Title: Variability in cell-to-cell signaling dynamics to transcriptional regulatory phenotype

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Dynamics in signaling pathways and transcriptional regulatory response are variable within isogenic cell population responding to same stimulus, and within the same cell over a repeated stimulus. However, the overall cellular decision making process is robust. Computational efforts, in general, have typically considered the variability at the signaling and gene regulatory levels in isolation from one another. Here we seek to bridge the two scales with the goal of identifying the information encoding aspects of the signaling dynamics that significantly alter gene regulation. We employ a combination of Monte Carlo simulations, variance based global sensitivity analysis, and decision tree analysis to explore the role of encoded information in dynamical features of multiple transient signaling pathways. In addition, we also develop a framework to quantify the amount of information transfer in these pathways and identify key information elements that trigger a specific downstream response. Simulations of cell-to- cell variability in signaling dynamics reveals two distinct downstream regulatory phenotypes sustained vs transient transcription factor activation. Using decision tree analysis, we identified the key dynamical features of signaling dynamics that control this digital type of downstream response. In addition, the effects of global variability were elucidated by global sensitivities. The results show that dynamical features of signaling dynamics play a significant role in regulating the downstream response and demonstrate that network interactions transform the variability in signaling dynamics to yield a structured variation and robustness in gene regulation.