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### The symphony of gene regulation

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## Chapter 6 Conclusions

This dissertation contributes to our understanding of gene regulation, both in terms of individual interactions as well as from a topological perspective, and how gene expression noise plays a crucial role in any gene regulatory system. Our contributions are both in the design and application of computational models that generate biological hypotheses as well as in testing them using specific wet-lab experiments.

The first contribution of this dissertation is in understanding how gene regulation is encoded in the wiring of the gene regulatory and protein interaction networks during HIV infection of the human host. We quantify regulatory structure using network topology and show that large-scale network properties and small-scale network patterns can explain specific biological behavior, such as human immune response and virus immune system evasion.

The second contribution of this dissertation is in understanding how individual gene regulatory interactions are encoded in DNA sequence in yeast. Specifically, we make use of the stochastic nature of gene expression to infer mechanisms of gene regulation from steady state protein distributions and temporal gene activity. We use computer simulations as well as wet-lab measurements to study the mapping between promoter DNA sequence, gene expression and gene expression noise, by measuring single-cell activity of a set of native, mutant and synthetically designed promoters *in vivo* and *in silico*.

We found that there are multiple ways to achieve the same change in the mean expression level of a gene, but with different effects on the cell-to-cell variability of gene expression in yeast. Our computer model suggests that this is the result of different, albeit DNA encoded, mechanisms of gene regulation. Notably, we found that different native promoters can have the same mean expression level, but vastly different amounts of noise by having different DNA sequence. Moreover, we found that the way in which noise changes with expression, when a gene is induced, is gene-specific and highly dependent on promoter DNA sequence.

We found that a combination of activation and repression can result in a unique transcriptional state of low expression and low noise, where usually low expression is accompanied with high noise. In addition we found that further noise reduction can be achieved by protecting against extrinsic noise from the regulator. Our computer simulations suggested that coupling between activator and repressor, for example when they are the same molecule, would reduce the sensitivity to fluctuations in the activity of the transcription factor. Measurements in the lab confirmed this prediction. To the best of our knowledge we are the first to identify such a mechanism.

In addition, we investigated the effect on the temporal dynamics of gene expression and steady state gene expression noise of two different DNA encoded mechanisms of gene expression change in yeast. In specific, we measured, using time-lapse microscopy and flow-cytometry, the gene expression activity of a set of synthetically designed promoters in which gene expression was increased through increasing the binding site affinity of the activating TF or by decreasing the binding affinity of nucleosomes that compete for binding with the TF. We hypothesized that the first mechanism would increase the time the gene was active and that the second mechanism would increase the frequency of activity. Computational models suggested that the first mechanism would increase the noise while the second mechanism would decrease the noise, where both mechanisms would cause an increase in mean expression level. Measurements of temporal gene expression in microscopy and steady state protein distributions in flow-cytometry confirmed our hypotheses.

The work presented in this dissertation has contributed to the understanding of how DNA sequences encode for gene expression, gene expression noise, and the interaction between genes, and in turn how gene interactions give rise to complex network structures. It will be very interesting to use this knowledge to develop a quantitative model that predicts, from DNA sequence, expression and noise in a gene network in which multiple genes regulate each other.