ParaDockS: A Framework for Molecular Docking with Population-Based Metaheuristics

René Meier,*[,†,‡,⊥] Martin Pippel,[†,⊥] Frank Brandt,[¶] Wolfgang Sippl,[†] and Carsten Baldauf*[,§,||,¶]

Department of Pharmaceutical Chemistry, Martin-Luther Universität Halle-Wittenberg, Wolfgang-Langenbeck-Strasse 4, 06120 Halle/Saale, Germany, Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 21a/II, 8010 Graz, Austria, Biotechnologisches Zentrum der TU Dresden, Tatzberg 47/49, 01307 Dresden, Germany, CAS-MPG Partner Institute for Computational Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, 320 Yue Yang Road, 200031 Shanghai, P. R. China, and Heidelberg Institute for Theoretical Studies (HITS), Schloss-Wolfsbrunnenweg 33, 69118 Heidelberg, Germany

Received December 1, 2009

Molecular docking is a simulation technique that aims to predict the binding pose between a ligand and a receptor. The resulting multidimensional continuous optimization problem is practically unsolvable in an exact way. One possible approach is the combination of an optimization algorithm and an objective function that describes the interaction. The software ParaDockS is designed to hold different optimization algorithms and objective functions. At the current stage, an adapted particle-swarm optimizer (PSO) is implemented. Available objective functions are (i) the empirical objective function p-Score and (ii) an adapted version of the knowledge-based potential PMF04. We tested the docking accuracy in terms of reproducing known crystal structures from the PDBbind *core set*. For 73% of the test instances the native binding mode was found with an rmsd below 2 Å. The virtual screening efficiency was tested with a subset of 13 targets and the respective ligands and decoys from the directory of useful decoys (DUD). ParaDockS with PMF04 shows a superior early enrichment. The here presented approach can be employed for molecular docking experiments and virtual screenings of large compound libraries in academia as well as in industrial research and development. The performance in terms of accuracy and enrichment is close to the results of commercial software solutions.

INTRODUCTION

Molecular interactions define all manifestations of life. Accordingly, knowledge of such processes is of paramount importance to current life science research and development in fields as diverse as medicine, biotechnology, and crop science. Upcoming challenges like fast-evolving infectious diseases, personalization of medicine, development of tailor-made enzymes or substrates, as well as the development of crop protective agents mark the need for rapid approaches that feature computational techniques.

Already since the late 1990s, computational approaches have gained considerable attention in the area of drug design.[1,2] In silico techniques from computational chemistry, bioinformatics, and systems biology apparently offer the chance to tackle these problems and to respond faster and in a more resource-conserving way than classical, pure wet-lab approaches. Molecular docking plays a key-role among the variety of approaches and techniques because it offers the chance to gain knowledge on the actual binding pose, the situation at atomic level that defines binding and function.

The three-dimensional structure of the complex formed by protein and ligand is key to the prediction of activities based on physicochemical models that describe the spatial and energetical properties of binding. Still, the high dimensionality and the complicated nature of the problem result in complex energy landscapes with many local minima. These features prohibit an analytic approach to molecular docking and thus, search strategies are employed to find the native pose of ligand and receptor. Most docking approaches generate a large number of complexes and evaluate their quality in terms of binding. Molecular docking thus means the generation and evaluation of molecular complexes to predict binding poses of protein ligand complexes. A way to categorize docking approaches follows the treatment of this high dimensionality:

- The ligand can be subdivided into rigid fragments. These are subsequently reassembled within the binding pocket. Such fragment-based techniques are used by FlexX,[3] Surflex,[4] and eHiTS.[5]
- The docking of ensembles of rigid ligand conformations results in high speed, but has its drawback in the fact that the biologically active conformation of a compound has to be part of the precalculated conformational ensemble. Examples are Fred[6] and early versions of Dock.[7,8]
- Heuristics-based techniques aim for the global minimum of an objective function, assuming this optimum is the effective complex. The search space of the algorithm is

* To whom correspondence should be addressed: E-mail: rene@paradocks.org (R.M.); caba@paradocks.org (C.B.).
† MLU Halle-Wittenberg.
‡ RCPE Graz.
¶ BIOTEC TU Dresden.
§ CAS-MPG PICB, Shanghai.
|| HITS, Heidelberg.
⊥ These authors contributed equally to this work.

10.1021/ci900467x
Published on Web 04/26/2010

defined by the degrees of freedom of ligand and protein. Population-based metaheuristics, mainly genetic algorithms (GA), are used by programs like GOLD[9] and AUTODOCK.[10]

Following the line of heuristic-based approaches, alternative search strategies have been proposed. The recently introduced docking program PLANTS[11,12] uses ant-colony optimization (ACO). Based on the AUTODOCK software, a number of particle-swarm optimization (PSO) approaches were presented: AUTODOCK with ClustMPSO,[13] SODOCK,[14] and PSO@AUTODOCK.[15] PSO is inspired by social behavior of animals, for example, bird flocking or fish schooling and was first suggested by Eberhart and Kennedy.[16] Intuitively, the PSO appears perfectly suited to tackle the continuous search space of protein ligand interaction within the molecular docking problem. This assumption is well supported by the performance and success of the published docking methodologies employing PSO variants. Of special interest is the easy adaptability of PSO, and other population-based metaheuristics, for parallel approaches, especially with the current rise of multicore CPU architectures.

The interaction between ligand and protein is described by a mathematical model, the objective or energy function. Important terms are the solvation energies of the protein, the ligand, and their complex ΔG_{sol}^{prot}, ΔG_{sol}^{lig}, and $\Delta G_{sol}^{complex}$, the change in entropy ΔS between bound and unbound state, the interaction energy ΔG_{int}, and the energy change in ligand and protein while the interaction is formed $\Delta\lambda$. All these terms contribute to the binding free energy according to eq 1[17]

$$\Delta G_{bind} = \Delta G_{sol}^{complex} - \Delta G_{sol}^{prot} - \Delta G_{sol}^{lig} + \Delta G_{int} - T\Delta S + \Delta\lambda \quad (1)$$

Practical considerations prohibit the correct estimation of ΔG_{bind}: (i) the large numbers of the individual contributions have to be balanced to avoid errors in the small values of the binding energy, especially with some contributions being only roughly estimated like entropy, and (ii) exact calculation demands a complete sampling of the conformational space for the ligand in the binding pocket, a very time-consuming task that is not feasible for high-throughput molecular docking of compound libraries.[17,18] Thus, a variety of approaches has been introduced that try to correctly rank of protein ligand poses toward the global optimum, the native state. In a test case, this means the reproduction of the X-ray structure. The available approaches can be categorized as follows:

- Force field-derived objective functions are based on the description of nonbonded interactions of established force fields. The terms used are based on physical laws and are accurate representations of the enthalpic contributions. DOCK[7,8] describes the nonbonded interactions partially with terms from the AMBER[19] force field. Within GOLD, the contributions of van der Waals-type interactions (vdW) are estimated by soft 8−4-Lennard-Jones potentials.[9]
- Empirically derived objective functions consist of a number of physics-inspired terms that describe, for example, hydrogen-bonds, ionic interactions, hydrophobic effects, entropy, π-stacking, or π-cation-interactions. These functions are trained to reproduce representative test sets. An advantage of empirical objective functions is their usually fast computational evaluation. GoldScore is in parts an empirically derived scoring function,[9] further examples are SCORE1[20] and X-SCORE.[21]
- Knowledge-based potentials stem from statistical evaluations of large data sets, for example, Protein Database. In contrast to the above-mentioned approaches, there is no limitation to the specifically described interactions because knowledge-based approaches try not to model individual interaction types. Rather, potentials intrinsically include all effects that can be extracted from experimentally derived structures. Well-accepted examples are BLEEP,[22,23] PMF[24] and PMF04,[25] and DRUGSCORE.[26]

Obviously, there is a multitude of energy functions and optimization algorithms available and many new developments can be expected in the future. To us, this clearly renders the need for a platform that allows the convenient incorporation of existing and new approaches either to describe ligand−receptor interaction or to search for the native pose. Even though a wide variety of programs to solve the molecular docking problem exists, there are disadvantages:

- Closed source distributions cover the approaches used for computations for the interaction, as well as for sampling and for energy estimation. This makes results and approaches not comparable and limits progress.
- Restricted licensing policies hinder the redistribution of self-developed code.
- Monolithic code and outdated programing standards limit the extension and further development of several existing approaches.

Our newly developed docking software has the chance to avoid these issues and to satisfy the needs of users and developers from industry and academia. The development of the Parallel Docking *S*uite (PARADOCKS) software follows these rules:

- PARADOCKS will be distributed as open source code under a nonrestrictive license (GPL).
- Design and implementation should result in an as far as possible platform and operating system independent software.
- If actively maintained programs or libraries are available for certain problems, they will be used.
- Parallel computer systems, compute clusters, and multicore workstations become more and more widespread, thus parallel data processing is a major goal of PARADOCKS.
- The program should be usable with automated pipelines for virtual screening and drug design.

Within this article we will describe the PARADOCKS framework for molecular docking. The Materials and Methods section will introduce basic design principles and their implementation and will cover specifics regarding the implementation of optimization algorithms and objective functions. The latter two will be illustrated by example implementations of a PSO, as well as the p-Score and PMF04[25] objective function. The Results section deals with the assessment of the docking accuracy as well as testing the applicability for virtual screening of PARADOCKS.

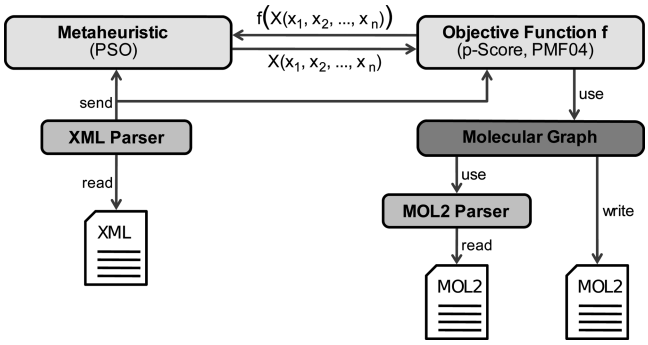


Figure 1. PARADOCKS design scheme. Boxes represent classes and arrows represent the interfaces.

MATERIALS AND METHODS

Problem Description. We approximate the ligand as a flexible molecule and the receptor as rigid. The interaction between ligand and receptor is described by an objective function that depends on three types of degrees of freedom: (i) The position of the ligand molecule is described by three values x, y, z in Cartesian coordinate space. (ii) The rotational degrees of freedom are modeled as a quaternion $H = x_1 + x_2i + x_3j + x_4k$. This representation overcomes the gimbal lock problem of Euler angles which, under special conditions, results in the loss of one degree of freedom. Unit quaternions are a non singular representation of rotations and widely used in the field of three-dimensional computer graphics.[27] (iii) The flexibility of the ligand is accounted for by free rotation of torsion angles (single bonds) of the ligand. This results in a variable number of degrees of freedom that depends on the size and topology of a molecule, meaning conformers of a molecular conjugation. The resulting dimensionality of the continuous search space is therefore $7 + T$ (with T being the torsion number). The goal of a molecular docking simulation is the prediction of the native bound structure of a ligand in the binding site of its receptor, which is assumed to be the global optimum of the search space. It is an accepted approach to solve this molecular docking problem, namely the finding of the native pose, using an optimization algorithm.

Framework Design. The PARADOCKS software is written in C/C++ and consists of modular functional units. Communication is realized via interfaces (cf. Figure 1). Parallel data processing is implemented via the Message Passing Interface (MPI). The input files are in XML format for simulation setup and in MOL2 format[28] for ligand and receptor coordinates. Subsequently, a molecular graph is created for the ligand. Information on position, orientation, and conformation of the ligand is stored in a $7 + T$-dimensional vector. The information is passed to the objective function for energy evaluation. The energy value (fitness of the solution) is passed back to the metaheuristic and a new iteration starts with the generation of new solutions. PARADOCKS can hold different objective functions and optimization algorithms. In addition, basic paradigms can be changed; this includes an increase of the number of degrees of freedom (e.g., by receptor flexibility), the linking to external programs for energy evaluation, or even the employment of multiobjective optimization.

Our aim is to present well working and robust software for molecular docking. Beyond that, we want to invite other scientists to participate in a joint development effort to improve the program and to expand its functionalities. To enable that we publish the source code of PARADOCKS under the GNU General Public License (GPLv2)[29] to ensure its free use, the freedom to modify the underlying code, and the redistribution. All parts of the program are as generic as possible and should at least be fit for all metaheuristics-based docking approaches. Implementation of new approaches, namely, energy functions or search strategies is therewith limited to the respective core functionalities, generic components need only little to no modification. All public classes and functions as well as the application programming interface (API) are documented by the documentation system Doxygen.[30] We supply an advanced algorithm for the atom type deduction based on topology subgraph matching similar to the SMARTS[31] system. The parsing of MOL2 files is performed by a robust algorithm based on an Extended Backus-Naur Form[32] grammar. To allow easy testing of self-implemented approaches, we provide an rmsd calculation program for small molecules which takes molecular symmetry into account.

Optimization Algorithm. By design, PARADOCKS is able to be used with different optimization algorithms. Based on promising results by others,[13–15] we decided to use particle swarm optimization as an exemplary optimizer implementation. The algorithm implemented here follows PSO as introduced by Eberhart and Kennedy.[16] Optimization starts with a population of random solutions; the search for optima is facilitated by updating generations, making the swarm virtually fly through the search space. The best position in search space so far (best solution achieved) is tracked for the individual particle as well as for the whole swarm. With the change of generations of the swarm, the particles are accelerated toward these best solutions. These accelerations are weighted by random terms. The algorithm is shown in Algorithm 1 and features two modifications to the original algorithm: (i) an inertia weight c_0 decreasing linearly over time[33] and (ii) the reinitialization with random position and velocity of particles leaving the area of interest (the proximity of the binding pocket). Initialization distributes the particles equally in the search space. After evaluation of the objective function, positions of each particle get adjusted toward the best configuration in the particle's history as well as toward the configuration of the current best particle of the swarm. The linearly decreasing inertia weight c_0 in our implementation is intended to force exploration of the search space and convergence to the global minimum (exploitation).

Algorithm 1: Particle Swarm Optimization
for every particle P **do**
  $P_X \Leftarrow$ random_ position ()
  $P_V \Leftarrow$ random_velocity ()
  $P_{BX} \Leftarrow P_X$
  $P_{BF} \Leftarrow f(P_X)$
end for
$i \Leftarrow 0$
while $i <$ maximum iterations **do**
  for every particle P **do**
    if molecule not in binding pocket **then**
      $P_X \Leftarrow$ random_position ()
    end if
    $N \Leftarrow$ neighborhood_best (P)

$$P_V \Leftarrow \left(c_0 - \frac{i}{\text{maximum iterations}}\right)P_V + c_1 r_1(P_{BX} - P_X) + c_2 r_2(N_{BX} - P_X)$$

$P_X \Leftarrow P_X + P_V$
$F^* \Leftarrow f(P_X)$
if F^* better P_{BF} **then**
$P_{BF} \Leftarrow F^*$
$P_{BX} \Leftarrow P_X$
end if
end for
end while

LEGEND: P_X = particle position; P_V = particle velocity; P_{BX} = best position of the particle; P_{BF} = best fitness of the particle; $f(x)$ = fitness function; c_0 = inertia weight; c_1 = cognitive weight; c_2 = social weight.

Objective Functions. *p-Score.* The p-Score objective function is an empirically derived energy function. The docking energy E_{dock} is dissected into

$$E_{dock} = E_{vdW} + E_{estate} + E_{internal} \quad (2)$$

The van der Waals (vdW)-type interactions are modeled by a Lennard-Jones potential calculated for pairs of the ligand $\mathscr{L}$ and protein $\mathscr{P}$ atoms

$$E_{vdw} = \sum_{i\in\mathscr{P}}\sum_{j\in\mathscr{L}}\left[\left(\frac{d_{0ij}}{d_{ij}}\right)^8 - 2\left(\frac{d_{0ij}}{d_{ij}}\right)^4\right] \quad (3)$$

The optimal vdW distance d_{0ij} between atoms i and j is the sum of the vdW radii of atom i and atom j. d_{ij} is the actual distance between atoms i and j. The 8−4 form of the potential is "softer".[34] The resulting reduced penalty for close contacts accounts for a limited flexibility of the receptor without explicitly modeling receptor flexibility.[35] $E_{internal}$ is defined as an 8−4 potential of the same form as E_{vdW}. But with the difference that only destabilizing positive values contribute to E_{dock}. $E_{internal}$ acts solely as penalty for internal vdW clashes.

The second contribution to the p-Score docking energy describes electrostatic interactions. This type of interaction is crucial for a correct description of specificity and affinity and hence crucial for molecular docking. The strength of the interaction depends on orientation and distance and thus E_{estat} is calculated by an angle- and distance-dependent potential

$$E_{estat} = \sum_{i\in\mathscr{P}}\sum_{j\in\mathscr{L}} f(d_{ij})f(\theta_{1ij})f(\theta_{2ij}) \quad (4)$$

In all cases, the energy contribution depends on the distance d_{ij} of the atom pairs i and j. The function terms $f(\theta_{1ij})$ and $f(\theta_{2ij})$ are not needed (set to 1) for ionic interactions as there is no angle dependency for this type (cf., Figure 2a), whereas lone-pair or hydrogen bond interactions demand modeling of the angle dependency. The description distinguishes between potentials for ionic interactions and hydrogen bonding with freely rotatable or frozen donor and acceptor atoms. A donor or acceptor atom is considered to be frozen if it is within a chain of heavy atoms, otherwise, if it is the terminal of a chain of heavy atoms, its lone pair or hydrogen can rotate freely. In the case of a freely rotatable hydrogen or lone pair θ_{1ij} and θ_{2ij} are calculated between the heavy atoms of the hydrogen bond as shown for atom j in Figure 2b and atom i in Figure 2c. For frozen donor and acceptor atoms the angles θ_{1ij} and θ_{2ij} correspond to the angle between the hydrogen or lone pair, respectively, and the two heavy atoms of the hydrogen bond as shown in Figure 2d. The linear potentials follow the formulas

$$f(d_{ij}) = \begin{cases} 1 & d_{ij} \le (d_{0ij} - k_1) \\ (1/k_1)\cdot(d_{0ij} - d_{ij}) & (d_{0ij} - k_1) < d_{ij} \le d_{0ij} \\ 0 & d_{ij} > d_{0ij} \end{cases} \quad (5)$$

$$f(\theta_1) = \begin{cases} (1/k_2)\cdot(k_2 - |\theta_1 - k_i|) & 0 \le |\theta_1 - k_i| \le k_2 \\ 0 & |\theta_1 - k_i| > k_2 \end{cases} \quad (6)$$

$$f(\theta_2) = \begin{cases} (1/k_3)\cdot(k_3 - |\theta_2 - k_j|) & 0 \le |\theta_2 - k_j| \le k_3 \\ 0 & |\theta_2 - k_j| > k_3 \end{cases} \quad (7)$$

The last term of eq 2, $E_{internal}$, evaluates the ligand conformation for vdW-clashes by using an 8−4-Lennard-Jones potential for all ligand atoms i and j which have at least 4 bonds distance

$$E_{internal} = \sum_{i\in\mathscr{L}}\sum_{j\in\mathscr{L}}\left[\left(\frac{d_{0ij}}{d_{ij}}\right)^8 - 2\left(\frac{d_{0ij}}{d_{ij}}\right)^4\right] \quad (8)$$

PMF04. PMF04 is a knowledge-based objective function. This allows the exploitation of the vast amount of experimentally determined protein−ligand structures as a basis for molecular docking. Muegge et al. have shown the capability of statistical potentials for molecular docking by implementing PMF scoring[24] into the DOCK4 program.[36] We implemented the statistical potential PMF04[25] for molecular docking with PARADOCKS. PMF04 is derived from 6611 protein ligand complexes and describes the interactions of 17 protein atom types with 34 ligand atom types in form of pairwise potentials

$$W_{ij}(d_{ij}) = -\ln\frac{g_{ij}(d_{ij})}{g_{ref}} \quad (9)$$

with $g_{ij}(d_{ij})$ the density of the atom pair ij in distance d_{ij} and g_{ref} the average density of atom pair ij. For a detailed description, we point to the original publication.[25] We will continue with the necessary adaptations to use PMF04 as an objective function for molecular docking with PARADOCKS. The original close distance penalty of 3 kcal/mol is far too low for use with molecular docking, since its use results in overlapping of the ligand with receptor atoms after optimization. To circumvent this, the repulsion part of an 8−4 Lennard-Jones-potential has been added as the close distance penalty of PMF04. The Lennard-Jones-potential $E_{internal}$ (cf., eq 8) describes the conformation of the ligand. The docking energy E_{dock} is calculated as follows:

$$E_{dock} = E_{PMF04} + a\cdot E_{internal} \quad (10)$$

with

$$E_{PMF04} = \sum_{i\in\mathscr{P}}\sum_{j\in\mathscr{L}} W_{ij}(d_{ij}) \quad (11)$$

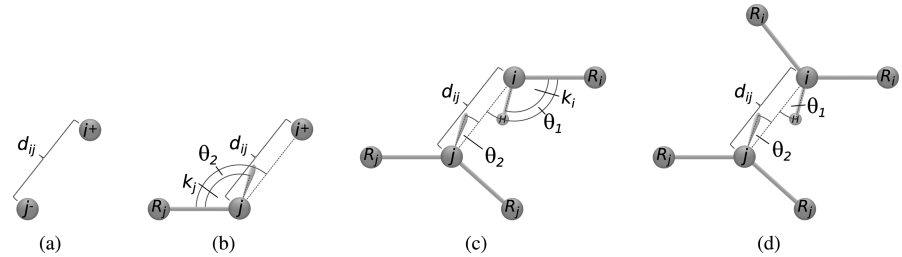


Figure 2. p-Score differentiates between multiple possibilities for electrostatic interactions, for example, (a) ionic interactions, (b) cation−lone pair interactions, (c) frozen acceptor and rotatable donor, and (d) frozen acceptor and donor.

RESULTS AND DISCUSSION

Parameter selection for the PSO and the objective functions, as well as the benchmarking for docking accuracy and virtual screening performance of PARADOCKS, were performed under the following paradigm: a useful molecular docking setup has to distinguish the quality of different poses of a receptor−ligand pair, as well as the quality of different potential ligands with respect to a receptor. The actual performance was compared to GOLD;[9] for further comparison, we point the reader to recent articles that feature extensive performance analysis of docking algorithms.[15,37–39] Parameter selection was performed on the (*Astex Diverse Set*[40]). For the evaluation of the docking accuracy, the PDBbind *core set*[41] was used; for assessing the virtual screening performance the directory of useful decoys (DUD)[42]) was employed. For all docking setups, identical initial coordinates of the ligand and the receptor were used. Where necessary, hydrogens were added to the crystal structures with the MOE program.[43] The initial conformations and orientations of all ligands were randomized.

Parameter Selection. *Particle Swarm Optimizer.* We found a limit of 150 000 iterations and a number of 20 particles to be sufficient for a good sampling and robust results. The search efficency is best with a cognitive weight $c_1 = 1.0$, a social weight $c_2 = 3.4$, and a constricting inertia weight c_0 ranging from 1.0 to 0.2. These parameters were selected in systematic tests of parameter combinations. The complex of the HIV-1 reverse transcriptase and its inhibitor TNK-651 (PDB 1JLA)[44] served as a typical example with 7 rotatable bonds and therefore average dimensionality. Because of its nondeterministic nature, every molecular docking experiment was repeated 400 times to generate comparable average results (this computation takes about four hours on a single 2.53 GHz Intel Xeon CPU). The average of the optimized score was compared and the parameter combination with the best average score is listed above.

p-Score. The parameters for p-Score were derived based on the assumption that an energy function for molecular docking has to evaluate the X-ray structures of a training set always better than alternative structures. The p-Score parameters to be optimized were the optimal vdW distances d_{0ij} as used in eqs 3 and 8 and k_1, k_2, and k_3 as in eqs 5−7.

The Astex Diverse Set,[40] a collection of high resolution (<2.5 Å) crystal structures of proteins and their drug-like ligands, was used as training set. For each protein ligand pair of the test set, 50 ligand conformations (decoys) with an rmsd relative to the X-ray structure above 2 Å and at least 22 decoys with an rmsd < 2 Å were generated. All decoys differed with an rmsd > 2 Å from each other. In the following, each of the up to 80 decoys per protein ligand pair was evaluated with an parameter set for the p-Score objective function. To indicate the quality of a parameter set, the ratio between decoys evaluated better or worse than the crystal structure was estimated

$$\mathrm{QP} = \frac{\text{number of decoys scored better than crystal structure}}{\text{number of decoys scored worse than crystal structure}}$$

An initial set of parameters was taken from X-SCORE[21] and improved by means of a randomized local search minimizing QP until no substantial changes of QP were observed anymore. The parameter optimization result was QP = 0.051, meaning that in more than 95% of all cases the crystal structure scores better than the decoys. The quality of the resulting vdW parameters can be seen in the fact that for 89% of all ligands in the PDBbind core set[41] we find at least one generated conformation which has an rmsd of less than 2 Å to the X-ray structure. The resulting vdW distances d_{0ij} and the electrostatic parameters k_1, k_2, and k_3 for the p-Score function can be found in the Supporting Information.

PMF04. Factor $a = 0.25$ of eq 10 was found by an exhaustive search with the objective of accumulating docking poses from the Astex diverse set that have an *rms*d below 2 Å to the X-ray structure.

Docking Accuracy. The PDBbind core set[41] contains 210 protein ligand pairs in 70 groups. Each group consists of proteins whose sequences are highly similar but that are complexed with ligands of low, medium, or high affinity, respectively. PARADOCKS runs were repeated 50 times per complex, and default parameters for the PSO were used. GOLD was used with automatic parameter settings with a selected search efficiency of 100%. The results of the docking simulations were clustered with a 2 Å rmsd cutoff and compared to the respective X-ray structures. A histogram plot of the results is shown in Figure 3, and numerical values are given in Table 1. 58% of the PMF04 dockings and 63% of the p-Score dockings found the native pose (GOLD 69%) within the three highest-ranking clusters.

We observe a significant decrease of the docking accuracy with the increase of the number of freely rotatable bonds; this effect is also observed for GOLD, but to a lesser extent than for PARADOCKS (cf., Figure 4a). There are two possible reasons for this effect: (*i*) The simple description of the ligand's conformation in p-Score and in our implementation of PMF04 might lead to the observed decrease in docking accuracy for ligands with more than 10 rotatable bonds. (*ii*) The same increase of torsional degrees of freedom leads as well to a substantially larger search space to sample. The simplified description of the ligand by avoiding van der Waals clashes is sufficient to predict meaningful ligand conformations. After fitting of the ligand conformations to

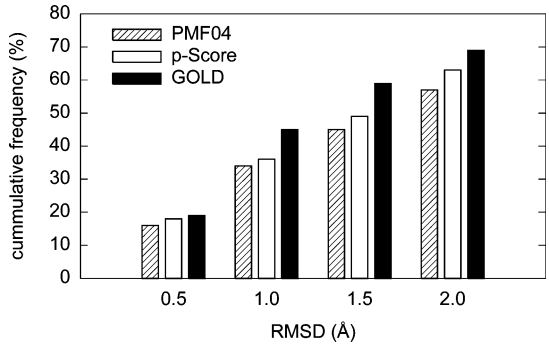


Figure 3. Comparison of the docking accuracy of PARADOCKS with p-Score and PMF with GOLD on the PDBbind core set. The data is plotted as an additive histogram for the highest ranked three clusters.

Table 1. Docking Quality of PARADOCKS with the Scoring Functions p-Score and PMF04 in Comparison to GOLD[a]

	native pose in clusters		
docking approach	1	1 and 2	1, 2, and 3
PARADOCKS/PMF04	47%	52%	58%
PARADOCKS/p-Score	52%	61%	63%
GOLD	62%	69%	69%

[a] The threshold for the native pose is a rmsd of 2 Å.

the X-ray structure, for 89% of all ligands in the PDBbind core set,[41] we find at least one conformer with an rmsd below 2 Å. The suggested standard settings for the optimization work well on average-sized problems. For ligands with more than ten torsional degrees of freedom, adapted docking settings should be used.

However, 75% of the substances listed in the world drug index (WDI)[45] have less than ten freely rotatable bonds (cf. Figure 4(b)). The general characteristics of drug molecules, as summarized, among others, by Lipinsky et al.[46] or Veber et al.[47] point toward smaller molecules with less than ten rotatable bonds as well.

Virtual Screening Performance. In virtual screening experiments, molecular docking is employed to find potent lead structures from large compound libraries. Thus it is of paramount importance to avoid false positive solutions. To thoroughly analyze the virtual screening performance of ParaDockS we selected a subset of 13 targets from the directory of useful decoys (DUD)[42] as described by Cheeseright et al.,[48] with at least 15 clusters of active compounds for each target. The 13 targets are: angiotensin-converting enzyme (ace), acetylcholinesterase (ache), cyclin-dependent kinase 2 (cdk2), epidermal growth factor receptor (egfr), factor Xa (fxa), HIV reverse transcriptase (hivrt), enoyl-acyl carrier protein reductase (inha), P38 mitogen-activated protein (p38), phosphodiesterase 5 (pde5), platelet-derived growth factor receptor kinase (pdgfrb), src tyrosine kinase (src) and vascular endothelial growth factor receptor (vegfr2). The data sets were downloaded from DUD in mol2 file format.[49] For PARADOCKS we used the default PSO settings with 30 repeats per instance with PMF04 and p-Score, in addition, the results of the p-Score dockings were rescored with PMF04. For GOLD the genetic algorithm with ten repeats was used with each of the three available energy functions GoldScore, ChemScore, and the Astex Statistical Potential (ASP). The virtual screening perfomance is now assessed by the ability to distinguish known-active compounds (P) from the selected decoys (N). For each compound in the sorted row, the true positive rate (TPR) and the false positive rate (FPR) were calculated. Solutions that score better or equal than that particular compound are defined as positive solutions. Active compounds within the range of positive solutions are true positives (TP) and decoys within the range of defined positive solutions are false positives (FP). TPR and FPR are calculated according to

$$\mathrm{TPR} = \frac{\mathrm{TP}}{P} \tag{12}$$

and

$$\mathrm{FPR} = \frac{\mathrm{FP}}{N} \tag{13}$$

The receiver operator characteristic (ROC) diagrams resulting from plotting the TPR and FPR values are shown in Figure 5. Ideally, ROC curves show a steep early ascent, almost parallel to the y -axis and then, close to the maximal value for y, continue parallel to the x -axis. Such a behavior can be exemplary seen for PARADOCKS with p-Score/PMF04 on the hivrt data set and for GOLD with GoldScore on the cox2 data set. However, most of the curves exhibit an sigmoidal shape. A good metric to assess the overall quality of a screening approach is the area under the ROC curve (AUC). The AUC gives the probability that a randomly chosen active is ranked higher than a randomly chosen inactive by the respective method. In Table 2 the AUC values are given, the methods exhibit similar perfomance. GOLD with ChemScore[50] and the Astex statistical potential (ASP)[51]

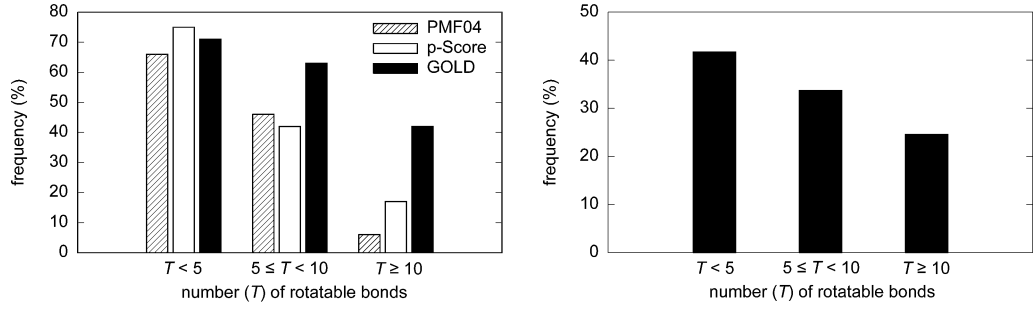


Figure 4. (a) The fraction of successful dockings (rmsd of 2 Å or better) of the PDBbind core set for PARADOCKS with p-Score and PMF, respectively, and with GOLD as a function of the number of rotatable bonds of the ligand. (b) Distribution of compounds in the WDI[45] with respect to the number of rotatable bonds.

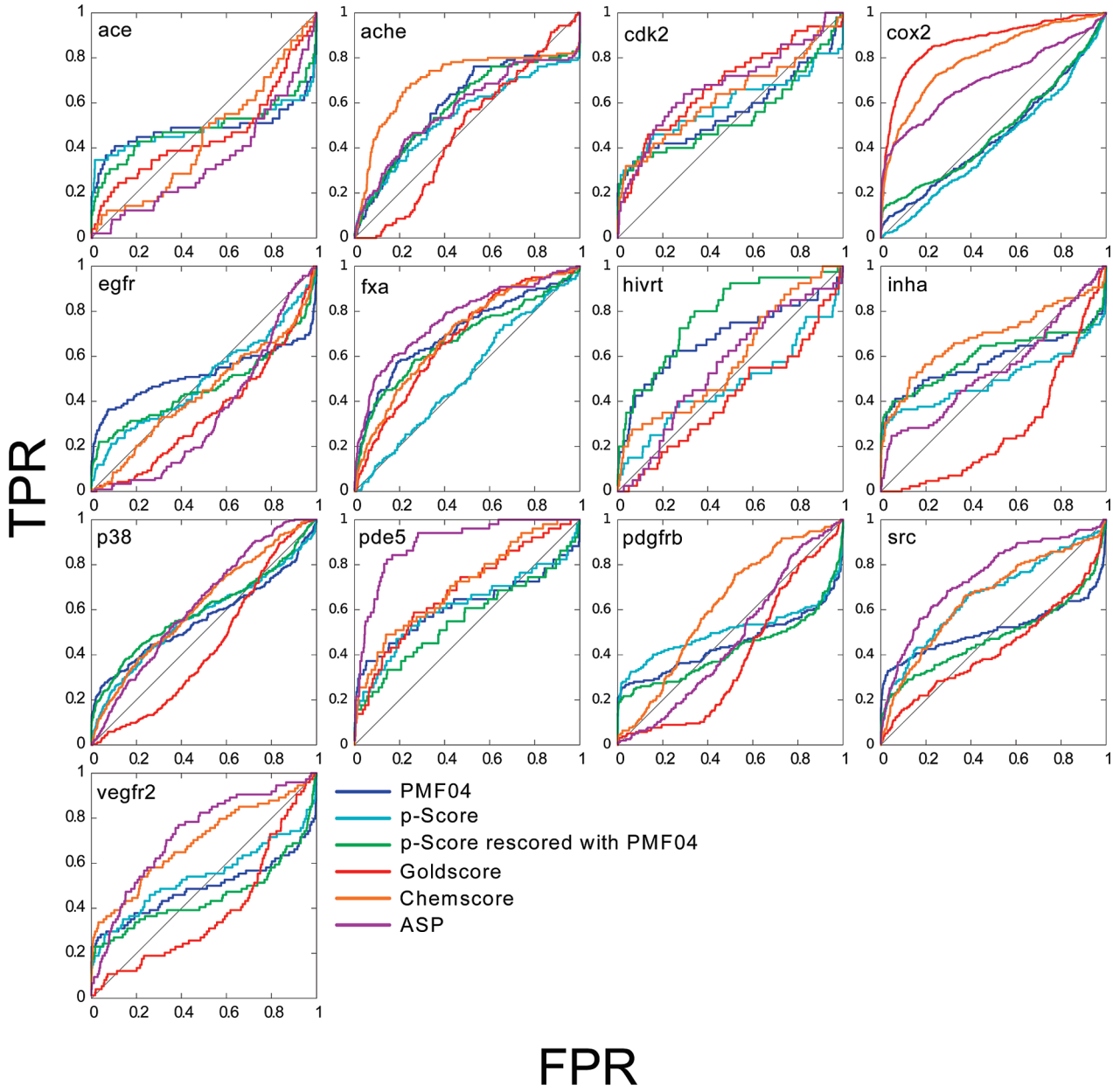


Figure 5. ROC curves to compare the performance of the different VS methods in PARADOCKS and GOLD. The lines are colored as follows: PARADOCKS with PMF04 in blue, PARADOCKS with p-Score in cyan, PARADOCKS docked with p-Score and rescored with PMF04 in green, GOLD with GoldScore in red, GOLD with ChemScore in orange, GOLD with ASP in purple.

Table 2. AUC Values for the ROC Curves[a]

target	PMF04	p-Score	p-Score/PMF04	GoldScore	ChemScore	ASP	DOCK
ace	0.49	0.49	0.49	0.46	0.44	0.34	**0.68**
ache	0.60	0.54	0.58	0.47	**0.69**	0.57	0.68
cdk2	0.56	0.59	0.54	**0.68**	0.63	**0.68**	0.57
cox2	0.46	0.42	0.48	**0.87**	0.80	0.71	0.82
egfr	0.52	0.50	0.47	0.36	0.46	0.37	**0.57**
fxa	0.71	0.51	0.68	0.69	0.72	**0.78**	0.73
hivrt	0.68	0.47	**0.78**	0.41	0.59	0.55	0.68
inha	0.58	0.50	0.60	0.29	**0.70**	0.56	0.27
p38	0.56	0.57	0.60	0.45	0.63	**0.64**	0.42
pde5	0.61	0.61	0.56	0.69	0.73	**0.90**	0.56
pdgfrb	0.45	0.51	0.42	0.39	**0.63**	0.49	0.36
src	0.51	0.66	0.48	0.44	0.67	**0.76**	0.48
vegfr2	0.49	0.54	0.45	0.39	0.70	**0.73**	0.38
Average	0.56	0.53	0.55	0.51	**0.65**	0.62	0.55

[a] The highest AUC value for each test set is highlighted in bold numbers. The screening method is abbreviated by the scoring method in use. Results for DOCK were taken from ref 48.

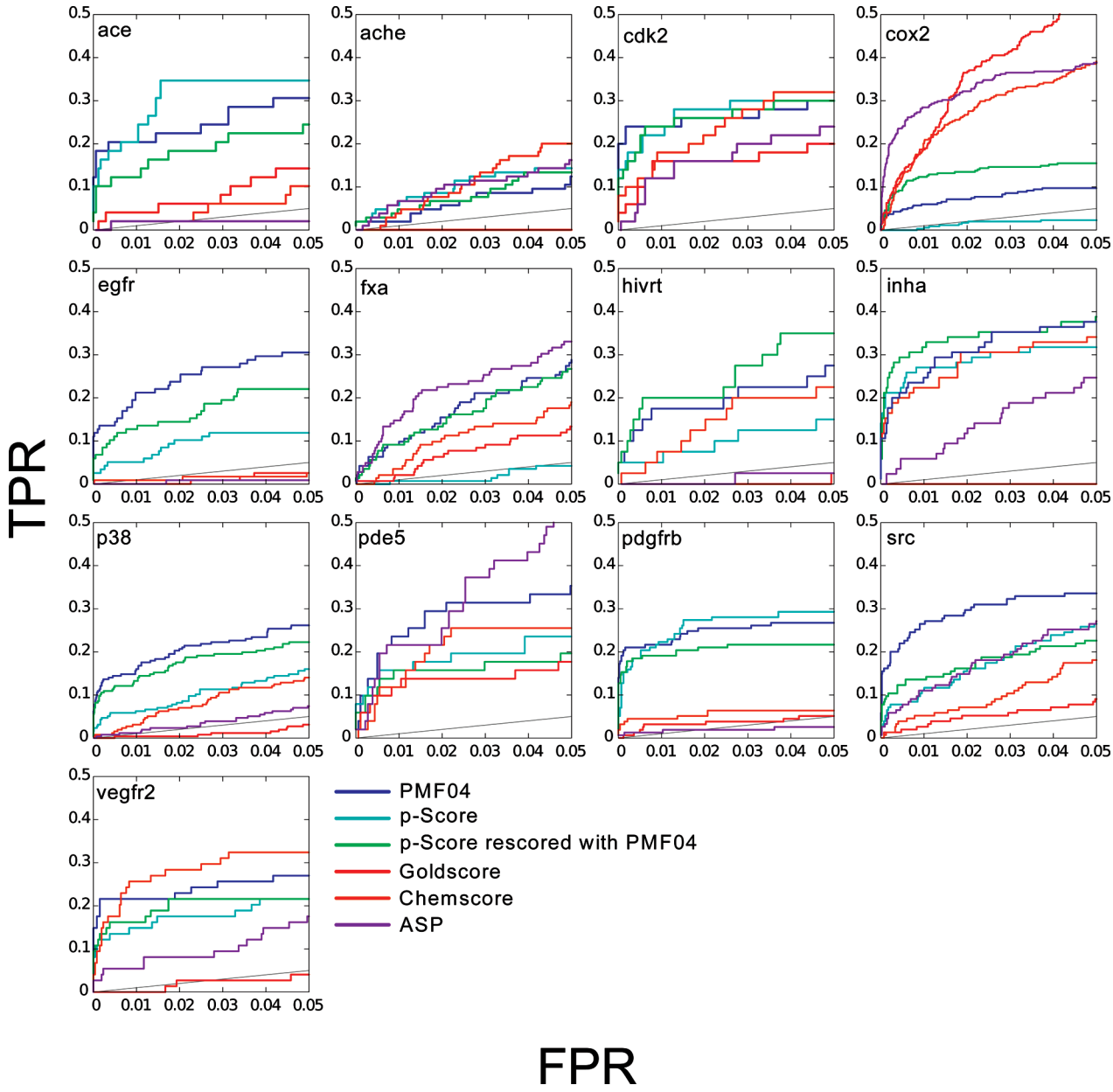


Figure 6. The first 5% of the ROC curves enlarged to compare the early enrichment of the different VS methods in PARADOCKS and GOLD. The lines are colored as follows: PARADOCKS with PMF04 in blue, PARADOCKS with p-Score in cyan, PARADOCKS docked with p-Score and rescored with PMF04 in green, GOLD with GoldScore in red, GOLD with ChemScore in orange, GOLD with ASP in purple.

show average values above 0.6, DOCK averages at 0.55, and PARADOCKS reaches 0.56 with PMF04, 0.53 with p-Score, and 0.55 with PMF04-rescored p-Score results. It is worth mentioning that PARADOCKS is hardly producing strong outliers with AUC values significantly below 0.5.

For practical reasons, the enrichment within the few top-ranking solutions is of great interest; economic demands allow only the processing of a limited number of compounds. ROC enrichment[52] is defined as the ratio of TPR to FPR for a given range of decoys and gives a good measure for the "early" enrichment in a virtual screening experiment. The advantage of ROC enrichment values is their independence from the composition of the test set. Most of the ROC curves in Figure 5 are sigmoidal, where it is striking that PARADOCKS with PMF04 produces mainly very steep ascending ROC curves. The magnification in Figure 6 puts the focus on the top-ranking 5% of solutions and highlights the high early enrichment. Especially for the very early enrichment (upper 1%) in Table 3, the superiority of PARADOCKS is clear, especially in combination with the PMF04 objective function. At 5% ROC enrichment (cf., Table 4) the advantage of PARADOCKS is still significant.

In Figure 7, exemplary docking results of two active compounds to the HIV reverse transcriptase are shown. The binding pocket of HIV-RT is narrow, and the shown docking results in Figure 7 are correct. Although the deviations of the predicted structures from the crystal structure are small, the ranking is not necessarily good. The ligand emivirine in Figure 7a is ranked sixth of 1437 by PMF04-rescoring of p-Score results but on position 1310 by GoldScore. The ligand nevirapine in Figure 7b is ranked on position 98 by PMF04, on position 286 by GoldScore, and on position 1012 by p-Score.

Timings and Parallel Efficiency. The computing time is of innate importance for the application of molecular docking techniques especially when performing virtual screenings

Table 3. ROC Enrichment Values at 1% for PARADOCKS, GOLD, and DOCK (from ref 48) across the 13 Selected DUD Targets[a]

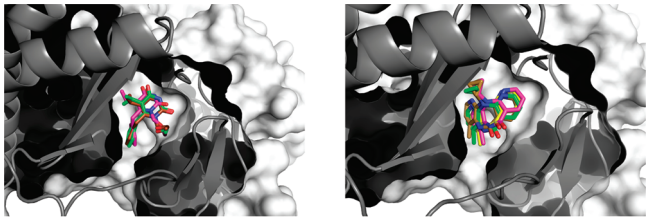
target	PMF04	p-Score	p-Score/PMF04	GoldScore	ChemScore	ASP	DOCK
ace	**44.1**	35.2	17.6	4.4	2.1	2.1	8.7
ache	1.9	**6.4**	4.0	0.0	4.0	**6.4**	0.0
cdk2	**61.0**	32.0	39.5	16.4	16.4	16.4	10.6
cox2	6.6	0.9	16.1	23.4	21.9	**58.5**	16.9
egfr	**24.7**	5.6	16.6	0.0	0.8	0.0	4.1
fxa	11.7	0.7	11.7	2.2	3.7	**20.1**	9.5
hivrt	24.0	5.5	**31.4**	0.0	5.5	0.0	6.2
inha	45.9	45.9	**91.2**	0.0	40.5	6.6	0.0
p38	**24.2**	6.8	18.1	0.4	3.3	1.2	0.0
pde5	**39.4**	25.8	20.7	12.7	16.4	31.9	7.7
pdgfrb	**47.2**	35.8	35.8	3.4	4.9	1.3	0.0
src	**48.9**	10.3	20.1	2.7	5.8	11.4	1.0
vegfr2	**55.2**	23.1	30.9	1.3	35.7	7.8	2.1

[a] The screening method is abbreviated by the scoring method in use. The highest ROC enrichment value for each test set is highlighted in bold numbers.

Table 4. ROC Enrichment Values at 5% for PARADOCKS, GOLD, and DOCK (from 48) across the 13 Selected DUD Targets[a]

target	PMF04	p-Score	p-Score/PMF04	GoldScore	ChemScore	ASP	DOCK
ace	7.1	**8.3**	5.0	3.0	2.1	0.4	3.9
ache	2.2	3.0	2.8	0.0	**4.4**	3.0	1.6
cdk2	6.4	6.9	6.9	4.3	**7.5**	4.8	3.0
cox2	2.0	0.5	3.3	**12.3**	8.6	9.0	10.0
egfr	**6.9**	2.5	4.9	0.5	0.5	0.2	3.5
fxa	5.5	0.8	5.5	2.5	3.8	**7.0**	5.1
hivrt	5.6	3.2	**8.4**	0.5	4.4	0.5	3.1
inha	**8.9**	7.5	**8.9**	0.0	7.8	5.0	0.0
p38	**5.8**	3.2	4.9	0.6	2.8	1.4	0.4
pde5	7.9	5.3	3.8	3.3	5.8	**10.4**	6.2
pdgfrb	6.1	**6.8**	4.8	1.0	1.3	0.5	0.2
src	**7.7**	5.6	4.8	1.7	3.7	5.6	0.4
vegfr2	6.5	5.1	5.1	1.1	**8.0**	3.8	0.8

[a] The screening method is abbreviated by the scoring method in use. The highest ROC enrichment value for each test set is highlighted in bold numbers.



(a) (b)

Figure 7. Visualization of example docking results from the virtual screening experiments: (a) the ligand binding domain of the HIV reverse transcriptase (PDB 1RT1) in complex with Emivirine (green) and the docking results with p-Score (magenta), and GoldScore (brown) and (b) the ligand binding domain of the HIV reverse transcriptase (PDB 1VRT) in complex with Nevirapine (green) and the docking results with PMF04 (yellow), p-Score (magenta), and GoldScore (brown).

with large libraries of compounds. To compare the timings, a docking simulation with 50 consecutive runs of a test instance (PDB 1JLA, HIV-1 reverse transcriptase and TNK-652)[44] was performed on an HP server (2.53 GHz Intel Xeon CPUs). PARADOCKS with p-Score finishes after about one hour. With PMF04 the timing is almost the same, the advantage of the simpler energy function is reduced due to the all-atom description. GOLD solves the given problem in slightly less than half an hour.

Parallel computing offers a chance for speed-up and is of special interest as there is a clear trend toward multicore CPUs in servers and workstations. In initial studies on parallel efficiency with artificial molecular docking setups we observed almost linearly scaling parallel efficiency with up to 512 CPU cores.[53] However, in the current version the amount of computing time needed to evaluate the interaction was greatly reduced compared to these initial tests. The current parallel implementation suffers from communication overheads; neither the optimization algorithm nor the objective functions are, at the current stage, optimized toward parallel processing. PARADOCKS with 4 CPU cores reaches the speed of GOLD with 1 CPU core. While the amount of simultaneous processes for many commercial solutions is limited by the number of licenses purchased, PARADOCKS is free software and not limited in the number of processes. This allows to overcome the current speed limitations by data parallel computation. Further details on timings and parallel performance can be found in the Supporting Information.

CONCLUSIONS

In the previous sections, we have introduced the molecular docking software PARADOCKS. The main feature, the open and easy extendable design, offers the possibility to implement one's own approaches. In addition, the sofware is equipped with a robust particle swarm optimizer and the two objective functions PMF04 and p-Score. PARADOCKS does not need extensive preprocessing of the input data. Input and output of structures as well as parameters and results is

organized in a way that makes the inclusion into existing virtual screening pipelines easy. The code is well structured and is documented by an automatic documentation system to allow easy familiarization. Furthermore, developers of optimization algorithms and scoring approaches will find the open and modular design of the PARADOCKS framework tailored for easy implementation and testing.

The performance was evaluated for three issues critical for molecular docking and virtual screening: accuracy, screening performance, and speed. In all three disciplines PARADOCKS is reaching very promising results. The docking accuracy, tested on reproducing the PDBbind core set, reaches up to 73% with p-Score. To assess the virtual screening performance, extensive testing with 13 targets of the DUD was performed. The early enrichment performance of PARADOCKS with the PMF04 objective function is superior to all other tested approaches. Summarizing, p-Score appears well suited for more accurate evaluations, while PMF04 is apparently well suited for rapid evaluations and high enrichment in virtual high throughput screenings. The particle swarm optimizer performs well and is robust. It offers a straightforward way for parallelization, but with current objective functions the communication overhead is high.

Although PARADOCKS is ready for production use, the software is under constant development. This first status report would be incomplete without an outlook on upcoming improvements and future development directions:

- Improvements of the description of the ligand conformation for the p-Score and PMF04 objective function are planned.
- The receptor flexibility will be accounted for by an explicit modeling of side chain flexibility.
- Further optimization techniques, for example, differential evolution, will be implemented and their performance analyzed.
- Improved load balancing and reduced communication will increase the parallel efficiency. The use of computationally more demanding objective functions will increase the parallel efficiency as well.
- The output of resulting structures will be changed to a trajectory-like format.

PARADOCKS is free software and published under the GNU General Public License (GPLv2).[29]

DOWNLOAD

Please refer to http://www.paradocks.org to download the PARADOCKS source code and to find additional information.

ACKNOWLEDGMENT

The authors, especially F.B. and C.B., gratefully acknowledge the support of this work by M. Teresa Pisabarro (BIOTEC, TU Dresden). The authors thank Daniel Merkle (SDU Odense) and Robert Günther (Universität Leipzig) for inspiring and fruitful discussions and Scott Edwards (PICB Shanghai) for proof reading of the manuscript. C.B. is grateful for a Feodor Lynen fellowship by the Alexander von Humboldt foundation. F.B. and C.B. are grateful for support by Klaus Tschira Foundation during their stay at BIOTEC, TU Dresden. Computational resources at the Centre for Information Services and High Performance Computing of TU Dresden and at the Computing Centre of Martin-Luther-Universität Halle-Wittenberg are gratefully acknowledged. The trademark "Paradocks" is owned by ParaDocks Omnimedia GbR (Freiburg, Germany); we are grateful for the permission to use this name for the molecular docking software.

Supporting Information Available: Data on ligand conformations, timings and parallel efficiency, the active compounds of the two described virtual screening test sets, and p-Score parameters. This information is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES AND NOTES

(1) Bajorath, F. Integration of virtual and high-throughput screening. *Nat. Rev. Drug Discovery* **2002**, *1*, 882–894.
(2) Klebe, G. Virtual ligand screening: strategies, perspectives and limitations. *Drug Discovery Today* **2006**, *11*, 580–594.
(3) Rarey, M.; Kramer, B.; Lengauer, T.; Klebe, G. A fast flexible docking method using an incremental construction algorithm. *J. Mol. Biol.* **1996**, *261*, 470–489.
(4) Jain, A. N. Surflex: Fully automatic flexible molecular docking using a molecular similaritybased search engine. *J. Med. Chem.* **2003**, *46*, 499–511.
(5) Zsoldos, Z.; Reid, D.; Simon, A.; Sadjad, B. S.; Johnson, A. P. eHiTS: an innovative approach to the docking and scoring function problems. *Curr. Protein Pept. Sci.* **2006**, *7*, 421–435.
(6) McGann, M. R.; Almond, H. R.; Nicholls, A.; Grant, J. A.; Brown, F. K. Gaussian docking functions. *Biopolymers* **2003**, *68*, 76–90.
(7) Kuntz, I. D.; Blaney, J. M.; Oatley, S. J.; Langridge, R.; Ferrin, T. E. A geometric approach to macromolecule-ligand interactions. *J. Mol. Biol.* **1982**, *161*, 269–288.
(8) Shoichet, B. K.; Kuntz, I. D. Matching chemistry and shape in molecular docking. *Protein Eng.* **1993**, *6*, 723–732.
(9) Jones, G.; Willett, P.; Glen, R. C.; Leach, A. R.; Taylor, R. Development and validation of a genetic algorithm for flexible docking. *J. Mol. Biol.* **1997**, *267*, 727–748.
(10) Morris, G. M.; Goodsell, D. S.; Halliday, R. S.; Huey, R.; Hart, W. E.; Belew, R. K.; Olson, A. J. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *J. Comput. Chem.* **1998**, *19*, 1639–1662.
(11) Korb, O.; Stützle, T.; Exner, T. E. An ant colony optimization approach to flexible proteinligand docking. *Swarm Intelligence* **2007**, *1*, 115–134.
(12) Korb, O.; Stützle, T.; Exner, T. E. Empirical Scoring Functions for Advanced Protein-Ligand Docking with PLANTS. *J. Chem Inf. Model.* **2009**, *49*, 84–96.
(13) Janson, S.; Merkle, D.; Middendorf, M. Molecular docking with multi-objective particle swarm optimization. *Appl. Soft. Comput.* **2008**, *8*, 666–675.
(14) Chen, H. M.; Liu, B. F.; Huang, H. L.; Hwang, S. F.; Ho, S. Y. SODOCK: Swarm optimization for highly flexible protein-ligand docking. *J. Comput. Chem.* **2007**, *28*, 612–623.
(15) Namasivayam, V.; Günther, R. PSO@AUTODOCK: A fast flexible molecular docking program based on swarm intelligence. *Chem. Biol. Drug Des.* **2007**, *70*, 475–484.
(16) Kennedy, J.; Eberhart, R. Particle swarm optimization. *Proc. IEEE Int. Conf. Neural Networks* **1995**, *4*, 1942–1948.
(17) Muegge, I.; Rarey, M. Small Molecule Docking and Scoring. *Rev. Comput. Chem.* **2001**, *17*, 1–60.
(18) Böhm, H. J.; Stahl, M. The Use of Scoring Functions in Drug Discovery Applications. *Rev. Comput. Chem.* **2002**, *18*, 41–87.
(19) Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, U. C.; Ghio, C.; Alagona, G.; Profeta, S.; Weiner, P. A new force field for molecular mechanical simulation of nucleic acids and proteins. *J. Am. Chem. Soc.* **1984**, *106*, 765–784.
(20) Böhm, H. J. The development of a simple empirical scoring function to estimate the binding constant for a protein-ligand complex of known three-dimensional structure. *J. Comput.-Aided Mol. Des.* **1994**, *8*, 243–256.
(21) Wang, R. X.; Lai, L. H.; Wang, S. M. Further development and validation of empirical scoring functions for structure-based binding affinity prediction. *J. Comput.-Aided Mol. Des.* **2002**, *16*, 11–26.
(22) Mitchell, J. B. O.; Laskowski, R. A.; Alex, A.; Thornton, J. M. BLEEP - potential of mean force describing protein-ligand interactions: I. Generating potential. *J. Comput. Chem.* **1999**, *20*, 1165–1176.

(23) Mitchell, J. B. O.; Laskowski, R. A.; Alex, A.; Forster, M. J.; Thornton, J. M. BLEEP - potential of mean force describing protein-ligand interactions: II. Calculation of binding energies and comparison with experimental data. *J. Comput. Chem.* **1999**, *20*, 1177–1185.
(24) Muegge, I.; Martin, Y. C. A general and fast scoring function for protein-ligand interactions: a simplified potential approach. *J. Med. Chem.* **1999**, *42*, 791–804.
(25) Muegge, I. PMF scoring revisited. *J. Med. Chem.* **2006**, *49*, 5895–5902.
(26) Gohlke, H.; Hendlich, M.; Klebe, G. Knowledge-based scoring function to predict proteinligand interactions. *J. Mol. Biol.* **2000**, *295*, 337–356.
(27) Shoemake, K. Animating rotation with quaternion curves. *Proc. 12th Annu. Conf. Comput. Graphics Interactive Tech.* **1985**, 245–254.
(28) Tripos L. P. *Tripos Mol2 File Format*; Tripos: St. Louis, MO, 2007; http://www.tripos.com/tripos_resources/fileroot/mol2_format_Dec07.pdf (accessed November 30, 2009).
(29) *GNU General Public License*, version 2; Free Software Foundation, Inc.: Boston, MA, 1991; http://www.gnu.org/licenses/gpl-2.0.txt (accessed November 6, 2009).
(30) Doxygen—Source code documentation generator tool. http://www.stack.nl/~dimitri/doxygen (accessed October 3, 2009).
(31) SMARTS—A language for describing molecular patterns. http://www.daylight.com/dayhtml/doc/theory/theory.smarts.html (accessed October 3, 2009).
(32) ISO/IEC 14977 Information technology—Syntactic metalanguage—Extended BNF. http://standards.iso.org/ittf/PubliclyAvailableStandards/s026153_ISO_IEC_14977_1996(E).zip (accessed October 3, 2009).
(33) Shi, Y.; Eberhart, R. Parameter selection in particle swarm optimization. LNCS. *Proc. 7th Annu. Conf. Evol. Program., San Diego, CA* **1998**, *1447*, 591–600.
(34) Bytheway, I.; Kepert, D. L. The mathematical modelling of cluster geometry. *J. Math. Chem.* **1992**, *9*, 161–181.
(35) Ferrari, A. M.; Wei, B. Q.; Costantino, L.; Shoichet, B. K. Soft docking and multiple receptor conformations in virtual screening. *J. Med. Chem.* **2004**, *47*, 5076–5084.
(36) Muegge, I.; Martin, Y. C.; Hajduk, P. J.; Fesik, S. W. Evaluation of PMF scoring in docking weak ligands to the FK506 binding protein. *J. Med. Chem.* **1999**, *42*, 2498–503.
(37) Friesner, R. A.; Banks, J. L.; Murphy, R. B.; Halgren, T. A.; Klicic, J. J.; Mainz, D. T.; Repasky, M. P.; Knoll, E. H.; Shelley, M.; Perry, J. K.; Shaw, D. E.; Francis, P.; Shenkin, P. S. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem.* **2004**, *47*, 1739–1749.
(38) Kellenberger, E.; Rodrigo, J.; Muller, P.; Rognan, D. Comparative evaluation of eight docking tools for docking and virtual screening accuracy. *Proteins* **2004**, *57*, 225–242.
(39) Moitessier, N.; Englebienne, P.; Lee, D.; Lawandi, J.; Corbeil, C. R. Towards the development of universal, fast and highly accurate docking/scoring methods: A long way to go. *Br. J. Pharmacol.* **2007**, *153*, 7–26.
(40) Hartshorn, M. J.; Verdonk, M. L.; Chessari, G.; Brewerton, S. C.; Mooij, W. T.; Mortenson, P. N.; Murray, C. W. Diverse, high-quality test set for the validation of protein−ligand docking performance. *J. Med. Chem.* **2007**, *50*, 726–741.
(41) Wang, R.; Fang, X.; Lu, Y.; Wang, S. The PDBbind database: collection of binding affinities for protein−ligand complexes with known three-dimensional structures. *J. Med. Chem.* **2004**, *47*, 2977–2980.
(42) Huang, N.; Shoichet, B. K.; Irwin, J. J. Benchmarking sets for molecular docking. *J. Med. Chem.* **2006**, *49*, 6789–6801.
(43) *MOE 2007.09*; Chemical Computing Group Inc.: Montreal, PQ, Canada, 2009.
(44) Ren, J.; Nichols, C.; Bird, L.; Chamberlain, P.; Weaver, K.; Short, S.; Stuart, D. I.; Stammers, D. K. Structural mechanisms of drug resistance for mutations at codons 181 and 188 in HIV-1 reverse transcriptase and the improved resilience of second generation non-nucleoside inhibitors. *J. Mol. Biol.* **2001**, *312*, 795–805.
(45) *World Drug Index*; Thomson Scientific: Philadelphia, PA, 2001.
(46) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **1997**, *23*, 3–25.
(47) Veber, D. F.; Johnson, S. R.; Cheng, H. Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D. Molecular properties that influence the oral bioavailability of drug candidates. *J. Med. Chem.* **2002**, *45*, 2615–2623.
(48) Cheeseright, T. J.; Mackey, M. D.; Melville, J. L.; Vinter, J. G. FieldScreen: Virtual screening using molecular fields. Application to the DUD data set. *J. Chem. Inf. Model.* **2008**, *48*, 2108–2117.
(49) *DUD A Directory of Useful Decoys*; University of California; San Francisco, CA, 2006; http://dud.docking.org/r2 (release date October 22, 2006).
(50) Eldridge, M. D.; Murray, C. W.; Auton, T. R.; Paolini, G. V.; Mee, R. P. Empirical scoring functions 1: The development of a fast empirical scoring function to estimate the binding affinity of ligands in receptor complexes. *J. Comput.-Aided Mol. Des.* **1997**, *11*, 425–445.
(51) Mooij, W. T. M.; Verdonk, M. L. General and targeted statistical potentials for protein-ligand interactions. *Proteins* **2005**, *61*, 272–287.
(52) Nicholls, A. What do we know and when do we know it. *J. Comput.-Aided Mol. Des.* **2008**, *22*, 239–255.
(53) Brandt, F. A Parallel Framework for High-Throughput Automated Docking. Diploma thesis, TU Dresden, 2007.

CI900467X