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Comparative analysis of some models of gene regulation in mixed-substrate microbial growth

Atul Narang*

Department of Chemical Engineering, University of Florida, Gainesville, FL 32611-6005, USA

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Abstract

Mixed-substrate microbial growth is of fundamental interest in microbiology and bioengineering. Several mathematical models have been developed to account for the genetic regulation of such systems, especially those resulting in diauxic growth. In this work, we compare the dynamics of three such models (Narang, 1998a. The dynamical analogy between microbial growth on mixtures of substrates and population growth of competing species. Biotechnol. Bioeng. 59, 116–121; Thattai and Shraiman, 2003. Metabolic switching in the sugar phosphotransferase system of *Escherichia coli*. Biophys. J. 85(2), 744–754; Brandt et al., 2004. Modelling microbial adaptation to changing availability of substrates. Water Res. 38, 1004–1013). We show that these models are dynamically similar—the initial motion of the inducible enzymes in all the models is described by the Lotka–Volterra equations for competing species. In particular, the prediction of diauxic growth corresponds to "extinction" of one of the enzymes during the first few hours of growth. The dynamic similarity occurs because in all the models, the inducible enzymes possess properties characteristic of competing species: they are required for their own synthesis, and they inhibit each other. Despite this dynamic similarity, the models vary with respect to the range of dynamics captured. The Brandt et al. model always predicts the diauxic growth pattern, whereas the remaining two models exhibit both diauxic and non-diauxic growth patterns. The models also differ with respect to the mechanisms that generate the mutual inhibition between the enzymes. In the Narang model, mutual inhibition occurs because the enzymes for each substrate enhance the dilution of the enzymes for the other substrate. The Brandt et al. model superimposes upon this dilution effect an additional mechanism of mutual inhibition. In the Thattai and Shraiman model, the mutual inhibition is entirely due to competition for the phosphoryl groups. For quantitative agreement with the data, all models must be modified to account for specific mechanisms of mutual inhibition, such as inducer exclusion.

Keywords: Mathematical model; Mixed substrate growth; Diauxic growth; Lac operon; Lotka–Volterra model

1. Introduction

When microbial cells are grown in a batch culture[1] containing a mixture of two carbon sources, they often exhibit *diauxic* growth, which is characterized by the appearance of two exponential growth phases separated by a lag phase called *diauxic lag* (Monod, 1947). The most well-known example of this phenomenon is the batch growth of *Escherichia coli* on a mixture of glucose and lactose (Fig. 1a). Early studies by Monod showed that in this case, the two exponential growth phases reflect the sequential consumption of glucose and lactose (Monod, 1942). Moreover, only glucose is consumed in the first exponential growth phase because the synthesis of the *peripheral* enzymes for lactose is somehow abolished in the presence of glucose. These enzymes include lactose permease, which catalyzes the transport of lactose into the cell, and β-galactosidase which catabolizes the intracellular lactose into products that feed into the glycolytic pathway. In contrast to the peripheral enzymes for lactose, which are uniquely associated with lactose, the enzymes of the glycolytic pathway are common to both glucose and lactose.

During the period of preferential growth on glucose, the peripheral enzymes for lactose are diluted to very small

*Tel.: +1 352 392 0028; fax: +1 352 392 9513.
E-mail address: narang@che.ufl.edu.
URL: http://narang.che.ufl.edu.

[1]Batch cultures refers to growth of the cells in a well-stirred container with no inflow or outflow of nutrients and cells.

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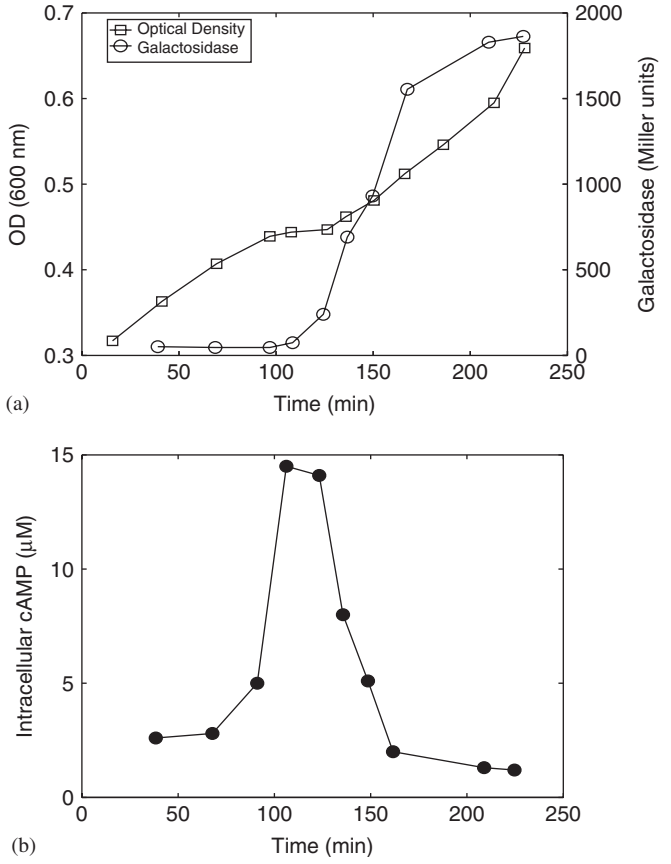

Fig. 1. Diauxic growth of *E. coli* on a mixture of glucose and lactose (Inada et al., 1996): (a) The optical density (□) shows two exponential growth phases separated by a diauxic lag ($60 \lesssim t \lesssim 160$ min). The levels of β-galactosidase (○), a peripheral enzyme for lactose, remain low until the beginning of the diauxic lag. (b) Evolution of the intracellular cAMP levels during the experiment shown in (a). The intracellular cAMP levels (●) during the first phase of exponential growth on glucose ($t \lesssim 60$ min) are similar to the intracellular cAMP levels during the second phase of exponential growth on lactose ($t \gtrsim 160$ min).

levels. The diauxic lag reflects the time required for the cells to build up the peripheral enzymes for lactose to sufficiently high levels. After the diauxic lag, one observes the second exponential phase corresponding to consumption of lactose.

It turns out that even in the absence of glucose, the peripheral enzymes for lactose are synthesized only if lactose is present in the environment. The mechanism for the synthesis or *induction* of the lactose-specific enzymes in the presence of lactose and absence of glucose was discovered by Monod and coworkers (Jacob and Monod, 1961). It was shown that the genes corresponding to the peripheral enzymes for lactose are contiguous on the DNA and transcribed in tandem, an arrangement referred to as the *lac* operon. In the absence of lactose, there is no transcription of the *lac* operon because a molecule called the *lac* repressor is bound to a specific site on the *lac* operon called the *operator*. This prevents RNA polymerase from attaching to the operon and initiating its transcription. In the presence of lactose, transcription of the *lac* operon is triggered because allolactose, a product of β-galactosidase, binds to the repressor. The allolactose-repressor complex is incapable of binding to the operator, which then becomes available for transcription (Ptashne and Gann, 2002, Chapter 1).[2]

Given the foregoing mechanism for *lac* transcription in the presence of lactose alone, it seems plausible that the key to the resolution of the glucose–lactose diauxie is the mechanism by which the transcription is abolished in the presence of glucose. This mechanism is not fully understood (Stülke and Hillen, 1999). Until recently, there were two models for glucose-mediated inhibition of *lac* transcription:

(1) *cAMP activation*: This model postulates that a complex consisting of cyclic AMP (cAMP) and catabolite repression protein (CRP) must bind to a specific site on the *lac* operon before it can be transcribed. When glucose is added to a culture growing on lactose, the cAMP levels somehow decrease. This reduces the binding of the cAMP-CRP complex to the *lac* operon, thus diminishing its transcription.
(2) *Inducer exclusion*: According to this model, enzyme IIA^{glc}, a peripheral enzyme for glucose, is dephosphorylated in the presence of glucose. The dephosphorylated enzyme IIA^{glc} inhibits lactose uptake by binding to the lactose permease, the transport enzyme for lactose. This reduces the intracellular concentration of allolactose, and hence, the transcription rate of the *lac* operon.

Experiments by Aiba and coworkers have shown that the cAMP activation model is not tenable (Inada et al., 1996). The cAMP levels are the same during growth on glucose and lactose (Fig. 1b). Moreover, the *lac* operon is not transcribed even if cAMP is added to a culture growing on glucose and lactose, and last but not the least, diauxic growth persists in mutants whose machinery for cAMP activation has been completely abolished (Inada et al., 1996, Figs. 4 and 5). This has led to the hypothesis that inducer exclusion alone is responsible for inhibiting *lac* transcription. However, the data shows that inhibition of lactose uptake by inducer exclusion is relatively mild. Indeed, in *E. coli* ML30, the activity of lactose permease is inhibited no more than ~40% at saturating concentrations of glucose (Cohn and Horibata, 1959a, Table 2). More generally, Saier and coworkers found that in *S. typhimurium*, inducer exclusion by glucose inhibits the synthesis of the peripheral enzymes for melibiose, glycerol, maltose,

[2]A similar mechanism serves to induce the genes for glucose transport (Plumbridge, 2003, Fig. 4). In the absence of glucose, transcription of the *ptsG* gene, which codes for the transport enzyme, $IIBC^{glc}$, is inhibited because a repressor molecule called Mlc is bound to the operator site on the gene. Upon entry of glucose, $IIBC^{glc}$ is dephosphorylated. The dephosphorylated $IIBC^{glc}$ sequesters Mlc away from the operator, thus liberating the gene for transcription.