Mutational robustness of gene regulatory networks: interplay between transcription factor – target gene and protein-protein interactions

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An organisms' persistence in the face of changing conditions requires a balance between robustness and evolvability. This is particularly important for developmental processes, in which gene regulatory networks (GRNs) play a key role. In this talk we investigate the effects of changes in network interactions (network rewiring) on the behaviour of GRN's.

In a GRN, transcription factors (TFs) regulate each others expression, and that of downstream target genes. Here we analyze the robustness of GRNs upon rewiring of the network of interactions, i.e. mutational robustness. In most modeling studies of robustness of GRNs, protein-protein interactions between TFs are not included, only regulatory interactions between TFs and their target genes. However, because TFs often regulate DNA as dimers, it is important to understand the impact of these protein-protein interactions on network stability and evolvability. In particular, the way in which different types of mutations reinforce or compensate each other is an important aspect. Compensatory effects of different types of mutations have indeed been observed experimentally, e.g. the evolution of transcriptional circuits where a combination of a change in cis-regulation and protein-protein interaction leads to an alternative GRN with the same function has been described (Tsong 2006).

Our approach consists of modeling GRNs using ordinary differential equations containing transcriptional regulation, protein-protein interactions of transcription factors, and decay terms. We study the mutational robustness of ensembles of randomly generated networks upon network rewiring. The network behaviour turned out to be more sensitive to rewiring in protein-protein interactions as compared to rewiring in regulatory interactions. Furthermore, robustness of networks to mutations in transcription factor – target gene interactions seems to be correlated with robustness to mutations in protein-protein interactions.
Importantly, analysis of combinations of network rewiring steps (where a mutation is followed by a second mutation) indicates that a combination of a protein-protein rewiring and a transcription factor-target gene rewiring has a much higher probability to be compensatory (i.e. to lead to an overall small effect on the resulting stable state) than combinations of two protein-protein rewiring steps.

We place our results in perspective by comparison with networks without protein-protein interactions and by comparison with parameter sensitivity analysis. As a test case, we do a quantitative study of rewiring effects for the model of a gene regulatory network that controls floral organ formation in Arabidopsis thaliana (van Mourik, submitted).

References:
Tsong et al., Nature 2006, 443, 415-420.
Van Mourik et al., revised manuscript submitted to BMC Systems Biology.