Accurate predictions, properly integrated with experimental data

The prediction of the structure of a protein–protein complex from key to cellular functioning. This can be particularly interesting in recognition and the mechanism of protein association, which are could give new insights into the basic principles of molecular biology (Bonvin, 2006; Deremble and Lavery, 2005; Gray, 2006).

one of the major challenges in current computational structural...
FRODOCK: a new approach for fast rotational protein–protein docking

orientational search, a large number of docked conformations with favorable surface complementarity can be obtained. This initial shape-based scoring function has been further enhanced by including additive correlation terms to consider electrostatics [FTDOCK (Gabb et al., 1997), DOT (Moent et al., 1999) and Molfit (Heifetz et al., 2002)], solvation [ZDOCK (Chen et al., 2003)] or even statistical interaction potentials [PIPER (Kozakov et al., 2006)].

Despite significant progress in the FFT-based methods, there is room for improvement in both speed and accuracy of the grid-based scoring function. The efficiency of the 6D FFT-based search depends on several factors. The computational cost increases with size, scaling at O(V log N), where N is the number of grid cells. The efficiency also decreases with the number of considered interaction potential terms, given that the global energy is computed as a sum of independent FFT correlation functions. Moreover, several rigid-body searches might be performed if the flexibility is explicitly considered or if alternative homology structures are used as docking templates. Thus, the FFT-based search process can take several hours or even more if the sampling is relatively large or several candidates must be docked.

The docking efficiency can be further improved by accelerating the rotational search using spherical harmonics (SH). In the Hex docking correlation algorithm (Ritchie and Kemp, 2000), the rotational docking is accelerated by correlating spherical polar basis functions (SPF) that model the surface shape and charges of docking molecules. Very recently, the same authors (Ritchie et al., 2008) presented several improvements for calculating multidimensional multi-property rotational FFT docking SPF correlations. Inspired by the efficiency achieved by this approach, here we have adapted our original Fast Rotational Method (FRM) (Kovacs and Wriggers, 2002; Kovacs et al., 2003), which was previously successfully used to fast fit atomic structures into electron microscopy (EM) density maps (Garzon et al., 2007), to protein–protein docking. This approach permitted a superior efficiency and a more exhaustive search by speeding up the three rotational degrees of freedom using SH and a convenient formulation of the 3D rotation group.

The application of FRM to protein–protein docking has derived and the competitive docking accuracy achieved on standard protein–ligand complexes with a simple translational scanning. A parallel version of this method termed FRODOCK (Fast ROtational DOCKing) was presented several improvements for calculating multidimensional multi-property rotational FFT docking SPF correlations. Inspired by the efficiency achieved by this approach, here we have adapted our original Fast Rotational Method (FRM) (Kovacs and Wriggers, 2002; Kovacs et al., 2003), which was previously successfully used to fast fit atomic structures into electron microscopy (EM) density maps (Garzon et al., 2007), to protein–protein docking. This approach permitted a superior efficiency and a more exhaustive search by speeding up the three rotational degrees of freedom using SH and a convenient formulation of the 3D rotation group.

1 METHODS

Global energy optimization was performed by 6D (3D rotations + 3D translations) rigid-body exhaustive search of the orientations of a fixed ligand with respect to a mobile receptor. The docking criterion is the minimization of a scoring function based on the interaction energy and composed of several terms. Considering only the rotational part, each energy term can be calculated by a correlation function defined as an integral of the form:

$$E(R) = \int f \cdot \Delta g$$

(1)

where $f$ and $g$ correspond to the interaction potential parts of the receptor and ligand, respectively. The operator $\Delta g$ denotes rotation of $g$ by $R$ defined by canonical Euler angles $\phi$, $\theta$ and $\psi$. On the unit sphere, the interaction potential can be expressed in terms of SH functions, $Y_{lm}(\theta, \phi)$, and its corresponding coefficients $\hat{f}_{lm}(R)$ and $\hat{g}_{lm}(R)$:

$$f(\theta, \phi, \lambda) = \int \hat{f}_{lm}(R) Y_{lm}(\theta, \phi) \, d\theta \, d\phi$$

(2)

where $r$ is the radius of the unit sphere; $\lambda > 0$ and $-\lambda \leq \theta, \phi \leq \lambda$ are the SH degree and order, and $\beta$ and $\lambda$ are the co-latitude and longitude, respectively. Instead of employing SPF functions Ritchie and Kemp, (2000), here the SH transformation is done discretely in concentric spherical layers (like onion shells) as previously described in (Kovacs and Wriggers, 2002). This radialization process permits a novel volumetric description of an interaction potential defined into a 3D grid in terms of harmonic radial functions.

The correlation docking function can be expressed in terms of an inverse Fourier transform of the SH functions (Garzon et al., 2007; Kovacs and Wriggers, 2002; Kovacs et al., 2003):

$$E(R) = FT^{-1} \sum_{l=0}^{\infty} \sum_{m=-l}^{l} \phi_{lm}(R) \cdot \delta_{lm}(R)$$

(3)

where $\phi_{lm}$ is the real coefficient that defines the matrix elements of the irreducible representations of the 3D rotation group. This expression can be computed very efficiently by pre-calculating such coefficients and by using as upper limit of integration the maximum shell radius for which a given potential has non-zero values. In addition to a very fast calculation of the rotational docking correlation, Equation (3) permits a deep and exhaustive rotational search. Note that rotational sampling step is limited by twice of the bandwidth (tw) used in the harmonic expansion of the correlated potentials (Equation (2)). For example, a bandwidth of 32 corresponds to a sampling rotational step of 5.6° which implies the scanning of more than 60 000 distinct rotations.

This fast exhaustive rotational search combined with an implicit translational scan was successfully employed by us to fit atomic structures into low-resolution EM maps (Garzon et al., 2007). In that case, we cross-correlated two electron density maps: one that corresponded to the experimental EM map and another that corresponded to a lower-resolution version of the atomic structure. In the case of protein–protein docking, a receptor potential pre-calculated in a 3D grid is correlated with a ligand force-field property defined at their atomic coordinates. Being $L_i$, such atomic property, the correlation contribution of the ligand, $g$, can be expressed as a summationary function of the form $\sum_i L_i \cdot \delta_{pi}$, where $\delta_{pi}$ is a delta function of the atom $i$ centered at its coordinate position. From this expression the spherical coefficient of the ligand can be reduced to (see Supplementary Appendix for details):

$$\hat{g}_{lm}(R) = \sum_{i=1}^{N} L_i \int_{0}^{\pi} \delta_{pi}(\theta) \cdot Y_{lm}(\theta, \phi) \, d\theta \, d\phi$$

(4)

Integrating Equation (4) into (3):

$$f'_{lm} = \int_{0}^{2\pi} \hat{f}_{lm}(R) \cdot \delta_{lm}(R) \cdot \sum_{i=1}^{N} L_i \cdot \delta_{pi}(u_\theta) \, d\theta$$

(5)

With this expression we avoid the implicit calculation of the SH coefficients of the ligand from a potential grid map as it is done with the receptor. However, we need to perform a summatory over all the ligand atoms, which can be costly if this number is too high. To overcome this problem and improve the overall efficiency, the integration is done over the atoms grouped...
The binding energy during complex formation was approximated by three coefficients, which gives us a new and efficient way to perform the rotational part of the protein-docking field. However, the translational space could be greatly reduced in particular if any of the ligand atoms are located at a distance bigger than the minimum radius of the ligand and smaller than the maximum radius at all the grid points close to the receptor surface (defined by atoms with solvent accessible surface area, SASSA > 0). The BSA was computed on the grid as the SASSA difference with and without these atom probes. For the L property, we utilized the SASSA of the ligand. In the same way, the desolvation contribution of the ligand with respect to the receptor was estimated but now using its accessible surface as reference. Thus, the total interaction desolvation energy is given by a sum of two correlation functions as Equation (12), of which they model the receptor–ligand and the ligand–receptor desolvation.

2.2 Implementation details

The method was implemented in three consecutive steps:

(1) **Generation of pre-calculated grid maps:** Three grid potentials were computed from the receptor coordinates (van der Waals, electrostatic and desolvation), whereas only one was needed from the ligand coordinates (desolvation). Several ad-hoc tools have been developed in order to pre-compute such potential maps. Atomic properties such as van der Waals radius, charges etc. were taken from the CHARMM 19 force field. The SASSA calculations were performed using analytical methods (Busa et al., 2005).

(2) **Performing the docking 6D search:** Once the grid maps were pre-calculated, the docking was performed with a single tool called FRODOCK, which implements the new methodology presented in the Methods section for 6D exhaustive docking search. The rotational

\[ P_W(p) = \sum_i P_W(i)p(i) \] (9)

and

\[ P_W(i)p = \begin{cases} P_W^(0)(i)p & \text{if } P_W^(0)(i)p \leq 0 \\ \frac{P_W^(0)(i)p}{P_W^(0)(i)p + \sum_j P_W(j)p} & \text{if } P_W^(0)(i)p > 0 \end{cases} \] (10)

where \( d_{ij} \) denotes the distance between the coordinates of atom \( i \) to a given grid point \( p \), \( P_{\text{full}} \) is a repulsive potential cut-off and \( A_i \) and \( B_i \) are constants. Using this expression and considering only the heavy atoms, the receptor van der Waals potential map was pre-computed using a generic C atom probe with radius 2.0 Å to model the ligand presence. By computing the receptor SH coefficients \( f_{\text{rev}}(r) \) from this grid, and making use of the ligand atoms mass as ligand scalar property \( L_i \), the van der Waals docking contribution for a given translational point was evaluated using Equation (7).

The electrostatic contribution was calculated in a similar way. To this end, only the partial charges are needed for the ligand, whereas for the receptor an electrostatic grid potential is approximated using a modified Coulomb’s law. Such grid potential is defined by

\[ P_L(p) = \sum_i B_L(i)p(i) \] (11)

where \( \varepsilon = 4\pi \) is a distance-dependent dielectric constant and \( q_i \) are the receptor partial charges. The soft van der Waals potential used here allows certain overlap between atoms, which can result in unrealistic large electrostatic energy terms. To alleviate this, the electrostatic values were clamped in a range of ±10 kcal/mol.

The docking desolvation energy is defined by the transfer of surface residues from water to protein–protein interface. Here this was estimated as a sum of per-atomic contributions proportional to the buried solvent accessible surface area, BSA; hence, the grid points of the receptor desolvation energy potential were calculated using

\[ P_D(p) = \sum_i B_D(i)p(i) \] (12)

where \( \sigma_i \) is the atomic solvation parameter for atom type \( i \) as previously calculated from linear fitting to experimental o/w and t/w transfer energies (Abagyan, 1997) and finally optimized for rigid-body docking (Fernandez-Recio et al., 2004). To estimate the receptor buried surface upon binding we modeled the presence of the ligand by locating generic probes of 1.7 Å radius at all the grid points close to the receptor surface (defined by atoms with solvent accessible surface area, SASSA > 0). The BSA was computed on the grid as the SASSA difference with and without these atom probes. For the L property, we utilized the SASSA of the ligand. In the same way, the desolvation contribution of the ligand with respect to the receptor was estimated but now using its accessible surface as reference. Thus, the total interaction desolvation energy is given by a sum of two correlation functions as Equation (12), of which they model the receptor–ligand and the ligand–receptor desolvation.
The chosen docking setup that splits the exhaustive search in translational and orientational degrees, thus avoiding pre-alignment situations with reference/original structures upon binding. To effectively test the method, the docking and certain degree of smoothness is even desirable in order to model small rigid-body docking, a detailed shape description is probably not required, the method. Bandwidths above 32 quickly deteriorate the performance and order: shape, desolvation and electrostatics. Other parameters, such as the binding energy in our rigid-body protein–protein docking are, in decreasing results suggested that the most important energetic contributions to the free interaction energy terms (Kozakov, WW, WE, WE, for which we found optimal values of 1.0, 0.3 and 0.5, respectively. As expected, the optimization results suggested that the most important energetic contributions to the free binding energy in our rigid-body protein–protein docking are, in decreasing order: shape, desolvation and electrostatics. Other parameters, such as the radialization step size of the spherical layers used in the SH expansions (fixed to 1 Å), the bandwidth (32) and the translational step size (2 Å), were chosen to have high efficiency without compromising the accuracy of the method. Bandwidths above 32 quickly deteriorate the performance and they did not improve the docking results. Note that for this type of initial rigid-body docking, a detailed shape description is probably not required, and certain degree of smoothness is even desirable in order to model small structural changes upon binding. To effectively test the method, the docking was repeated 50 times for each complex, with distinct random initial ligand orientations, thus avoiding pre-alignment situations with reference/original complexes.

An additional validation benchmark was compiled with available rigid-body test cases of the latest CAPRI experiments, which were not already included in the Weng’s benchmark. This additional benchmark included targets T11 and T12 of the cohesin–dockerin complex of the cellulose (PDB ID 1OHZ), T13 of the SAG1–antibody complex (PDB ID 1YNT), T14 of the protein Ser/Thr phosphatase-1 bound to MYPPT1; T18 xylanase-TAXI complex (PDB ID 1T6G); T19 of ovine prion-Fab complex (PDB ID P1RX); T25 of Arti-GTP-AR0Hcap10 (PDB ID 259); T26 TolBPer (PDB ID 2HQS) and T27 Hip2 bound to a UBC9 (PDB 2D05). For targets T11 and T19, homology models previously built by ICM were used as ligand probes [details of modeling are described in (Fernandez-Recio et al., 2005)]. The ligand (RMSDl) and interface (RMSDI) root mean square deviations were computed following CAPRI criteria (Mendez et al., 2003). For computing the RMSDl, the receptors were superimposed using all the C atoms, with the exception of the T3 case. In this case only the binding domain of the ligand was considered for the RMSDl calculation, as the other domain, which is not relevant for the interaction, is moved with respect to the bound reference state. A ligand or receptor residue is considered to be at the interface if any of its atoms is within 10 Å of an atom of the receptor or the ligand, respectively. Contacts are defined in the same way but with a shorter distance of 5 Å. None of the interface or contacts residues that fulfill such distance restraints have been excluded by any other criterion.

3 RESULTS
The global success rates shown in Figure 1 provided a first overall view of the performance of our new docking approximation on the unbound 76 targets from Weng’s benchmark. We had on average a probability of 90% to find at least an acceptable solution (RMSDl ≤ 10 Å) within the 10 000 predictions made for all 50 runs of each docking case, with a probability of 67% for finding a medium quality solution (RMSDl ≤ 5 Å). These success rates smoothly diminished to 78 and 53% for finding acceptable and medium solutions, respectively, within top 1000. When only the top 100 were considered, FRODOCK maintains excellent success rates of 51 and 30%, respectively. In a closer view, it can be seen a clear different behavior depending on the complex type: whereas at least one acceptable solution can be found below the first 500 predictions (100% success rate) for enzyme–substrate cases (Fig. 1A; E, solid line), for antibody–antigen (dotted lines) the success rate drops to 78% for top 1000, and it falls even more (63%) for the other type (O, dashed line). These differences are more accentuated when looking at the top 100, in which we found success percentages of 92, 50 and 22% for E, A and O categories, respectively. It is well known that surface complementarity, which is the main docking driving force in this method (as in the majority of rigid docking methods), is a stringent criterion with enzyme–substrate and antibody–antigen docking cases. Nevertheless, it is much less effective with the O type docking cases, which contain the most heterogeneous and difficult test cases of the three categories. Similar observations can be made by looking at RMSDl instead of RMSDl (see Supplementary Fig. S1).

Several acceptable solutions have been found in almost all docking cases (see Supplementary Table S1 and S2). There are only five known difficult cases (1BGX, 1RTX, 1SBB, 1HE8, 1IB1) in which practically no acceptable solutions were found with RMSDl ≤ 10 Å or RMSDl ≤ 4 Å within 10 000 default predictions yielded by FRODOCK. There are also poor accuracy cases such as 1KLU in which some of the predictions are lost because they are ranked beyond the considered 10 000 predictions and/or their RMSD fell out of the limits to consider the solution as acceptable.
As expected, this variation becomes larger as predictions are made farther away from the experimental structures. Variations in the rank, RMSD, and RMSD_L are observed, with values of 0.55 and 0.04 being obtained for rank, RMSD_L, and RMSD_D, respectively, for E cases (Table S1), average standard deviation values of 13, 5, and 2 Å, respectively, for O cases these values are 306, 0.89 and 0.06, respectively. Nevertheless, only in a few cases, such as 1JPS, 1GCQ or 1MLO, different solution sets can be obtained with an average RMSD_L variation larger than 3 Å. This, otherwise relatively minor, amplification of the solution space is essentially the same in all the 50 runs, thus demonstrating the robustness of the method. Only in a few cases, such as 1IPS, 1GCQ or 1MLO, different solution sets can be obtained with an average RMSD_L variation larger than 3 Å. This, otherwise relatively minor, degeneration of solutions is likely a result of grid interpolation errors amplified by the clustering of the solutions.

We tested the comparative efficiency of FRODOCK in the case HyHel-5/lysozyme, previously used as a timing reference in a very recent version of HEX (Rüdiger et al., 2008), which to our knowledge is the fastest protein-protein exhaustive docking search available. Our approximation is 10% slower than Hex, which takes ~27 min to perform this docking in a standard 2.2 MHz linux workstation. This docking tool slightly outperforms FRODOCK, most likely because it uses a more efficient two-stage protocol using 3D shape FFT scans with bandwidth 20 followed by 1D shape plus electrostatics rescoring with a bandwidth 30. Nevertheless, if FRODOCK employed the two equivalent shape and electrostatic terms used in HEX, the docking time could be reduced to 18 min. In this particular case, FRODOCK found the first acceptable solution at positions 32th and 30th, with and without desolvation, respectively. The different nature of the docking methodology and the diverse parameters employed, including different size of the translational and rotational steps, made difficult a thorough comparison of the docking performance. Nevertheless, it is clear that both methods have comparable performance at least in this representative example.

On the same case, the FFT standard ZDOCK (versions 2.3.1 or 3.0.1) docking tool takes more than two hours (using a dense sampling with -d option). In any case, we implemented a parallel version that can take advantage of multiple processors. This version can speed up the docking calculations several folds (see Supplementary Fig. S2). HEX could follow similar strategy but its two-step protocol will be slightly more complex to parallelize than our direct translation space split in multiple processors.

### 3.1 Validation of docking method on CAPRI targets

For validation purposes, we also tested how FRODOCK would have performed in the CAPRI experiments. For that, we applied our docking protocol to the CAPRI targets 11, 12, 13, 18, 19, 25, 26 and 27. In four of nine of the CAPRI test cases, the method predicted at least one acceptable solution within the top 10 (Table 1). Moreover, two of these cases (T19, T25) achieved medium quality by CAPRI standards, and another two (T12, T14) even achieved high accuracy. The goodness of these predictions can be observed in Figure 2B, D, F and G. Acceptable solutions for targets T11 (Fig. 2A) and T13 (Fig. 2C) were also found at 26th and 23rd position, respectively. In the three remaining cases we still found acceptable solutions within the top 500 positions (Fig. 2E, H, I). From these solutions, and using further refining protocols, it is feasible to improve their ranking to top positions. The simplest and most common way to achieve this would be through the screening of the predictions with available experimental information of the complex. For example, in the difficult case of TAXI-Niger Xilanase complex (T18), the successful CAPRI predictions were obtained using an experimental restraint for residues Glu79 and Glu170, which were known to be at the interface. If we use this restraint to filter out the FRODOCK solutions without these two residues at the interface, the first prediction is now ranked 10th with a RMSD_L of 2.6 Å. Following a similar strategy, we obtained top ranked solutions for targets T26 and T27 (see details in Table 1). In summary, these results validate the excellent performance of our initial exhaustive search-docking tool.

### 4 DISCUSSION

We have developed an initial-stage rigid-body docking program called FRODOCK, which optimizes van der Waals, desolvation, and electrostatics interaction potentials by using a new fast rotational docking algorithm based on SH combined with a systematical translational search.

We have shown that, on a standard benchmark set, our new approach can place an acceptable solution (RMSD_L ≤10 Å) within the top 100 solutions in more than half of the cases (51%), and within the top 20 solutions in almost a third of the cases (30%). These results...
Table 1. Results obtained with CAPRI test cases

<table>
<thead>
<tr>
<th>Ligand RMSD</th>
<th>Interface RMSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 Å</td>
<td>&lt; 3 Å</td>
</tr>
<tr>
<td>N</td>
<td>Rank</td>
</tr>
<tr>
<td>T11</td>
<td>16</td>
</tr>
<tr>
<td>T12</td>
<td>13</td>
</tr>
<tr>
<td>T13</td>
<td>70</td>
</tr>
<tr>
<td>T14</td>
<td>8</td>
</tr>
<tr>
<td>T18</td>
<td>6</td>
</tr>
<tr>
<td>T19</td>
<td>13</td>
</tr>
<tr>
<td>T25</td>
<td>31</td>
</tr>
<tr>
<td>T26</td>
<td>11</td>
</tr>
<tr>
<td>T26</td>
<td>7</td>
</tr>
<tr>
<td>T27</td>
<td>25</td>
</tr>
<tr>
<td>T27</td>
<td>4</td>
</tr>
</tbody>
</table>

N denotes the number of solutions, and rank the position of the first solution found within the RMSD limit shown in the top of the column. The fvat and fnat, the interface ratios were calculated as described in Mendez et al. (2003). In all cases the RMSDs were calculated using C atoms.

* Filter results of T14 considering only the predictions in which residue K14 of Hip2 is at ≤ 5 Å from residue E179 of Niger Xilanase.

* Filter results of T36 considering only the predictions in which residue H246 and T292 of TolB are present in the complex contact interface.

* Filter results of T27 considering only the predictions in which residue K14 of Hip2 is at ≤ 5 Å from residue C93 of Ubc9.

Test cases in bold had at least a solution ranked in the top ten predictions.

are very competitive, as compared to other exhaustive protein-protein docking approaches. In a comparative blind docking on the same cases of the Weng’s benchmark, HEX found 16 acceptable solutions within the top 20 orientations, and 24 cases within the top 100 (Richie et al., 2008). FRODOCK results were better, finding 20 and 38 acceptable solutions within the same ranges (see Table S1). HEX also significantly improved the number of acceptable solutions by constraining the search to focus the calculation around the receptor binding site, e.g. up to 28/42 with one constraint. Despite evident benefits of employing constraints during the search, in terms of complexity reduction and enhanced performance, in this work we have chosen to focus on the most general and challenging problem defined by the blind 6D exhaustive docking search.

Apart from procedural differences, ZDOCK and FRODOCK have similar docking accuracy. On the 76-case docking test used here, ZDOCK 3.0 (Mintseris et al., 2007) obtained 13 and 24 cases (see Table S2), respectively, which are very competitive, as compared to other exhaustive protein-protein docking approaches. In a comparative blind docking on the same cases of the Weng’s benchmark, HEX found 16 acceptable solutions within the top 20 orientations, and 24 cases within the top 100 (Richie et al., 2008). FRODOCK results were better, finding 20 and 38 acceptable solutions within the same ranges (see Table S1). HEX also significantly improved the number of acceptable solutions by constraining the search to focus the calculation around the receptor binding site, e.g. up to 28/42 with one constraint. Despite evident benefits of employing constraints during the search, in terms of complexity reduction and enhanced performance, in this work we have chosen to focus on the most general and challenging problem defined by the blind 6D exhaustive docking search.

Apart from procedural differences, ZDOCK and FRODOCK have similar docking accuracy. On the 76-case docking test used here, ZDOCK 3.0 (Mintseris et al., 2007) obtained 13 and 24 cases (see Table S2), respectively, which are very competitive, as compared to other exhaustive protein-protein docking approaches. In a comparative blind docking on the same cases of the Weng’s benchmark, HEX found 16 acceptable solutions within the top 20 orientations, and 24 cases within the top 100 (Richie et al., 2008). FRODOCK results were better, finding 20 and 38 acceptable solutions within the same ranges (see Table S1). HEX also significantly improved the number of acceptable solutions by constraining the search to focus the calculation around the receptor binding site, e.g. up to 28/42 with one constraint.
Fig. 2. Docking predictions for rigid-body CAPRI targets T11 (A); T12 (B); T13 (C); T14 (D); T18 (E); T19 (F); T25 (G); T26 (H) and T27 (I) The orientations of predicted ligand (in red) and the corresponding crystal structure (in green) are shown after superposition of their receptors (surface representation in gray). The displayed predictions correspond to the first ranked acceptable solution of Table 1.
but they do not perform an exhaustive search, and therefore there is always the possibility of losing the correct docking pose.

In summary, the competitive docking accuracy and efficiency achieved by our approach can eventually open up new application windows, especially regarding large-scale structural modeling of protein complexes (Aloy and Russell, 2006; Zhu et al., 2008). In this context, a tool capable of reducing the protein–protein docking search to a few minutes will be critical to effectively address future high-throughput approaches. Further method improvements will include merging with scoring protocols such as ICM (Abagyan and Totrov, 1994) and psyDock (Cheng et al., 2007), together with local refinement and rescoring of the atomic coordinates of the FRODock predicted complex in order to generate more realistic solutions.

Funding: Spain grants BFU2007-65977 and CAM-BIO-0214-2006 (to P.C.) and BIO2008-02882 (to J.F.R.) and by NIH grant R01-GM071872 (to R.A.).

Conflict of Interest: none declared.

REFERENCES


