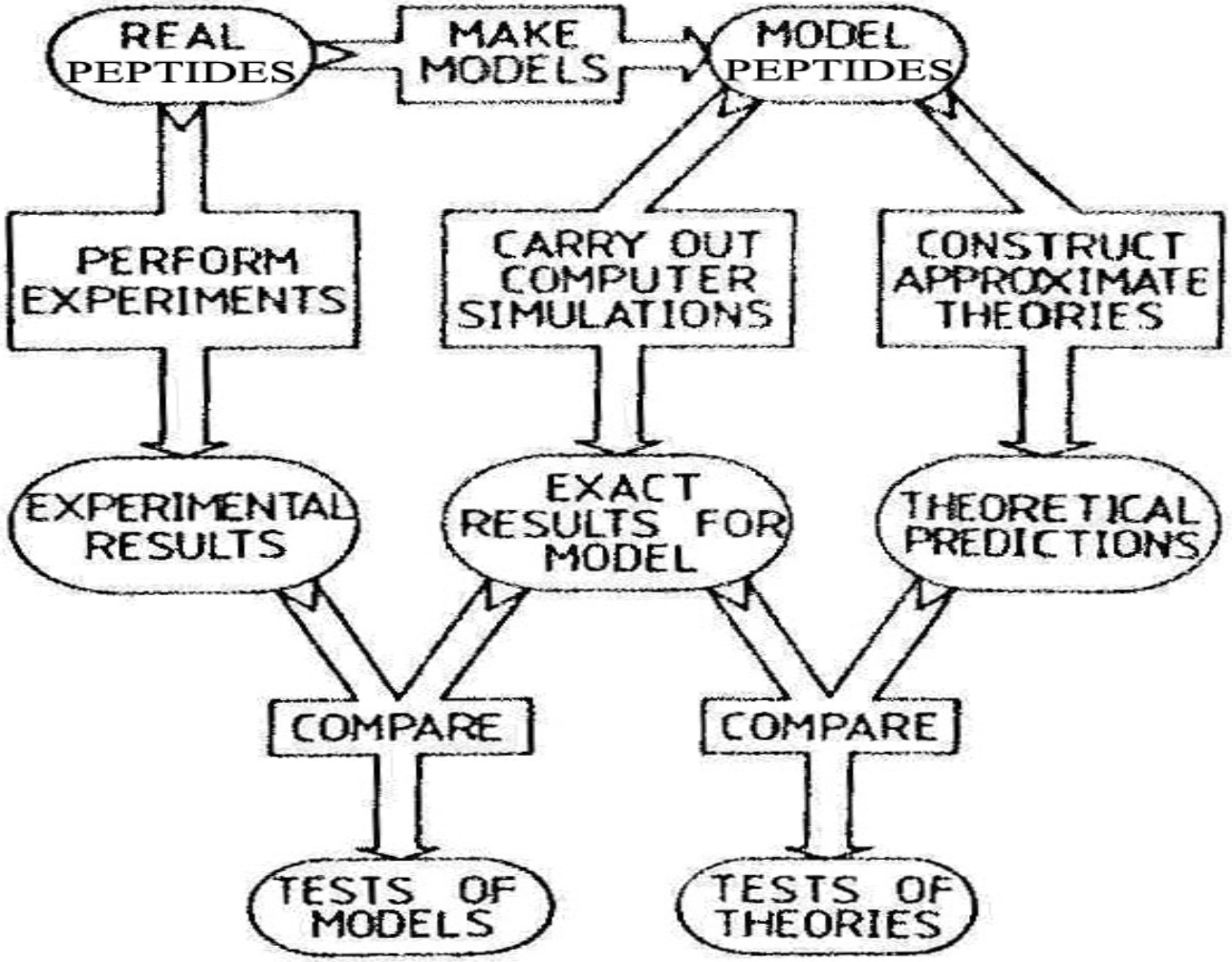
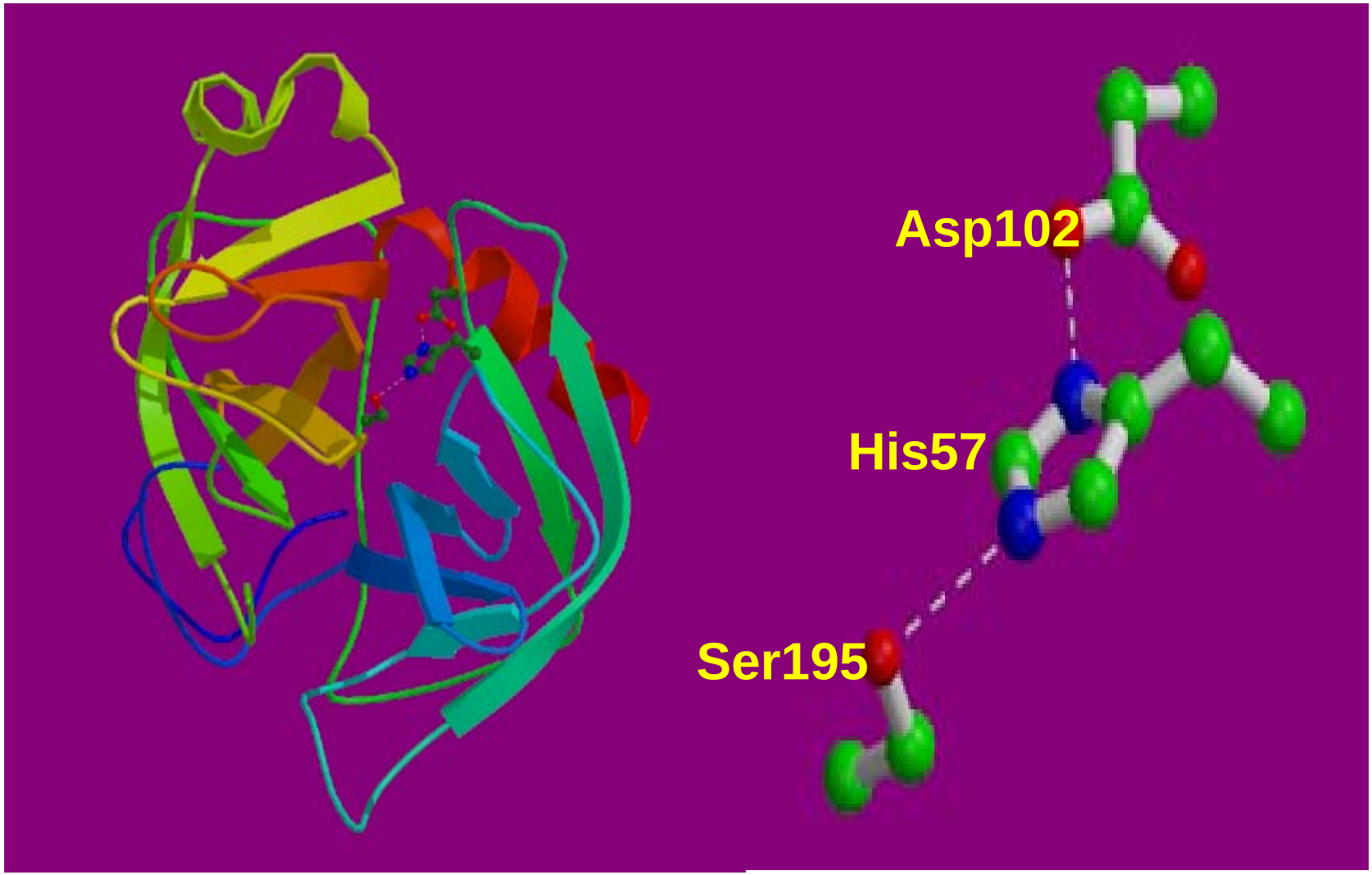
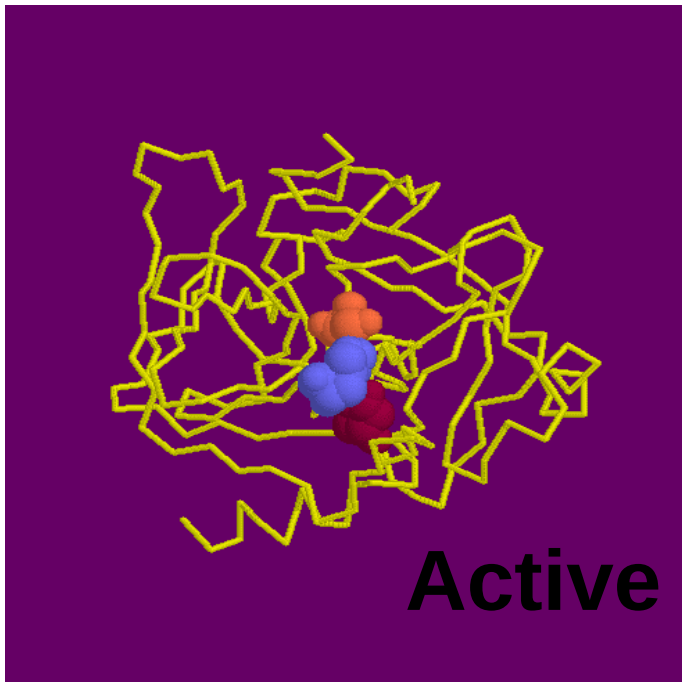
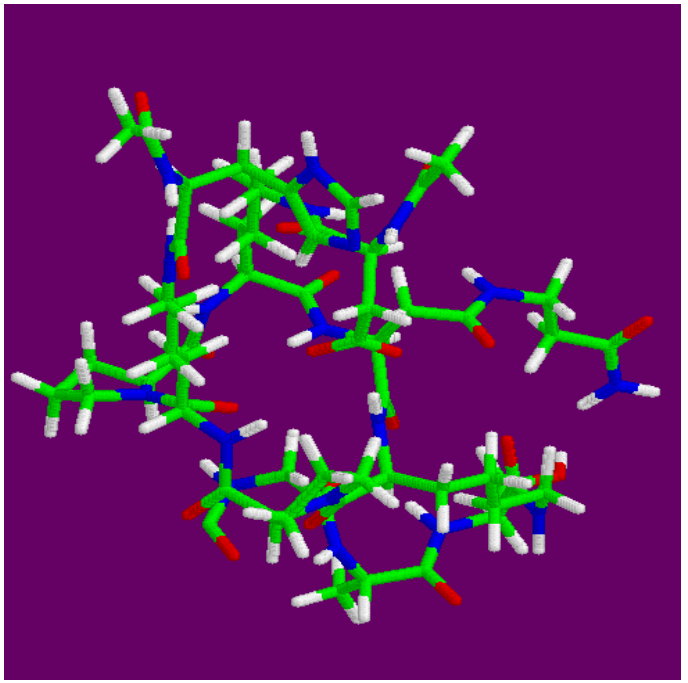
Theozymes - Compuzymes



chymotrypsin



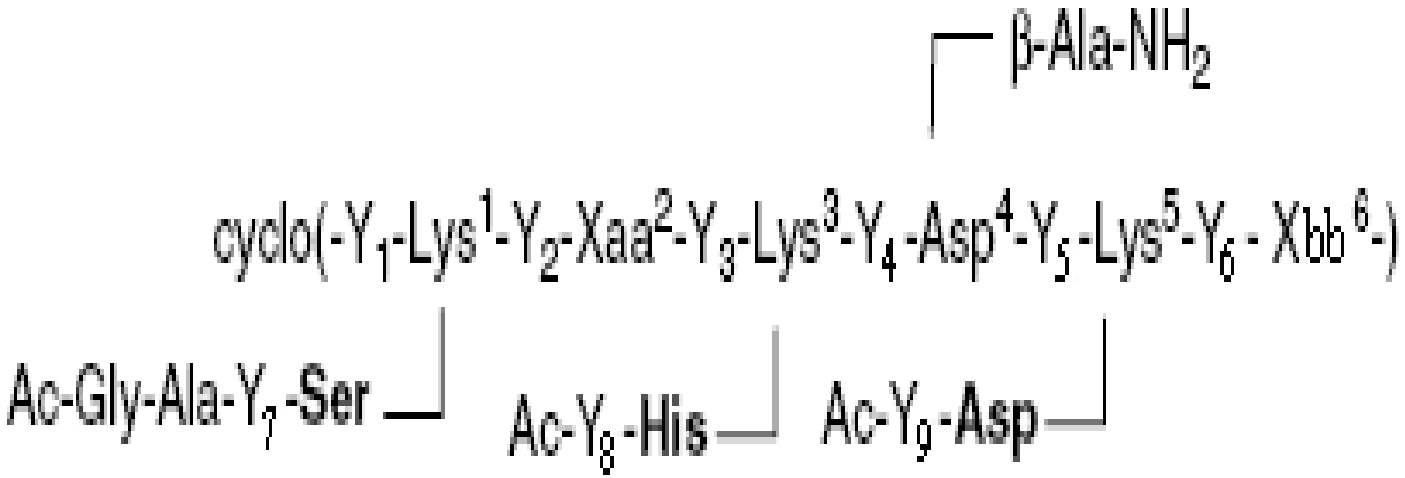




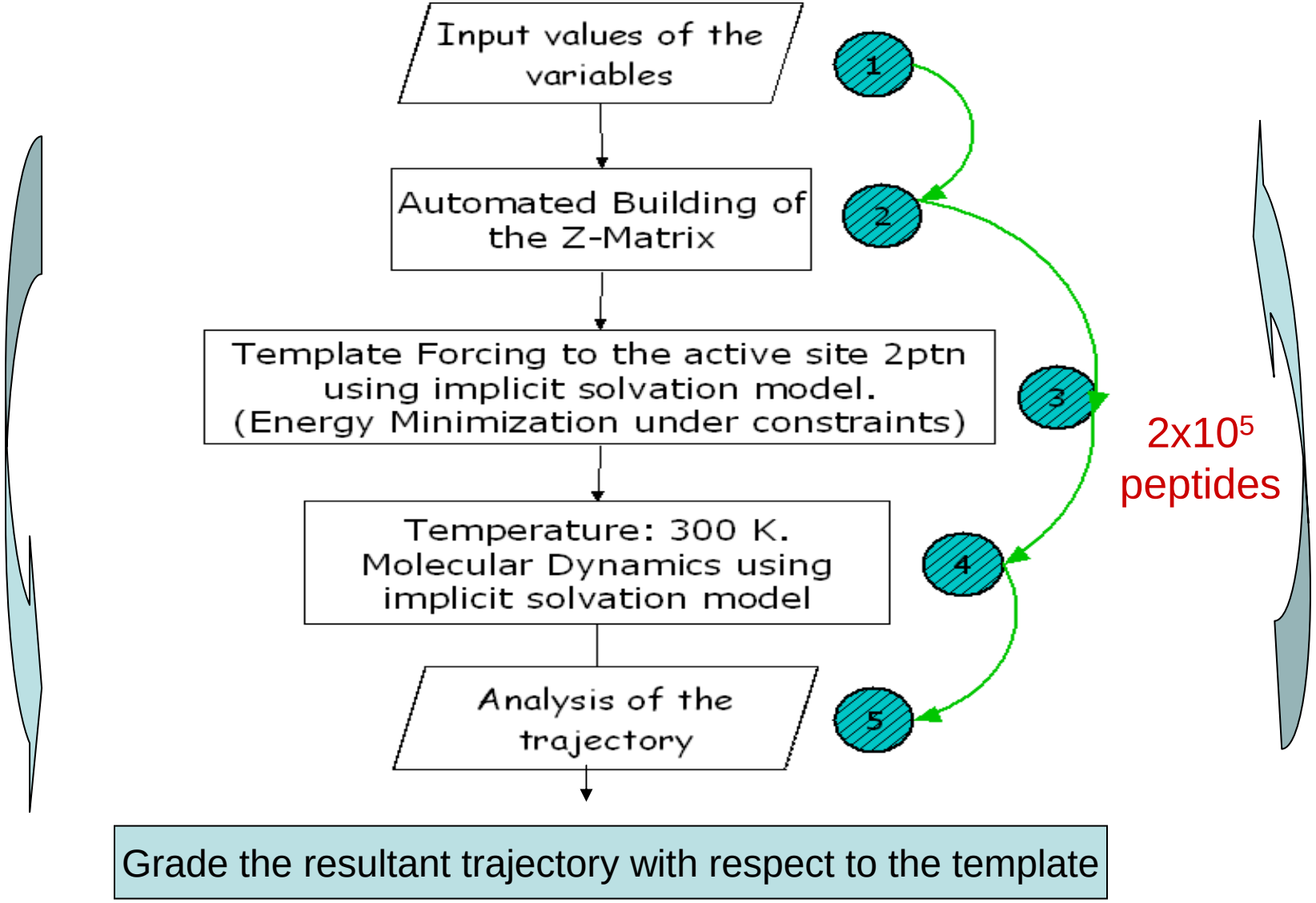
Chymotrypsin
245 aminoacids

Peptide-template
12 aminoacids

Molecular template for chymotrypsin



Flowchart


Input values of the variables
1
Automated Building of the Z-Matrix
2
Template Forcing to the active site 2ptn using implicit solvation model. (Energy Minimization under constraints)
3
2x10^5 peptides
Temperature: 300 K. Molecular Dynamics using implicit solvation model
4
Analysis of the trajectory
5
Grade the resultant trajectory with respect to the template

The application (TAS) (1/5)

- TrypsinActSite(TAS) is a new tool that provides an integrated framework to build and predict the best mimetic for the serine protease, chymotrypsin.

The application (TAS) (2/5)

- An extension of the well-known software TINKER (Ponder, J.W) (http://dasher.wustl.edu/tinker/) that:
- (a) constructs branched cyclic peptides of a certain pattern

The application (TAS) (3/5)

- (b) guides the peptides to adopt a conformation similar to the active site

The application (TAS) (4/5)

- (c) subjects the molecules to unconstrained molecular dynamics (implicit solvation environment)

The application (TAS) (5/5)

- (d) grades the resultant trajectories with respect to the actual trypsin spatial arrangement of the active site.

Results

INPUT

	Comments
/opt	# Installation path of TINKER
1	# Version of TINKER (4.1)
Gly	# Xaa peptide (Fig. 1)
Gly	# Xbb peptide (Fig. 1)
1	# Choice 1 (specific D/L chirality)
L L D L L D L D D	# Peptide 1 (Y1- … -Y9)
L D L L D L L D D	# Peptide 2 (Y1- … -Y9)
D L L D L L L L L	# Peptide 3 (Y1- … -Y9)
D L D D L D D D L	# Peptide 4 (Y1- … -Y9)
	# Leave this line blank to continue
220000	# The total time of MD (fs)
1	# Time step length (fs)
2	# Time between dumps (ps)
300	# Temperature (K)
SASA	# Implicit Solvation model
amber99	# Force Field

OUTPUT

Peptide	RMSd(%)	**d**1(%)	**d**2(%)	**d**3(%)
1	97	4	0	27
2	12	4	0	2
3	1	0	0	0
4	11	10	1	15
Amber99/GBSA				
1	9	10	4	7
Charmm27/GBSA				
1	4	0	0	0
Charmm27/SASA				
1	100	99	0	15
Amber99/ONION				
1	100	100	0	100

TAS + GRIDS

- TAS is especially suited for distributed computing.
- The package can screen over $2 \cdot 10^5$ substances, exhibiting the pattern (template) for possible mimetics of chymotrypsin.
- This computer process can be easily distributed.

Future Enhancements of TAS

Next editions will take into account

a. the simulation of other active sites
b. the choice of the number of the amino acids being in the circle
c. hydrogen bond directionality constraints
d. the binding site topology