Over the last few decades, we have identified the activators and repressors driving transcriptional programs in development. Further, live-imaging studies have revealed that most developmental genes are expressed in a punctuated fashion, with bursts of gene expression surrounded by periods of transcriptional silence. Yet, while previous studies have determined which bursting parameters (frequency, duration, or amplitude) are controlled by transcription factors, how this control is implemented at the molecular level remains unknown. Such knowledge is a necessary step toward reaching a predictive understanding that makes it possible to calculate transcriptional dynamics from knowledge of the arrangement of binding sites for these transcription factors on regulatory DNA.

In this talk, I will present how we are combining experimental, theoretical, and computational approaches to shed light on how the precise timing of the recruitment of transcription factors to the promoter determines output transcriptional dynamics in embryos of the fruit fly Drosophila melanogaster. Specifically, we use theoretical modeling to show how protein-protein cooperativity can bridge the widespread disconnect between fast transcription factor binding and slow transcriptional bursting. We test these predictions through a new method for simultaneously measuring transcription factor binding at target loci and the resulting output transcriptional activity of these loci in single living cells. Our approach sets the stage for uncovering an “anatomy of a burst” that maps the precise timing and ordering of the diverse molecular players that drive the transcriptional process, paving the way to developing predictive models of cellular decision-making in development.