Molecular Docking in Drug Discovery

Article *in* Journal of Pharmaceutical Research International · June 2021

DOI: 10.9734/jpri/2021/v33i30B31639

7 authors, including:

Deepak Khobragade
Datta Meghe Institute of Medical Sciences (Deemed University)
42 PUBLICATIONS **162** CITATIONS
SEE PROFILE

Sagar Wankhede
JSPM's Charak College of Pharmacy and Research, Wagholi, Pune, India
66 PUBLICATIONS **816** CITATIONS
SEE PROFILE

Ashwini Armarkar
Datta Meghe Institute of Pharmacy,Wardha
6 PUBLICATIONS **9** CITATIONS
SEE PROFILE

Journal of Pharmaceutical Research International

33(30B): 46-58, 2021; Article no.JPRI.68704
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Molecular Docking in Drug Discovery

Rani T. Bhagat[1*], Santosh R. Butle[2], Deepak S. Khobragade[1], Sagar B. Wankhede[1], Chandani C. Prasad[1], Divyani S. Mahure[1] and Ashwini V. Armarkar[1]

[1]Datta Meghe College of Pharmacy, Datta Meghe Institute of Medical Sciences (Deemed to be University) Salod, Sawangi, Wardha-442107, India.
[2]School of Pharmacy, Swami Ramanand Teerth Marathwada University Nanded-431606, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author RTB designed overall study about this manuscript and analyse the manuscript. Authors SRB, DSK and SBW wrote some part of manuscript. Authors CCP and DSM she give suggestions at that time of manuscript preparation. Author AVA spellings correction. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i30B31639
Editor(s):
(1) Dr. Ana Cláudia Coelho, University of Trás-os-Montes and Alto Douro, Portugal.
Reviewers:
(1) Manish R.Bhise, Dr. Rajendra Gode college of Pharmacy, India.
(2) Hemant Kumar Singh Yadav, RAK Medical and Health Sciences University, United Arab Emirates.
(3) A Sanjeeva Kumar, Orotta College of Medicine and Health Sciences, Asmara, Eritrea.
Complete Peer review History: http://www.sdiarticle4.com/review-history/68704

Review Article

Received 14 March 2021
Accepted 19 May 2021
Published 03 June 2021

ABSTRACT

In last few years the Computer Aided Drug Design and Discovery is many success rates. In academics and many pharmaceutical industries for drug lead discovery they adopt the Computational Drug Design. The modern era of drug discovery and development structural information play an important role. For visualization of 3D-structure of molecule different docking program are developed. The docking score is analysed by using computer-based drug design software. It is structure based virtual screening method for the orientation, conformation, position into a structure of target molecule. Ligand and Protein docking is new concept. Molecular docking method complication is optimization of lead molecule, biological pathway evaluation and de Novo drug design.

Keywords: Molecular docking; binding; receptor; rigid; flexible.

**Corresponding author: E-mail: raniteksinhbhagat@gmail.com;*

1. INTRODUCTION

The Suitable orientation of ligand molecule overs the receptor molecule to build a stable complex is called as molecular docking [1-7]. This orientation utilized for the binding affinity prediction and strength of connection of ligand and protein by using scoring function. The drug receptor interaction predicts the affinity and activity of molecule [8-17]. It plays vital role in drug design and drug discovery. It is minimized overall free energy of system. New drug discovery and development is very challenging task. With the help of In-Silico method new drug discovery occurs [18-27]. For the rapid gaining of drug discovery process the computer-based drug design should be used. It is useful in structural biology of molecule and computational drug design [28-35]. It is used to anticipate the 3-Dimensional structure of molecule. With the help of scoring function currently rank candidates docking for large libraries compound perform the virtual screening [36-42].

2. COMPUTER AIDED DRUG DESIGN

It is computer-based technique used in the computational chemistry to discover, enhance or study of drug and related biologically active molecule is called as (CADD) Computer Aided Drug Design.

1. It is most useful in new drug design.
2. It provides knowledge about the chemical and biological properties of ligands and targets.
3. It is used to find and improve novel drug.
4. Discovery of in-silico filters for prediction of undesirable properties like poor activity and poor Pharmacokinetic and Toxicity of drug molecule.
5. It is used for the optimization of novel drug targets. CADD is being used to find hits
6. By using chemical scaffolds to find out novel Virtual screening is applied for new drug molecules.

3. STRUCTURE-BASED DRUG DESIGN

Structure-based computer aided drug design depend on the knowledge of the target protein structure to calculate interaction energies for all tested compounds [43-46]. In structural data-base is crystalized target proteins are available. structure- based is to design compounds that bind with minimal energy by specifically and tightly to the target [47-57]. A broader terminology, Virtual high-throughput screening, is a computer-based screening tool that allows screening of a large library of similar chemical compounds for a particular biological activity [58-65]. Virtual high-throughput screening comes in many forms, including: chemical similarity search, selecting compounds by predicted biologic activity through quantitative structure-activity relationship (QSAR) models or pharmacophore mapping, and virtual docking of compounds against protein target of interest [66-74]. By using computational tools in the lead optimization phase of drug development is significant and cost benefit. Application of computational tools in hit-to-lead optimization while reducing the number of compounds that must be synthesized and tested *In vitro* [75-79].

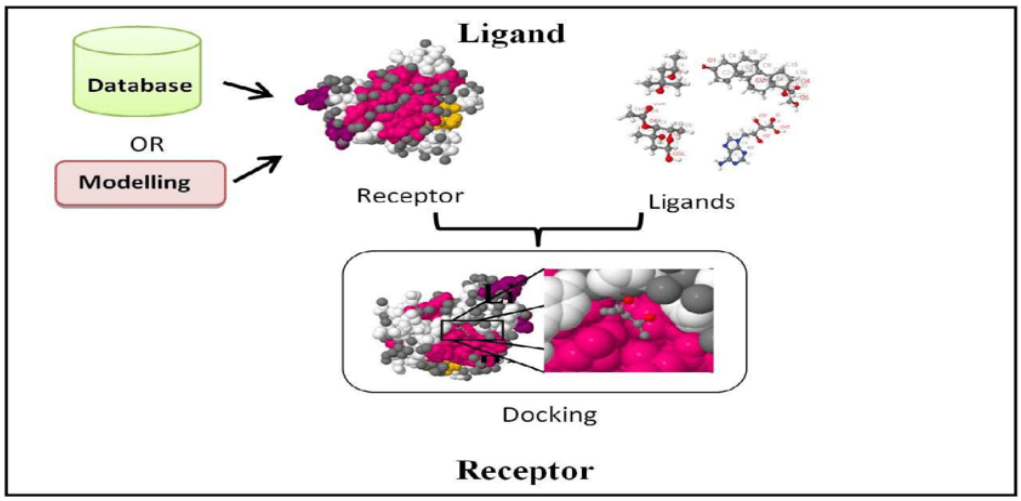

Fig. 1. Commuter aided drug design model

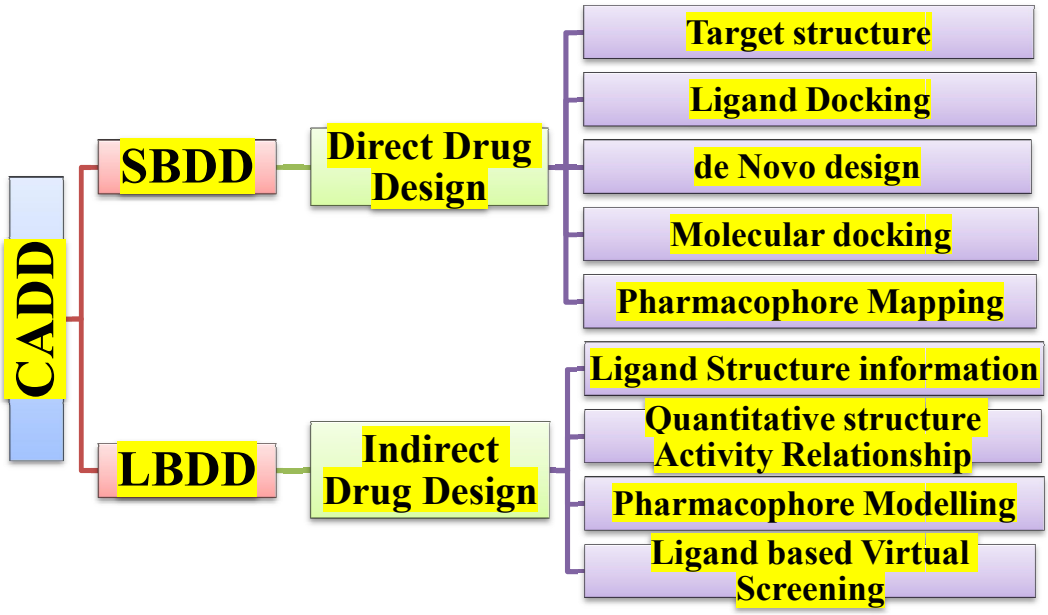

Fig. 2. Drug design structure

4. LIGAND-BASED DRUG DESIGN

Ligand-based exploits the knowledge of known active and inactive molecules for chemical similarity searches or quantitative structure-activity relation (QSAR). Ligand-based, is ideal where the 3D structure of the target proteins are not available.

Structural-Based Computer Aided Drug Design:

Steps includes:

(1) For docking Preparation of the target protein and compound library,
(2) Determining a Proper binding pose for each compound, and
(3) Ranking the docked structures of molecules.

To predicts the orientations or conformations of a receptor-ligand complex by using the Molecular docking and it is a structural based computer simulation procedure and used to predict the binding affinity between the molecules in the complex.

Table 1. Difference between rational drug design and computer aided drug design

Rational Drug Design	Computer Aided Drug Design
1. It is Time consuming Method.	1. It is Time saving Method
2. It is very slow Process and less Accuracy.	2. It is very Rapid Process and More Accuracy.
3. It is costly process.	3. It is cost effective process.
4. It required More manpower.	4. It Required Less manpower
5. In this Finding New medication Based On knowledge of Biological Target.	5. In this Finding New Medication Based on Structure and Ligand based.
6. It is not used for Drug repurposing.	6. It is Useful for Drug Repurposing.
7. Ligand Receptor Interaction is not evaluated.	7. Ligand receptor Interaction is Evaluated.
8. It is not helpful for the Rapid designing and discovery of New Therapeutic Entity.	8. It is helpful for the Rapid designing and discovery of New Therapeutic Entity.
9. In this Do not need to know the Biological target structure.	9. In this need to know the Biological target structure.

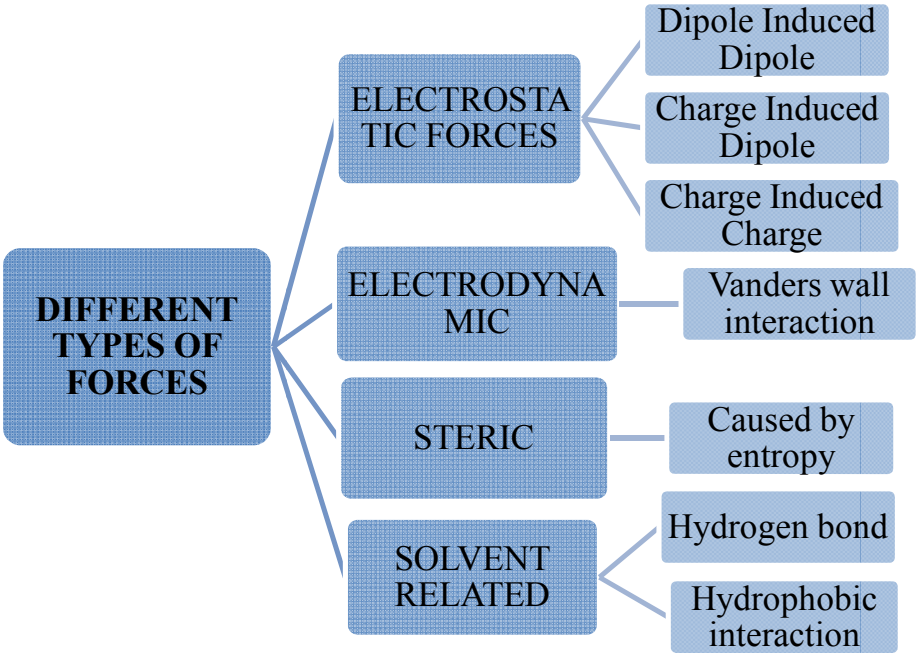

Fig. 3. Interactions different types

5. TYPES OF MOLECULAR DOCKING

1 Search Algorithm: The experimentation method determines the binding modes and number of configurations creates. For docking analysis, the Monte Carlo method, fragment and genetic based, systemic searches is applied.

- **a.** Rigid Docking
- **b.** Flexible Docking

2. Rigid Docking: In this docking the receptor and ligand molecule both are fixed. Docking is performed.

3. Flexible Docking: In this docking the ligand and the receptor both are movable. It is conformationally flexible. Each rotation the energy is calculated. Each conformation surface cell occupancy is calculated. After that the most optimum binding pose is selected.

4. Scoring Function: The binding affinity is directly corresponding to the binding score. The best binders are best scoring ligands. It can be experimental, knowledge and molecular mechanics based. Docking Scoring is play important role in designing of drug:

a) Knowledge-based and
b) Energy component methods

a) **Knowledge-based scoring function** uses the statistics of the observed inter-atomic contact frequencies in a large database of the crystal structure of protein-ligand complexes. Molecular interactions close to the maximum frequency of interactions in the data-base will have a high binding affinity [80-85]. A molecular interaction with a low binding affinity in data base will have a low frequency of interaction.

b) **Energy component scoring method** is based on the mathematical assumption that change in free energy upon binding of a ligand to a protein target (DG bind) is the sum of the free energy for ligand-protein interaction, ligand-protein and solvent interaction, conformational changes in the ligand and protein and the motion in the ligand and protein target during complex formation [86-90].

6. MOLECULAR DOCKING MECHANICS STEPS

In In-Silico method studied the intermolecular interaction between 2 drug molecules. The protein receptor is Macromolecule. It acted as an inhibitor. The following steps involved in docking process are as.

Step I – Preparation of protein and Ligand: From Research Collaboratory Structural Bioinformatics Protein data bank (PDB) downloading the 3D-structure of the Protein. After that downloaded structure should be pre-processed. From the cavity removal of the water molecules, the charges stabilization, missing residues filling, add hydrogen atom side chains generation.

Step II –Ligand Preparation: By using different databases such as ZINC, Pub Chem Ligands molecule can be downloaded. It can be draw in Chem sketch tool in mol file. Then utilized LIPINSKY'S RULE OF 5 for this ligand molecule. It is used for the drug like and unlike molecules. It increases the high chance of success rate and decrease the failure due to drug likeness properties for molecules.

Step III- Grid Generation: In this all factors like site, rotatable group, excluded volumes, constraints kept constant. The number of genetic operations performed (crossover, migration, mutation) is the key parameter in determining. Binding Cavity Prediction are to be done.

Step IV –Prediction of Active site: The active site of protein molecule should be predicted. after that Preparation of protein, the water molecules and hetero atoms if present they are removed from cavity.

Step V- Docking: Ligand and protein interactions are analyzed. Best docking score should be selected.

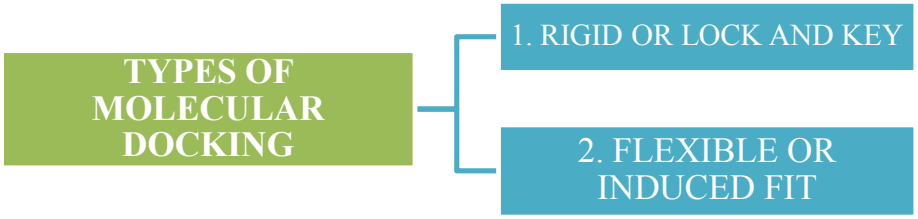

Fig. 4. Types of molecular docking

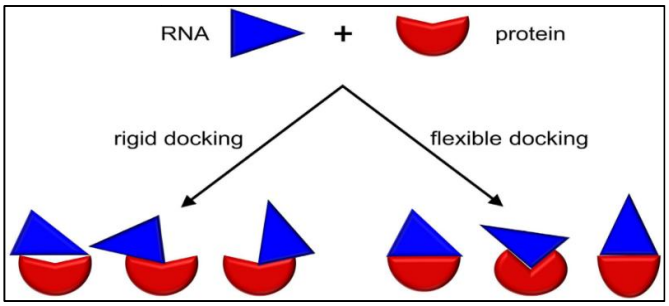

Fig. 5. Flexible Docking

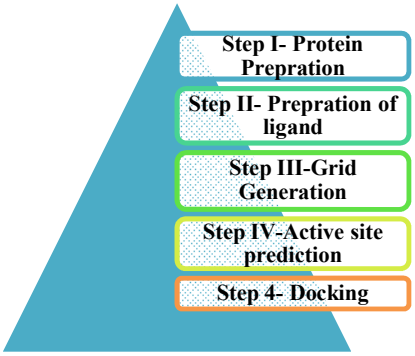

Fig. 6. Molecular docking mechanics steps

Table 2. Difference between lipinsky's rule and muegge rule

Properties	Lipinsky's rule of 5	Muegge RULE
Molecular weight	< 500 g/mol	780.94 g/mol
Log P	< 5	3.92
H- bond donor	< 5	6
H- bond acceptor	< 10	14
Polar surface area	< 140 A^0	203.06 A^0

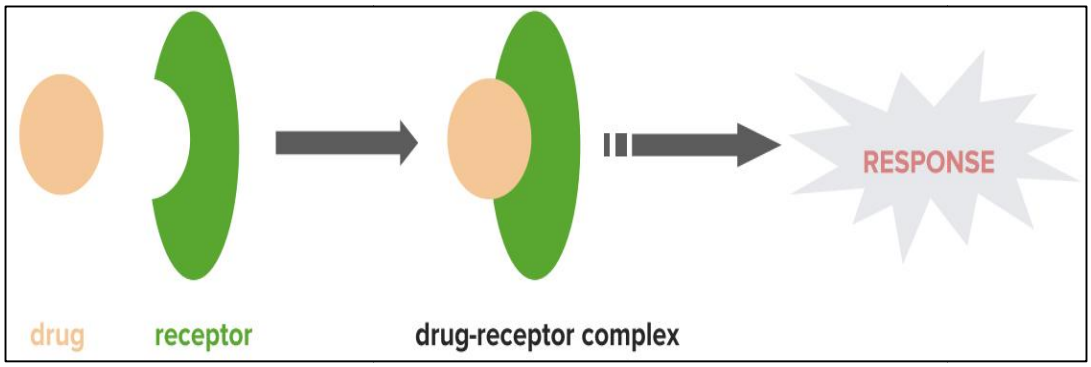

Fig. 7. Drug receptor response

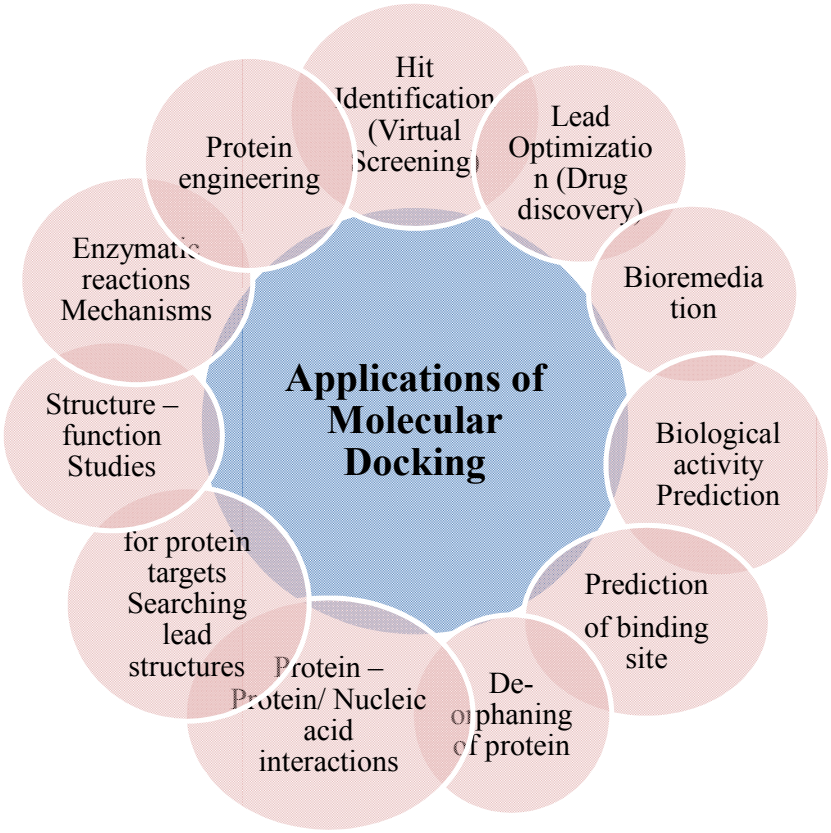

Fig. 8. Application of molecular docking

Table 3. Docking software

Sr No.	Program	Docking Approach	Scoring Function	Advantages	Disadvantages	Licence Term
1.	Auto Dock	Genetic algorithm and Simulated Annealing	force-field methods	Small cavities opened for hydrophobic ligands	Polar flexible ligand	Free for Academic Use
2.	Dock	fitting of Shape	Chem Score	Known binding site	Slow speed	Free for Academic Use
3.	Flex X	Construction Increment	Flex X Score,	Small cavities opened for hydrophobic ligands	More flexible ligands	Commercial Free evaluation (6week)
4.	FRED	fitting of Shape	Piece wise Linear Potential,	High speed, large binding site	Polar ligands	Free for Academic Use
5.	Glide	Sampling of Monte Carlo	Glide Score, Glide Comp	Flexible Hydrophobic ligands	Ranking very slow	Commercial
6.	GOLD	GA searching	Gold and Chem Score	Small Hydrophobic ligands	Large cavity ligand ranking	Commercial
7.	Ligand Fit	Sampling Monte Carlo	Ligand Score	Known binding site	Slow speed	Commercial

7. DISCUSSION AND CONCLUSION

Molecular Docking provides different tools used for drug design and discovery. The medicinal chemist easy to visualization of molecules structural databases. It successfully predicts the binding of ligands within receptor. These drugs make molecular docking process in drug design. It is time-saving, cost-effective. It is used for the novel drug development [91-95]. It Is Very Useful for Future Medicinal Chemist to Discover the Novel Drug Design and Novel Drug Development Process. Molecular docking method complication is optimization of lead molecule, biological pathway evaluation and de Novo drug design. In this review mention all information regarding molecular docking. Malaria, Heart failure, Cancer and other infectious diseases are public health challenges in most countries due to the emergence of drug resistance strains, thus necessitating the need for novel effective remedies [96-100]. Identification of new indication from existing drug and application newly identified drug to treatment of disease. Computational drug design, a cost- effective and less time-consuming approach, is a validated and reliable alternative to the cost expensive and time-consuming conventional method of drug discovery. Malaria, Heart failure, Cancer and other infectious diseases are public health challenges in most countries due to the emergence of drug resistance strains, thus necessitating the need for novel effective remedies. Identification of new indication from existing drug and application newly identified drug to treatment of disease. Computational drug design, a cost- effective and less time-consuming approach, is a validated and reliable alternative to the cost expensive and time-consuming conventional method of drug discovery. It is become powerful alternative strategy to discover and develop novel drugs from existing drug with the help of Computer Aided Drug Design (CADD).

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

RB thanks to the Head of the Pharmaceutical chemistry school of pharmacy, SRTMU Nanded

for their guidance for making manuscript. I would like to special thanks Datta Meghe College of Pharmacy, Datta Meghe Institute of Medical Sciences (Deemed to be University) Salod (H) Wardha for financial support.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERANCES

1. Jorgensen WL. The many roles of computation in drug discovery. Science. 2004;303(5665):1813–1818. [PubMed] [Google Scholar]
2. Bajorath J. Integration of virtual and high-throughput screening. Nat Rev Drug Discov. 2002;1(11):882–894. [PubMed] [Google Scholar]
3. Walters WP, Stahl MT, Murcko MA. Virtual screening - an overview. Drug Discov. Today. 1998;3:160–178. [Google Scholar]
4. Langer T, Hoffmann RD. Virtual screening: An effective tool for lead structure discovery? Curr Pharm Des. 2001;7(7):509–527. [PubMed] [Google Scholar]
5. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: Methods and applications. Nat Rev Drug Discov. 2004;3(11):935–949. [PubMed] [Google Scholar]
6. Gohlke H, Klebe G. Approaches to the description and prediction of the binding affinity of small-molecule ligands to macromolecular receptors. Angew Chem Int Ed Engl. 2002;41(15):2644–2676. [PubMed] [Google Scholar]
7. Moitessier N, Englebienne P, Lee D, Lawandi J, Corbeil CR. Towards the development of universal, fast and highly accurate docking/scoring methods: a long way to go. Br J Pharmacol. 2008;153(Suppl 1):S7–26. [PMC free article] [PubMed] [Google Scholar]
8. Brady GP Jr, Stouten PF. Fast prediction and visualization of protein binding pockets with PASS. J Comput Aided Mol Des. 2000;14(4):383–401. [PubMed] [Google Scholar]
9. Mezei M. A new method for mapping macromolecular topography. J Mol Graph Model. 2003;21(5):463–472. [PubMed] [Google Scholar]
10. Fischer E. Einfluss der configuration auf die wirkung derenzyme. Ber. Dt. Chem. Ges. 1894;27:2985–2993. [Google Scholar]
11. Koshland DE Jr. Correlation of structure and function in enzyme action. Science. 1963;142:1533–1541. [PubMed] [Google Scholar]
12. Hammes GG. Multiple conformational changes in enzyme catalysis. Biochemistry. 2002;41(26):8221–8228. [PubMed] [Google Scholar]
13. Rarey M, Kramer B, Lengauer T, Klebe G. A fast flexible docking method using an incremental construction algorithm. J Mol Biol. 1996;261(3):470–489. [PubMed] [Google Scholar]
14. Morris GM, Goodsell DS, Halliday RS, Huey R, Hart WE, Belew RK, Olson AJ. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. Journal of Computational Chemistry. 1998;19(14):1639–1662. [Google Scholar]
15. Jones G, Willett P, Glen RC, Leach AR, Taylor R. Development and validation of a genetic algorithm for flexible docking. J Mol Biol. 1997;267(3):727–748. [PubMed] [Google Scholar]
16. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, Repasky MP, Knoll EH, Shelley M, Perry JK, Shaw DE, Francis P, Shenkin PS. Glide: a new approach for rapid, accurate docking and scoring. 1 Method and assessment of docking accuracy. J Med Chem. 2004;47(7):1739–1749. [PubMed] [Google Scholar]
17. McGann MR, Almond HR, Nicholls A, Grant JA, Brown FK. Gaussian docking functions. Biopolymers. 2003;68(1):76–90. [PubMed] [Google Scholar]
18. Shoichet BK, McGovern SL, Wei B, Irwin JJ. Hits, leads and artifacts from virtual and high throughput screening. Molecular Informatics: Confronting Complexity; 2002. [Google Scholar]
19. Bailey D, Brown D. High-throughput chemistry and structure-based design: Survival of the smartest. Drug Discov Today. 2001;6(2):57–59. [PubMed] [Google Scholar]

20. Kuntz ID, Blaney JM, Oatley SJ, Langridge R, Ferrin TE. A geometric approach to macromolecule-ligand interactions. J Mol Biol. 1982;161(2):269–288. [PubMed] [Google Scholar]
21. Halperin I, Ma B, Wolfson H, Nussinov R. Principles of docking: An overview of search algorithms and a guide to scoring functions. Proteins. 2002;47(4):409–443. [PubMed] [Google Scholar]
22. Coupez B, Lewis RA. Docking and scoring--theoretically easy, practically impossible? Curr Med Chem. 2006;13(25):2995–3003. [PubMed] [Google Scholar]
23. Kontoyianni M, Madhav P, Suchanek E, Seibel W. Theoretical and practical considerations in virtual screening: A beaten field? Curr Med Chem. 2008;15(2):107–116. [PubMed] [Google Scholar]
24. Brooijmans N, Kuntz ID. Molecular recognition and docking algorithms. Annu Rev Biophys Biomol Struct. 2003;32:335–373. [PubMed] [Google Scholar]
25. ten Brink T, Exner TE. Influence of protonation, tautomeric, and stereoisomeric states on protein-ligand docking results. J Chem Inf Model. 2009;49(6):1535–1546. [PubMed] [Google Scholar]
26. Cross JB, Thompson DC, Rai BK, Baber JC, Fan KY, Hu Y, Humblet C. Comparison of several molecular docking programs: pose prediction and virtual screening accuracy. J Chem Inf Model. 2009;49(6):1455–1474. [PubMed] [Google Scholar]
27. Li X, Li Y, Cheng T, Liu Z, Wang R. Evaluation of the performance of four molecular docking programs on a diverse set of protein-ligand complexes. J Comput Chem. 2010;31(11):2109–2125. [PubMed] [Google Scholar]
28. Perola E, Walters WP, Charifson PS. A detailed comparison of current docking and scoring methods on systems of pharmaceutical relevance. Proteins. 2004;56(2):235–249. [PubMed] [Google Scholar]
29. Sherman W, Day T, Jacobson MP, Friesner RA, Farid R. Novel procedure for modeling ligand/receptor induced fit effects. J Med Chem. 2006;49(2):534–553. [PubMed] [Google Scholar]
30. Jiang F, Kim SH. "Soft docking": matching of molecular surface cubes. *J Mol Biol.* 1991;219(1):79–102. [PubMed] [Google Scholar]
31. Claussen H, Buning C, Rarey M, Lengauer T. FlexE: Efficient molecular docking considering protein structure variations. J Mol Biol. 2001;308(2):377–395. [PubMed] [Google Scholar]
32. Alonso H, Bliznyuk AA, Gready JE. Combining docking and molecular dynamic simulations in drug design. Med Res Rev. 2006;26(5):531–568. [PubMed] [Google Scholar]
33. Sander T, Liljefors T, Balle T. Prediction of the receptor conformation for iGluR2 agonist binding: QM/MM docking to an extensive conformational ensemble generated using normal mode analysis. J Mol Graph Model. 2008;26(8): 1259–1268.
[PubMed][Google Scholar]
34. Subramanian J, Sharma S, BR C. A novel computational analysis of ligand-induced conformational changes in the ATP binding sites of cyclin dependent kinases. J Med Chem. 2006;49(18):5434–5441. [PubMed] [Google Scholar]
35. Subramanian J, Sharma S, BR C. Modeling and selection of flexible proteins for structure-based drug design: backbone and side chain movements in p38 MAPK. *ChemMedChem.* 2008;3(2):336–344. [PubMed] [Google Scholar]
36. R, Ginalski K. Can we trust docking results? Evaluation of seven commonly used programs on PDBbind database. J Comput Chem; 2010.
DOI: 10.1002/jcc.21643. [PubMed] [Google Scholar]
37. McConkey BJ, Sobolev V, Edelman M. The performance of current methods in ligand-protein docking. Current Science. 2002;83:845–855. [Google Scholar]
38. Goodford PJ. A computational procedure for determining energetically favorable binding sites on biologically important macromolecules. J Med Chem. 1985;28(7):849–857.
[PubMed] [Google Scholar]
39. Kastenholz MA, Pastor M, Cruciani G, Haaksma EE, Fox T. GRID/CPCA: A new computational tool to design selective

ligands. J Med Chem. 2000;43(16):3033–3044.
[PubMed] [Google Scholar]

40. Levitt DG, Banaszak LJ. Pocket: A computer graphics method for identifying and displaying protein cavities and their surrounding amino acids. J Mol Graph. 1992;10(4):229–234.
[PubMed] [Google Scholar]
41. Laskowski RA. Surfnet: A program for visualizing molecular surfaces, cavities, and intermolecular interactions. J Mol Graph. 1995;13(5):323–330. 307–328.
[PubMed] [Google Scholar]
42. Glaser F, Morris RJ, Najmanovich RJ, Laskowski RA, Thornton JM. A method for localizing ligand binding pockets in protein structures. Proteins. 2006;62(2): 479–488. [PubMed] [Google Scholar]
43. Ewing TJ, Makino S, Skillman AG, Kuntz ID. DOCK 4.0: Search strategies for automated molecular docking of flexible molecule databases. J Comput Aided Mol Des. 2001;15(5):411–428. [PubMed] [Google Scholar]
44. Welch W, Ruppert J, Jain AN. Hammerhead: fast, fully automated docking of flexible ligands to protein binding sites. Chem Biol. 1996;3(6):449–462. [PubMed] [Google Scholar]
45. Schnecke V, Kuhn LA. Virtual screening with solvation and ligand-induced complementarity. Perspectives in Drug Discovery and Design. 2000;20:171–190. [Google Scholar]
46. Zsoldos Z, Reid D, Simon A, Sadjad BS, Johnson AP. eHiTS: An innovative approach to the docking and scoring function problems. Curr Protein Pept Sci. 2006;7(5):421–435. [PubMed] [Google Scholar]
47. Miranker A, Karplus M. Functionality maps of binding sites: A multiple copy simultaneous search method. Proteins. 1991;11(1):29–34.
[PubMed] [Google Scholar]
48. Eisen MB, Wiley DC, Karplus M, Hubbard RE. HOOK: A program for finding novel molecular architectures that satisfy the chemical and steric requirements of a macromolecule binding site. Proteins. 1994;19(3):199–221.
[PubMed] [Google Scholar]
49. Bohm HJ. LUDI: Rule-based automatic design of new substituents for enzyme inhibitor leads. J Comput Aided Mol Des. 1992;6(6):593–606.
[PubMed] [Google Scholar]
50. Goodsell DS, Lauble H, Stout CD, Olson AJ. Automated docking in crystallography: Analysis of the substrates of aconitase. Proteins. 1993;17(1):1–10.
[PubMed] [Google Scholar]
51. Hart TN, Read RJ. A multiple-start monte carlo docking method. Proteins. 1992;13(3):206–222.
[PubMed] [Google Scholar]
52. Goodsell DS, Olson AJ. Automated docking of substrates to proteins by simulated annealing. Proteins. 1990;8(3):195–202. [PubMed] [Google Scholar]
53. Abagyan R, Totrov M, Kuznetsov D. ICM-A new method for protein modeling and design: Applications to docking and structure prediction from the distorted native conformation. J. Comput. Chem. 1994;15:488–506. [Google Scholar]
54. McMartin C, Bohacek RS. QXP: Powerful, rapid computer algorithms for structure-based drug design. J Comput Aided Mol Des. 1997;11(4):333–344.
[PubMed] [Google Scholar]
55. Accelrys Inc., San Diego, CA, USA.
56. Oshiro CM, Kuntz ID, Dixon JS. Flexible ligand docking using a genetic algorithm. J Comput Aided Mol Des. 1995;9(2):113–130. [PubMed] [Google Scholar]
57. Verdonk ML, Cole JC, Hartshorn MJ, Murray CW, Taylor RD. Improved protein-ligand docking using gold. Proteins. 2003;52(4):609–623.
[PubMed] [Google Scholar]
58. Brint AT, Willett P. Algorithms for the Identification of three-dimensional maximal common substructures. J. Chem. Inf. Comput. Sci. 1987;27:152–158. [Google Scholar]
59. Fischer D, Norel R, Wolfson H, Nussinov R. Surface motifs by a computer vision technique: Searches, detection, and implications for protein-ligand recognition. Proteins. 1993;16(3):278–292. [PubMed] [Google Scholar]
60. Norel R, Fischer D, Wolfson HJ, Nussinov R. Molecular surface recognition by a computer vision-based technique. Protein Eng. 1994;7(1):39–46. [PubMed] [Google Scholar]

61. Miller MD, Kearsley SK, Underwood DJ, Sheridan RP. FLOG: A system to select 'quasi-flexible' ligands complementary to a receptor of known three-dimensional structure. J Comput Aided Mol Des. 1994;8(2):153–174. [PubMed] [Google Scholar]

62. Diller DJ, Merz KM., Jr. High throughput docking for library design and library prioritization. Proteins. 2001;43(2):113–124. [PubMed] [Google Scholar]

63. Burkhard P, Taylor P, Walkinshaw MD. An example of a protein ligand found by database mining: Description of the docking method and its verification by a 2.3 A X-ray structure of a thrombin-ligand complex. J Mol Biol. 1998;277(2): 449–466.
[PubMed][Google Scholar]

64. DesJarlais RL, Sheridan RP, Dixon JS, Kuntz ID, Venkataraghavan R. Docking flexible ligands to macromolecular receptors by molecular shape. J Med Chem. 1986;29(11):2149–2153. [PubMed] [Google Scholar]

65. Kuntz ID, Leach AR. Conformational analysis of flexible ligands in macromolecular receptor sites. J. Comput. Chem. 1992;13:730–748. [Google Scholar]

66. Kollman PA. Free energy calculations: Applications to chemical and biochemical phenomena. Chem. Rev. 1993;93:2395–2417. [Google Scholar]

67. Aqvist J, Luzhkov VB, Brandsdal BO. Ligand binding affinities from MD simulations. Acc Chem Res. 2002;35(6):358–365. [PubMed] [Google Scholar]

68. Carlson HA, Jorgensen WL. An extended linear response method for determining free energies of hydration. J Phys Chem. 1995;99:10667–10673. [Google Scholar]

69. Shoichet BK, Stroud RM, Santi DV, Kuntz ID, Perry KM. Structure-based discovery of inhibitors of thymidylate synthase. Science. 1993;259(5100):1445–1450. [PubMed] [Google Scholar]

70. Michel J, Verdonk ML, Essex JW. Protein-ligand binding affinity predictions by implicit solvent simulations: a tool for lead optimization? J Med Chem. 2006;49(25):7427–7439.
[PubMed] [Google Scholar]

71. Briggs JM, Marrone TJ, McCammon JA. Computational science new horizons and relevance to pharmaceutical design. Trends Cardiovasc. Med. 1996;6:198–206. [PubMed] [Google Scholar]

72. Bohm HJ. Prediction of binding constants of protein ligands: a fast method for the prioritization of hits obtained from design or 3D database search programs. J Comput Aided Mol Des. 1998;12(4):309–323. [PubMed] [Google Scholar]

73. Gehlhaar DK, Verkhivker GM, Rejto PA, Sherman CJ, Fogel DB, Fogel LJ, Freer ST. Molecular recognition of the inhibitor AG-1343 by HIV-1 protease: Conformationally flexible docking by evolutionary programming. Chem Biol. 1995;2(5):317–324. [PubMed] [Google Scholar]

74. Verkhivker GM, Bouzida D, Gehlhaar DK, Rejto PA, Arthurs S, Colson AB, Freer ST, Larson V, Luty BA, Marrone T, Rose PW. Deciphering common failures in molecular docking of ligand-protein complexes. J Comput Aided Mol Des. 2000;14(8):731–751. [PubMed] [Google Scholar]

75. Clark KP. Ajay, Flexible ligand docking without parameter adjustment across four ligand- receptor complexes. J Comput Chem. 1995;16:1210–1226. [Google Scholar]

76. Taylor JS, Burnett RM. DARWIN: A program for docking flexible molecules. Proteins. 2000;41(2):173–191. [PubMed] [Google Scholar]

77. Cornell WD, Cieplak P, Bayly CI, Gould IR, Merz KM, Ferguson DM, Spellmeyer DC, Fox T, Caldwell JW, Kollman PA. A second generation force field for the simulation of proteins, nucleic acids, and organic molecules. J. Am. Chem. Soc. 1995;117:5179–5197. [Google Scholar]

78. Weiner SJ, Kollman PA, Case DA, Singh UC, Ghio C, Alagona G, Profeta S, Jr., Weiner P. New force field for molecular mechanical simulation of nucleic acids and proteins. J. Am. Chem. Soc. 1984;106:765–784. [Google Scholar]

79. Brooks BR, Bruccoleri RE, Olafson BD, States DJ, Swaminathan S, Karplus M. CHARMM: A program for macromolecular energy, minimization, and

dynamics calculations. J. Comput. Chem. 1983;4:187–217. [Google Scholar]

80. Srinivasan J, Cheatham TE, Cieplak P, Kollman PA, Case DA. Continuum solvent studies of the stability of DNA, RNA, and phosphoramidateâ^'DNA Helices. Journal of the American Chemical Society. 1998;120(37):9401–9409. [Google Scholar]
81. Kollman PA, Massova I, Reyes C, Kuhn B, Huo S, Chong L, et al. 3rd calculating structures and free energies of complex molecules: Combining molecular mechanics and continuum models. Acc Chem Res. 2000;33(12):889–897. [PubMed] [Google Scholar]
82. Still WC, Tempczyk A, Hawley RC, Hendrickson T. Semianalytical treatment of solvation for molecular mechanics and dynamics. J. Am. Chem. Soc. 1990;112(16):6127–6129. [Google Scholar]
83. Guimaraes CR, Mathiowetz AM. Addressing limitations with the MM-GB/SA scoring procedure using the WaterMap method and free energy perturbation calculations. J Chem Inf Model. 50(4):547–559. [PubMed] [Google Scholar]
84. Singh N, Warshel A. Absolute binding free energy calculations: On the accuracy of computational scoring of protein-ligand interactions. Proteins. 2010;78(7):1705–1723. [PMC free article] [PubMed] [Google Scholar]
85. Gabb HA, Jackson RM, Sternberg MJ. Modelling protein docking using shape complementarity, electrostatics and biochemical information. J Mol Biol. 1997;272(1):106–120. [PubMed] [Google Scholar]
86. Jain AN. Scoring noncovalent protein-ligand interactions: a continuous differentiable function tuned to compute binding affinities. J Comput Aided Mol Des. 1996;10(5):427–440. [PubMed] [Google Scholar]
87. Head RD, Smythe ML, Oprea TI, Waller CL, Green SM, Marshall GR. VALIDATE: A new method for the receptor-based prediction of binding affinities of novel ligands. J. Am. Chem. Soc. 1996;118:3959–3969. [Google Scholar]
88. Gehlhaar DK, Moerder KE, Zichi D, Sherman CJ, Ogden RC, Freer ST. De novo design of enzyme inhibitors by Monte Carlo ligand generation. J Med Chem. 1995;38(3):466–472. [PubMed] [Google Scholar]
89. Eldridge MD, Murray CW, Auton TR, Paolini GV, Mee RP. Empirical scoring functions: I. 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(5):425–445. [PubMed] [Google Scholar]
90. Muegge I, Martin YC. A general and fast scoring function for protein-ligand interactions: A simplified potential approach. J Med Chem. 1999;42(5):791–804. [PubMed] [Google Scholar]
91. Mitchell JBO, Laskowski RA, Alex A, Thornton JM. Bleep-potential of mean force describing protein-ligand interactions: I. generating potential. J. Comput. Chem. 1999;20(11):1165–1176. [Google Scholar]
92. Ishchenko AV, Shakhnovich EI. SMall Molecule Growth 2001 (SMoG2001): An improved knowledge-based scoring function for protein-ligand interactions. J Med Chem. 2002;45(13):2770–2780. [PubMed] [Google Scholar]
93. Feher M, Deretey E, Roy S. BHB: A simple knowledge-based scoring function to improve the efficiency of database screening. J Chem Inf Comput Sci. 2003;43(4):1316–1327. [PubMed] [Google Scholar]
94. Verkhivker G, Appelt K, Freer ST, Villafranca JE. Empirical free energy calculations of ligand-protein crystallographic complexes. I. Knowledge-based ligand-protein interaction potentials applied to the prediction of human immunodeficiency virus 1 protease binding affinity. Protein Eng. 1995;8(7):677–691. [PubMed] [Google Scholar]
95. Wallqvist A, Jernigan RL, Covell DG. A preference-based free-energy parameterization of enzyme-inhibitor binding. Applications to HIV-1-protease inhibitor design. Protein Sci. 1995;4(9):1881–1903. [PMC free article] [PubMed] [Google Scholar]
96. Gohlke H, Hendlich M, Klebe G. Knowledge-based scoring function to predict protein-ligand interactions. J Mol

Biol. 2000;295(2):337–356. [PubMed] [Google Scholar]

97. DeWitte RS, Shakhnovich EI. SMoG: de Novo Design Method Based on Simple, Fast, and Accurate Free Energy Estimates. 1 Methodology and Supporting Evidence. J. Am. Chem. Soc. 1996;118:11733–11744. [Google Scholar]

98. Charifson PS, Corkery JJ, Murcko MA, Walters WP. Consensus scoring: A method for obtaining improved hit rates from docking databases of three-dimensional structures into proteins. J Med Chem. 1999;42(25):5100–5109. [PubMed] [Google Scholar]

99. Feher M. Consensus scoring for protein-ligand interactions. Drug Discov Today. 2006;11(9-10):421–428. [PubMed] [Google Scholar]

100. Clark RD, Strizhev A, Leonard JM, Blake JF, Matthew JB. Consensus scoring for ligand/protein interactions. J Mol Graph Model. 2002;20(4):281–295. [PubMed] [Google Scholar]

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/68704