



The Symphony of Gene Regulation

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Summary

Genomes of even the simplest of organisms are comprised of many genes, the units of genetic information that are stored in the DNA code. One of the biggest challenges in the post-genomic era is to infer biological function from DNA sequence. A genome is like a musical composition. It is comprised of many parts, some of which are played at the same time while others must be played at different times. Therefore, the correct execution of a symphony requires an orchestra to play in harmony - the score dictates 'who' plays 'what' and most importantly 'when'. Likewise, the observed complexity of biological functioning lies in the way genes are directed and organized. The functioning of a single gene only makes sense when we take into account 'when' the gene is active and 'whom' it interacts with.

In order to advance our understanding of gene regulation (when?) and gene interaction (with whom?) we have studied two different biological systems: Infection of the human host with HIV-1 and transcriptional regulation in baker's yeast.

For HIV-1 infection we have studied the interaction network that arises from the multitude of cellular interactions that take place between viral and human genes and proteins during infection. We have found that the topology of this network, in terms of global structure and local re-occurring patterns can be used to study HIV-1 infection. In specific we found that the network structure shows how the cellular machinery of the human immune system tries to inhibit virus infection and replication, and that the virus in turn tries to evade the host's immune response. Taken together our results shed light on how HIV-1 infection occurs by hijacking the host cellular machinery. In addition, using protein interaction data and a bioinformatics algorithm we predicted novel cell surface proteins in human lymphocytes that potentially interact with HIV. This set constitutes a well-founded starting point for experimental testing of cell and tissue susceptibility to different HIV strains.

To understand individual gene interactions and how control of gene expression occurs we studied transcriptional regulation in baker's yeast by measuring the activity of genes in individual cells. We focused on the promoter region of the DNA to unravel the 'language' of transcriptional control. Assisted by a quantitative model that we developed, we found that phenotypic cell-to-cell variability, or 'noise', in gene activity between cells that have the same genotype is a result of specific transcriptional mechanisms that are encoded in the promoter DNA sequence. We showed that genes have a unique relationship between their transcriptional activity and their noise.

Next, using a micro-fluidic microscopy platform measuring single-cell expression of a set of synthetic designed promoters over time we investigated the effect of two different DNA sequence changes on temporal gene expression. We found that both adding a binding site of a transcriptional activator and adding a sequence that increases the accessibility of the DNA to activators increase transcriptional activity, however with opposing effects on the cell-to-cell variability. Evolution can therefore operate on several mechanisms for changing gene expression that result in systems with different stochastic properties. Taken together we found that even very small changes in the promoter DNA sequence can give rise to large differences in the noise of gene expression.

Hence, the work presented in this dissertation has contributed to the understanding of how DNA sequence encodes for gene activity and its variability between cells, as well as how interactions of genes give rise to complex network structures.