# The yeast metabolic cycle is coupled to cell division cycle Start across diverse strains

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**The yeast metabolic cycle is a synchronous rhythm observed in *Saccharomyces cerevisiae* grown under slow-growth aerobic chemostat conditions. It is known to couple to the cell division cycle, despite both cycles having different frequencies. Multiple interpretations have been proposed for the nature and purpose of this coupling. By quantitatively measuring the metabolic and cell cycle oscillations of multiple strains, we demonstrate strain-specific coupling between metabolic shifts and DNA replication. These data support a model in which metabolic shifts couple to cell cycle Start and the ratio of time spent in different metabolic cycle phases is proportional to the growth rate.**

***Keywords* — Saccharomyces cerevisiae, yeast metabolic cycle, cell cycle, coupled oscillations, systems biology**

## I. Introduction

The yeast metabolic cycle has been observed since 1969 [1] and consists of a synchronous oscillation in which yeasts growing aerobically alternate between building storage carbohydrates during a low-oxygen-consumption phase (LOC) and their rapid consumption in a high-oxygen-consumption phase (HOC), with large oscillations in the transcriptome content [2,3]. The cell division cycle couples to this oscillation despite having a different period from the yeast metabolic cycle. Specifically, a subpopulation of cells passes through cell cycle Start once per metabolic cycle [4]. The nature of this coupling has been a matter of debate in the scientific literature with DNA replication observed in both HOC and LOC depending on the strain examined and growth conditions used [4]. Understanding the nature of and reasons for this coupling stands to shed light on the nature of coupled oscillations in biological systems.

## II. Methods & Results

### A. Metabolic Cycle Analysis

Previous research on the yeast metabolic cycle was performed in different strains under different chemostat conditions. We wished to determine which behaviors were invariant across strains and which showed strain-specific variation. We selected two previous lab strains, as well as two wild isolates, to measure and analyze yeast metabolic cycle and cell division cycle events. These strains were grown under identical conditions at a set of varied growth rates. We measured yeast metabolic cycles via quantitative measurements of dissolved oxygen concentration.

We found that the HOC phase length changed little with decreasing growth rate, whereas LOC phase length extends asymptotically as the growth rate slows. This quantitative relationship was invariant across all strains, although the period and dissolved oxygen profile of the metabolic cycle differed between strains. Closer examination revealed that the fraction of time spent in HOC has a positive relationship with growth rate, projecting to ~100% at the growth rate associated with the switch from respiration to fermentation.

### B. Cell Cycle Analysis

The cell division cycle was analyzed across strains and growth rates by sampling and fixing cells at 10-minute intervals over the course of several yeast metabolic cycles. We stained for DNA content with SYTOX Green to identify populations of cells in G1 (before DNA replication) and S/G2 (after replication) at each time-point. We found DNA replication could occur in LOC or HOC depending on the strain and growth rate. Each strain, however, has a characteristic delay between entry into HOC phase and initiation of DNA replication. This delay changes very little with differences in HOC length or growth rate.

## III. Conclusions

All tested yeast strains exhibited a metabolic cycle, which primarily varies with growth via changes in the length of LOC and exhibits a pulse of DNA replication once per cycle. This pulse comes after a strain-specific delay following HOC entry and can occur in either LOC or HOC.

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