BPS3031

Computational Drug Design

Comprehensive Study Notes

HD 83 • Monash University

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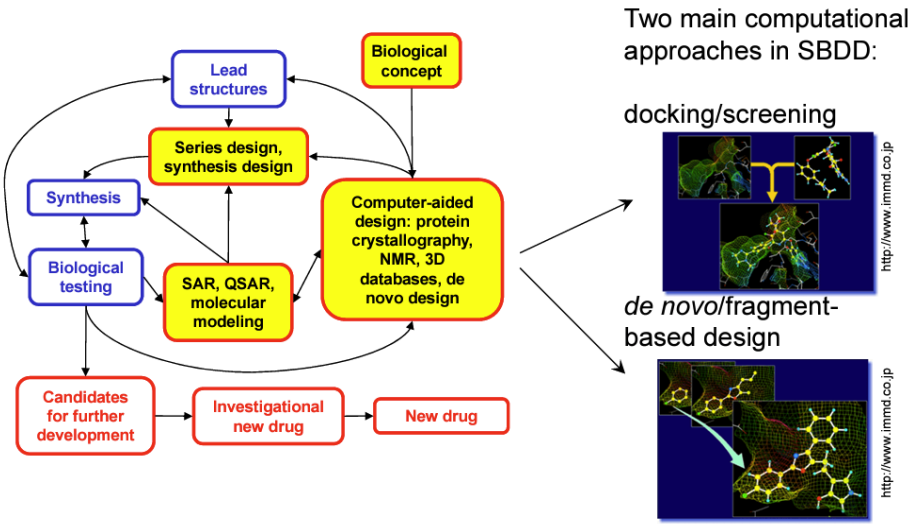
Structure-based drug design

Structure-based drug design (SBDD) = a drug design strategy based on the three-dimensional (3D) structure of the target (from X-ray or NMR studies or protein modelling).

- Uses technological advances
  - X-ray (high-throughput crystallisation, robotics)
  - NMR
  - Protein modelling (improvements in algorithms' performance, CASP)RMS
  - Advances in molecular biology, robotics, electronics, etc.
  - Completion of the human genome
  - Development of and advancements in combinatorial chemistry and high-throughput screening
  - Increase in computer power, parallelization
  - Cloud and grid computing, GPUs
  - Algorithm developments, in particular, AI

SBDD workflow



Advantages of SBDD

- Requires only the availability of 3D information for macromolecular drug target
- Does not require biological data, LBDD does
- Does not require pre-synthesized compounds
- Compounds can be virtual
  - Reduce cost
  - Adding the ability to screen virtual libraries with the use of defined diversity
- Computational
  - Hardware is relatively cheap
  - Screening is done fast
- Performed early in the drug design process
- Performed before candidates are synthesised
- Used for preliminary screening

Molecular docking

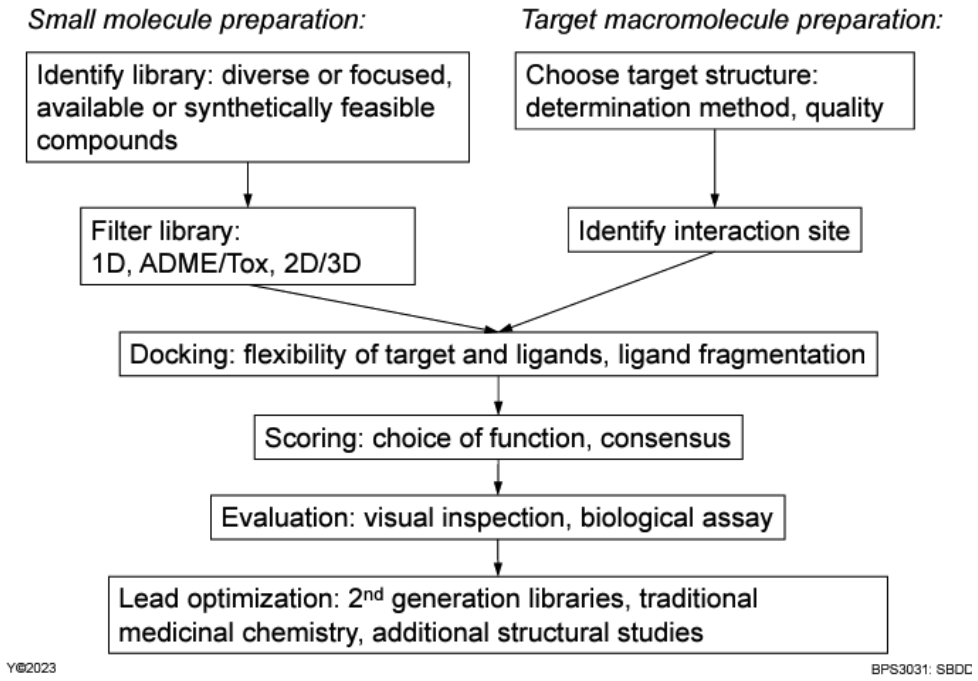
- What: fitting molecules together in a favourable configuration to produce a complex.
- Aspects
    - exploration of conformational space of a ligand (and, increasingly, of a protein), for example:
        - conformational analysis of small molecules independent of their receptor binding
        - incremental build approach which takes into account 3D information on the drug target
    - orientation search (seeking the best spatial fit between a ligand and a receptor)
    - energy minimization/geometry optimization of a docked complex
    - ranking and scoring (comparing docked complexes in terms of spatial complementarity, energy, binding affinity etc.)
        - Scoring is for poses, ranking is for ligands
        - 1 target/1 ligand ⇒comparing multiple poses (scoring)
            - poses = structures, scores ≡ energies, activities
        - 1 target/many ligands ⇒comparing multiple ligands (ranking)
            - many target/many ligands ⇒ selectivity
- Aim
    - correct prediction of either or both:
        - accurate structure of the complex(es)
        - biological/pharmacological activity of the drug candidate(s)
- Areas of application of docking:
    - hit identification
    - lead optimization
    - study of molecular recognition, drug action, and metabolism

Virtual screening (in silico screening)

- the use of high-performance computing to analyse large chemical databases to identify possible drug candidates.
- Successful due to enrichment nature of screening (tackles the shortcomings of scoring functions and the challenges of docking problem [challenge of predicting and analysing the binding interactions between compound and target])
- Adaptive response from rational drug design and HTS/combinatorial chemistry
    - Its rational (with regards to the ligand and receptor structures and interactions) and can process many compounds relatively efficiently)
- Complementary approach to HTS
- Comparisons made to random screening
- Knowledge-driven
    - Nature of the binding site of the receptor (SBDD)
    - Type of potential drug candidate (LBDD)
- Encompassing a variety of computational screens
    - Simple: fast filtering, molecular similarity
    - Sophisticated: docking and scoring
- SBDD vs LBDD
    - 3D structure of the receptor known → receptor-based compound screening (structure-based VS)

    - biological activity of ligands known → pharmacophore-based compound screening (ligand-based VS)
- Reality:
    - Too many possible structures to prepare through chemical synthesis or generate in silico
    - Need methods to reduce the size of screening libraries while maintaining compounds with desirable properties for potential drug leads

Virtual screening workflow



Drug likeness and Lipinski's rule of 5

- Relationships between structure and ADME/toxicity
- Properties:
    - LogP, MW, rotatable bonds, H-bond donors/acceptors, aqueous solubility, BBB permeation
- Approach:
    - Filter virtual libraries to remove compounds with poor druggability from consideration early in the drug discovery process
- ADME/tox filtering:
    - Lipinski's rule of 5 and similar filters
    - ADME properties prediction
    - Toxicity prediction
    - Functional group filters
- Lipinskis rule of 5
    - MW < 500 g/mol
    - Low-medium lipophilicity, LogP < 5
    - HBD (OH and NH) ≤ 5
    - HBA (O and N) ≤ 10
- Other improvements
    - Log D instead of Log P
    - PSA < 140 angstroms squared

- Other filters
    - Functional group filters
        - Remove reactive and/or toxic fragments, potential metabolic liabilities, and other undesirable groups
            - E.g. nitro groups, long aliphatic chains, alkyl halides, acid or sulfonyl halides, anhydrides
    - 2D similarity to known ligands
        - Low chance of novelty
    - 3D pharmacophore search:
        - Chemical characteristics of the binding site can be analysed to determine the functional groups for protein-ligand interactions
            - Receptor-based pharmacophore models
        - Only compounds with appropriate chemical features complementary to the receptor-based pharmacophore model are retained

Diverse or focused Virtual libraries

- Diverse VL
    - Formed when there is no information on potential ligands
    - Desired with:
        - Varied types of groups and their relative orientations
        - Degree of difference between members of a library
- Focused VL
    - Formed when there is some information on active ligands is available
        - Typically second generation VL constructed around a hit located from a more diverse VL
        - Small size
        - Low in diversity
        - Greater depth of diversity in a local region of structural space

Post-processing

- Occurs after virtual screening and docking and scoring
- Virtual inspection to discard undesirable structures:
    - High lipophilic molecules are difficult to test because of their low solubility
    - If many of the docked structures belong to one chemical class, not necessary to test them all
    - Fast docking tools cannot produce reliable solutions for all compounds
        - Can adopt unreasonable docked binding modes = docking to the outer surface of the protein or having strained conformations

Enrichment factor

- Decides whether VS was successful by comparing it to random selection
- Looks at the top 10% of ranked compounds and compares the number of actives to the number of actives expected to be included in a random selection of the same size
    - Note: can be calculated at other percentages (e.g. 2% or 5%)
- Used to compare different methods
    - E.g. EF (10%) of Glide SP vs EF (10%) of Glide XP

PREVIEW

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The full set is 118 pages, covering every topic with all diagrams and a clickable table of contents.

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