Title of Project:	Unravelling and modelling mechanisms that control noise in gene expression using RNA-binding proteins in S. cerevisiae
Cell Mechanism Supervisor Name	Sander Granneman
Quantitative Supervisor Name	Peter Swain

Summary of project

Microbes are constantly subjected to changes in their environment and have to rapidly alter their transcriptome to adapt efficiently. Post-transcriptional regulation by RNA-binding proteins (RBPs) plays a key role during this adaptation. By shaping the expression of stress-responsive genes, RBPs are thought to enable organisms to respond faster to environmental changes than transcriptional control alone.

We have recently shown in S. cerevisiae that RBPs Nrd1 and Nab3 can pre-maturely terminate transcription of stress-responsive genes, which has a pronounced effect on their steady-state expression kinetics. The biological significance of this observation, however, remains unclear. The ability to accurately regulate levels of expression during stress is often limited by the stochastic nature of transcriptional regulation. This stochasticity can lead to substantial cell-to-cell variability (noise) in gene expression, which can be detrimental to fitness.

We hypothesize that Nrd1/Nab3 may affect the kinetics of gene expression to reduce this noise. Our recent time-lapse microscopy studies of cell-to-cell variability in mutant strains strongly support this model.

Therefore, the goals of our project are to quantify the extent of noise suppression and unravel the mechanism behind it, to develop a single-cell reporter of transcriptional activity to determine if noise suppression occurs during transcription, and to determine how prevalent this activity might be in yeast through finding the requirements for efficient noise suppression using a mathematical model.

The project is interdisciplinary, involving yeast genetics, biochemistry, quantitative microscopy, mathematical modelling, and analysis of both single-cell time-lapse data and large next-generation sequencing data.

What quantitative skills will the student acquire or develop during their PhD project?

The student will learn how to employ CRISPR to make genomic mutations in yeast, to perform CRAC analyses to monitor the interaction between RBPs and their direct RNA substrates, to generate next generation sequencing libraries, to perform time-lapse microscopy experiments for quantifying cell-to-cell variability in RNA and protein levels, and to analyse the resulting data using the Python and R programming languages.