Molecular Dynamics Simulation of the D102A Variant of Chymotrypsin

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1 Introduction

Almost one third of all proteases can be classified as serine proteases [1]. These protiens are named for the nucleophilic Ser residue at the active site. Serine proteases fall into two broad categories based on their structure – chymotrypsin-like (trypsin-like) or subtilisin-like [2]. Chymotrypsin-like proteases are the most abundant in nature and can be found in eukaryotes, prokaryotes, archae, and viruses. They are involved in many critical physiological processes, such as hemostasis, apoptosis, digestion, and reproduction [1].

In order to hydrolyze a peptide bond, these well-studied enzymes must overcome three major mechanistic barriers: (1) amide bonds are extremely stable due to electron donation from the amide nitrogen to the carbonyl; (2) water is a poor nucleophile and proteases always activate water via a general base; (3) and amines are poor leaving groups because proteases protonate the amine prior to expulsion [1].

To overcome these three reaction barriers, serine proteases contain a group of three residues called the catalytic triad that use hydrogen bonding to increase reaction favorability. In chymotrypsin, the triad is composed of serine, histidine, and aspartate, and is part of a larger hydrogen bonding network [1].

Mutagenesis experiments of catalytic triad residues show decreased catalytic activity; substitution of Ser195 or His57 with Ala effectively disables the triad [1]. For this project, we hypothesize that the Asp-His hydrogen bond restrains the conformational flexibility of the His ring so that it can more strongly hydrogen bond to Ser, thus activating serine for a nucleophilic attack.

To test this, we carried out two all-atom molecular dynamics simulations of two chymotrypsin series variants: the wild type sequence, and with Asp-102 substituted for alanine (mutation D102A). This enabled us to determine rotamer distributions of the His side chain and the time-dependent frequencies of His-Ser bond formations.

2 Methods

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3 Results

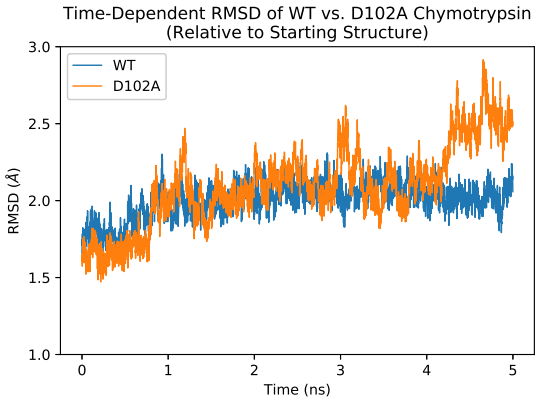


Figure 1: RMSD of wild-type (WT) and D102A simulations

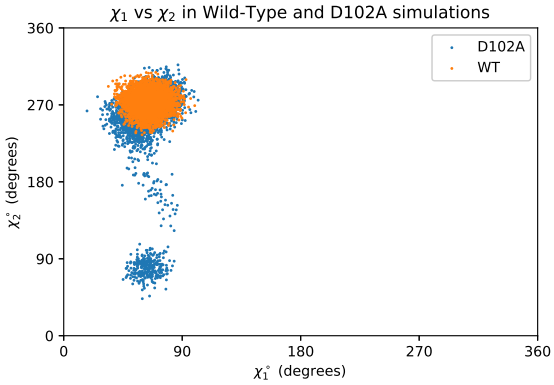
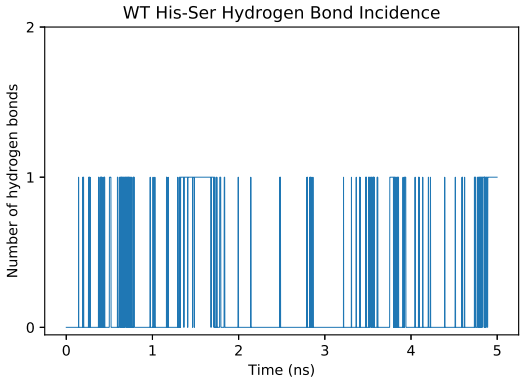


Figure 2:



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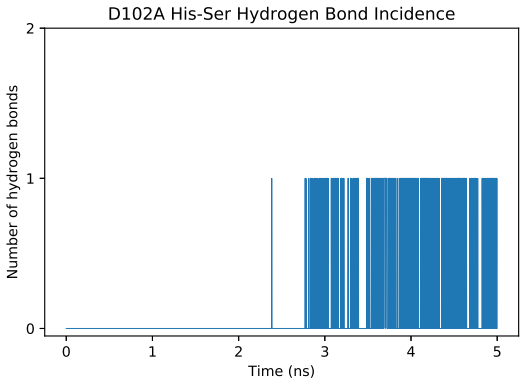

Figure 4:

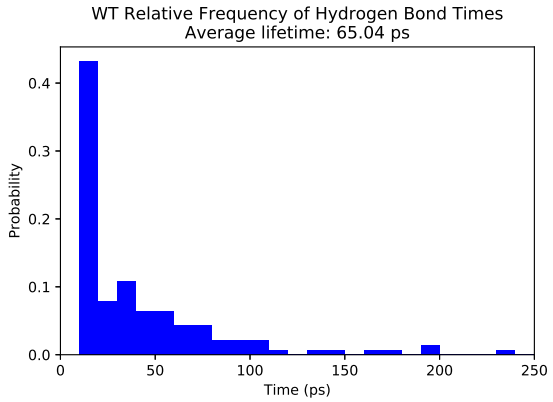

Figure 5:

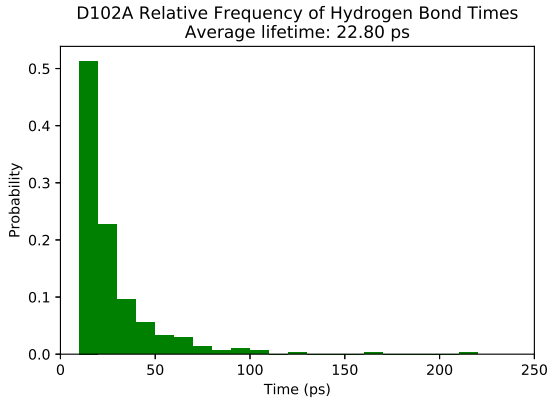

Figure 6:

4 Conclusion

Acknowledgements

5 References

References

[1] Hedstrom L. Serine protease mechanism and specificity. Chemical reviews. 2002 Dec 11;102(12):4501-24.

[2] Madala PK, Tyndall JD, Nall T, Fairlie DP. Update 1 of: Proteases universally recognize beta strands in their active sites. Chemical reviews. 2011 Apr 8;110(6):PR1-31.

A Hydrogen Bond Lifetime Code

Minted portion to be added later.