

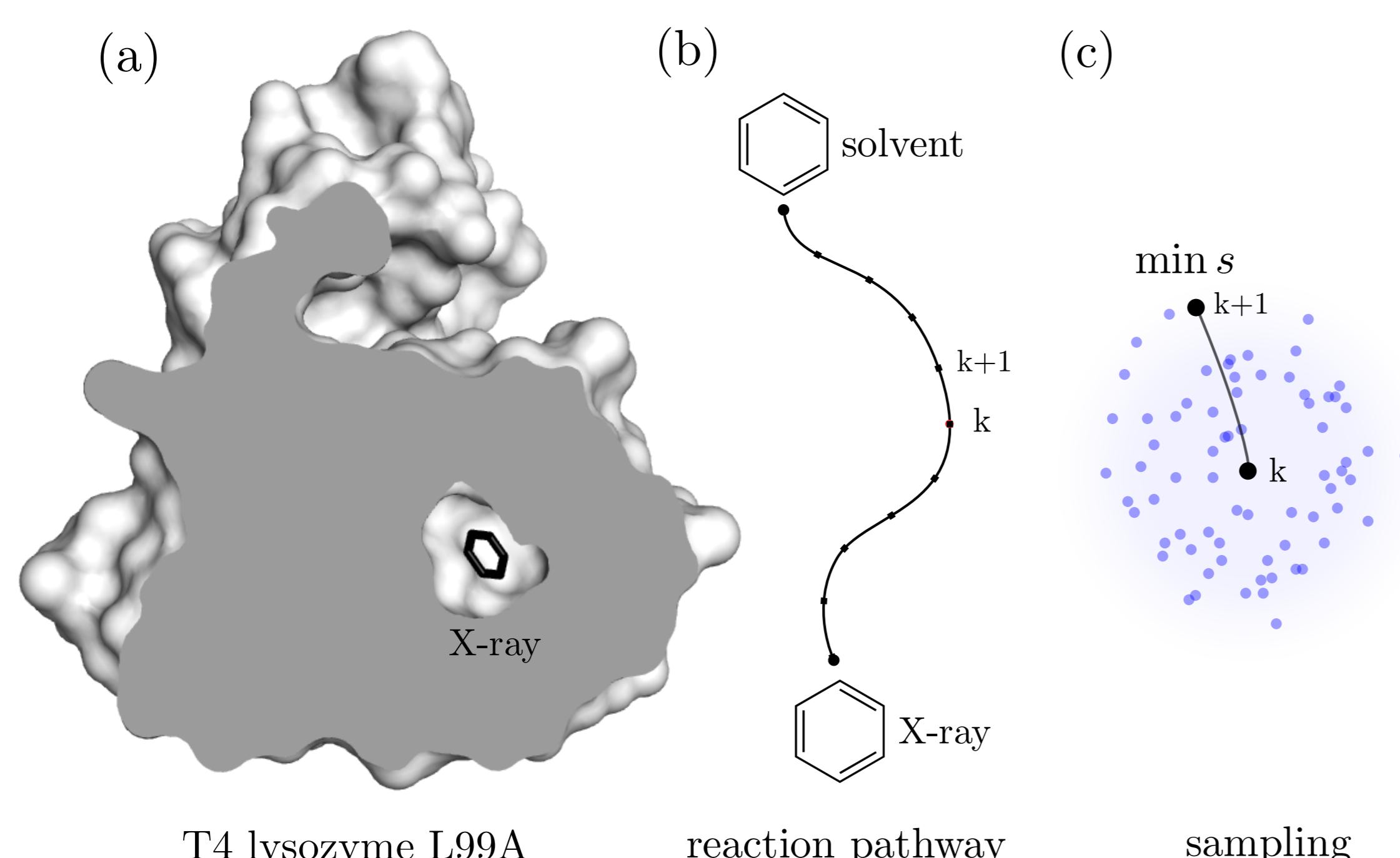
# Ligand Dissociation Pathways in T4 Lysozyme L99A

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## How to Find an Exit Tunnel?



For each of  $i$ th pair of ligand-protein atoms the partial loss function is defined as  $\exp(-r_i)/r_i$ , where  $r_i$  is the distance between the atoms and it is given by  $r_i = \lambda \|x_k - y_l\|$

The loss function is the following:

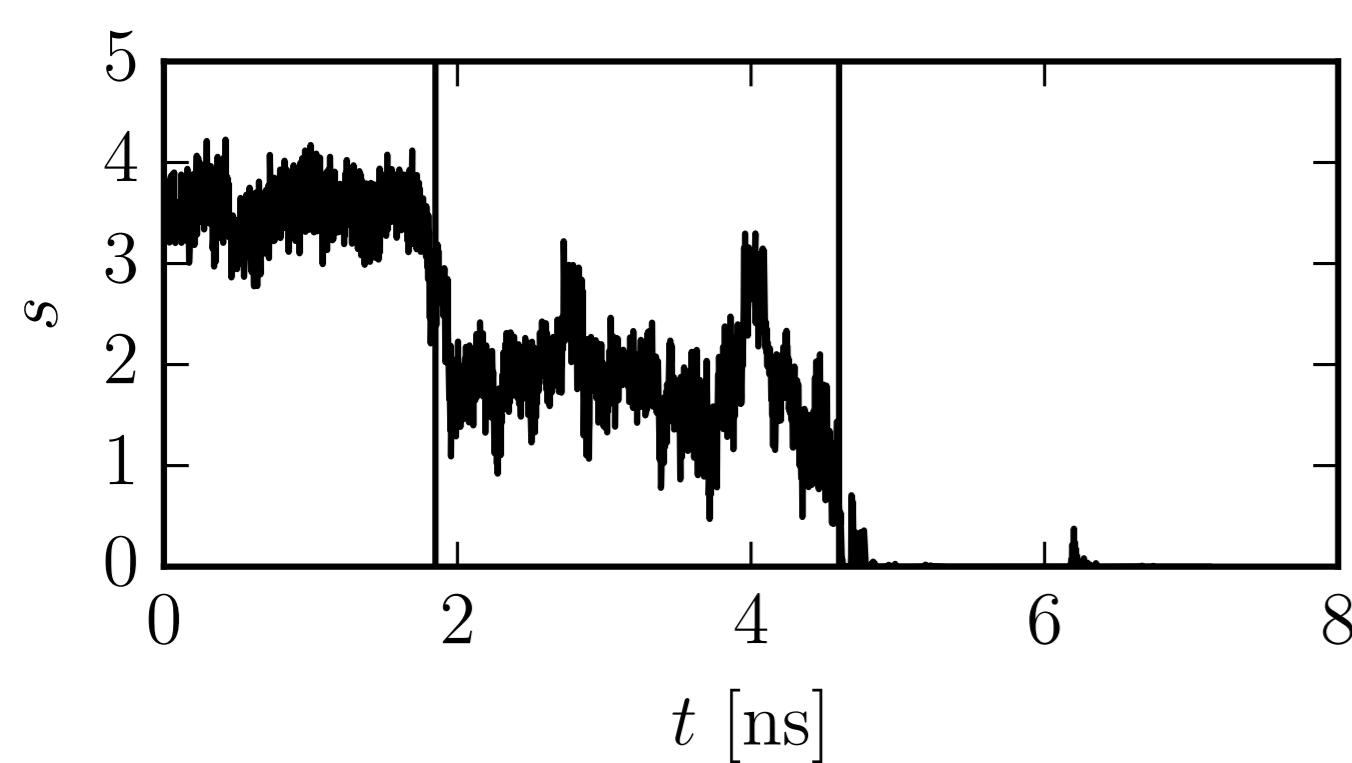
$$s = \sum_{i=1}^P \frac{\exp(-r_i)}{r_i}, \quad (1)$$

where  $P$  is the number of ligand-protein atom pairs.

The loss function is optimized during MD simulations using the Metropolis–Hastings algorithm with the Boltzmann factors:

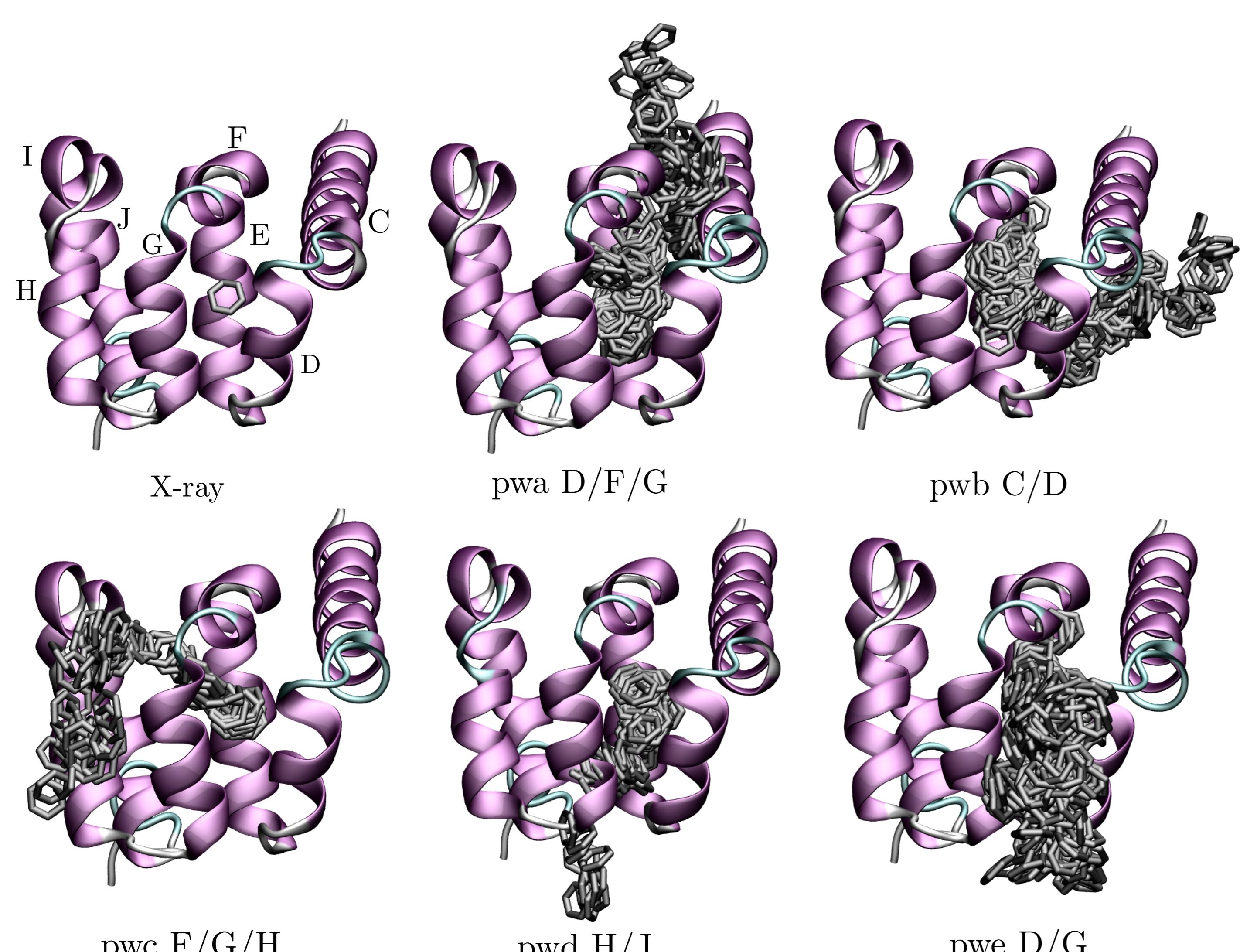
$$p = \begin{cases} \exp(-\beta(s(x') - s(x))) & \text{if } s(x') > s(x) \\ 1 & \text{otherwise} \end{cases} \quad (2)$$

where  $x'$  is a randomly chosen neighboring position of the ligand and  $\beta = 1/T(t)$  is a parameter introduced to decrease the probability of acceptance of a worse solution as the minimization procedure proceeds.

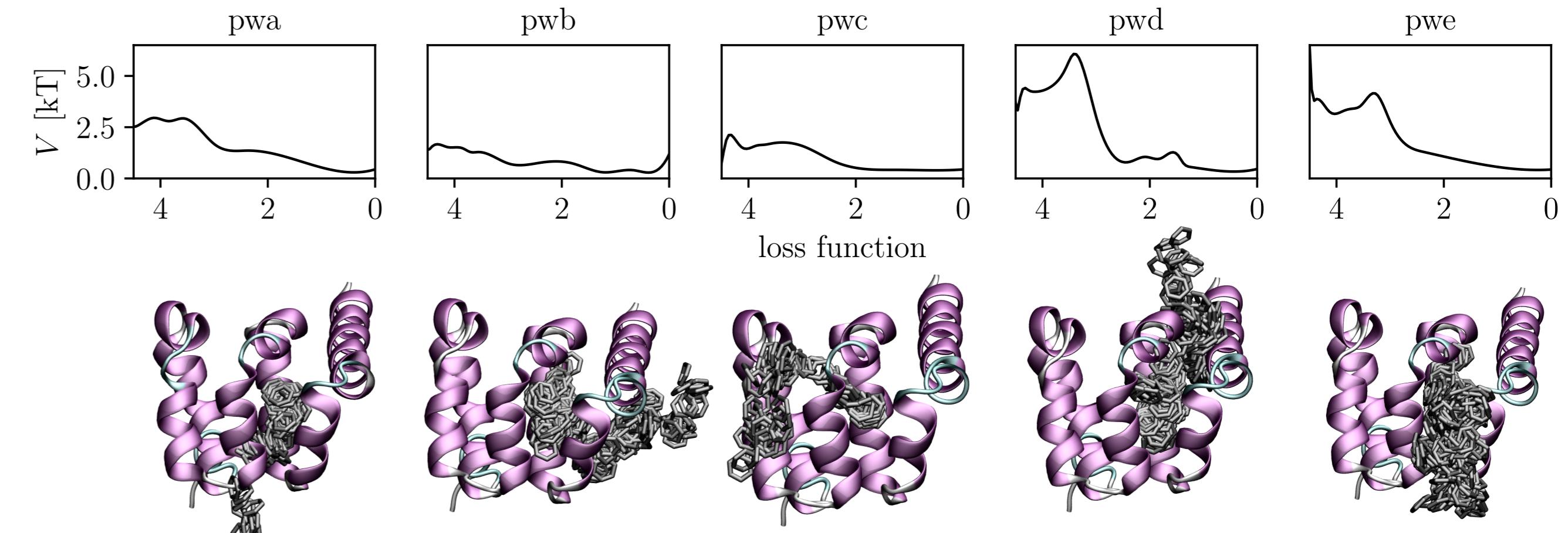


- Enhanced sampling and non-convex optimization;
- Biasing toward the minimum of the loss function;
- Loss function describes interactions in a ligand-protein system;

## Ligand Dissociation Pathways



## Are Transient Pathways Heterogeneous? [3]



Reaction pathways of the benzene unbinding from the lysozyme L99A mutant classified in five clusters. In the upper panel the bias potential is shown as a function of the minimized loss function. The bottom panel depicts atomistically the reaction pathways.

## maze: A Module for Plumed 2 [3]



maze is a code that implements enhanced sampling methods for simulating the reaction pathways of ligand unbinding. It is made as a module for Plumed 2, an engine for free energy calculations of atomistic systems.



Fork maze from Github.



Ask us on Gitter.

## References

- [1] J. Rydzewski, O. Valsson, *J. Chem. Phys.* 150 (2019).
- [2] J. Rydzewski, ..., H. Grubmüller, *J. Chem. Theory Comput.* 14, 2843 (2018).
- [3] J. Rydzewski, *Submitted* (2019).

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All the data and PLUMED input files required to reproduce the results reported in this study will be available on PLUMED-NEST ([www.plumed-nest.org](http://www.plumed-nest.org)), the public repository of the PLUMED consortium.