Molecular mechanisms of stochastic chromatin effector interaction dynamics
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Aim: In this interdisciplinary PhD project, we aim to develop a theoretical model based on single molecule measurements, to analyze and predict the chromatin signaling outcomes of multivalent epigenetic effector proteins.

Background: Chromatin, the nucleoprotein complex encompassing the eukaryotic genetic material, is highly chemically modified. Combinations of these post-translational modifications form a molecular language, interpreted by protein ‘readers’ or effectors, which results in a defined biological output. Due to the critical role of chromatin in cell function, differentiation and disease a deeper insight into these processes is of critical importance for the development of advanced treatments.

We recently developed a single-molecule assay based on total internal reflection microscopy (Kilic et al., Nature Commun., 2015) that allows to directly monitor effector protein interaction dynamics with modified chromatin fibers. We investigated the dynamic interactions of one such effector, heterochromatin protein 1 (HP1), with its cognate histone mark, H3 trimethylated at lysine 9 (H3K9me3) in chromatin fibers. A first study demonstrated how heterochromatin protein 1 (HP1), a key component of the gene repression machinery, is recruited to histone 3 (H3) tri-methylated at lysine 9 (H3K9me3) through multivalent interactions. These developments now set the stage for more detailed investigations into the mechanism of PTM readout by effectors.

Project: Our goal is to quantitatively predict signaling outcomes, based on a chemical understanding of effector affinity, avidity, concentration, chromatin architecture and modification state, as well as to characterize the role of noise in the system. In this PhD project, the student will perform single-molecule measurements and develop a theoretical framework to integrate quantitative interaction data to obtain a molecular description of chromatin signaling. Such a quantitative investigation will then allow us to integrate the chromatin node into quantitative models of signaling networks for systems biology studies.

If you have a background in biophysics, systems biology or related fields and are interested, send a cover letter, CV and the contact information of 3 referees to beat.fierz@epfl.ch or vassily.hatzimanikatis@epfl.ch