Computational Drug Discovery

Modern drug discovery is a tedious process that is often limited by the expense and time of screening a target. Computational drug discovery provides an alternative method for generating hits to a target, by allowing:

- **Rapid screening**: computational technology and speed is still advancing
- **Enormous numbers of compounds**: search huge databases and use combinatorial chemistry for new molecules
- **Less effort and cost**: don’t have to buy as many compounds or as much equipment

• Hydroxymethyltransferase (SHMT)

Scores (max, min, etc.) were calculated. Each of the molecules, ranked by chemistry for new molecules

Enormous numbers of compounds and speed is still advancing

Rapid screening

Has a cofactor: Vitamin B\(_6\) (pyridoxal phosphate, PLP)

Can be inhibited by displacing PLP with a stronger-binding molecule

Structure of SHMT dimer, assembled from PDB 1BJ4

Identifying Drug Candidates: 2 Approaches

Pharmacophore Matching

Molecular Dynamics

Evaluate Drug Candidates: 2 Approaches

Scoring Aflinities: Finding the Best Function

Known actives and decoys for 101 targets

Scoring functions: different interactions

Create consensus score

Receiver operating characteristics (ROC) curves

Apply to SHMT

Molecular dynamics (MD) is the simulation of molecular motion, keeping track of positions and trajectories.

We used the MD package AMBER 12 to simulate the "pulling out" of PLP or drug molecules, in a process called steered molecular dynamics (SMD).

We compared the affinity for PLP in human and E. coli SHMT, to determine if a human inhibitor is feasible.

To overcome inadequate sampling in SMD, we used umbrella sampling and weighted histogram analysis which combine many small simulations into a single, more accurate measurement.

MD Simulations

Umbrella sampling shows that pulling PLP to a distance of 40 A from a starting position of about 7 A from E. coli SHMT takes about 30 kcal/mol while human SHMT only requires about 20 kcal/mol.

Suggests that generally the E. coli SHMT binds its cofactor 50-60% more strongly than human SHMT.

References


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Sample high-ranking drug candidates

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Target: SHMT

We used computational drug discovery techniques on the enzyme serine hydroxymethyltransferase (SHMT), which:

- Is a cancer enzyme
- Handles glycine/serine metabolism
- Is in a pathway that drives tumorigenesis
- Has a cofactor: Vitamin B\(_6\) (pyridoxal phosphate, PLP)

Can be inhibited by displacing PLP with a stronger-binding molecule

Structure of SHMT dimer, assembled from PDB 1BJ4

Scoring and Simulation Results

Each of the 4 scoring functions (ad4, Vina, custom, fast) produced a list of molecules, ranked by binding affinity, for each of the 101 targets.

Cumulative belief and statistical consensus scores (max, min, etc.) were calculated. The ROC curve shows the effectiveness of each function:

- Area under the ROC curve (AUC) represents the probability that the function will rank an active compound as more likely to succeed than an inactive one.
- AUCs computed by simple arithmetic average over all 101 targets.
- The function with highest AUC, Vina, and the cumulative function were used to rank the list of SHMT candidate inhibitors from docking and matching.

MD Simulations

Umbrella sampling shows that pulling PLP to a distance of 40 A from a starting position of about 7 A from E. coli SHMT takes about 30 kcal/mol while human SHMT only requires about 20 kcal/mol.

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Future Directions

- The highest-scoring compounds have been listed and are undergoing umbrella sampling.
- Their affinities will be compared to PLP.
- Promising compounds will be purchased and evaluated further.

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ZINC10536317

Sample high-ranking drug candidates

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