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Effect of Amino Acid Type on Peptide Structure

Abstract

Through intramolecular interactions, amino acids largely dictate a peptide's structure and flexibility, both of which play significant roles in a peptide's binding properties and function. This model explored the effects of three major residue types (uncharged hydrophilic, hydrophobic, and charged) on peptide structure in solution, by utilizing a bead-spring model and the relevant potentials, including Lennard-Jones and screened Coulomb, to describe amino acid interactions. As indicated by contact maps and MD movies, MD simulations of fifteen residue peptides with varied amino acid configurations captured the relevant structural interactions, such as a hydrophobic core versus a flexible peptide made up solely of uncharged hydrophilic residues. Modeling these structural interactions can aid the design of peptides for a specific task, such as fitting in the catalytic region of an enzyme.

Background

Since structure plays an important role in peptide function, understanding the major intramolecular interactions can aid the engineering of a peptide for a desired task. For example, a peptide may require a specific conformation, such as an inflexible core or a loop structure, to bind with high affinity to an antibody or enzyme catalytic region. This study used molecular dynamics (MD) simulations of a bead-spring polymer model to explore the effect of uncharged hydrophilic, hydrophobic, and charged residues on the peptide's most probable structural configurations, as described by contact maps and movies.

Methodology

A bead-spring model was chosen to describe a fifteen residue peptide composed of different amino acids and each residue was described by a single bead. In addition to Hooke's law for covalent bonds (1), different potentials described each of the three amino acid types in an implicit solvent. For interactions between uncharged hydrophilic residues and between different types of amino acids, the Weeks-Chandler-Andersen (WCA) potential [1] was used (2). Interactions between charged residues included the WCA potential and a screened Coulomb potential (3), and a Lennard-Jones (6-12) potential (4) captured hydrophobic-hydrophobic interactions.

$$u(r_{ij}) = \tfrac{1}{2}k^0(r_{ij} - r_0)^2 \text{, where } k^0 \text{ is } \frac{k}{k_B T} \quad (1)$$

$$u(r_{ij}) = 4\varepsilon^0\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right] \text{, where } \varepsilon^0 \text{ is } \frac{\varepsilon}{k_B T} \quad (2)$$

$$u(r_{ij}) = 4\varepsilon^0\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right] + \frac{\lambda_B q_1 q_2}{r_{ij}}\exp\left[\frac{-r_{ij}}{\lambda_D}\right] \quad (3)$$

$$u(r_{ij}) = 4\left(5\varepsilon^0\right)\left[\left(\frac{\sigma}{r_{ij}}\right)^{12} - \left(\frac{\sigma}{r_{ij}}\right)^{6}\right] \quad (4)$$

k is the spring constant and r_0 the equilibrium bond length, which were set equal to 70 kcal/mol Å^2 and 3.8 Å, respectively [2]. r_{ij} represents the distance between particle *i* and *j*, and σ is the particle diameter (set equal to 2.5 Å based on the average size of amino acids within the peptide backbone not including the R group). λ_D is the screening length, while λ_B is the Bjerrum length (7 Å in water at room temperature),

and q_1 and q_2 represent the residue charges (set to ±1). The well depth ε^0 was set to 1 for the WCA potential while the L-J potential used to describe the interaction between hydrophobic residues in water involved an ε^0 of 5 because the contact energies of two hydrophobic residues has been shown to range from approximately -3 to -7 k_BT with a tryptophan-tryptophan contact roughly equal to -5 k_BT [3]. To determine the screening length, a physiologic salt concentration (140 mM NaCl) was assumed to calculate a λ_D of 8.12 Å using equation 5 [4].

$$\lambda_D(nm) = \frac{0.304}{\sqrt{I(M)}} \quad \text{, where I is the ionic strength in molarity} \qquad (5)$$

To save on computational time, cutoff values (Table 1) for using the WCA and L-J potentials depended on σ, and were chosen based on convention (i.e. where the L-J potential is $1/60^{th}$ of its minimum). For the charged residues the WCA potential was only included within the WCA cutoff, and outside this cutoff, the screened Coulomb potential only was calculated for interactions within the Coulombic cutoff, which was chosen to be where the potential approximately equaled 0.01.

Table 1: Cutoff Values for Different Potentials

Cutoff	Value (Å)
R_{WCA}	$2^{1/6}\sigma$
R_{LJ}	2.5σ
R_C	26.5

Equipped with these potentials and the cutoff values, MD simulations were conducted for four different configurations (Table 2) of amino acids within a 15 residue peptide. These different configurations included a peptide composed purely of noninteracting hydrophilic residues (H) and adding in charged (P for positive and N for negative) or hydrophobic (Ph) residues. Finally, a peptide consisting of all three types, similar to a peptide of research interest, was also simulated. For each configuration, three separate trials were conducted and each trial resulted in a unique matrix of the probability of observing two particles within a minimum distance of 5 Å normalized by the total number of observations. This relatively stringent minimum distance allowed room for salt bridges (typically around 2.8 Å) and hydrophobic interactions, while ignoring the size of the amino acid R groups. Using the averaged values over the three trials, a contact map was generated for each configuration. In addition to creating contact maps, MD movies were generated to evaluate structure and flexibility differences between peptide configurations. In these movies, the end-to-end distance was periodically evaluated for the different peptides.

Table 2: Peptide Configurations Simulated

Peptide	Configuration
A	H,H,H,H,H,H,H,H,H,H,H,H,H,H,H
B	H,P,P,P,P,H,H,H,H,H,N,N,N,N,H
C	H,Ph,Ph,H,H,Ph,Ph,Ph,Ph,Ph,H,H,Ph,Ph,H
D	H,P,H,H,Ph,Ph,H,Ph,Ph,N,H,H,P,Ph,N

Results and Discussion

The four different peptide configurations resulted in significantly different heat maps describing the probability of contact between amino acids (Figure 1). With purely uncharged hydrophilic amino acids, the peptide proved highly flexible, as seen in the MD movie created. The uniform distribution of particle contacts (Figure 1a) demonstrated that no clear preferred structure exists for this peptide. By adding oppositely charged hydrophilic particles on the ends of the peptide, the peptide appears to form a loop with the ends coming together (Figure 1b). An optimum distance for the interaction of the positive and negative particles appeared to exist, as indicated by the highest contact probability observed for the 4^{th} and 12^{th} amino acids. This interaction of the ends led to a more consistent and, on average, shorter end-to-end distance (movie) than the purely uncharged hydrophilic peptide; however, the peptide also retained a degree of flexibility. The peptide composed of hydrophobic and uncharged hydrophilic amino acids proved highly inflexible due to the peptide condensing in upon itself to form a hydrophobic core of amino acids almost always in contact with each other (Figure 1c). Additionally, the end-to-end distance changes minimally throughout the course of the simulation (movie). Finally, the peptide composed of all four types of amino acids showed interesting structural properties (Figure 1d). The N-terminal part remained

flexible but interacted only slightly with the remainder of the peptide. Again a hydrophobic core formed with the central hydrophobic amino acids almost always in contact with each other and also in contact with the C-terminal hydrophobic residue. Additionally, the C-terminal positive particle appeared to interact with the two negatively charged residues with a similar probability. This caused an interesting shift in the end-to-end distance from the positive charge interacting with the last amino acid versus the 10^{th} amino acid (movie).

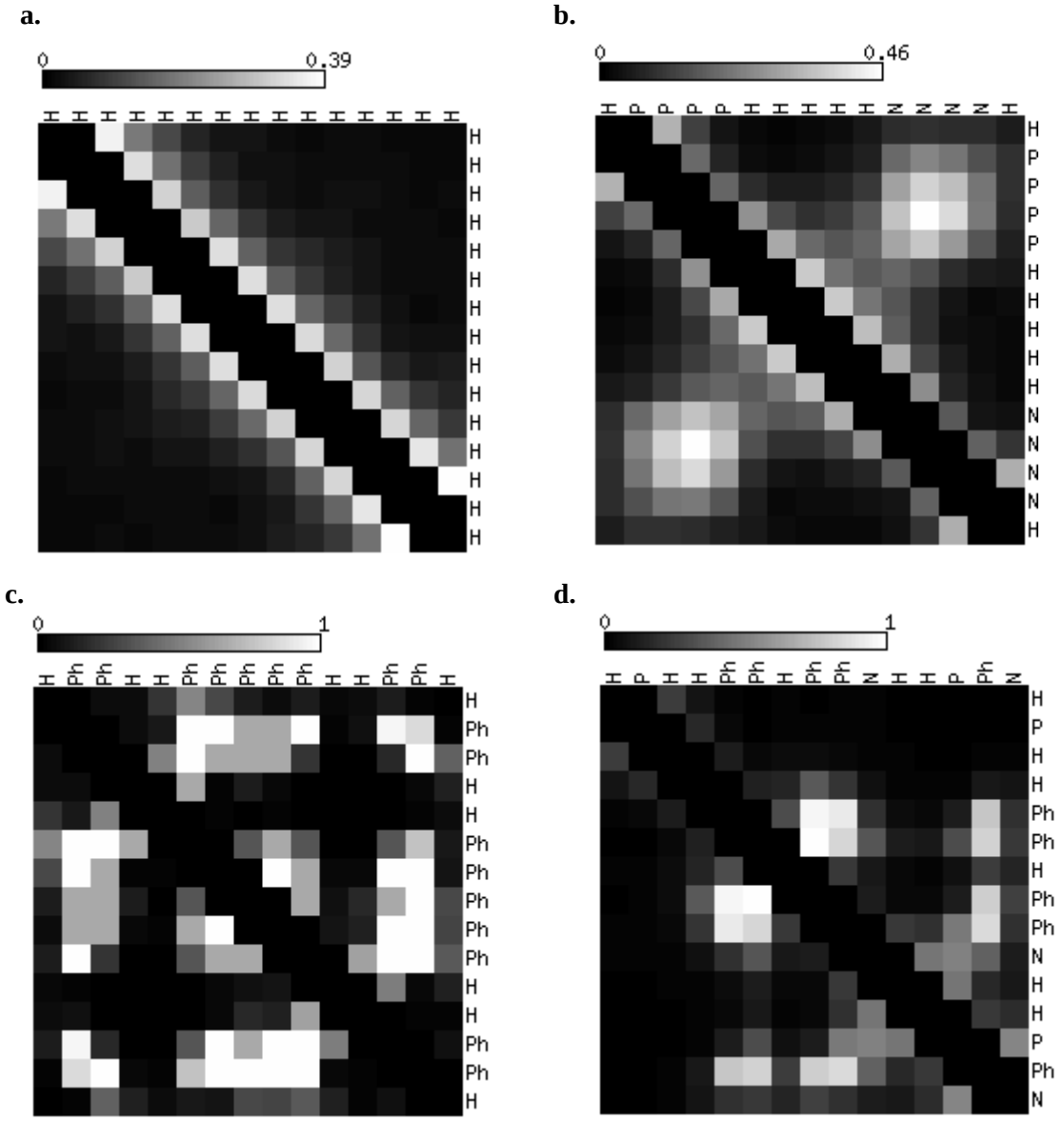

Figure 1: Contact maps generated to describe the intramolecular interactions observed for the four different peptide configurations. A higher intensity (lighter color) reflects a higher contact probability. Residue abbreviations: H-uncharged hydrophilic, P-positive hydrophilic, N-negative hydrophilic, Ph-hydrophobic.

Conclusion

Based on the contact maps and MD movies generated, the hydrophobic residues appear to impart an inflexible structure to the peptide. The charged residues also impart structure but allow for more flexibility within the peptide than seen with the hydrophobic amino acids. This flexible loop structure could be valuable for fitting into an enzyme's catalytic region. To improve this model, one could start

adding in more detail to the individual amino acids. So, instead of using one hydrophobic potential to describe all hydrophobic interactions, this potential could be altered based on a specific amino acid's hydrophobicity. This would provide a better approximation to a specific amino acid's properties based on its R group. Additionally, to add more detail with regard to size as well as amino acid properties, one could introduce a two-bead or three-bead model to describe each amino acid. Finally, instead of using an implicit solvent one could actually simulate the peptide in atomistic water.

Movie

The movie depicts the four different fifteen residue peptides simulated. Throughout the movie, one can compare the structure and flexibility of each peptide and the end-to-end distances of the peptides that are depicted periodically. Uncharged hydrophilic residues are shown in grey, hydrophobic residues in purple, positively charged residues in red, and negatively charged particles in blue.

References:

1. Weeks JD, Chandler D, Andersen HC, Role of Repulsive Forces in Determining the Equilibrium Structure in Simple Fluids. *J Chem Phys.* 1971: 54(12): 5237-5247
2. Korkut A, Hendrickson WA. A Force Field for Virtual Atom Molecular Mechanics of Proteins. *PNAS*. 2009;106(37):15667–15672.
3. Miyazawa S, Jernigan RL. Residue-Residue Potentials with a Favorable Contact Term and an Unfavorable High Packing Density Term, for Simulation and Threading. *J Mol Biol*. 1996;256:623–644.
4. Israelachvili J., *Intermolecular and Surface Forces*, Academic Press Inc., 1985, ISBN 0-12-375181-0