

Computational Intelligence Methods for Docking Scores

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Abstract: Computer-aided drug design (CADD) methodologies have proven to be very effective, greatly enhancing the efficiency of small molecule drug discovery and development processes. These methods include quantitative structure-activity relationship and pharmacophore models, quantitative structure-property relationship models, as well as *in silico* docking studies. While docking studies very often correctly identify the binding mode of a ligand, they have reduced success in predicting binding affinities. Development of improved and more efficient strategies for scoring binding affinity is a very active area of research. Here we review the utility of computational intelligence approaches such as artificial neural networks, fuzzy logic, and evolutionary computation to the calculation of improved docking scores.

Keywords: Computational intelligence, evolutionary algorithms, artificial neural networks, fuzzy logic, docking scores, *in silico* docking, high-throughput screening, virtual screening.

INTRODUCTION

By current estimates, it costs more than \$1.3 billion and takes 12-15 years to bring a new drug to market [1, 2]. On average, far less than 1% of screened compounds (from lead discovery and lead optimization) enter preclinical development. For every 250 compounds in preclinical development, 5 survive to enter clinical testing with only 1 approved drug by the FDA after an average of 15 years of total research and development. Typically, discovery and pre-clinical development takes 3-6 years to achieve an investigational new drug (IND) filing whereas clinical trials can last up to 10 years or more before the product reaches the market [2, 3]. A simplified preclinical drug discovery and development workflow is presented in Fig. (1).

Protein-ligand docking is routinely applied in pre-clinical drug discovery in order to: a) generate “focused” or “enriched” compound libraries *via* high-throughput virtual screening and b) optimize “hits” into lead series. Lead optimization includes testing of structure-activity relationship (SAR) hypotheses as well as evaluation of novel scaffolds and core templates [4, 5]. The selected compounds are then synthesized or purchased and screened experimentally. Each compound in a focused library is selected after considering structural and physical properties that will increase its probability of having activity for the specific target as well as its ultimate survivability through pre-clinical development [6]. Additional filters based on predicted physico-chemical properties, such as Lipinski’s “Rule-of-Five” are often applied in an attempt to improve the absorption, distribution, metabolism, excretion and toxicology (ADMET) profiles of compounds that are important for survival through later stage drug development [7, 8].

The overall goal for lead discovery is to find novel structures and preferably novel structure classes that have activity

for a target of interest. Docking software used in lead discovery must therefore be able to correctly identify molecules that can fit in a binding and/or active site and more importantly identify those that do not. Rank ordering of compounds by activity is not as important as being able to generate a relatively “small” set of compounds containing as many true actives with as few false positives as possible.

Lead optimization is an iterative process of design, testing and evaluation in which the hits identified in lead discovery are optimized in order to increase their binding affinities (K_d), ideally into the low nanomolar (nM) range. Additionally, alternative templates or scaffolds are often evaluated to ensure novelty and patentability as well as synthetic accessibility. Because of the importance of enhancing survivability through pre-clinical development, compounds are also optimized in order to enhance their “drug-likeness”. The ADMET properties most often optimized at this stage include: solubility (e.g., aqueous, saline, plasma, organic solvents); aqueous/organic phase partition coefficients (logP); acid dissociation constants; intestinal absorption (e.g., CACO2 cell assay); membrane penetration and *in vivo* efficacy in cell models; as well as toxicology (e.g., cytochrome P450 assays). Often optimizing a compound for these ADMET properties *decreases* its potency for the target protein.

For lead optimization, protein ligand-docking is most useful in assisting medicinal chemists in the development and testing of SAR hypotheses. Unlike lead discovery, lead optimization involves studying a single series of closely related chemical structures having a gradient of activity. Very often the differences in the chemical and structural features between active compounds and less active ones are subtle [9]. The demands on docking software for lead optimization are therefore much greater than for lead discovery. In particular, it is very important that the scoring functions be able to correctly rank-order compounds. In practice, while docking software does a very good job of correctly identifying the binding modes of ligands, their scoring functions have much less success in predicting binding affinities [9-14]. Development of improved and more efficient strategies is a very

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Fig. (1). A typical pre-clinical drug discovery and development workflow. In lead discovery diverse screening libraries are screened. Docking and QSAR methodologies are often used to generate focused libraries to increase efficiency. In lead optimization, scaffolds identified in lead discovery are optimized to increase potency and ADME properties. SAR hypotheses are generated and tested in an iterative manner. Docking and QSAR modeling play an important role in this process. Pre-clinical development focuses on *in vivo* optimization as well as further optimization of ADME and toxicological properties. The goal is to advance a drug candidate to an initial new drug (IND) filing to begin clinical testing.

active area of research. One rather new development has been the interest in applying existing tools and techniques from the field of computational intelligence [15].

Computational intelligence is a broad field in computer science focusing on the development of machine learning approaches for the automatic selection of features and optimization of models. The tools and techniques of this field include artificial neural networks, fuzzy logic, and evolutionary computation [16-20]. In this paper we will review the utility of some of the more popular applications of computational intelligence to docking scores.

This paper is organized as follows. The next section presents a brief overview of protein-ligand binding and summarizes existing scoring functions. The following section introduces general concepts of computational intelligence and the section following presents examples of their application to scoring functions. The final section will be a discussion of

future directions in the development of more accurate scoring functions and the conclusions.

SCORING FUNCTIONS

A docking experiment consists of an exploration of the conformational space of a ligand and a target protein in order to find the global free energy minimum on a very complex potential energy landscape. Multiple binding modes representing local free energy minima, called poses, are generated and evaluated with a scoring function that assesses both steric as well as chemical interactions in order to guide the conformational searching algorithm of the docking software. The chemical interactions assessed include hydrophobic and Van der Waals, electrostatic, as well as H-bonding interactions. Ideally, the best scores should be assigned to "correct" poses - or ones that are consistent with an x-ray crystal or NMR structure.

There are currently more than 60 docking programs. Some commonly used docking programs include: AutoDock, DOCK, FlexX, FRED, Glide, GOLD, ICM, LUDI, MOE, LibDock, LigandFit, Molegro, Pro_Leads QXP, and Surflex. For additional detail regarding docking algorithms we refer the reader to the following reviews [9, 14, 21-23].

These same scoring functions used for evaluating poses can also be used to predict the ligand's relative binding affinity. Ideally, more active compounds should bind tighter and have higher scores. This is the fundamental assumption and the basis for using docking experiments for lead discovery and lead optimization. Unfortunately, as has been extensively discussed in the literature, this is often *not* the case [9-14]. Scoring functions are typically classified into three categories: a) force field, b) empirical, or c) knowledge-based. Consensus scores are often generated from some linear (or nonlinear) combination of scoring functions. There are currently more than 30 scoring functions available. Some of the most commonly used functions are presented in Table 1.

Protein-Ligand Binding

Traditionally, protein-substrate binding has been thought of in terms of either the "lock-and-key" [24] or the "induced-fit" models [25]. The "conformation selection" model has been proposed in which ensembles of conformations of both ligands and binding sites coexist. Binding occurs between those conformations (of both ligand and binding site) that are complementary in shape [26]. This model is consistent with recent studies that have suggested that more accurate docking results are obtained using a holo-enzyme structure containing a ligand in the active site than from either an apo-enzyme or a homology model [27-30]. It is important to note that experimentally-determined bound conformations are not necessarily the lowest energy conformations. In the simplest case, the binding process between a ligand (L) and a protein (P) is given as:



and the binding constant K_b is given by:

$$K_b = \frac{[L \cdot P]}{[L][P]} \quad (2)$$

The Gibbs free energy (ΔG_b) for this binding is given by:

$$\Delta G_b = \Delta H - T\Delta S = -RT \ln K_b \quad (3)$$

The dissociation constant, K_d , is inversely proportional to K_b :

$$K_d = \frac{1}{K_b} \quad (4)$$

Ideally, a potent inhibitor should be a very tight binder, so the inhibition constant K_i should be much smaller than the K_d of the substrate. K_i , the inhibition constant, and K_d can both be determined experimentally [31].

The free energy of binding, ΔG_b , is a function of the intermolecular hydrogen bonds as well as the electrostatic and (relatively) weak Van der Waals interactions between complementary poses of a ligand and a protein [32]. However, any modeling of a binding process in an aqueous environment needs to take into account the energy required to

"desolvate" the area(s) of contact between the ligand and the binding site. In general, the favorable hydrogen bonding as well as electrostatic and Van der Waals interactions between the ligand and binding site do not come close to compensating for the loss of favorable interactions with the solvent water molecules when binding occurs.

Table 1. Some Commonly Available Scoring Functions

Scoring Function	Type	Docking Program
LUDI [36, 37]	Empirical	
Autodock [38]	Empirical	Autodock
ChemScore [39]	Empirical	GOLD, FRED, Pro_Leads
eHiTS [40]	Empirical	eHits
FlexX [41]	Empirical	FlexX
F-Score [41]	Empirical	
GlideScore [42, 43]	Empirical	Glide
Hammerhead [44]	Empirical	Hammerhead, LigandFit, Surflex
HINT [45]	Empirical	
LigScore [46]	Empirical	LigandFit
PLP [47]	Empirical	LigandFit, FRED
SCORE [48]	Empirical	
SCORE 3.0 [49]	Empirical	PSI-DOCK
ScreenScore [50]	Empirical	FRED
SIE [51]	Empirical	
Autodock [38]	Force Field	Autodock
DockScore [55]	Force Field	Dock
D-Score [56]	Force Field	
GOLDScore [57, 58]	Force Field	Gold
G-Score [56]	Force Field	
ICM [59]	Force Field	ICM
QXP [60]	Force Field	QXP, MCDOCK
RankScore [61]	Force Field	FITTED
SIE [51]	Force Field	
VALIDATE [62]	Force Field	
ASP [200]	Knowledge Based	GOLD
BLEEP [65]	Knowledge Based	
DrugScore [63, 64]	Knowledge Based	
M-Score [66]	Knowledge Based	
PLP [44, 67]	Knowledge Based	LigandFit, FRED
PMF [68-71]	Knowledge Based	LigandFit
SMoG [72, 73]	Knowledge Based	
X-Score [52]	Consensus/Empirical	

In aqueous solution, water molecules in direct contact with the solvent accessible surface areas of both the ligand and the protein are known as hydration shell waters. The

hydration shell waters of both the ligand as well as the binding site are, in general, more ordered than the bulk solvent waters. For waters in proximity to non-polar surface areas, this increased order is due to stronger hydrogen bonding (very similar to surface tension). For waters in proximity to charged or polar regions, the favorable electrostatic interactions “lock” the waters in place, also decreasing their entropy. When a ligand binds, these “ordered” waters are released, increasing entropy and thus favorably contributing to ΔG_b (equation 3). This “hydrophobic effect” more than compensates for the unfavorable energetic terms of desolvation [33]. In fact, the hydrophobic effect is considered to be the largest contributor to binding affinity [34]. Protein-ligand specificity is primarily due to structural complementarity of the ligand and the protein, hydrogen bonding, as well as electrostatic and Van der Waals interactions.

Hydrogen bonding requires some additional consideration with regards to scoring functions that model ΔG_b . As discussed above, hydrogen bonds generally contribute to specificity but *not* significantly to binding affinity [34]. A desolvation penalty must be paid when water is “removed” from the ligand and the protein binding sites resulting from the loss of hydrogen bonds between the ligand and/or protein and solvent waters. This penalty is *approximately* balanced by the hydrogen-bonding energy gained through ligand-protein interactions. A significant cost in free energy due to these enthalpic contributions is therefore paid for *via* unsatisfied hydrogen bonds, which reduces the overall binding free energy.

Scoring functions also need to address entropic contributions from the ligand and protein. These include translational, rotational, vibrational, as well as conformational entropic losses of the ligand and protein when they form a complex. Because of these factors, the “internal energies” of the ligand and protein in a complex are often higher than they are in their “free” solvated states [34]. This is consistent with a mechanism of action for enzymes that use the binding energy to “tweak” substrates closer to transition state structures in order to lower the activation energy and thus speed up the reaction.

As an example, there is a linear correlation ($R^2 = 0.88$) between the differences in conformational (e.g., “internal”) energies between the bound conformations of several HIV-1 protease inhibitors and their gas-phase minimized conformations *vs* their experimentally determined binding affinities [35]. From this analysis it was observed that the most potent, tightly bound inhibitors had the largest deviations from their gas phase minimized conformations, suggesting that the free energy of binding, ΔG_b , is compensating for the less energetically favorable conformations. In practice, it is often difficult to directly compare experimentally determined ΔG_b values with calculated values as these will differ based on experimental conditions such as temperature, concentrations, pH, pressure, ionic strength, etc. Additionally, it is also very difficult to model all the factors involved (especially the entropic and solvent terms). Fortunately, for screening or lead optimization purposes, it is less important to get the correct value than it is to correctly rank ligands with respect to their binding affinities. Often the free energy of binding is simply calculated as follows:

$$\Delta G_b = G_{complex} - (G_{ligand} + G_{protein}) \quad (5)$$

The next sections will describe the different approaches used in the most common scoring functions.

Empirical Scoring Functions

Empirical scoring functions decompose the free energy of binding into the contributions from hydrogen bonding, Van der Waals interactions, electrostatics, hydrophobic interactions as well as the entropies of the ligand and binding site. These factors are each scaled by constants that have been “calibrated” by regression of experimentally-determined binding affinities. One potential concern when using empirical scoring functions is their general applicability when attempting to correctly score compounds from scaffolds that differ from those used during model training. A “typical” empirical scoring function is as follows:

$$\Delta G_b = \Delta G_{H-bond} + \Delta G_{vdw} + \Delta G_{elec} + \Delta G_{hydrophobic} + \Delta G_{conformation} \quad (6)$$

where the Van der Waals term (ΔG_{vdw}) most often uses a Lennard-Jones 6-12 potential (although this varies) and $\Delta G_{conformation}$ refers to the conformational free energy lost when a ligand binds. The most common empirical scoring functions include: LUDI [36, 37]; Autodock [38] (this also contains force field components); ChemScore [39]; eHiTS [40]; FlexX [41]; F-Score [41]; GlideScore [42, 43]; Hammerhead [44]; HINT [45]; LigScore [46]; PLP [47]; SCORE [48]; SCORE 3.0 [49]; ScreenScore [50]; SIE [51]; and X-Score [52].

Force Field Based Scoring Functions

Another equation used to calculate the free energy of binding is

$$\Delta G_b = E_{forcefield} - T\Delta S_{solute} + \Delta G_{solvent} \quad (7)$$

$E_{forcefield}$ is often calculated using molecular mechanics force fields such as the ones used in CHARMM [53] and AMBER [54]. This term estimates the internal energies, the coulombic interactions including the Van der Waals interactions as well as hydrogen bonding. The entropy and solvent terms are calculated separately using a variety of techniques [14, 34]. These are often treated with terms from empirical scoring functions as in AutoDock [38]. A typical force field generated energy term, such as the one used in AMBER [54] is presented below:

$$\begin{aligned} E_{forcefield} = & \sum_{bonds} K_r (r - r_{eq})^2 + \sum_{angles} K_\theta (\theta - \theta_{eq})^2 \\ & + \sum_{dihedrals} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] \\ & + \sum_{nonbond} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\epsilon R_{ij}} \right] \\ & + \sum_{H-bonds} \left[\frac{C_{ij}}{R_{ij}^{12}} - \frac{D_{ij}}{R_{ij}^{10}} \right] \end{aligned} \quad (8)$$

where K_r , K_θ , A_{ij} , B_{ij} , C_{ij} , D_{ij} are constants, r is the bond length, r_{eq} is the equilibrium bond length, θ is the angle, θ_{eq} is the equilibrium angle, ϕ is the dihedral angle, n is the pe-

riodicity, q_i and q_j are atomic charges, ϵ is the dielectric constant and R_{ij} is the distance between the atoms. One major weakness of force-field based scoring functions is that larger ligands are often scored better simply because of their larger size. Another weakness is that distances are often limited in order to speed up the calculations which can affect estimation long range binding interactions. Examples of force-field based scoring functions include: Autodock [38]; DockScore [55]; D-Score [56]; GOLDScore [57, 58]; G-Score [56]; ICM [59]; QXP [60]; RankScore [61]; SIE [51]; and VALIDATE [62].

Knowledge-Based Scoring Functions

Knowledge-based scoring functions are generated by converting the frequencies of ligand atom - protein atom interaction pairs into free energies using Boltzmann distributions. These are called potentials of mean force (PMF). Atom types can be defined based upon their environments attempting to model complex, non-linear binding interactions. These scoring functions are efficient computationally and are therefore useful in virtual screening. Perhaps more importantly, knowledge-based functions are not limited by structure class of ligand (as empirical scoring functions can sometimes be) nor by the structure of the protein (as is the case with force-field based scoring functions). The major weakness of knowledge-based scoring functions is that under-represented atom interactions in the Protein Data Bank (PDB) (e.g., metals or halogens) will not be modeled or scored. In essence, these scoring functions are statistical in nature and work best when the numbers of interactions are large. Additional terms are often added, to account for solvation, solvent molecules, and to better correlate with experimental data. A typical knowledge based scoring function such as the one used in DrugScore [63, 64] is

$$\Delta W = \gamma \left[\sum_{k_i} \sum_{k_l} \Delta W_{ij}(r) \right] + (1-\gamma) \left[\sum_{k_i} \Delta W_i(SAS, SAS_o) + \sum_{k_l} \Delta W_j(SAS, SAS_o) \right] \quad (9)$$

where SAS is the solvent accessible surface, ΔW_{ij} is the interaction term between k_i ligand atoms of type i and k_l protein atoms of type j and γ is an adjustable parameter optimized empirically to be 0.5. Examples of force field-based scoring functions include: BLEEP [65]; DrugScore [63, 64]; M-Score [66]; PLP [47, 67]; PMF [68-71]; and SMOG [72-73].

Consensus Scoring

As each scoring function has its own strengths and weaknesses, it is difficult to identify one that will work well across different classes of protein targets. Recent studies have compared docking programs and scoring functions across a wide range of targets [50, 74-97]. In these comparisons, "decoys" or false positives that are similar in structure to true actives are often used in an attempt to simulate more realistic screening conditions [98]. The results of these studies suggest that there does not seem to be *one* docking program or *one* scoring function that works best in all cases [99]. Many of the more popular docking programs (e.g., Autodock, FlexX, FRED, Glide, Gold, LigandFit, MoeDock and MolDock - to name a few) all seem to do a fairly good job obtaining "correct" poses - or at least ones that are con-

sistent with experimental structure data [91]. Scoring functions, on the other hand, tend to have rather poor correlations with experimental binding or inhibition data with Pearson correlation coefficients often much less than 0.5. From a very practical point of view, the selection of a docking program is perhaps less important than selection of the scoring function to use for a particular target of interest [100, 101]. For novel targets or for targets where experimental data is scarce, this can be difficult or even impossible. In these cases, preliminary docking studies will have to be performed using one or more scoring function(s). As experimental data becomes available, the choice of scoring function can be re-evaluated.

Some guidance for initial selection of scoring function can come from an analysis of the binding pocket. In practice, scoring functions tend to emphasize either: a) hydrogen-bonding interactions or b) hydrophobic and Van der Waals interactions. Selection of the best scoring function will therefore depend in part upon the types of intermolecular protein-ligand interactions present in the specific target of interest. For example GOLDScore, Xscore, PLP (1&2), as well as the Molegro scoring functions all have highly weighted hydrogen-bonding terms and seem to work well in targets where hydrogen-bonding plays an important role in binding [102, 103]. On the other hand, scoring functions like ChemScore, which emphasize Van der Waals and hydrophobic interactions, seem to work better for binding sites with large non-polar surface areas. In a recent study, several different scoring functions were evaluated for use in virtual screens against thymidine kinase and estrogen receptor [76]. The PMF and FlexX scoring functions seemed to work best for the relatively polar thymidine kinase active site while DockScore worked best for the apolar estrogen receptor binding site. Consensus scoring was introduced as a way to offset the weaknesses of individual scoring functions [104]. This approach works best when the scoring functions combined have terms that are *not* significantly correlated [105]. Consensus scoring has been implemented in many of the commercially available docking packages (e.g., Accelrys, Autodock and Tripos) as well as in stand-alone packages such as X-Score [52].

QSAR, COMPUTATIONAL INTELLIGENCE AND MACHINE LEARNING

Given the difficulties discussed above, there is great interest in the development of improved scoring strategies to more accurately predict protein binding affinities [9, 14, 27]. One relatively new and promising approach is the application of tools and techniques borrowed from the field of computational intelligence [15, 106]. The advantage of these approaches is that predictive models can be built for processes that are extremely complex and where our understanding of the fundamentals is limited [107]. For drug discovery, these approaches are used to predict experimental activities based on descriptors or features. This requires a method of supervised learning using a set of descriptors or features coupled with experimental values such as binding activities. This section presents a brief introduction to QSAR, artificial neural networks, fuzzy logic, evolutionary algorithms, as well as machine learning.

QSAR Models

Since its introduction in 1969 [108], QSAR models have proven to be very effective in predicting experimental activities based on molecular descriptors or features. Examples of these calculated descriptors often include: counts of features (e.g., hydrogen bond acceptors, hydrogen bond donors, aromatic ring systems, carbonyl groups, basic nitrogens, carboxyl groups, etc.); physico-chemical properties including dipole moment, volume, polarizabilities, water-octanol partition coefficients, solubility, molecular weight, melting point, boiling point, heat of sublimation, molar refractivity, etc.; topological indices and atom connectivities such as branching indices, kappa shape indices, electrotopological state indices, atom-pairs, topological torsions, etc.; surface areas both polar and non-polar; and calculated intramolecular energies (both quantum mechanical as well as empirical). There are literally thousands of molecular descriptors currently available. To be useful to the medicinal chemist, the large number of descriptors needs to be decreased in order to build a robust and predictive QSAR model. A variety of techniques are typically employed for this purpose including multiple linear regression (MLR), partial least squares regression (PLS), and principle component analysis (PCA). These approaches require an assumption that the features and activity are linearly separable. Artificial neural networks have proven useful for selection of features that are nonlinearly correlated to small molecule activities [106, 109-116].

A pharmacophore is the three dimensional substructure of an active compound or structure class that is both necessary and sufficient for bioactivity. Pharmacophore modeling involves aligning a set of active compounds structurally against a target. Common structural and chemical features are then identified that most commonly include: hydrogen bond donors and acceptors, charged or polar groups, and aromatic groups. The distances and angles between the features are then calculated and used to generate a pharmacophore model. Compounds can be screened against this model and scored by how well they fit the model.

Comparative molecular field analysis (CoMFA) is a variation of pharmacophore modeling where the structural alignment is performed in a lattice of grid of points to which a molecular force field is applied [117]. An interaction energy is calculated for the molecule at each point that typically has steric, electrostatic and hydrophobic terms. As is the case for simple QSAR models, PCA and/or PLS are typically used to decrease the number of descriptors and the model is generated. Comparative molecular similarity indices analysis (CoMSIA) is very similar to CoMFA but is based on molecular similarity instead of interaction fields [118].

Artificial Neural Networks

Artificial neural networks (ANNs) are a computer science paradigm that makes use of an abstract modeling of the neuronal structure of the brain as a tool for pattern recognition [119-121]. ANNs (or more commonly referred to as simply "neural networks" in the computer science community) are transfer functions that accept some number of input features and yield some output decision. These models can be used to learn a relevant mapping of inputs to output deci-

sions over a training set of examples. For example, with respect to QSAR, the input can be various physico-chemical descriptors such as polar surface area (PSA), dipole moment, solubility, octanol-water partition coefficients, number of hydrogen bonds, etc. with the output being a decision concerning the likelihood of activity or relative binding affinity [109]. A typical ANN architecture consists of an input layer, one or more hidden layers, and an output layer (Fig. 2). A linear neural network model would have no hidden layer, with the input nodes being directly connecting to the output node(s). As long as the input-output mapping is not one-to-many (i.e., the same input having varying output), there exists a neural network that will map every input pattern to its appropriate output pattern.

Fig. (2). An artificial neural network architecture using six input nodes, two hidden layers, and one output node. This architecture is a feed-forward multi-layer perceptron. Other architectures are possible making use of recurrence, a variable number of connections, variable number of nodes, nodes per layer, layers, processing elements internal to each node, and so forth.

Given the ease with which QSAR features can be calculated, the modeler then is required to determine which features should be included or excluded from the model as input. In addition, the weights of importance for each of these features (and all of their combinations) with respect to maximizing predictive accuracy on the output decision over the training examples may be unknown. A process of optimization is typically used to vary the weights and/or architecture of the neural network to minimize the mean squared error between the predicted output and actual values over the training set. There are a wide variety of training algorithms for this purpose, the most common of which is a method of

backpropagation for weight adjustment [122]. Once defined, the best model resulting from training is tested over a validation set of held-out examples not used during training and the model can be re-designed if necessary. In some cases a second held-out testing set of data is used to assess final predictive accuracy.

Fuzzy Systems

Fuzzy systems (also known as “fuzzy logic”) attempts to capture the uncertainty and imprecision that are not easily quantified by other methods. Based on fuzzy set theory [123, 124], fuzzy algorithms have proven useful for clustering or classification in bioinformatics [125-129] where they are used to handle uncertainties in rule-based representations. For example, for drug activity prediction, a fuzzy model representation might take the form:

IF the RMSD of the pose from the template is CLOSE TO 2Å and the score is CLOSE TO 8.00

THEN the decision of active is TRUE

or

IF the score is ACTIVE and compliance to the Rule of Five is MOSTLY TRUE

THEN the decision of drug-likeness is TRUE

Fuzzy systems are extremely powerful when the inputs being used to generate the model do not separate cleanly into discrete values or are subjective. Instead of forcing the inputs or continuous variables into partitions based on user defined discrete intervals, a fuzzy system can be designed to represent membership in vaguely defined partitions. This is useful when the discrete interval boundaries are largely subjective and/or difficult to determine empirically. There are many sub-disciplines of fuzzy logic theory that have been developed to handle linguistic variables, and many of these are appropriate for use in biological problems such as drug docking. For example, the differences between what are known as type-1 and type-2 fuzzy sets are clearly outlined in the literature [130] and are beyond the scope of this survey. Additional information on fuzzy logic types can be found in [131, 132].

Fuzzy systems have been applied to docking and screening in a variety of ways, although this is a relatively novel application area [133]. For example, the similarity between small molecules used for docking can be approximated using fuzzy rules based on overlapping shape or area rather than discrete values. This can be useful for identifying clusters of compounds with similar side chain conformation, even without the requirement of energy minimization approaches, which can be computationally expensive [134]. In some cases fuzzy clustering approaches can be more effective than Bayesian neural network approaches for small molecule clustering, and this gives the possibility for significant advancement in the near future in this area [135].

Evolutionary Computation

Evolutionary algorithms (EAs) are typically computer-based representations of natural evolution as a population-based optimization process (Fig. 3). EAs commonly make use of random variation and selection as a means for discov-

ering solutions to complex problems. The basic principle of EAs is appealingly simple: 1) an initial population of solutions is generated, typically at random, 2) a portion or all of the individuals in the current population are altered at random using variation operators akin to mutation and/or recombination, 3) the worth of each individual in the population is evaluated with respect to a fitness function that is pre-defined by the user and a user-specified percentage of worst solutions are removed from the population, 4) the remaining solutions are used as “parent” solutions to generate “offspring” solutions with variation as described above, and 5) the process returns to step 2 unless a halting criterion has been met, such as exceeding a user-specified number of generations or available time. The various methods of evolutionary computation include: evolutionary programming [136]; evolution strategies [137]; genetic algorithms [138-140]; genetic programming [141]; particle swarm optimization [142]; ant-colony optimization [143]; and differential evolution [144, 145]. Each approach has its own advantages and disadvantages relative to specific problems. The “No Free Lunch” theorem indicates that no single optimization approach will work best over all problems [146]. This is actually a very similar result to the realization noted above that there seems to not be one single drug docking algorithm that works best for all drug discovery problems.

Fig. (3). A flow diagram of a standard evolutionary algorithm. The loop of variation, scoring, and, generation of parent solutions for the next “generation” of evolution continues until a termination criterion is satisfied.

Evolved Artificial Neural Networks and Evolved Fuzzy Systems

In addition to optimizing solutions to a particular problem, evolutionary computing can also be used to optimize neural networks [147, 148]. The evolutionary algorithm optimizes the connections (and weightings) between the input layer, the hidden layer(s), and the output layers and scores each ANN based on mean squared error between the predicted and actual outputs. Likewise, evolutionary algorithms can be used to optimize fuzzy classifiers or fuzzy inputs. Evolutionary computing can also be used to evolve the selec-

tion of features to be used in a model simultaneous with the optimization of that model's architecture [149-152].

Other Common Approaches for Machine Learning

Support vector machines (SVM) have recently been used for prediction of compound activities [153-155]. Support vector machines represent the input descriptors/features as vectors that are projected onto higher-dimensional space. An optimal hyperplane is then constructed separating the actives and inactives. The hyperplane is used to predict the activity of new compounds that are tested [156-158]. Another technique recently used is that of Naïve Bayesian categorization [159-161]. Naïve Bayesian categorization is based on Bayes' rule for conditional probability and is useful to classify compounds as active or inactive. The models are statistical in nature and are based on the frequency of the descriptors in the training set.

APPLICATIONS OF COMPUTATIONAL INTELLIGENCE AND MACHINE LEARNING TO SCORING FUNCTIONS

Current efforts for improving scoring functions with computational intelligence and machine learning techniques and applications can be categorized into one of the following four areas: development of improved solvation and entropy terms; consensus scoring; pre- and/or post-filtering (often with QSAR and CoMFA models); and finally optimization of novel target specific scoring functions.

Improved Solvation and Entropy Terms

It is well accepted that scoring functions contain simplifications and approximations that limit their ability to fully account for entropic and solvent effects and thus do not accurately calculate ΔG_b [9, 14, 27, 34]. The scores that are generated by these functions are *not* the binding free energies - although they may be proportional to them to varying degrees. However, these scores are useful as a direct measure of how well a ligand's pose complements the binding site and thus are extremely useful for selection of poses during the docking process. Recent efforts to optimize scoring functions have focused on adding/improving these entropy and solvent terms. Very often, computational intelligence techniques have been employed for descriptor selection and model optimization. Several current examples of this approach are listed below.

LigScore1 & 2, are widely used scoring functions included in Accelrys software (LigandFit) [46]. These scoring functions were developed (including feature selection) and optimized using EAs. In another recent example, a combination of PLS, ANNs, and EAs were used in the design of new QXP scoring functions by optimizing the solvent and entropy terms [162]. More recently a function for rapid scoring using an MD-averaged grid and the accessible surface area (FURSMASA) was developed using a combination of EAs and molecular dynamics simulations [163]. In validation experiments, all three examples performed well in comparison to existing methods. These validation experiments included large compound databases containing COX-2, HIV-1 protease as well as p38 inhibitors and decoys.

Consensus Scoring

As discussed previously, there has recently been interest in developing novel consensus scores. Computational intelligence and machine learning techniques have been used successfully to perform feature selection and optimization of the weightings for each term in the model. The scores (as well as relevant underlying terms) of each scoring function become the features in these models. Often, additional terms such as solvent and entropy terms, are added into these models. Recent examples include PLS analysis and SVMs. Targeted consensus scores were recently generated using partial least squares analysis for specific targets that included matrix metalloproteinases (MMP) [78] and acetylcholinesterase [164]. In the MMP study, PCA (using the different scores from the scoring functions) was used for pose selection in the PLS model. The acetylcholinesterase study simply used the pose with the top consensus score. PLS was also used to generate a more general scoring function based on 129 ligand-protein complexes spanning seven protein families [165]. SVMs were used recently to generate consensus scores for a several proteins including serine proteases, metalloenzymes and nuclear hormone receptors [166]. A method for feature selection was developed for choosing scoring functions that were complementary and enhanced enrichment.

Pre- & Post-Screening Filtering

Pre- and post-filters are routinely used in docking studies [8, 160, 167, 168]. These filters range from simple substructure searches for toxic or reactive groups to models based on physico-chemical and/or predictive ADME-tox properties (similar to the Rule-of-Five). A more sophisticated model using ANNs has proven to be useful at predicting reactive compounds and false positives [169]. Structural interaction fingerprints have also been used to filter docking results. These fingerprints create a binary string to represent the three dimensional structural binding information from a protein-ligand complex [170, 171]. These are computationally efficient and are useful in large virtual screens.

Perhaps the most successful approach has been the use of QSAR and pharmacophore models, including CoMFA and CoMSIA, to score docked poses [172-182]. The top scoring pose(s), are selected either by a single or by a consensus scoring function. Feature selection and the iterative process of model building are absolutely critical and can be time consuming processes. Again, EAs [183] and ANNs [184] have proven to be of great assistance at these tasks. Alternatively, QSAR models can be used to filter out compounds before docking [185]. The reported correlation coefficients for the validation of these approaches are often $R^2 > 0.90$. This represents a significant improvement over the performance of individual scoring functions where a $R^2 > 0.7$ is considered "good".

Novel Target Specific Scoring Functions

Most available scoring functions were designed to work across a very broad and diverse set of protein classes. From experience, it is clear that these will work better on some protein classes (as well as ligand structure classes) than on

others. There is currently great interest in developing target-specific scoring functions [9, 14, 15, 27, 100, 101] and a wide variety of techniques have been used. These include using: QSAR methodologies (both 2D and 3D) including MLR, PLS and PCA; Naïve Bayes; ANNs; and EAs. Traditional 1D- and 2D-QSAR methodologies such as MLR, PLS and PCA have proven to be useful in generating targeted scoring functions [61, 186-188]. COMBINE is perhaps the most well known of these [189-191]. There is even an example of an approach based on design of experiments methodology [192]. These methods all use or generate descriptors that are specific to the protein-ligand interactions with the target of interest in order to generate the QSAR models. As discussed previously, ANNs and EAs can be very useful in feature selection and QSAR model development. It should be no surprise that both ANNs [193, 194], EAs [195] and even fuzzy systems [196-198] have been used to customize scoring functions.

Other researchers have developed scoring functions using 3D- and 4D-QSAR methods. These techniques use target specific force fields for docking and/or scoring. Recently, adaptation of fields for molecular comparison (AFMoC) methodology modeled HIV-1 protease inhibitors with enhanced accuracy over other scoring functions [199]. This approach used a CoMFA-like force field that was tailored for HIV-1 protease. Finally, naïve Bayesian statistics have also been used in the generation of novel scoring functions [158-160]. This approach combined 2D descriptors (connectivity fingerprints) with scoring functions and applied Bayesian statistics to improve the enrichment for compounds tested against a variety of tyrosine kinases.

FUTURE DIRECTIONS

As discussed throughout this review, there is currently great interest in the generation of improved scoring functions. For lead discovery, these scoring functions must be able to minimize the number of false positives while remaining computationally efficient. For lead optimization, these scoring functions must be able to correctly rank order compounds by biological activity. Unfortunately, most scoring functions often do not have adequately modeled entropy and solvent terms. Scoring functions are, however, very good at modeling the complementarities between a binding site and a pose. More importantly, currently available scoring functions are often unable to correctly rank order compounds and have high numbers of false positives.

Several successful efforts to optimize scoring functions have focused on the entropic and solvent terms in the scoring function. Depending upon the scoring function, the methodology varies. Several examples were presented where computational intelligence techniques have been used for feature selection, model development, and optimization for both the individual terms as well as the scoring function as a whole. This is a very fruitful area for future research.

As it is clear that no scoring function works equally well across all protein classes, there also is a growing interest in developing targeted or customized scoring functions for specific targets or target protein classes including different compound scaffolds. For customized scoring functions to be adopted widely by the screening community, individual users must be able to *easily* generate their own customized

scoring functions. Ideally these capabilities should be built into the docking software itself. As an example, some software packages already allow for users to generate their own consensus scores (e.g., Accelrys, Tripos, Autodock). Molegro allows users to develop and use their own scoring functions with tools for performing MLR and for creating ANN models. All too often, however, rescoring poses with a different scoring function than the one that comes with the software package requires exporting the poses and the target binding site to yet another software package. Docking software packages should provide more flexibility for the development and/or use of user defined scoring functions.

Feature selection and model optimization are areas where computational intelligence techniques are of great use. In particular evolutionary computation can be used to quickly and efficiently select features and optimize models. A very powerful approach is to combine EAs with other modeling approaches such as ANNs [148] or fuzzy systems.

CONCLUSIONS

Here we reviewed the recent applications of computational intelligence methods to the development of scoring functions. This is a relatively new and promising area of research. There is a great opportunity for the development of novel approaches and methodologies that will increase the likelihood of finding and optimizing novel inhibitors using docking and scoring.

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