Parsimonious Gene Regulatory Network modeling reveals mRNA half-life control of the pathogen-responsive transcriptome

Alexander Hoffmann

Signaling Systems Laboratory, San Diego Center for Systems Biology (SDCSB), University of California San Diego (UCSD), La Jolla, CA 92093, USA

Although advances in high throughput experimentation have progressed rapidly, an unresolved challenge of mammalian Systems Biology is to develop models that predict "-omic" datasets. In this study, we applied the scientific principle of parsimony to develop a mechanistic modeling framework for the complex gene regulatory network (GRN) that controls cellular responses to pathogens. We found that transcriptomic responses to pathogens are largely accounted for by just three signal-responsive transcription factors functioning surprisingly independently, rather than synergistically. However, we found that the control of mRNA halflife, both constitutively as well as signal inducibly, determines the specificity of cellular responses to pathogens, indicating the limitations of promoter-only models for gene expression. We anticipate that the parsimonious framework will allow for an increasingly detailed understanding of signal responsive gene expression programs, and the linking of "top-down" and "bottom-up" Systems Biology approaches to predict complex biological function.