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Glycolytic Oscillations in Individual Yeast Cells

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Abstract

Oscillations in the concentration of yeast glycolytic intermediates have been intensively studied since the 1950s, but these studies have so far been limited to observations of average oscillatory behavior in synchronized cultures. Hence, it has remained unknown whether the onset of oscillations is a collective property of the population which requires a high cell density, or if individual cells can oscillate also in isolation. To determine the mechanisms behind oscillations, cell-cell interactions and synchronization, and to investigate the role of cell-cell heterogeneity, oscillations have to be studied on the single-cell level.

The aims of this project were to determine whether individual cells in isolation can oscillate and if there is large heterogeneity among individual cells, to determine if a fluid flow affects the oscillatory behavior, to identify the precise conditions required for oscillations to emerge in individual cells, to investigate the mechanism behind oscillations, and to elucidate the mechanism behind synchronization, its robustness to cell heterogeneity and its universality with respect to different chemical species.

In this work it was shown that glycolytic oscillations can be induced and studied in individual, isolated yeast cells by combining optical tweezers for cell positioning, microfluidics for environmental control and fluorescence microscopy for detection. My single-cell data revealed large heterogeneity and four categories of cell behavior were identified. It was also verified that the oscillatory behavior was determined by the concentrations of glucose and cyanide in the extracellular environment rather than the flow rates used in the microfluidic flow chamber.

Varying the concentrations of glucose and cyanide, the precise conditions for oscillations to emerge in individual cells were determined and it was shown that individual cells can oscillate also at conditions where no oscillations are detected in populations. This indicates that loss of oscillations in a population can be caused by desynchronization rather than by loss of oscillations in individual cells. Investigation of single-cell responses using a detailed kinetic model showed that the onset of oscillations could be described by allosteric regulation of the enzyme phosphofructokinase by AMP and ATP.

To determine the mechanism behind synchronization and to assess its robustness and universality, entrainment of oscillations in individual yeast cells by periodic external perturbations was investigated. It was found that oscillatory cells synchronize through phase shifts and that the mechanism is insensitive to cell heterogeneity (robustness) and similar for different types of external perturbations (universality).

The results presented in this work have advanced our understanding of the complex set of reactions in energy metabolism and the mechanisms through which cells oscillate, communicate, and synchronize. Pursuing these studies will hopefully not only give further information about glycolysis in yeast, but also about energy metabolism, oscillations, and communication in other biological systems, such as oscillatory insulin secretion from islets of β-cells.

Keywords: Optical manipulation, microfluidics, fluorescence microscopy, single cell analysis, *Saccharomyces cerevisiae*, glycolysis, oscillations, NADH, heterogeneity, synchronization, robustness, universality
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