REVIEW ARTICLE

Docking: A Powerful Approach for the Discovery of Anti-cancerous Drugs

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ABSTRACT

The discovery of drug and its development is a labor-intensive, time-consuming, and costly process. Customarily it was hard to choose the best synthetic moiety of accumulating that assumes a powerful job in treating or forestalling malignancy. In India, the death rate is extremely high in this way, the advancement of novel and intense anti-cancerous drugs is vital and henceforth, we need to apply different computational techniques for lead age and streamlining during the time spent medication disclosure along these lines. We utilize atomic mooring as it saves time just as the expense and assists with deciding little particles based leads with better pharmacological action and lessening results for an explicit sickness objective. Docking helps distinguish proof of novel accumulates of restorative interest. This survey depicts different kinds of mooring, different virtual products utilized for mooring, steps associated with mooring utilizing autodock 4.2, and how it is generally utilized in anti-cancer examination.

Keywords: Anti-cancerous drugs, Autodock 4.2, Docking, Drug Discovery, Softwares used.

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INTRODUCTION

Cancer refers to a group of diseases. It involves abnormal growth of cell with spreading properties.[1] It contrasts with benign tumors, which do not spread.[2]

Cancer forms a subset of neoplasm.[3] Neoplasm or tumour is a group of cells with unregulated growth properties and forms a mass or lump.[4] It develops when normal cells in a specific part of the body starts to grow out of control. Generally, this is due to the damage of DNA. In cancer cells DNA is not repaired. This may be possibly due to a person in contact with something in the environment like smoking, UV radiation etc. Changes can reduce the risk of cancer development in lifestyle.[5] If cancer is detected early, it is easy for treatment.[6]

As the mortality rate in India is very high, the development of new drugs with efficient therapeutic effect is crucial. Selecting the compound that can effectively treat or prevent cancer earlier was very difficult.[7] But now, there are various computational methods such as docking that helps in drug discovery with less labour-intensive and less time consumption.[8] Docking helps distinguish proof of new accumulates of restorative interest, anticipate ligand-target communications at an atomic level, or portray structure-action connections (SAR).[9] Sub-atomic docking has been demonstrated to be fruitful in discovering novel anti-cancer mixes against different protein targets, such as BCR-ABL tyrosine kinase, Chk1, FKBP, protein tyrosine phosphatase (PTP) and EGFR too.[10] To know the kind of mixes that are to be secluded, sort of mixes that can be liable for the natural action, sort of explicit objective and the particular hindrance component, a computational atomic docking approach can be utilized with the ideal protein target.[11]

DOCKING

It is a method in which the orientation of one molecule to another when bound to each other to form a stable complex with therapeutic activity is performed. Orientation depends on the binding affinities of two molecules. It is beneficial in structure-based drug design.[12]

Principle of Docking

It is based on the interactions due to binding affinities of two molecules to form a stable complex with pharmacological and therapeutic activities with reduced side effects in drug designing, drug discovery, and drug development using

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computation methods. Two continuous steps achieve it, i.e., sampling conformations (ligand and protein binding) and scoring function (ranking of the highest among the generated conformations).[13]

Types of Docking

Rigid Docking

In this the molecules are rigid. The orientation here is done in 3D space in terms of scoring function.

Flexible Docking

In this the molecules are flexible. Here, the orientation, and conformations, are determined.[14]

METHODOLOGY

1) Rigid Ligand and Rigid Receptor Docking

In this the inquiry space is exceptionally less; alluding just three translational and three rotational levels of opportunity.[15] In this sort van der Waals, electrostatics, H-holding just as hydrophobic i.e., water loathing communications are considered.[16]

2) Flexible Ligand and Rigid Receptor Docking

In those the van der Waals, H-holding, electrostatic communications, collaborations between useful gatherings, conformational entropy and desolvation terms are thought of. Autodock 4.0 is best fitted here for noticing the adaptability of the receptor by the receptor by permitting the development of side chains.[17]

3) Flexible Ligand and Flexible Receptor Docking

When the receptor is additionally adaptable the expense is high for this sort of arrangement. The inner development is firmly connected with the coupling nature. This is a difficult technique. It very well may be finished by 'delicate docking'. It decreases the van der Waals repugnance energy term in scoring capacity to take into account a level of iota molecule cover among receptor and ligand.[18]

4) Local Move Monte Carlo Sampling for Flexible Receptor Docking

Neighborhood move is otherwise called window move.[19] In this technique, one twist point is changed and six ensuing twists are changed while the rest anchor stays as is to protect all bond lengths just as angles.[20]

APPROACHES

1. FRAGMENT BASED METHOD

In this the ligand are separated into protons or small fragments. The docking is then performed for these fragments and linked together.

2. DISTANCE GEOMETRY

Here in this, the intermolecular distances are grouped together, followed by 3 D structures being calculated.

3. MATCHING APPROACH

In this the ligand is placed at the target site which best suits or fits it and optimization is checked.

4. LIGAND FIT APPROACH

Here the ligand is fitted in the active protein site for considering shape.

5. POINT COMPLIMENTARITY APPROACH

In this the shape or chemical is being observed between the ligand and protein interaction.

6. BLIND DOCKING

In this, the whole surface of the protein is scanned and possible binding sites are observed.

7. INVERSE DOCKING

In this the toxicity and side effects of the macromolecule and the target are determined and then matched for the conduction of binding interactions between them.[21]

MOLECULAR DOCKING MODELS

1. LOCK AND KEY THEORY

Here, the substrate attaches to the macromolecule due to specific interaction like a key that fits the lock due to its unique stereochemical features.

2. THE INDUCED-FIT THEORY

In this the ligand and target undergo small conformational changes up to a limit till they are ready to fit each other.

3. THE CONFORMATION ENSEMBLE MODEL

Here the proteins can undergo large conformational changes an also can adapt from one state to the another.[22]

STEPS INVOLVED IN MOLECULAR DOCING USING AUTODOCK 4.2

Requirements-[26] Windows XP or Windows 7, MGL tools, Cygwin,[27] Discovery studio visualizer, binary files, Auto Dock 4.2, Auto grid, Java[28]

SOFTWARES USED[23-25]

Table 1: Softwares of Docking

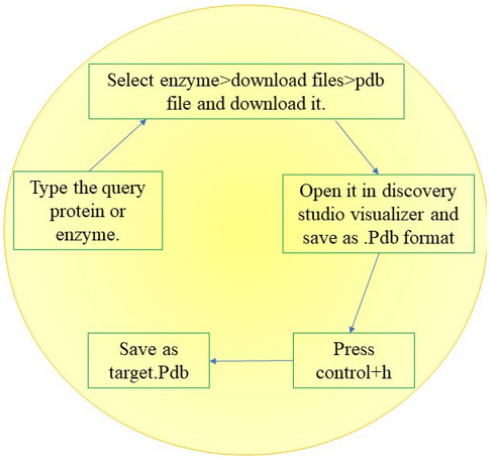
Softwares Used	*Downloading Links*
1. DOCK (1982, 2001)	http://dock.compbio.ucsf.edu/
2. FLEX (1996)	https://sourceforge.net/projects/flex/
3. Hammerhead (1996)	https://hammerhead-rhythm-station.en.softonic.com/
4. Surflex (2003)	https://www.biopharmics.com/downloads/
5. SLIDE (2002)	https://kuhnlab.natsci.msu.edu/software/slide/index.html
6. AutoDock (1990, 1998)	http://autodock.scripps.edu/downloads/autodock-4-2-x-installation-on-windows
7. ICM (1994)	https://www.molsoft.com/download.html
8. MCDock (1999)	http://autodock.scripps.edu/
9. GOLD (1997)	https://www.filehorse.com/download-proshow-gold/
10. GemDock (2004)	http://gemdock.life.nctu.edu.tw/dock/download.php
11. Glide (2004)	https://trustrevizion163.weebly.com/blog/glide-docking-software-free-download
12. Yucca (2005)	https://sourceforge.net/projects/yucca/

Following steps are involved: -

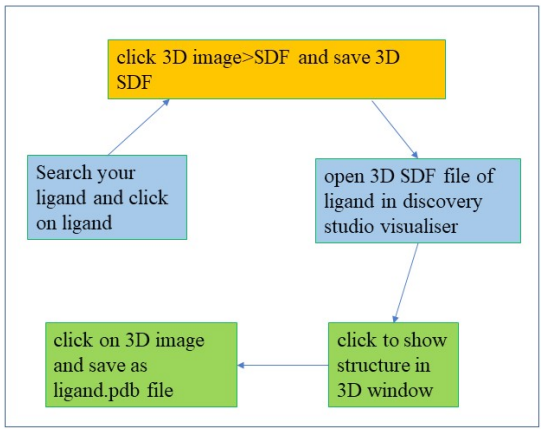
Initializing Molecules

Protein molecule is initialized by addition of H atoms. On the other hand, for ligand molecule detection of rotatable bonds. Then open the protein molecule and change its view from line to surface so that it can easily set to grid box.

RETRIEVING TARGET.PDB FILES FROM MAJOR PROTEIN DATABASES

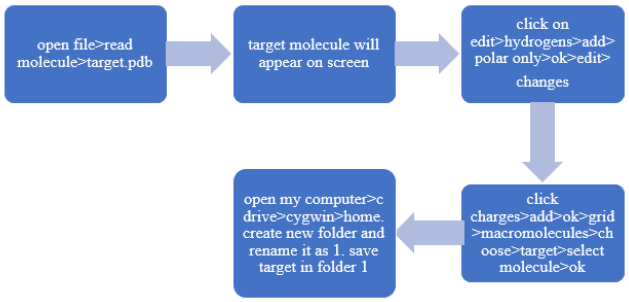


RETRIEVING LIGAND.PDB FILES FROM MAJOR LIGAND DATABASES

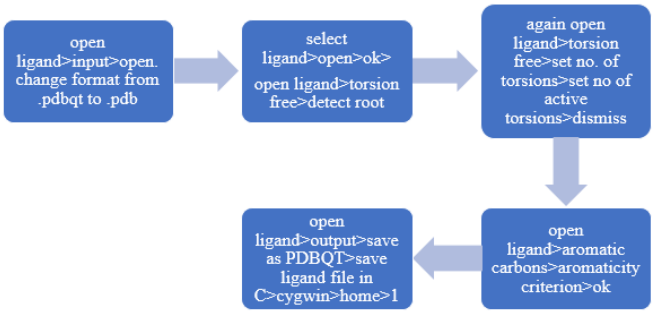


PREPARING PDBQT FORMAT FOR TARGET AND LIGAND, GRID AND DOCKING PARAMETER FILE USING AUTODOCK 4.2

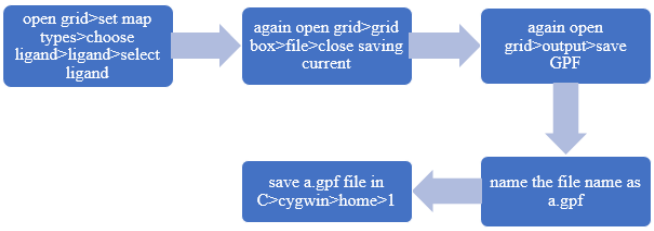
PREPARATION OF TARGET.PDBQT FILE



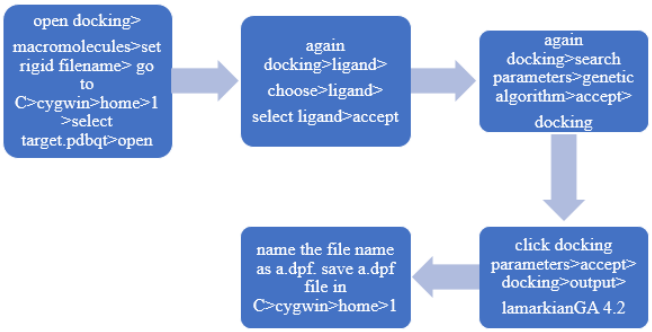
PREPARATION OF LIGAND.PDBQT FILE



PREPARATION OF GRID PARAMETER FILE



PREPARATION OF DOCKING PARAMETER FILE



USING CYGWIN FOR MOLECULAR DOCKING

Open Cygwin. Use these commands highlighted by copy and paste in Cygwin and press enter after each command.

(cd..)cd<space>..

(Is)Is<space>

(cd 1) cd<space>1(or foldername)<space>

(Is)Is<space>

(autogrid4.exe -p a.gpf -l a.glg &)

Autogrid(tab)<space>-p<space>a.gpf<space>-l<space>a.glg&

(tail -f a.glg &) tail<space>-f<space>a.glg<space>&

(autodock4.exe -p a.dpf -l a.dlg &)

Autodock(tab)<space>-p<space>a.dpf<space>-l<space>a.dlg&

(tail -f a.dlg &) tail<space>-f<space>a.dlg<space>&

Copy target.pdb file in C>Cygwin>home>1

Copy and paste the following commands in Cygwin window and press enter after each command:

(grep '^DOCKED' a.dlg | cut -c9- >a.pdbqt)

(cut -c-66 a.pdbqt> a.pdb)

(catTarget.pdb a.pdb | grep -v '^END ' | grep -v '^END$' > complex.pdb)

Close cygwin window

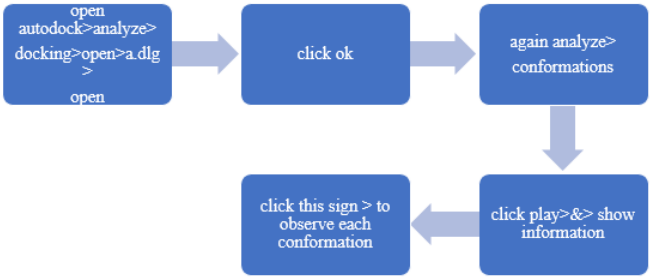
Click ok

ANALYZING INTERACTION ENERGY

After the successful execution of autodock. The result was formed in the ten next conformations. This is observed by

selecting the "play, ranked by energy" option. And the final file is saved as "result.pdb" file.[29]

ANALYZING RESULTS



RETRIEVING LIGAND-ENZYME INTERACTION COMPLEX .PDB

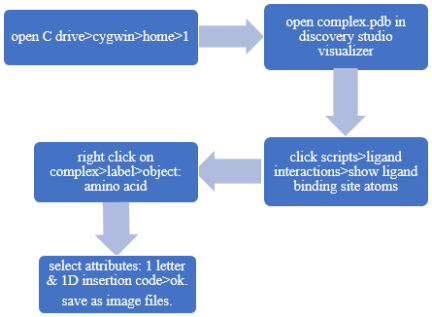


Table 2: Research on Docking of various Anti-cancerous Drugs

S. No.	*Type of cancer*	*Ligand (drugs)*	*Target*	*Docking software*	*Result*	*Ref. No.*
1	Lymphoma cancer	crizotinib, sunitinibmalate, tandutinib	ALK (human anaplastic lymphoma cancer kinase)	Argus lab d	crizotinib derivatives and sunitinib derivatives were detected with significant energy value even better than many of the conventional drugs.	30
2	Breast cancer	raloxifene and toremifene	human estrogen receptor	HEX	Raloxifene derivative and Toremifene derivative were detected and proved better compared to many of the available marketed drugs.	31
3	Anti-cancer agent	modified colchine derivatives	Human cancer cell lines	Autodock	Some of the colchine analogues are more potent than unmodified colchicine.	32
4	human colorectal carcinoma cancer and breast cancer	heterocyclic benzimidazole molecule	human colorectal carcinoma cancer and ER-alpha for breast adenocarcinoma cancer cell lines	Maestro version 11.5	drugs were identified according to the energy levels and then followed up by comparing with the standard drug.	33
5	Anti-cancer agent	The docking is performed for boswellic acid as well as ursolic acid	receptor human cyclin dependent kinase 2	Argus lab	The energy level or docking score of boswellic acid is good as compared to ursolic acid when performed	34
6	Anti-cancer property	Aloesin, barbaloin, curcumin and emodin	topoisomerase 1, a 91-KDa monomer containing 765 amino acids	Autodock 4	it was found that emodin was best amongst all to treat the deadly disease cancer.	35
7	antitumour effect on urothelial bladder cells	matrine and cisplatin	Urothlial bladder cells	CDOCKER model in DS2.5	the results obtained show that both of these inhibit urothelial bladder cells' growth in ratio 2000:1. These shows effect by arresting cell cycle.	36
8	Breast cancer	23 3D pubchem structure of furanocoumarin compounds	3 D structure obtained from protein data bank	autodock	Xanthotoxol was best in scoring function followed by bergapten, angelicin, psoralen and isoimperatorin for breast cancer.	37
9	Kidney cancer	aspirin, celecoxib, dexamethasone and diclofenac.	proinflammatory protein S100A8	Affymetrix hugene 1.0 ST arrays	The results show that S100A8 protein has anti-cancer therapeutic effect.	38
10	Brain, lung and skin cancer	6-hydroxylglavones	1QH4, 2ITO and 2VCJ proteins	autodock	The result shows that it is highly effective based on scoring functions obtained.	39
11	Non-small cell lung cancer	traditional Chinese medicinal compounds	epithelial growth factor receptor protein (EGFR)	autodock	as a result, triptolide was found for its anti-proliferative potency.	40

S. No.	*Type of cancer*	*Ligand (drugs)*	*Target*	*Docking software*	*Result*	*Ref. No.*
12	Anti-cancerous activity	paclitaxel, etoposide and topotecan	tubulin protein	Schrödinger software	etoposide is the best drug for tubulin.	41
13	Anti-cancer activity	Xanthones and their analogues	Cancer cell lines such as A549, HepG2, U251	autodock	Shows positive result	42
14	Anti-cancer activity	Thymoquinone (TQ)	Phosphate and tensin homolog located on chromosome 10q23 (PTEN)	autodock	It showed the binding energy of -7.37 Kcal with 3 hydrogen bonds	43
15	Anti-cancer activity	72 cytotoxic compounds	Melanoma cell line SK-MEL-2	autodock	AN2 and AC4 shows a better binding score for the target.	44
16	NON-MELANOMA SKIN CANCER	Ibuprofen, butanoic acid	3D structures of human COX-2	autodock	e morin compound exhibited better binding energy of -32.9528 kJ/mol against PPARα followed by COX-2 (binding energy: −18.4311 kJ/mol) and PPARγ (binding energy: −17.4228 kJ/mol) when compared to their cocrystallized ligands.	45
17	Brain, lung and skin cancer	Hydroxylated flavones and its derivatives	1QH4, 2ITO and 2VCJ protein	autodock	The docking results show that 6-hydroxyflavanone capable of interacting with 1QH4, 2ITO and 2VCJ proteins.	46
18	Skin cancer	(heptadecanoic acid, 16 methyl-, methyl esters; 9,12-octadecadienoic acid; cis-9-octadecenoic acid) derived from the fungus *Trichoderma*	Skin Cancer Protein (4,5-Diarylisoxazole HSP90 Chaperone)	autodock	heptadecanoic acid, 16 methyl, methyl ester was the most potent when compared to the standard drug "dyclonine".	47
19	human skin squamous cell carcinoma	20 hit compounds	Aquaporin-3 (AQP3) protein	autodock	the compound (1-(4-methoxyphenoxy)-3-((4-methoxyphenyl) amino) propan-2-ol) has good free binding energy.	48
20	Kidney cancer	drugs	S100A8	autodock	S100A8 protein is a potential target for therapeutic activity in kidney cancer.	49
21	Antihypertensive activity	ethyl 1-benzenesulfonyl -2-[(e)-2- (2 methylphenyl) ethenyl] indole -3-carboxylate	Human renin	Molegro Virtual Docker (MVD)	This ligand showed the highest score and a strong binding affinity towards the protein.	50
22	Renal carcinoma	Rutin, curcumin	CCND1	autodock	CCND1 will act as a potential therapeutic target.	51
23	Colon cancer	GLTP - Nilotinib, PTPRN - Venetoclax, VEGFA - Venetoclax and FABP6 - Abemaciclib.	CDK4/6 protein	autodock	the FABP6 gene showed positive results during docking.	52
24	papillary renal cell carcinoma	60 drug candidates	C3 and ANXN1 proteins	autodock	Vorinostat showed best results.	53
25	Anti-inflammatory agents	Dimethylpyridine Derivatives	anti-COX-1/COX-2	autodock	the best therapeutic activity was observed by PS18, PS19, PS33, PS40 and PS41.	54
26	Breast cancer	Compound Kushen injection (CKI)	HSD11B1, DPP4, MMP9, CDK1, MMP2, PTGS2, and CA14.	Cytoscape 3.6.1	DPP4 had strong binding activity with matrine, alicyclic protein, sophoridine, and MMP9 had a strong binding activity with adenine and sophoridine.	55

S. No.	*Type of cancer*	*Ligand (drugs)*	*Target*	*Docking software*	*Result*	*Ref. No.*
27	Urothelial bladder cancer	Matrine and cisplatin	Fibronectin, Vimentin, Bcl-2, Caspase-3, p-Akt, p-PI3K, VEGFR2, and VEGF proteins	CDOCKER module in DS 2.5	combination of matrine and cisplatin showed the best results.	56
28	Cervical cancer	ligand like Vasicinone, Oleanic acid and Chavicol	target protein DNMT1 (PDB ID: 4WXX)	Autodock vina software	Vasicinone was the best compound against DNMT1 with its minimum binding energy.	57
29	Human cervical cancer	Polyphenolic compounds	Caspase 3-HeLa Cell Line Protein	Hex 8.0.0	Coumarin showed best positive results during docking.	58
30	Oral cancer	ARRB1, FLNA, CALM3, and HTT	proteins	Autodock	HTT and CALM3 showed positive results as compared to others.	59
31	Oral cancer	Dihydrohelenalin	receptor protein DNMT1	AutoDock Vina software	Dihydrohelenalin (CID: 3032910) was the only compound that can inhibit the activity of DNMT1 (PDB ID: 4WXX).	60
32	Oral cancer	*Limonia acidissima* is widely known as wood apple	HER2 (human epidermal growth factor 2) is one of the proteins	autodock	Limonia acidissima is widely known as wood apple against oral cancer an in-silico approach. The compounds of wood apple showed their anti-cancer properties against HER2 protein which could be used for further analysis.	61
33	Cancer treatment	Antimicrobial peptides (AMPs)	Human cadherin-1 protein	patchdock	AMPs have good activity with human cadherin -1 protein.	62
34	Mitochondrial dysfunction	kaempferol, quercetin, eugenol, oxyresveratrol, tanshinone 2a, catechin, epicatechin, cinnamaldehyde, and emodin	inner mitochondrial membrane protein, CyPD	autodock	emodin was observed best by strong affinity as compared to others.	63
35	Oral squamous cell carcinoma	Caffeic acid and caffeine	P 53, bcl 2, bax and casapase 9	Hex 6.0 docking software	This shows good receptor ligand interactions	64
36	Anti-cancer properties	(7-hydroxy-4′-methoxy-3,11-dehydrohomoisoflavanone, 4,4′-dihydroxy-2'-methoxychalcone, 7,4′-dihydroxy-3,11-dehydrohomoisoflavanone, luteolin, quercetin-3-methyl, kaempferol-3-O-β-d-xylopyranoside and kaempferol3-O-α-l-rhamnopyranosyl-(1→2)-β-D-xylopyranoside)	Tyrosine kinase (TK), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMP)	Autodock vina	the phytochemicals showed positive and good results during the docking.	65

Role of Docking in Anticancer Research

Docking is done for drug design, drug discovery, and drug development to reduce the cost and time, and it is not labor intensive.

CONCLUSION AND FUTURE PERSPECTIVES

Docking programming projects workers have demonstrated to assume a critical job for drug configuration, drug disclosure and advancement of medication in different anti-cancerous divisions. It is an Insilco structure-based technique. Subsequently, the contextual analysis and many examples of overcoming adversity show that one can discover in writing, identified with PC supported medication plan, that in-silico approaches, blend with biophysical information, trial high throughput screening and science/toxicology/clinical examinations are an imperative instrument during the time spent medication revelation. It aids dynamic, conceptualizing novel thoughts and quickly investigating them to test a theory, carrying answers for issues that can't be evaluated tentatively either because the trials is too hard to even think

about designing or because it would be excessively expensive. Docking should be done to investigate normal mixes moreover.

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