**REINDEER: A Protein-Ligand Feature Generator Software for Machine Learning Algorithms**

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**Abstract**

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1- Introduction

In the past decade, we have witnessed a proliferation of data-driven approaches for designing protein-ligand scoring functions, which scientists apply to predict the binding affinity of a protein-ligand complex. These new scoring functions employ traditional machine learning (ML) and deep learning algorithms (DL) for deriving a non-linear relationship between binding affinity quantity and a representation of the protein-ligand complex [1-9].

A designed scoring function can be evaluated based on its ability to perform four tasks: scoring, ranking, docking, and screening. The first two tasks involve predicting binding affinity values, while the other two tasks evaluate the scoring function's ability to distinguish between native or near-native poses and decoys, as well as true binders from non-binders [10, 11]. The PDBbind dataset [12], DUD-E [13], and DEKOIS2.0 [14] are among the popular datasets for training and testing, in spite of the fact that there are some hidden biases in these datasets [15, 16].

In the ML case, it is needed to represent a protein-ligand complex in terms of a feature vector by applying feature engineering techniques, while in the DL case, these representations are mostly learned end-to-end during the training phase.

RF-Score [17], ECIF∷LD-GBT [18], and multi-shelled ECIF [19] are ML-based scoring functions that exploit the occurrence of interatomic contacts and ligand descriptors in ECIF∷LD-GBT case to generate a feature vector for ML algorithms like Random Forest (RF) or Gradient Boosting Decision Trees (GBT). ET-Score [20] and its’ enhanced versions, i.e., GB-Score [21] and ENS-Score [22], employed distance-weighted interatomic contacts and Extremely Randomized Trees (ERT) for constructing an ML-based scoring function. ∆vinaRF20 [23], ∆vinaXGB [24] and ∆LinF9XGB [25] employ some Autodock Vina empirical terms alongside other descriptors, e.g., RDKit descriptors for ligand, for feature generation procedures, and RF and eXtreme Gradient Boosting (XGB) algorithms as learners. Proteo-chemometrics IFPs [26] and PLEC-FP [27] apply different generalized versions of extended-connectivity fingerprints (ECFPs) for protein-ligand representation. SMPLIP-Score [28] utilizes a featurization method to vectorize and embed the interaction fingerprint pattern between the ligand‑binding site environment and fragments of ligands. TB-IECS [29] employs some theory-based energy terms, e.g., van der Waals, for making a representation for an XGB algorithm. OPRC-GBT [30], AGL-Score [31], PPS-ML [32], EISA-Score [33], and PerSpect ML [34] are examples of ML-based scoring functions that utilize topology principles and invariants for generating feature vectors for a protein-ligand complex.

Unlike ML algorithms, DL methods have the capability to learn an end-to-end representation of a protein-ligand complex. Seo et al. [35], AEScore [36], and BCL-AffinityNet [37] are among the recent examples of DL-based scoring functions that utilize different variants of Feed-Forward Neural Networks (FFNNs). For the recent examples of Convolutional Neural Networks (CNNs) –based scoring functions, we can mention Jones et al. [38], DeepDTAF [39], AA-Score [40], and OnionNet-2 [41]. GIGN [42], PIGNet2 [43], CarsiDock [44], and GAABind [45] can be categorized as instances of Graph Neural Networks (GNNs) –based binding affinity estimators.

Emphasis of ML-based

Lack of package to feature engineering

Comparing to existence one, use table, ML-PLIC paper

Reason for selection of these methods, exclusion of enery term based like DeltaVinaRF20, new, geometry-based

Last paragraph of introduction

2- Theory

Occurrence of Interatomic Contact

Occurrence of interatomic contact (OIC) was introduced by Ballester et al. for developing the RF-Score scoring function [17]. In this technique, the authors represented a protein-ligand complex by counting the number of occurrences of a specific pair of protein and ligand atoms below a distance threshold. Ten elemental atom types (H, C, O, N, F, P, S, Cl, Br, and I) were allocated for protein and ligand , although in its original implementation, the Hydrogen element was omitted. The following formula calculates the occurrence (1):

|  |  |
| --- | --- |
|  | (1) |

Where xi,j is the number of contacts between i and j atom types. k and l are protein and ligand atoms belonging to the i and j atom types. dkl is the Euclidean distance between k and l atoms, and Θ is the Heaviside step function that counts contacts below dcutoff=12 Å. The feature vector contains 50 integer-valued features.

Distance-Weighted Interatomic Contact

Distance-weighted interatomic contact (DWIC) was employed by ET-Score [20] for vectorial representation of a protein-ligand complex and further used by GB-Score [21] and ENS-Score [22]. Like OIC, ten elemental atom types are chosen for both ligand and protein. However, protein atom types are further augmented by considering the nature of amino acid side chains. To reflect the different characteristics of amino acids, they are classified into four groups (Charged (c), Polar (p), Amphipathic (a), and Hydrophobic (h)):

Charged={Arg, Lys, Asp, Glu}

Polar={Gln, Asn, His, Ser, Thr, Cys}

Amphipathic={Trp, Tyr, Met}

Hydrophobic={Ile, Leu, Phe, Val, Pro, Gly, Ala}

Therefore, each elemental protein atom type belongs to four groups. As an example, CP denotes a carbon atom of polar residues. At its’ core, DWIC is similar to OIC in the feature generation by considering atom types pair of protein and ligand, but, in DWIC, the Heaviside step function is replaced by a function, which differentiated close and distant interatomic contacts by applying an inverse-square factor. The following equation (2) describes this function:

|  |  |
| --- | --- |
|  | (2) |

The definition of symbols is similar to equation (1), and like OIC, dcutoff=12Å is applied. The DIWC feature vector includes 200 float-valued features.

Extended Connectivity Interaction Features

Extended Connectivity Interaction Features, or concisely ECIF, share the same essence, like DIWC, with OIC [18]. However, ECIF applies different atom type representations and dcutoff value (6Å) and only retains the counting atom type pairs scheme of OIC. The authors defined atom types in ECIF by considering the atom environment. Atom symbol, explicit valence, number of attached heavy atoms, number of attached hydrogens, aromaticity, and ring membership were employed for this definition, which results in 22 and 70 atom types for protein and ligand, respectively. The final feature vector comprises 1540 integer-valued features.

Protein–Ligand Extended Connectivity Fingerprints

Wójcikowski et al. [27] introduced protein–ligand extended connectivity fingerprints (PLEC FPs) for encoding a 3D structure of a protein-ligand complex to a fingerprint. To achieve this, PLEC FP utilizes the atom environment concept that underlies the ECFP. Here, atomic identifiers are atomic mass, total number of connections, number of heavy-atom neighbors, number of attached hydrogen atoms, and formal charge. PLEC consists of two steps. In the first step, protein and ligand atoms within a certain threshold (4.5 Å) are identified, then hashed entities are built for each atom by using ECFP. In the second step, a pair of hashed protein and ligand atoms are hashed to a final bit. In the REINDEER software, the required depths of ECFP for ligand (R1) and protein (R2) are set to 1 and 5, and the noniterative ECFP algorithm from Proteo-chemometrics interaction fingerprints is used (see Proteo-Chemometrics Interaction Fingerprints for more information). The final feature vector is a 211-bit string (2048 dimensions).

Proteo-Chemometrics Interaction Fingerprints

Proteo-chemometrics interaction fingerprints (PrtCmm IFPs) method combines ECFPs with proteo-chemometrics approaches. In this procedure, protein and ligand are separately characterized for the construction of a predictive model. Despite the PLEC FPs technique, which generates fingerprints by considering and hashing atom pairs in protein-ligand complex, the current method generates fingerprints for ligand and protein separately and concats them together. Also, the PrtCmm IFPs method applies a novel noniterative (NI) ECFP algorithm to remove the information collision possibility and nested-hash operations. This new algorithm hashes the average properties of atoms in each neighborhood for making identifiers. It is worth mentioning that atomic mass, total number of connections, number of heavy-atom neighbors, number of attached hydrogen atoms, and formal charge are considered properties of an atom [26]. The current implementation of PrtCmm IFPs in REINDEER uses R1=1 and R2=1 (the same radius for ligand and protein), 29-bit string, and NI ECFP for making fingerprints. The final feature vector is constructed by the concatenation of two 512-bit strings.

3- Method

4- Case Study

5- Conclusion

6- References

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