Project #2

Title: Mathematical modeling of dysfunctional glucose metabolism in diabetes

Description: In obesity and diabetes, increased glucose metabolism occurs in tissues in a dysregulated or unscheduled way such that increased formation of the reactive metabolite, methylglyoxal (MG), occurs. Accumulation of MG modifies proteins to increase unfolding and activates the unfolded protein response (UPR), low-grade inflammation, insulin resistance and vascular disease. We recently discovered high glucose concentration stabilizes hexokinase-2 (HK2) to proteolysis in muscle, adipose tissue and vascular sites to initiate dysfunctional glucose metabolism – a process called "*HK2-linked glycolytic overload and unscheduled glycolysis*". We want to simulate the dysregulation of glucose control *in silico* to explore the key features and identify where to intervene with drugs for effective therapy.

In this project we will start with an established mathematical model of glucose metabolism in liver cells, hepatocytes, and add on to these reactions of MG formation and metabolism. We will explore the important determinants of MG formation. We will then make adaptation to model the formation of MG in pancreatic beta-cells and also vascular cells (by replacing glucokinase with hexokinase 1 and HK2 and other changes). The outcome will be an improved understanding of how to improve treatments to prevent and treat type 2 diabetes and vascular complications of diabetes.
Techniques used: computer-based mathematical modeling, data and literature mining.

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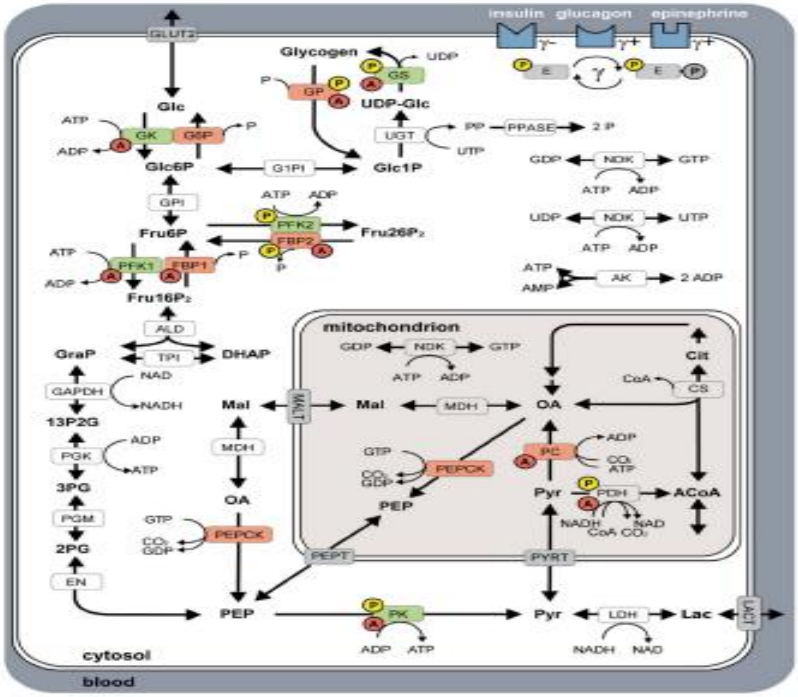

Figure 1. Overview of human hepatocyte model consisting of glycolysis, gluconeogenesis and glycogen metabolism. Metabolic model compartmentalized in blood, cytosol and mitochondrion (from Koenig et al., 2012 – see below).

References: König, M., Bulik, S. AND Holzhütter, H.-G. (2012) Quantifying the Contribution of the Liver to Glucose Homeostasis: A Detailed Kinetic Model of Human Hepatic Glucose Metabolism. PLOS Computational Biology 8, e1002577.
Rabbani, N., Xue, M. and Thornalley, P.J. (2022) Hexokinase-2-linked glycolytic overload and unscheduled glycolysis – driver of insulin resistance and development of vascular complications of diabetes. Internat J Molec Sci 23, 2165.