BIOCHEMISTRY SEMINAR

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"Transcription factor dynamics in gene expression: the long and short of it"

Abstract: Transcription factors (TFs) regulate gene expression by binding to specific DNA sequences within a complex and heterogenous chromatin environment to assemble transcriptional machinery at specific genomic loci. The mechanisms by which TFs bind to their target sequences on dynamic chromatin to regulate gene expression remains elusive. Single-molecule tracking (SMT) has emerged as a powerful approach to explore chromatin and transcription factor dynamics and their interaction in living cells. We used single-molecule tracking to directly measure the interaction dynamics of a broad spectrum of transcription factors, including steroid hormone receptors, chromatin remodelers and architectural proteins in live cells. We found that TFs follow power-law distributed binding times, suggesting that most TFs interact with chromatin with a broad range of binding affinities, rather than the conventional model of specific and non-specific binding affinities. Using machine-learning based analysis of single molecule diffusion, we show that chromatin displays two distinct low-mobility, highly sub-diffusive states. Our experimental observations are consistent with a minimal active copolymer model for interphase chromosomes. Remarkably, we find that a diverse set of transcription factors, co-regulators and remodelers also exhibit two distinct low-mobility states. Our studies further reveal that the lowest mobility state requires an intact DNA binding domain and oligomerization domains, while protein-protein interactions between TFs and coregulators define the higher mobility state. Finally, we present some recent results on how mechanical properties of the microenvironment shape chromatin mobility and TF dynamics. Together, our results elucidate how transcription factor and chromatin mobility regulates transcriptional activation in mammalian cells.

Bio: Dr. Arpita Upadhyaya is Professor of Physics and co-director of the Biophysics program at the University of Maryland, College Park. She graduated from the Birla Institute of Technology and Science, India, with a Master of Physics and Bachelor of Engineering. She obtained her Ph.D. in Physics at the University of Notre Dame where she studied the process of cellular rearrangements during morphogenesis using theories of phase separation in liquids. She was then a Pappalardo Fellow in the Department of Physics at MIT where she studied the biophysics of force generation by the cellular cytoskeleton. In her lab at UMD she investigates how cellular mechanics and forces enable a cell to sense and respond to its physical environment. Dr. Upadhyaya's lab uses high-resolution live cell imaging of single molecule movements and cellular force generation to uncover the biophysics of receptor signaling, mechanosensing and gene expression in immune cells and cancer cells.

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