AI Driven Drug Repurposing Module

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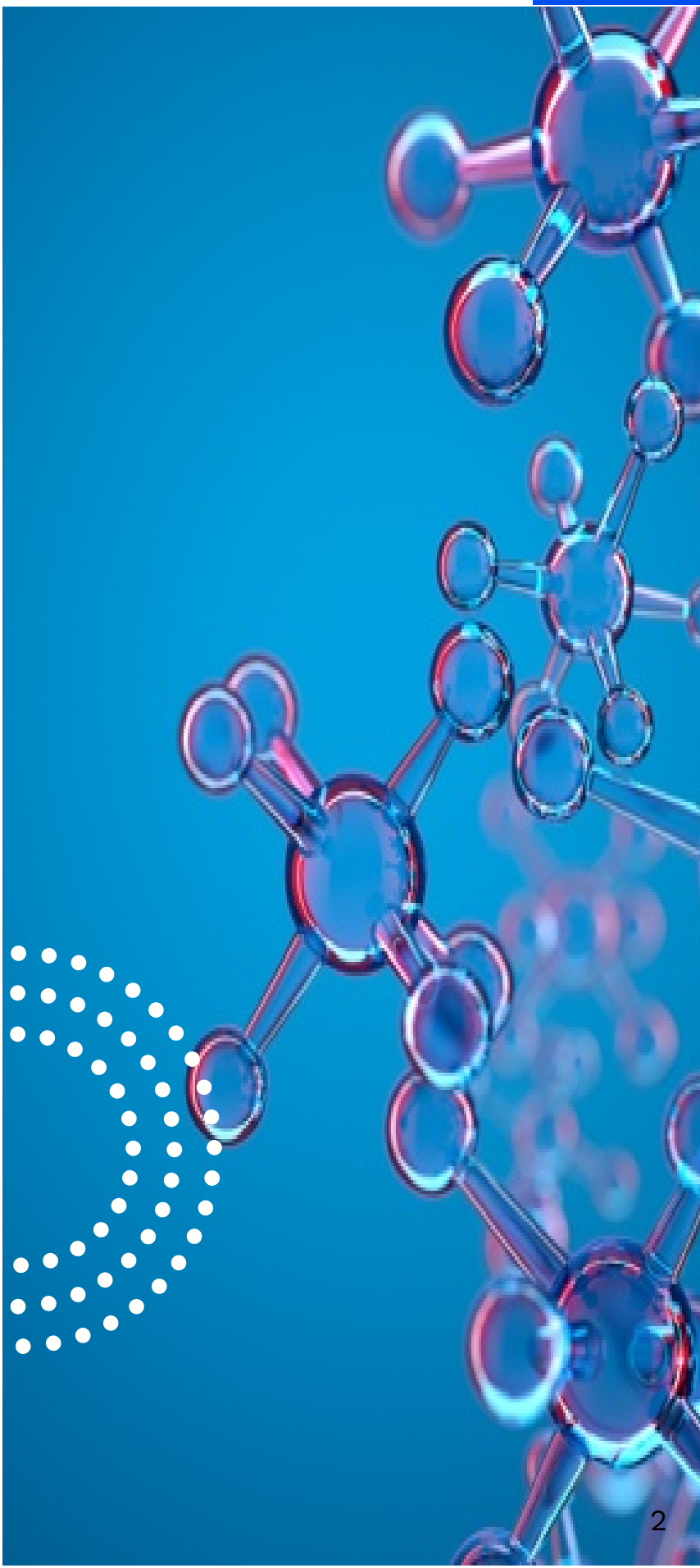


Introduction

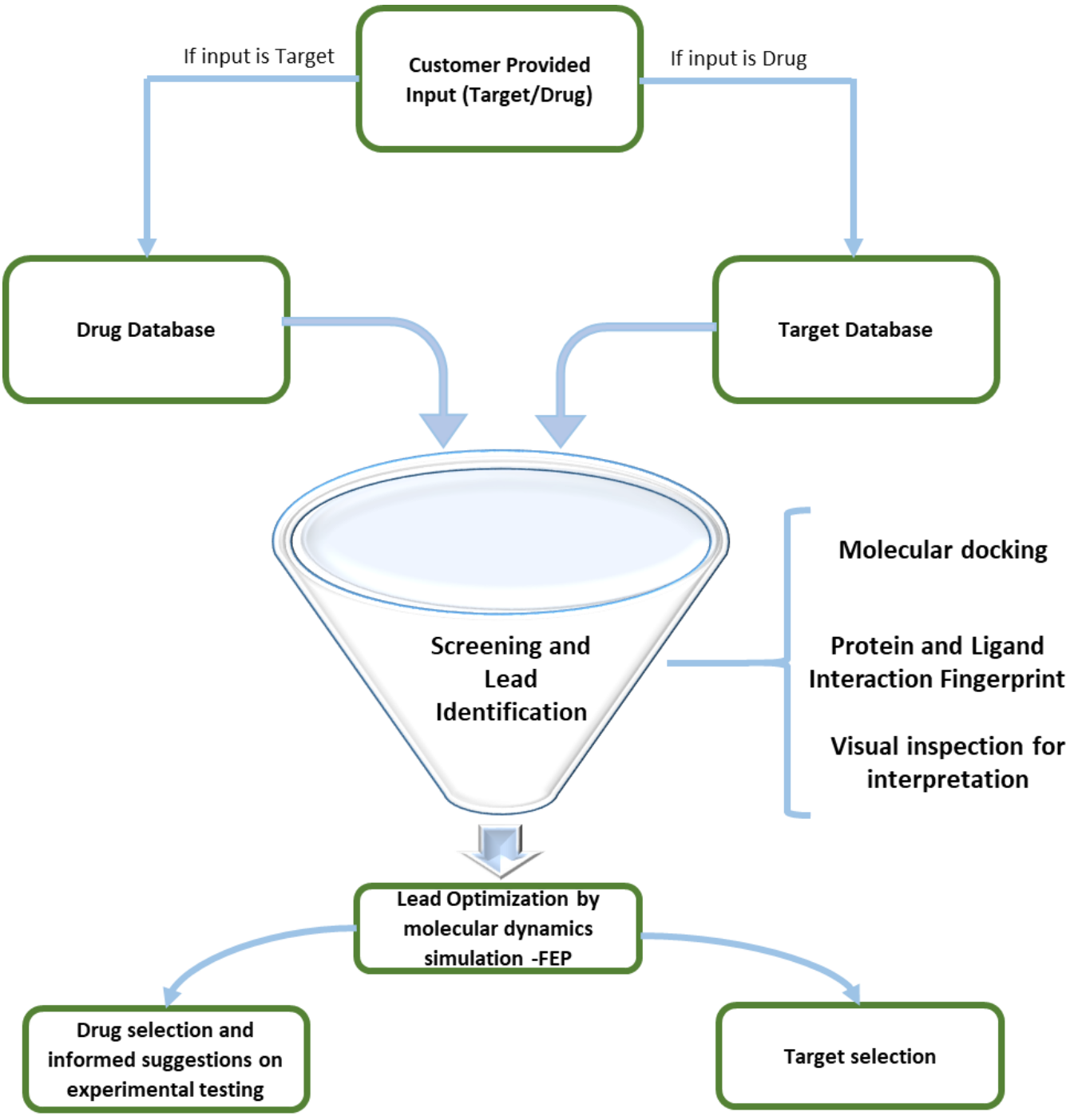
Drug Repurposing / Repositioning accelerates the traditional drug discovery process by using drugs, that are clinically safe and approved for a specific medical condition, for another different therapeutic application. By choosing FDA-approved drugs we can very well avoid the preclinical, phase I and II trials, thereby drastically reducing the cost and time spent on drug discovery. The cost of identifying a new drug from scratch takes around ~ 2 -3 billion whereas repositioning a drug takes ~ ~300 million thus providing a rapid return on investment.

> The most fruitful basis of the discovery of a new drug is to start with an old drug.- James Black

We at Medvolt, imply cutting-edge machine learning and artificial intelligence approaches to further speed up the drug repurposing strategy. The use of artificial intelligence benefits from the usage of big data with sophisticated algorithms in taking the right decision in almost every step of drug repurposing thereby helping in preventing failure at a later stage. Medvolt's drug repurposing module does not follow a generalizable computational framework, rather it is customizable based on the needs and hence it offers uniqueness to every project.

1. Reference: Pushpakom, S., Iorio, F., et al. "Drug repurposing: progress, challenges and recommendations." Nat Rev Drug Discov, 2019, 18, 41–58.

Big picture of drug repurposing module workflow



Medvolt's drug Repurposing Module offers two approaches - Target-based drug repurposing and Compound-based drug repurposing.

Compound-based drug repurposing

If the input is the drug, we suggest the novel therapeutic area of the implication of the drug-using our compound-based drug repurposing approach.

Target database

We have an exclusive target database comprising structurally prepared and validated targets with respective disease details curated from literature using deep neural networks and natural language processing software. Our database is updated regularly to include almost all therapeutic areas.

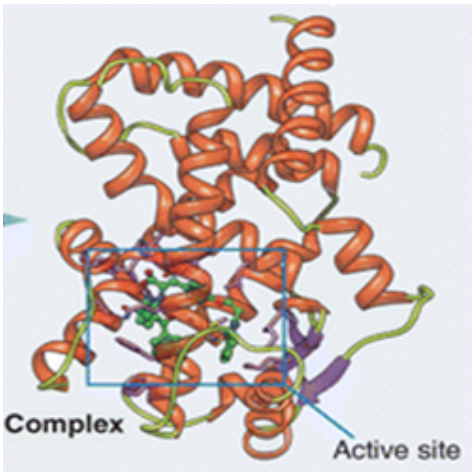
Target-based filtering and Lead identification

We perform molecular docking and protein-ligand interaction fingerprint (PLIF) analysis for screening and identification of potential therapeutic targets for our input drug.

1. **Molecular Docking**

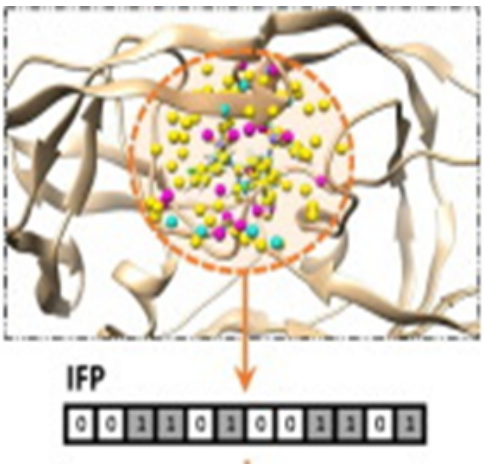
Preparation of input compound is done before molecular docking. The input compound is docked to all the targets in the database. Docking is done to identify the best binding mode of ligand showing good interactions with active site residues of the target, thereby having excellent binding energy and binding affinity values. The ranking is done based on the docking scores.

We subsequently remove those targets with which our drug compound does not show favorable good interactions as well as low docking scores. Visual inspection of the docking results can help the user pick the best target with good, favorable interaction for further development.



2. Protein & ligand Interaction fingerprint

Most molecular docking tools perform these two functions. 1. Docking of the ligand and identification of energetically admissible poses. 2. The scoring function assesses the binding free energy for each pose.[2]



Though most of the famous docking programs perform fairly well in generating sound poses, most often the scoring functions fail to evaluate the binding energy precisely. Hence, it is a good practice to employ post-docking filters making use of different types of the structure–activity relationship of protein and ligand to overcome docking failures. Here, we use one filter based on three-dimensional protein–ligand interaction fingerprints (PLIF). Plif assess the docking pose of the ligand to check for interactions with target protein similar to that of reference ligand. Thus it helps to retrieve those active compounds which are considered inactive by docking tool because of their low docking scores [2].

2. Reference: C. Da and D. Kireev, "Structural Protein–Ligand Interaction Fingerprints (SPLIF)", J Chem Inf Model, 2014, 54 (9), 2555-2561

Lead Optimization

We use molecular dynamics (Free energy perturbation- FEP) studies to optimize the leads.

FEP

We use the Free energy perturbation - thermodynamic integration method to accurately estimate delta G, the free energy of binding. We decouple the bound ligand in multiple intermediate lamda windows and estimate delta G change between ligand-bound and unbound to give the delta G of binding. Literature shows that this method has reported a root mean square error value of less than 1 kcal/mol.

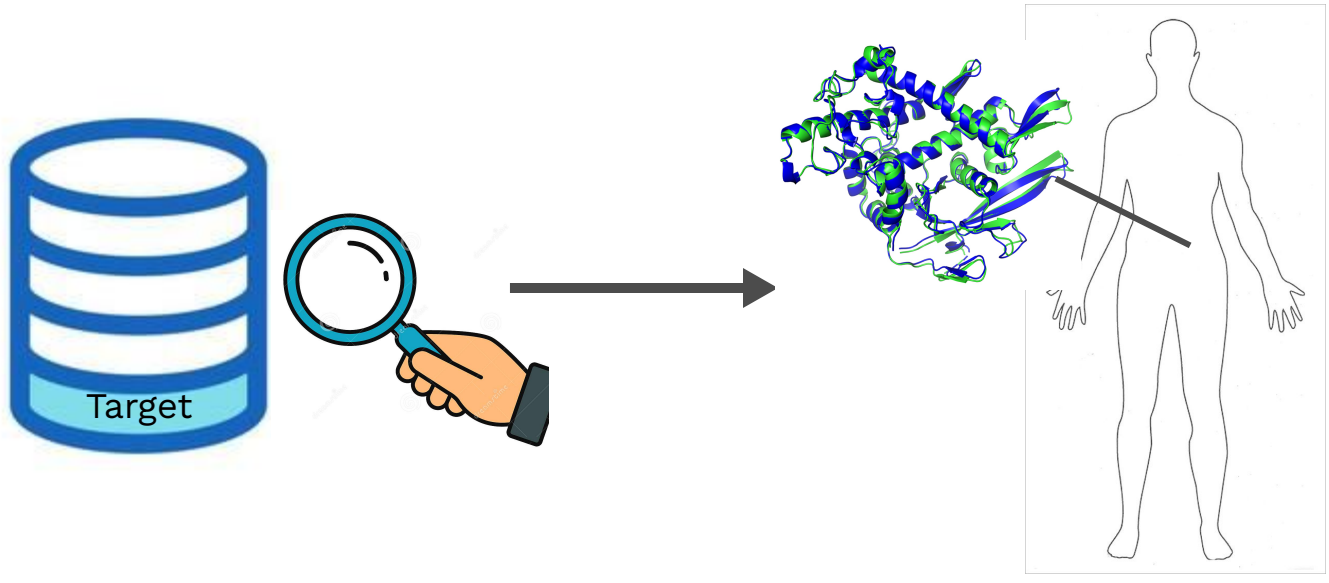
The absolute binding free energy (ΔG_{bind}) was calculated as

$\Delta G_{bind} = \Delta G_{comp} - \Delta G_{lig}$.

FEP successfully calculates the binding energy of the protein-ligand complex guiding the small molecule drug discovery.

Outcome

Our compound-based drug repurposing approach with state of art techniques helps the user to pick the specific therapeutic target for successful repositioning of the drug. The module opens a new therapeutic window for every investigational drug and FDA-approved drug.



Target-based drug repurposing approach

If the input is a target, we identify a potentially safe drug-using target-based drug repurposing approach.

Drug database

We have a specially developed database for drugs using sophisticated AI algorithms. Our drug database includes FDA-approved and investigational drugs. The database is periodically updated to facilitate access to up-to-date records of both FDA-approved and investigational drugs.

Drug-based filtering and Lead identification

We perform molecular docking and PLIF analysis for screening and identification of novel drugs for our input Target. Our user-friendly visualization tools can help the user carefully pick the potent drug with ease.

Lead Optimization

We use molecular dynamics (FEP) studies to optimize the leads. The ranking of the leads is done based on the FEP scores. Users can pick top-scoring leads for further pre-clinical trials.

Outcome

Our target-based drug-repurposing module can be effectively used to identify potent drugs and can accelerate the drug development process. Also, our module will be very helpful for clients who would like to discover novel drugs for rare diseases. Rare diseases are those that affect only a small number of people worldwide and there are as many as 7000 rare diseases worldwide. Generally, pharmaceutical companies do not invest their time and money to find a cure for these rare diseases [3]. Our module will help those clients crying out for innovation in the treatment of rare diseases as well as other common, deadliest diseases with AI-driven state of art techniques.

Highlights

1. Both the Target and drug databases has a broad spectrum of data covering all therapeutic area and are updated periodically.
2. We have picked state of art techniques and AI algorithms to get reliable results.
3. Our user-friendly interface and visualization tools can provide hazel-free progress.
4. Our domain experts will be there to support and provide suggestions to derive a proper decision at every step of discovery.
5. Every project we undertake will be unique in every way and can be customized based on the client's preference.

3. Reference: C. Darcy Jimenez, “Healx:”, https://www.pharmaceutical-technology.com/analysis/healx-ai-drug-repurposing-rare-disease/