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SET-UP AND COMPARISON OF DYNAMIC SIMULATION WITH DIFFERENT APPLICATIONS

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ABSTRACT

This paper examines the possibilities of building up dynamic simulations for the glycolysis of the Saccharomyces Cerevisiae with two different applications. In one of the two applications it was possible to set up the metabolic simulation in different resolutions and confront the results with the published data. All the three simulation models supply adequate results like in tendencies and as in dimensions, compared to the measured data. The linked models of individual enzyme-reactions could result in the accumulation or run-out of intermediate components. This effect disappears if the detailed model is built from elemental reactions. In this case a huge amount of kinetic and balance parameter needs identification. The examined case shows well the difficulties of the clearing with common components taking part in numerous cell processes, in a selected part-process. The main advantage of the detailed metabolic model is that it contains direct enzyme and enzyme-complex information. This allows the extension of the model with more real or theoretical reactions.
Keywords: dynamic, simulation, comparison, Saccharomyces Cerevisiae

INTRODUCTION

The development of the biology and informatics today makes the detailed dynamic simulation of cell's metabolic processes possible. Many software packages are available and part of them are free for research. It is very useful in the orientation between the available software- packages and a comparative study appeared in a recent past (*Alves et al.,* 2006).

Csukás et al. (2001) and (*Csukás*, 2001) developed a new method for direct computer mapping of various processes in the '90s. This method makes the handling of large hybrid models available. The contact of a generic simulator to a genetic algorithm makes the identification of undetermined models also possible (*Csukás and Balogh*, 1998).

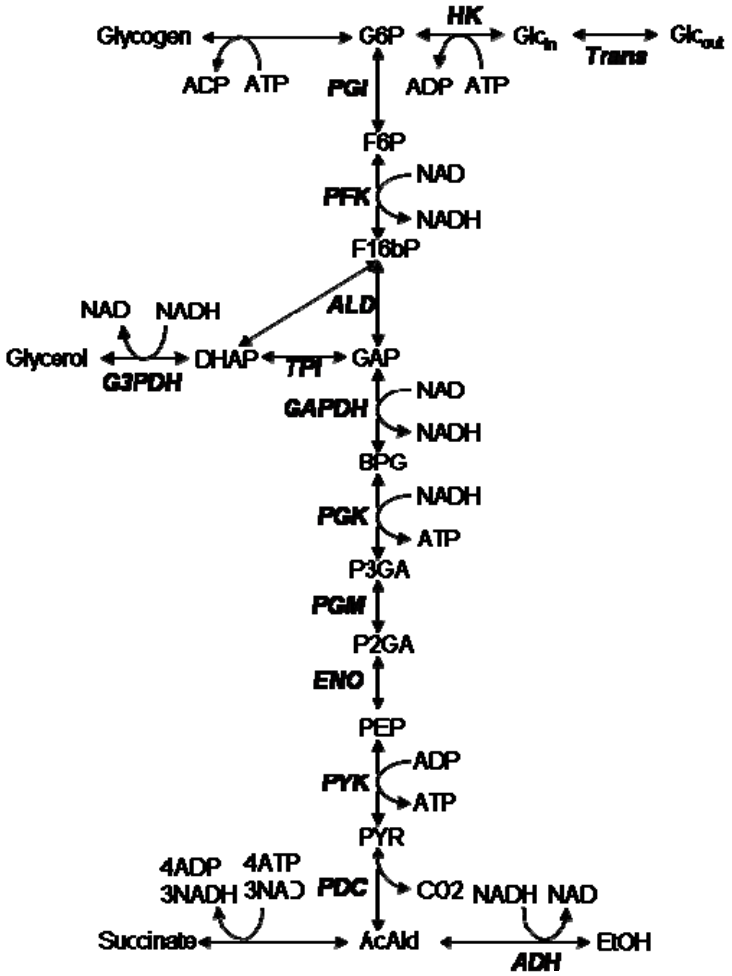
In this work we compare the COPASI software package selected by the recommendation of the literature (*Alves et al., 2006*) and the generic simulator used on the Department of Information Technology of the University of Kaposvár through an example of a metabolic part-process, which is examined particularly with measures as well. With the generic simulator it is possible to examine the elemental processes in the highest resolution (*Csukás*, 2000).

MATERIALS AND METHODS

We examined the details of the metabolic processes of the Saccharomyces Cerevisiae (*Figure 1*). Besides the examined alcohol-fermentation main process, there are side processes resulting in glycogen, trehalose, glycerine and succinate. Teusink examined how accurate a complete model could be if enzyme-kinetics coherence was determinated for each enzyme as the basic elements of the complete model (*Teusink et al.*, 2000). He found that the difference between measured and calculated values was less than 100% in 50% of the cases. This result makes the free integration of the data of the measured enzyme-reactions questionable.

Figure 1

Metabolic processes of the Saccharomyces Cerevisiae



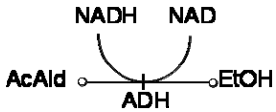
Source: Based on *Teusink* et al., 2000 data

The COPASI software-package we used to build our model is a group of specialized applications developed for modeling of biochemical networks. The software handles the compartments automatically and it is able to calculate stationary phase and to optimize the parameters by given options. There are more methods available to identify the parameters, among others two variants of the genetic algorithms. The set-up of the application is simple, the input of the data occurs in tables. Even the survey of very complicated models is easy trough the different organized reports and summaries. By the running of the application we can save the results into files or tables, or we can display the process on graph. The application organizes the used equations and makes them user friendly through its display method. It is also possible to work with built-in and own implementation of reaction-equations as well.

The application used at the University of Kaposvár is more common and flexible, but less clear and user friendly than the COPASI. The simulator application communicates through an MS EXCEL interface. It reads and also publishes the data and the results through EXCEL objects. We used the application in two different ways. The modules of the low-resolution version are matching the Teusink-model and the COPASI model as well. By the high-resolution version we detailed all the gross processes to basic processes. That links the following steps together naturally, and do not describe the processes as elements. The detailed model contains only the following types of elemental reactions: 1→1, 1→2, 2→1 and 2→2. The gross description of enzyme reaction of the alcohol dehydrogenase can be seen on the second figure and on the third figure performs the same reaction's detailed solution.

Figure 2

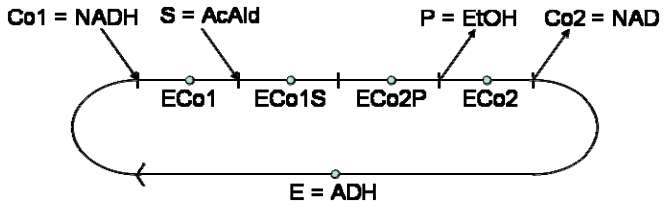
Enzyme reaction of the alcohol dehydrogenase



Source: *Teusink et al.*, 2000

Figure 3

Detailed presentation of the enzyme reaction of the alcohol dehydrogenase



RESULTS AND DISCUSSION

Not all of the needed data were present in measures or in the literature as we built up the models. We had to identify these data by all the three models. And even so we could use estimated data in some equations only. The data of the COPASI and the low-resolution other model was calculated mainly from the literature (*Teusink et al.*, 2000; *Barnett,* 2003). In the low-resolution model the concentration of the ATP, ADP, AMP, NADH and NAD was constant. In the high-resolution model we identified all the kinetic and balance parameters of the basic processes.

In the examined network and even in the not observed cell-processes many reactions use or produce ATP, ADP, AMP, NADH and NAD components. These components affect the speed of the examined reaction very significantly. There are three different solutions to treat this problem:

- One of them is that we calculate with a constant concentration to the observed component, thinking on the homeostasis of the physique. The cell will maintain the balance between the different components. This solution is not usable because both the glycolysis and the belonging processes are responsible for the major changing of the component's concentrations.
- The other solution is when we set the system working free and we do not have any influence on the concentration of these materials. In that case the model has not any limitation to keep materials between fixed values. This solution is also inapposite because the overproduction or the run-out of a material in a process is not possible in the organism.
- The third solution tries to keep a balance with a fictitious process between these materials inhibiting their overproduction or run-out. This process works, however, between arbitrary rules, and does not always match perfectly to the theoretical process.

So all the three solutions have some weaknesses, and none of them were determinate to optimal usage in the models.

By the COPASI model the third method gave the best results, as by the generic simulator we declared the concentration of the components constant, inspired by the first method. The main results of the models can be seen on *Figure 4 - Figure 7* compared to the measured data.

The data show that the results are relatively similar even with different simulation programs and solution-methods. Despite the user-friendly interface and a lot of pre-made solution-methods, it is much more difficult to simulate a complete process with the COPASI application, because it's premade contexts are not always usable, however, the implementation of the model needs much less time, but the model will be more inaccurate. The specialized application with a prepared generic simulator results in more accurate values. The identification is possible in both models. That allows to determinate the parameters according to the results and the measured data of the experiments. The high resolution model handles the interaction more naturally between the part-processes. The high resolution generic simulation model came close to the measured data at the best.

Figure 4

Co_2 evolution in the created models

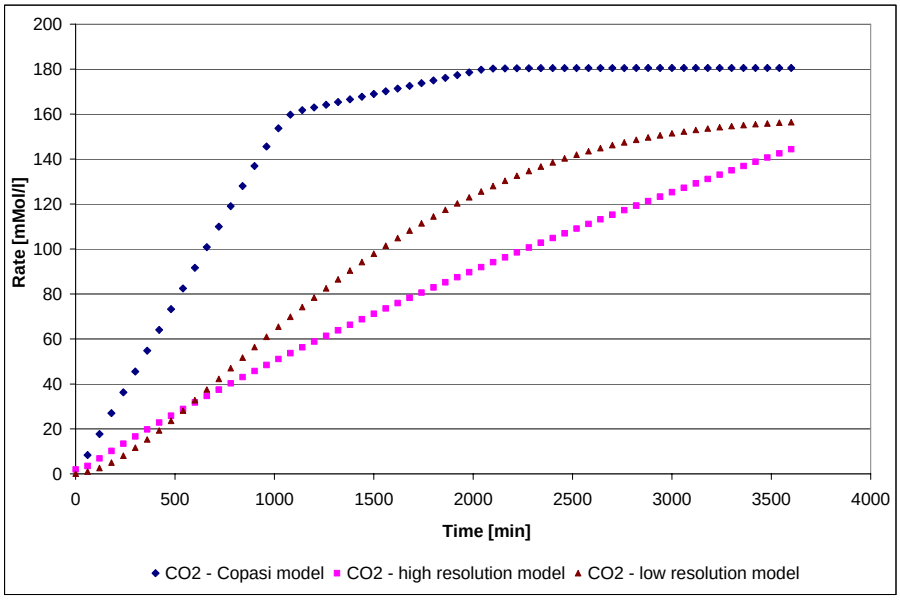
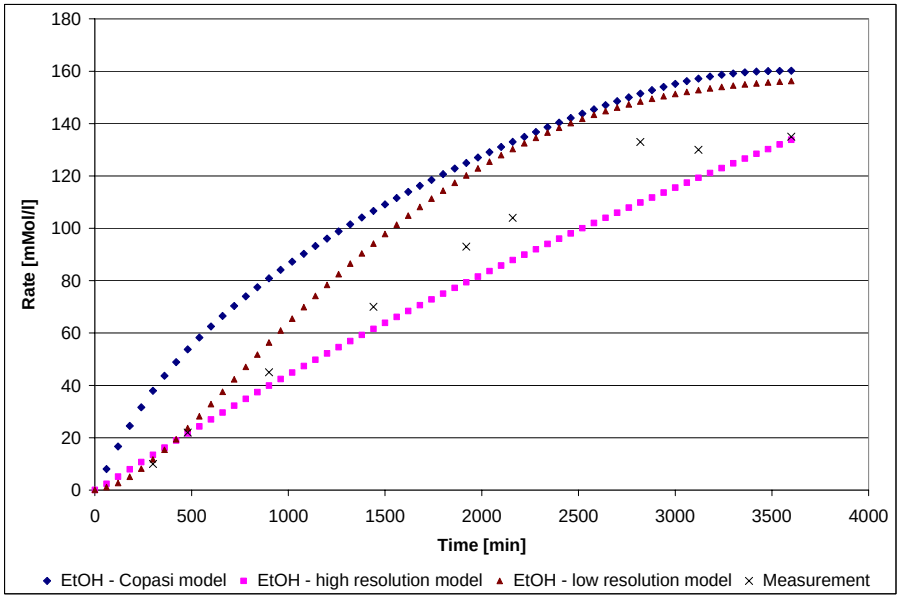


Figure 5

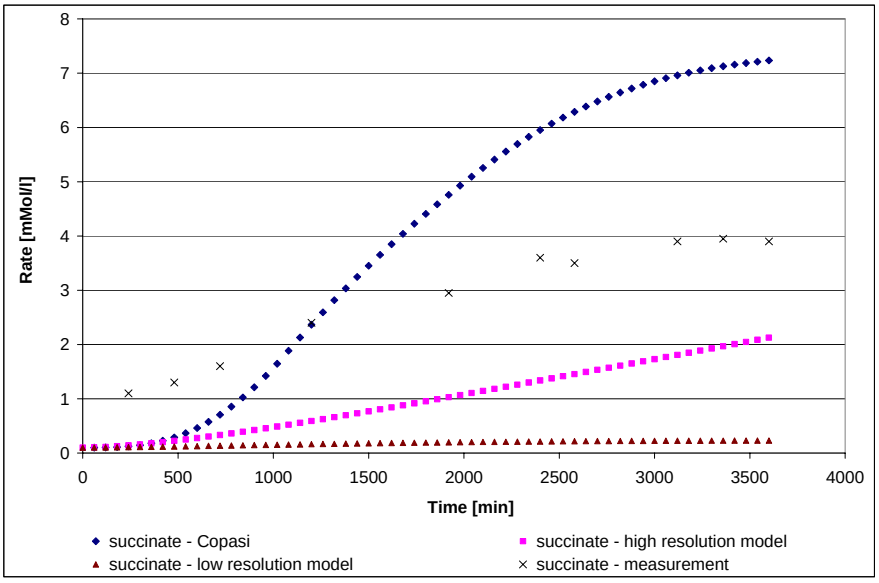
Ethanol production in the created models and measured data



Source: *Teusink et al.*, 2000 and own data

Figure 6

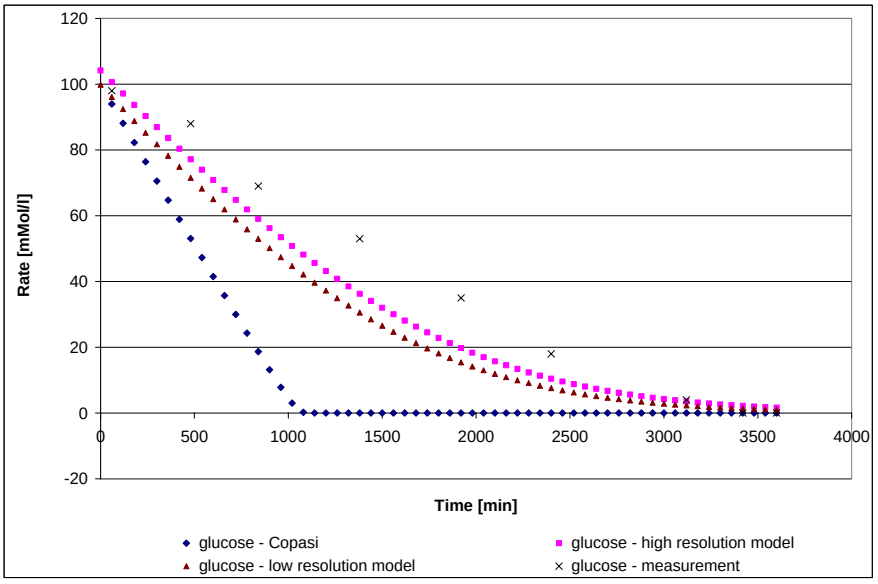
Succinate production in the created models and measured data



Source: *Teusink et al.*, 2000 and own data

Figure 7

Glucose consumption in the created models and measured data



Source: *Teusink et al.*, 2000 and own data

CONCLUSIONS

The biggest handicap of the complete process simulation is that it cannot be extended, or it can be, but with a lot of work and difficulties. It is not good by the modeling of the effect of a new or modified component, because during the new process the model must work with new equations. This is absolutely not problem by the high resolution model, because all the thing to do is to complete the model with new components and/or elemental processes, so it can follow the real process more accurately than before.

The other question is the isolation of the modeled process. The examined system in the cell is not completely isolated, other, not observed materials and processes can have an effect on it. So the examined system could produce components which exist temporarily in the process, and can have an effect on one or more observed and not observed processes. The same system could work in many different ways. In our case we supposed to the production of ethanol and CO_2. But the processes of an organism are not regularly linear. The process can change, and can effect in an absolutely new way depending on the needs of the organism (*Schuster*, 2000). This possibility makes, in part, the best model also incidental. By the description of the elemental processes of the model and the functional processes, we assumed the static operation of the cell.

The assumption that the cell has concentrated parameters, so every molecule could meet every other molecule with some kind of plausibility, also enhances the inaccuracy of the model. There are micro-compartments inside the cell, where the reactions follow each other like on a production line because of the sequencing of the enzymes (*Al-Habori*, 1995). These compartments can be found on different places in the cell, and the muster of the compartments has a great effect on the speed of the reactions (*Ellis*, 2001).

Right after that we can put up the question: are we entitled to use chemical and kinetic models to map the biological processes? The question is not answered yet. But through our examination and the literature we can declare that the modeling and the simulation of the metabolic processes gives help to the development of the biotechnology and life science.

Of course the development of the simulation technology has economic advantages as well. Complicated experiments using huge amounts of special materials to examine a single process of a cell are not cheap. It is not always possible to develop the production and the efficiency on macro level. Sometimes a little modification has much bigger effect on the production. The simulation is the right answer to find out how and where to modify. Better methods and solutions of the simulation processes can take closer to the required result with less risks and costs.

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