EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 3
107-112
Year: 2019

COMPUTER AIDED DRUG DESIGN: A COMPUTATIONAL METHOD FOR DRUG DISCOVERY AND DEVELOPMENT

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Article Received on 09/01/2019 **Article Revised on 29/01/2019** **Article Accepted on 19/02/2019**

ABSTRACT
Computer aided drug design (CADD) or insilico design is the application of computational or computer modeling in drug design. Drug is a biomolecule that can bind to a target receptor resulting to pharmacological response. The purpose of drug design is to predict the binding ability and strength at which a molecule can bind to target of an interest. Computer aided drug design may be applied at stages such as hit identification using virtual screening, hit-to-lead optimization of affinity and selectivity and lead optimization. Utilizing computational techniques have given rise to remarkable progress in drug discovery.

KEYWORDS: Computer aided drug design, insilico design, ligand, drug discovery.

INTRODUCTION
Computer aided drug design (CADD) or insilico design is the application of computational or computer modeling in drug design or more specifically ligand design (drug invention and development).[1] Drug is an organic small molecule that can bind to biological molecule usually protein or nucleic acid in other to induce or inhibit its function resulting in physiological and psychological change in the body. A ligand is a molecule that can bind tightly to its target. A ligand should possess properties such as bioavailability, metabolic half-life, side effects, before it can become safe and effective.[2,3] The basic aim of drug design is to predict if a given molecule will bind to a target and at what strength.[1]

Computer aided drug design may be used in drug discovery at stages such as hit identification using virtual screening, hit-to-lead optimization of affinity and selectivity and lead optimization of other pharmaceutical properties while maintaining affinity.[1,3] The three major roles of CADD in drug discovery are: large number of compounds can be reduced into smaller sets of active compounds that can be experimentally tested; lead optimization in other to check for absorption, distribution, metabolism, excretion, and the potential for toxicity[4]; novel compounds can be designed by piecing together fragments into novel chemo types.[3] The discovery of drugs through CADD has been applied to design of anticancer agents (thymidylate syntheses inhibitors)[5], antiviral agents (HIV protease inhibitors)[6], antiglaucoma agents (carbonic anhydrase inhibitors)[7], neutrophil elastase inhibitors.[8]

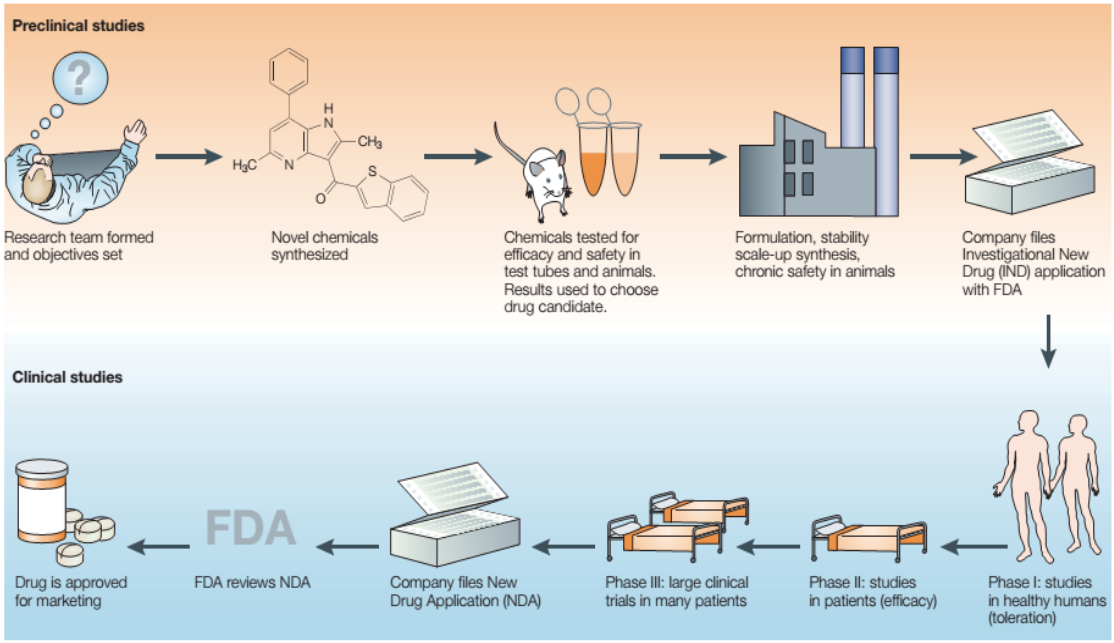

Figure I: Steps in drug discovery.[9]

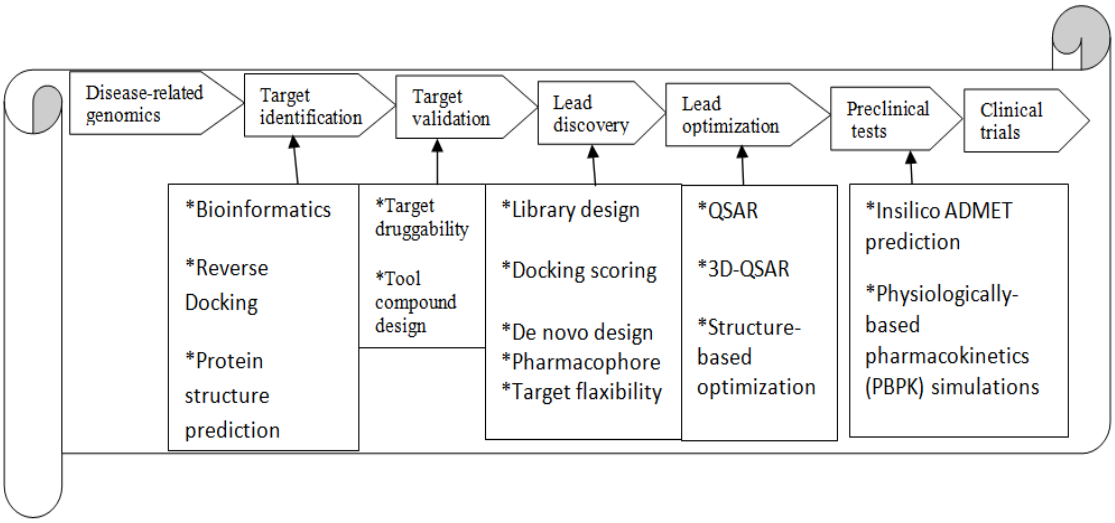

Figure II: CADD techniques in different stages of drug discovery.[10]

Classification of computer aided drug design

CADD can be classified into structure-based and ligand-based. Structure-based CADD has its foundation on the knowledge of 3D structure of biological target of interest.[3,11,12] The 3D structure of the target can be obtained from x-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy.[2,13] The desired biological effect that occurs when a molecule interacts with a specific protein is as a result of its favorable interaction with the binding site of the target protein is the main hypothesis of this approach.[13] Structure-based computer aided drug design (SBCADD) can further be grouped into molecular docking and de novo ligand design. Steps in SBCADD include acquiring a 3D structure of the desired protein, identification of the binding or active site (binding pocket of the receptor), ligand-receptor fit analysis and new leads design.[14,15] Structure-based tools such as virtual high throughput screening and direct docking methods on targets can easily be used when the structure of the lead compound is known.[3] But when information about the target structure is not known, computational method such as homology may be applied. [3]

Homology modeling also called comparative modeling (template-based modeling) involves designing an experimental 3D structure of protein from its amino acid sequence using known protein template.[16,17] The observations that form the bases of homology modeling are protein structure is individually determined by its amino acid sequence (theoretically, knowledge of the sequence can help to obtain the structure).[18]

Evolutionarily, 3D protein structure is more conserved than its sequence.[19] Homology modeling involves the following steps.[17]:
Template identification and amino acid sequence alignment (programs such as BLAST or FASTA can be employed to obtain the modeling template and the corresponding sequence alignment).

Alignment correction: after the template has been identified, sophisticated method such as multiple sequence alignment can be employed to get a better alignment and more additional information.

Backbone generation: once the alignment has been completed, backbone creation can be carried out by copying the template residues that show up in the alignment with the model sequence.

Loop modeling: modeling regions of the target sequence that are not aligned with a template.

Side-chain generation: compare the side-chain conformations (rotamers) of residues that are conserved in structurally similar proteins.

Model optimization: it requires a sequence of rotamer prediction and energy minimization steps.

Model validation: this involves the verification of the model so as to estimate errors in a structure.

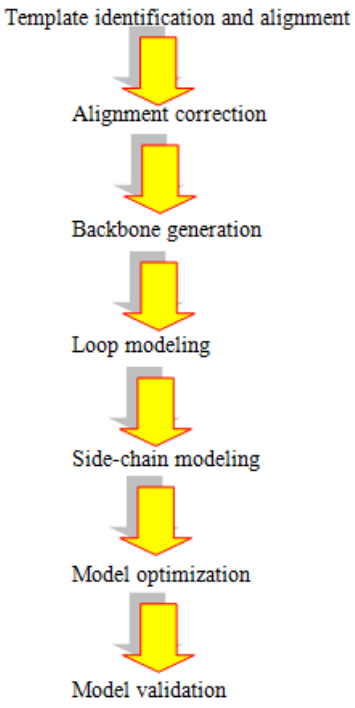

Figure III: Steps in homology modeling.

Molecular docking
This method predicts the structure of the stable complex formed when one molecule bind with another molecule[20] and to explicate it fundamental biochemical processes.[21,22] It also predicts the binding configuration of ligands to appropriate binding site and makes it possible to characterize the behavior of ligands (small molecules) in the target binding site.[23] Two approaches use for docking techniques are shape complementarity (shape matching: the surface structural characteristics of the ligands and the target provides their molecular interaction) and simulation (the ligand and target is being separated by physical distance and then ligand is allowed to bind to the target active site after definite number of "moves" in its conformational space).[24] The two components of molecular docking are search algorithm and scoring functions. The search algorithm involves using computational resources to explore all possible orientations and conformations of the protein bound with the ligand. Conformational search strategies are stochastic torsional searches, molecular dynamics simulations and genetic algorithm. The scoring functions help to differentiate the correct binding conformation in the presence of all other poses.[25] Also, the scoring function is used to rank the binding affinities of each compound and should be able to calculate the free energy.[25] Scoring function include: empirical, knowledge based, or molecular mechanics based. Docking methodologies include:[20,24]

i. Rigid ligand and rigid receptor docking: the ligand and the receptor (protein target) are treated as rigid bodies.
ii. Flexible ligand and rigid receptor docking: the ligand is treated flexible while the receptor is made to be constant or rigid.
iii. Flexible ligand and flexible receptor docking: both the ligand and the receptor are treated as flexible

Applications of molecular docking include: virtual screening (hit identification), lead optimization (binding mode or a pose), bioremediation, prediction of K_A (biological activity?), chemoinformatics, binding site prediction (blind docking), drug-DNA interaction, binding site identification, protein-protein interaction and enzymatic reactions.[26,27] Molecular docking has been applied in identifying the role of Human Leukocyte Antigen (HLA) in idiosyncratic adverse drug reactions.[27] It has been used to predict the functionality of G protein-coupled receptors and drug molecules in order to inhibit the growth of cancer stem cells.[27] Also, Examples of docking tools are Auto Dock[28], DOCK[29], Flex X[30], GOLD (Genetic Optimization for Ligand Docking)[31], Glide (Grid-based Ligand Docking with Energetics)[32], Surflex[33], ICM (Internal Coordinate Modelling)[34], MVD (Molegro Virtual Docker)[35], Fred (Fast Rigid Exhaustive Docking)[36], LigandFit[37], FITTED (Flexibility Induced Through Targeted Evolutionary Description)[38], GlamDock[39], vLifeDock[40] and iGEMDOCK.[41]

Other structure-based techniques are virtual high-throughput screening, atomic detail docking and molecular dynamics simulations.

Structure-based virtual high-throughput screening (SB-vHTS)

This involves data base searching for the potential hit. SB-vHTS selects ligands predicted to bind to the target site (binding site). The main steps in SB-vHTS are:[3]

(i) Preparation of the target protein.
(ii) Search libraries or compound database.
(iii) Determination of a favorable binding site for each compound.
(iv) Rating the docked structures.[42]

Molecular dynamics simulations

This is the use of Newtonian physics to understand atom or protein motions and its conformational changes for drug discovery. Molecular dynamics enables scientists to study macromolecules such as proteins, nucleic acids (RNA and DNA) and biological membranes. Steps in molecular dynamics simulation are:[43]

i. Ppreparation of initial model of receptor-ligand system.
ii. Estimate molecular forces acting on each atom.
iii. Position each atom according to those forces based on Newton's law of motion.
iv. Advance simulation time by one or two fs.

Molecular dynamics software that bear the same name as their force field are AMBER.

(Assisted Model Building and Energy Refinement)[44], CHARMM (Chemistry at Harvard Macromolecular Mechanics)[45] and NAMD.[46,47]

Ligand based drug design (LBDD)

This is an indirect drug design that is employed in the absence of the 3D receptor information, but depends on the knowledge of other molecules that are known to interact with target of interest.[48,49] Popularly used LBDD tools are 3D structure-activity relationships (3D QSAR) and pharmacophore modeling.[3]

Quantitative structure-activity relationships (QSAR)

QSAR is a computational tool that shows the supposed correlation between chemical structures and biological activity in a given chemicals.[3,50] The basic assumption of QSAR is that there is an intrinsic relationship between molecular structure and biological activity. Also QSAR is a predictive statistical tool with chemical activity encoded in form of molecular descriptors. Mathematically, QSAR can be represented as

Activity = *f*(physiochemical properties and/or structural properties) + error

The QSAR procedure include the following.[51]

a. Converting molecular structures into mathematical descriptors.
b. Identification of physico-chemical properties with descriptors representative of molecular properties.
c. Mapping molecular descriptors into properties and developing of a QSAR model.
d. Validation of the QSAR model

Pharmacophore mapping

This is a technique in which the basic molecular properties that are related to biological activity of a compound of interest.[3] The International Union of Pure and Applied Chemistry (IUPAC) formally defined a pharmacophore as "the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target structure and to trigger (or to block) its biological response".[52] Steps for developing pharmacophore model include:[3,53]

a. Database search can be employed to identify the active compounds that can bind to the required target
b. Essential atom type and their connectivity is defined for a 2D pharmacophore model.
c. The conformations are defined using IUPAC nomenclature for 3D pharmacophore model.
d. Common characteristics required in binders can be known using ligand alignment.
e. Pharmacophore model building.
f. Ranking of the pharmacophore models and selecting the best models.
g. Pharmacophore models validation.

CONCLUSION

CADD is of immense importance in drug discovery. Different methods of CADD depends on target or protein of interest and the available resources. The field of CADD is rapidly evolving with various computational techniques to aid in drug discovery. This will make a good impact in individual's health through the discovery of therapeutics.

ACKNOWLEDGEMENTS

My profound gratitude goes to Prof. Okoro, U.C. and Chief Lolo Marcilina N. Ugwu (Ugochinyere 1 of Awhum kingdom). I also appreciate all those that have contributed to the success of this work.

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