Can AI discover the drugs of the future?

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The Biggest Crisis of the Contemporary Science

The number of researchers in the world who know both graduate-level mathematics and molecular-level biology is smaller than the number of fields medalists!

The rule of life has been there for billions of years but very little is known about it!

None knows the existence and uniqueness of mathematical foundation for life!

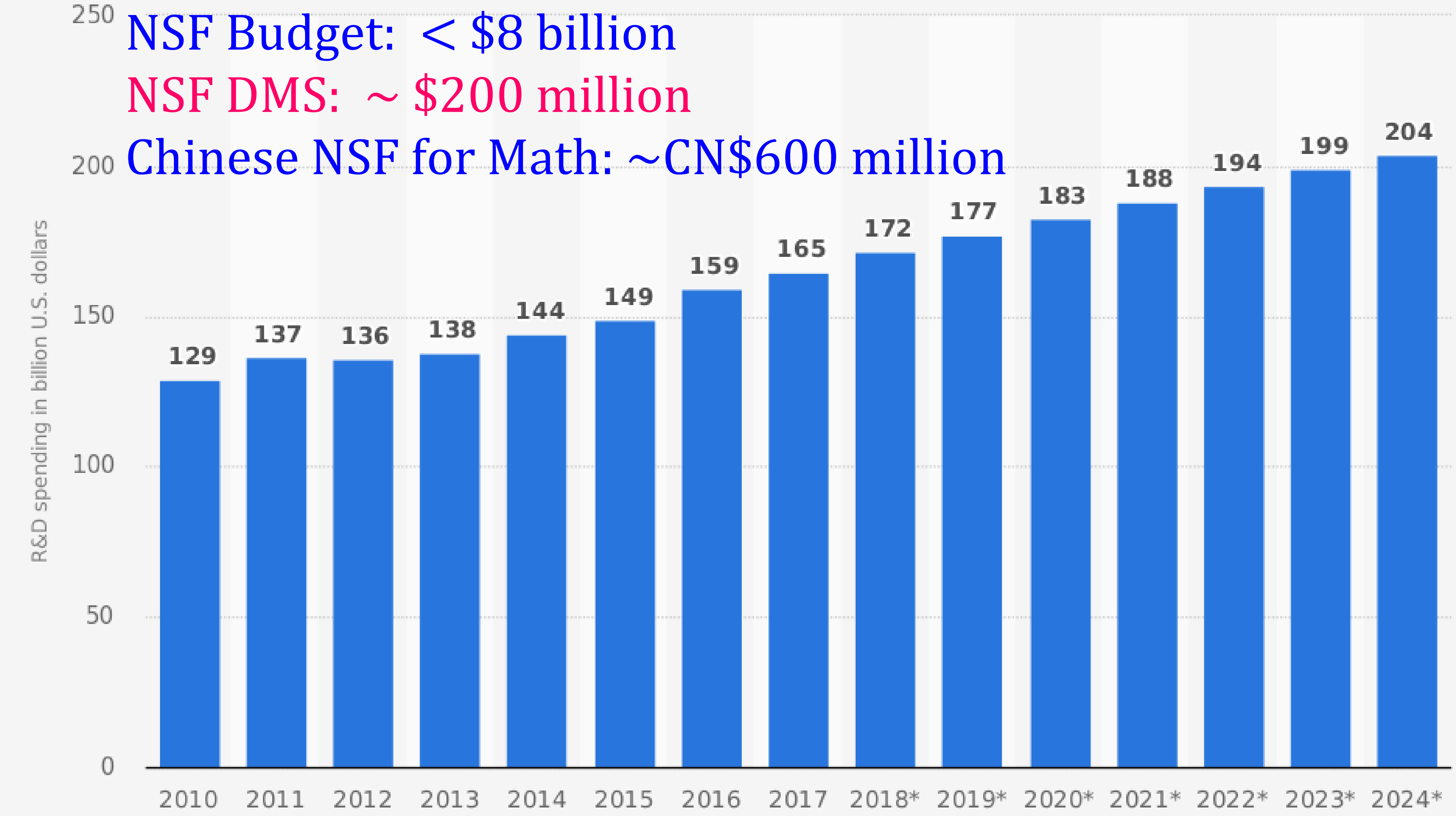
A Brief Summary of Modern Biological Science

1960 2000 2019

Organismal biology (i.e., nonliving organisms, living organisms, developmental biology, morphology, anatomy, physiology, and medicine)	Molecular organismal biology, organomics, connectomics, foodomics, physiomics, pharmacogenomics, …
Ecology	Molecular ecology
Evolution (i.e., life, and evolutionary biology)	Molecular evolution
Molecular and cellular biology (i.e., cell biology, biochemistry, molecular biology, and genetics)	Omics (e.g., genomics, proteomics, metabolomics, metagenomics, lipidomics, glycomics, transcriptomics, epigenomics, …)

Macroscopic Mesoscopic Microscopic

Total global spending on pharmaceutical research and development from 2010 to 2024 (in billion U.S. dollars)



NSF Budget: $<$ \$8 billion

NSF DMS: $\sim$ \$200 million

Chinese NSF for Math: ~CN\$600 million

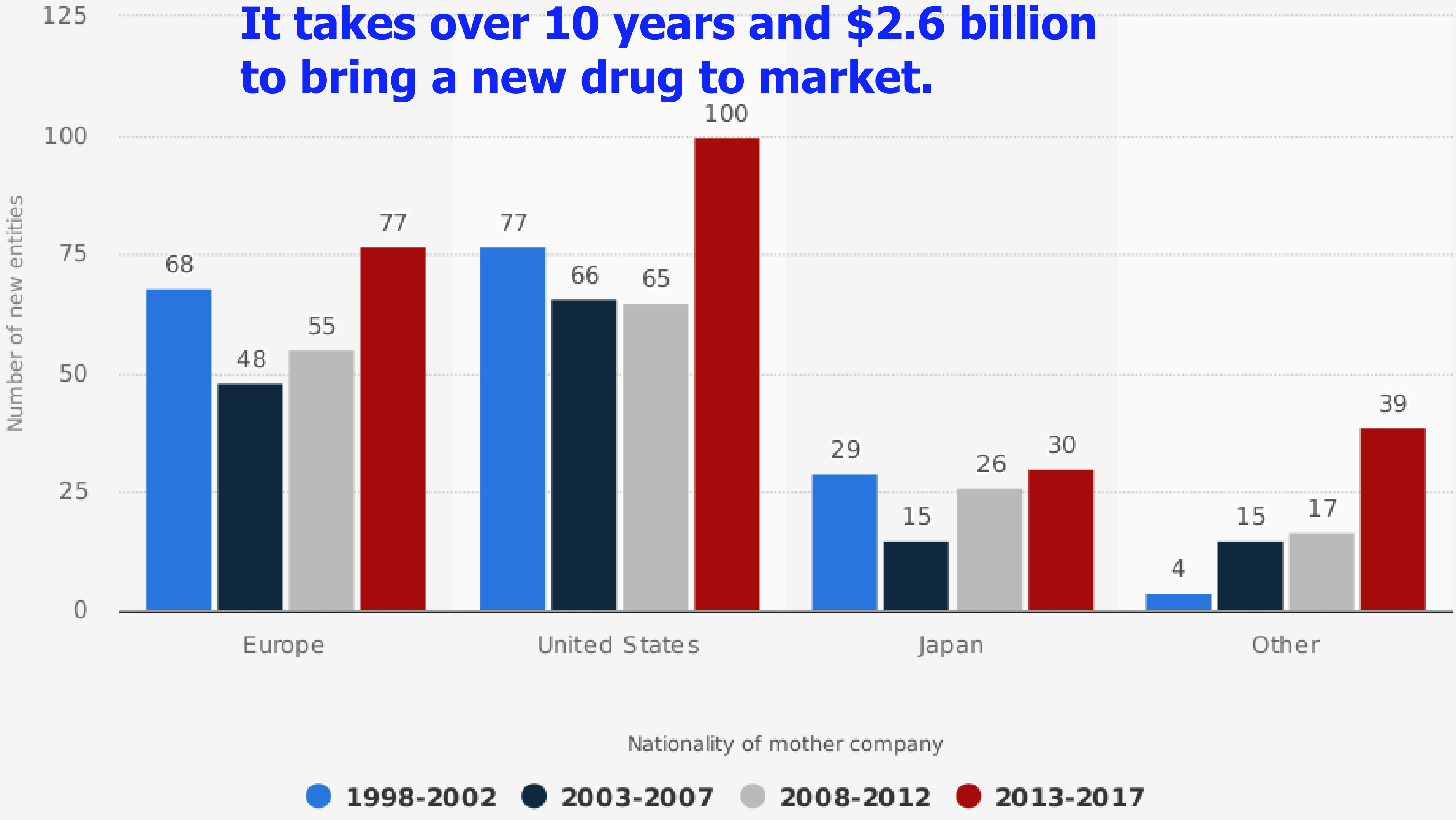
Funding for mathematical research is $\sim\varepsilon^3$

Source
Evaluate
© Statista 2019

Additional Information:
Worldwide; Evaluate (EvaluatePharma); as of May 2018

statista

Number of new chemical or biological entities developed between 1992 and 2017, by region of origin



It takes over 10 years and $2.6 billion to bring a new drug to market.

Source
EFPIA
© Statista 2018

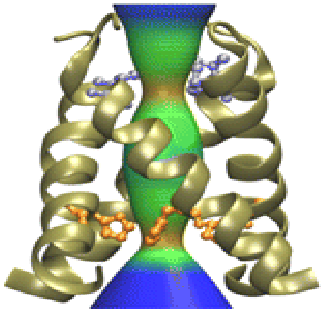
Additional Information:
Worldwide

Drug design and discovery

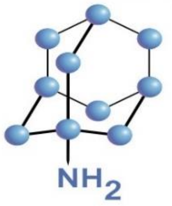
1) Disease identification (physiology)
2) Target hypothesis (biochem./mole. biol.)
3) Virtual screening: drug pose, binding affinity, solubility, partition coefficient, toxicity, and side-effects (biophysics/bioinformatics)
4) Drug structural optimization in the target binding site (biochemistry/biophysics/synthetic chem.)
5) Preclinical *in vitro* and *in vivo* test
6) Clinical trials
7) Optimize drug's efficacy, pharmacokinetics, and pharmacodynamics properties (quantitative systems pharmacology)

Influenza -- flu virus

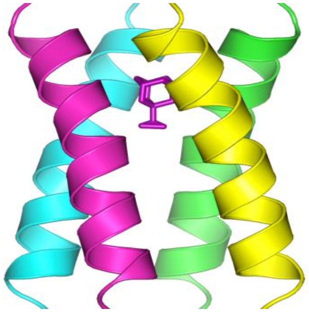
M2 channel



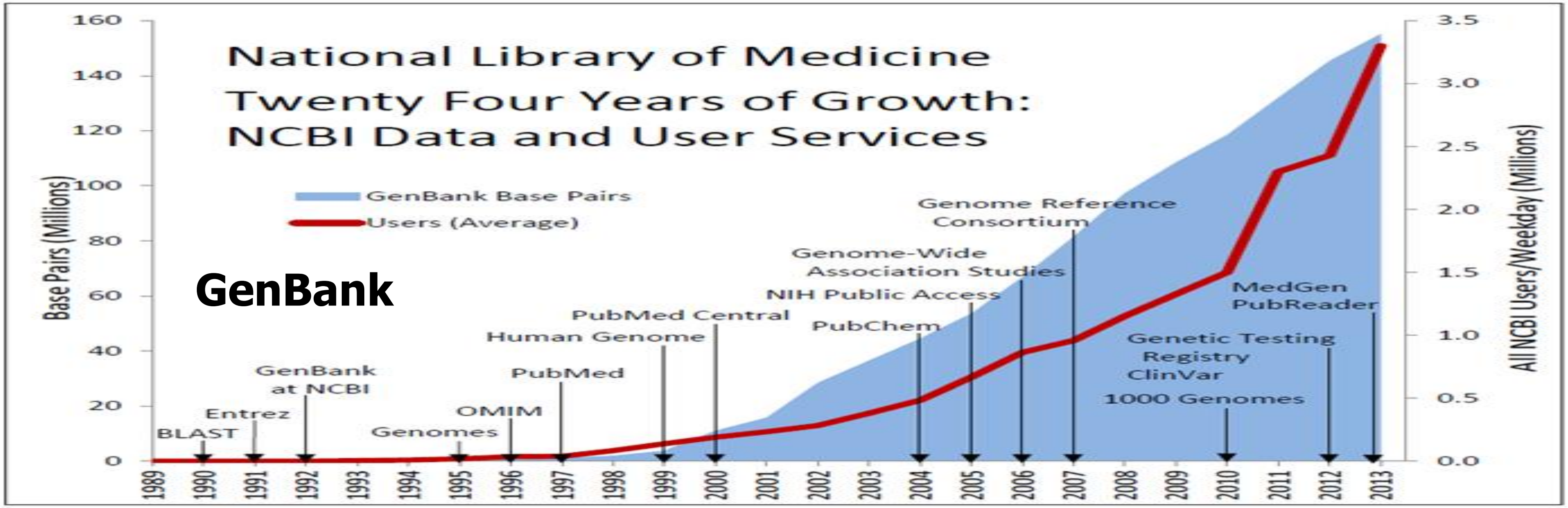
Amantadine



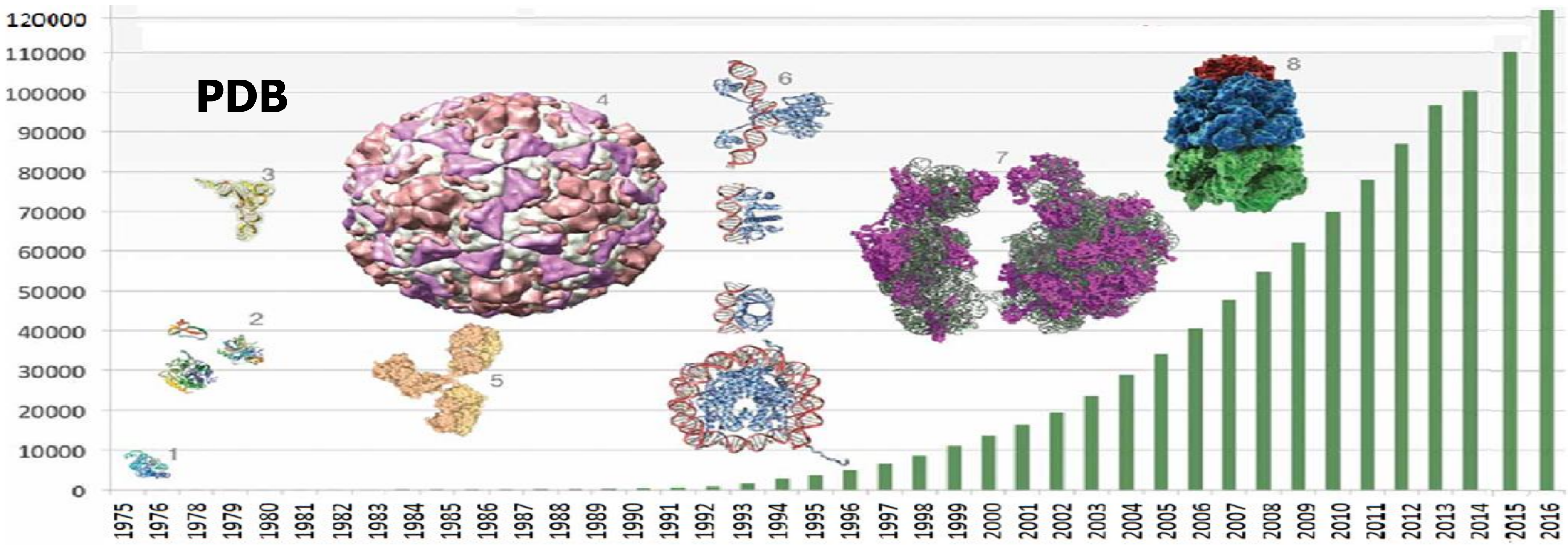
M2-A complex



Biological data



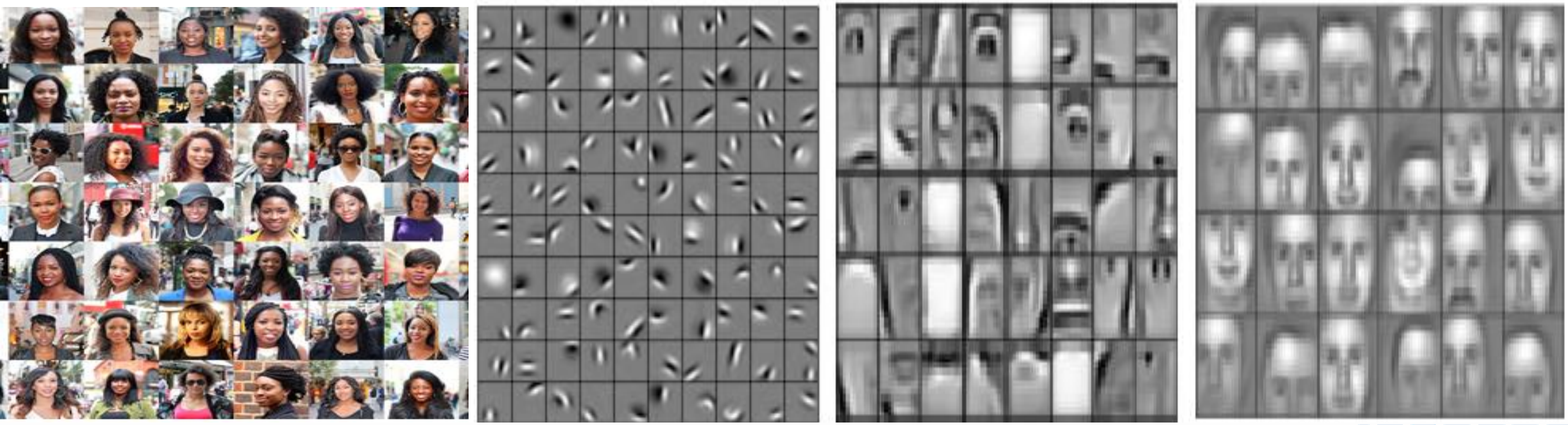
GenBank

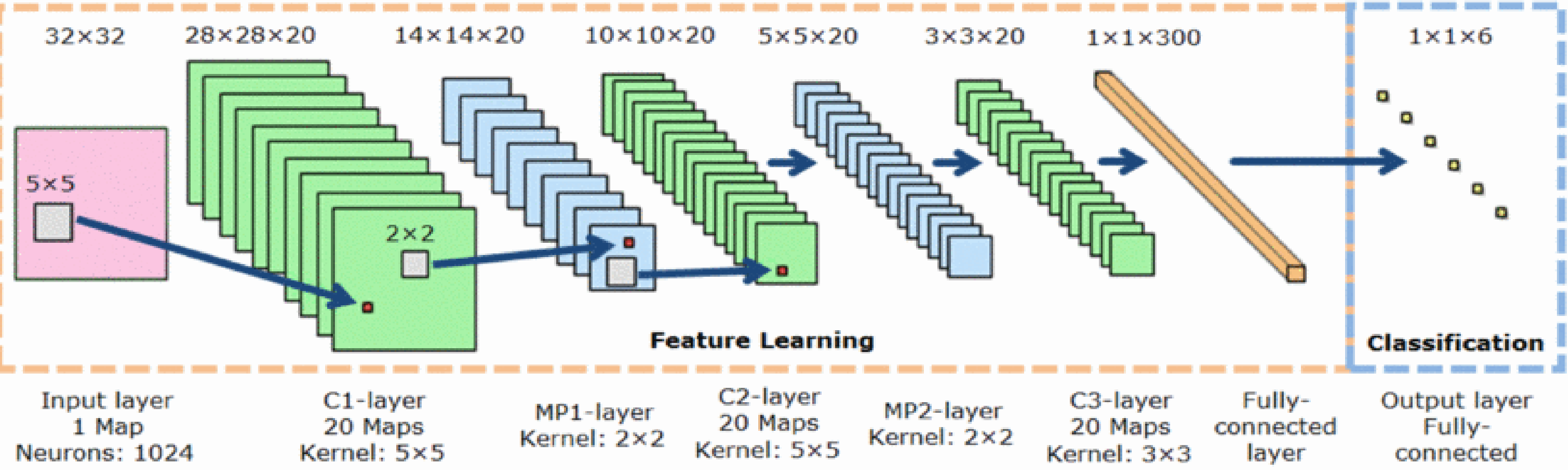


PDB

Artificial Intelligence & Deep learning

Bryson and Ho (Backpropagation 1969); Fukushima (Neo-Cognitron 1980); LeCun (CNN 1998); Hopfield (RNN 1982); Hochreiter and Schmidhuber (LSTM 1997); Goodfellow et al (GAN 2014); Autoencoder; Image translation, …

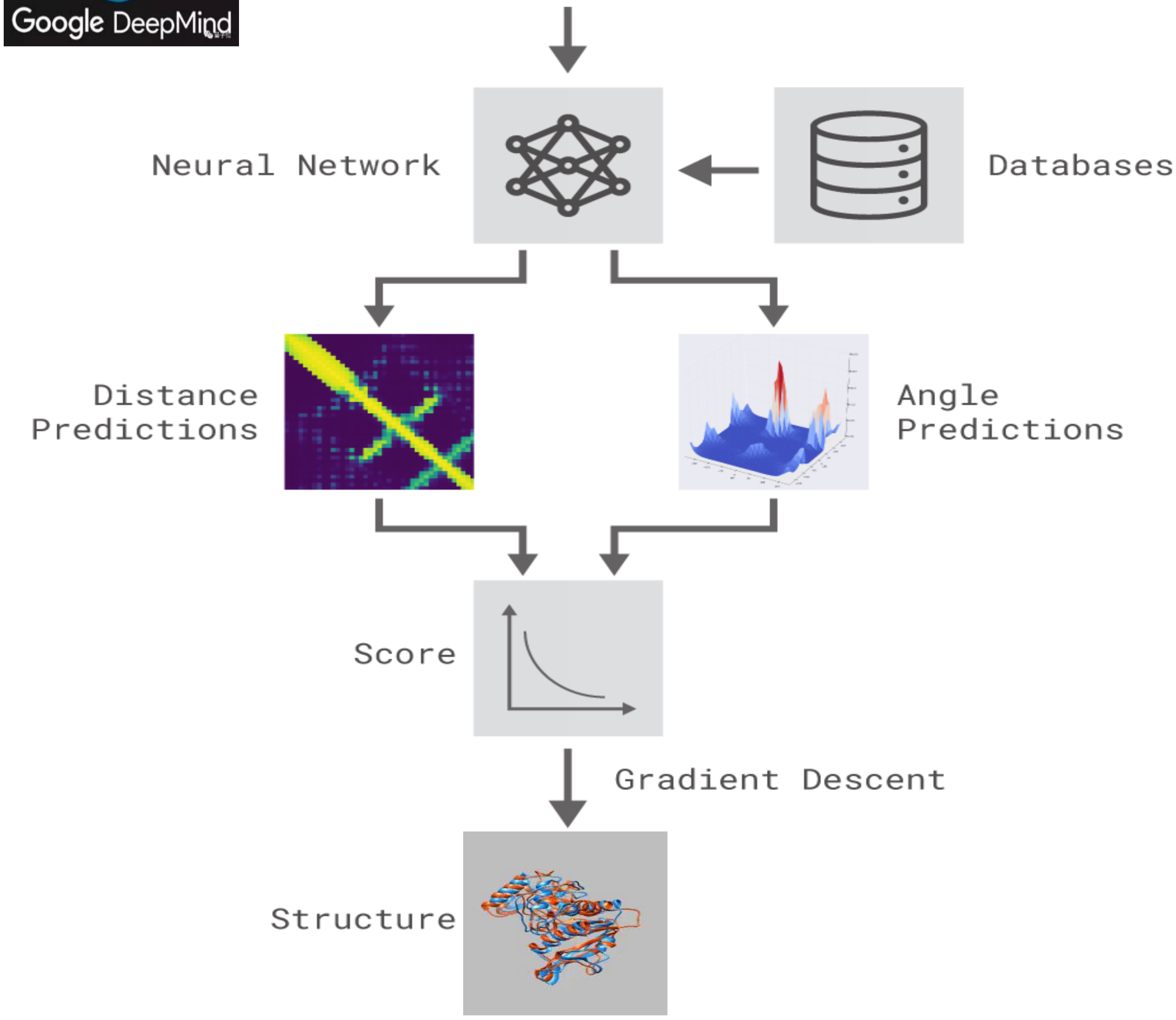




ALPHA FOLD won 25 of 43 contests and was ranked 1St among 98 competitors in CASP 13.

Protein Sequence

SQETRKKCTEMKKKFKNCEVRCDESNHCVEVRCSDTKYTLC



Neural Network

Databases

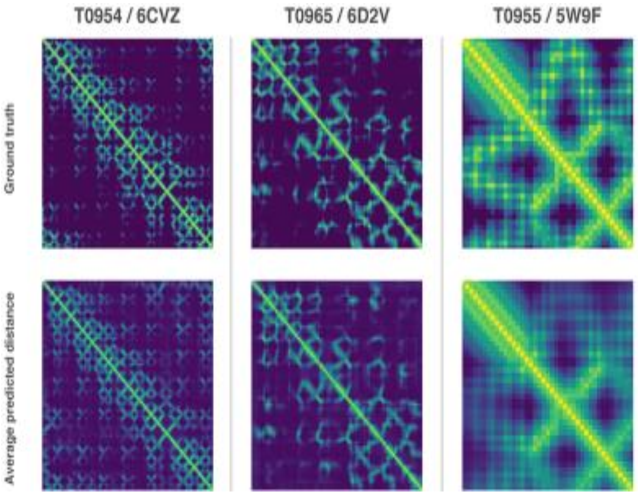
Distance Predictions

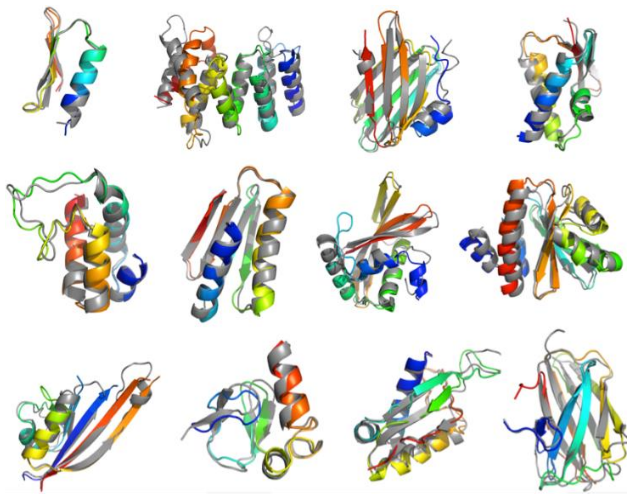
Angle Predictions

Score

Gradient Descent

Structure





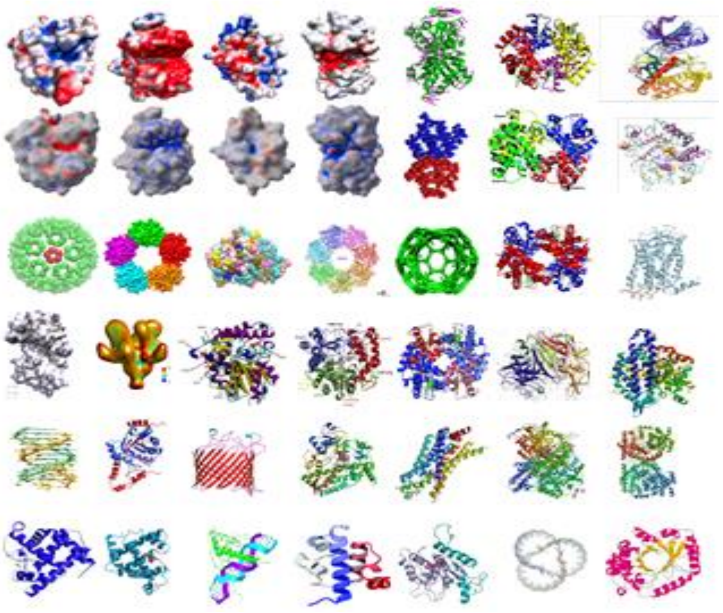
How to do deep learning for 3D biomolecular data?

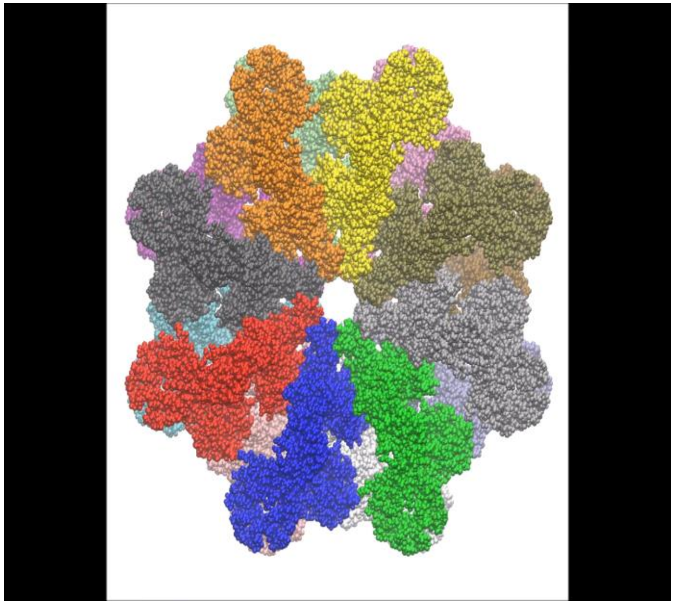
Obstacles for deep learning of 3D biomolecules:

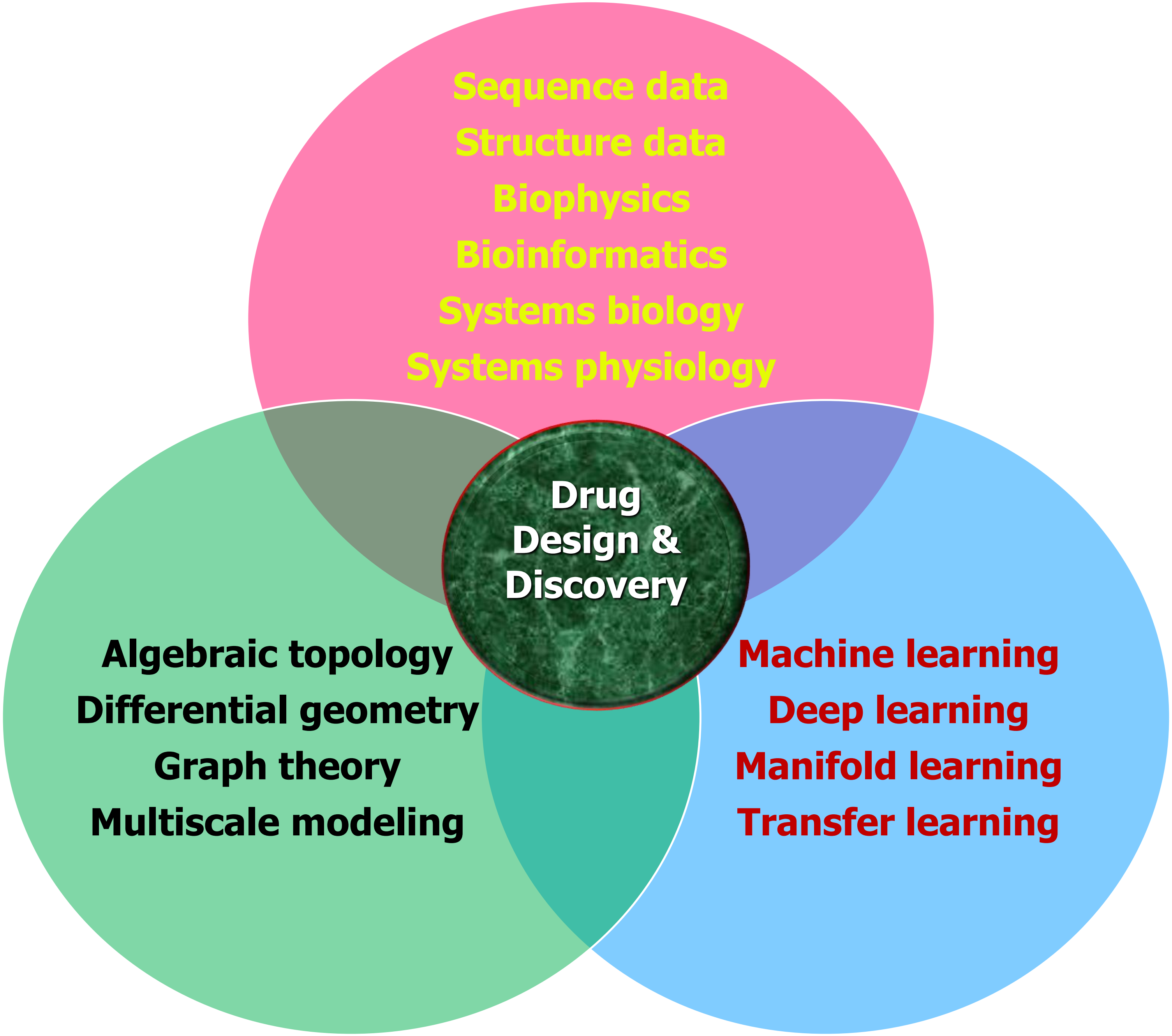
- **Geometric dimensionality: $\mathbb{R}^{3N}$, where *N* ~5000 for a protein.**
- **Machine learning dimensionality: > 1024^3*m*, where *m* is the number of atom types in a protein.**
- **Molecules have different sizes --- non-scalable.**
- **Complexity: intermolecular & intramolecular interactions**

Solution:

- **Geometric simplification, dimension reduction & scale unification**







Sequence data
Structure data
Biophysics
Bioinformatics
Systems biology
Systems physiology

Drug
Design &
Discovery

Algebraic topology
Differential geometry
Graph theory
Multiscale modeling

Machine learning
Deep learning
Manifold learning
Transfer learning

Two schools of thinking

Given a protein with *N* atom and an average of *n* electrons in each atom

Fundamentalism

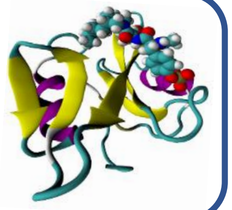
Quantum Mechanics $\mathbb{R}^{3Nn+3N}$

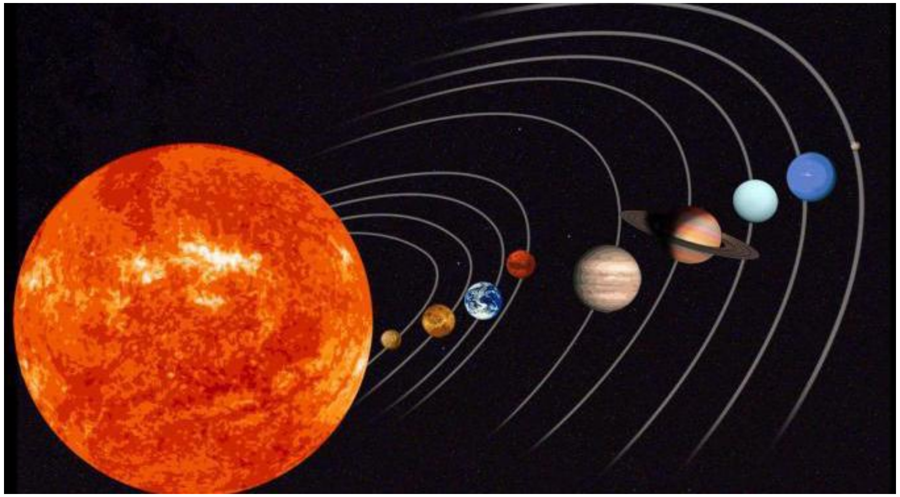
QM/MM $\mathbb{R}^{K}$ $3N < K < 3N(n+1)$

Molecular Mechanics $\mathbb{R}^{3N}$

Multiscale Coarse-grain $\mathbb{R}^{M}$ $(3<M<3N)$

Poisson-Boltzmann, PNP, etc. $\mathbb{R}^{3}$





Differentiable Manifold $\mathbb{R}^{2}$

Algebraic Topology $\mathbb{R}^{1}$

Graph Theory $\mathbb{R}^{0}$

Geo-Top Indices $\mathbb{R}^{0}$

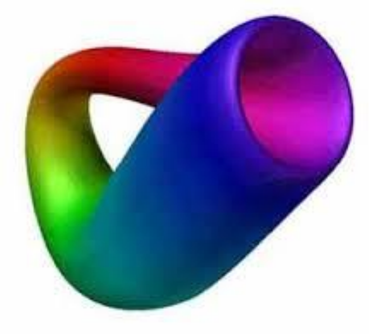
Reductionism

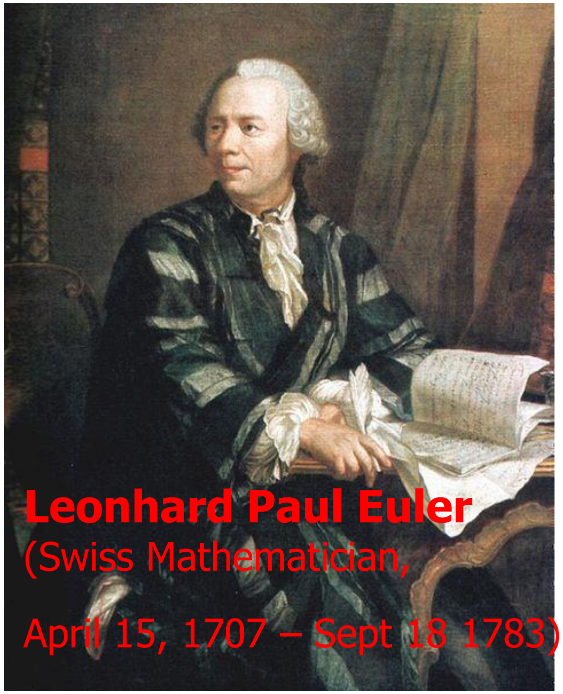
Basic hypothesis: Intrinsic physics lies on low-dimensional manifolds in a high dimensional space

Classical Topology

Möbius Strips (1858)

Klein Bottle (1882)

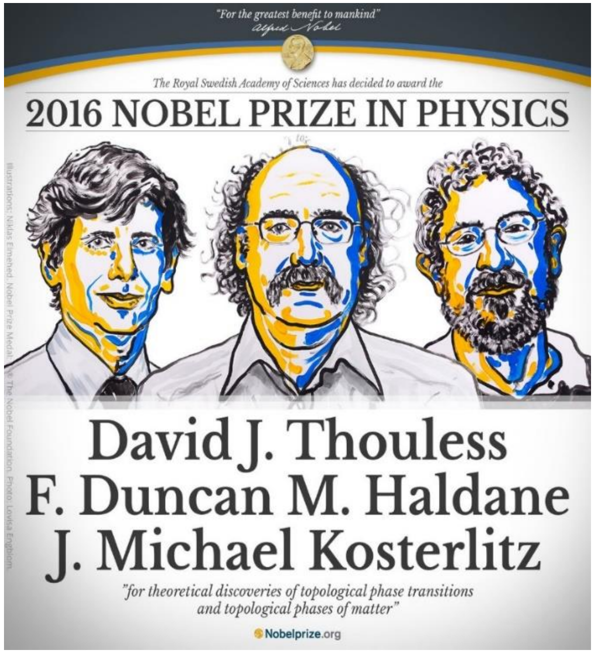




Leonhard Paul Euler
(Swiss Mathematician,
April 15, 1707 – Sept 18 1783)

Torus

Double Torus



"For the greatest benefit to mankind"

Alfred Nobel

The Royal Swedish Academy of Sciences has decided to award the

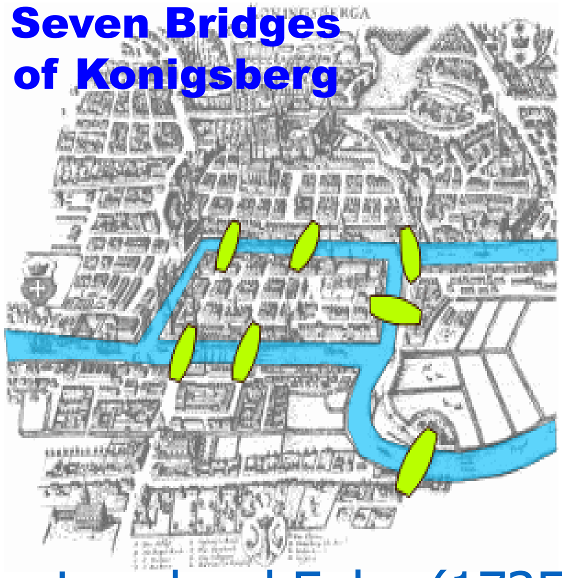
2016 NOBEL PRIZE IN PHYSICS

David J. Thouless
F. Duncan M. Haldane
J. Michael Kosterlitz

"for theoretical discoveries of topological phase transitions and topological phases of matter"

Nobelprize.org

Augustin-Louis Cauchy,
Ludwig Schläfli,
Johann Benedict Listing,
Bernhard Riemann, and
Enrico Betti



Seven Bridges of Konigsberg

Leonhard Euler (1735)

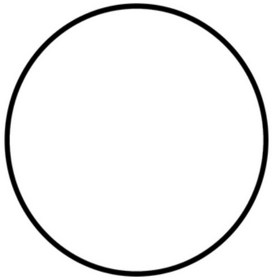
Topological invariants: Betti numbers

β_0 **is the number of connected components.**
β_1 **is the number of tunnels or circles.**
β_2 **is the number of cavities or voids.**

Point

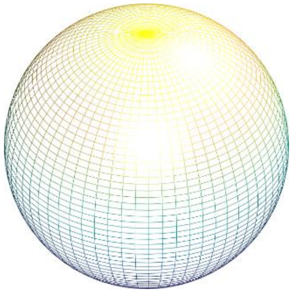
$\beta_0 = 1$
$\beta_1 = 0$
$\beta_2 = 0$

Circle



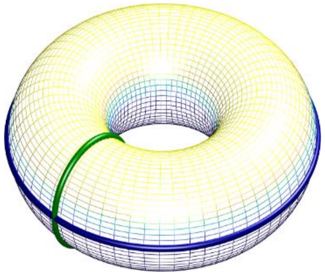
$\beta_0 = 1$
$\beta_1 = 1$
$\beta_2 = 0$

Sphere



$\beta_0 = 1$
$\beta_1 = 0$
$\beta_2 = 1$

Torus

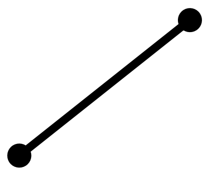


$\beta_0 = 1$
$\beta_1 = 2$
$\beta_2 = 1$

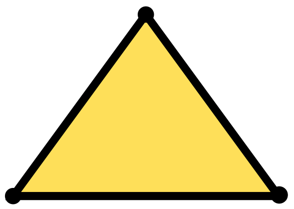
Vietoris-Rips complexes of planar point sets

Simplexes:

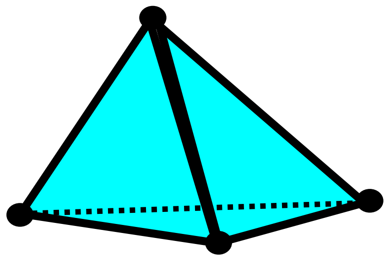
0-simplex



1-simplex

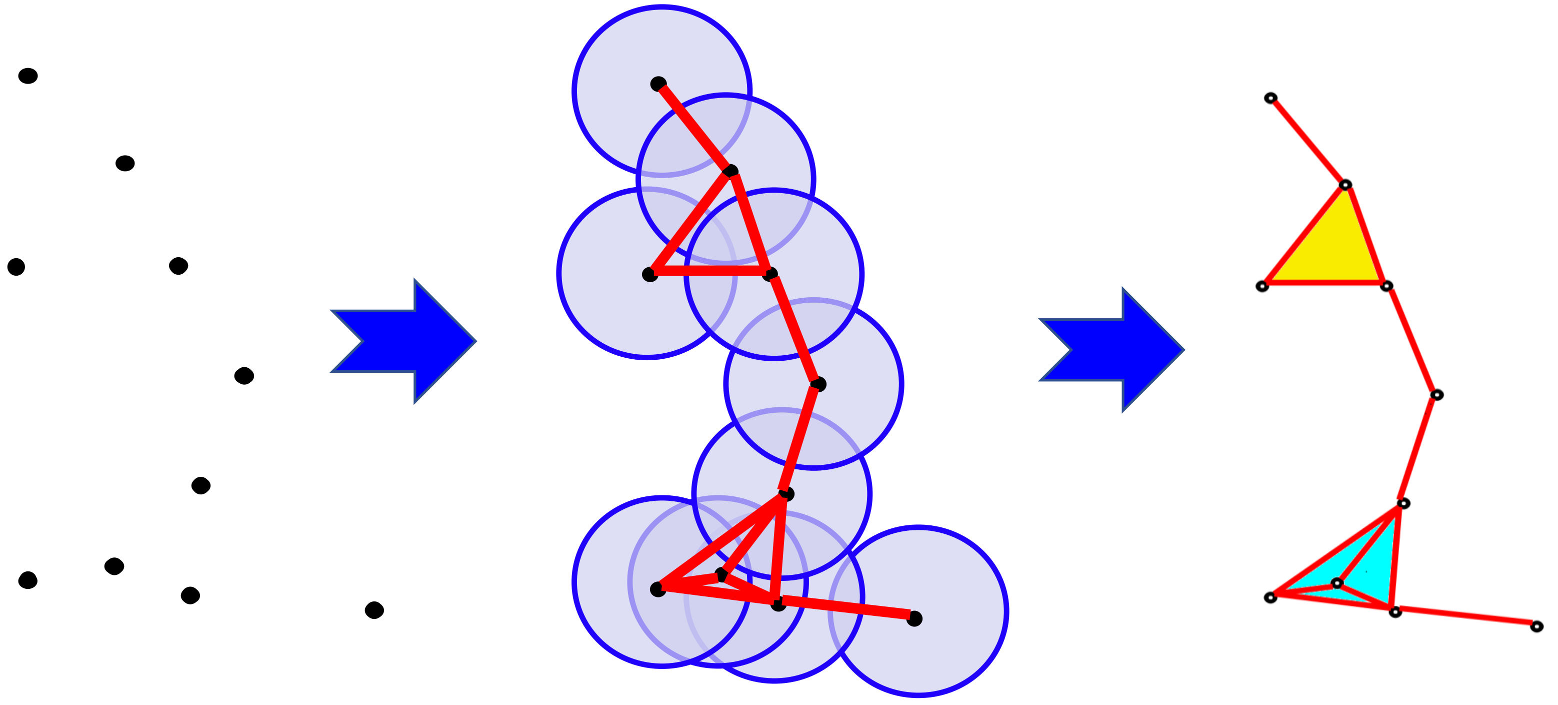


2-simplex



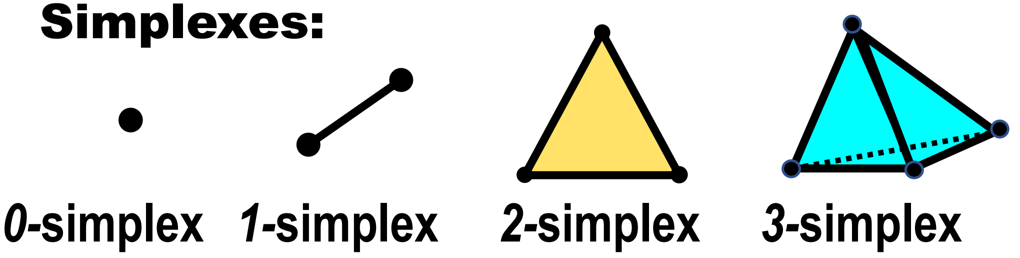
3-simplex

Simplicial complexes of ten points:



Persistent homology

Simplexes:



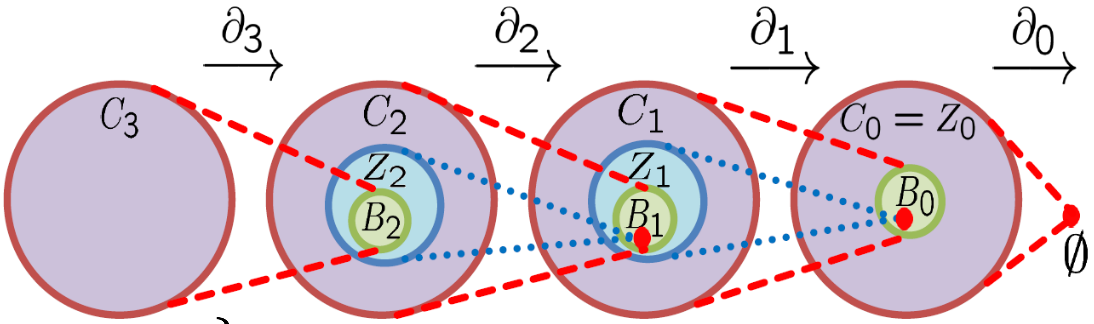
Frosini and Nandi (1999), Robins (1999), Edelsbrunner, Letscher and Zomorodian (2002), Zomorodian and Carlsson (2005), Edelsbrunner and Harer, (2007) Kaczynski, Mischaikow and Mrozek (2004), Ghrist (2008), ...

k-chain: $K = \left\{ \sum_j c_j \sigma_j^k \right\}$

Chain group: $C_k(K, \mathbb{Z}_2)$

Boundary operator:

$$\partial_k \sigma^k = \sum_{j=0}^{k} (-1)^j \{v_0, v_1, \ldots, \widehat{v_j}, \ldots, v_k\}$$

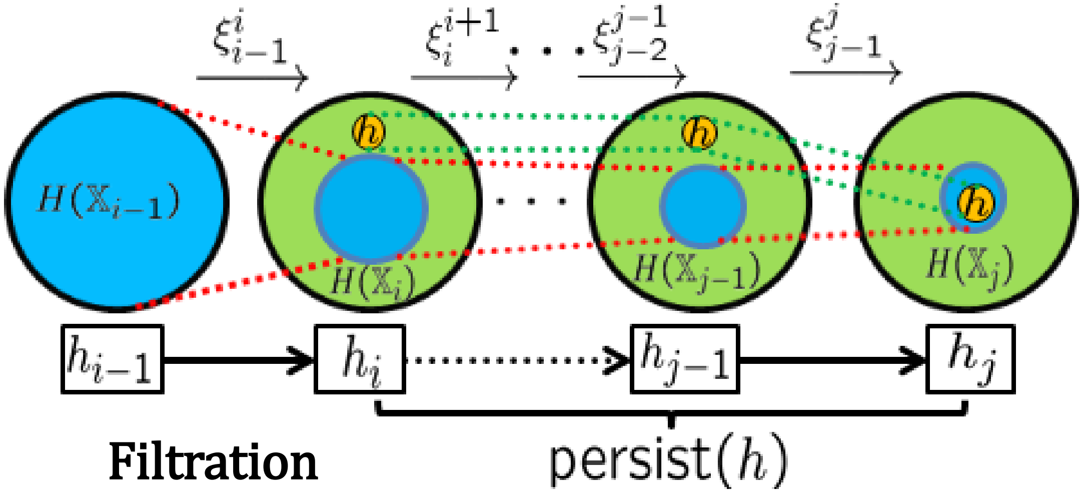

$\xrightarrow{\partial_3}$
$\xrightarrow{\partial_2}$
$\xrightarrow{\partial_1}$
$\xrightarrow{\partial_0}$
C_3
C_2
Z_2
B_2
C_1
Z_1
B_1
$C_0 = Z_0$
B_0
$\emptyset$

Cycle group: $Z_k = \text{Ker } \partial_k$

Boundary group: $B_k = \text{Im } \partial_{k+1}$

Homology group: $H_k = \frac{Z_k}{B_k}$

Betti number: $\beta_k = \text{Rank}(H_k)$

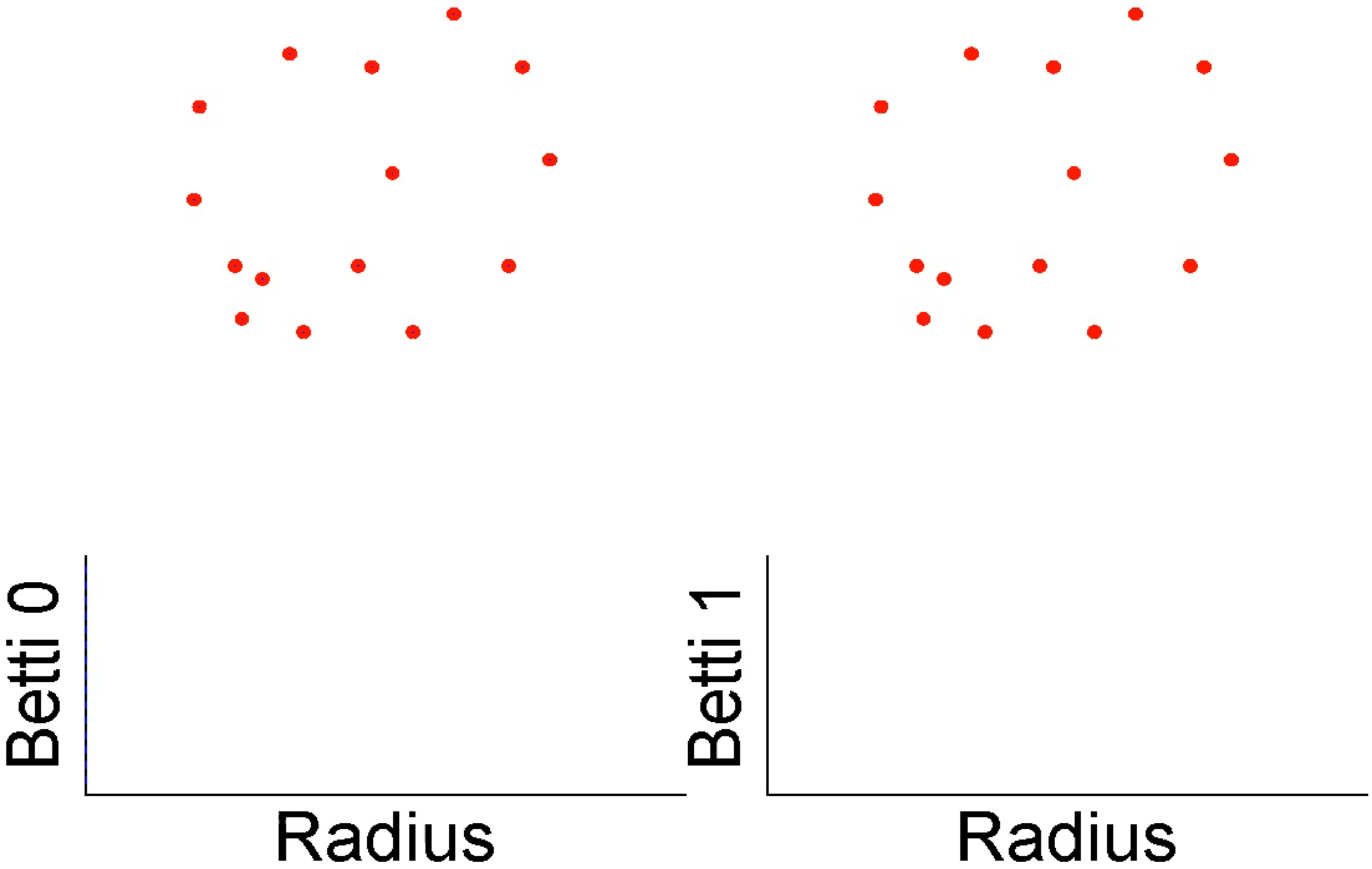


Xia, Wei, IJNMBE, 2014;
Xia, Feng, Tong, Wei, JCC, 2015

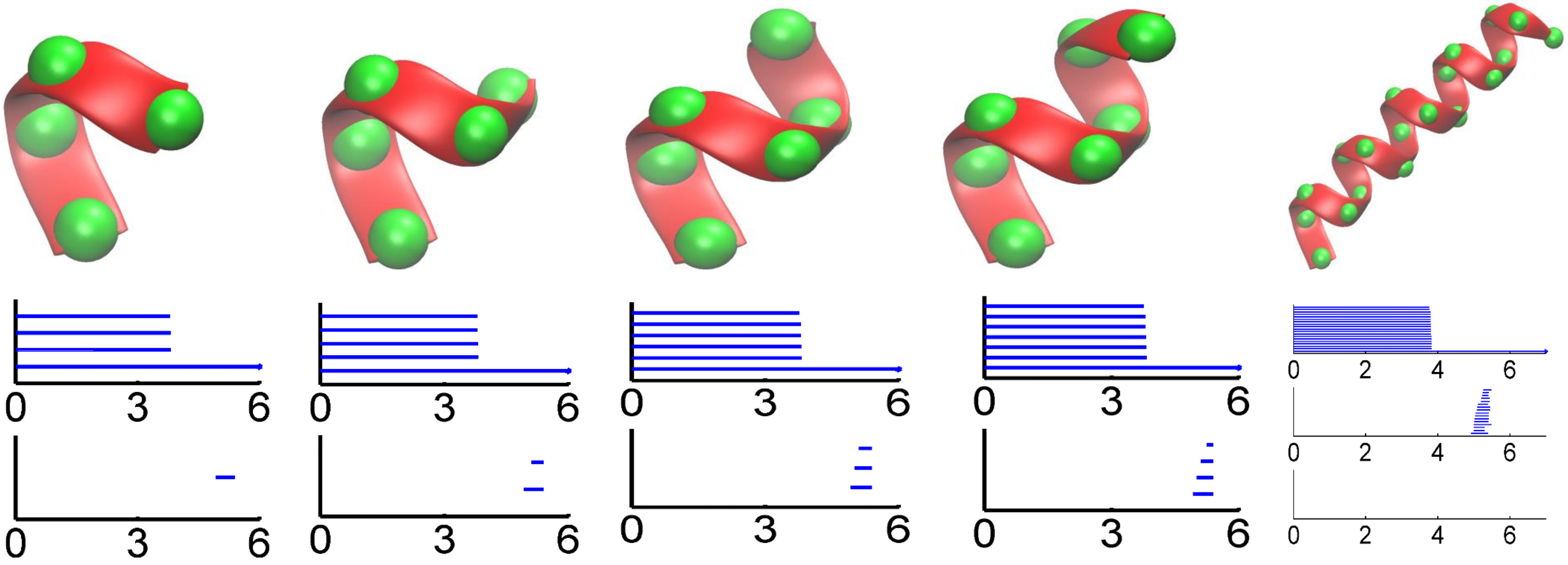
Algebraic Topology

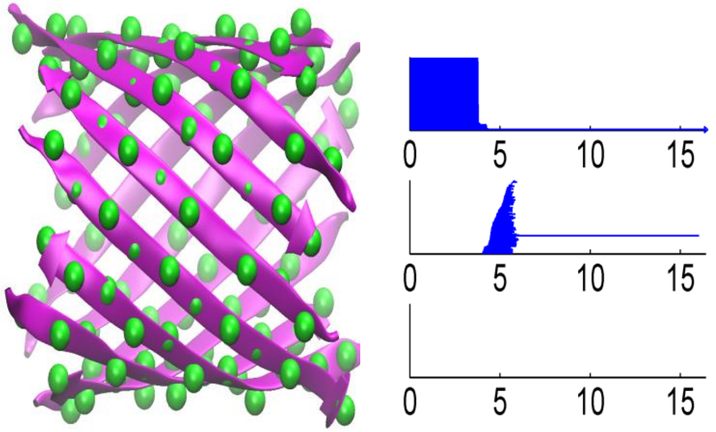
Vietoris-Rips complexes, persistent homology and topological fingerprint

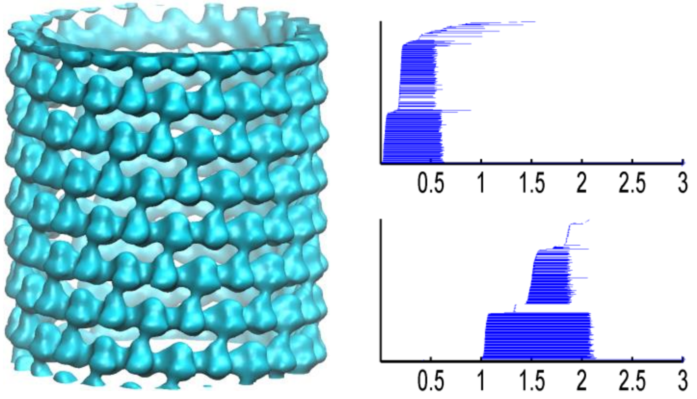
(Xia, Wei, 2014)



Topological fingerprints of an alpha helix



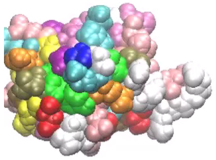


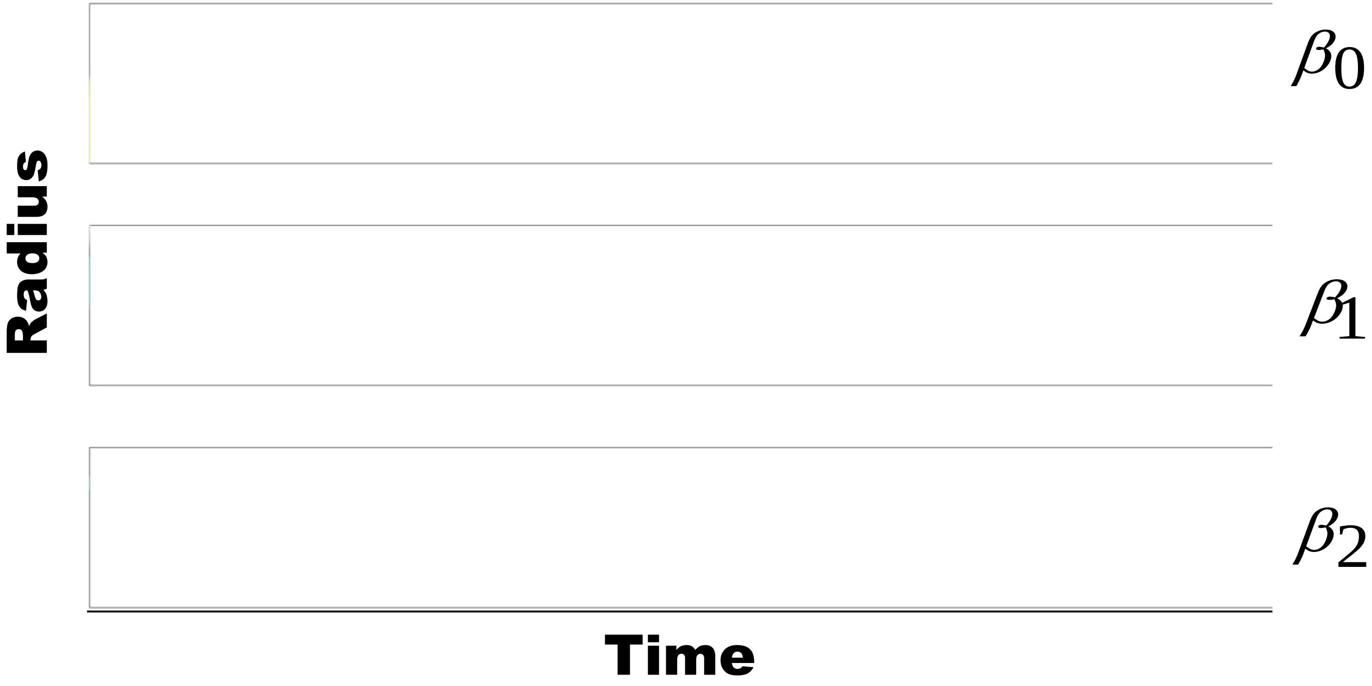


(Xia & Wei, IJNMBE, 2014, 2015)

Algebraic Topology

2D persistent homology of protein 1UBQ unfolding

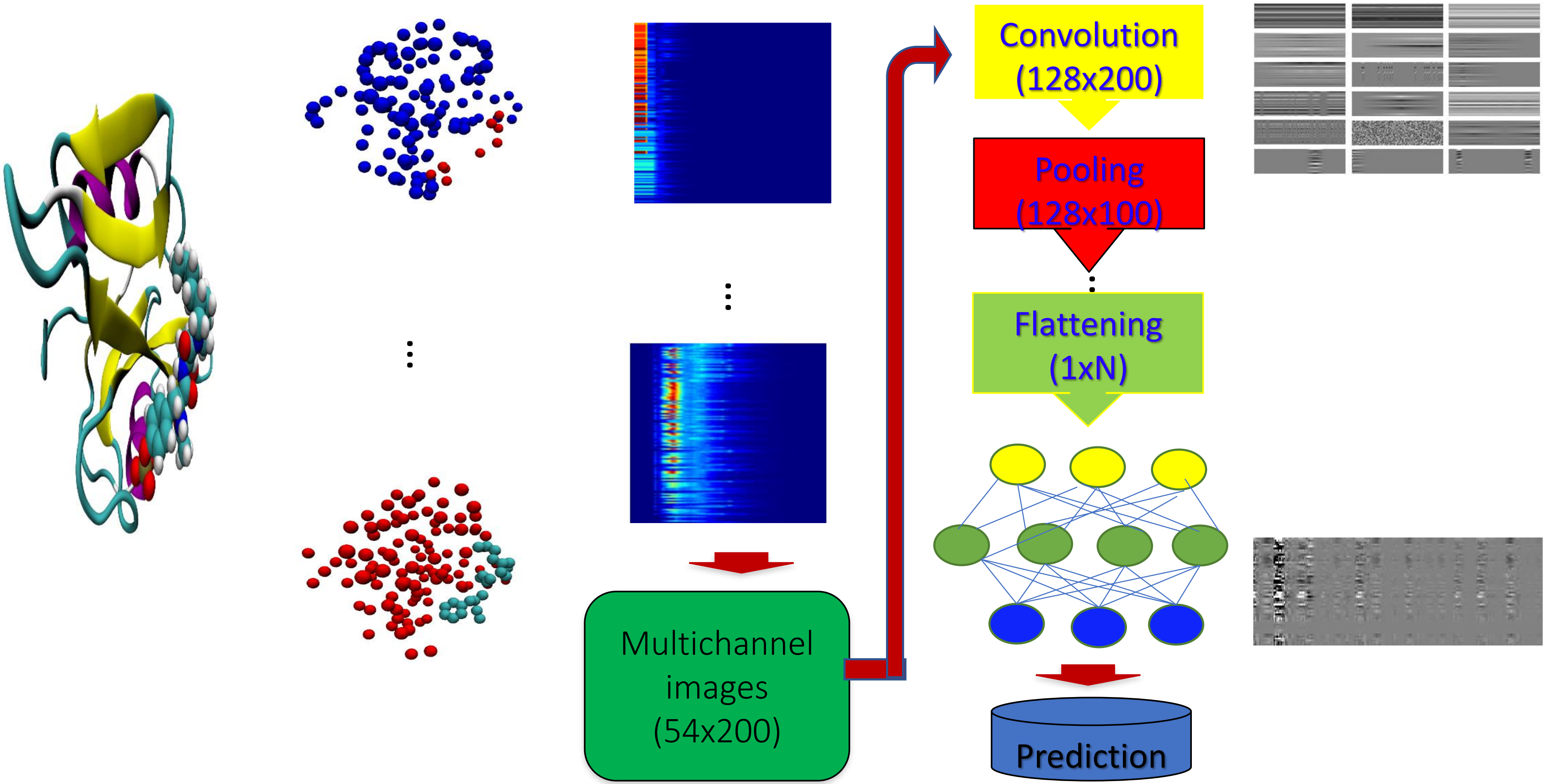




(Xia & Wei, JCC, 2015)

Kelin Xia

Topological convolutional deep Learning architecture



Convolution (128x200)

Pooling (128x100)

Flattening (1xN)

Multichannel images (54x200)

Prediction

Original protein-ligand Complex

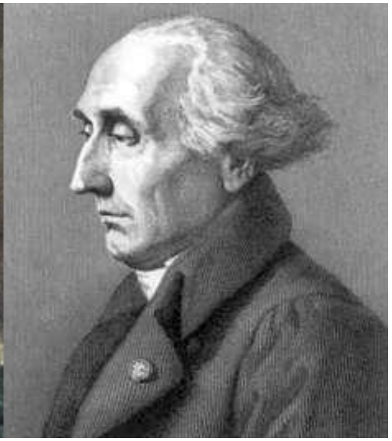
Classify atoms into element specific groups

Generate topological, DG & graph fingerprints

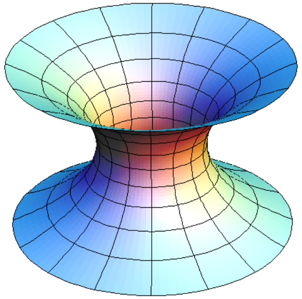
Convolutional deep learning neural network

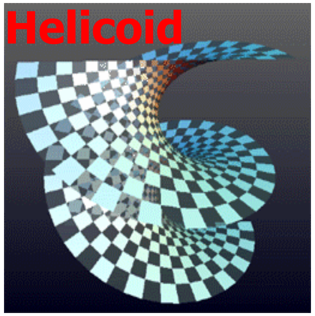
(Cang & Wei, PLOS CB, 2017)

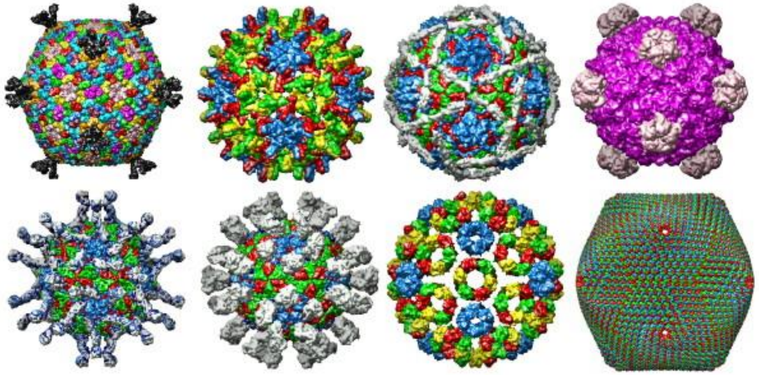
Leonhard P. Euler
(Swiss Mathematician,
April 15, 1707 – Sept
18 1783



Joseph L. Lagrange
(Italian Mathematician,
January 25 1736 –
April 10, 1813)



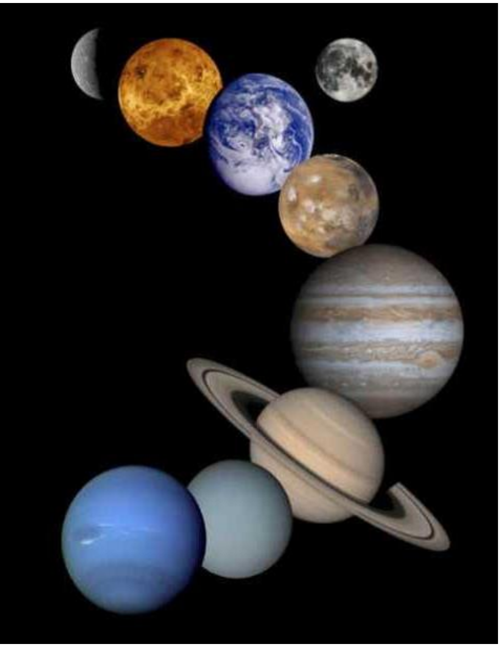


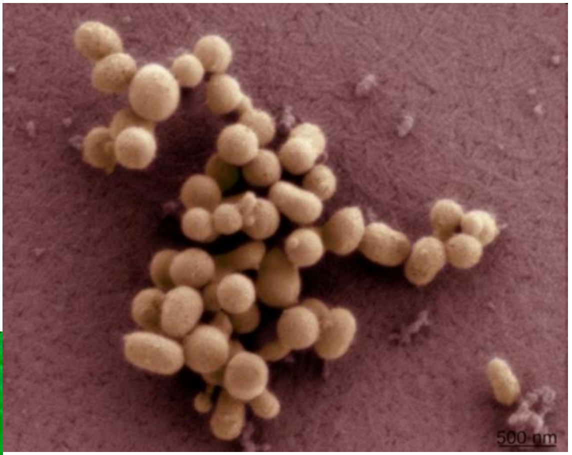


Viral morphology

Minimal Surfaces

A way to minimize energy and maximize stability



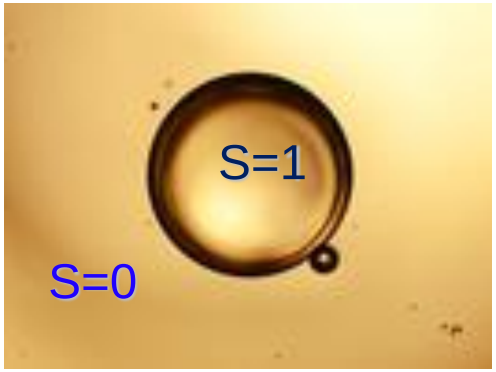


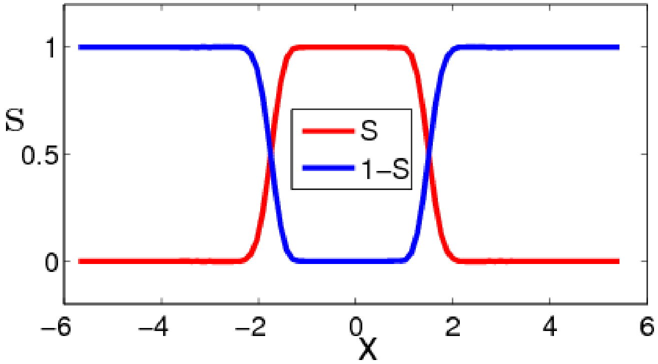
Man-made life,
Mycoplasma
mycoides

Differential geometry based minimal surface model

$$G=\int \gamma[\text{area}]\,d\boldsymbol{r} \qquad \text{area}=|\nabla S|$$

where G is the surface energy, gamma (γ) is the surface tension, and S is a surface characteristic function:

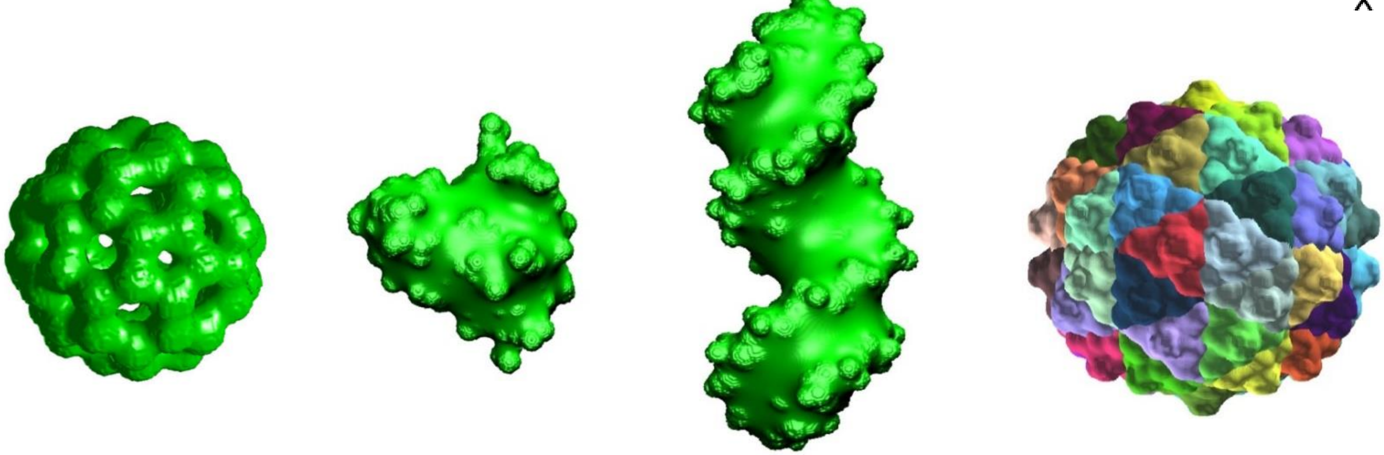




Generalized Laplace-Beltrami flow:

$$\frac{\partial S}{\partial t}=|\nabla S|\left[\nabla\cdot\frac{\gamma\nabla S}{|\nabla S|}\right]$$

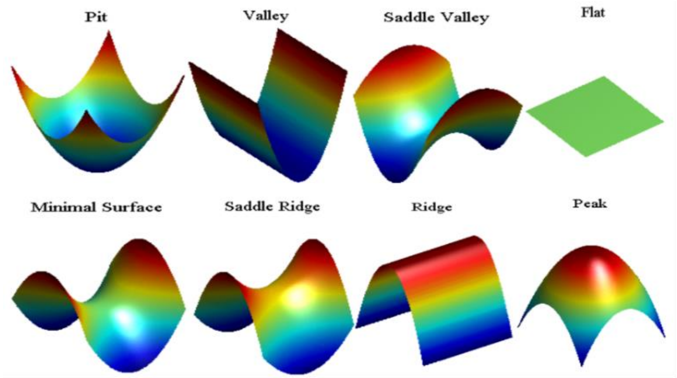
Mean curvature



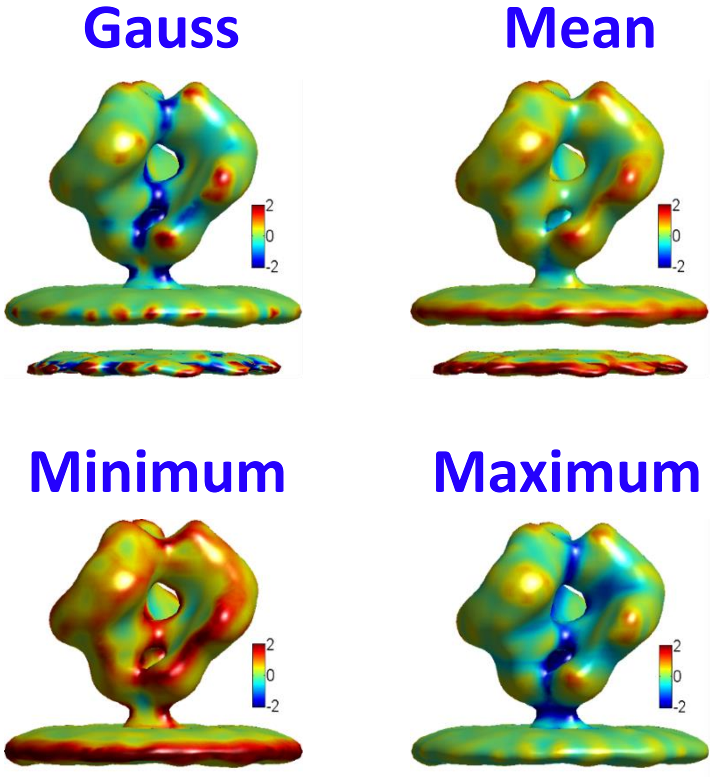
Shan Zhao

(Bates, Wei, Zhao, 2006; JCC,2008; Zhao, Cang, Tong & Wei, Bioinformatics 2018)

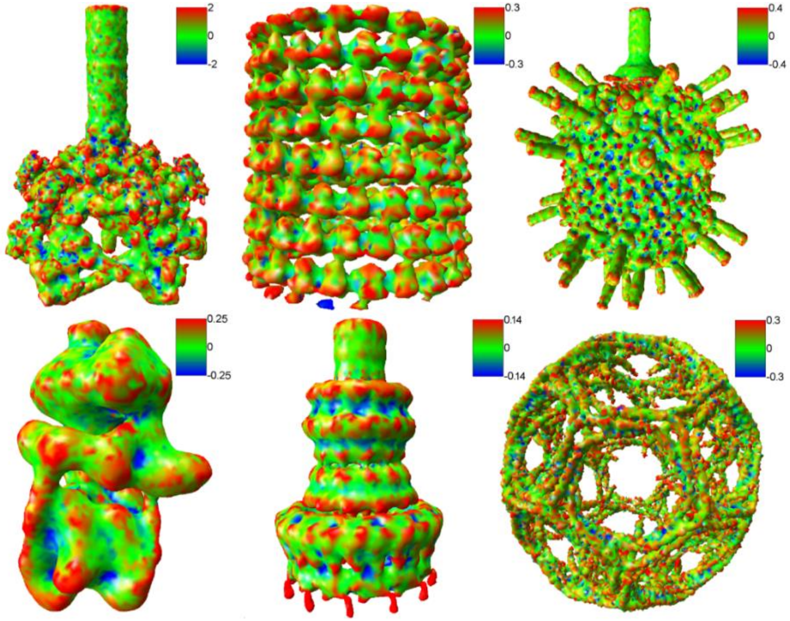
Differential Geometry



Kelin Xia



Mean curvatures of subcellular structures



(Feng, Xia, Tong and Wei, JCP, IJNMBI,2012)

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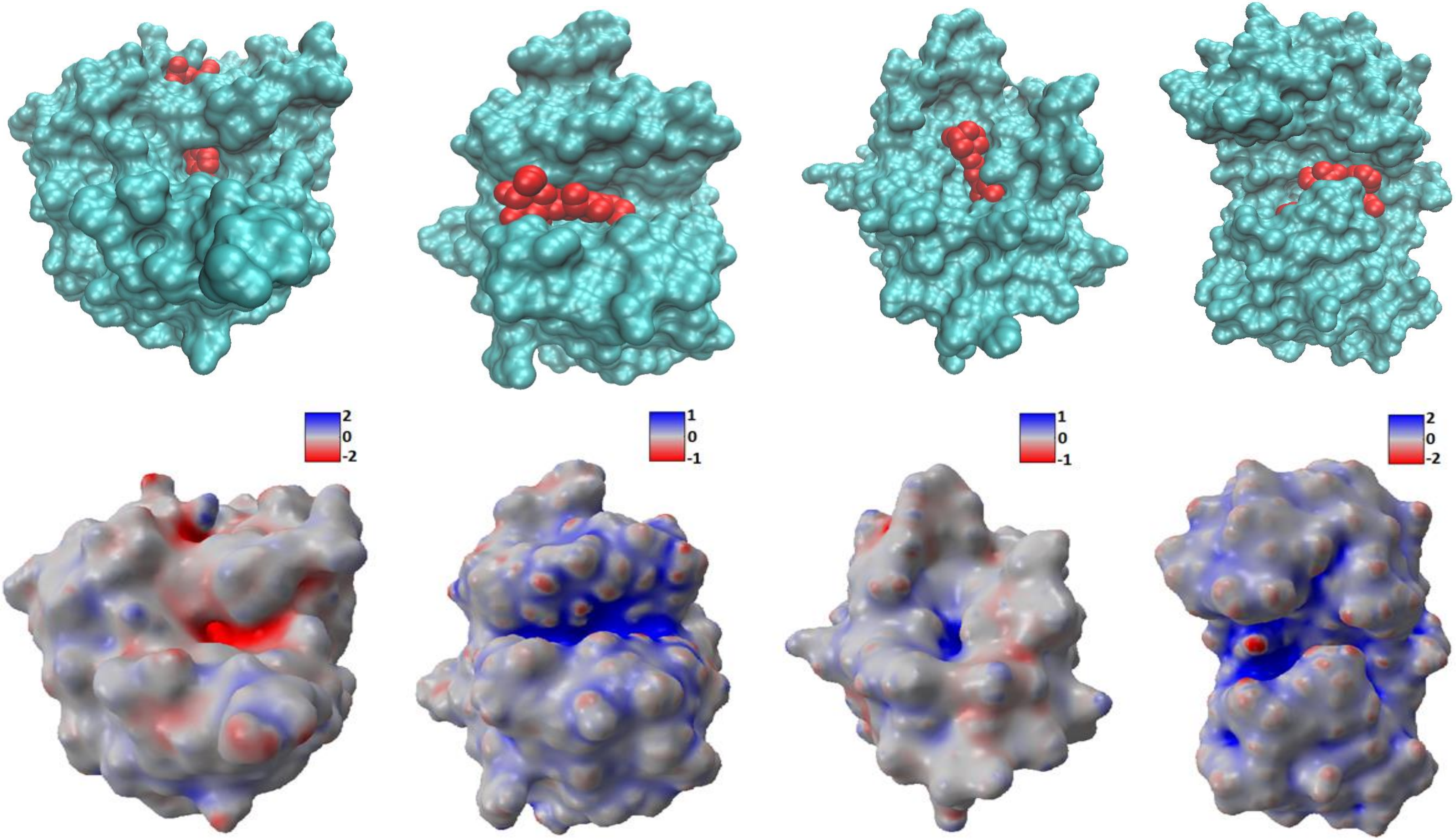
Protein binding site prediction by the product of curvature and electrostatics

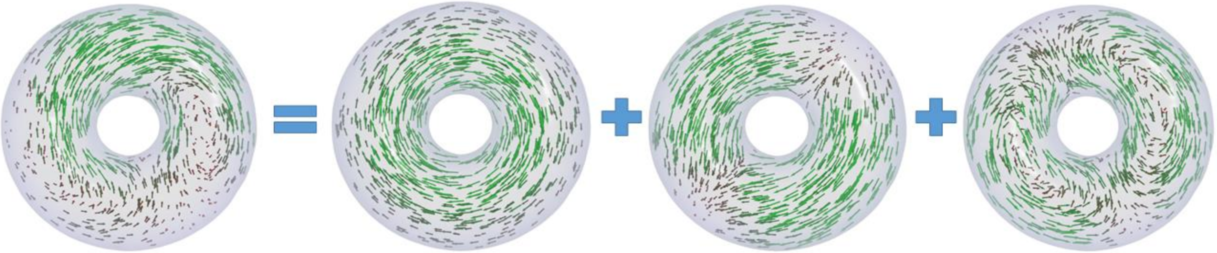


(Xia, Feng, Tong & Wei, JCP 2013; Zhao, Cang, Tong & Wei, Bioinformatics, 2018)

de Rham-Hodge theory and discrete exterior calculus

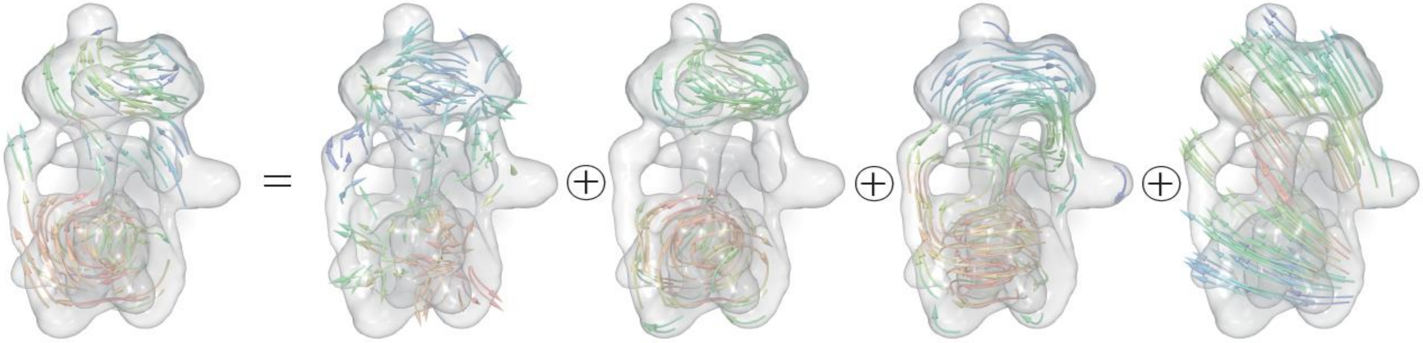
Hodge decomposition:

(Zhao, Wang, Tong & Wei, 2018)



A vector field = Harmonic + curl-free + divergent-free

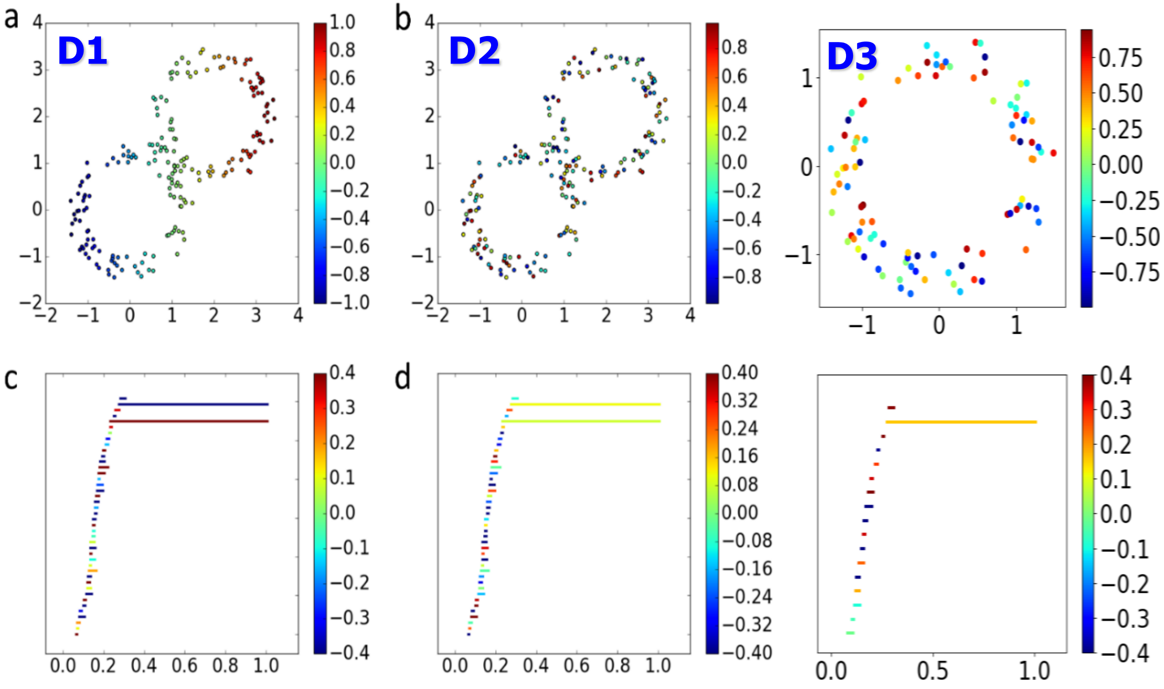
Cryo-EM data:

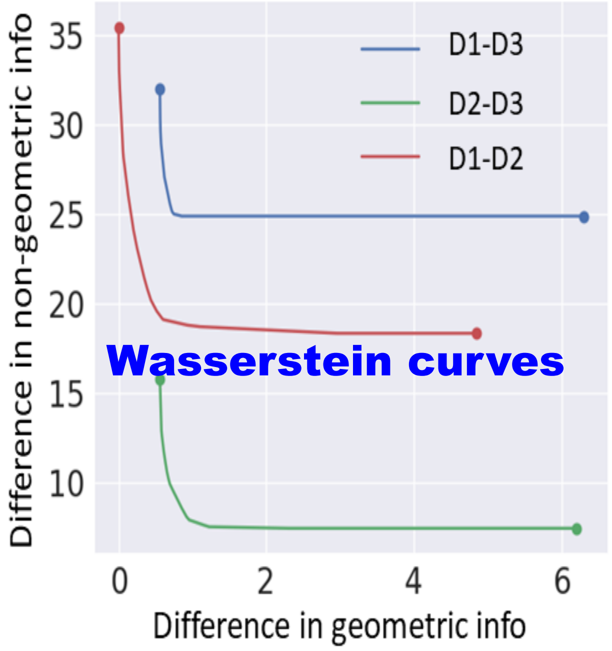


$$\begin{tikzcd}
\text{0-Form} \arrow[r, "d_0"] \arrow[d, shift right, "\star_0"'] & \text{1-Form} \arrow[r, "d_1"] \arrow[d, shift right, "\star_1"'] & \text{2-Form} \arrow[r, "d_2"] \arrow[d, shift right, "\star_2"'] & \text{3-Form} \arrow[d, shift right, "\star_3"'] \\
\text{Dual 3-Form} \arrow[u, shift right, "\star_0^{-1}"'] & \text{Dual 2-Form} \arrow[l, "d_0^T"'] \arrow[u, shift right, "\star_1^{-1}"'] & \text{Dual 1-Form} \arrow[l, "d_1^T"'] \arrow[u, shift right, "\star_2^{-1}"'] & \text{Dual 0-Form} \arrow[l, "d_2^T"'] \arrow[u, shift right, "\star_3^{-1}"']
\end{tikzcd}$$

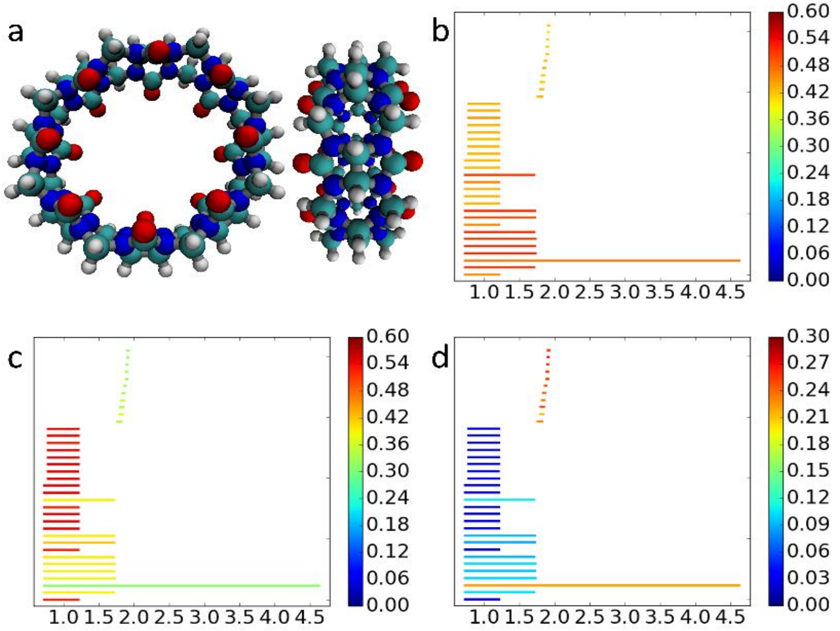
$$\begin{tikzcd}
\text{point-based scalar field} \arrow[r, "\nabla"] \arrow[d, leftrightarrow, "\star"] & \text{edge-based vector field} \arrow[r, "\nabla\times"] \arrow[d, leftrightarrow, "\star"] & \text{face-based vector field} \arrow[r, "\nabla\cdot"] \arrow[d, leftrightarrow, "\star"] & \text{cell-based scalar field} \arrow[d, leftrightarrow, "\star"] \\
\text{cell-based scalar field} & \text{face-based vector field} \arrow[l, "\nabla\cdot"'] & \text{edge-based vector field} \arrow[l, "\nabla\times"'] & \text{point-based scalar field} \arrow[l, "\nabla"']
\end{tikzcd}$$

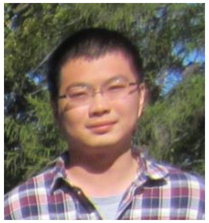
Persistent cohomology





Wasserstein curves



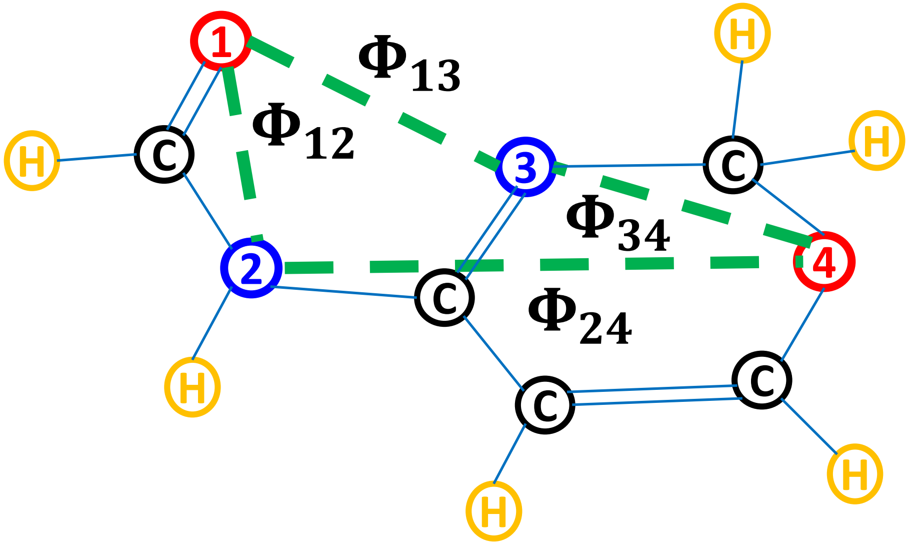


Zixuan Cang

(Cang & Wei, 2018)

Algebraic Graph Theory for Biomolecules

Molecular graph G(V,E)



Adjacency matrix of $G(V_{ON},E)$

$$\begin{bmatrix} 0 & \Phi_{12} & \Phi_{13} & 0 \\ \Phi_{12} & 0 & 0 & \Phi_{24} \\ \Phi_{13} & 0 & 0 & \Phi_{34} \\ 0 & \Phi_{24} & \Phi_{34} & 0 \end{bmatrix}$$

Eigenvalues: $\lambda_1^A, \lambda_2^A, \ldots$

Can one hear the shape of a drum?

Laplacian matrix of $G(V_{ON},E)$

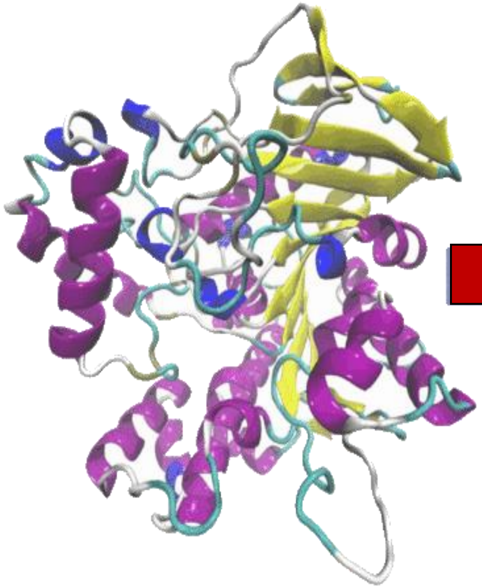
$$\begin{bmatrix} \Phi_{12}+\Phi_{13} & -\Phi_{12} & -\Phi_{13} & 0 \\ -\Phi_{12} & \Phi_{12}+\Phi_{24} & 0 & -\Phi_{24} \\ -\Phi_{13} & 0 & \Phi_{13}+\Phi_{34} & -\Phi_{34} \\ 0 & -\Phi_{24} & -\Phi_{34} & \Phi_{24}+\Phi_{34} \end{bmatrix}$$

Eigenvalues: $\lambda_1^L, \lambda_2^L, \ldots$

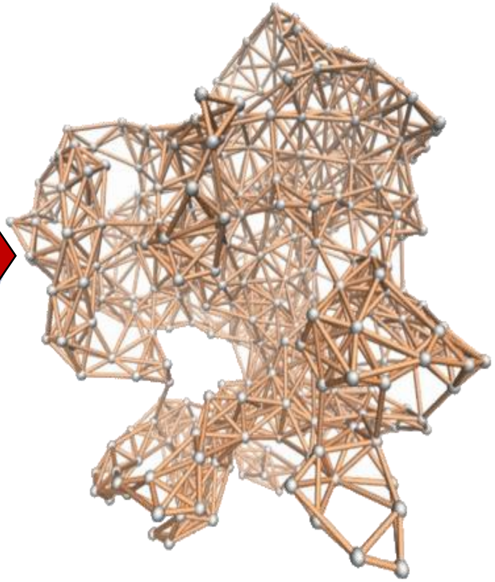
(Nguyen and Wei, 2018)

Algebraic graph theory for biomolecules

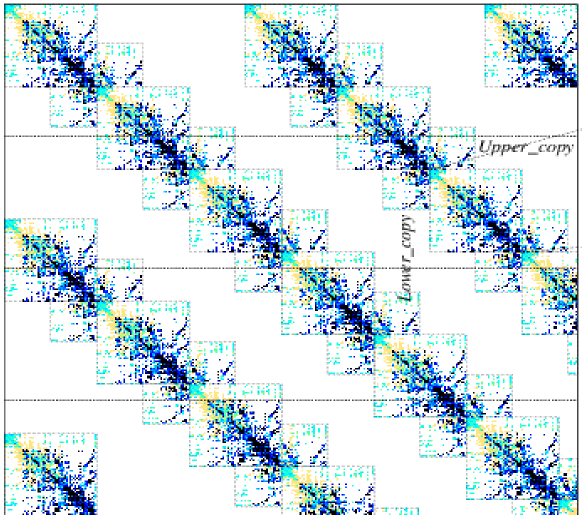
Protein



Hypergraph representation



Laplacian matrices and adjacency matrices



Eigenvalue multiplicities in Laplacian and adjacency matrices are associated with structural self-similarity, stability, flexibility and activity and hotspots, etc.

Corresponding eigenvalues $\lambda_1^L, \lambda_2^L, \ldots$ $\lambda_1^A, \lambda_2^A, \ldots$

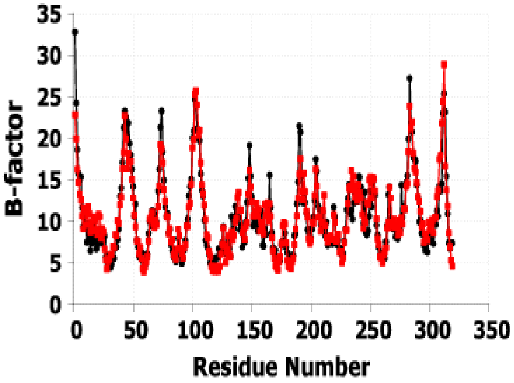
Mark Kac: Can one hear the shape of a drum?

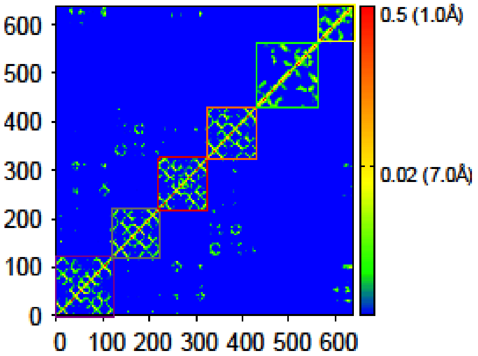
Can one hear the interaction of molecules?

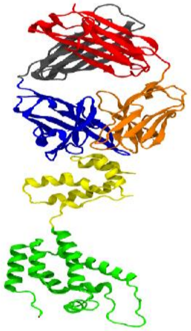
Geometric Graph Theory

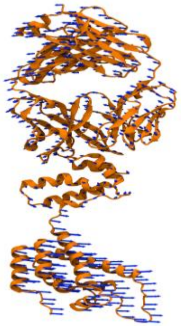
- **Multiscale weighted colored graphs (MWCG)**
- MWCG is about 40% more accurate than Gaussian network model (GNM) in B-factor prediction, based on 364 proteins.

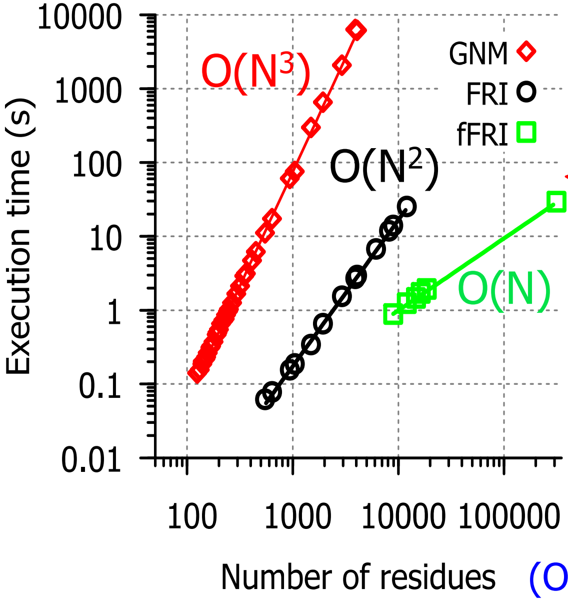
K. Opron

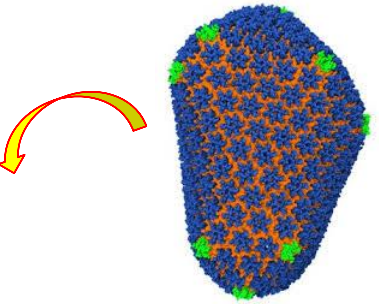












HIV capsid (313,236 residues) would takes GNM 120 years to compute!

$$
\Gamma_{ij}(\Phi) = \begin{cases} -\Phi(r_{ij},\eta), & i \neq j, \\ -\sum_{j,j\neq i}^{N} \Gamma_{ij}, & i = j \end{cases}
$$

$$
\Phi(r_{ij},\eta) = 1, \quad r_{ij} \to 0
$$

$$
\Phi(r_{ij},\eta) = 0 \quad r_{ij} \to \infty
$$

$$
\Phi(r_{ij},\eta) = e^{-(r_{ij}/\eta)^{\kappa}}
$$

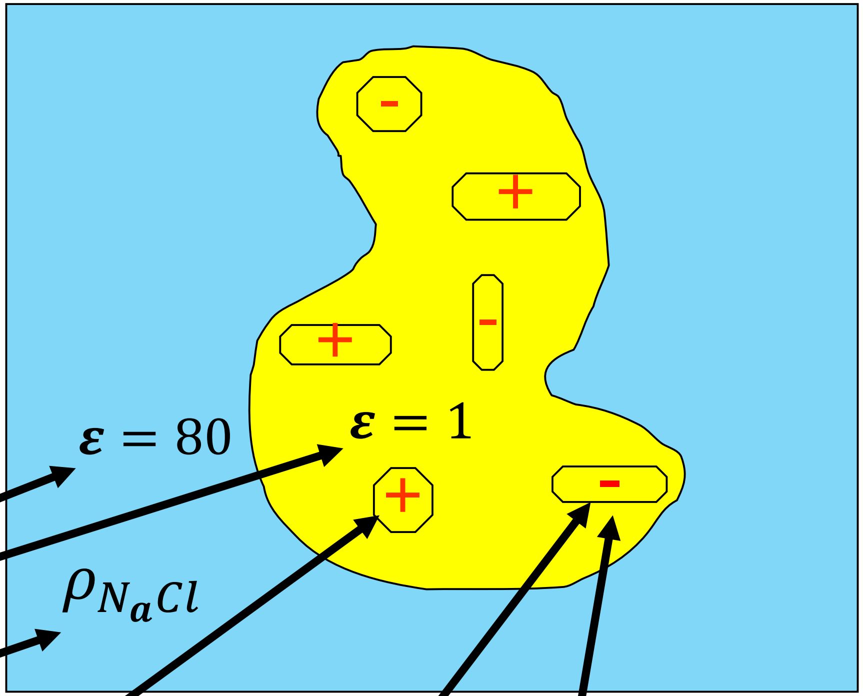
$$
B_i^{FRI} = a\left(\Gamma_{ii}(\Phi)\right)^{-1}
$$

(Opron, Xia and Wei, JCP, 2013; JCP 2014; JCP, 2015; Nguyen, et al, JCIM, 2017, Bramer and Wei, JCP, 2018. Nguyen and Wei, 2018)

Multiscale: The Poisson-Boltzmann equation

- Discontinuous dielectric constant at the interface
- Non-smooth interface (geometric singularity)
- Singular charges (delta functions)

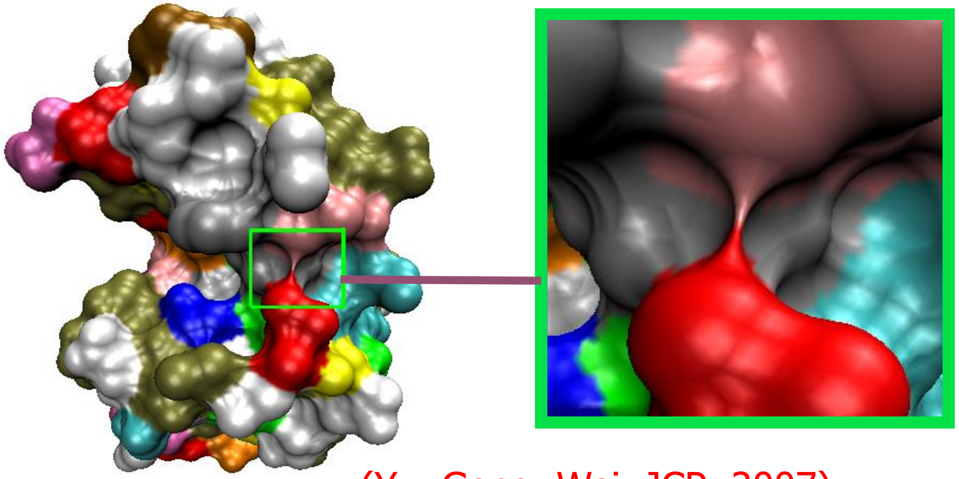
Chern et al, 2003; Geng, Yu, Wei, JCP, 2007; Geng, Zhao, JCP 2017


-
+
-
+
$\boldsymbol{\varepsilon} = 80$
$\boldsymbol{\varepsilon} = 1$
+
-
ρ_{N_aCl}

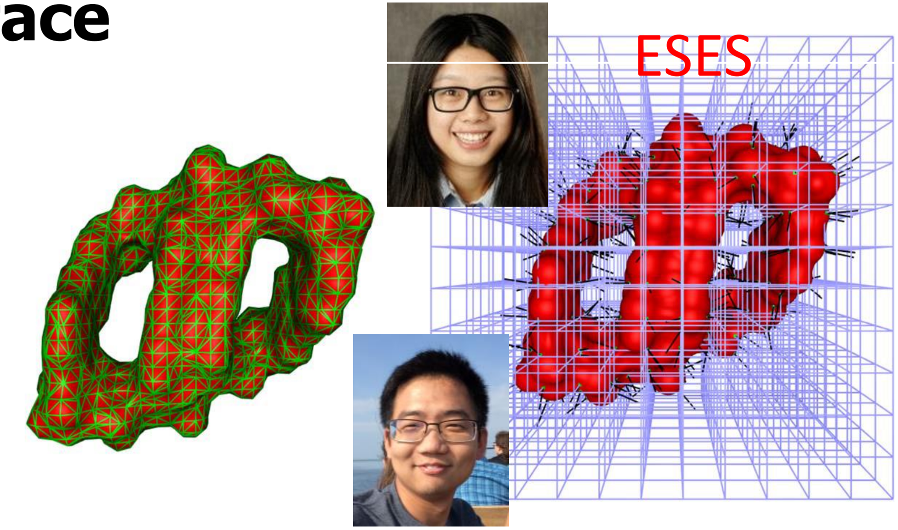
$$-\boldsymbol{\nabla}\cdot(\boldsymbol{\varepsilon}(\boldsymbol{r})\boldsymbol{\nabla}\boldsymbol{\phi}) = \sum_{\boldsymbol{i}} q_{\boldsymbol{i}} c_{\boldsymbol{i}} \boldsymbol{e}^{-\frac{q_i\phi}{kT}}$$

$$+\sum_{\boldsymbol{i}}\Big(\underbrace{Q_{\boldsymbol{i}}\delta(\boldsymbol{r}-\boldsymbol{r}_{\boldsymbol{i}})}_{\text{Point charge}} - \underbrace{\boldsymbol{d}_{\boldsymbol{i}}\cdot\boldsymbol{\nabla}\delta(\boldsymbol{r}-\boldsymbol{r}_{\boldsymbol{i}}) + \boldsymbol{\Theta}_{\boldsymbol{i}}:\boldsymbol{\nabla}\boldsymbol{\nabla}\delta(\boldsymbol{r}-\boldsymbol{r}_{\boldsymbol{i}})}_{\text{Charge polarization (Amoeba)}}\Big)$$

MIBPB for solving the Poisson equation with protein interface

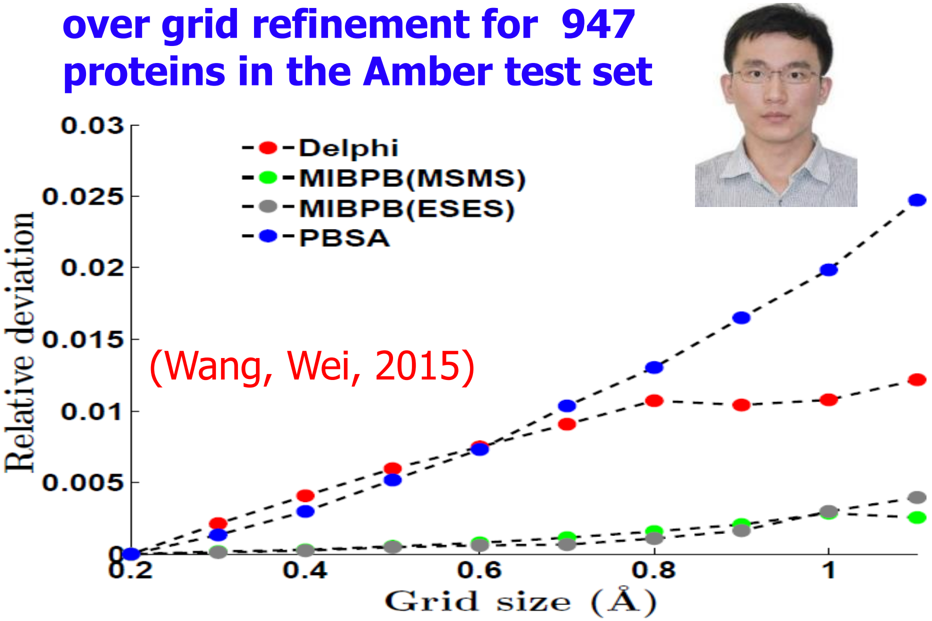


(Yu, Geng, Wei, JCP 2007)



(Liu, Wang, Zhao, Tong, Wei, JCC 2017)

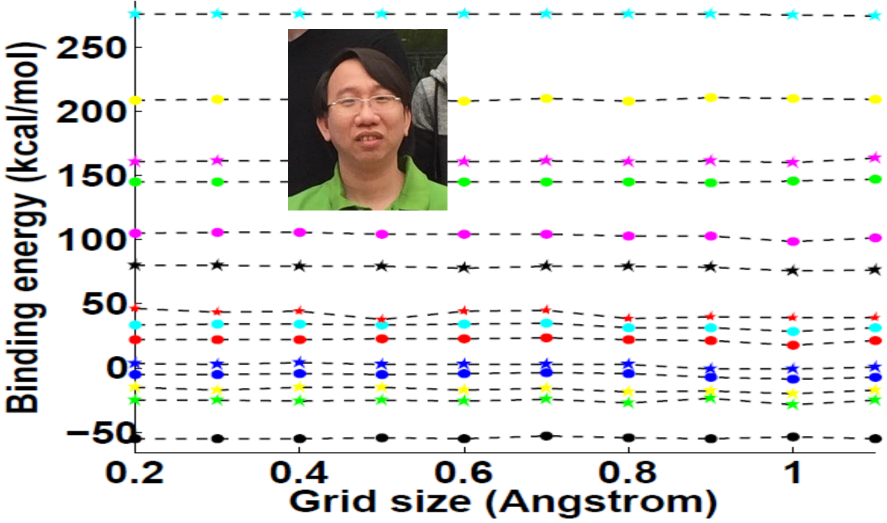
Relative solvation energy deviations over grid refinement for 947 proteins in the Amber test set

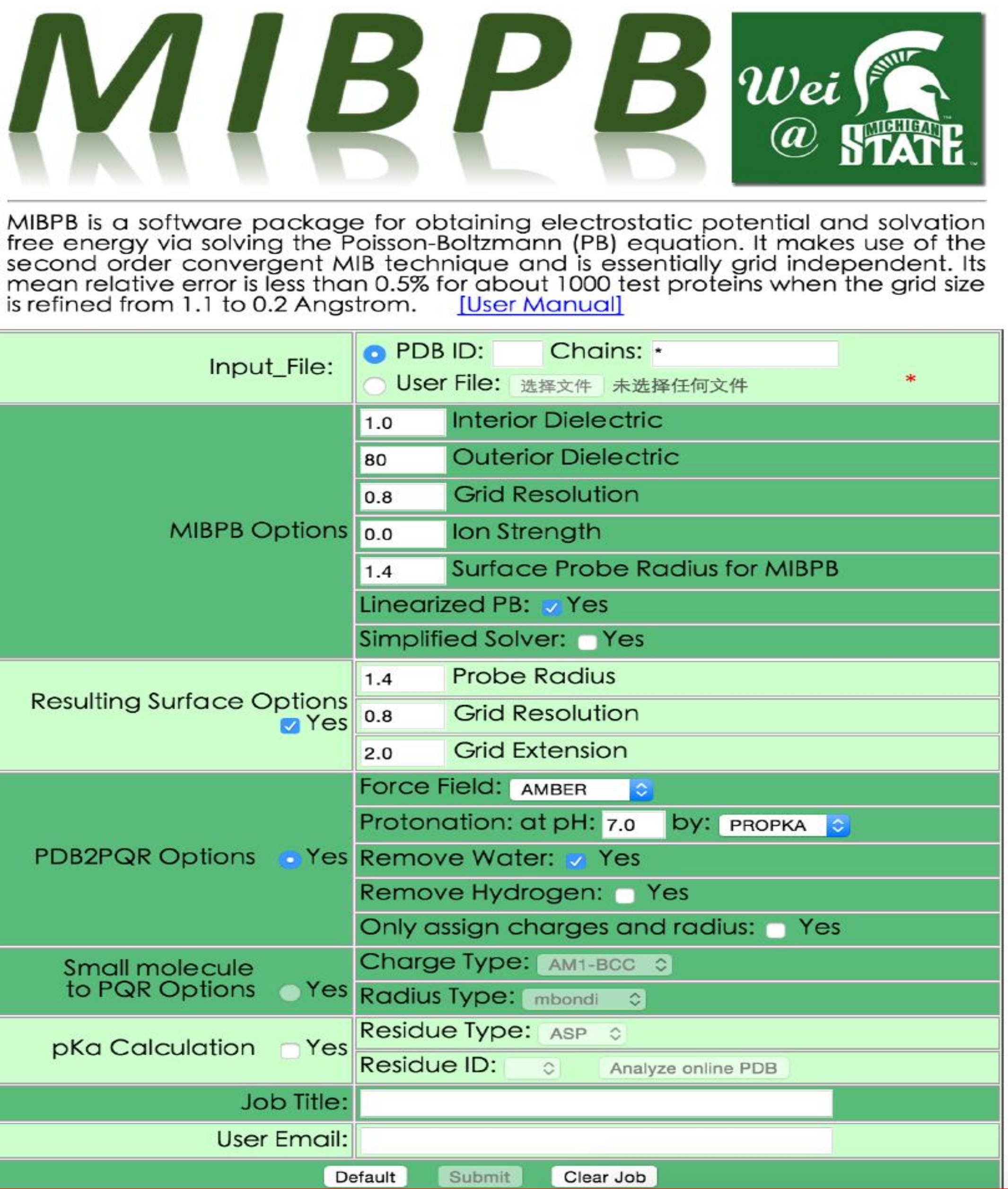


(Wang, Wei, 2015)

Electrostatic binding energies of 14 RNA-protein complexes over grid refinement

(Nguyen, Wang, Wei, JCC, 2015)



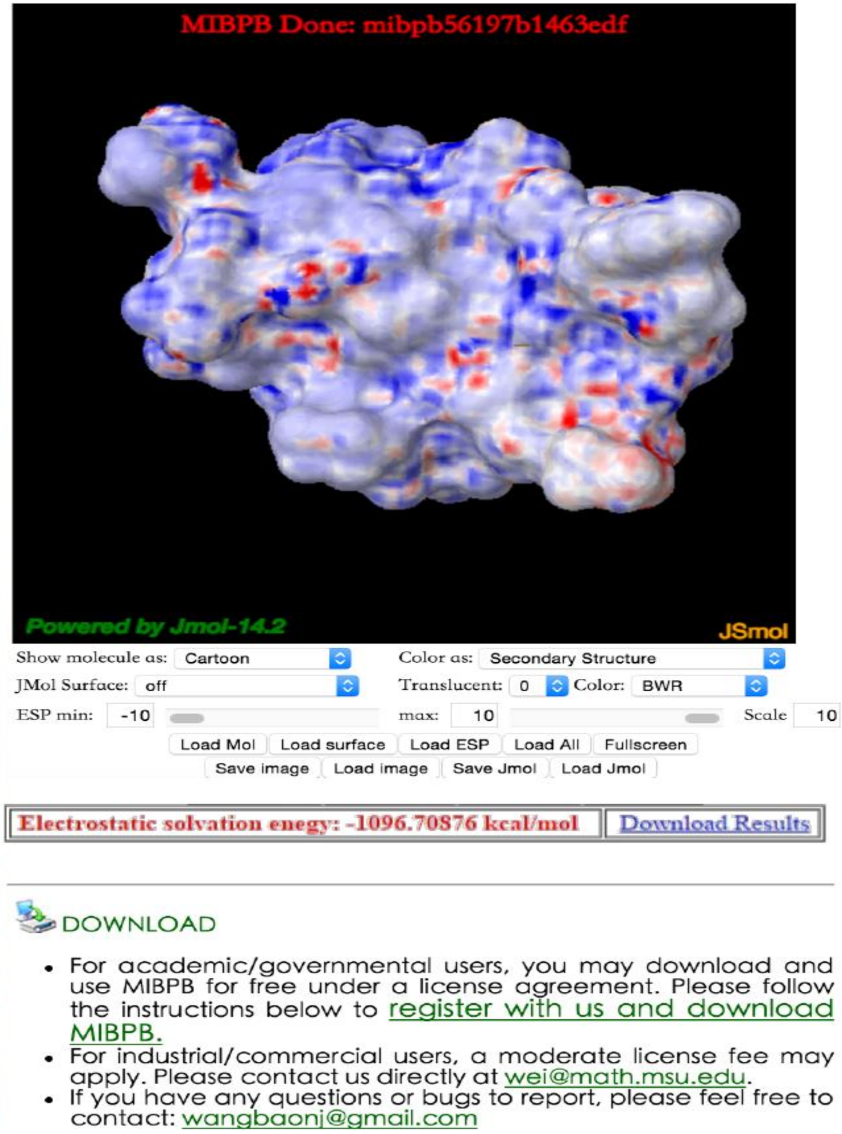


MIBPB

Wei @ Michigan State

MIBPB is a software package for obtaining electrostatic potential and solvation free energy via solving the Poisson-Boltzmann (PB) equation. It makes use of the second order convergent MIB technique and is essentially grid independent. Its mean relative error is less than 0.5% for about 1000 test proteins when the grid size is refined from 1.1 to 0.2 Angstrom. [User Manual]

Input_File:	● PDB ID: Chains: * ○ User File: 选择文件 未选择任何文件 *
MIBPB Options	1.0 Interior Dielectric 80 Outerior Dielectric 0.8 Grid Resolution 0.0 Ion Strength 1.4 Surface Probe Radius for MIBPB Linearized PB: ☑ Yes Simplified Solver: ☐ Yes
Resulting Surface Options ☑ Yes	1.4 Probe Radius 0.8 Grid Resolution 2.0 Grid Extension
PDB2PQR Options ● Yes	Force Field: AMBER Protonation: at pH: 7.0 by: PROPKA Remove Water: ☑ Yes Remove Hydrogen: ☐ Yes Only assign charges and radius: ☐ Yes
Small molecule to PQR Options ○ Yes	Charge Type: AM1-BCC Radius Type: mbondi
pKa Calculation ☐ Yes	Residue Type: ASP Residue ID: Analyze online PDB
Job Title:	
User Email:	



MIBPB Done: mibpb56197b1463edf

Show molecule as: Cartoon Color as: Secondary Structure

JMol Surface: off Translucent: 0 Color: BWR

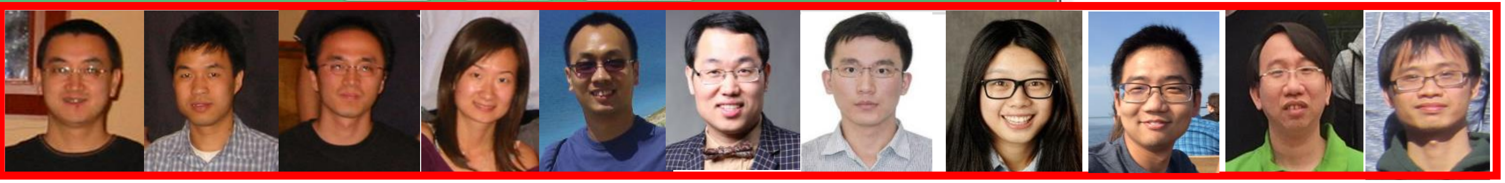
ESP min: -10 max: 10 Scale 10

Electrostatic solvation energy: -1096.70876 kcal/mol Download Results

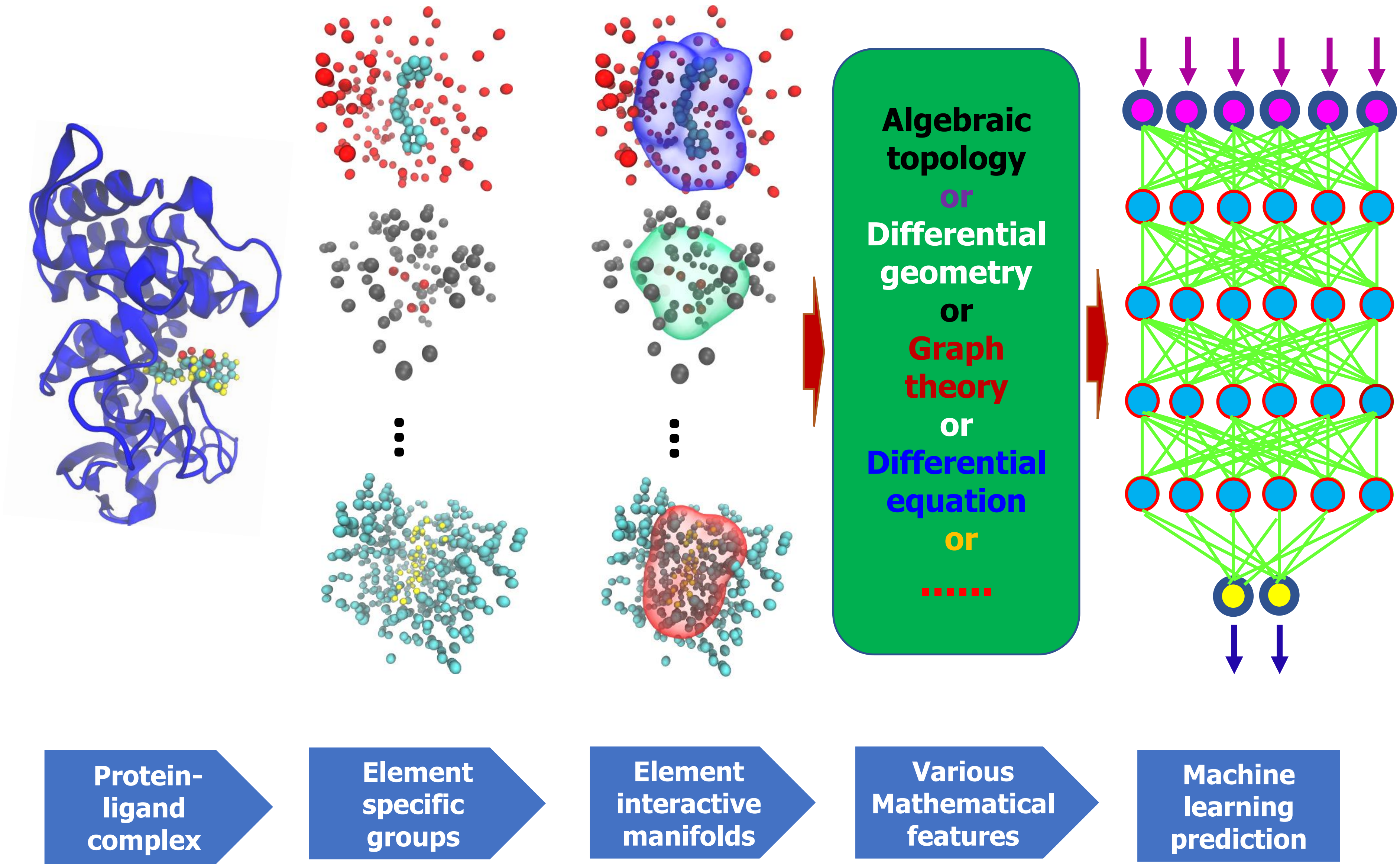
DOWNLOAD

- For academic/governmental users, you may download and use MIBPB for free under a license agreement. Please follow the instructions below to register with us and download MIBPB.
- For industrial/commercial users, a moderate license fee may apply. Please contact us directly at wei@math.msu.edu.
- If you have any questions or bugs to report, please feel free to contact: wangbaonj@gmail.com

(Wang, Zhao, Wei, 2015)



Mathematical deep learning



Algebraic topology
or
Differential geometry
or
Graph theory
or
Differential equation
or
……

Protein-ligand complex

Element specific groups

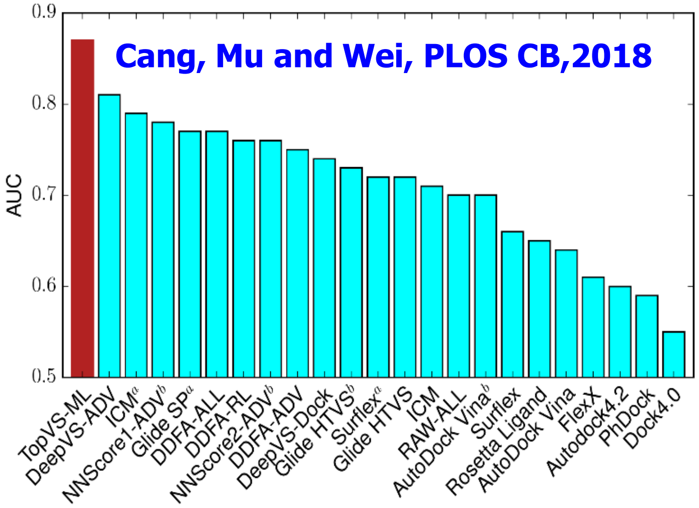
Element interactive manifolds

Various Mathematical features

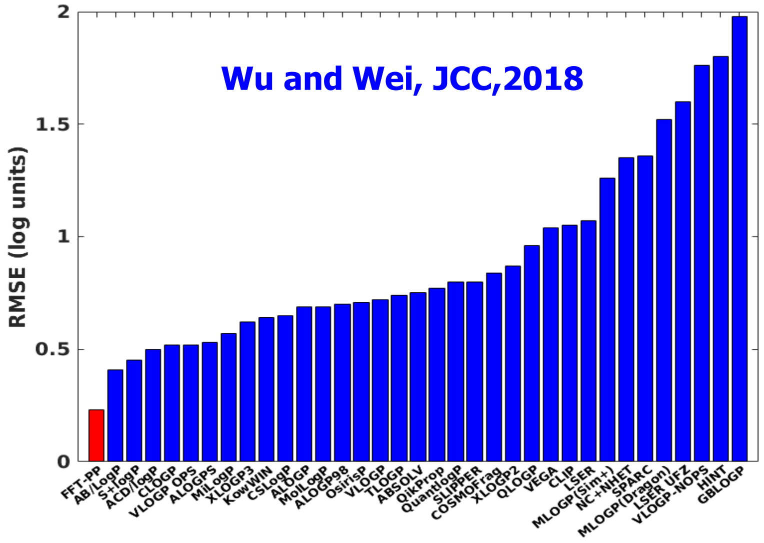
Machine learning prediction

Topological learning based predictions

Classification of ligands & decoys DUD database 128,374 protein-ligand/decoy pairs


Cang, Mu and Wei, PLOS CB,2018

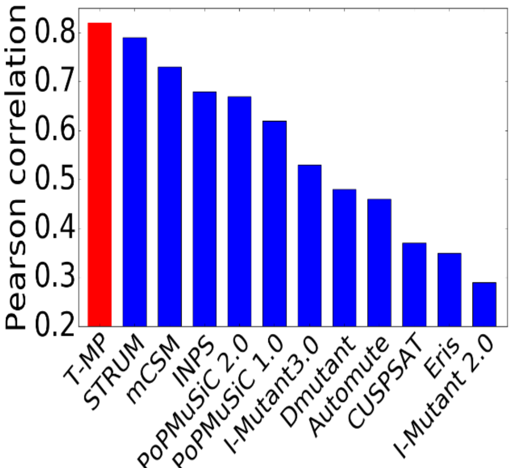
Prediction RMSD of LogP (Star set)

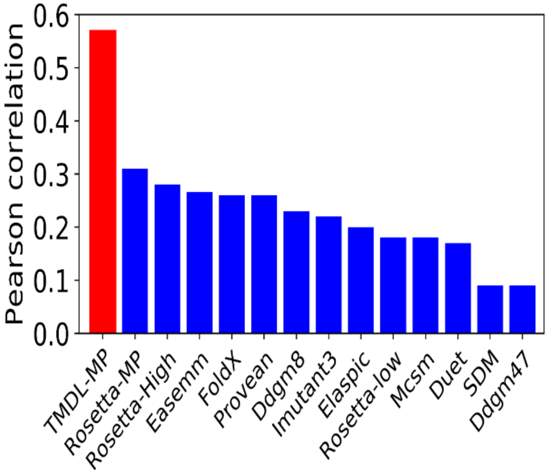

Wu and Wei, JCC,2018

Predicting mutations on 2648 globular proteins

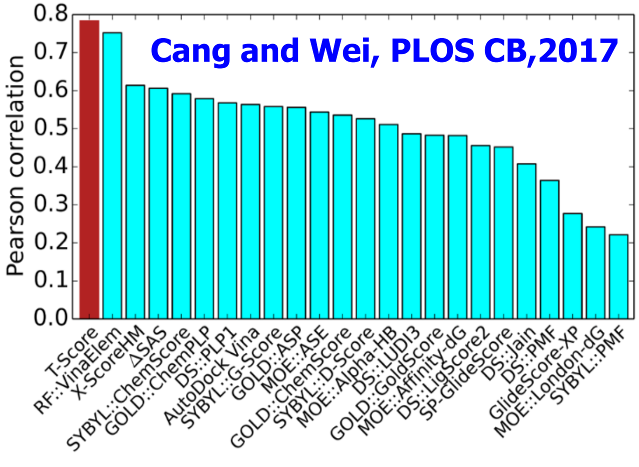
Predicting mutations on 223 membrane proteins

(Cang and Wei, Bioinformatics, 2017)



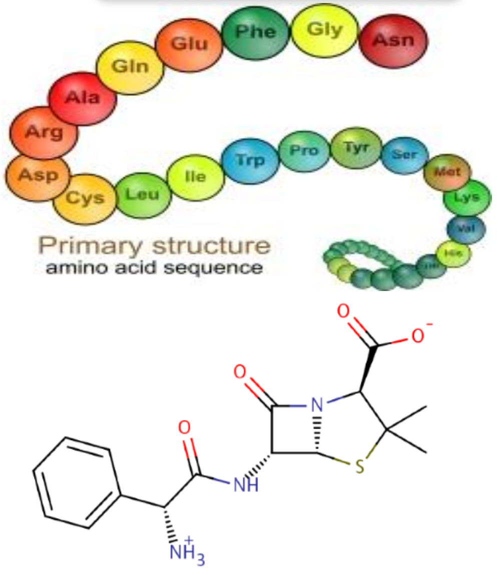


Binding affinity prediction of PDBBind v2013 core set of 195 protein-ligand complexes

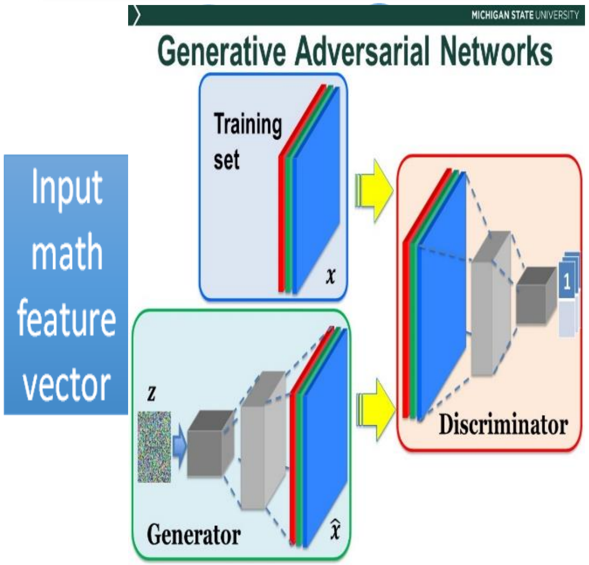

Cang and Wei, PLOS CB,2017

Drug Design Data Resource (D3R) Grand Challenge

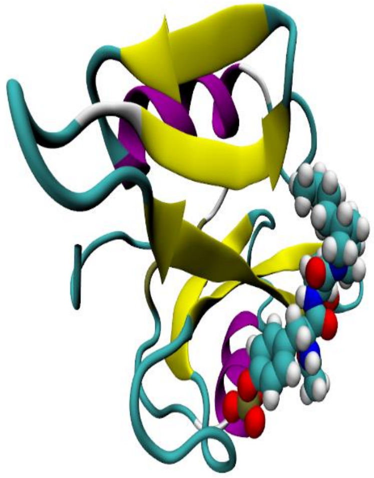
Given data



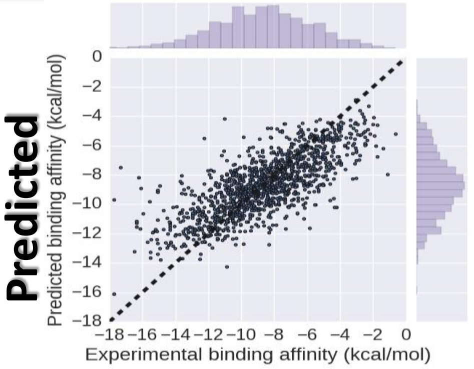
Math based GAN


MICHIGAN STATE UNIVERSITY
Generative Adversarial Networks
Input math feature vector
Training set
x
z
Generator
x̂
1
Discriminator

Predicted complex

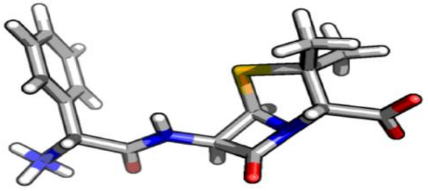


Final predictions to be compared with experiments

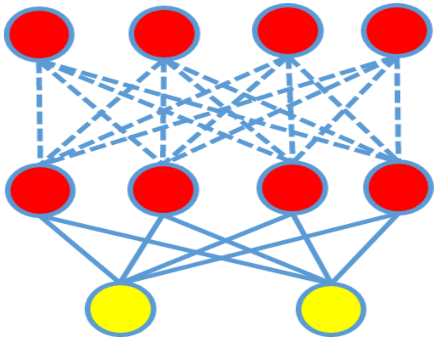


Predicted

Experimental

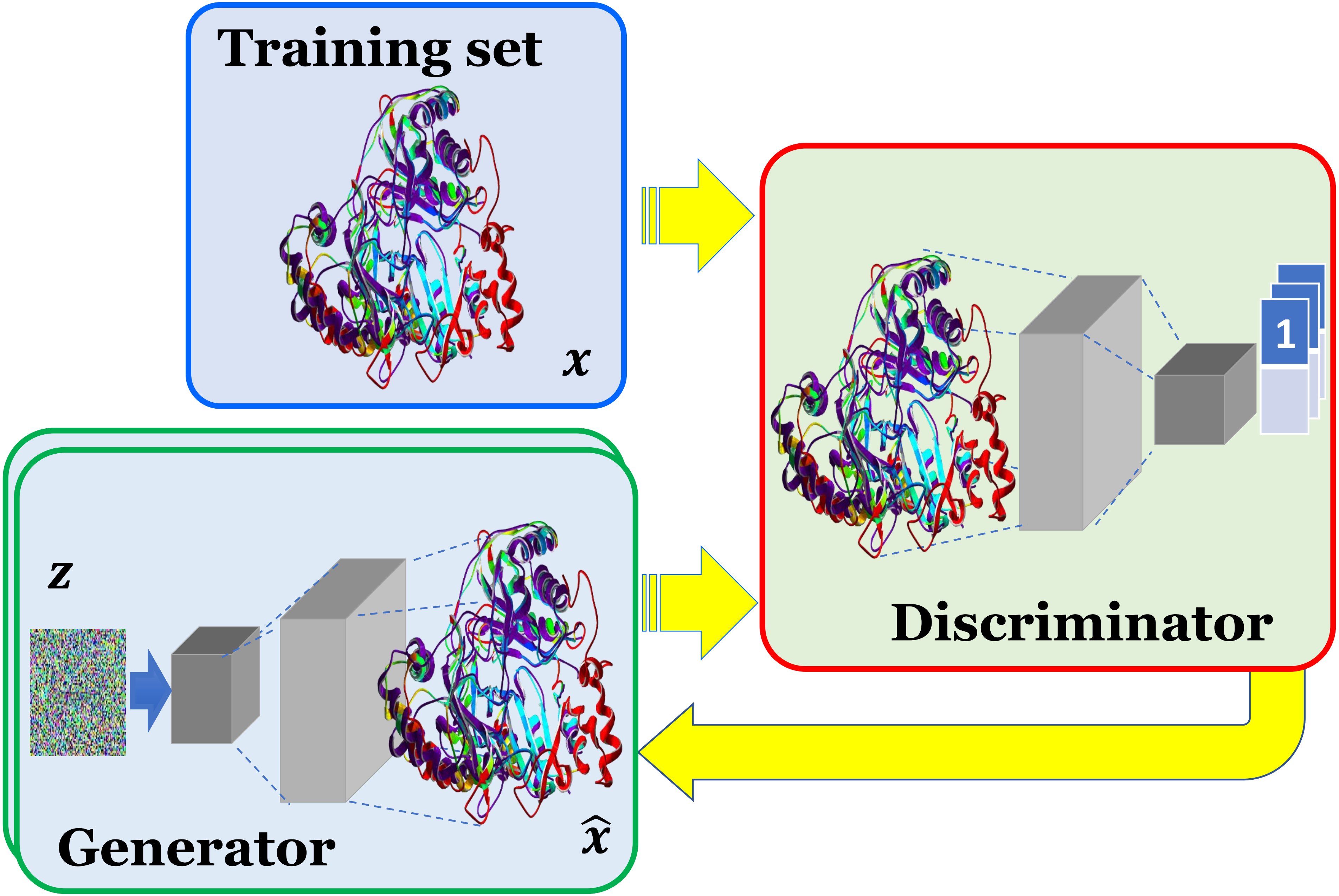


Drug pose



(Nguyen et al, JCAMD, 2018)

Generative Adversarial Networks for Drug Design



Training set

x

Discriminator

z

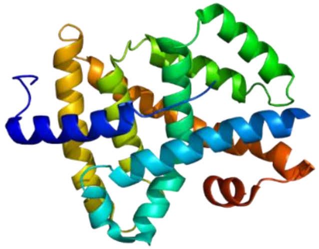
Generator

$\hat{x}$

D3R Grand Challenge 2 (2016-2017)

Given: Farnesoid X receptor (FXR) and 102 ligands

Tasks: Dock 102 ligands to FXR, and predict their poses, binding free energies and energy ranking



Stage 1

Pose Predictions (partials)

Scoring (partials)

Free Energy Set 1 (partials)

Free Energy Set 2 (partials)

Stage 2

Scoring (partials)

Free Energy Set 1 (partials)

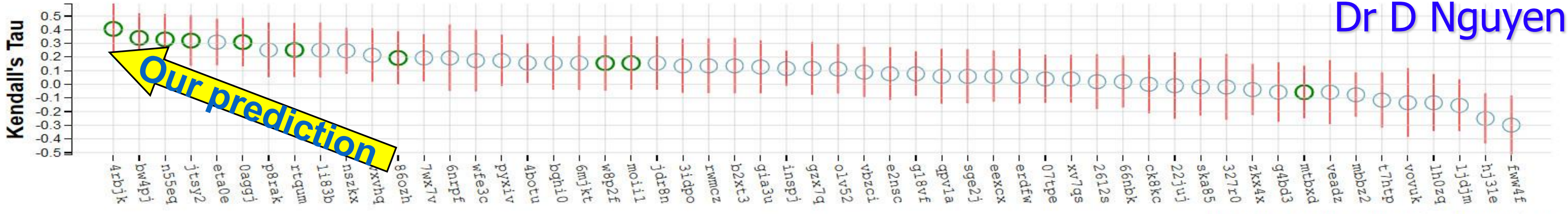
Free Energy Set 2 (partials)

Dr D Nguyen

(Nguyen et al, JCAMD, 2018)

Grand Challenge 2

Free Energy Set 1 (Stage 2) - Kendall's Tau



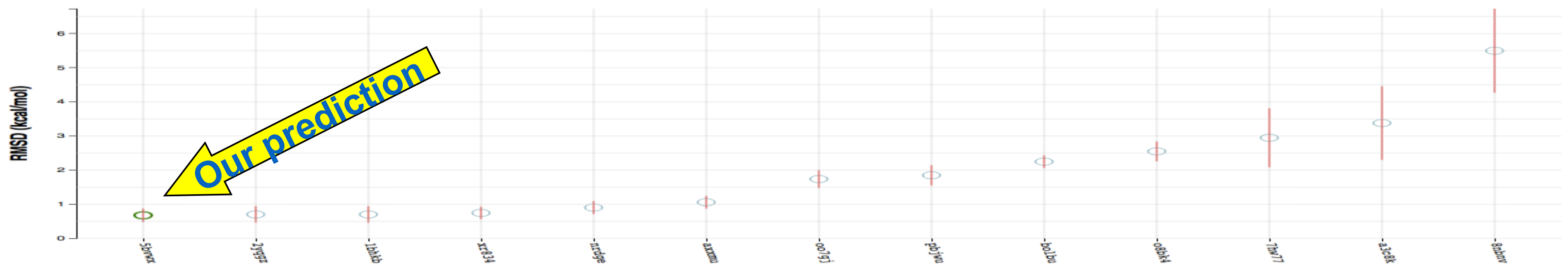
Receipt ID

Filled circle indicates an incomplete set of predictions

Green circle indicates your predictions (requires login)

Grand Challenge 2

Free Energy Set 1 (Stage 1) - RMSD



Receipt ID

Green circle indicates your predictions (requires login)

D3R Grand Challenge 3 (2017-2018)

(Nguyen et al, JCAMD, 2018)

Pose Prediction

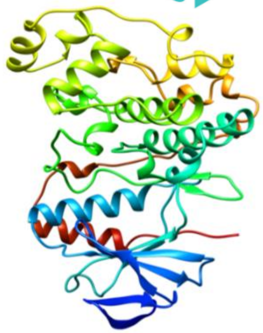
Cathepsin Stage 1A

Pose Predictions (partials)

Cathepsin Stage 1B

Pose Prediction

Cathepsin S



Kinase: p38-α

Affinity Rankings excluding Kds > 10 μM

Cathepsin Stage 1

Scoring (partials)

Free Energy Set

VEGFR2

Scoring (partials)

JAK2 SC3

Scoring

Free Energy Set

Cathepsin Stage 2

Scoring (partials)

Free Energy Set

JAK2 SC2

Scoring (partials)

TIE2

Scoring

Free Energy Set 2

p38-α

Scoring

ABL1

Scoring (partials)

Active / Inactive Classification

VEGFR2

Scoring (partials)

JAK2 SC3

Scoring

Free Energy Set

JAK2 SC2

Scoring (partials)

TIE2

Scoring (partials)

Free Energy Set 1

p38-α

Scoring (partials)

ABL1

Scoring (partials)

Affinity Rankings for Cocrystalized Ligands

Cathepsin Stage 1

Scoring (partials)

Free Energy Set

Cathepsin Stage 2

Scoring (partials)

Free Energy Set

Zixuan Cang

Dr D Nguyen

D3R Grand Challenge 4 (2018-2019)

Pose Predictions

BACE Stage 1A

Pose Predictions (Partials) 2/3 🥇 2/3 🥈

BACE Stage 1B

Pose Prediction (Partials) 2 /2 🥈 1/2 🥉

Affinity Predictions

Cathepsin Stage 1

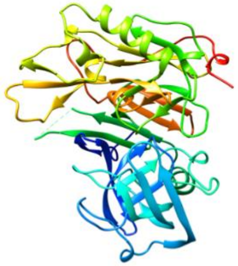
Combined Ligand and Structure Based Scoring 2/5 🥇 2/3 🥈 2/4 🥉

Dr. Kaifu Gao Dr. D Nguyen

Ligand Based Scoring (No participation)

Structure Based Scoring 2/4 🥇 3/3 🥈 3/3 🥉

Free Energy Set 1/7 🥇 1/7 🥈 2/5 🥉



BACE Stage 1

Combined Ligand and Structure (No participation)

Ligand Based Scoring (Partials) (No participation)

Structure Based Scoring (Partials)(No participation)

Free Energy Set (No participation)

BACE Stage 2

Combined Ligand and Structure

Ligand Based Scoring (No participation)

Structure Based Scoring (Partials)

Free Energy Set 3/4 🥈 1/4 🥉

Algebraic topology

Differential topology

Geometric topology

Differential equation

Algebraic graph

Structural graph

Exyreme graph

Geometric algebra

Number theory

Algebraic geometry

Differential geometry

Distance geometry

Lie algebra

Biology became microscopic (i.e., molecular) in 1960s and added an omics dimension around the dawn of the millennium.

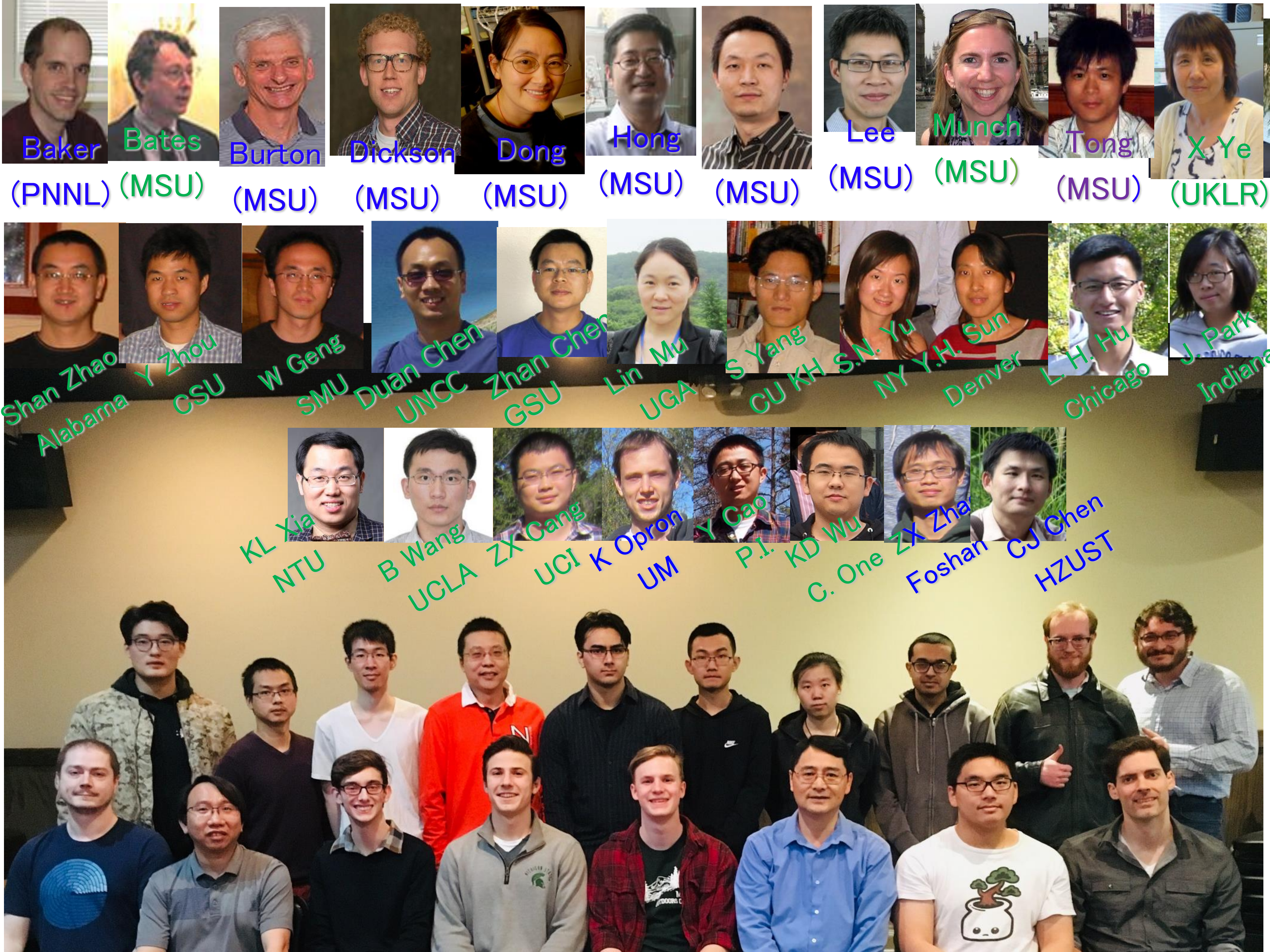
Driving by mathematics, biology is transforming from qualitative, phenomenological and descriptive to quantitative, predictive and analytical.

The last frontier of science is biology, while the last frontier of biology is mathematics.

Complex analysis

Real analysis

Stochastic analysis


Baker
(PNNL)
Bates
(MSU)
Burton
(MSU)
Dickson
(MSU)
Dong
(MSU)
Hong
(MSU)
(MSU)
Lee
(MSU)
Munch
(MSU)
Tong
(MSU)
X Ye
(UKLR)
Shan Zhao
Alabama
Y Zhou
CSU
W Geng
SMU
Duan Chen
UNCC
Zhan Chen
GSU
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