**Maik Kschischo**
University of Applied Sciences Koblenz, RheinAhrCampus, Remagen, Germany, D-53424
e-mail: kschischo@rheinahrcampus.de
**Matthias Kahm**
University of Applied Sciences Koblenz, RheinAhrCampus, Remagen, Germany, D-53424
e-mail: kahm@rheinahrcampus.de
**Clara Navarrete**
University of Gothenborg, Department of Cell- and Molecular Biology, Medicinaregatan 9C, Box 462 SE 405 30, Sweden
e-mail: b92naroc@uco.es
**José Ramos**
University of Cordoba, Avenida Menendes Pidal, 14071 Cordoba, Spain
e-mail: mi1raruj@uco.es

## Actuators of yeast potassium homeostasis

Potassium is the most abundant cation in living cells and is involved in a variety of essential cellular processes including translation, endocytosis and even cell cycle regulation. Changes of external and internal $K^+$ concentrations change the membrane potential required for the transport of molecules across the plasma membrane, affect the pH and osmolarity of the cytosol and induce changes of the cell volume [1]. Metabolic decarboxylation processes release $CO_2$, which affects the pH, the bicarbonate concentration, the proton buffer capacity and the potassium transport [2].

To gain a deeper understanding of the complex interplay between these variables we developed an ordinary differential equation model of potassium control in the yeast *Saccharomyces cerevisiae*. The basic model covers the thermodynamic constraints on the operation of the major potassium transport systems and the proton ATPase Pma1. Regulation mechanisms where only partly included as many of them are either unknown or not sufficiently characterized. This basic model qualitatively reproduces known aspects such as the hyperpolarisation in *trk1,2*$\Delta$ mutants and potassium starved cells, as well as the potassium uptake energized by the Pma1 driven proton extrusion.

To make quantitative predictions we calibrated the model to potassium starvation experiments given in [3]. For cells grown in a medium with high $K^+$ and shifted to $K^+$ free medium, a decrease of the intracellular $K^+$ content and cell volume was measured. While the external potassium drop occurs in minutes, the internal $K^+$ is slowly reduced during several hours.

The regulatory control of the various transport systems under potassium starvation conditions is not well understood. To identify potential control mechanisms and points of applications we regarded the experimental time course $K^+_{data}(t)$ as a signal which has to be tracked by the model $K^+_{sim}(t)$. More precisely, we determined a time dependent input function $p(t)$ that solves the minimization problem

$$|| K^+_{sim}(p(t), \theta, t) - K^+_{data}(t) || = \text{Min}\,. \tag{1}$$

Each transport protein or any other component of the model for which such an input function exists was regarded as a potential actuator for potassium control.

We found that the (i) the proton pump Pma1 and the (ii) the $CO_2$ system are the most likely actuators of potassium homeostasis. In addition, we found evidence that yeast cells sense external potassium rather than internal potassium, what is also supported experimentally. To demonstrate the consistency of our predictions we successfully designed a modified PI-controller which reproduces the experimental time courses of internal potassium. This PI controller mimics the unknown details of signalling and gene expression changes required for the maintenance of homeostasis.

In summary, we present a mathematical model which provides testable predictions about unknown regulatory mechanisms necessary for homeostatic control of potassium in *S. cerevisiae*. We also believe that our tracking approach to mathematical modeling has general applicability. It is a versatile strategy to detect unmodeled dynamics and their points of application.

## References

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