



Modelling Snf1 regulation in *Saccharomyces cerevisiae*



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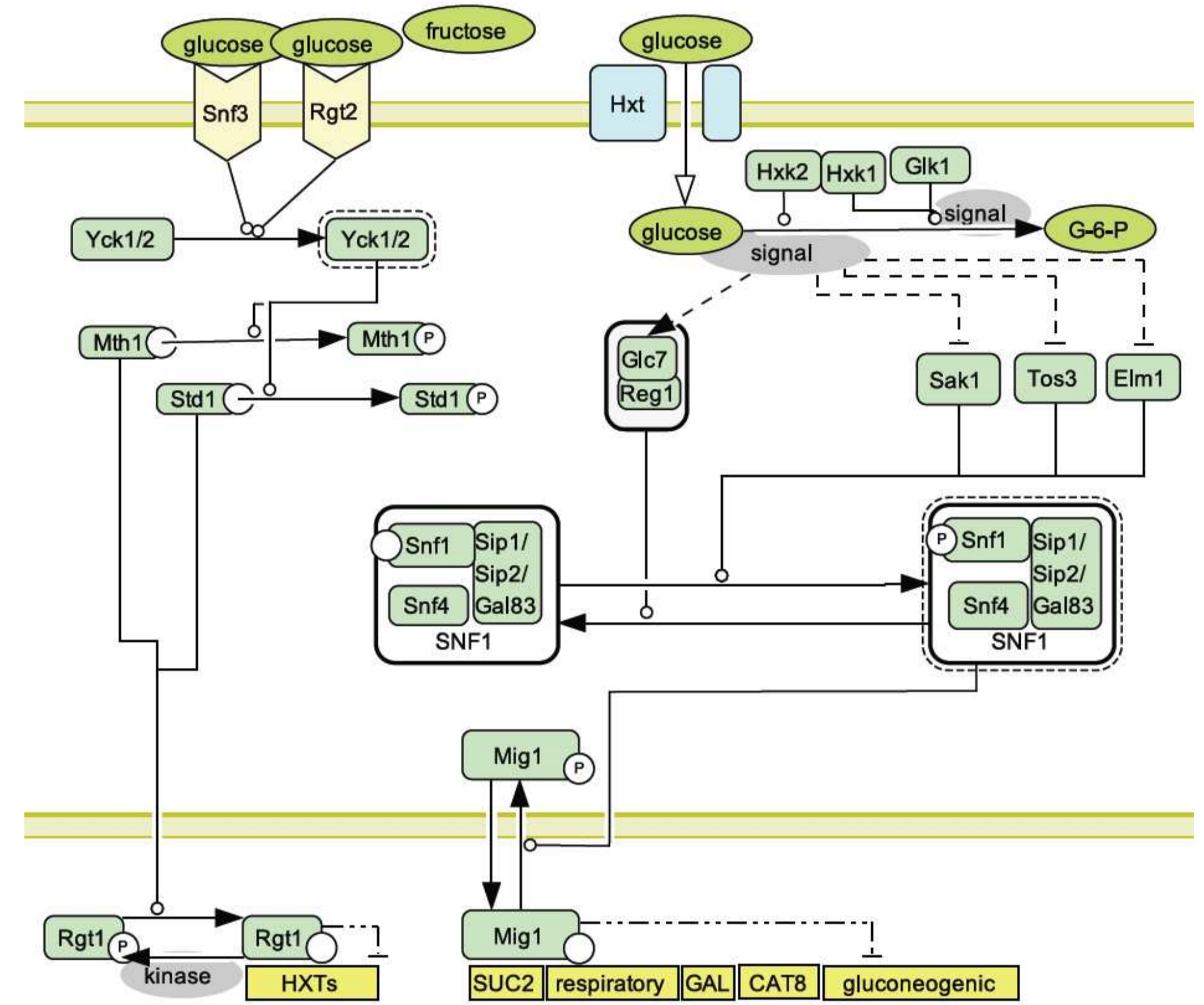
Background

The AMP-activated-protein-kinase (AMPK) signaling pathway plays a central role in monitoring the cellular energy status and controlling energy production and consumption. The yeast AMPK orthologue Snf1 is best known for its role in glucose repression/derepression. One ultimate goal of the study of these pathways is to generate a computational model able to support drug development, targeted at advancing diseases such as obesity and type II diabetes. In this work, we focus on a quantitative dynamic model describing the Snf1 activation/deactivation pathway.

Model

Snf1 plays a main role in transcriptional activation and repression of gene expression:

- Glucose depletion → Snf1 activation by phosphorylation through its upstream kinases Sak1, Tos3, Elm1. Activation of Snf1 → Inactivation of the repressor Mig1 via phosphorylation → Expression of genes involved in alternative carbon utilization.
- Glucose abundance → Snf1 deactivation by dephosphorylation through its upstream phosphatase Reg1/Glc7. Deactivation of Snf1 → Mig1 remains active → Repression of genes involved in the utilization of alternative carbon sources.

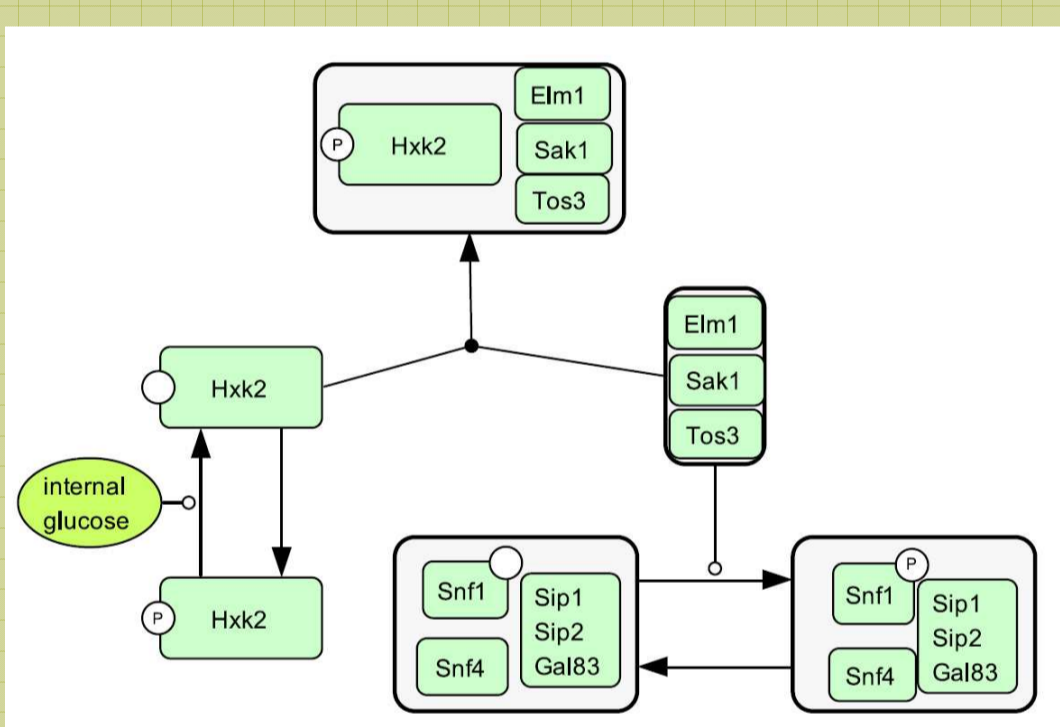


Key Questions

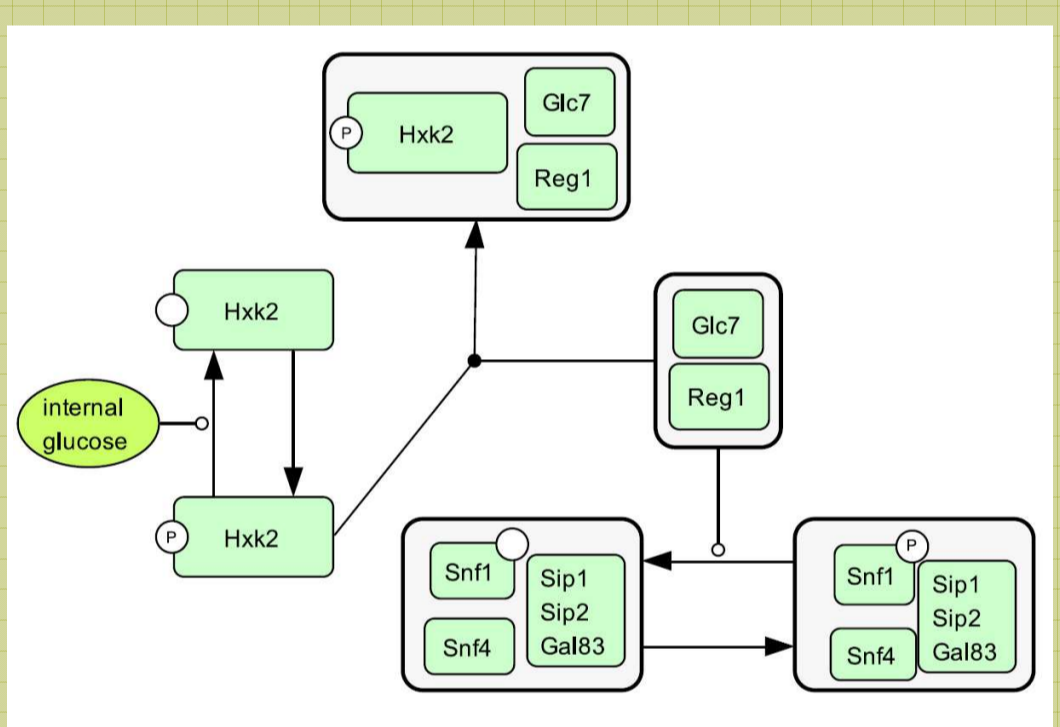
- Does regulation of Snf1 occur via its phosphatase or its kinase or both?
- How are the kinase and phosphatase of Snf1 regulated?
- Which role do the hexokinases play?
- Can the huge variety of hexosetransporters (Hxts) be summarized in one pool?

Hypotheses

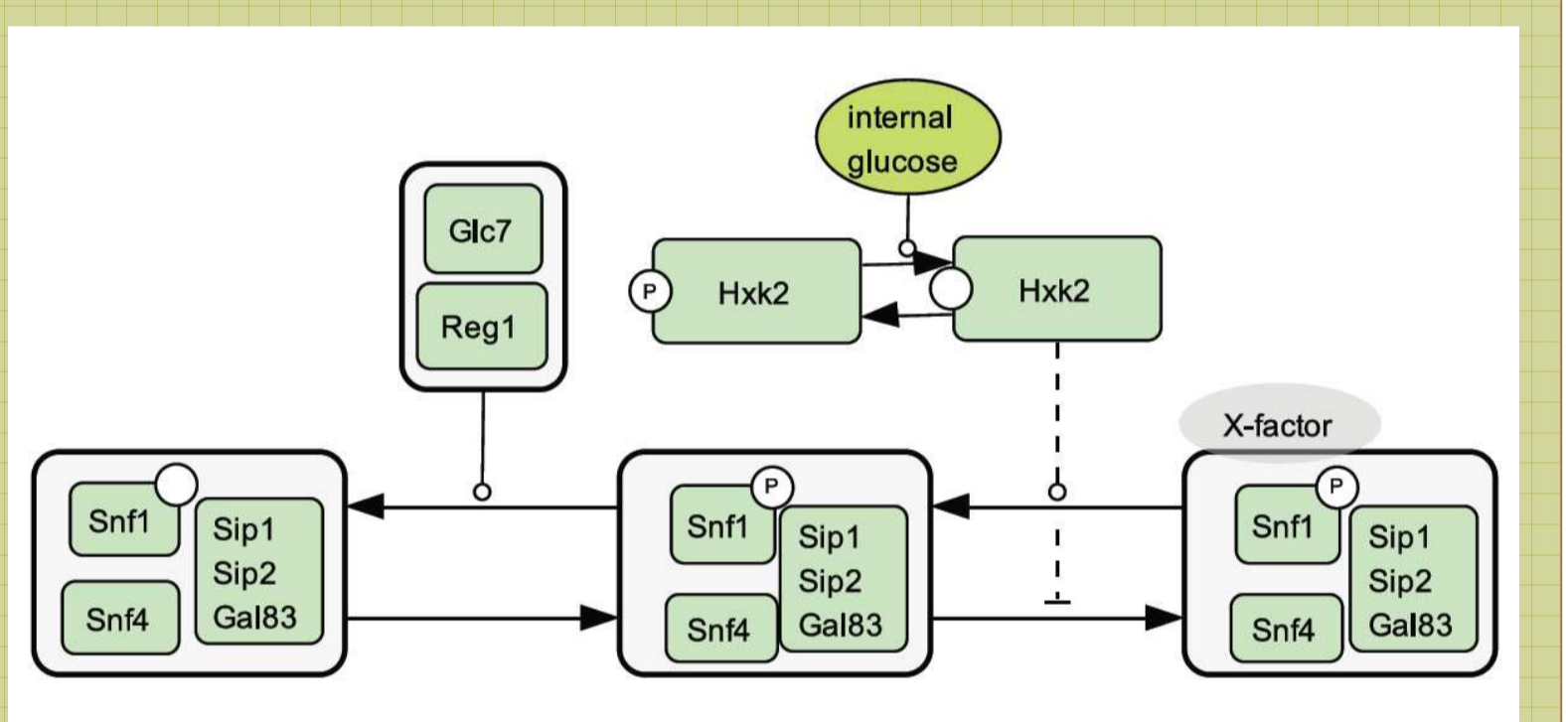
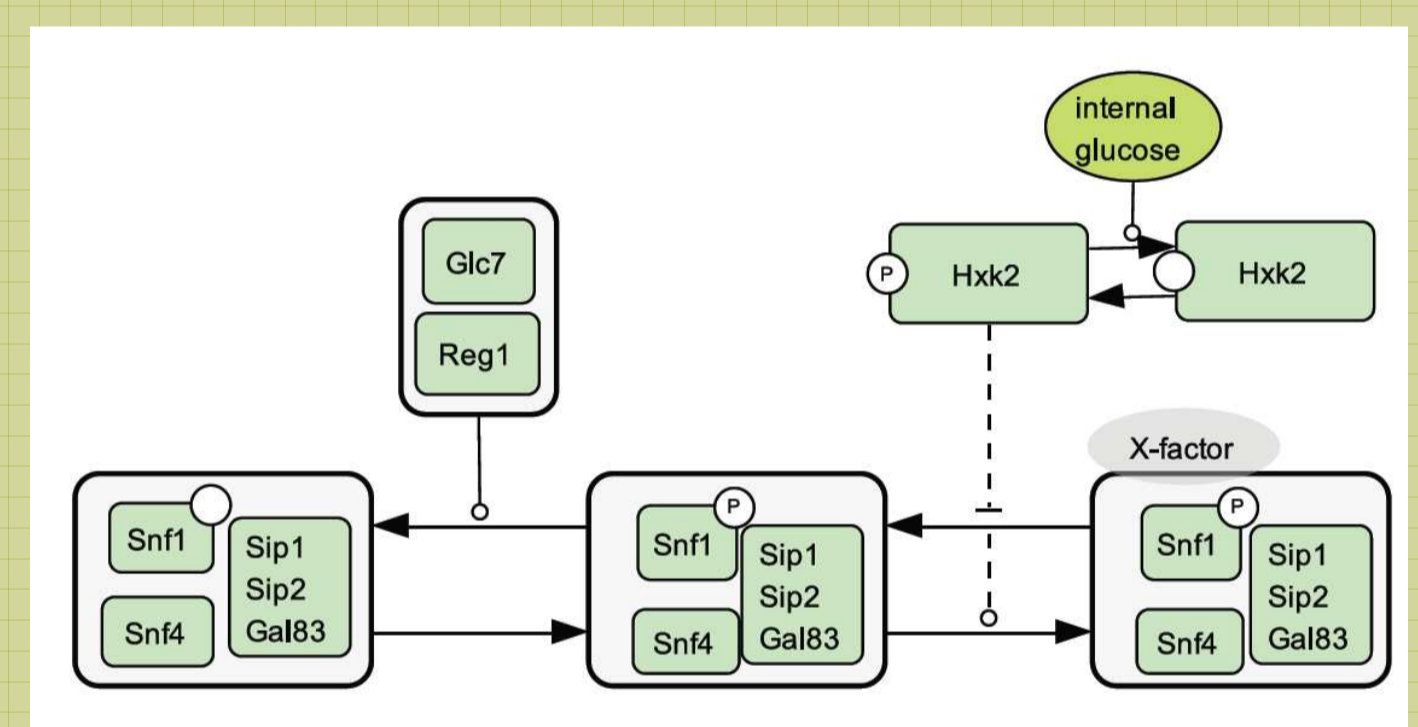
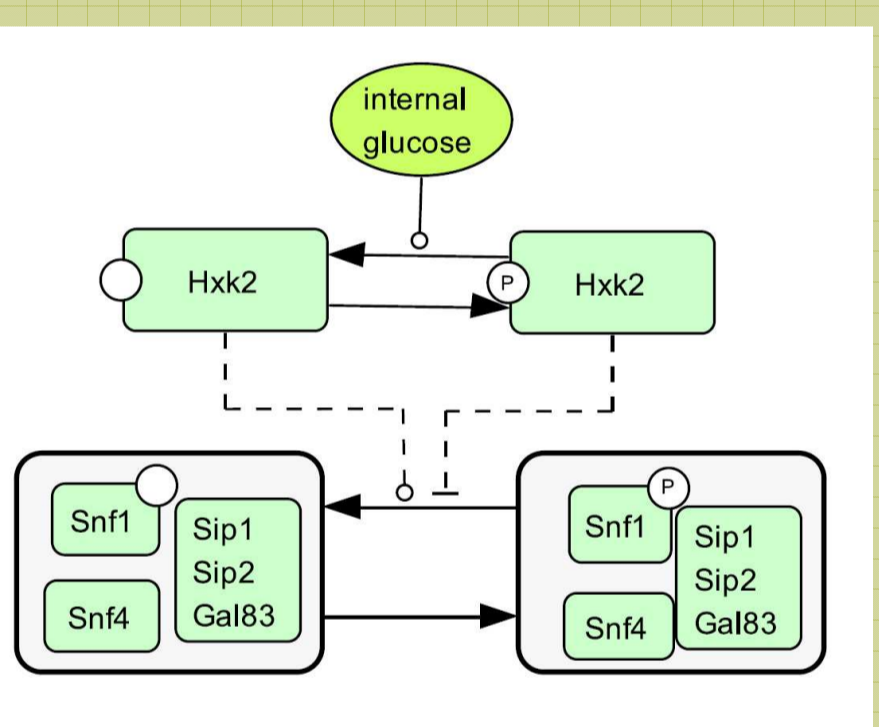
Regulation by complex formation:



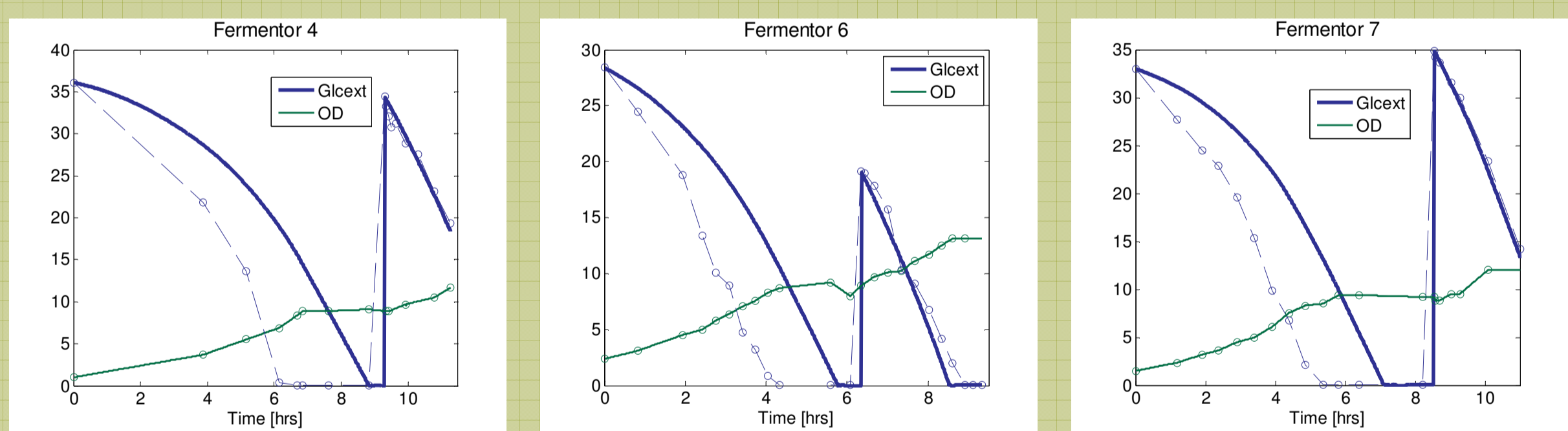
Regulation directly from Hxks:



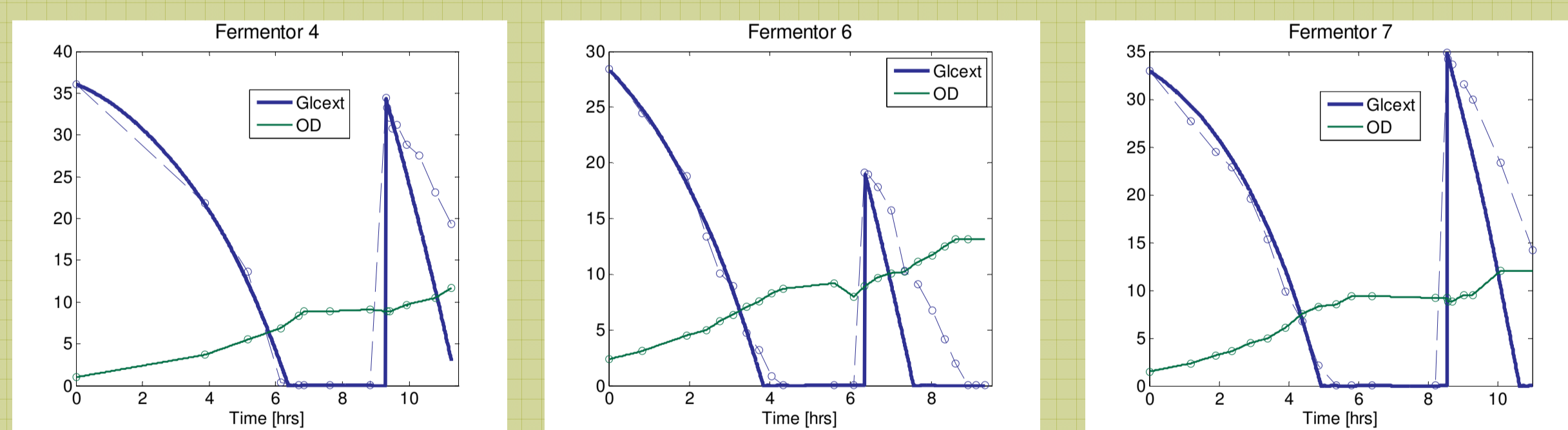
Regulation directly from Hxks with respect to the X-factor:



Modelling approach to slow for glucose consumption:



Modelling approach to fast for glucose consumption after the pulse:

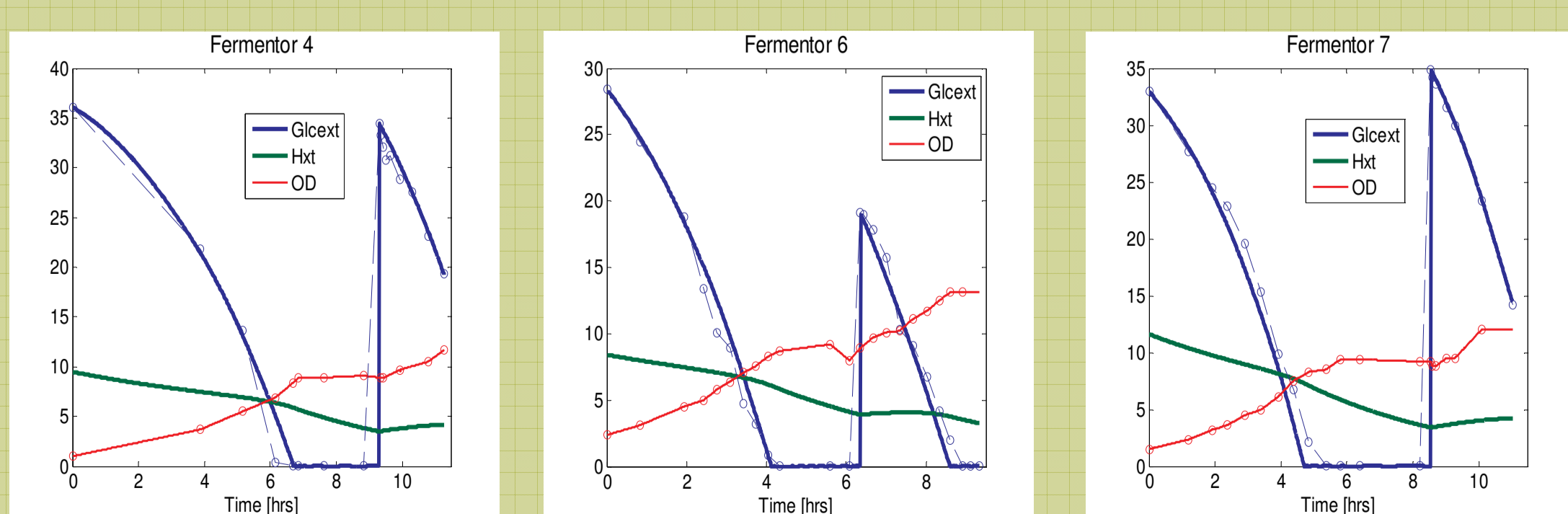


Showing the influence of a decreasing amount of Hxts during glucose depletion.

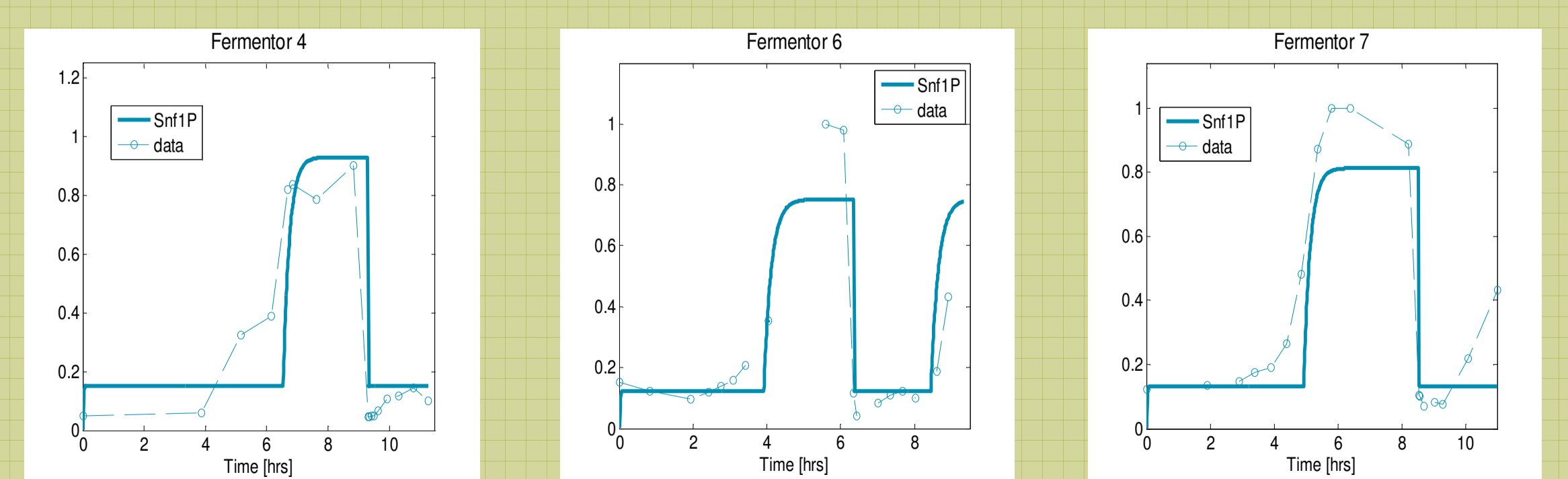
Results

- Experimental data for extracellular glucose, OD, and Snf1P provided the basis for modelling.
- The model correctly reproduces the experimentally measured Snf1 activation and deactivation responses.
- To reproduce *in silico* the glucose correctly, we included synthesis and degradation reactions for the Hxts.

Modelling the glucose repression derepression under consideration of changing Hxts levels. The Hxts were modelled using an ODE consisting of a production term depending on the amount of glucose and a degradation term:



Modelling results for the Snf1 activation and deactivation (considering the Hxts):



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