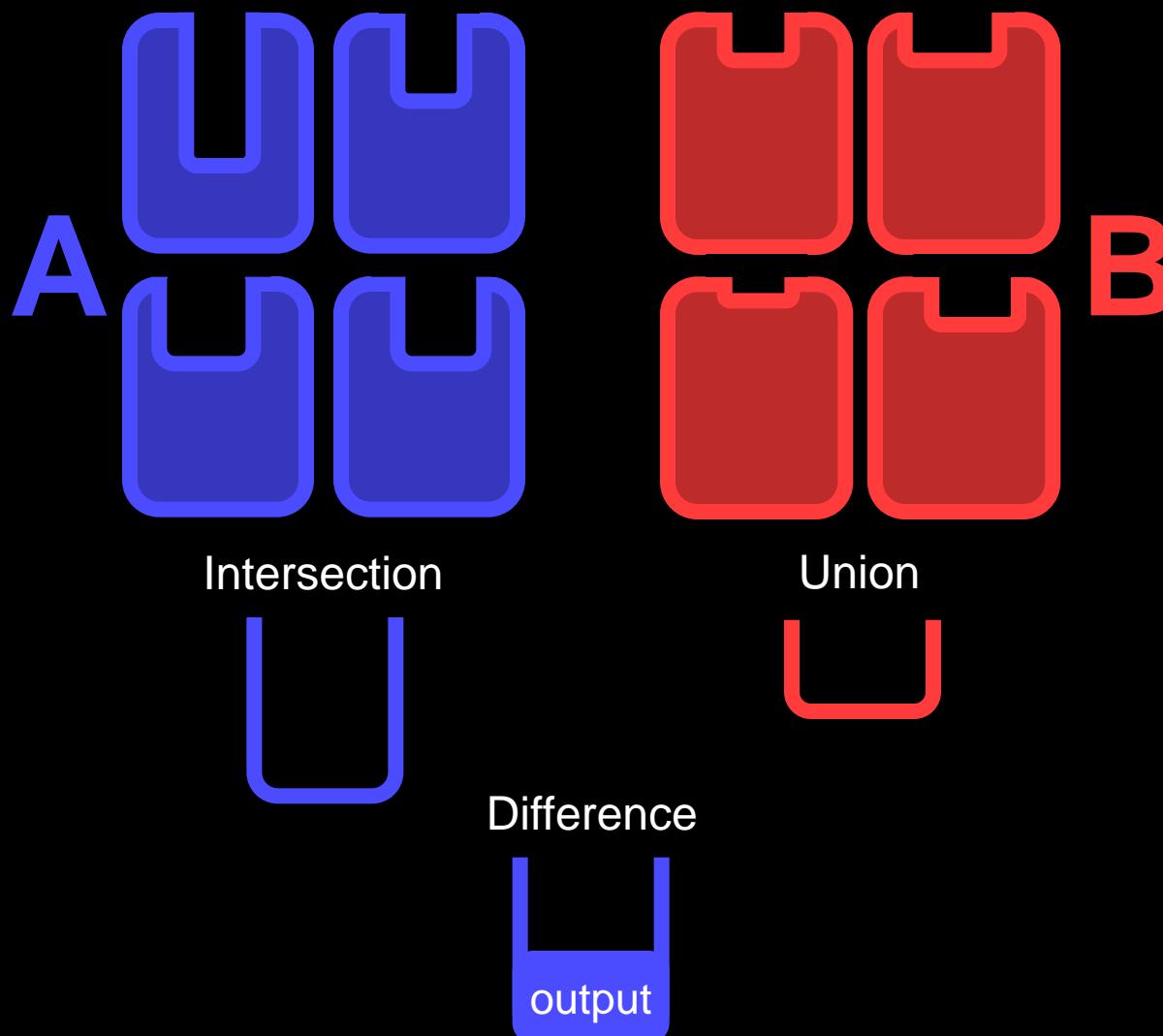
VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

What is the maximum extent of B?



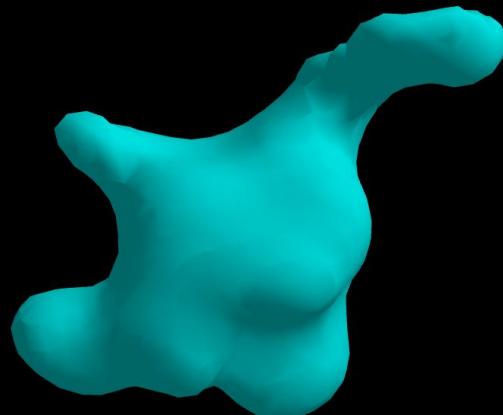
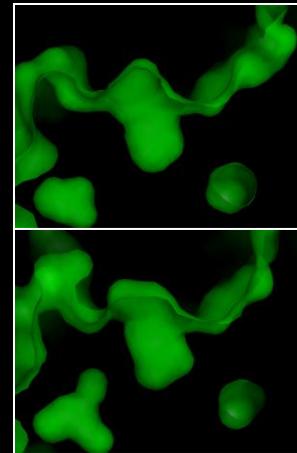
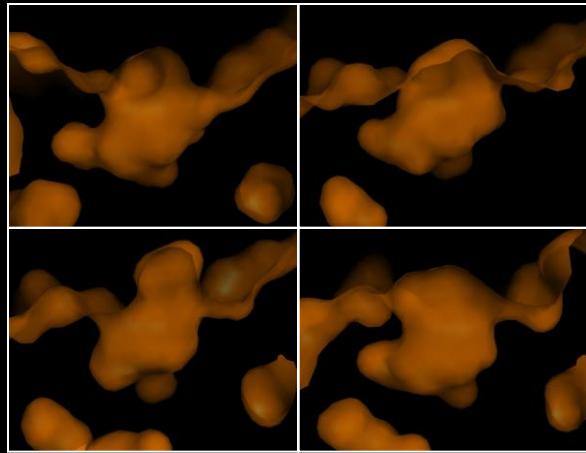
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All parts of A that are not in any part of B

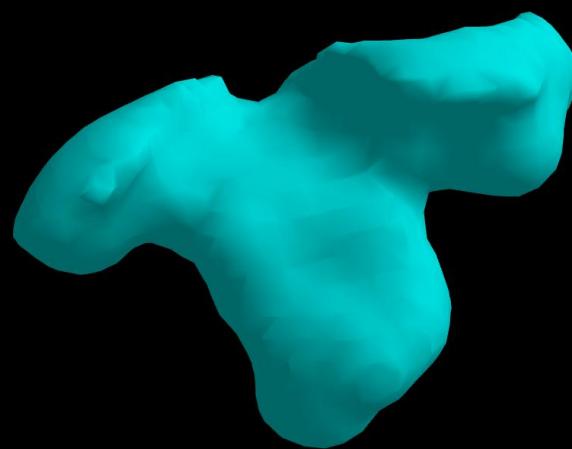


VASP: A Volumetric Analysis of Surface Properties Yields Insights into Protein-Ligand Binding Specificity. Brian Chen and Barry Honig. *PLOS Computational Biology*. 6(8): e1000881.

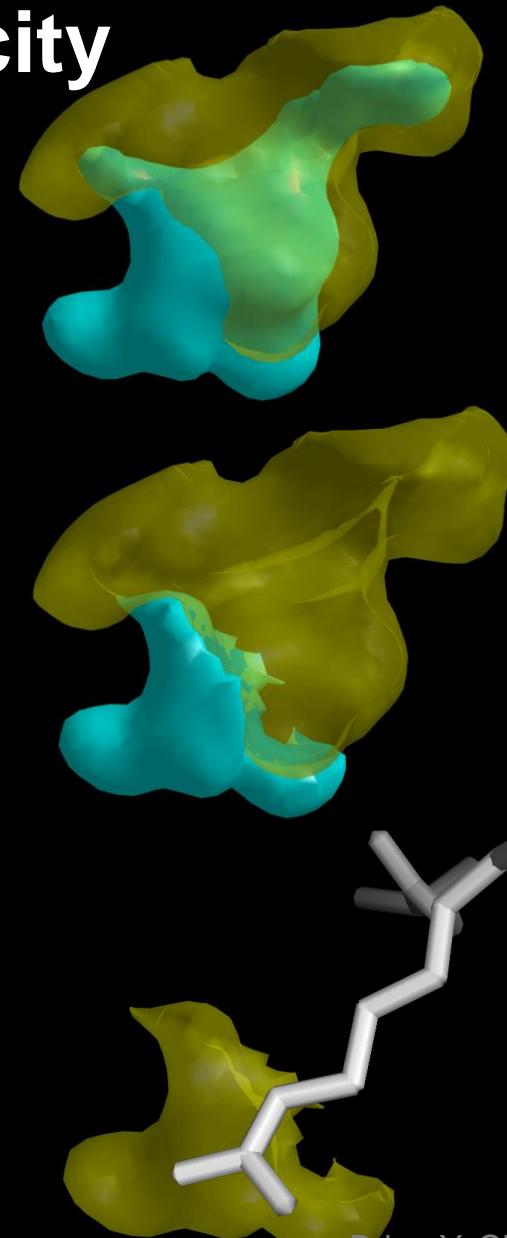
VASP finds subcavities in trypsins and elastases that influence specificity



Trypsin Intersection



Elastase Union



Brian Y. Chen

Computers can help us understand protein function

Structure
Alignment

Functional
Site
Comparison

Structure
Prediction

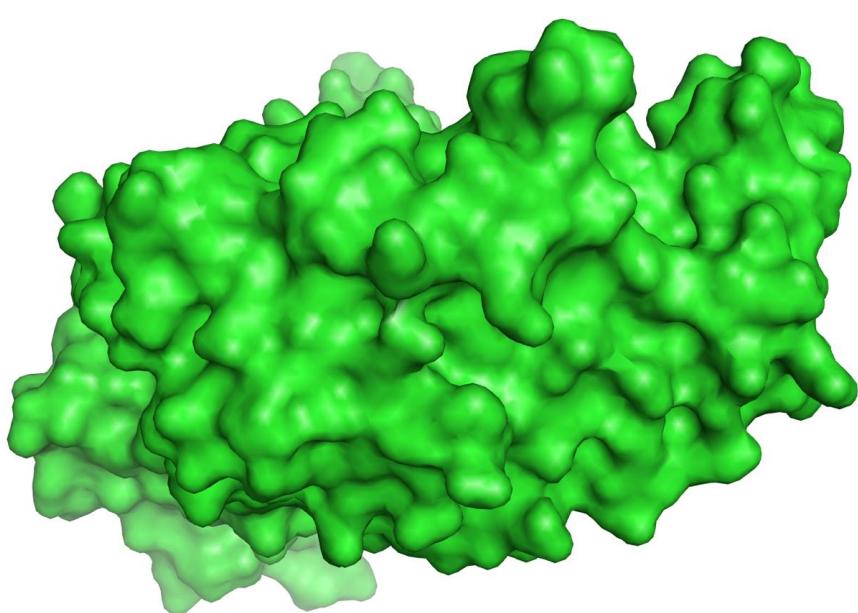
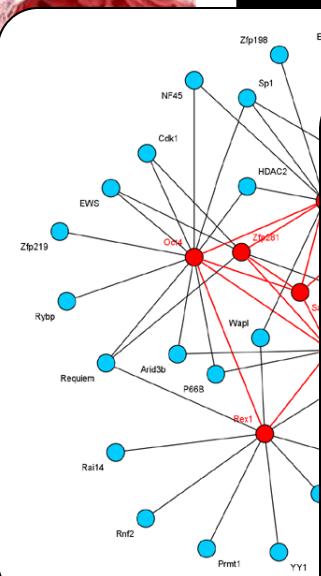
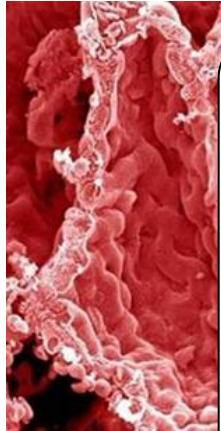
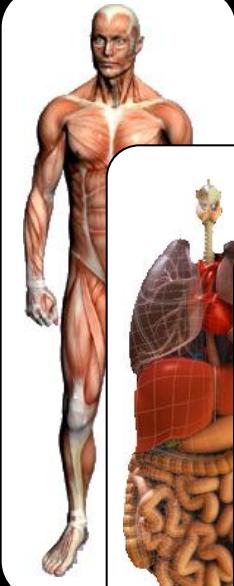
Structural
Bioinformatics

Molecular
Simulation

Integrative
Methods

Docking

Protein function forms a basis for analyzing bigger systems and harder biological problems



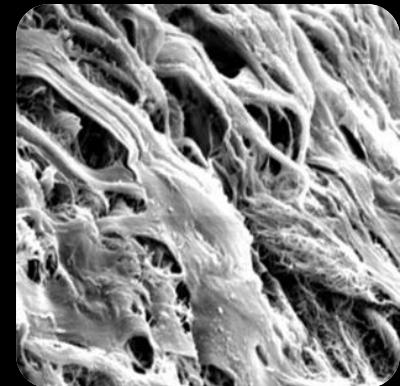
Drug Design



Biofuels



Biomaterials



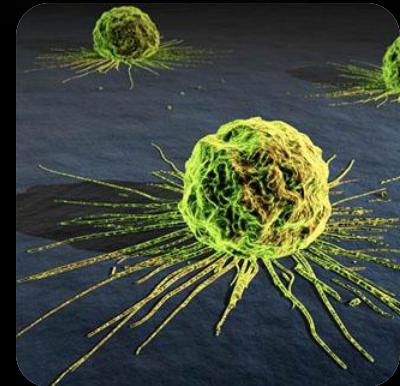
Protein functions drive technology



Medical Diagnostics



Agriculture



Cancer

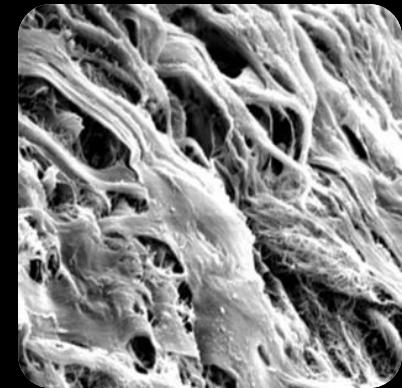
Drug Design



Biofuels



Biomaterials



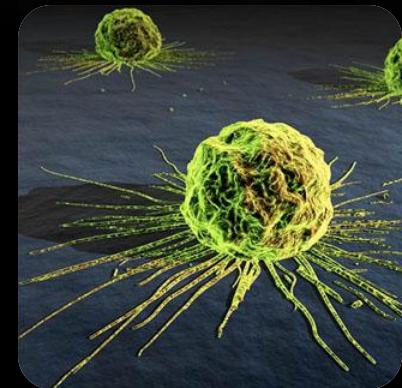
Bioinformatics impacts many problems



Medical Diagnostics



Agriculture



Cancer

Spring 2011: Introduction to Bioinformatics

- An introduction to combining computation with biology to solve biological problems
- Recommended for BioS, BioE, CSE, and Math students.
- **No programming experience required**
- Semester Project on a Genome or Algorithm of your choice
 - Extra Credit for Collaborative Interdisciplinary Projects
- Topics include:
 - Sequence Alignment, Multiple Sequence Alignment
 - Phylogenetic Trees and Reticulate Evolution
 - DNA Sequencing and DNA Microarrays
 - Gene Regulatory Networks
 - Genome Annotation, The Cancer Genome Atlas
 - Transcription Factor Binding Site Prediction

Fall: Structural Bioinformatics

- A survey of geometric algorithms for understanding protein functions from structure
- Recommended for BioS, BioE, CSE, Math seniors, grad students.
- **No programming experience required**
- Semester Project on finding similar functional sites
 - Interdisciplinary Collaboration with experts in other fields
- Topics include:
 - Whole structure alignment and the Space of Protein Folds
 - Protein surfaces, cavities, and electrostatics
 - Protein-protein, Protein-DNA interfaces, interactions
 - Protein Structure Prediction, Simulation, Docking
 - Structural Bioinformatics in Pharmaceutical discovery
 - Function annotation, active site prediction, geometric matching

Questions

Questions