

Development of a hybrid All-Atom/Coarse-Grained force field to study biliverdin conformational changes within bacteriophytochromes

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Phytochromes are a large family of photoreceptor proteins composed of three domains: PAS, GAF, and PHY¹. The GAF domain binds the linear tetrapyrrole chromophore biliverdin via a cysteine residue. Biliverdin, a bile pigment derived from heme breakdown², acts as a chromophore by absorbing light in the red to far-red range. This enables phytochromes to toggle between states with absorption maxima varying by 50 to 70 nm, depending on chromophore configuration³. Biliverdin exists in two distinct conformations, known as extended and compact (**Figure 1**) and understanding the conformational changes of biliverdin within the protein is important to identify the key amino acids that stabilize each conformation. Such knowledge could guide the design of mutated protein structures to enhance the red shift, improving their usability for deep-tissue imaging.

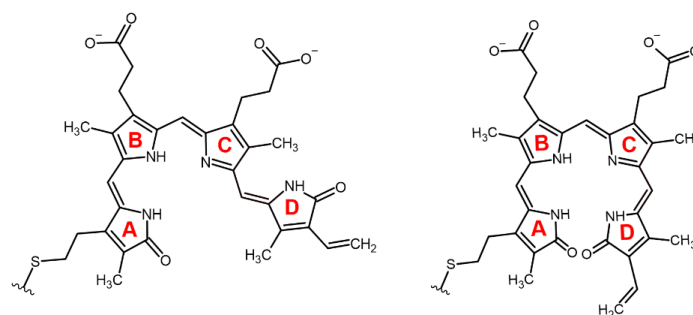


Figure 1: (left) extended biliverdin conformation and (right) compact biliverdin conformation.

However, these large-scale conformational transitions are computationally demanding. To address this challenge, we developed a hybrid all-atom/coarse-grained force field, combining ff14SB for the atomistic regions and SIRAH^{4,5} for the coarse-grained parts. This approach ensures that the cavity and the amino acids interacting with biliverdin are accurately represented while enabling efficient umbrella sampling simulations to explore the conformational landscape.

References

- (1) Chernov, K. G.; Redchuk, T. A.; Omelina, E. S.; Verkhusha, V. V. Near-Infrared Fluorescent Proteins, Biosensors, and Optogenetic Tools Engineered from Phytochromes. *Chem. Rev.* **2017**, *117* (9), 6423–6446. <https://doi.org/10.1021/acs.chemrev.6b00700>.
- (2) McDonagh, A. F. Turning Green to Gold. *Nat. Struct. Biol.* **2001**, *8* (3), 198–200. <https://doi.org/10.1038/84915>.
- (3) Shu, X.; Royant, A.; Lin, M. Z.; Aguilera, T. A.; Lev-Ram, V.; Steinbach, P. A.; Tsien, R. Y. Mammalian Expression of Infrared Fluorescent Proteins Engineered from a Bacterial Phytochrome. *Science* **2009**, *324* (5928), 804–807. <https://doi.org/10.1126/science.1168683>.
- (4) Machado, M. R.; Barrera, E. E.; Klein, F.; Soñora, M.; Silva, S.; Pantano, S. The SIRAH 2.0 Force Field: Altius, Fortius, Citius. *J. Chem. Theory Comput.* **2019**, *15* (4), 2719–2733. <https://doi.org/10.1021/acs.jctc.9b00006>.
- (5) Klein, F.; Soñora, M.; Helene Santos, L.; Nazareno Frigini, E.; Ballesteros-Casallas, A.; Rodrigo Machado, M.; Pantano, S. The SIRAH Force Field: A Suite for Simulations of Complex Biological Systems at the Coarse-Grained and Multiscale Levels. *J. Struct. Biol.* **2023**, *215* (3), 107985. <https://doi.org/10.1016/j.jsb.2023.107985>.