Predicting protein dynamics of cryptochrome using generative models

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1. Introduction

Protein dynamics, the different conformations in which a protein moves within an animal's body, can provide insight into its function [1, 2]. These dynamics can be represented by the distributions of protein conformations and the stability of different structural states [3]. We are interested in the cryptochrome protein, which is one of the candidates for magnetoreception of migratory birds [4, 5]. By exploring the structural conformations of the cryptochrome, we can possibly explore whether a radical pair can readily form and whether it is important in magnetoreception [5, 6].

2. Predicting protein dynamics

Traditionally, molecular dynamics (MD) simulations have been used to sample protein conformations by computing atom-atom interactions [7, 8, 9]. However, MD is limited by the extensive computational time required to sample the full range of possible conformations for large proteins. To address this, we employ machine learning generative models to generate cryptochrome conformations using an initial structure from the European robin. Recent works proposed different machine learning algorithms that can generate protein conformations instead of running molecular dynamics simulations. In this work, we show the result of using the Str2str model [10] which uses the diffusion process to estimate the distribution of the protein structures. The resulting generated conformations, as shown in figure 1, cover regions of the structural distribution that MD simulations alone could not sample. This shows that the generated protein conformations are informative and can be used to refine the landscape of protein distribution. It can also be used as an initial protein structure in short MD simulations to verify stable conformations of the protein. However, some structures are visually different from the initial protein structure and may possibly be biologically unrealistic. In addition, we identified previously unobserved dynamic regions within the protein, as shown in figure 3, that could suggest potential functional roles in the future.

Further validation is needed to assess the biological feasibility of these generated conformations through experiments and additional simulations. Our approach can be extended to predict cryptochrome dynamics in other migratory birds and fish, offering insights into the molecular mechanisms that make cryptochrome essential for magnetoreception in migratory species.

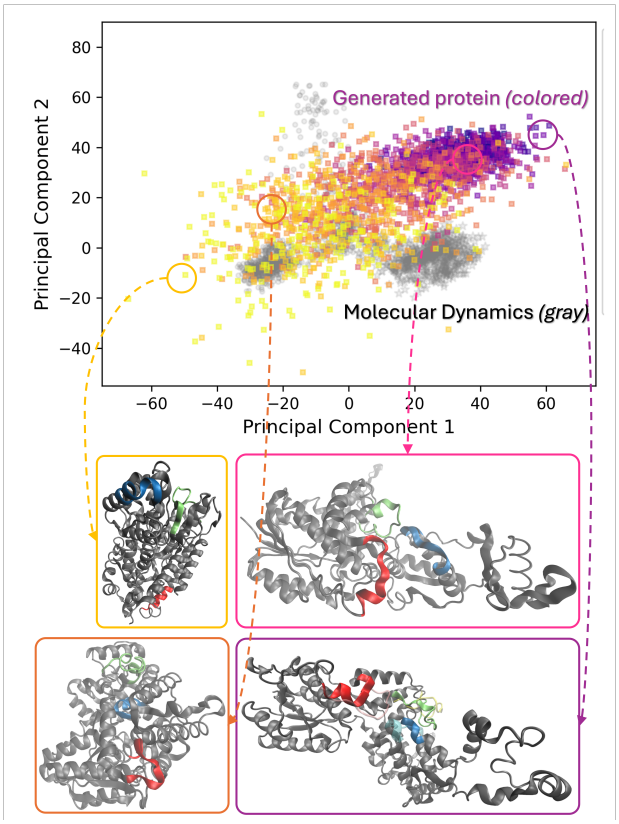

Fig. 1: Distribution of the conformations of the cryptochrome protein simulated using molecular dynamics (gray) and generated using Str2Str model (colored). Generated samples cover areas in the distribution that were not sampled by molecular dynamics. The distribution of the protein conformations were estimated from the first two principal component of back-bone atom locations of each of the residue in a centered and aligned protein. Visually, some generated samples are too compact or too unrolled compared to the protein structure from MD simulations as shown in figure 2 (b). This suggests that some conformations may not be physically realizable.

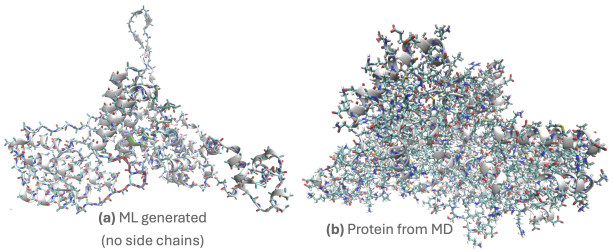

Fig. 2: Visualization of the cryptochrome protein ErCry4 from a snapshot of an MD simulation.

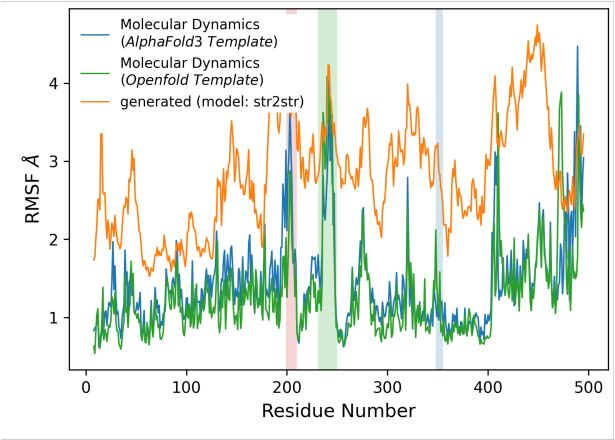

Fig. 3: Root mean square fluctuation of each residue in the cryptochrome of the european robin based on molecular dynamics (blue and green) and generated by str2str model (orange). The molecular dynamics simulations were run from an initial structure predicted by Alphafold3 [11] (blue) and an initial structure predicted by Openfold [12] (blue)

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