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Limited by sensing-A minimal stochastic model of the lag-phase during diauxic growth

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Abstract

Many microbes when grown on a mixture of two carbon sources utilise first and exclusively the preferred sugar, before switching to the less preferred carbon source. This results in two distinct exponential growth phases, often interrupted by a lag-phase of reduced growth termed the *lag-phase*. While the lag-phase appears to be an evolved feature, it is not clear what drives its evolution, as it comes with a substantial up-front fitness penalty due to lost growth. In this article a minimal mathematical model based on a master-equation approach is proposed. This model can explain many empirically observed phenomena. It suggests that the lag-phase can be understood as a manifestation of the trade-off between switching speed and switching efficiency. Moreover, the model predicts heterogeneity of the population during the lag-phase. Finally, it is shown that the switch from one carbon source to another one is a sensing problem and the lag-phase is a manifestation of known fundamental limitations of biological sensors.

Keywords: diauxic growth, Brownian computers, stochastic systems, biological sensors

1. Introduction

Diauxic growth is the phenomenon whereby a population of microbes, when presented with two carbon sources, exhibits bi-phasic exponential growth intermitted by a *lag phase* of minimal growth. Originally, the phenomenon was described by Monod [1] demonstrating diauxie with glucose and lactose in *E.coli*. In his experiments Monod showed that the population first grows exponentially on glucose until all glucose is exhausted, then enters the lag-phase of no growth before resuming exponential growth on lactose. The duration of the lag-phase can be substantial (order of magnitude of a generation time).

Diauxic growth and the network that controls it has since been subject to intense experimental [2, 3, 4, 5, 6, 7, 8] and theoretical [5, 9, 10, 11] investigation. There are two main mechanisms responsible for two phase growth in bacteria, both of which depend on the *phosphotransferase* (PTS) system [12]: (*i*) Regulation of metabolic genes via global transcription regulators, especially cAMP. (*ii*) Direct uptake mediated inducer exclusion. In *E.coli* the levels of dephospho $EIIA^{glc}$ increase during glucose uptake. $EIIA^{glc}$ inactivates the uptake of the secondary sugars (i.e. lactose) and in this way prevents the induction of the relevant uptake system.

Diauxic growth is generally believed to be an adaptation to optimise growth in multi-nutrient environments. Indeed, there is a clear argument that sequential uptake is beneficial in that it maximises the share of the higher quality nutrient for the lineage. Yet, by the same token one would have to conclude that a lag-phase is detrimental in that it is not at all conducive to the