Using accelerated molecular dynamics to retrieve conformational ensemble of Alamethicin

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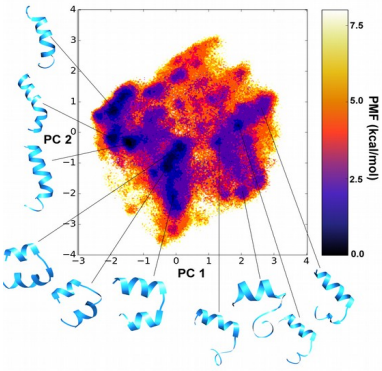
The use of enhanced sampling molecular dynamics simulations to facilitate the folding of peptides and proteins is a relatively new approach which has quickly gained momentum in recent years. One such technique, namely accelerated molecular dynamics introduced by Hamelberg et al. [1], can make accessible different intermediate states visited during peptide folding by lowering the energy barrier between them. In other words, the dynamic path from the unfolded state to all intermediates and finally to the near-native state is "flattened" by introducing a non-negative boost to the potential. This approach has been applied by Miao et al., [2] to elucidate the native structures of fast-folding small peptides from their unfolded states.



The molecule, Alamethicin, chosen in this study belongs to the class of peptaibols that are 7-20 residue long, non-ribosomally synthesized amphipathic molecules showing interesting membrane perturbing activity. It is important to elucidate the structure and dynamics of such peptaibols due to their potential antimicrobial effects and future application. However, all peptaibols including Alamethicin, consist of non-proteinogenic amino acids like aminoisobutyric acid (Aib), D-isovaline (Div), hydroxy-proline (Hyp) and C-terminal alcohol residues like phenylalaninol (Pheol), valinol, etc. which are not readily available within the residue libraries of most simulation software. In this study, we parameterized Aib and Pheol and constructed the unfolded structure of alamethicin to be simulated using accelerated MD simulation for its comparison with the native form available from the Protein Data Bank. We performed three consecutive 1 micro seconds (µs) long simulations. N-terminal folding was observed within the first 100 nano seconds (ns) while the C-terminal folding could only be achieved almost after 800 ns. It took 1 µs to attain the near-native conformation which usually may take several micro seconds worth of classical MD to produce the same results. Another important observation is the significant time spent by the peptide existing as a highly curved helical conformation (resembling a hairpin motif as shown in the figure). The figure describes free energy landscape of alamethicin calculated using principal component analysis based on torsional angles in stead of Cartesian coordinates. The curved conformation is an energetically stable state and would require an energy "boost" of roughly 2.5 kcal mol^{-1} to attain backbone linearity which is the native state. This technique has proven beneficial in order to obtain the complete conformational ensemble of such dynamic peptides. It can be concluded that accelerated MD simulation techniques are suitable for the elucidation of peptaibol structures and understanding their folding dynamics.

[1] D. Hamelberg, J. Mongan, J. A. McCammon, *J Chem Phys*, **2004**, *120*, 11919-11929.
[2] Y. Miao, F. Feixas, C. Eun, J. A. McCammon, *J Comp Chem*, **2015**, *36*, 1536-1549.