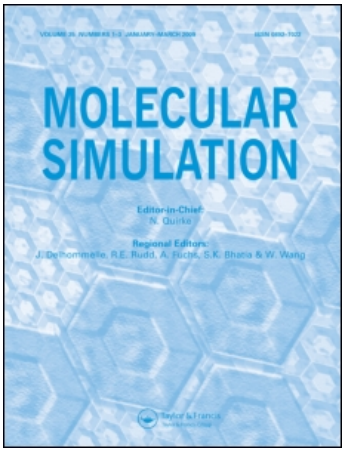

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LysinebasedTrypsinActSite(LysTAS): A configurational tool of the TINKER software to evaluate Lysine based branched cyclic peptides as potential chymotrypsin-mimetics

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1. Introduction

Serine proteases are members of a large class of proteolytic enzymes found in many organisms that have an important role in many biochemical processes, such as protein catabolism, digestion, blood pressure regulation, etc.

Recently a Lysine based branched cyclic peptide synthesis has been reported; the peptide's choice was assisted by computer aided molecular design [1]. LysinebasedTrypsin-ActSite(LysTAS) is a new tool that automated the above mentioned processes; it works as an extension of the well-known software TINKER (http://dasher.wustl.edu/tinker/) [2]. The package builds peptidomimetic molecules that satisfy a particular design (figure 1) and grades them against chymotrypsin's active site's topology.

At this stage we omitted the modelization of the binding site despite its obvious significance in catalysis. Our intention is to construct a leader compound with serine protease-like activity without further specificity. The concept behind this is Menger spatiotemporal hypothesis and the most recent "NAC" [3]. According to this approximation the ability of an enzyme to bind to the substrate (formation of the Michaelis complex (MC)) [4] by acquiring an approximate conformation is the most crucial step towards catalysis.

2. Overview of the application

This application: (a) constructs branched cyclic peptides of a certain pattern; (b) guides the peptides to adopt a conformation similar to the active site; (c) subjects the molecules to unconstrained molecular dynamics (implicit solvation environment); and (d) grades the resultant trajectories with respect to the actual trypsin spatial arrangement of the active site.

The first part is the automated builder of branched cyclic peptides. It constructs the peptide molecules that satisfy the pattern in figure 1. The peptide model comprises a cyclic hexapeptide-carrier on which the active site residues can be attached to the Lys—NεH groups.

Template forcing was used for guiding each peptide (the catalytic triad of the molecule) to adopt a specific conformation, similar to the trypsin active site, referred to as the template.

The molecular segment used as template was the side-chain heavy atoms of the catalytic triad residues (Asp, His, Ser) and was extracted from the crystal structure of trypsin -pdb entry code 2ptn- as a typical representative of the serine protease family.

The implicit solvation technique is fully parametrical. The user can choose the implicit solvation model, the temperature of the simulation, the simulation time, the time interval for the dynamics steps, the interval between coordinate/trajectory.

The heavy atoms of the catalytic triad residues in the enzyme are superimposed to the corresponding heavy atoms of the peptide model's catalytic triad: then the RMS distances (in Cartesian coordinates) are measured in order to assign a similarity score. This comparison refers to 12 atoms belonging to the side chain heavy atoms of the three residues in the active site: Ser, His and Asp. C^{β} atoms are included, so

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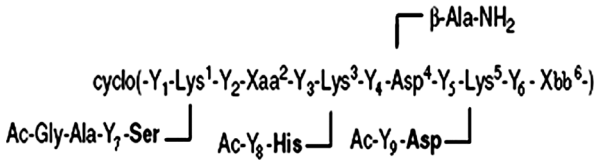

Figure 1. Peptides modelled as serine protease mimics. Active site residues Ser, His and Asp are in bold. Y_i denotes the D/L chirality and Xaa, Xbb can be any of the 20 aminoacids.

His residue contributes six atoms, Asp four atoms and Ser two atoms. All RMS measurements mentioned throughout this paper refer to the above definition.

The criterion for a frame of the trajectory to count it as one with a favorable topology is:

$$\mathrm{RMSd}_i = \mathrm{RMS}[\mathrm{frame}_i^{\text{implicit solution}} - \mathrm{TEMPLATE}] \leq 2\text{Å}.$$

The application measures the distances between the atoms of the active site residues that are responsible for the hydrogen bonds throughout the simulation, as an additional criterion of similarity. The criterion for the hydrogen bonding's distance is <3 Å [5]. Wallace *et al.* [6] suggested a RMS distance of <2 Å from the functional template.

The molecule with Xaa = Gly, Xbb = Gly and the following set of chiralities $X_1,\ldots,X_9$ = L–L–L–L–L–L–L–L–D (figure 1) was used for validation purposes and its simulated implicit solvation trajectories (various solvation models, see manual) was similar to those reported in Ref. [1].

The programme LysTAS provides an automated way to search for bioactive compounds. This software offers to the scientific community a flexible, open source tool capable of investigating any molecule belonging to the set that exhibit the pattern of figure 1 (2×10^5 molecules).

As far as we know there are no other open source programmes that provide automated building of branched peptides. Also the programme could be used as a springboard for the exploration of further capabilities by interested developers.

LysTAS is implemented in Perl and is thus linux platform independent.

Availability: LysTAS (including the associated manual) is free for academic use at http://users.uoi.gr/btatsis

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