# A Wonderful Christmas with Mysterious Oscillations[1]

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It has been known for many decades that budding yeast cells can spontaneously synchronize their metabolism and cell division when grown in continuous cultures. This synchrony is most commonly and conveniently observed as oscillations in the oxygen consumption of the culture that can last over many weeks, as long as the culture is fed with fresh growth media. Yet the complexity of this mysterious phenomenon has resisted scientific curiosity for many decades and shifted it to the periphery of mainstream research.

My work on cell growth brought me to these mysterious oscillations, and I became fascinated by them and their challenge. At the time, it was suggested that their role is to separate DNA replication in time from the periods of intense oxygen consumption and reactive oxygen species production, and thus reduce the mutation rate. This sounded simple and intuitively appealing, so I did not pay much attention to the controversy in the literature. I just liked the appealing idea. Yet, when I started synchronizing yeast in the lab and looking at my own data, I could not reconcile them with restricting DNA to the low oxygen consumption phase. After checking meticulously everything in my experiments and not finding artifacts, I finally read carefully enough the published evidence and found that it was consistent with my data (Slavov and Botstein, 2011) but could not convince me that DNA replication is sequestered away from the phase of high oxygen consumption. Now that made the whole phenomenon all that more mysterious and compelling to me. I really wanted to understand these oscillations!

I analyzed all my data and came up with my own hypothesis, but that was not enough; the complexity of the phenomenon could have misled me, so I needed a direct experimental test, ideally in a simple system that we understand well. It was very clear both from my data and data from many other labs published over 4-5 decades that the metabolic cycling in continuous cultures is correlated with partial cell division cycle synchrony. Thus, my idea was to simply synchronize cells with respect to their cell division cycle and measure oxygen consumption. Measurements of oxygen consumption during the division cycle were done in the 1960-1980s, but the data was from cells that mostly ferment (a very different growth condition) and not nearly as quantitative as what can be achieved nowadays. After considering all methods for synchronizing the cell division cycle of yeast, I decided to use a nutritional pulse as the most physiological method with the

[1] The published version of this essay can be found at: https://www.pubchase.com/essays

fewest artifacts. Instead of producing the intended cell division cycle synchrony, however, my experiments resulted in metabolic cycling without cell division cycling! At first, of course, that was a great surprise. Multiple repetitions of the experiment turned the observation into an exciting finding. Doing the sampling was time-consuming and demanding in the extreme, but I was so eager to know what was happening that I spent Christmas Day of 2010 collecting samples, the ones that ultimate were used for our article. It is still the longest, the happiest and the most exciting Christmas Day I have had in my life.

The results of the experiments gave an answer that I find very convincing. I felt we had learned something exciting, at least incredibly exciting for me, and I wanted to share it with colleagues who might be interested in it and incorporate their feedback before we submitted our article for review. I was shocked by the emotional responses that our work elicited, but that is a subject for another essay.

In retrospect, the work behind our *PNAS* article (Slavov *et al*, 2011) was a thrilling and rewarding journey. It certainly did not resolve the whole mystery but gave us insightful glimpses into the complexity of metabolic regulation and a delightfully memorable Christmas Day, one that I would love to repeat.

# References

Slavov N, Botstein D (2011) Coupling among growth rate response, metabolic cycle, and cell division cycle in yeast. *Mol Biol Cell* **22**: 1997–2009

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