Molecular Dynamics Simulations of Peptides and Proteins

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Background

- Molecular dynamics (MD) is a useful computational method used to model molecular interactions.
- In general, MD simulations go through 3 steps:
  - Energy Minimization
  - Equilibration
  - Production
- Force field – set of parameters and functions used to determine energies and forces associated with molecular interactions.
- Total energy must be conserved.

$$V_{\mathrm{AMBER}} = \sum_{i}^{n_{\mathrm{bonds}}} b_i(r_i - r_{i,\mathrm{eq}})^2 + \sum_{i}^{n_{\mathrm{angles}}} a_i(\theta_i - \theta_{i,\mathrm{eq}})^2 + \sum_{i}^{n_{\mathrm{dihedrals}}} \sum_{n}^{n_{i,\max}} (V_{i,n}/2)[1 + \cos(n\phi_i - \gamma_{i,n})]$$
$$+ \sum_{i<j}^{n_{\mathrm{atoms}}}{}' \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) + \sum_{i<j}^{n_{\mathrm{atoms}}}{}' \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}},$$

Figure 1. Hamiltonian of the AMBER force field.[1]

Introduction

- This study aimed to investigate the dynamics involved in the binding of naringenin with TtgR, a sensory protein, as a means to further understand why the binding occurs.
- Familiarization with computational chemistry methods was first needed before studying naringenin binded to TtgR.
- The following programs and softwares were learned using an alanine dipeptide:
  - AMBER (Assisted Model Building and Energy Refinement) – a collection of softwares used to run molecular dynamics simulations and define molecular interaction parameters[2]
  - LEaP – a program within AMBER that creates a complete description of a desired molecule and prepares files for AMBER simulations
  - VMD (Visual Molecular Dynamics) – a program used to visualize molecules and simulations performed with programs such as AMBER
- A visual representation of naringenin in complex with TtgR was created using VMD.

MD Simulation of Alanine Dipeptide

Simulation conditions:
- Solvated with 630 water molecules
- 10000 MD steps (0.002 ps timesteps)
- 300 K temperature (through Langevin thermostat)
- 1 atm pressure (through Berendsen barostat)

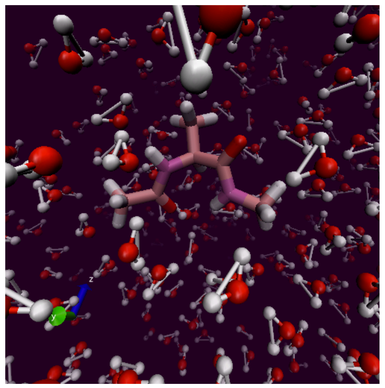

Figure 2. Alanine dipeptide interacting with water (left). The interaction was visualized using VMD. C – pink, N – mauve, H – white, O – red.

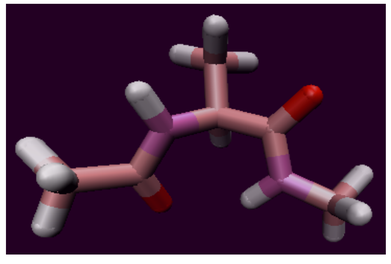

Figure 3. Alanine dipeptide (right). C – pink, N – mauve, H – white, O – red.

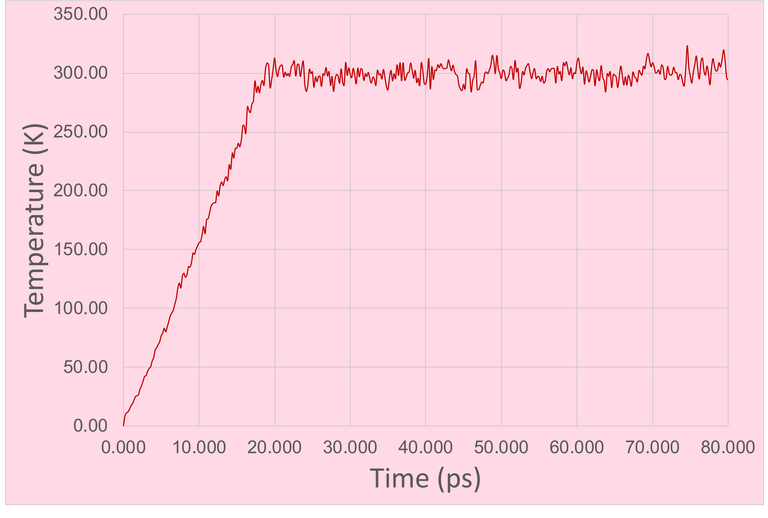

Figure 4. Stabilization of alanine dipeptide temperature through heating.

Future Work

- Naringenin is a flavonoid found in citrus fruits[3] and plant roots[4] and possesses antimicrobial properties.[3] Naingenin also may help with the management of metabolic syndrome.[4]
- Naringenin can bind to TtgR, a protein involved in the regulation of the transcription process of bacteria. TtgR helps keep out harmful substances out of bacteria cells. Through binding, naringenin can enter bacteria cells and cause damage.[3]
- A simulation will be performed with naringenin and TtgR using the same process as alanine dipeptide.

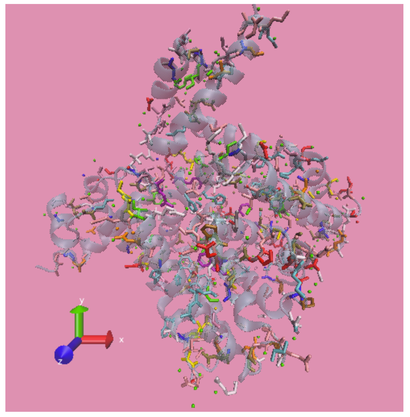

Figure 5. Naringenin in complex with TtgR visualized using VMD (right). PDB ID: 2UXU.

References

[1]Madej, B. D.; Walker, R. An Introduction to Molecular Dynamics Simulations Using AMBER. https://ambermd.org/tutorials/basic/tutorial0/index.htm#Run_AmberMD_sander. (Accessed July 23, 2020).
[2]D.A. Case, K. Belfon, I.Y. Ben-Shalom, S.R. Brozell, D.S. Cerutti, T.E. Cheatham, III, V.W.D. Cruzeiro, T.A. Darden, R.E. Duke, G. Giambasu, M.K. Gilson, H. Gohlke, A.W. Goetz, R. Harris, S. Izadi, S.A. Izmailov, K. Kasavajhala, A. Kovalenko, R. Krasny, T. Kurtzman, T.S. Lee, S. LeGrand, P. Li, C. Lin, J. Liu, T. Luchko, R. Luo, V. Man, K.M. Merz, Y. Miao, O. Mikhailovskii, G. Monard, H. Nguyen, A. Onufriev, F.Pan, S. Pantano, R. Qi, D.R. Roe, A. Roitberg, C. Sagui, S. Schott-Verdugo, J. Shen, C.L. Simmerling, N.R.Skrynnikov, J. Smith, J. Swails, R.C. Walker, J. Wang, L. Wilson, R.M. Wolf, X. Wu, Y. Xiong, Y. Xue, D.M. York and P.A. Kollman (2020), AMBER 2020, University of California, San Francisco.
[3]Alam, M. A.; Subhan, N.; Rahman, M. M.; Uddin, S. J.; Rez, H. M.; Sarker, S. D. Effect of Citrus Flavonoids, Naringin and Naringenin, on Metabolic Syndrome and Their Mechanism of Action. *Adv. Nut.* **2014**, 5, 404-417.
[4]Alguel, Y. A.; Meng, C.; Teran, W.; Krell, T.; Ramos, J. L.; Gallegos, M.-T.; Zhang, X. Crystal Structures of Multidrug Binding Protein TtgT in Complex with Antibiotics and Plant Antimicrobials. *J. Mol. Biol.* **2007**, 369, 829-840.

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