Blockbuster drug design by blocking transition states

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Motivation

About TSAs

In the field of drug design, producing specific viral protease inhibitors by finding the transition state analogs(TSA) has become a mainstream approach[1]. The TSAs are the compounds with a chemical structure that mimic the transition state of the substrate molecule in an enzyme-catalyzed reaction. The theory states that during the enzyme-catalyzed reactions, the enzyme stabilizes a higher energy transition state intermediate causes the overall activation energy being lowered. The TSAs do not undergo the catalyzed reaction hence can bind stronger to the enzyme than the substrate.

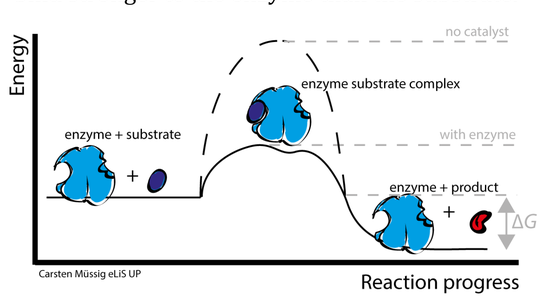


Figure.1[1] The energy profile of an enzyme-catalysed reaction. The enzyme substrate complex refers to the transition state intermediate.

Objectives

1. Build a molecular alignment algorithm using the shape of the molecules as the align criterion

- Find the single alignment of reference and database molecule in which their volume overlap is maximized.

2. Add Spherical Harmonics to refine the model(advanced)

-Add electron characteristic as one of the align criterion.

Methodology

Gaussian Representation & Total Volume Recurrence

- Each atom in the molecule is represented by a Gaussian function. Atoms are differed by their positions and spread α.
- Since the overlap of two Gaussians is a new Gaussian(Figure.2), it is possible to implement an iterative procedure to compute the higher level overlaps as needed in the volume estimation

$$V_{ab} = pp\exp(-\frac{\alpha\beta}{\alpha+\beta}\|a-b\|^2)\sqrt{(\frac{\pi}{\alpha+\beta})^3} \quad (1)$$

where p is the Gaussian weight (constant) and (a,α) and (b, β) are parameters of two gaussian[2].

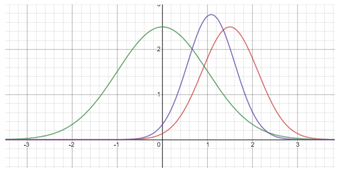


Figure.2 The overlap of two given Gaussians (red and green lines) is also a Gaussian (blue line).

- The total volume of a single molecule and the molecule-molecule overlap volume are respectively given by:

$$V = \sum_a V_a - \sum_{a,b} V_{ab} + \sum_{a,b,c} V_{abc} - \sum_{a,b,c,d} V_{abcd} + \cdots \quad (2)$$

$$V_{A,B} = \sum_{a\in A, b\in B} V_{ab} - \sum_{a,b\in A, c\in B} V_{abc} - \sum_{a\in A, b,c\in B} V_{abc} + \sum_{a,b\in A, c,d\in V} V_{abcd} - \cdots \quad (3)$$

Optimal Alignment

Initial Orientation-Quaternion Introduced

- The principal axes of the molecule are obtained by the eigenvector of the SVD of its mass matrix.
- Translate the molecules such that their CoMs coincide, leaves the alignment with angular dependence only.
- Rigid-body rotation is applied through quaternion algebra, which turns Eq.1 to:

$$V_{ab} = pp\sqrt{(\frac{\pi}{\alpha+\beta})^3}\exp(-\frac{\alpha\beta}{\alpha+\beta}q'Aq) \quad (4)$$

- Where q is the unit quaternion and A is a matrix sole depends on the centres of Gaussians a and b.

Gradient-Ascent

- The simple formulae for volume imply that computing the gradient and Hessian is straightforward[2],

$$\nabla_q V_{ab}(q) = -2V_{ab}Aq \quad (5) \qquad \nabla_q{}^2 V_{ab}(q) = 2V_{ab}(2Aqq'A - A) \quad (6)$$

which only depend on the already computed volume, the matrix A and the quaternion q.

Stimulated Annealing

- Additional stimulated annealing is required to get rid of the local optimum.
- The temperature and the number of iterations are self-regulated during the procedure.

Key Results

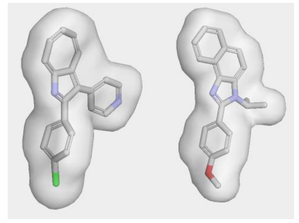


Figure.3 Two optimal aligned molecules, which are selected from the database, the similarity score is 0.78.

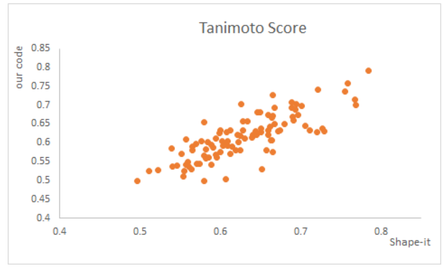
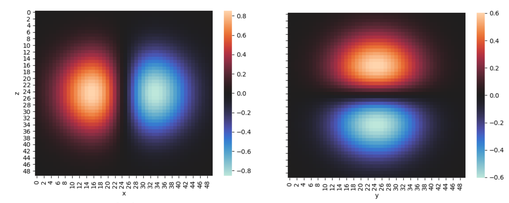


Figure.4 The Tanimoto score comparison for our algorithm and SHAPE-IT. Random noise is because the SVD function in SHAPE-IT is different from numpy's, causes the initial rotation axis being different.



(a) (b)

Figure.5 (a). The orbital overlap between px and s. (b). The orbital overlap between pz and s.

Future Implications

- Our work would give a reference point for better precision in 3D molecular alignment procedure once the Spherical Harmonics is added.
- Further TSAs matching processes for any given enzyme can be done based on our program.

[1] Schramm, V. (2018). Enzymatic Transition States and Drug Design. Chemical Reviews, 118(22), 11194-11258. https://doi.org/10.1021/acs.chemrev.8b00369
[2] Silicos-it | Shape-it™. Silicos-it.be.s3-website-eu-west-1.amazonaws.com. (2021). Retrieved 2 March 2021, from http://silicos-it.be.s3-website-eu-west-1.amazonaws.com/software/shape-it/1.0.1/shape-it.html.