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Spatio-temporal dynamics of glycolysis in cell layers. A mathematical model

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ABSTRACT

Glycolytic oscillations occur in many cell types and have been intensively studied in yeast. Recent experimental and theoretical research has been focussed on the oscillatory dynamics and the synchronisation mechanism in stirred yeast cell suspensions. Here we are interested in the spatio-temporal organisation of glycolysis in cell layers. To this end we study a grid of a few thousand compartments each containing a cell. The intracellular dynamics is described by a core model of glycolysis. The compartments can exchange metabolites via diffusion. The conditions for oscillatory dynamics in a single compartment are investigated by bifurcation analysis. The spatio-temporal behaviour of the cell layer is studied by simulations. The model predicts the propagation of repetitive wave fronts induced by a substrate gradient. The formation of these waves crucially depends on the diffusive exchange of the reaction product between cells. Depending on the kinetic parameters complex spatio-temporal behaviour such as periodic termination of waves can arise. In these cases the cellular oscillation characteristics depend on the location of the cell in the array.

1. Introduction

Rhythmicity is a characteristic phenomenon in biological systems. Many examples for ultradian oscillations have been found on the cellular level, e.g. in metabolic, signalling and gene-regulatory networks (Goldbeter, 2002; Monk, 2003). One of the best studied metabolic rhythms are glycolytic oscillations. These have been intensively analysed experimentally as well as theoretically in populations of yeast cells and in cell extracts (Ghosh et al., 1971; Goldbeter and Lefever, 1972; Richard, 2003; Reijenga et al., 2005; Danø et al., 2007). Particular interest was directed towards the synchronisation of these oscillations in cell suspensions. There is strong evidence that individual cells communicate by exchanging glycolytic intermediates, especially acetaldehyde (Richard et al., 1996; Danø et al., 2007; Poulsen et al., 2007). Various theoretical models have been proposed to explain the experimentally observed fast synchronisation between cells (e.g. Wolf and Heinrich, 1997, 2000; Hynne et al., 2001; Danø et al., 2001). These investigations focus on the temporal dynamics in stirred cell suspensions. However, glycolytic oscillations have been observed in a variety of cell types, notably in muscle, heart and pancreatic β-cells, that are organised in tissues or organs (Tornheim and Lowenstein, 1973; O'Rourke et al., 1994; Tornheim, 1997). In these cases spatial aspects contribute to the overall dynamics. The relevance of spatial organisation was already shown for signalling processes including cAMP and calcium (Hess, 2000). The intercellular transduction of periodic cAMP signals is essential during the life cycle of *Dictyostelium discoideum*, and intra- and intercellular spatial aspects are critically involved in calcium signalling (Goldbeter, 1996; Sneyd et al., 1995; Höfer et al., 2001). An impressive example for the role of spatial organisation in metabolic systems has been detected in neutrophils where intracellular NADH waves are related to the production of reactive oxygen metabolites (Kindzelskii and Petty, 2002).

The ability of the glycolytic system to generate waves in a cell-free system was predicted early (Goldbeter, 1973) and confirmed experimentally in yeast extracts induced by local addition of substrates (Boiteux and Hess, 1980; Shinjyo et al., 1995; Mair et al., 2001). Recent experiments with yeast extracts in an open spatial reactor show interesting phenomena such as changing propagation directions of target patterns as well as the emergence of spiral waves in dependence on the substrate influx and the protein concentration (Bagyan et al., 2005, 2008; Lavrova et al., 2009).

First evidence for travelling waves in suspensions of intact yeast cells has been given by Jacobsen et al. (1980) in a quasi-one-dimensional system under continuous supply of substrate. The wave formation has been observed under conditions when the cells are in an oscillatory state confirming earlier observations on the relation of pattern formation and oscillations in yeast extracts (Boiteux and Hess, 1980).

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Here we study the spatio-temporal organisation of glycolysis in layers of intact cells resulting from local substrate addition, a system that could easily be studied experimentally. In particular, we are interested in conditions for wave propagation and complex patterns. According to the published experiments we describe the spatial glycolytic system as an array of coupled oscillators. Many theoretical studies of glycolysis concerning the oscillation mechanism, synchronisation effect and spatio-temporal behaviour in extracts started by using simplified two-variable models (Sel'kov, 1968; Goldbeter, 1973; Wolf and Heinrich, 1997; Lavrova et al., 2009). Along that line we describe the cellular glycolytic dynamics by a core model. We consider every cell to be embedded in a compartment of extracellular medium. In a first step we analyse the occurrence of oscillations in a single compartment. Subsequently, we use these results to investigate spatial phenomena in a cell layer of around 2400 cells.

2. The Model

In order to describe the situation in a cell layer, we study a two-dimensional grid of 49×49 compartments, each containing an individual cell. The extracellular metabolites can be exchanged via diffusion between adjacent compartments. The metabolite concentrations are assumed to be homogeneously distributed within each compartment and within the individual cells, respectively.

We use a two-variable model with an autocatalytic step for the description of the intracellular dynamics, see scheme in Fig. 1. The two variables lump the concentrations of upper and lower intermediates of glycolysis, respectively. The autocatalytic feedback summarises the extensive regulation of the enzyme phosphofructokinase which was found to underlie the generation of glycolytic oscillations. It is based on the positive effect of ADP and fructose-6-phosphate on that enzyme (Sel'kov, 1968). The concentrations of the substrate and the product of the autocatalytic reaction are denoted by X_i and Y_i within the cell, and X_i^{ex} and Y_i^{ex} in the extracellular medium within compartment i. The time dependent changes of these concentrations are governed by the differential equation system:

$$\frac{dX_i^{ex}}{dt} = J_i^{in} - \varphi J_i^{trans} - \sum_{j(i)} J_{i,j}^{diff,X} \tag{1a}$$

$$\frac{dX_i}{dt} = J_i^{trans} - v_{1,i} \tag{1b}$$

$$\frac{dY_i}{dt} = v_{1,i} - v_{2,i} - J_i^{exchange} \tag{1c}$$

$$\frac{dY_i^{ex}}{dt} = \varphi J_i^{exchange} - \sum_{j(i)} J_{i,j}^{diff,Y} \tag{1d}$$

For each compartment i the fluxes J_i^{in} and J_i^{trans} describe the external injection rate of the substrate X to the extracellular medium and the uptake rate of X from the extracellular medium into the cell. For the compartments i to which substrate is added externally, we assume $J_i^{in} \neq 0$, otherwise $J_i^{in} = 0$. The flux $J_i^{exchange}$ denotes the transmembrane exchange of the product Y between the extracellular medium and the cell. The parameter φ has been introduced to account for the volume ratio of the intra- and extracellular medium, and is defined as $\varphi = V/V^{ex}$. In Eqs. (1a) and (1d), $J_{i,j}^{diff,X}$ and $J_{i,j}^{diff,Y}$ give the diffusion fluxes of the compounds X and Y between the compartment i and its neighbouring compartments j. Summations are performed over all numbers $j(i)$ indicating a compartment j which is a direct neighbour of compartment i. The rates of the enzymatic reactions 1 and 2 are denoted by $v_{1,i}$ and $v_{2,i}$, respectively. Generally, the fluxes and reaction rates are described by mass action kinetics. In particular,

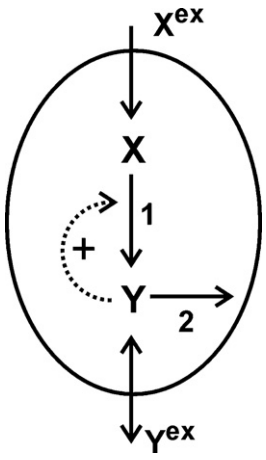

Fig. 1. Schematic representation of the glycolytic model in a single cell.

the following expressions are used:

$$J_i^{trans} = \frac{J^{max} X_i^{ex}}{X_i^{ex} + K_M} \tag{2a}$$

$$J_i^{exchange} = \kappa (Y_i - Y_i^{ex}) \tag{2b}$$

$$J_{i,j}^{diff,X} = d_X (X_i^{ex} - X_j^{ex}) \tag{2c}$$

$$J_{i,j}^{diff,Y} = d_Y (Y_i^{ex} - Y_j^{ex}) \tag{2d}$$

$$v_{1,i} = k_1 X_i \frac{\alpha + (Y_i/K)^n}{1 + (Y_i/K)^n} \tag{2e}$$

$$v_{2,i} = k_2 Y_i. \tag{2f}$$

In order to take the characteristic kinetic properties of the glucose transport into account, J_i^{trans} is described by a saturation function, with J^{max} and K_M denoting the corresponding maximal transport rate and the half saturation constant, see Eq. (2a). The parameter κ which enters Eq. (2b) for the passive transmembrane exchange of Y, is related to the membrane permeability P_Y, the cell surface area A and the cell volume V in the following way: $\kappa = AP_Y/V$. The diffusion rates of the intermediates are proportional to their concentration differences between adjacent compartments i and j. The constants d_X and d_Y in Eqs. (2c) and (2d) for the diffusion of X^{ex} and Y^{ex} are related to the diffusion coefficients D_X and D_Y as follows $d_X = D_X/L^2$ and $d_Y = D_Y/L^2$, with L describing the length scale of the compartments. The parameters k_1 and k_2 are the rate constants of enzymatic reactions 1 and 2. The autocatalytic effect of Y_i on its own production (see reaction 1 in Fig. 1 and Eq. (2e)) is described by a Hill function with the Hill coefficient n and a factor K related to the feedback strength. The parameter α accounts for a residual enzyme activity in the absence of the product. All parameters and variables are considered dimensionless.

3. Results

Starting point of our investigation is the four-variable model within one compartment (equation system (1) and (2) for $i = 1$, the subscript i is omitted in this case). A single compartment represents a cell in a cell layer or a dense solution with a finite relation of the intra- and extracellular volume φ. Note that it does not describe an isolated cell in a large or infinite extracellular volume. Such a case was studied experimentally and revealed that there are no oscillations in isolated cells (Poulsen et al., 2007; Danø et al., 2007).

The dependence of the systems dynamics on the kinetic parameters is studied by bifurcation analysis using the software package XPPAUT (Ermentrout, 2002). In Fig. 2 the result is shown for two