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The Yeast Metabolic Cycle, heterogeneous gene expression within synchronized cultures

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The Yeast Metabolic Cycle (YMC) is a model system of temporal compartmentalization of cellular and metabolic processes. After starvation and upon continuous glucose feeding in limiting concentration, cell populations of prototrophic strains of *Saccharomyces cerevisiae* undergo synchronized glycolytic and respiratory oscillations over time[1] characterizing the cycle. Additionally, previous studies showed that transcription and transcript levels of genes associated with particular pathways alternate during the YMC[1,2,3,4,5]. Over the years, the YMC has become a popular model system to study the principles underlying biological rhythms and clocks[6].

While most studies carried out on the YMC focused on understanding how synchronicity is achieved by looking at whole cell populations, often using sequencing techniques, here we demonstrate the importance of studying the YMC using single cell techniques. By the use of single molecule RNA fluorescence in situ hybridization[7], we examined pre-ribosomal RNA gene expression by RNA polymerase I in the synchronised YMC cell population. We obtain evidence for sub-populations of cells expressing different pre-rRNA transcript levels within synchronized cultures, supporting extensive cell-to-cell heterogeneity[5].

Next, we explored whether genes transcribed by RNA polymerase II behave in a similar way, using multiplex-RNA-FISH experiments on antagonistic oscillating transcripts of three recognized periodic genes[1], during distinct phases of the YMC. We observed similar trends in median transcript levels compare to measures formerly acquired by microarray and sequencing studies[1,5]. However, global changes in transcript levels along the YMC correspond to oscillations in transcription and transcript levels within cells, combined with a fluctuation in the number of cells within the population expressing these particular transcripts at variable levels. In other words, we detect variation in the gene expression patterns in individual cells from synchronized cultures. The non-expressing cells within the YMC population support a model where transcription itself is neither required nor sufficient to maintain the Yeast Metabolic Cycle.

We aim to fit a stochastic mathematical model of transcription to our quantitative data, to investigate further the concept of intrinsic timekeeping[8], explore how stochasticity might influence synchrony and describe the effect of changes in metabolism on transcription.

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