Title of the Presentation

Patrick Barth

Swiss Federal Institute of Technology (EPFL), Institute of Bioengineering and Ludwig Institute for Cancer Research
patrick.barth@epfl.ch

Proteins are the workhorses of life and are now often associated with a 3-dimensional architecture thanks to tremendous progress in experimental structure determination and prediction approaches. However, proteins are not static molecules. They often behave as switches, alternating between states that carry out distinct functions. Hence, switching is a powerful mechanism of biological regulation and typically occurs upon structural changes triggered by a wide variety of external stimuli (e.g. from photon absorption to the binding of drug molecules) through a process referred as allostery. Understanding how this switching behavior occurs at the molecular level remains challenging. The advent of deep learning offers new opportunities to explore and predict protein motions, but these approaches have mostly been applied to static representations of protein structures. We are developing computational approaches integrating protein design, molecular dynamics simulations and deep learning interpretation of protein motions to uncover the biophysical underpinnings of protein allosteric functions. Using these techniques, we are reprogramming the functions of natural receptors and designing new classes of switchable biosensors and ligands for basic, synthetic cell biology and therapeutic applications (e.g.[1,2,3,4,5]).

[1] Feng X., et al. (2017). Computational design of ligand-binding membrane receptors with high selectivity. Nature Chemical Biology, 13(7), 715–723.
[2] Yin J., et al. (2020). Structure of a D2 dopamine receptor–G-protein complex in a lipid membrane. Nature, 584(7819), 125–129.
[3] Chen K.-Y. M., et al. (2019). Computational design of G Protein-Coupled Receptor allosteric signal transductions. Nature Chemical Biology, 16(1), 77–86.
[4] Paradis J. S., et al. Computationally designed GPCR quaternary structures bias signaling pathway activation. Nature Communications 13, 6826 (2022).
[5] Jefferson R., et al. Computational design of ultrasensitive flexible peptide:receptor signaling complexes for enhanced chemotaxis. Nature Communications 14, 2875 (2023).