Persistent Path-Spectral Based Machine Learning for Protein-Ligand Binding Affinity Prediction

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Outline

Motivation

Persisitent Path Spectral(PPS)

Protein-Ligand Binding Affinity Prediction

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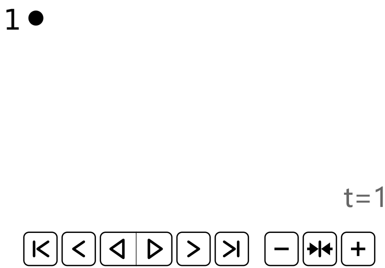

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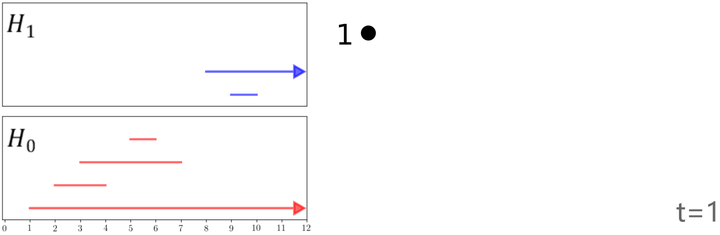

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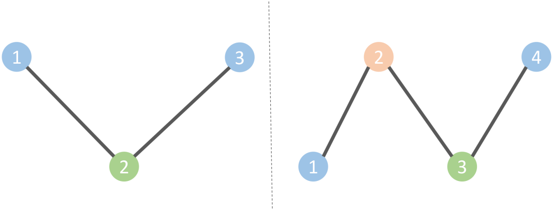

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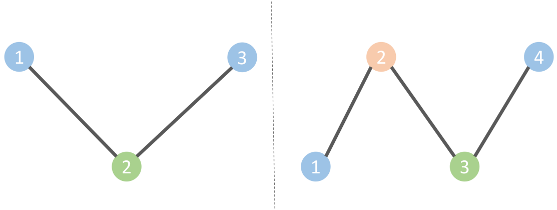

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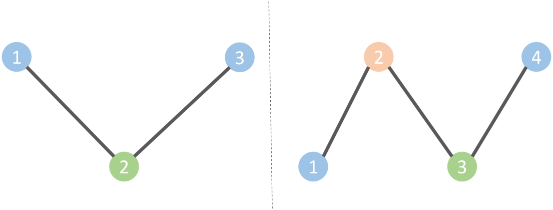

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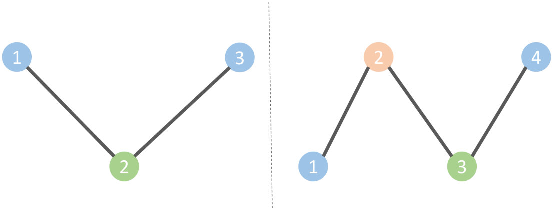

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- And test our model on issue of protein-ligand binding affinity prediction, PPS model can achieve competitive results.

Motivation

Persisitent Path Spectral(PPS)

Protein-Ligand Binding Affinity Prediction

Definition (Simplicial Complex)

An (abstract) simplicial complex C *is a pair* (V, C_V) *where* V *is a vertex set and* C *is a simplex set, such that every* $\sigma \in C_V$ *is a nonempty subset of vertex set , and every nonempty subset of* σ *is also* $\in C_V$*.*

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Definition (n-simplex walk,path)

A series of n-simplices $\sigma_1^n, \sigma_2^n, ..., \sigma_l^n, \sigma_{l+1}^n$ *(not must diverse) is called an* ***n-simplex walk*** *from* σ_1^n *to* σ_{l+1}^n *while* σ_i^n *and* σ_{i+1}^n *share an (n+1)-simplex for each* $i = 1, 2, ..., l$.

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Under another additional condition that these n-simplices are different from each other, this ***n-simplex walk*** *turns into an* ***n-simplex path****.*

Definition (shortest path)

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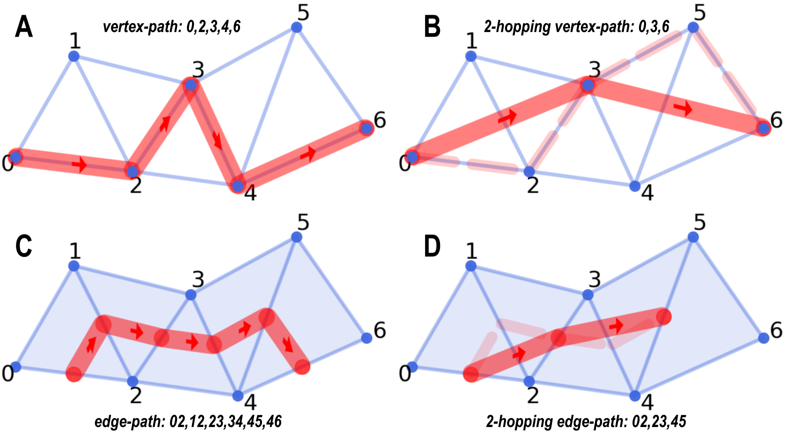
Example: hopping path of simplicial complex


A
vertex-path: 0,2,3,4,6
B
2-hopping vertex-path: 0,3,6
C
D
edge-path: 02,12,23,34,45,46
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0
1
2
3
4
5
6

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Given a simplicial complex C, which can be represented by $\{C_n\}_{n\geq 0}$, here C_n is the collection of all n-simplices. For a subset of C_n, donated as X_n, if there is a k-hopping n-simplex walk visiting every n-simplices of X_n at lowest, the subset X_n is defined as a ***k-hopping n-simplex connected component*** *of C, which denoted by* ***(k,n) connected component*** *for simplicity.*

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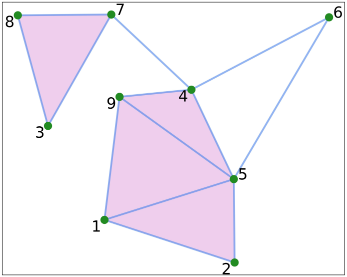

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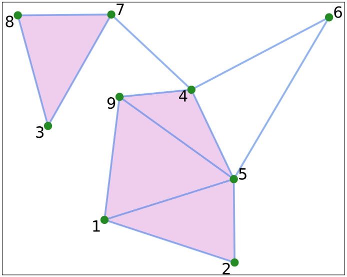

- 2-hopping vertex walk: $\{v_1, v_6, v_7, v_5, v_7, v_9, v_2, v_4, v_8, v_4, v_3\}$
- 3-hopping vertex walk: $\{v_3, v_9, v_8, v_5, v_3, v_6\}$; $\{v_2, v_7, v_1\}$; $\{v_4\}$

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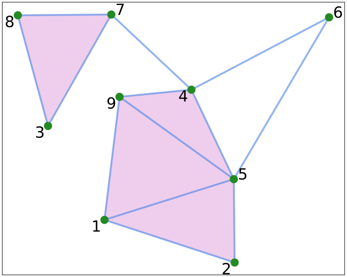

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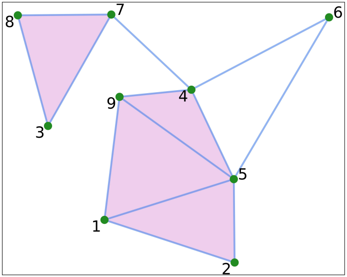

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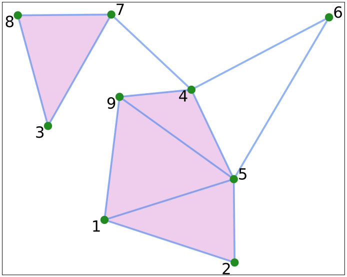

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- 3-hopping edge walk: $\{[1,2], [4,5], [2,5], [4,9]\}$
- seven (2,1) connected components, ten (3,1) connected components

Definition (k-path degree)

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The ***k-path n-simplex Laplacian matrix*** *L_k^n of simplicial complex C is a $N(C_n)$ order square symmetric matrix whose entries is shown as follows, denoted by* ***(k,n) path-Laplacian****.*

$$L_k^n(C)(i,j) = \begin{cases} \delta_k(\sigma_i^n) & , \; i = j \\ -1 & , \; d_{i,j}^n = k \\ 0 & , \; otherwise \end{cases} \tag{1}$$

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Theorem

The number of ***k-hopping n-simplex connected components*** *is the multiplicty of zero eigenvalue of* ***(k,n) path-Laplacian****.*

Example: Laplacian matrix of C_{20}

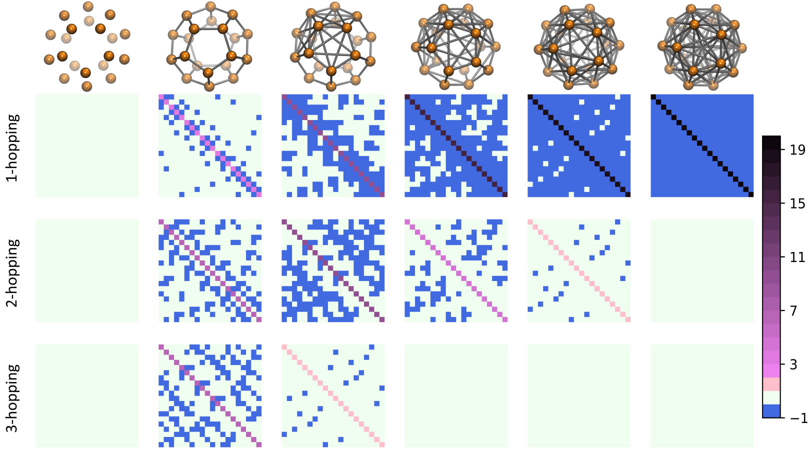
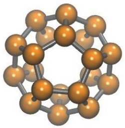
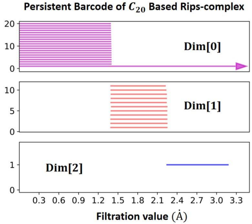
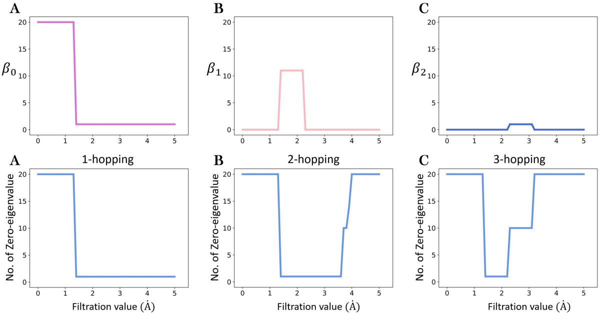


Figure: Vertex(0-simplex) path-Laplacian matrices with filtration values 1.0Å, 1.5Å, 2.3Å, 3.3Å, 3.7Å, 4.0Å.

Example: Persisitent feature of C_{20}







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Assume we have a filtration of simplicial complexes, which is a sequence of nested simplicial complexes

$$O_1 \subset O_2 \subset ... \subset O_t$$

where O_i is a sub-complex of $O_{i+1}(0 < i < t)$. For each O_i, we consider its (k,n) path-Laplacian matrix $L_k^n(O_i)$, then we get a sequence of path-Laplacian matrixes for each pair (k,n)

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Definition (persistent path spectral)

*The persistence and variance of the path-spectral information through the sequence of path-Laplacian matrixes is called the **persistent path-spectral** of the sequence of simplicial complexes.*

Example: Persisitent path-spectral of C_{20}

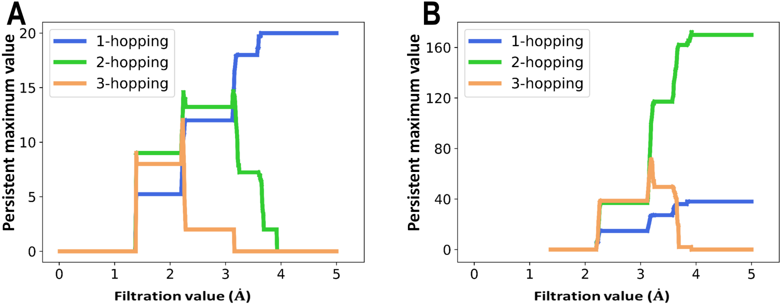

Figure: Persistent attribute curves from persistent path-spectral for C_{20}. Left is based on vertex, right is based on edge.

Motivation

Persisitent Path Spectral(PPS)

Protein-Ligand Binding Affinity Prediction

Protein-Ligand Complex and Affinity

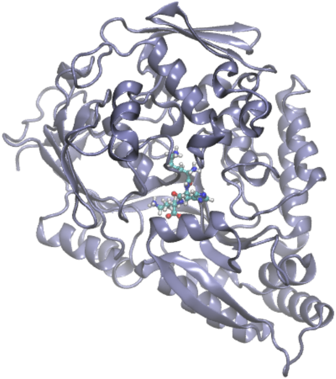

Figure: Protein-ligand complex ID: 1b3f.

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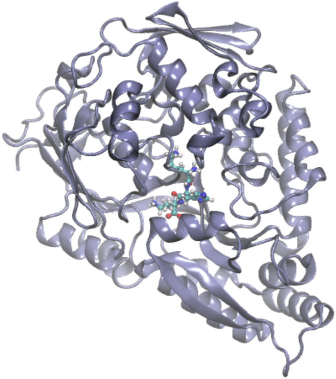

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- A protein-ligand complex is a complex of a protein bound with a ligand that is formed following molecular recognition between proteins that interact with each other or with various other molecules.
- The highest possible affinity from a protein towards the ligand, or target molecule, can be observed when the protein has a perfect mirror image of the shape of the target surface together with a charge distribution that complements perfectly the target surface.

Protein-ligand binding affinity prediction

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- However, this is extremely costly in the first screening of a compound, which requires a prohibitively enormous search space.
- To narrow the search space, there is an urgent need to develop more efficient computational approaches.

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1. One is the classical methods which usually use linear functions to model the relationship between experimental data and features. Classical methods can be divided into three groups:
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2. The other is artificial intelligence (AI) based methods which can capture nonlinear relationship between features and experimental data. AI based models can be grouped into two categories:
   - Machine learning models
   - Deep learning models

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- Euclidean distance and electrostatic distance functions are used to form the filtration of the representation.
- For each protein-ligand complex, 36 atom combinations are generated with protein atoms C, N, O, S and ligand atoms C, N, O, S, P, F, Cl, Br, I. And a filtered bipartite graph is constructed from every atom-combination where the distance is used as the filtration value for each edge.

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- For electrostatic interactions, H atoms are also taken into consideration and a total of 50 atom combinations are generated from electrostatic interactions.

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- We use persistent median value curve and persistent mean value curve of the persistent spectral with hopping 1, 2 and 3 as the features.

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- For the topological representation of a protein-ligand complex, use PPS to obtain feature, which can be combined with machine learning model.
- For the distance-based PPS model, the filtration goes from 0Å to 10 Å with a step of 0.1 Å, and for the electrostatic-based PPS model, the filtration goes from 0 to 1 with a step of 0.02.
- We use persistent median value curve and persistent mean value curve of the persistent spectral with hopping 1, 2 and 3 as the features.
- The size of features based distance-model is $\mathbf{21600 = 36(atom\text{-}combinations) \times 100(persistence) \times 3(hopping) \times 2}$, the size of features based electrostatic function is $\mathbf{15000 = 50(atom\text{-}combinations) \times 50(persistence) \times 3(hopping) \times 2}$. Combined model's feature size is $\mathbf{36600 = 21600 + 15000}$.

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No. of estimators	**Maximum features**	**Learning rate**	**Loss function**
40000	Square root	0.001	Least square
Minimum sample split	**Subsample size**	**Maximum depth**	**Repetition**
3	0.7	6	10

Table: Detailed parameters of GBT

Datasets

- The PDBbind database is a collection of the experimentally measured binding affinities exclusively for the protein-ligand complexes available in the Protein Data Bank(PDB).
- This type of knowledge is the much needed basis for many computational and statistical studies on molecular recognition.

Dataset	**Refined set**	**Training set**	**Test set (Core set)**
PBDbind-v2007	1300	1105	195
PDBbind-v2013	2959	2764	195
PDBbind-v2016	4057	3772	285

Table: Detailed information of the three PDBbind datasets, i.e., PDBbind-v2007, PDBbind-v2013, PDBbind-v2016.

Result

PDBbind-v2016	Dist	Charg	Dist+Charg
1-hopping	0.793(1.393)	0.808(1.359)	0.823(1.322)
2-hopping	0.792(1.392)	0.798(1.374)	0.810(1.347)
3-hopping	0.781(1.436)	0.800(1.375)	0.811(1.354)
(1,2,3)-hopping	0.829(1.287)	0.832(1.269)	0.843(1.248)

PDBbind-v2013	Dist	Charg	Dist+Charg
1-hopping	0.746(1.561)	0.760(1.534)	0.775(1.503)
2-hopping	0.753(1.535)	0.759(1.518)	0.767(1.497)
3-hopping	0.733(1.584)	0.725(1.606)	0.745(1.560)
(1,2,3)-hopping	0.778(1.478)	0.778(1.473)	0.791(1.444)

PDBbind-v2007	Dist	Charg	Dist+Charg
1-hopping	0.791(1.534)	0.800(1.509)	0.804(1.509)
2-hopping	0.793(1.500)	0.766(1.559)	0.791(1.497)
3-hopping	0.781(1.540)	0.776(1.547)	0.799(1.499)
(1,2,3)-hopping	0.818(1.142)	0.827(1.399)	0.827(1.399)

Table: PCCs and RMSEs of PPS-ML models on three datasets.

Result

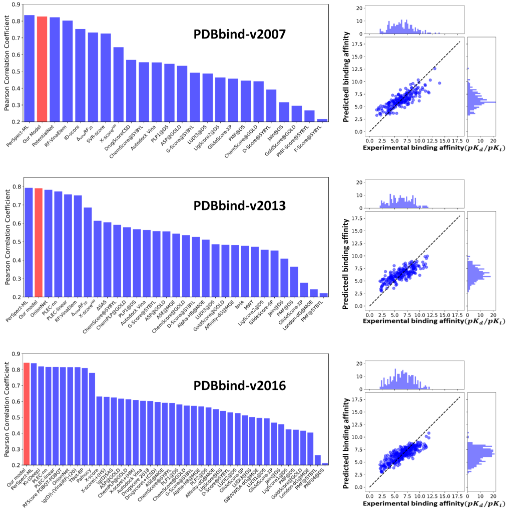

Figure: Performance of PPS-ML model on three datasets.

Result

- In our model, the feature size is 36600, which is much larger than the data size of three PDBbind datasets we used.
- We expanded the parameter step by 5 times for feature generation to do regression to alleviate overfitting problem.

Dataset	**Original size(36600)**	**Adjusted size(7320)**
PDBbind-v2016	0.843(1.248)	0.839(1.257)
PDBbind-v2013	0.791(1.444)	0.790(1.447)
PBDbind-v2007	0.827(1.399)	0.830(1.390)

Table: PCCs and RMSEs of PPS-ML model on three datasets based on different feature size.

Thank You!