Fundamental Concepts in Drug Discovery

Lecture-22

Outline

- Modeling and Simulation
- Drug Discovery- Concepts
- Pipeline
- Challenges
- ML Applications- Overview

Drug

- A drug is any chemical substance that causes a change in an organism's physiology or psychology when consumed.
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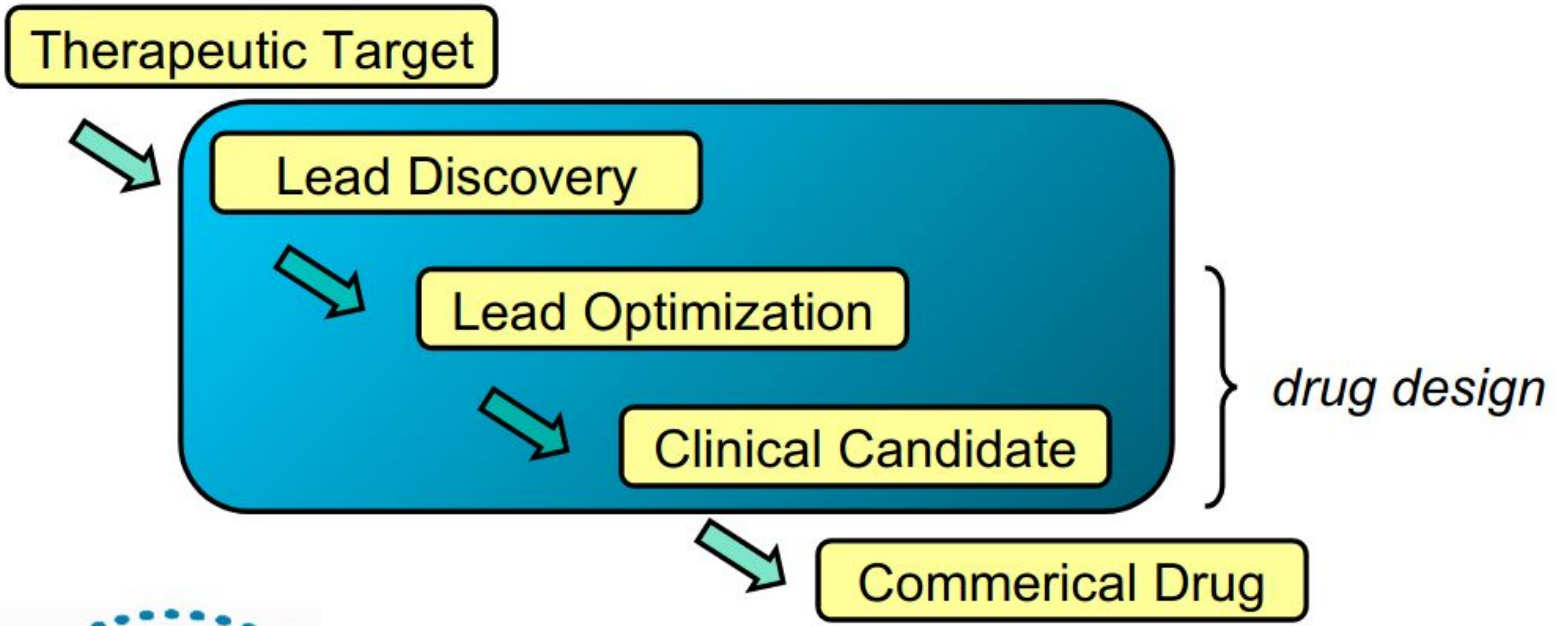
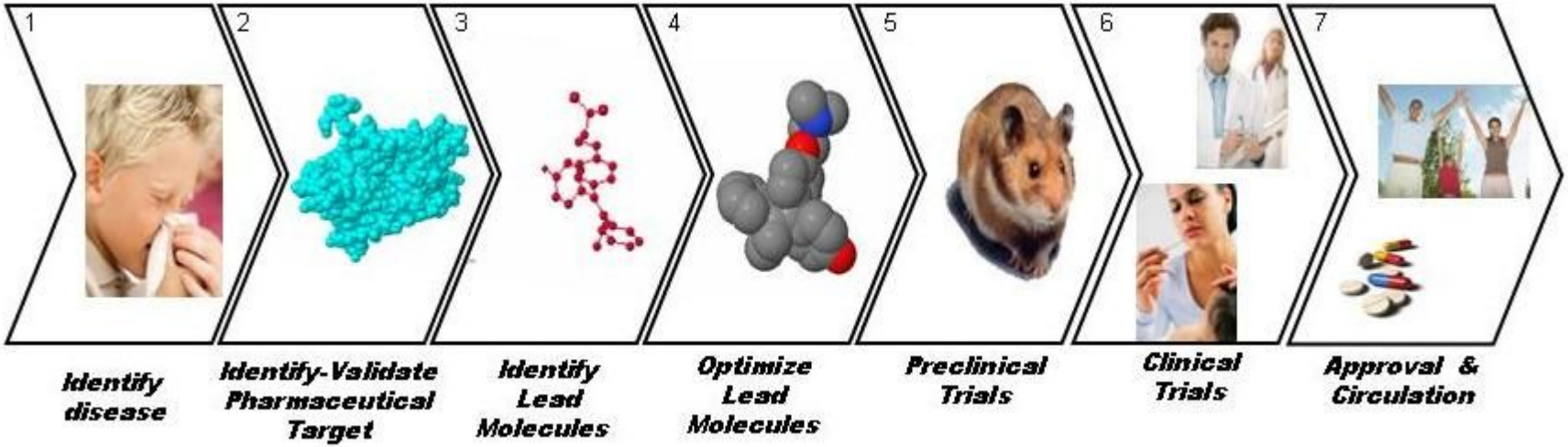
What is Drug Discovery

rational and targeted search for new drugs

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2
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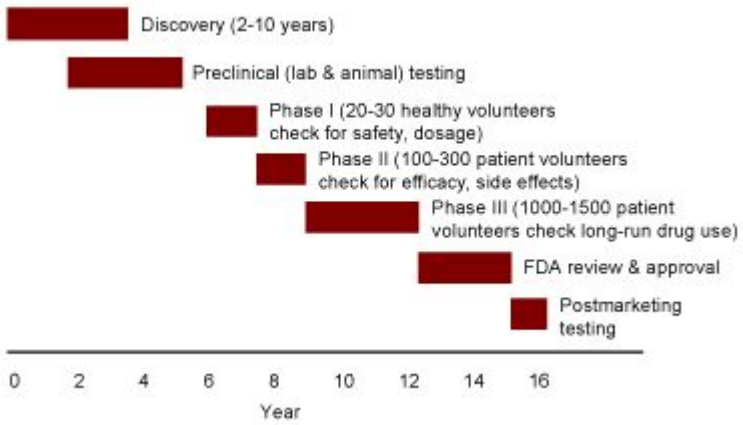
Identify disease
Identify-Validate Pharmaceutical Target
Identify Lead Molecules
Optimize Lead Molecules
Preclinical Trials
Clinical Trials
Approval & Circulation


Discovery (2-10 years)
Preclinical (lab & animal) testing
Phase I (20-30 healthy volunteers check for safety, dosage)
Phase II (100-300 patient volunteers check for efficacy, side effects)
Phase III (1000-1500 patient volunteers check long-run drug use)
FDA review & approval
Postmarketing testing
0
2
4
6
8
10
12
14
16
Year

The typical drug discovery and development process, involves an often arduous series of events that starts with perhaps 5,000 candidate drug molecules and ends with a single product that can be brought to market.

Because any technology that can shorten the discovery and development process has the potential to save the industry billions of dollars, there is considerable R&D involved in replacing or supplementing the drug discovery process with modeling and simulation.

Computer Aided Drug Discovery

CADD is a modern computational technique used in the drug discovery process to identify and develop a potential lead

To predict the toxicity of a candidate drug or to streamline the screening process

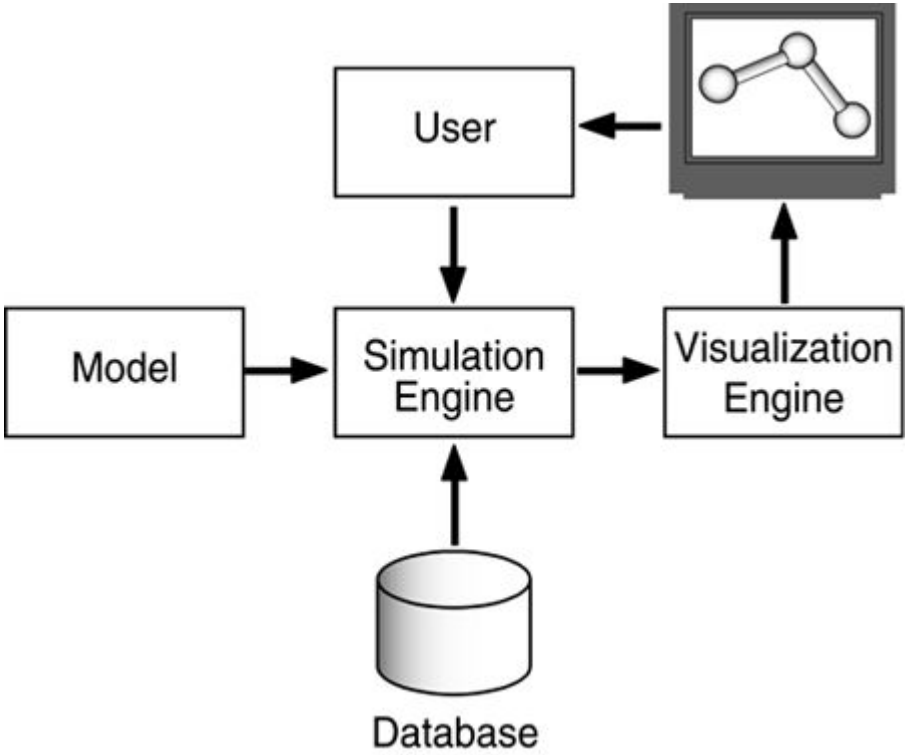
Modeling and Simulation

the model,which can be a mathematical equation, a logical description encoded as rules, or a group of algorithms that describes objects and their interrelationships in the real world

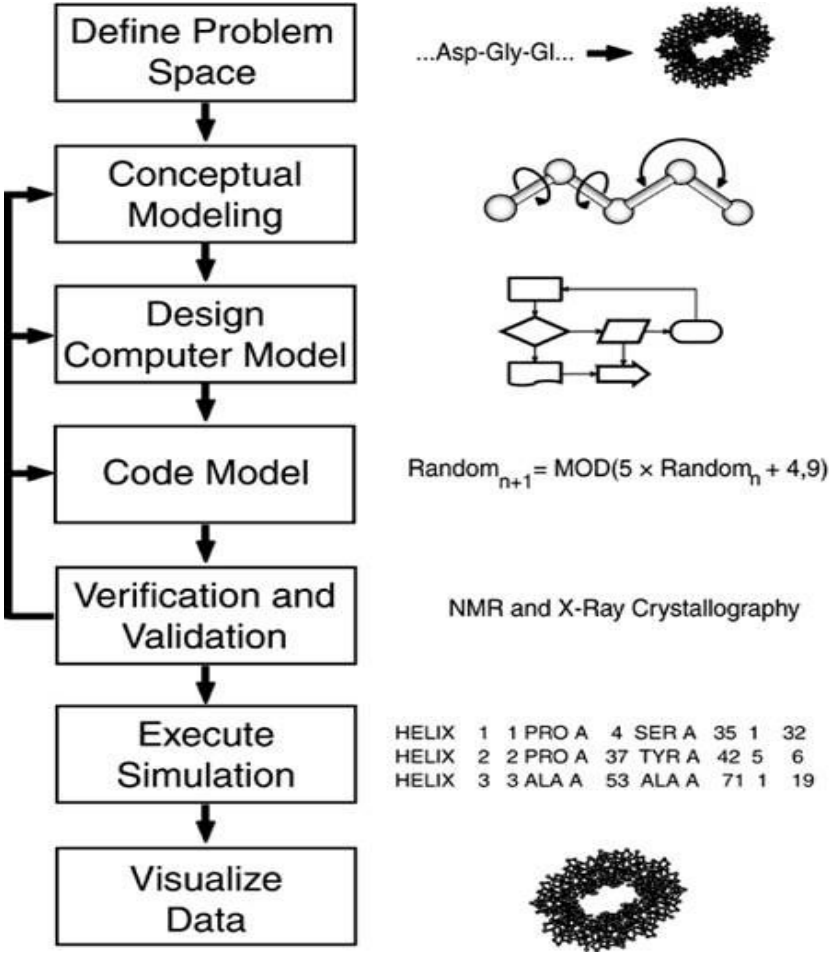
database consists of a large,complex system that contains libraries of data

Simulation engine create an output that corresponds to a condition in the real world, such as a description of the folding of a protein molecule in an aqueous solution

Visualization: Rasmol,



Basic Process



Simulation Perspectives

- Continuous Simulation: vary according to time (eg: current drug concentration in blood

$$[Drug]_{plasma} = \frac{Dose}{Volume_{plasma}} \times e^{-KT}$$

- Discrete Simulation: object or process arrives at a stage, waits in a queue until it receives attention, and then moves on to the next stage

Virtual Screening

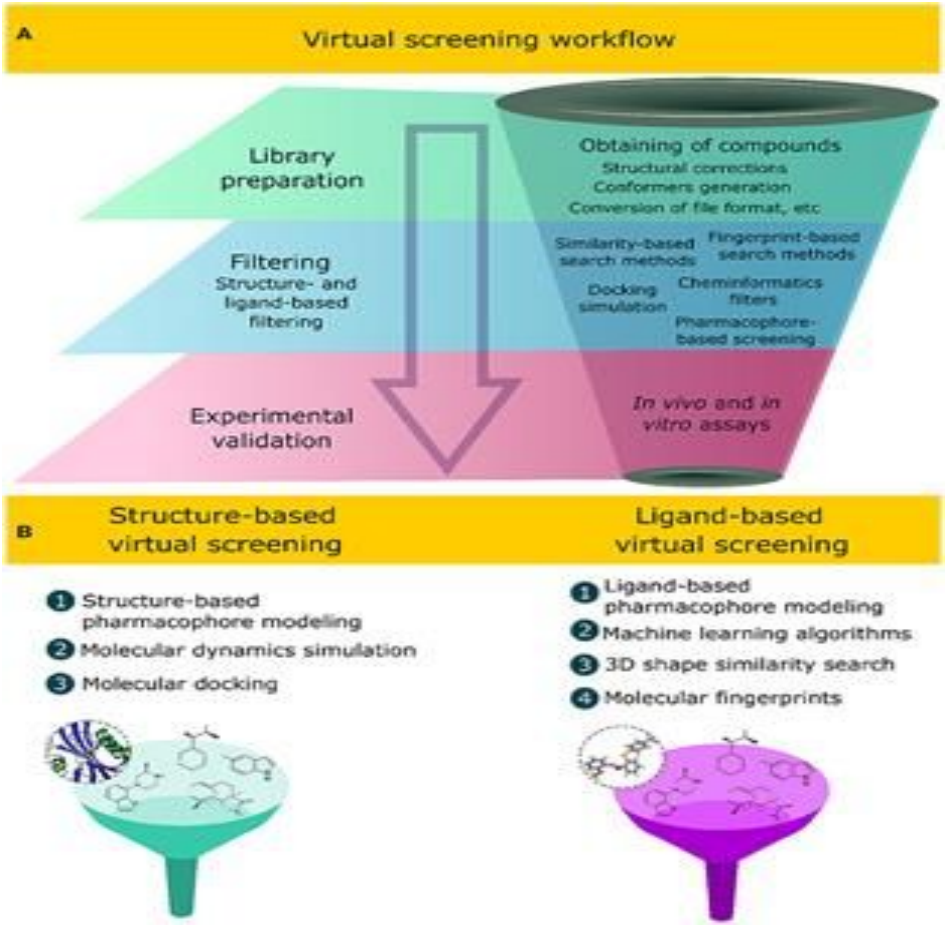
- Virtual screening (VS) is a computational technique used in drug discovery to search libraries of small molecules in order to identify those structures which are most likely to bind to a drug target, typically a protein receptor or enzyme
- Computational methods (Virtual Screening) are needed:
  - HTS is slow: HTS of corporate collections many months
  - HTS is expensive: Average cost US$1M per screen.Payne et al. 2007
  - Growing # of research targets no HTS until target validation
- VS can complement HTS by enriching libraries with likely ligands

Virtual Screening

- VS Search for molecules that modulate the function of a therapeutic target
- VS can predict selective drug binding: Drugs must selectively bind to their intended target, as binding to other proteins may cause harmful side-effects
- VS to predict whole-cell Activity

Approaches

- Ligand Based
- Structure Based



ML and DL tasks

- Database: ChemBL, PDB
- Tasks:
  - Encoding molecular interaction networks
  - Predicting active and inactive components
  - Regression over drug potency
  - Molecular structure prediction
  - Activity prediction
  - Target prediction

Thank you