Hypergraph based Persistent Cohomology(HPC) for molecular representations in drug design

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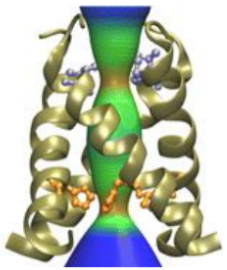
2020-12-16

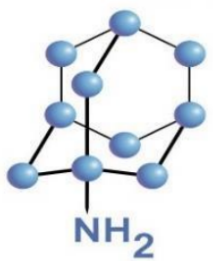
Outline

Drug design and discovery

General flow

1) Disease identification (physiology)
2) Target hypothesis (biochem./mole. biol.)
3) Virtual screening: 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 test
7) Optimize drug's efficacy, pharmacokinetics, and pharmacodynamics properties (quantitative systems pharmacology)





RCSB PDB
PROTEIN DATA BANK
171916 Biological Macromolecular Structures Enabling Breakthroughs in Research and Education

GEO Gene Expression Omnibus

GenBank
Celebrates 25 years of service

nature
International weekly journal of se
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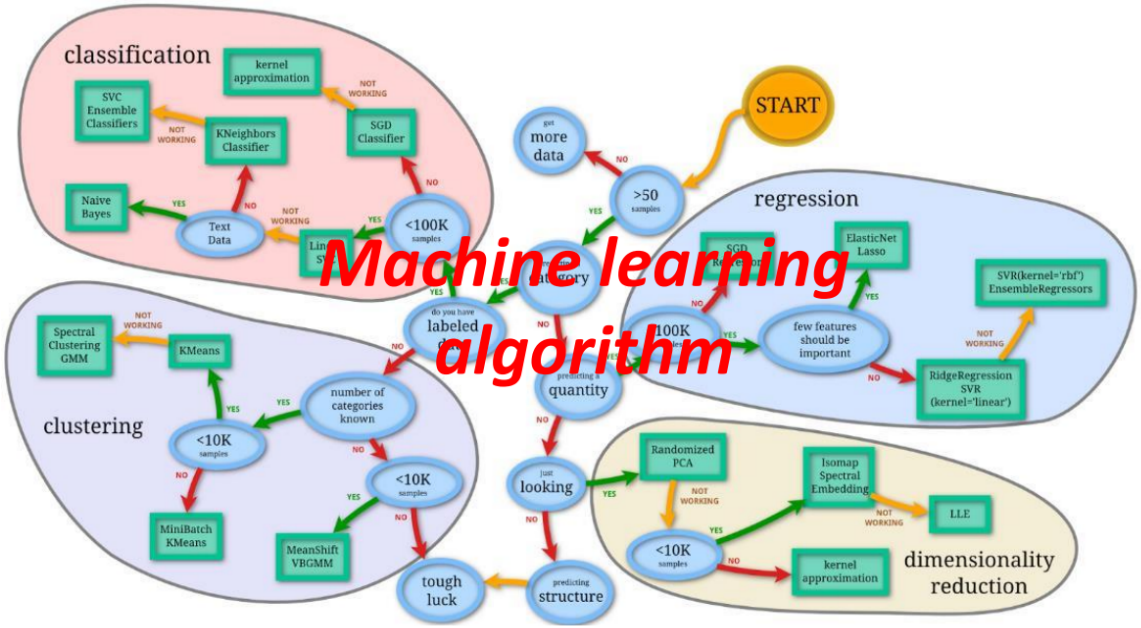
NATURE | NEWS

Gene data to hit milestone

With close to one million gene-expression data sets

How to deal with big data ?



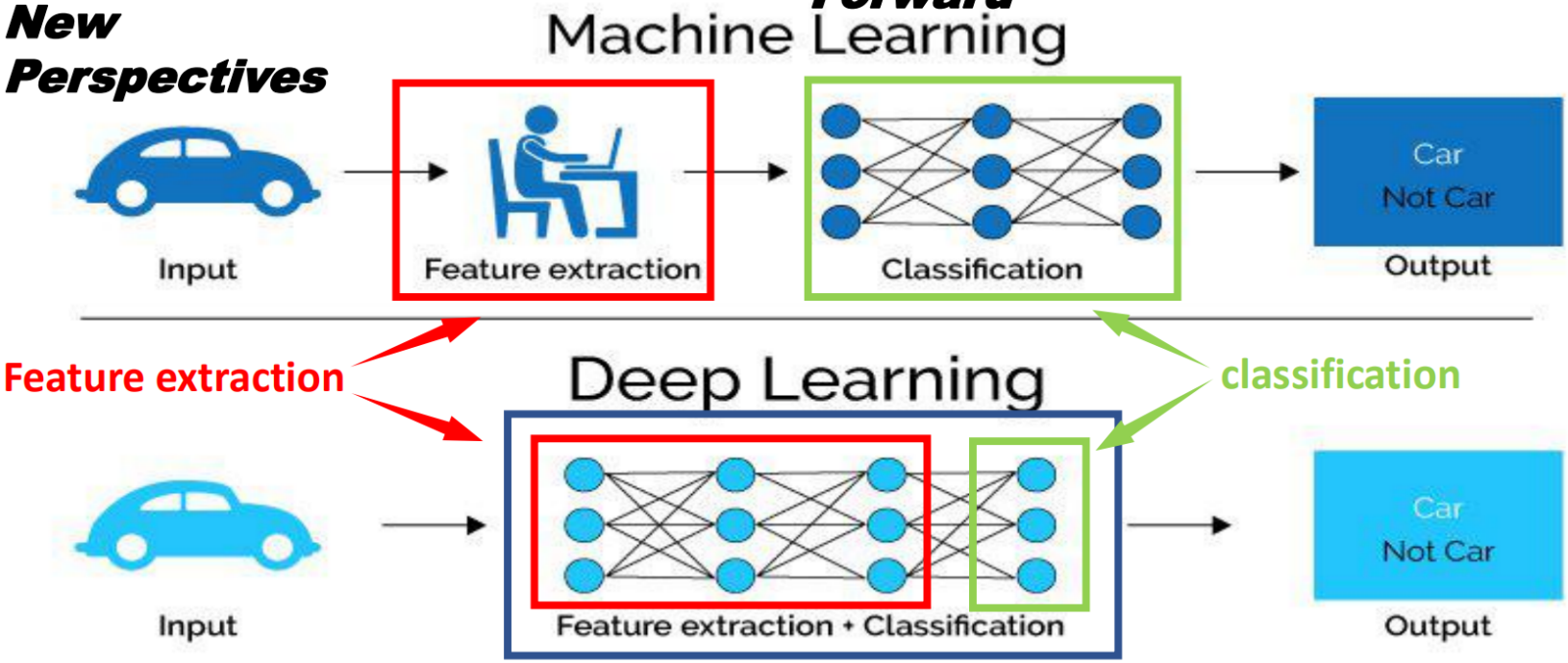
Feature extraction and feature learning

"The success of machine learning algorithms generally depends on data representation..."

Y. Bengio, etc,"Representation Learning: A Review and New Perspectives

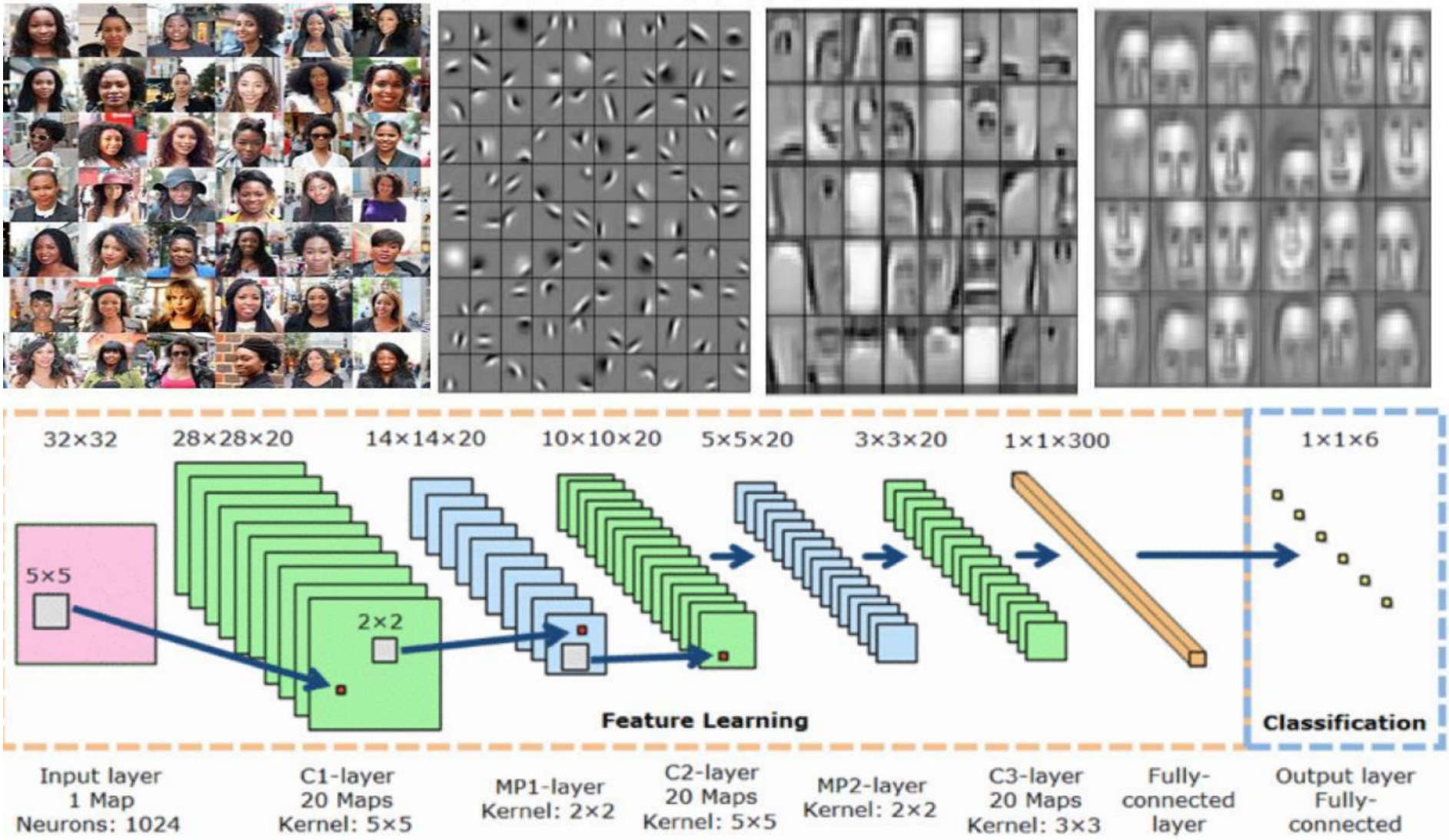
"The deep learning research aims at discovering learning algorithms that discover multiple levels of distributed representations..."

Y. Bengio, "Deep Learning of Representations: Looking Forward



Deep learning

Fukushima (1980) – Neo-Cognitron; LeCun (1998) – Convolutional Neural Networks (CNN);...



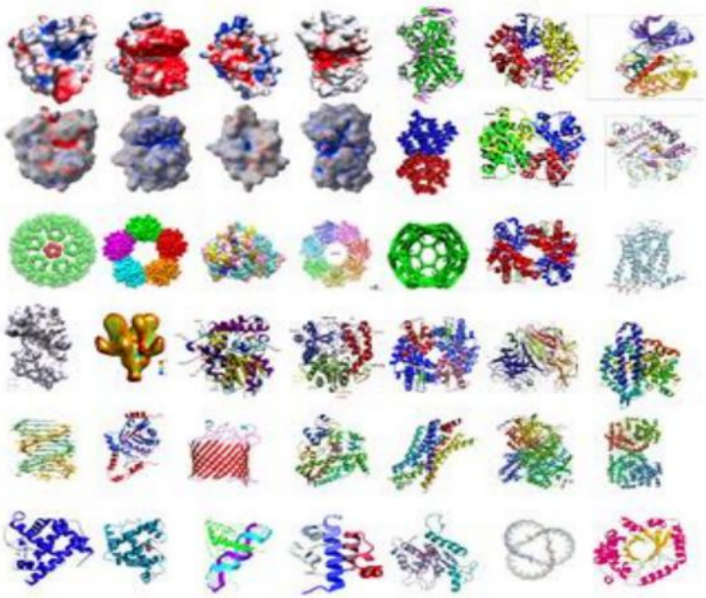
How to do deep learning for 3D biomolecular data?

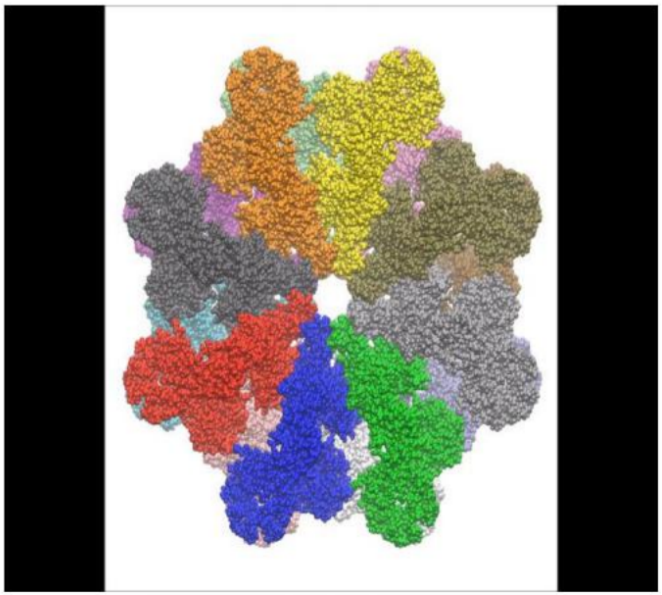
Obstacles for deep learning of 3D biomolecules:

- **Geometric dimensionality: R^{3N}, where N~5500 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: biochemistry & biophysics**

Solution:

- **Dimensionality reduction & unification (scalability)**
- **Topological simplification/geometric simplification/graph theory simplification**

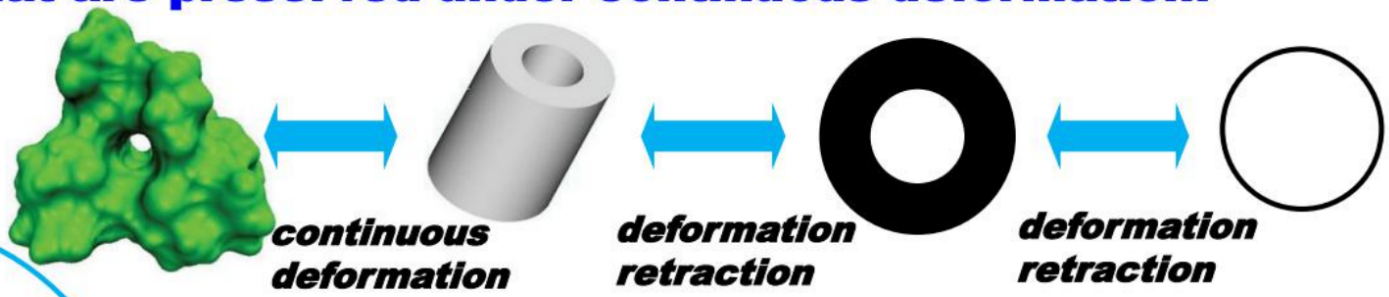


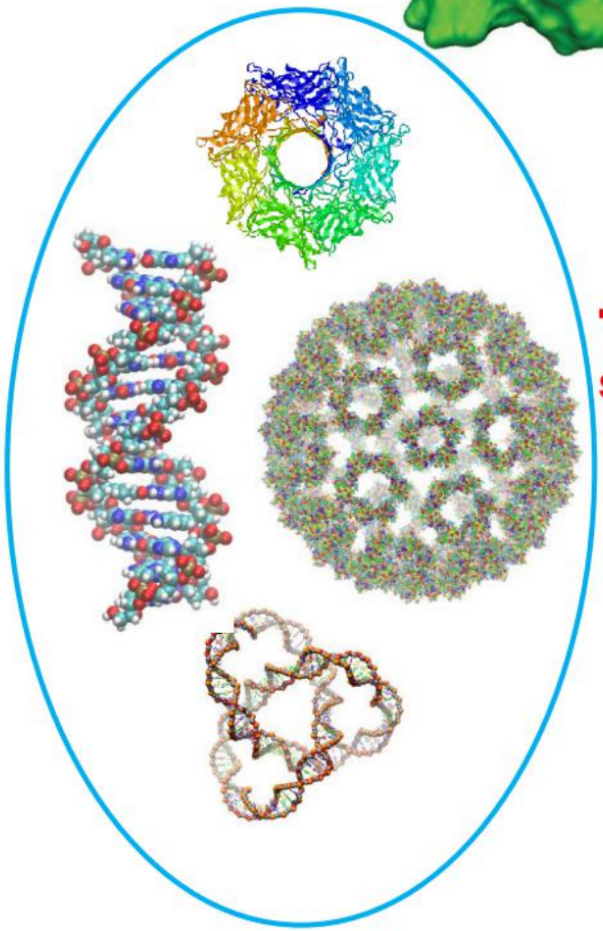


Topological invariant--Betti number

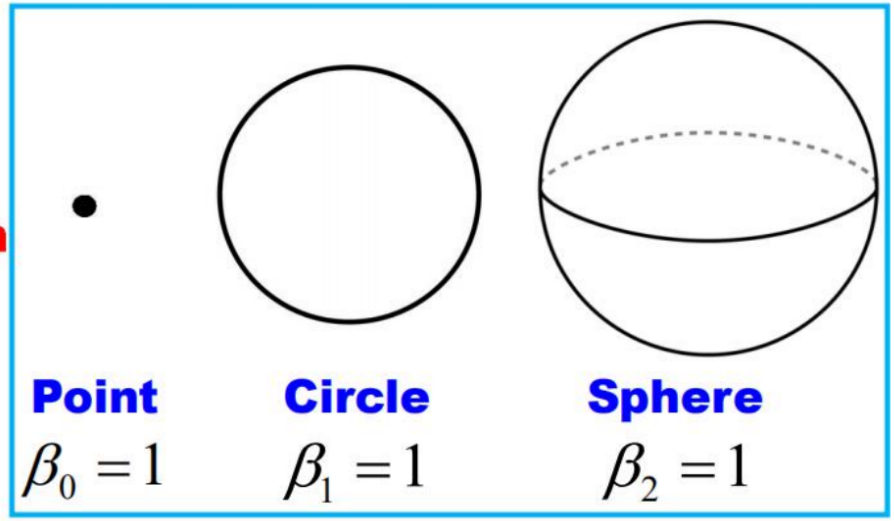
Properties that are preserved under continuous deformation!

Homotopy equivalent:





Topological simplification

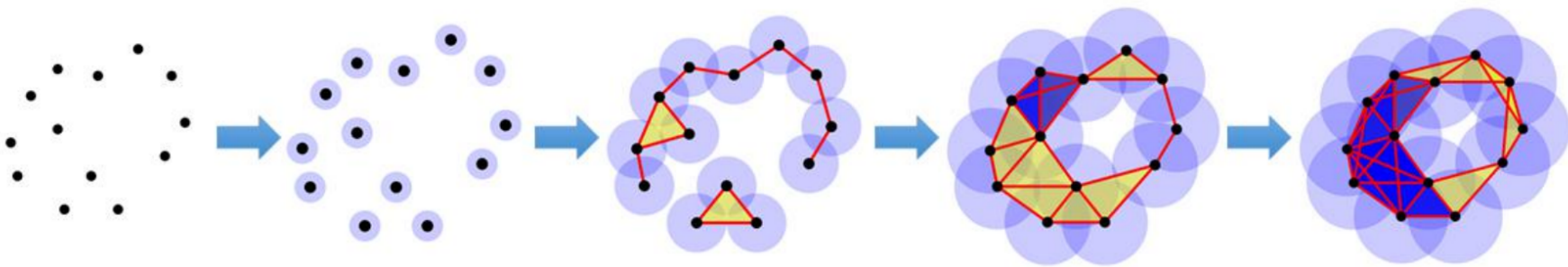


β_0 **is the number of connected components**

β_1 **is the number of tunnels or circles**

β_2 **is the number of voids or cavities**

Topological data analysis -- *Persistent homology*



filtration

Chain group: $C_n(K, Z_p)$

Boundary operator:

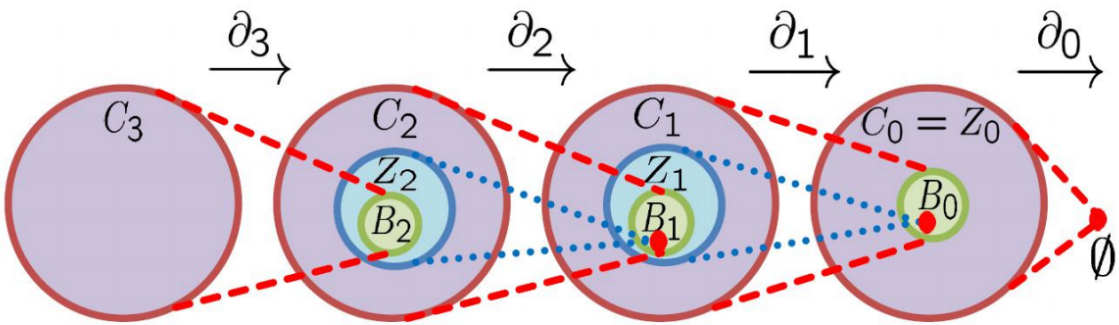
$$\partial_n(\sigma_n) = \sum_{i=0}^{n} (-1)^i \{v_0, v_1, \cdots, \hat{v}_i, \cdots v_n\}$$

$$Z_n = Ker\partial_n$$

$$B_n = \mathrm{Im}\,\partial_{n+1}$$

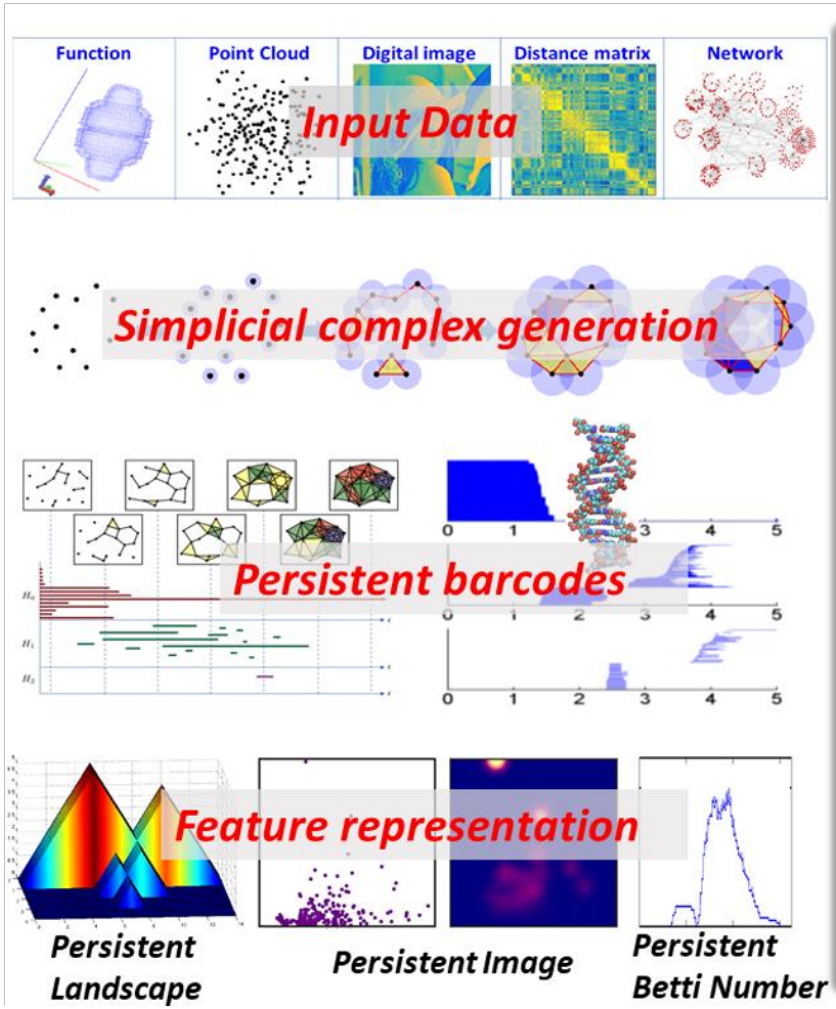
$$H_n = Z_n / B_n$$

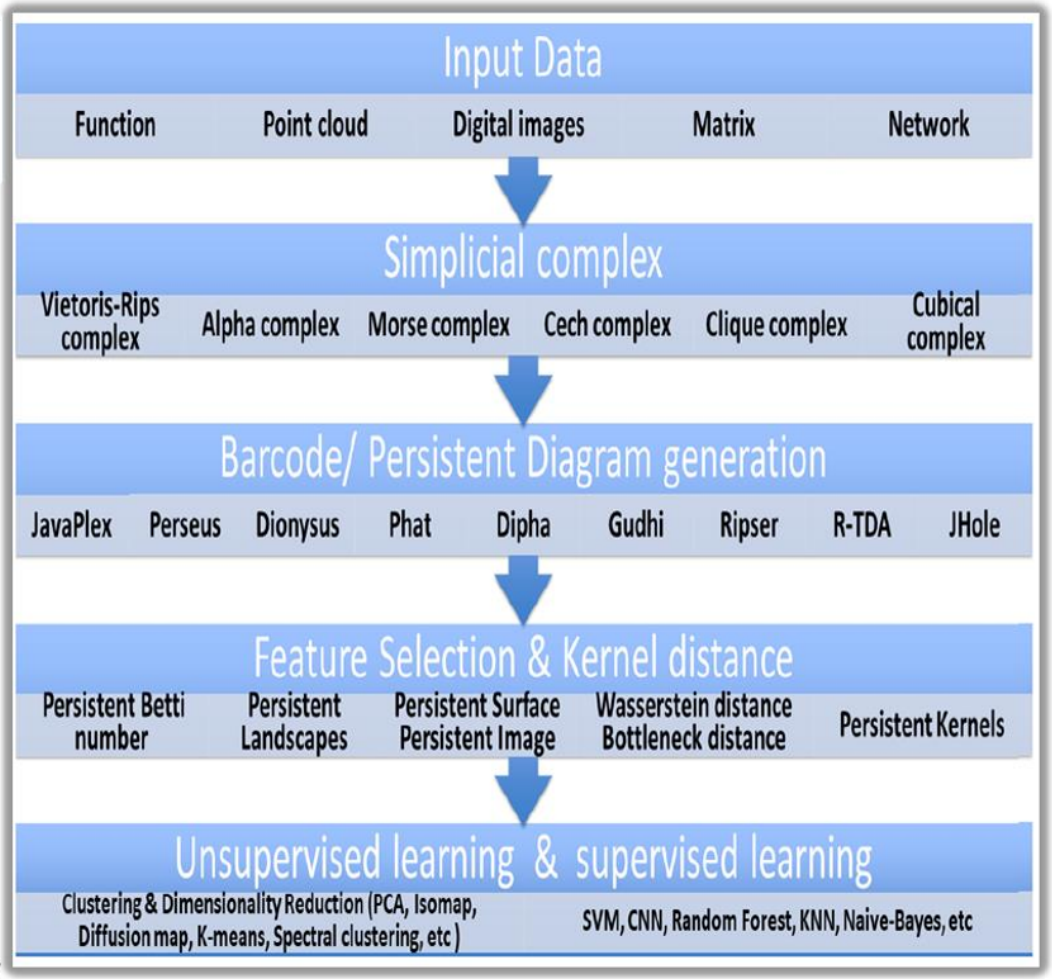
$$\beta_n = rank(H_n)$$



TDA based machine learning models

(Pun, Xia and Lee, arXiv, 2019)

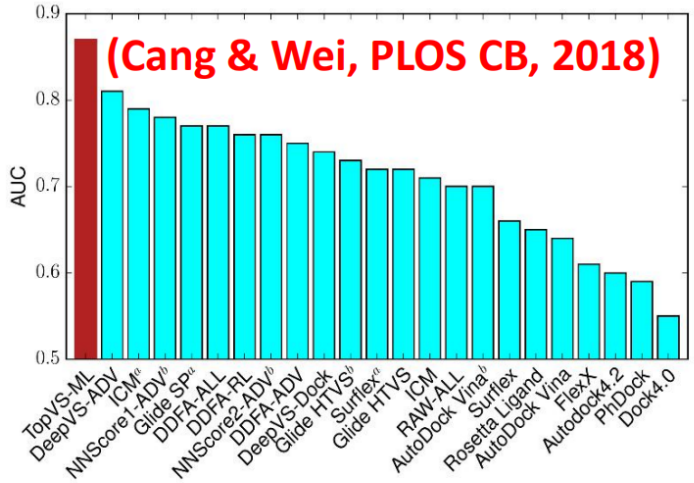


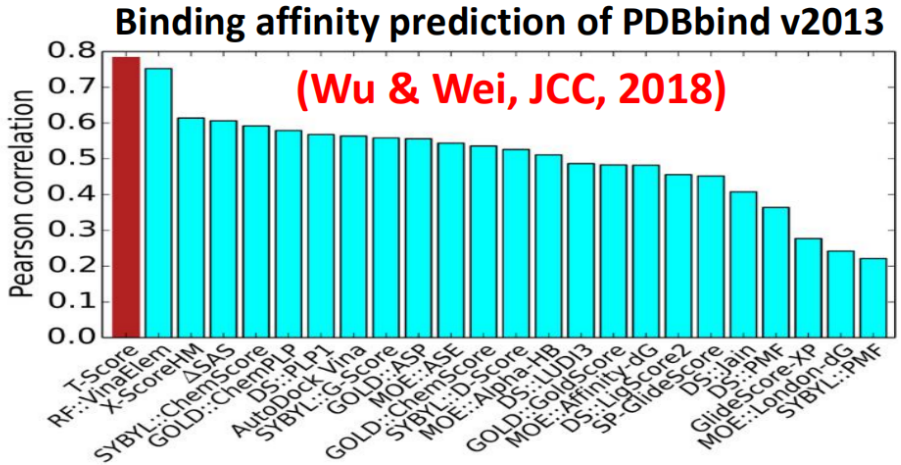


Recent progress in TDA based drug design

Guowei Wei
MSU, USA

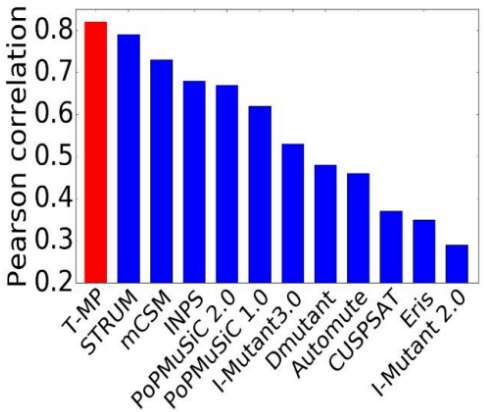
DUD database 128374 protein-ligand/decoy pairs

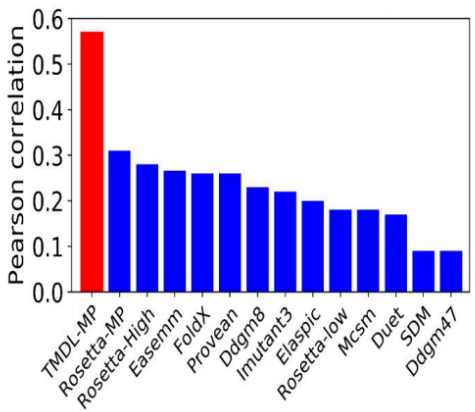




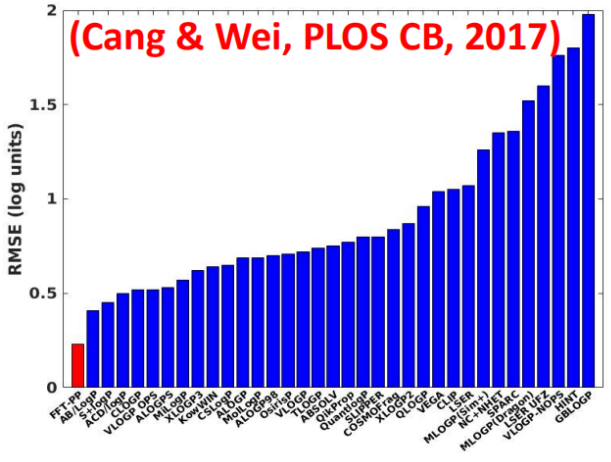
Prediction correlations for 2648 mutations on globular proteins

(Cang & Wei, PLOS CS, 2017)



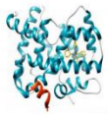


Prediction RMSD of logP(star set)



Recent progress in TDA based drug design

D3R Grand Challenge 2



Stage 1

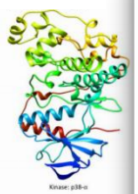
Pose Predictions (partials)
Scoring (partials)
Free Energy Set 1 (partials)
Free Energy Set 2 (partials)

Stage 2

Scoring (partials)
Free Energy Set 1 (partials)
Free Energy Set 2 (partials)

Wei Team's performance at D3R Grand Challenge

D3R Grand Challenge 3 (2017-2018)



Pose Prediction

Cathepsin Stage 1A
Pose Predictions (partials)

Cathepsin Stage 1B
Pose Prediction

Affinity Rankings excluding Kds > 10 μM

Cathepsin Stage 1
Scoring (partials)
Free Energy Set

Cathepsin Stage 2
Scoring (partials)
Free Energy Set

VEGFR2
Scoring (partials)

JAK2 SC2
Scoring (partials)

p38-α
Scoring

JAK2 SC3
Scoring
Free Energy Set

TIE2
Scoring
Free Energy Set 2

ABL1
Scoring (partials)

Active / Inactive Classification

VEGFR2
Scoring (partials)

JAK2 SC2
Scoring (partials)

p38-α
Scoring (partials)

JAK2 SC3
Scoring
Free Energy Set

TIE2
Scoring (partials)
Free Energy Set 1

ABL1
Scoring (partials)

Affinity Rankings for Cocrystalized Ligands

Cathepsin Stage 1
Scoring (partials)
Free Energy Set

Cathepsin Stage 2
Scoring (partials)
Free Energy Set

D3R Grand Challenge 4 (2018-2019)

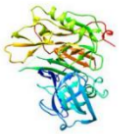
Pose Predictions

BACE Stage 1A
Pose Predictions (Partials) 1/2 3/3

BACE Stage 1B
Pose Prediction (Partials) 2/2 1/2

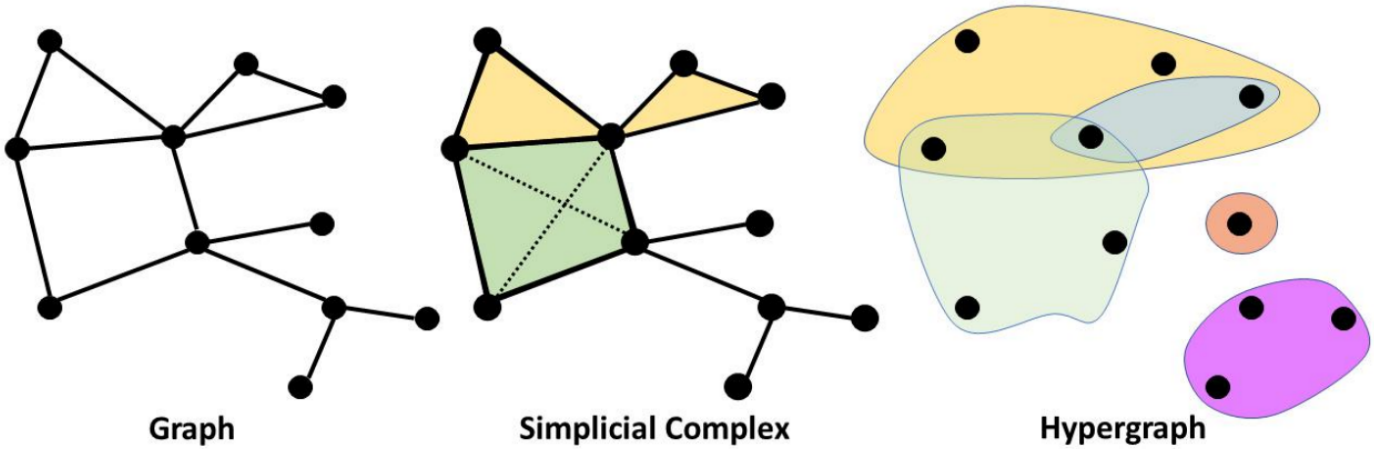
Affinity Predictions

Cathepsin Stage 1
Combined Ligand and Structure Based Scoring 2/5 2/3 2/4
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)

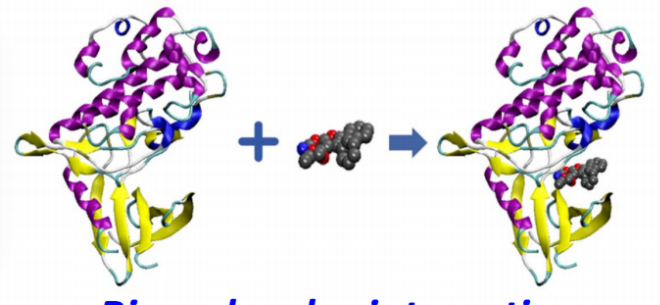
BACE Stage 2
Combined Ligand and Structure
Ligand Based Scoring (No participation)
Structure Based Scoring (Partials)
Free Energy Set 3/4 1/4



hypergraph is a generalization of simplicial complex,

how about doing persistence by hypergraph?

Recent progress in hypergraph



Biomolecular interactions characterized by hypergraph

Collaborator
Jie Wu
Math, HEBNU

The embedded homology of hypergraphs and applications (Bressan, Li, Ren & Wu, 2016)

Operators on random hypergraphs and random simplicial complexes (Ren, Wu & Wu, 2017)

A discrete Morse Theory for hypergraphs (Wu, Ren, Wang & Wu, 2018)

Hodge Decompositions for Weighted Hypergraphs (Ren, Wu & Wu, 2018)

Stability of persistent homology for hypergraphs (Ren & Wu, 2020)

Biomolecular hypergraph representation

The key idea is to describe atom interaction relations as hyperedges.

Take the protein-ligand interactions as an example. We denote the set of protein atoms, the set of ligand atoms, the hypergraph and the vertex set of the hypergraph as $V_P = \{v_i; i = 1, 2, ..., N_p\}$, $V_L = \{v_j; j = 1, 2, ..., N_l\}$, $\mathcal{H}$ and $V_{\mathcal{H}}$ respectively.

1. For the vertex set, we take $V_{\mathcal{H}} = V_L \cup V_P$
2. For the hyperedge set, we define an n-hyperedge in $\mathcal{H}$ as

$$\sigma^n = \begin{cases} \{\mathbf{v}_0, \mathbf{v}_1, ..., \mathbf{v}_n\}; \exists i, j, \mathbf{v}_i \in V_P, \mathbf{v}_j \in V_L, & n > 0 \\ \{\mathbf{v}_0\}; \mathbf{v}_0 \in V_{\mathcal{H}}, & n = 0. \end{cases} \tag{1}$$

For simplicity, we denote the hypergraph $(\mathcal{H}, V_{\mathcal{H}})$ as $\mathcal{H}$.

Example

Remark: for each n-hyperedge(n>0), there must be two vertices come from different molecules.

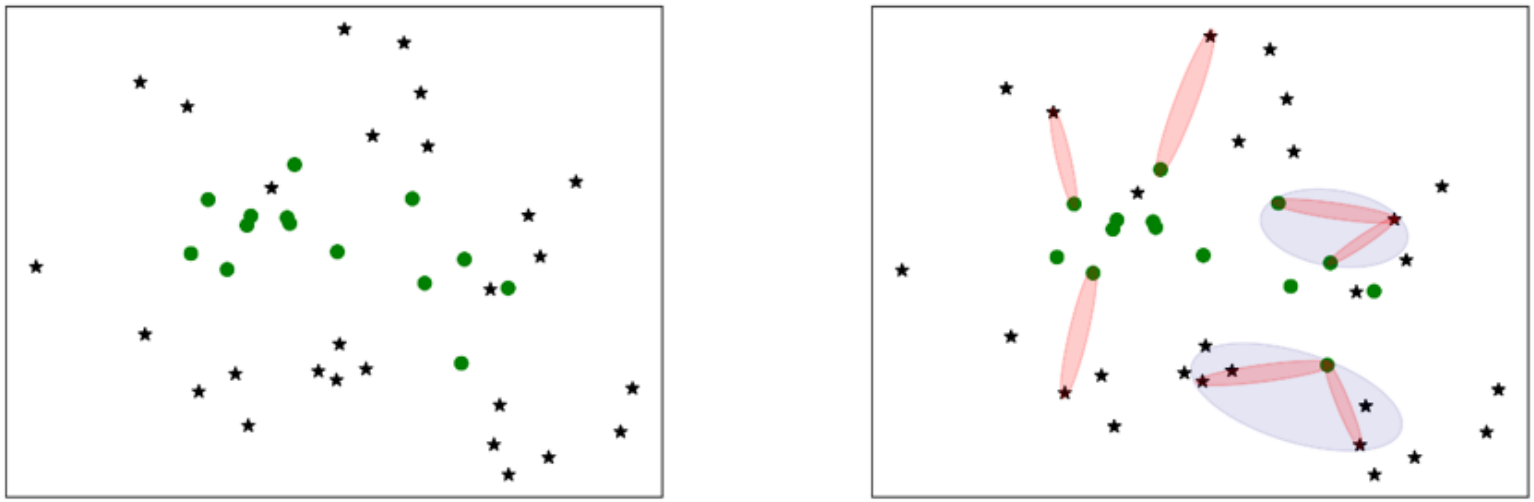


Figure: C-C pair of PDBID 3P2E with cutoff 5

Hypergraph filtration

The key point of all the persistent models is the filtration process. Here we assign nondecreasing filtration values for all the hyperedges, then the hypergraph together with these filtration values will naturally form a filtration process.

For the protein-ligand interactions, we use two steps to build the filtration.

1. we define interactive distance between two atoms $\mathbf{v}_i$ and $\mathbf{v}_j$ as

$$d(\mathbf{v}_i, \mathbf{v}_j) = \begin{cases} \|\mathbf{v}_i - \mathbf{v}_j\|, & \text{if } \mathbf{v}_i \in \mathbf{V}_P, \mathbf{v}_j \in \mathbf{V}_L \text{ or } \mathbf{v}_i \in \mathbf{V}_L, \mathbf{v}_j \in \mathbf{V}_P \\ g(\mathbf{v}_i, \mathbf{v}_j), & \text{otherwise.} \end{cases} \tag{2}$$

2. using the idea of Rips complex, the filtration value for a hyperdege $\sigma^n = \{\mathbf{v}_0, \mathbf{v}_1, ..., \mathbf{v}_n\}$ is defined as,

$$f(\sigma^n) = \begin{cases} \max_{0 \le i < j \le n} d(\mathbf{v}_i, \mathbf{v}_j), & n > 0 \\ 0, & n = 0. \end{cases} \tag{3}$$

Remark: different $g(v_i, v_j)$ can result in different filtration processes. I will give more explanation later. Here, we use this formular

$$g(\mathbf{v}_i, \mathbf{v}_j) = \begin{cases} \max_{\mathbf{v}_k \in V_P, \{\mathbf{v}_i, \mathbf{v}_j, \mathbf{v}_k\} \in \mathcal{H}_2} \{d(\mathbf{v}_i, \mathbf{v}_k), d(\mathbf{v}_j, \mathbf{v}_k)\}, & \text{if } \mathbf{v}_i, \mathbf{v}_j \in \mathbf{V}_L \\ \max_{\mathbf{v}_k \in V_L, \{\mathbf{v}_i, \mathbf{v}_j, \mathbf{v}_k\} \in \mathcal{H}_2} \{d(\mathbf{v}_i, \mathbf{v}_k), d(\mathbf{v}_j, \mathbf{v}_k)\}, & \text{if } \mathbf{v}_i, \mathbf{v}_j \in \mathbf{V}_P \end{cases} \tag{4}$$

Example

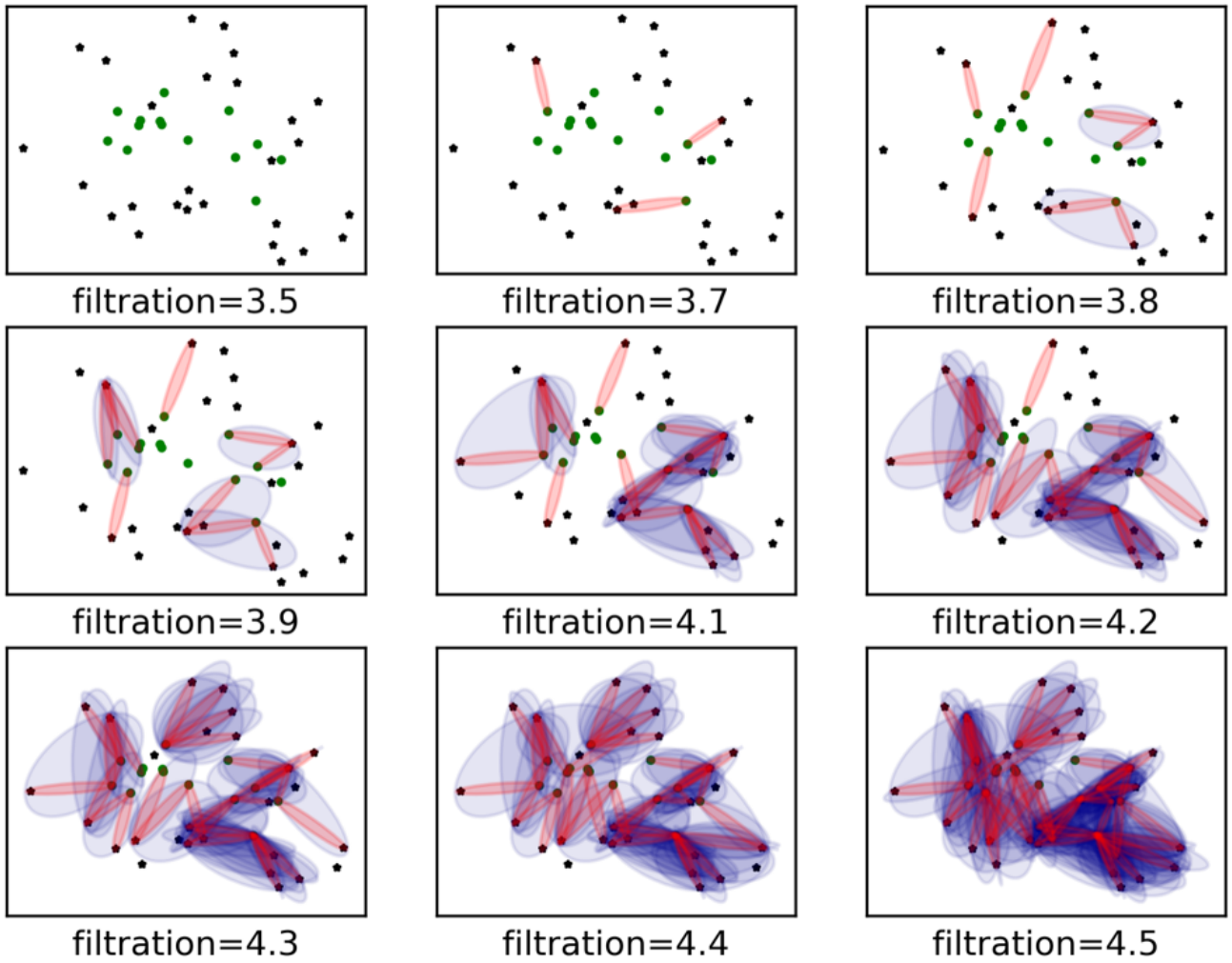


Figure: Hypergraph filtration for C-C pair of PDBID 3P2E

(Co)homology of the hypegraph

Given a hypergraph $\mathcal{H}$, its associated simplicial complex $K_{\mathcal{H}}$ is defined in 1991. In 2016, a more general definition — the embedded homology is proposed.

Here, we consider the embedded homology and corresponding persistent homology, for our hypergraph models.

Further, to incorporate the information that persistent homology cannot capture, we propose the hypergraph based persistent cohomology(HPC) and hypergraph based weighted persistent cohomology(HWPC).

Embedded homology of hypergraph

Definition (infimum chain complex)

Given a hypergraph $\mathcal{H}$, the infimum chain complex of $\mathcal{H}$ with coefficient R is defined as

$$Inf_n(\mathcal{H}, R) = \sum \{C_n |\ C_\star \text{ is a subchain complex of } R((K_{\mathcal{H}})_\star) \text{ and } C_n \subset R(\mathcal{H}_n)\}$$

which is the largest subchain complex of the chain complex of $K_{\mathcal{H}}$ that is contained in the graded modules $R(\mathcal{H}_\star)$

Definition (supremum chain complex)

Given a hypergraph $\mathcal{H}$, the supremum chain complex of $\mathcal{H}$ with coefficient R is defined as

$$Sup_n(\mathcal{H}, R) = \bigcap \{C_n |\ C_\star \text{ is a subchain complex of } R((K_{\mathcal{H}})_\star) \text{ and } R(\mathcal{H}_n) \subset C_n\}$$

which is the smallest subchain complex of the chain complex of $K_{\mathcal{H}}$ that contains $R(\mathcal{H}_\star)$ as a graded modules.

Proposition

Given a hypergraph $\mathcal{H}$, the infimum chain complex of $\mathcal{H}$ with coefficient R is given by

$$Inf_n(\mathcal{H}, R) = R(\mathcal{H}_n) \cap {\partial_n}^{-1}(R(\mathcal{H}_{n-1}))$$

Proposition

Given a hypergraph $\mathcal{H}$, the supremum chain complex of $\mathcal{H}$ with coefficient R is given by

$$Sup_n(\mathcal{H}, R) = R(\mathcal{H}_n) + \partial_{n+1}(R(\mathcal{H}_{n+1}))$$

Proposition

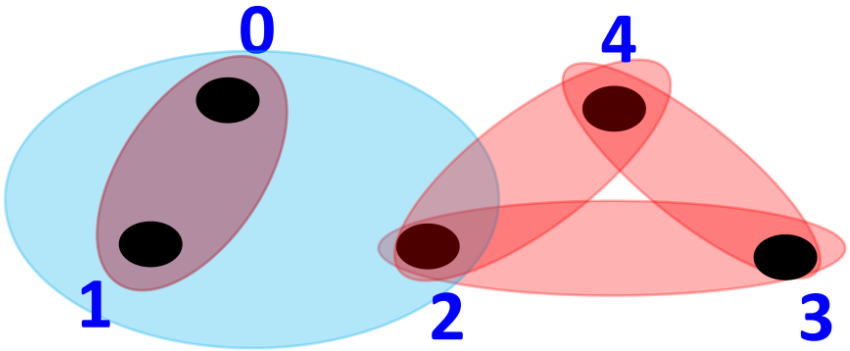
Given a hypergraph $\mathcal{H}$, the homology of the infimum chain complex of and supremum chain complex of $\mathcal{H}$ with coefficient R are isomorphic.

Definition (Hypergraph embedded homology)

Given a hypergraph $\mathcal{H}$, the n-th embedded homology of $\mathcal{H}$ with coefficient R is defined as

$$H_n(\mathcal{H}, R) = H_n(Sup_\star(\mathcal{H}, R)) = H_n(Inf_\star(\mathcal{H}, R))$$

$$C_0 = Z\{\{0\},\{1\},\{2\},\{3\},\{4\}\}$$
$$C_1 = Z\{\{0,1\},\{2,3\},\{2,4\},\{3,4\}\}$$
$$C_2 = Z\{\{0,1,2\}\}$$
$$A_0 = Z\{\{0\},\{1\},\{2\},\{3\},\{4\}\}$$
$$A_1 = Z\{\{0,1\},\{0,2\},\{1,2\},\{2,3\},\{2,4\},\{3,4\}\}$$
$$A_2 = Z\{\{0,1,2\}\}$$
$$\rightarrow A_3 \xrightarrow{\partial_3} A_2 \xrightarrow{\partial_2} A_1 \xrightarrow{\partial_1} A_0$$
$$S_n = C_n + \partial_{n+1}(C_{n+1}), I_n = C_n \cap \partial_n^{-1}(C_{n-1})$$



$$I_0 = Z\{\{0\},\{1\},\{2\},\{3\},\{4\}\}$$
$$I_1 = Z\{\{0,1\},\{2,3\},\{2,4\},\{3,4\}\}$$
$$I_2 = 0$$
$$S_0 = Z\{\{0\},\{1\},\{2\},\{3\},\{4\}\}$$
$$S_1 = Z\{\{0,1\},\{2,3\},\{2,4\},\{3,4\},\partial\{0,1,2\}\}$$
$$S_2 = Z\{\{0,1,2\}\}$$

$$H_0^s = Ker(\partial_0^s)/\mathrm{Im}(\partial_1^s)$$
$$= S_0/\mathrm{Im}(\partial_1^s)$$
$$= Z\{\{0\},\{1\},\{2\},\{3\},\{4\}\}/Z\{\{1\}-\{0\},\{3\}-\{2\},\{4\}-\{2\},\{4\}-\{3\}\}$$
$$= I_0/\mathrm{Im}(\partial_1^i)$$
$$= Ker(\partial_0^i)/\mathrm{Im}(\partial_1^i)$$
$$= H_0^i$$

$$H_1^s = Ker(\partial_1^s)/\mathrm{Im}(\partial_2^s)$$
$$= Z\{\{3,4\}-\{2,4\}+\{2,3\},\partial\{0,1,2\}\}/Z\{\partial\{0,1,2\}\}$$
$$= Z\{\{3,4\}-\{2,4\}+\{2,3\}\}$$
$$= Ker(\partial_1^i)/\mathrm{Im}(\partial_2^i)$$
$$= H_1^i$$

$$H_2^s = Ker(\partial_2^s)/\mathrm{Im}(\partial_3^s)$$
$$= Ker(\partial_2^s)$$
$$= 0$$
$$= Ker(\partial_2^i)/\mathrm{Im}(\partial_3^i)$$
$$= H_2^i$$

Embedded cohomology of hypergraph

Definition (Infimum cochain complex)

Given a hypergraph $\mathcal{H}$, we define the infimum cochain complex $Inf^*(\mathcal{H}, G)$ with coefficient G as

$$\mathrm{Inf}^n(\mathcal{H}, G) = (\mathrm{Inf}_n(\mathcal{H}, R))^* = Hom(\mathrm{Inf}_n(\mathcal{H}, R), G),$$

which the dual of $\mathrm{Inf}_n(\mathcal{H}, R)$.

Definition (Supremum cochain complex)

Given a hypergraph $\mathcal{H}$, we define the Supremum cochain complex $Sup^*(\mathcal{H}, G)$ with coefficient G as

$$\mathrm{Sup}^n(\mathcal{H}, G) = (\mathrm{Sup}_n(\mathcal{H}, R))^* = Hom(\mathrm{Sup}_n(\mathcal{H}, R), G),$$

which the dual of $\mathrm{Sup}_n(\mathcal{H}, R)$.

Proposition

Given a hypergraph $\mathcal{H}$, the cohomology of $Sup^\star(\mathcal{H}, G)$ and the cohomology of $Inf^\star(\mathcal{H}, G)$ are isomorphic.

Definition (Hypergraph embedded cohomology)

Given a hypergraph $\mathcal{H}$, we define the n-th embedded cohomology of $\mathcal{H}$ with coefficient G as

$$H^n(\mathcal{H}, G) = H^n(\mathrm{Sup}^\star(\mathcal{H}, G)) = H^n(\mathrm{Inf}^\star(\mathcal{H}, G)).$$

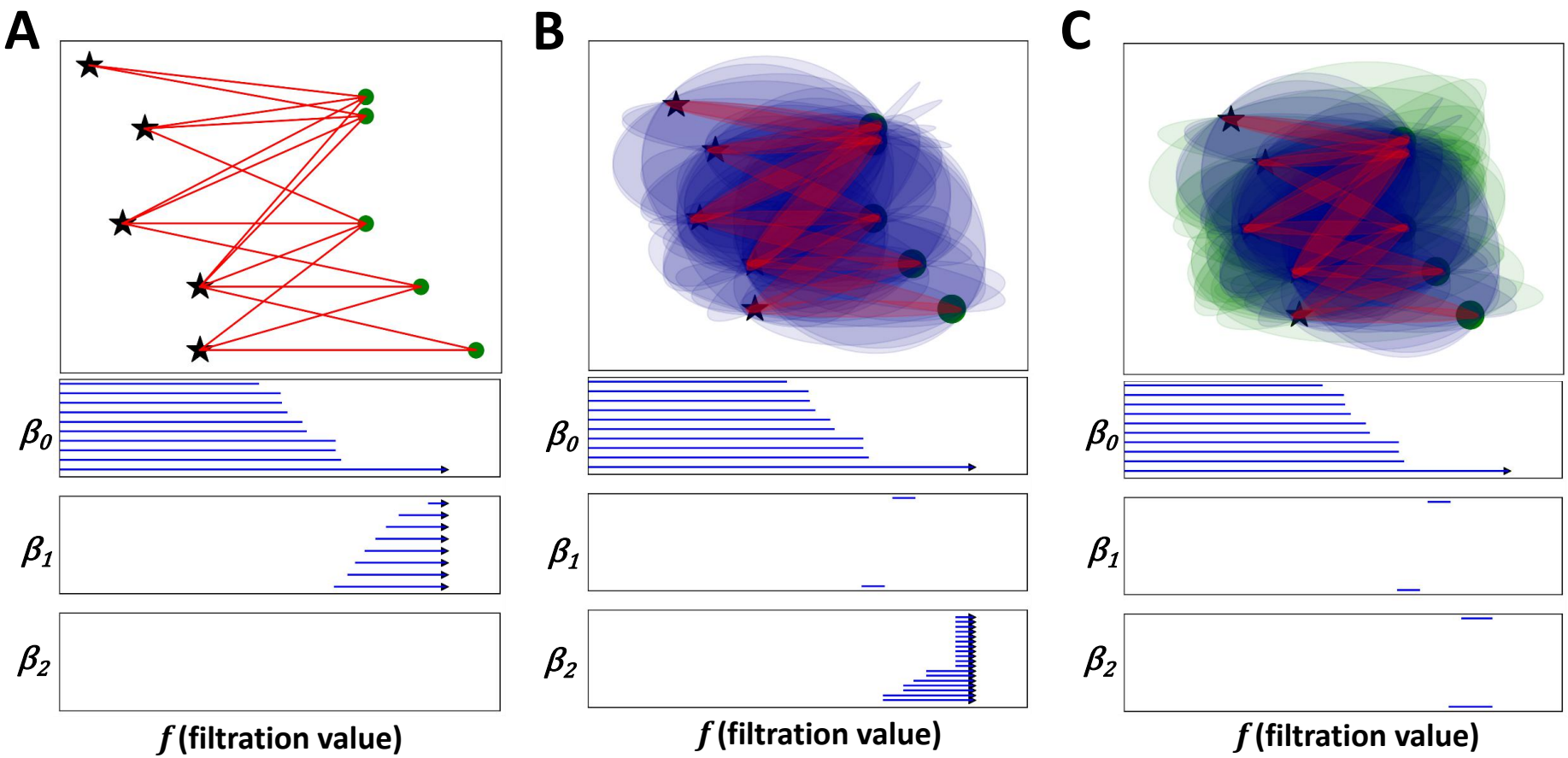
From now on, the coefficient R and G are both Z_2. So we have $\{\mathbf{v}_i, \mathbf{v}_j\} = -\{\mathbf{v}_i, \mathbf{v}_j\} = \{\mathbf{v}_j, \mathbf{v}_i\}$, which means that for any two n-hyperedges σ_n, $\sigma_{n'}$ $(0 \leqslant n \leqslant m)$, if the vertices of σ_n and $\sigma_{n'}$ are same. Then, $\sigma_n = \sigma_{n'}$.

Theorem

For an m-dimension hypergraph $\mathcal{H}$, its embedded cohomology is the simplicial cohomology of $K_{\mathcal{H}}$, if it satisfies the following two conditions.

1. *For each vertex of $\mathcal{H}$, it is a 0-hyperedge.*
2. *For each n-hyperedge $\sigma_n = \{\mathbf{v}_0, \mathbf{v}_1, ..., \mathbf{v}_n\}(1 \leqslant n \leqslant m)$ of $\mathcal{H}$, it has an associated ("face") set $\{\sigma^0_{n-1}, \sigma^1_{n-1}, ..., \sigma^n_{n-1}\}$ with $\sigma^i_{n-1}(0 \leqslant i \leqslant n) = \{\mathbf{v}_0, ..., \mathbf{v}_{i-1}, \mathbf{v}_{i+1}, ..., \mathbf{v}_n\}$ generated from σ_n by removing the vertex $\mathbf{v}_i$. It only allows at most one ("face") element (among the $n+1$ elements) from the set is not an $(n-1)$-hyperedge of $\mathcal{H}$.*

Hypergraph based persistent cohomology(HPC)



Bipartite graph ***Hypergraph(up to 2)*** ***Hypergraph(up to 3)***

Figure: Bipartite-graph VS hypergraph

HWPC

Weighted persistent cohomology has been proposed to incorporate more structure, physical, chemical and biological information into a unified representation, i.e., persistent cohomology enriched barcode[**?**]. Different from all previous models, here we consider a new weight scheme, derived from graph centrality, for persistent cohomology. More specifically, we define the weights for a 0-hyperedge $\sigma_0 = \{\mathbf{v}_i\}$ as,

$$w(\sigma_0) = \begin{cases} \sum_{\mathbf{v}_k \in V_L} e^{-\frac{\|\mathbf{v}_k - \mathbf{v}_i\|^2}{\eta^2}}, & \mathbf{v}_i \in V_P \\ \sum_{\mathbf{v}_k \in V_P} e^{-\frac{\|\mathbf{v}_k - \mathbf{v}_i\|^2}{\eta^2}}, & \mathbf{v}_i \in V_L \end{cases} \tag{5}$$

and an 1-hyperedge $\sigma_1 = \{\mathbf{v}_i, \mathbf{v}_j\}$ as,

$$w(\sigma_1) = e^{-\frac{\|\mathbf{v}_i - \mathbf{v}_j\|^2}{\eta^2}}. \tag{6}$$

The scale parameter η controls the influence range of the nodes. Smaller η values mean local interactions and larger η values mean global interactions.

Further, we define the weight for a 0-cohomology generator δ^0 as,

$$w(\delta^0) = \frac{\sum_{\sigma_0^i \in \mathcal{H}_0} \delta^0(\sigma_0^i) * w(\sigma_0^i)}{\sum_{\sigma_0^i \in \mathcal{H}_0} \delta^0(\sigma_0^i)}, \tag{7}$$

and an 1-cohomology generator δ^1 as,

$$w(\delta^1) = \frac{\sum_{\sigma_1^i \in \mathcal{H}_1} \delta^1(\sigma_1^i) * w(\sigma_1^i)}{\sum_{\sigma_1^i \in \mathcal{H}_1} \delta^1(\sigma_1^i)}. \tag{8}$$

Note that Z_2 is used in computation, and the term $\delta^1(\sigma_1^i)$ is either 0 or 1. For persistent cohomology enriched barcodes, each barcode represents a generator and is colored by the weight values defined above.
Computationally, our persistent cohomology enriched barcodes are calculated based on the associated simplicial complex. And the weights defined in Eqs. (5) and (6) are generalized to any 0-simplex and 1-simplex, respectively. Note that distance between two atoms from the same molecule is defined as Eq. (2). Similarly, weights for cohomology generators in Eqs. (7) and (8) are also extended to associated simplicial complex counterpartners.

HPC/HWPC base machine learning

Persistent barcodes from HPC and HWPC can be discretized into feature vectors. We combine these feature vectors with gradient boosting tree to build our HPC/HWPC-ML model.

For the discretization, we consider the binning approach. That is, The total number of the barcodes (i.e., Betti numbers for HPC) or the sum of the weight values of enriched barcodes (for HWPC) within each bin, is used as molecular descriptors.

Protein-ligand binding affinity prediction

A drug design process covers various steps, Among all the steps, one of the key issue is to identify ligands (drug) that have higher binding affinity with the target biomolecules. During the past few decades, a variety of empirical, physics-based, knowledge-based, and machine-learning-based models are proposed. The databank PDBbind (www.pdbbind.org.cn) is established to systematically evaluate and compare their performance for protein-ligand binding affinity prediction.

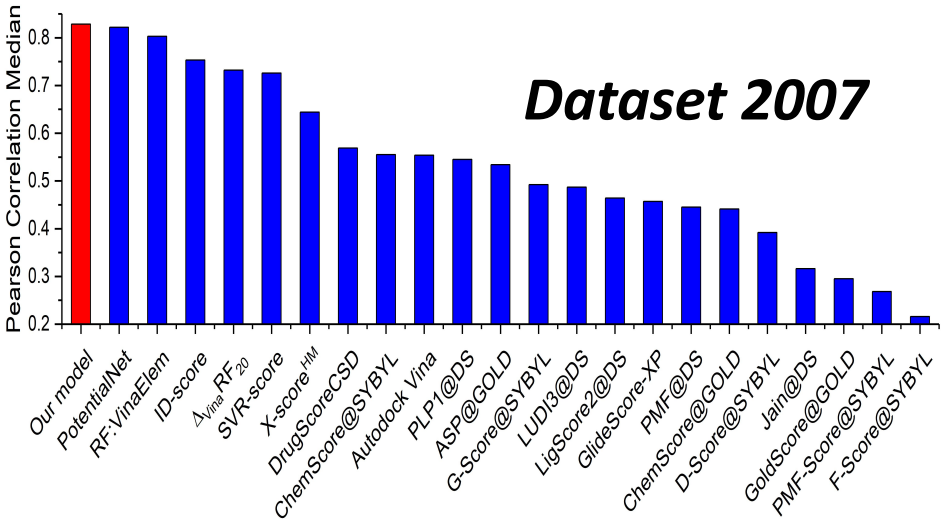
Parameter setting

We use our HPC/HWPC-ML to make the protein-ligand binding affinity prediction, the cutoff is 10.5Å, filtration region is [2.0Å,7.5Å] with bin size 0.1Å. In this way, the feature size are 3960=36×55×2×1, 7920=36×55×2×2 and 11880=36×55×2×3 for HPC, HWPC and combined-HWPC respectively. The parameter setting for GBT is as follows.

No. of Estimators	Learning rate	Max depth	Subsample
40000	0.001	9	0.7

Min_samples_split	Loss function	Max features	Repetitions
2	Least square	SQRT	10

Results

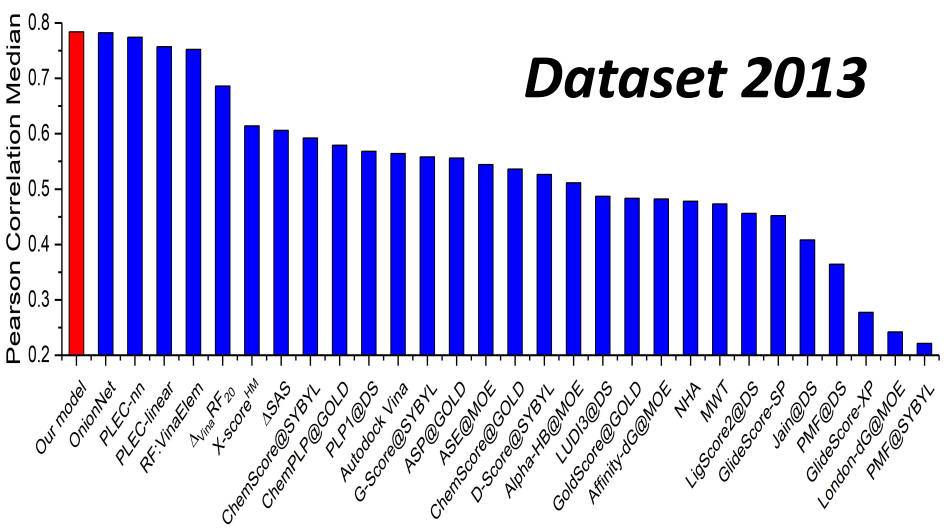


HPC/HWPC

+

GradientBoostingTree

	HPC	HWPC2.5	HWPC10	HWPC(2.5+10)
PDBbind2007	0.813(1.423)	0.823(1.418)	0.827(1.395)	0.829(1.403)
PDBbind2013	0.770(1.508)	0.780(1.498)	0.779(1.486)	0.784(1.483)
PDBbind2016	0.810(1.359)	0.825(1.322)	0.825(1.324)	0.831(1.307)



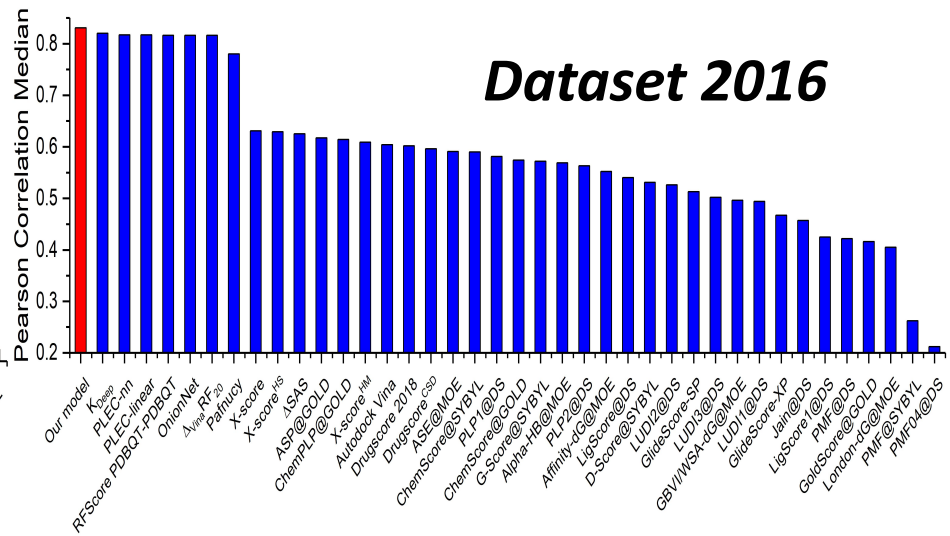


Figure: Comparison of our model with other traditional models

Thank You