Mathematical Biosciences 255 (2014) 33–42

Contents lists available at ScienceDirect

Mathematical Biosciences

journal homepage: www.elsevier.com/locate/mbs

Understanding bistability in yeast glycolysis using general properties of metabolic pathways

Robert Planqué [a,*], Frank J. Bruggeman [b], Bas Teusink [b], Josephus Hulshof [a]

[a] Department of Mathematics, VU University Amsterdam, De Boelelaan 1081, 1081 HV Amsterdam, The Netherlands
[b] Molecular Cell Physiology, Netherlands Institute of Systems Biology, VU University Amsterdam, De Boelelaan 1085, 1081 HV Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 29 November 2013
Received in revised form 3 June 2014
Accepted 4 June 2014
Available online 21 June 2014

Keywords:
Biochemical pathways
Differential equations
Bifurcation analysis
Glycolysis
Yeast

ABSTRACT

Glycolysis is the central pathway in energy metabolism in the majority of organisms. In a recent paper, van Heerden et al. [1] showed experimentally and computationally that glycolysis can exist in two states, a global steady state and a so-called imbalanced state. In the imbalanced state, intermediary metabolites accumulate at low levels of ATP and inorganic phosphate. It was shown that Baker's yeast uses a peculiar regulatory mechanism—via trehalose metabolism—to ensure that most yeast cells reach the steady state and not the imbalanced state.

Results: Here we explore the apparent bistable behaviour in a core model of glycolysis that is based on a well-established detailed model, and study in great detail the bifurcation behaviour of solutions, without using any numerical information on parameter values.

Conclusion: We uncover a rich suite of solutions, including so-called imbalanced states, bistability, and oscillatory behaviour. The techniques employed are generic, directly suitable for a wide class of biochemical pathways, and could lead to better analytical treatments of more detailed models.

Background

Cells need a robust supply of energy to maintain themselves and grow. The central pathway that provides cells with energy is glycolysis. In glycolysis, glucose is converted into pyruvate with a net production of 2 adenosine 5′-triphosphate (ATP) molecules per molecule of glucose. This net production is achieved in "lower" glycolysis after a first ATP investment in "upper" glycolysis (Fig. 1). Such "turbo-design" of glycolysis, used by many organisms, is inherently risky [2]. If lower glycolysis does not keep up with upper glycolysis, metabolic intermediates may accumulate, a situation we will refer to as an *imbalanced state* [1]. This leads to reduced ATP production, lower growth rates, even leading to cell death [3]. This phenotype has been observed in regulatory compromised pancreatic β-cells [4] and also in *Saccharomyces cerevisiae* yeast [5].

In yeast, an imbalanced state occurs in cells with a defect in trehalose 6-phosphate synthase (Tps1). Such cells cannot convert glucose 6-phosphate (G6P) into trehalose (see Fig. 1), and are not able to grow on excess glucose. These Tps1Δ mutants show an accumulation of the glycolytic intermediate fructose 1,6-bisphosphate (Fbp) at low concentrations of ATP and inorganic phosphate P_i.

Just how the trehalose pathway contributes to the overall functioning of glycolysis has been debated for a long time [6–8]. In a recent paper [1], van Heerden and colleagues have shown, using a combination of modelling and experiments, that trehalose metabolism acts as a transient regulatory mechanism, steering the dynamics of glycolysis away from the imbalanced state.

The model in [1] builds on a detailed model for yeast glycolysis [3] that had been used in a number of recent papers [9–13]. In [1], the model was extended to incorporate the usually neglected P_i dynamics. The first main result that came out of the numerical study was that the Tps1Δ mutants showed coexistence of two stable attracting states: next to the expected imbalanced state, a steady state corresponding to normally functioning glycolysis was also found. Whether dynamics converged to one state or the other was only found to depend on initial conditions.

This surprising result, which was verified experimentally and was even found in cells with normal trehalose biosynthesis [1], inspired the development of a smaller version of the detailed glycolysis model that could be studied analytically. In this paper, we study this core model of yeast glycolysis that is limited to the

* Corresponding author. Tel.: +31 705987832.
E-mail address: r.planque@vu.nl (R. Planqué).

http://dx.doi.org/10.1016/j.mbs.2014.06.006
0025-5564/

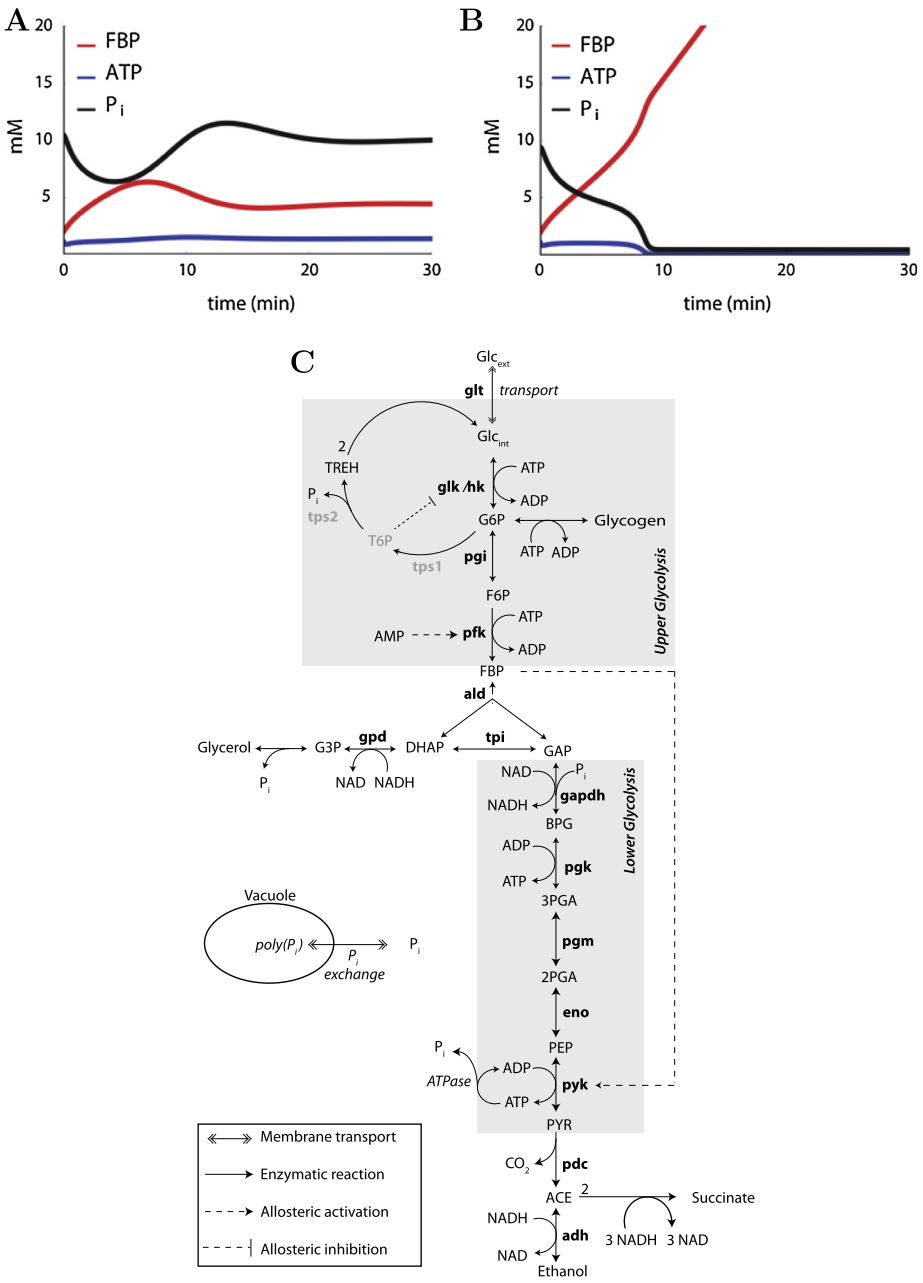

Fig. 1. (A and B) Examples of temporal dynamics for the core model of glycolysis, showing the concentrations of Fbp, ATP and P_i over time. (A) Regular dynamics; (B) imbalanced state. (C) Schematic illustration of glycolysis, showing upper and lower glycolysis, and the trehalose cycle. In Tps1Δ mutants, the trehalose cycle from G6P to Glc_{int} is knocked out. Abbreviations are found in the Supplementary Text. All panels adapted from [1].

dynamics of ATP, P_i and the glycolytic intermediate Fbp. We give a detailed analysis of the occurrence of regular steady states and their stability, of bistability between regular and imbalanced steady states, and of the occurrence of oscillatory behaviour (for which glycolysis is well-known [14]).

The methods we use are based on four common properties of metabolic networks, rather than on the specific structure in glycolysis reaction kinetics. In particular, these properties are the two-layered structure of stoichiometry and reaction kinetics, the use of conserved moieties, the appearance of enzyme concentrations as scalar factors in reaction rate functions, and the transformation properties of these rate functions. In the discussion, we explore to what extent these methods may be extended to more detailed models.

Results and discussion

A core model for yeast glycolysis

The core model studied in this paper considers the dynamics of Fbp, ATP, adenosine 5′-diphosphate (ADP) and P_i and is depicted in Fig. 2. Their respective concentrations are denoted by f, a, b and p. By assumption, $a + b = a_T$, a constant, and b will not feature in the subsequent equations.

The reaction velocity of the main glycolytic pathway up to Fbp, upper glycolysis, is mainly determined by the irreversible reaction catalysed by phosphofructokinase (PFK). PFK is a very complicated enzyme with highly nonlinear reaction kinetics [2], and has been studied extensively [2,15–19]. Lower glycolysis, the pathway