



## Constructing a Large Kinetic Model of the Hepatocyte Core Metabolism

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Subproject 2.2: Kinetic Model of the Hepatocyte

### Introduction

Kinetic models are necessary to understand the dynamics of the cell metabolism. Therefore a kinetic model of the core Hepatocyte should be formulated which includes energy and carbohydrate metabolism, amino acid synthesis and degradation, nucleotide metabolism and the detoxification of  $\text{NH}_3$ .

The kinetic network should be able to show characteristic Hepatocyte functions like

- blood glucose homeostasis
- ketone body synthesis
- $\text{NH}_3$  detoxification
- protein synthesis

### Metabolic Network

The core metabolism of the human Hepatocyte was reconstructed [Fig.1]. The resulting metabolic network is compartmentalized (cytosol, mitochondrion, blood) and consists of:

reactions	337	transporter	105
processes	22	regulations	123
compounds	180		

### Network Reconstruction and Validation

- Information retrieval from databases (Brenda, Kegg, HumanCyc, Reactome)
- Use of manually curated HepatoSys and textbook knowledge
- Structural validation (removing dead ends, isolated reactions, ...)
- Submodel creation and curation
- Functional analysis (FBA)

### Flux Balance Analysis (FBA)

FBA was used to validate the network. Sub networks of the full core model were created and different target fluxes optimized. In this process the basic functionality of the network was tested [Fig.2].

### Kinetic model

#### Kinetic data collection

For all reactions in the model the available kinetic data was obtained from databases (SABIO-RK [5], Brenda). A subset of kinetic parameters is shown in Fig.3.

#### Rate laws

- Detailed kinetic laws (if information available)
- Generalized Michaelis Menten Kinetics (if kinetic data, but no rate laws available)
- Otherwise mass action kinetics
- Regulations are integrated with simple mechanisms

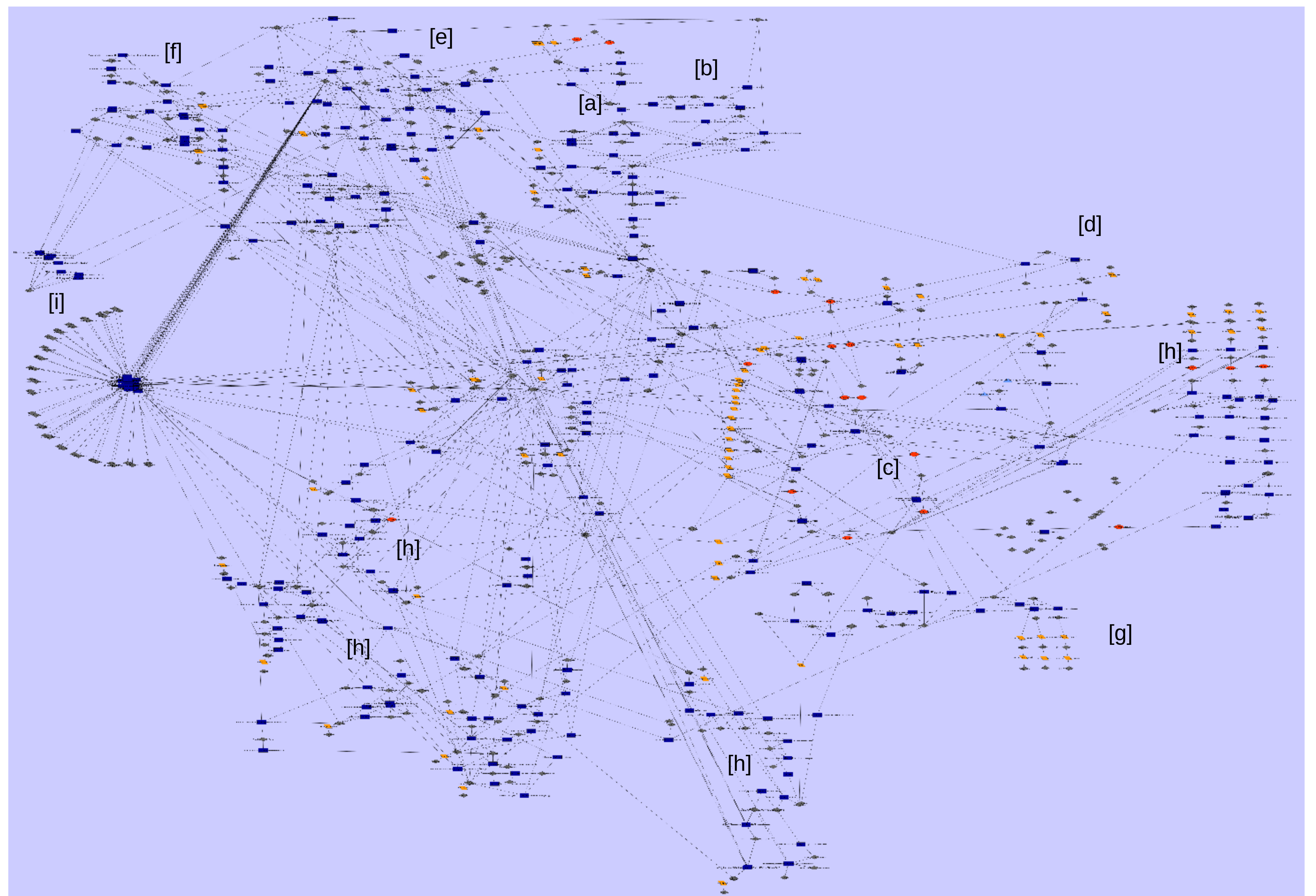


Fig.1: **Reconstructed metabolic network of core Human Hepatocyte metabolism:** Glycolysis and gluconeogenesis [a], pentose phosphate pathway [b], citrate cycle [c], urea cycle [d], purine metabolism [e], pyrimidine metabolism [f], ketone body synthesis [g], amino acid metabolism [h], protein synthesis [i] reactions: blue rectangle, processes: red octagon, transporter: orange parallelogram, compounds: grey rhombus regulations and flux objects not displayed, edges of compounds with highest degree not displayed

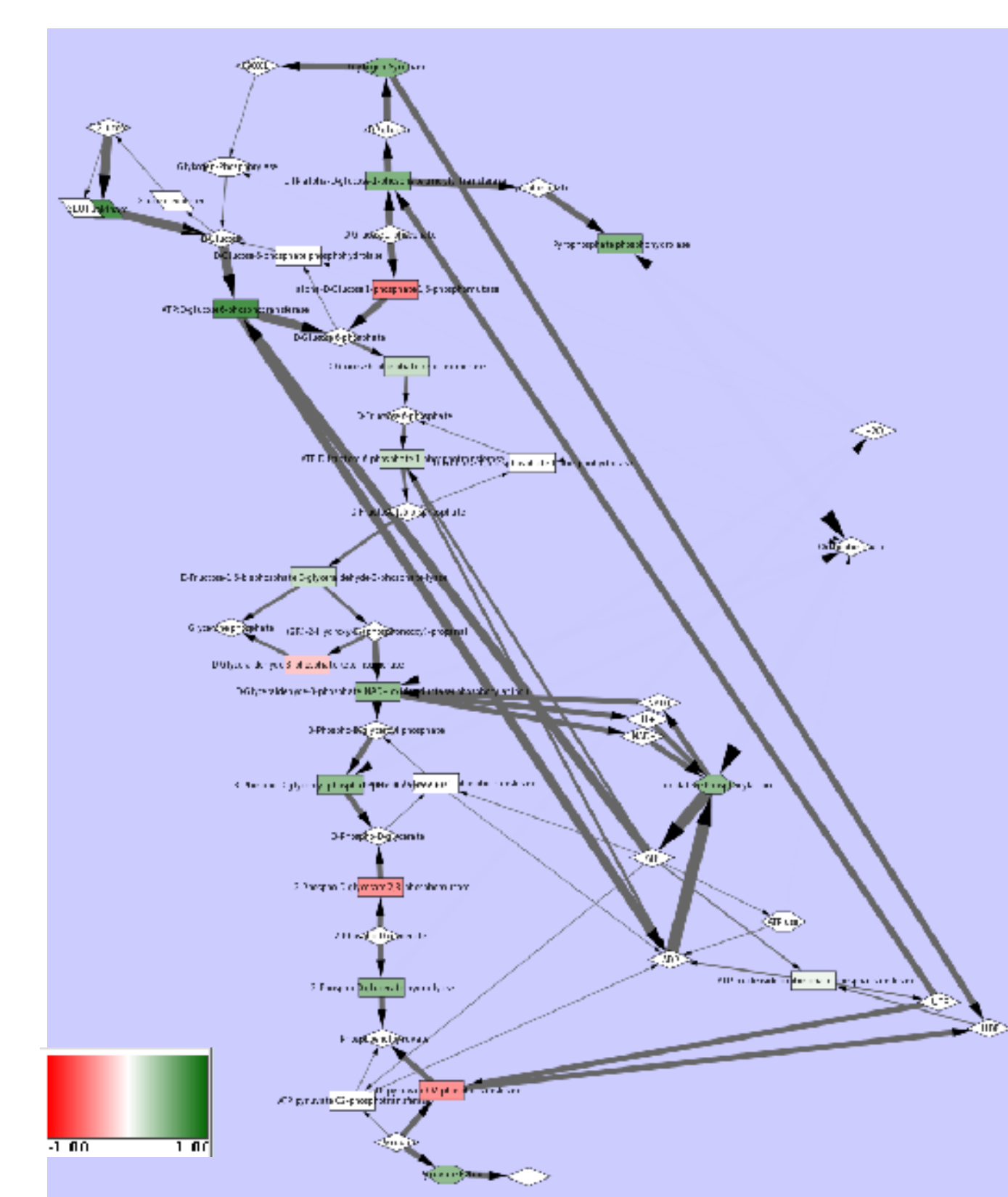


Fig.2: **Example FBA of submodel glycolysis.** Test if external glucose can be stored as glycogen. Targetflux: glycogen synthase Boundary Conditions: glucose import; pyruvate, glycogen export  
1. Extern **glucose can be stored as glycogen.**  
2. Glycogen synthesis is **coupled to glycolysis:** ATP, UTP needed for activation of glucose.  
Some glucose has to be metabolised to store glycogen.

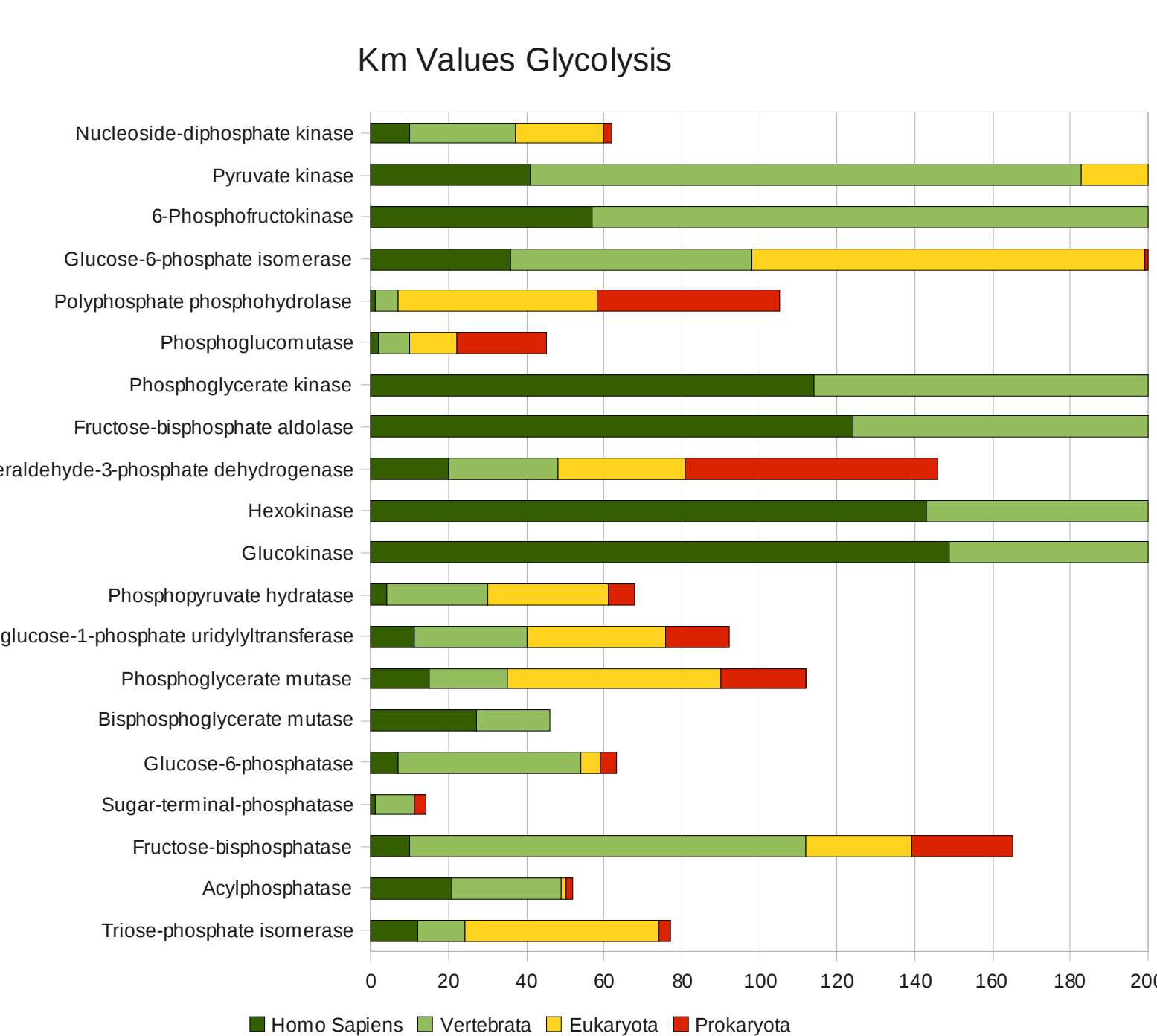


Fig.3: **Collected Km values** for reactions in submodel glycolysis.

Only key regulatory reactions have to be modelled in full detail [1,2] to reproduce the kinetic behaviour of the network. For some pathways detailed kinetic models have been developed in our group (Fig.4, [3,4]). This information is used to build the the full core metabolic network.

### Work in Progress

Working on test case glycolysis and gluconeogenesis (rate law formulation, integration of regulation and simulation). Applying the developed methods to all sub networks and the full core network in the future.

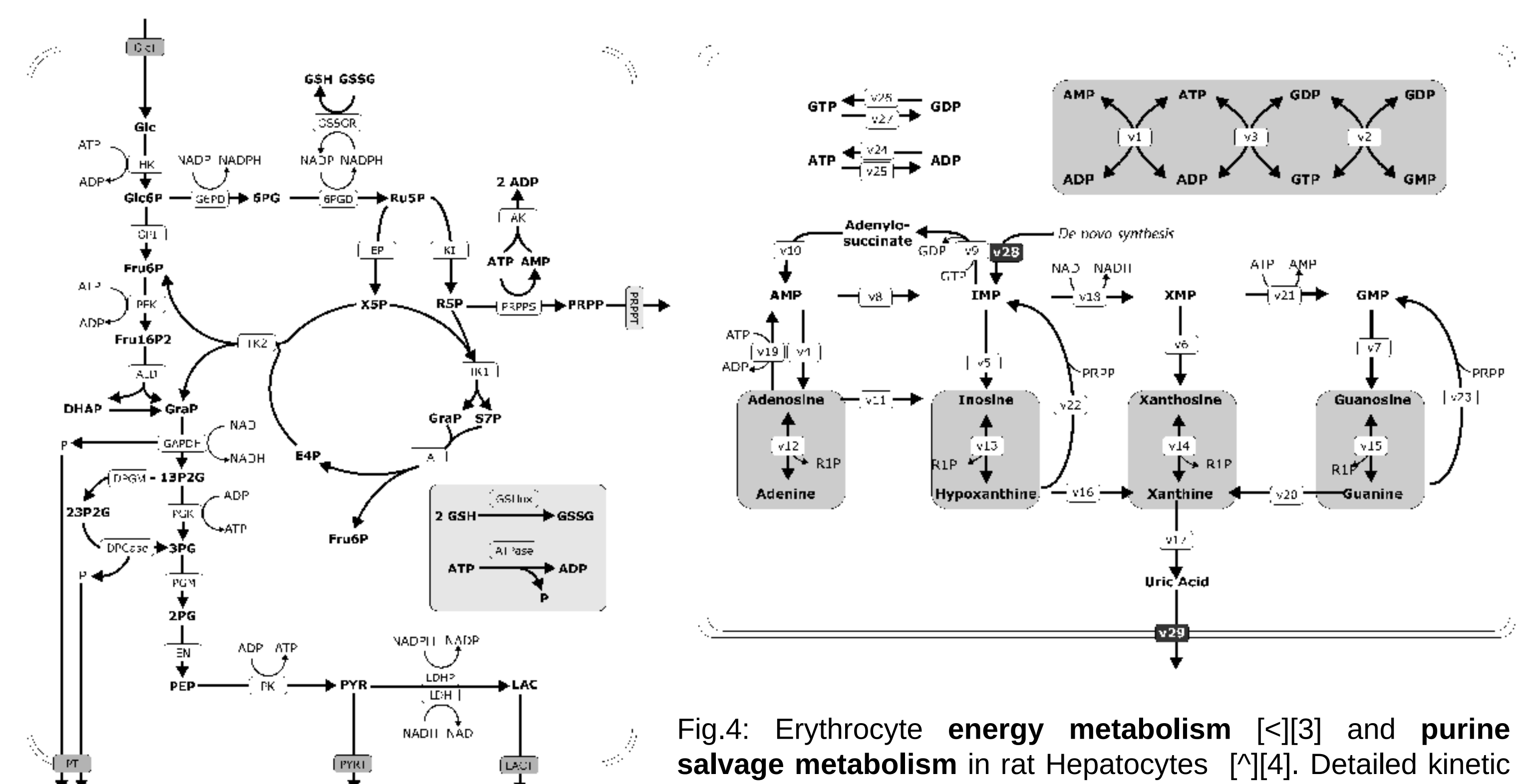


Fig.4: **Erythrocyte energy metabolism** [3] and **purine salvage metabolism** in rat Hepatocytes [4]. Detailed kinetic models for these sub networks available.

### References:

- [1] Kinetic hybrid models composed of mechanistic and simplified enzymatic rate laws, Sascha Bulik, Sergio Grimbs, Carola Huthmacher, Joachim Selbig and Hermann G. Holzhuetter; FEBS Journal (2008)
- [2] The stability and robustness of metabolic states: identifying stabilizing sites in metabolic networks Sergio Grimbs, Joachim Selbig, Sascha Bulik, Hermann-Georg Holzhuetter and Ralf Steuer; Mol Syst Biol. 2007;3:146. Epub 2007 Nov 13. (2007)
- [3] Use of mathematical models for predicting the metabolic effect of large-scale enzyme activity alterations. Application to enzyme deficiencies of red blood cells. Schuster R, Holzhuetter HG; Eur J Biochem. 1995 Apr 15;229(2):403-18. (1995)
- [4] Mathematical modelling of the purine metabolism of the rat liver. Bartel T & Holzhuetter HG; Biochim; Biophys Acta 1035, 331-339. (1990)
- [5] SABIO-RK: Integration and Curation of Reaction Kinetics Data Wittig U., Golebiewski, M., Kania, R., Krebs, O., Mir, S., Weidemann, A., Anstein, S., Saric, J. and Rojas, I. Lecture Notes in Bioinformatics, 4075: 94-103(2006).

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