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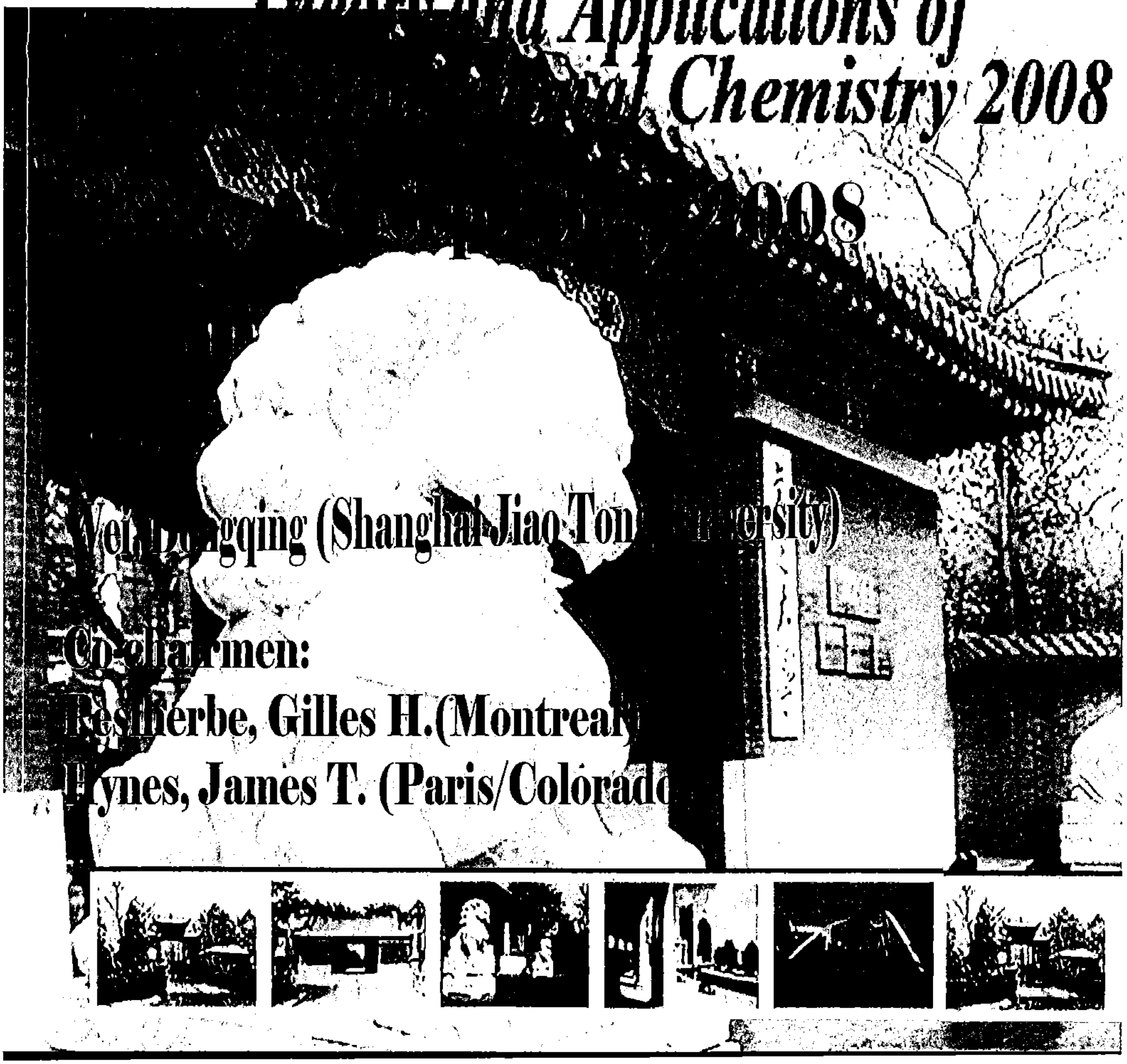

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A New Docking And Screening Method Using A New Operator Based Upon Bioinformatics

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Abstract. Many disease-protein targets have been found from biochemical experiments. Druggable compounds which inhibit or activate those significant protein targets must be researched rapidly. Many researches are using in-sillico screening program such as DOCK, AutoDock and GOLD using classical mechanical potentials. We report the new method using a new operator which uses simulated annealing based on bioinformatics on the protein-ligand flexible docking.

Keywords: operator, docking, screening, bioinformatics, and drug design
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Methods

We use docking engine based upon bioinformatics such as protein structure prediction and effective usage for many X-ray or NMR structures of protein-ligand complex. An amino acid sequence of the target protein which is query sequence are aligned in the filter of CE Z-Score 3.7 for biological similarity significant with the PDB database with some BLAST alignment methods. In the stage of ligand-docking, fingerprint (FP) is used as the basis set in the bioinformatics based simulated annealing. FP is composed of two, three or four atoms. Moreover this FP includes the information of atom-type such as used in Sybyl atom-type and bond-type. Next FP alignment score is defined to determine the docking pose of the ligand to be the most stable one. The docking process was shown in FIGURE 1. Moreover, a new operator was described in FIGURE 2.

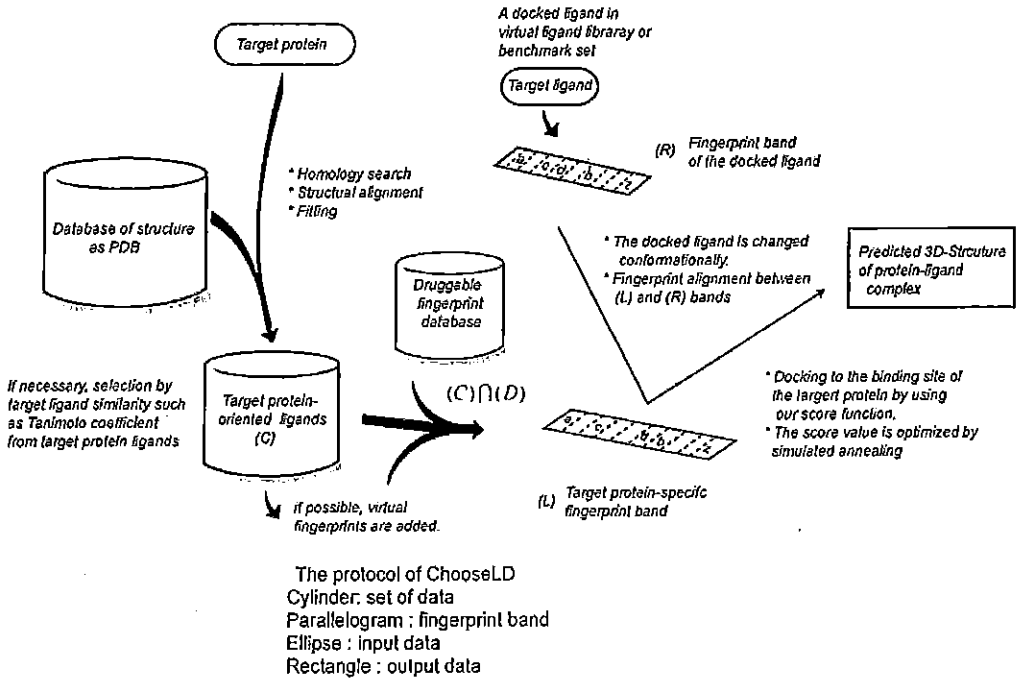

FIGURE 1. Scheme map of ChooseLD protein-ligand docking. Target ligand is docked to the isolated target protein, and the predicted ligand-protein 3D-structure is produced after the fingerprint alignment and the simulated annealing procedures.

$$
\begin{aligned}
FPAScore &= F(aligned\_fp, fp\_rmsd, molecule) \\
&= BaseScore(aligned\_fp, fp\_rmsd) \\
&\times fp\_volume(molecule) \\
&\times fp\_contact\_surface(molecule)
\end{aligned} \tag{1}
$$

$$
BaseScore(aligned\_fp, fp\_rmsd) = \frac{RawScore(aligned\_fp)}{1 + \ln(fp\_rmsd^{k1} + 1)} \tag{2}
$$

$$
fp\_volume(molecule) = \ln \frac{1.0 + nafp^{k2}}{1.0 + nap^{k3}} \tag{3}
$$

$$
fp\_contact\_surface(molecule) = \frac{\sum_{i=1}^{n} density\_of\_atom(atom(i))}{total\_density\_of\_atom(molecule)} \tag{4}
$$

FIGURE 2. The equation used to calculate the FPAScore. Equations (2), (3) and (4) are substituted for three terms in equation (1).

Results

we could make the docking and screening method based upon bioinformatics newly. The accuracy is almost similar to the GOLD and GLIDE docking methods most famous, and higher than the DOCK and AutoDock methods famous. The compared results were shown in FIGURE 3.

(a)

Tc Range	kI						failed PDBID
	1.0	2.0	3.0	4.0	5.0	6.0	
	success rate(%)						
0.56 - 0.08	46.0	54.6	57.6	58.9	56.3	58.6	1V4S, 1G9V
0.76 - 0.08	50.0	61.0	60.7	62.1	59.4	62.1	1V4S
0.96 - 0.08	55.6	62.1	64.4	65.2	65.8	64.8	1V4S
average	50.5	59.2	60.9	62.1	60.5	61.8	

(b)

Docking soft	success rate (%)		
	Corina	MINI	average
DOCK	21.6	20.6	21.1
AutoDock	26.2	27.0	26.6
GOLD ChemScoreSTD	45.5	45.3	45.4
GOLD GOLDScoreLib	44.1	44.9	44.5
GOLD GOLDScoreSTD	45.2	46.7	46.0
	success rate (%)		
ChooseLD TC 0.56 - 0.08			40.1
ChooseLD TC 0.76 - 0.08			44.8
ChooseLD TC 0.96 - 0.08			46.4

FIGURE 3. Success rates for two benchmark sets for Tanimoto coefficient (Tc) ranges, 0.56-0.08, 0.76-0.08 and 0.96-0.08. (a); 85 benchmark set. The k1 value in equation (2) in Fig. 2 was varied from 1.0 to 6.0. Docking calculation of 83, 84 and 84 protein targets succeed in above three ranges, respectively. Since family ligand sets were not found, the ligand-docking results were not obtained for 1V4S and 1G9V. (b); 133 benchmark set. The success rate of ChooseLD is compared with DOCK, AutoDock and GOLD. Corina and MINI show the method to determine initial ligand conformation. ChooseLD uses the furthest conformation from the experimental conformation. 116 protein targets were used in the 133 PDB targets

CONCLUSION

A new docking and screening method using a new operator based upon bioinformatics were made, and this method covers new docking poses different from classical mechanical potential methods.

REFERENCES

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