HUMBOLDT-UNIVERSITÄT ZU BERLIN

bachelor thesis

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Ein kombiniertes Modell für die Messung von extrazellulären Biomarkern mit Rückschluss auf die Aktivität des Hog-Pathways im Modelsystem saccharomyces cerevisiae

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1 Abstract

Hier kommt meine englische Zusammenfassung

2 Zusammenfassung

und hier meine Deutsche

Contents

3 Introduction

3.1 system biology

System biology is there for the extraction of a system wide understanding of living organismen. This includes the interaction of multiple proteins, genes, metabolits et cetera, which are measured in the laboratory. This approach gets more significant in the analysis of executed omics experiments which easily results in data in the gigabyte range (Zitieren: Toward an integrated ...).

Currently limitations of the system biology approach are the usages and constructions of mathematical equations which should represent the biological system. This is a trade off between reduction of the system of interest without dimishing the quality of the information value or reasonableness intended digital twin. Another important problem is that there does not exists a complete biological understanding and knowledge of all system component. The system biological appproach is therefore only a heuristic approach (zitieren!!!)

In-depth insights of an investigated system are e.g. useful for medicine and the biotechnology sector (cite: Toward an integrated software platform for systems pharmacology!!!!) because this results in the improvement of well constructed mathematical models of a cell system could be useful for the design of target-oriented medications.

An increase in external osmolarity leads to a cell volume reduction. The cell counteract this high osmotic pressure by increased intracellular glycerol as an osmolyte and restores in this way its volume.

Mathematical models *in silico* are further helpful to test laboratory experiments *in silico* to identify meaningful experiments by construction of DoE (Design of Experiment). This helps to save the resources (e.g. money, time) of the experimentalist and could results in a deeper understanding of the underlying biological system.

3.2 Saccharomyces cerevisiae

The yeast Saccharomyces cerevisiae (*S. cerevisiae*) is a unicellular eucaryotic organism and belongs to the class of fungi. It was the first eucaryotic organism where the whole genome had been full sequenced. In nature, the environment of S. cerevisiae varies in factors like temperatur, nutrient levels or osmolarity with the time and the cell must adapt with these changes. The Hog-Pahtway in yeast has a significant role in the adaption process after an osmotic stress exposure. It normalize the volume of the cell with an accumulation of the osmolyt glycerol inside, by closing the glycerol membran transporter Fps1and the production of glycerol.

3.3 state of the art

It already exists multiple models for the hog pathway (signaling module), ion transport (transport module) and the volume regulation (volume module) (!!! alles hier noch mit Zitaten belegen). The signaling module keeps tracks of the stress response signaling pathways
Each of these models describe a part of the cell system while assuming other important aspects of the system as constant (see picture 1).

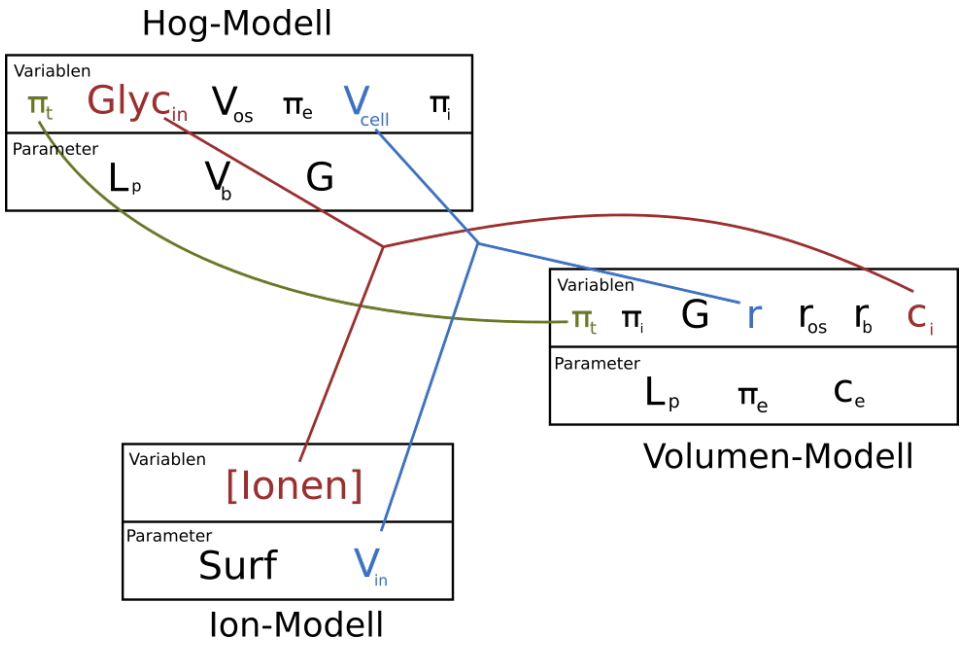

Figure 1: intersections of the three models

In our momentan state of knowledge, there is not yet a model which integrate this three modules into a single model. The combined model simulates the interaction between extra- and intracellular ionconcentration, changes in cell volume and the activity of the MAP cascade (???). The model senses the differences in the osmolarity between the cell and its environment and adapt with the important Hog pathway with the MAP cascade the cell volume and the intracellular osmolyt concentrations.

3.4 theory

The ion model consists out of a non-equivilibrium thermodynamic (NET) approach to model the transport of the ion over the plasma membrane.

In the ion model a glycerol stimulus is further simulated.

The cell volume depends essential on the relation of the internal, external and turgor pressure. The internal and external pressure π depends on the concentration c of the osmotic active substance in the corresponding areas correlated over the equation 1

$$\pi = c \cdot R \cdot T \tag{1}$$

4 material and methods

4.1 software development

Cause a simulation for the combined models could take several minutes and the thereafter calculation and handling of this results are not garanted to work in the process of a program development, I came up with the idea that the results must be safed after each simulation and the analysis of them should be run in another program, as

first program : simulation –> save data
second program : data –> analysis

For the construction of this workflow I implemented a database and connected. For the storing logic of the data I used a concept from CDISC for clinical trials which allowed me to construct the useful column names, data types and table in the database. Because a simulation of ODEs and algebraic equations can have pending sets of initial values, parameter values or equations terms, I expanded the concept of CDISC to the area of system biology and designed new data storage procedures. In picture (!!! Bild zeichnen lassen und hier einfügen) you can see the proposed workflow.
The intention for the implementation of CDISC to system biology was the fact, that the FDA is moving towards CDISC standards for regulatory submissions (!!!cite : forging new SDTM standards ... !!!!).

With this approach, you can analysis and try new codes snippets with the results of a long simulation in seconds.

5 Results

5.1 results of single models

Before merging the three models together it must be controlled whether each model is implemented correctly for itself. The pictures of the models simulation results are the guide for this. Sometimes there are discrepanies between the puplished model and the picture which should represent the model. Hereafter, the implementation process for each of the models is described.

5.1.1 Ion model

The challanges with the implementation of the ion model where, that the presented equation, initial values and parameters did not result in the intended system behaviour. After an in-depth analysis of the equation there where two anomalies:

1. the calculation of the change of the inner proton ion concentration has Bf as an undefined parameter
2. the fluxes have the wrong units

For solving the problem with the undefined parameter in (1) the ODE was constructed by deriving the formula for the calculation of the pH value for diluted solution

$$pH = -log_{10}([H^+])\frac{d}{dt}pH = -\frac{d}{dt}log_{10}([H^+]) = -\frac{1}{ln(10)}\frac{d}{dt}ln([H^+])$$

The published ion model has discrepancies in the parameter values of the phenomenological and stoichiometric coefficients and the calculation of the ion fluxes have the wrong units

5.2 merging of the models

In the process of merging models there exists some useful steps which are good descriped in (zitieren). Hereafter, the used essential steps a sketched:
One of the first steps in the process of model merging is the control whether there is a conflict between assumptions of the description of the biological systems.

5.3 combined model

For the analysis and validation of the merged model we choosed the nuclear phophorylated Hog1 (Hog1PPn) as the control substance. Hog1PPn is also used in the hog model as the output because it regulates the expression of hundred of genes (zitieren : Hog Model!!!)

6 Discussion

Discussion: It is assumed that there are not any temperature gradient which would results in a heat flux.

Currently, only the proton and the potassium transport are ATP driven. It is known that Na^+ is also excluded by the Ena1p pump, which extrudes potassium. A general extension of the implemented membran transport processes could benifits the insight of then model in response of a external stimulus.

An implementation of the CWI pathways could further improve the information value of the combined model.

7 Literaturverzeichnis

8 Danksagung

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