homeostasis of blood glucose

Computer simulations of central liver functions

by Matthias König and Hermann-Georg Holzhütter

The liver performs a multitude of important physiological functions such as synthesising plasma proteins, producing bile and hormones, detoxifying toxic compounds and precisely regulating the concentration of various substances in the blood (homeostasis). In particular, the liver plays a crucial role in the regulation of blood glucose levels.

Modelling hepatic glucose metabolism helps to understand central liver functions and basic regulation mechanisms and thereby provides insights in the role of the liver in systemic diseases such as diabetes.

Glucose regulation is vital

The concentration of glucose in the blood is maintained within a narrow range between 3 millimolars (mM) after prolonged fasting or extensive muscle activity and 9 mM after food intake. This homeostasis is crucial for the body. Too high concentrations of plasma glucose (hyperglycaemia) for an extended period result in protein modifications due to non-specific binding of sugar molecules to proteins (glycation), ultimately leading to tissue damage, especially in smaller blood vessels. On the other hand, too low concentrations (hypoglycaemia) result in under-supply of tissues and organs, first and foremost to the brain, which derives its energy almost entirely from glucose. Without the contribution of the liver to maintain the glucose levels under hypoglycaemia, we could only survive for a couple of minutes.

The blood glucose level – a dynamic quantity

The concentration of blood glucose is a dynamic quantity which is influenced by nearly all organs (figure 1). Its regulation is a challenge, since both utilisation (e.g. by muscle activity) and intake of glucose via food are subject to major fluctuations in the course of the day.

The hormones insulin and glucagon mainly regulate glucose homeostasis by adjusting both hepatic production and utilization of glucose and utilisation of glucose by muscle and fatty tissue. While insulin lowers the concentration of glucose, glucagon helps to counteract hypoglycaemia. The blood concentrations of insulin and glucagon change as direct response to alterations in glucose as their secretion by the pancreas is adjusted. An increase in blood glucose levels leads to an increase of insulin and a decrease in the glucagon concentration. Both hormones bind to receptors on the target organs, thereby activating signalling pathways that adapt glucose consumers and producers in a concerted manner to one another.

The liver's dual role in systemic glucose metabolism

The liver plays a dual role in glucose homeostasis (figure 2). On one hand, it produces hepatic glucose when the blood glucose level is too low (hypoglycaemia), for instance during extensive physical activity or prolonged fasting. On the other, if the levels are too high after meals (hyperglycaemia), the liver functions as a store and consumer of glucose. The liver can thus counteract systemic changes in blood glucose due to fluctuations in utilisation (sleep versus physical activity) and in glucose intake (fasting versus food uptake).

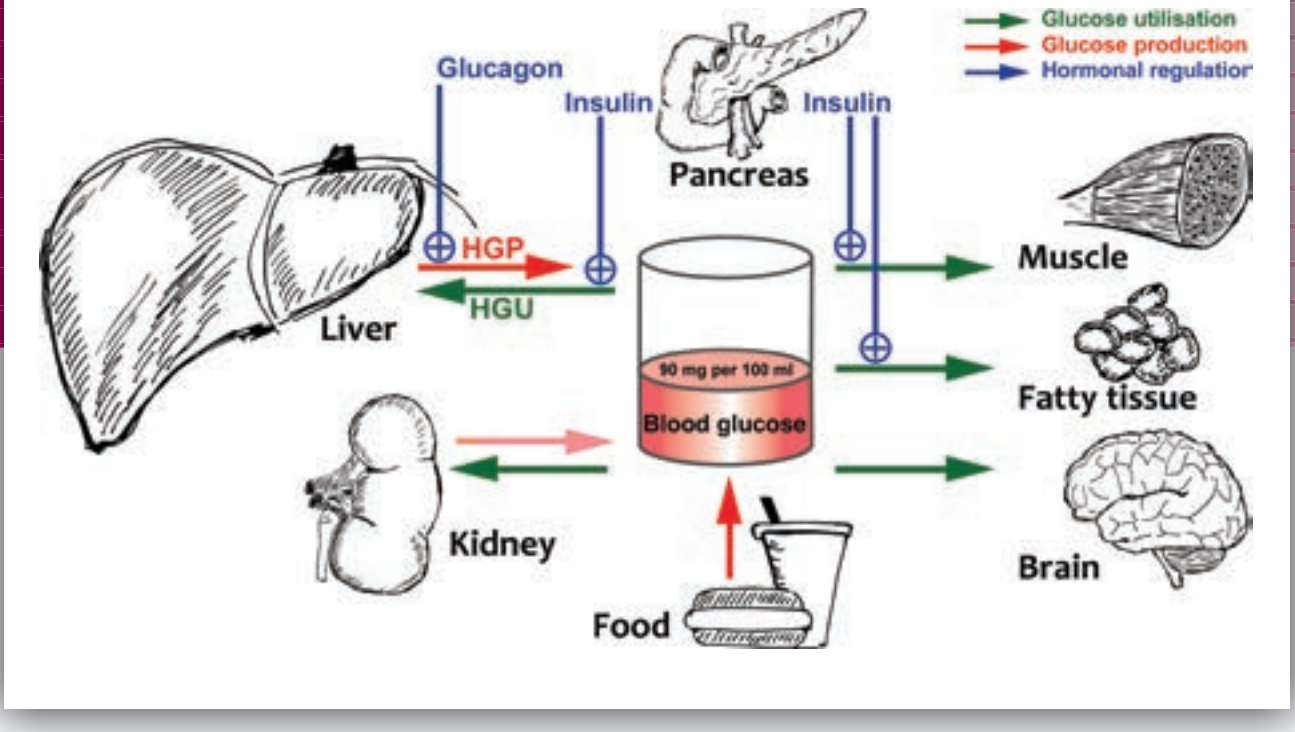

Figure 1: Homeostasis of the blood glucose level
The blood glucose concentration is decreased by glucose utilising organs and tissues (green) or increased by food uptake and glucose production (red). The glucose consumption of the brain is relatively constant in the course of the day, whereas the glucose requirement of muscles is subject to major fluctuations depending on activity. The liver can switch between production (hepatic glucose production, HGP) and utilisation (hepatic glucose utilisation, HGU) under normal physiological conditions. During extended periods of fasting the kidneys too can produce glucose. Insulin and glucagon, hormones secreted by the pancreas, play a central role in blood glucose regulation, firstly because control of utilisation by muscles and fatty tissue is insulin-dependent and secondly because HGU and HGP are adjusted by insulin and glucagon (Graphics: M. König).

Hepatocytes, the main liver cells, account for the bulk of the hepatic metabolic activity. Glucose metabolism in hepatocytes consists of the reactions of glycolysis (glucose degradation and subsequent conversion into fat or energy), gluconeogenesis, formation of glucose from precursors such as lactate, and the ability to store glucose as a polymer carbohydrate (glycogen). Hepatocytes form glycogen when blood glucose concentrations are high (glycogen synthesis) or release glucose from the glycogen store when glucose levels are low (glycogenolysis).

Due to the ability to either newly synthesize glucose or release from buffer stores, the body has implemented a system that can react quickly to fluctuations and counteract them.

The switch between glucose utilisation and production is controlled both by the hormones insulin and glucagon and by glucose itself in its role as a substrate, product, inhibitor and activator of reactions. In the liver insulin increases the activity of glucose-utilising metabolic pathways (HGU, glycolysis and glycogen synthesis) and reduces glucose-producing pathways (HGP, gluconeogenesis and glycogenolysis). Glucagon has the opposite effect. Insulin and glucagon act by changing the activity of key enzymes in glucose metabolism, such as pyruvate kinase or glycogen synthase.

Insulin and glucagon activate signalling cascades which result in changes of the phosphorylation state of key proteins that take effect within seconds or minutes accompanied by changes in activity, thereby permitting fast reaction to alterations in glucose utilisation or food uptake. Furthermore, over longer periods of hours, days or weeks modulation at the gene expression and protein levels take place that enable adaptation to states of fasting or to day and night rhythms.

Mathematic modelling of liver metabolism

Modelling liver metabolism is a central task of the Virtual Liver Network (www.virtual-liver.de), a large-scale national initiative of the German Federal Ministry of Education and Research (BMBF) which is of particular significance for establishing systems biology and systems medicine. The network aims to create a series of dynamic models of the human liver that, while not fully replicate its physiology, morphology and function, will represent key aspects in models (Holzhuetter *et*

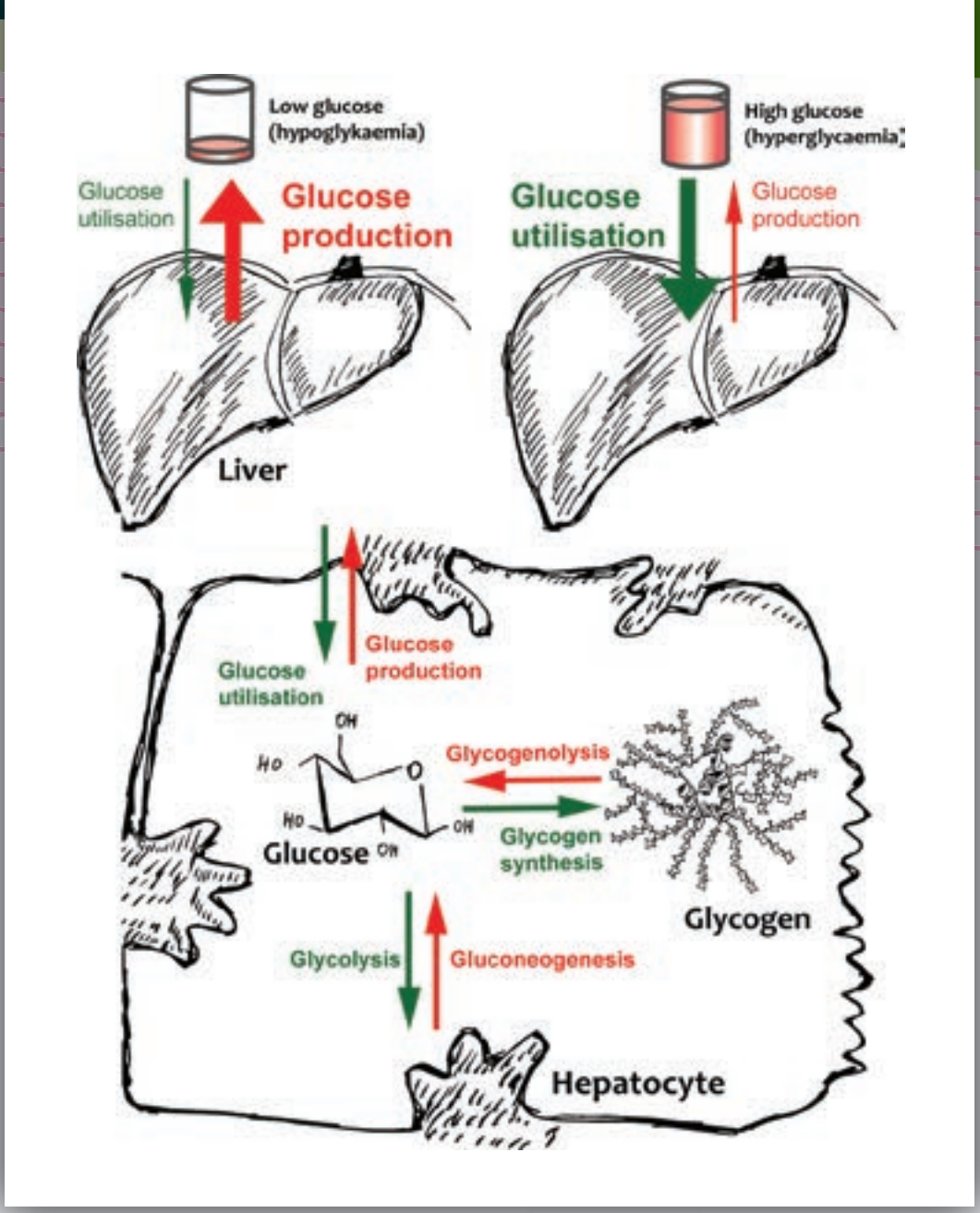

Figure 2: The liver's dual role in systemic glucose metabolism
The liver is able to switch between glucose production when blood glucose is low and glucose consumption when blood glucose is high. In hepatocytes, glucose can be used for energy production by means of glycolysis, or be synthesised *de novo* from precursors (gluconeogenesis). Furthermore, glucose can be stored as glycogen when the blood glucose levels are high (glycogen synthesis) or be released from glycogen when the blood glucose is low (glycogenolysis) (Graphics: M. König).

al., 2012). During this process, quantitative and qualitative data from all organisational levels will be integrated. One milestone in modelling the liver metabolism was the reconstruction of the hepatic reaction network HepatoNet1 (Gille *et al.*, 2010).

With the aim of gaining a better understanding of the central role played by the liver in glucose homeostasis, a detailed kinetic model of glucose metabolism was developed within the Virtual Liver Network (Koenig *et al.*, 2012; figure 3). The model includes hormonal control of glucose metabolism by insulin and glucagon via changes in the phosphorylation state of key enzymes, thereby linking hormonal control with metabolism. The mathematical core of the model is a description of individual processes by means of customary differential equations that make it possible to simulate the behaviour of metabolism over time.

Based on the kinetic properties of individual enzymes, the model describes the dual role of the liver as a producer (HGP) and utilizer (HGU) of glucose, depending on dynamic changes in blood glucose level and the hormones insulin and glucagon. It thus describes the systemic function of the liver in glucose metabolism (figure 3).

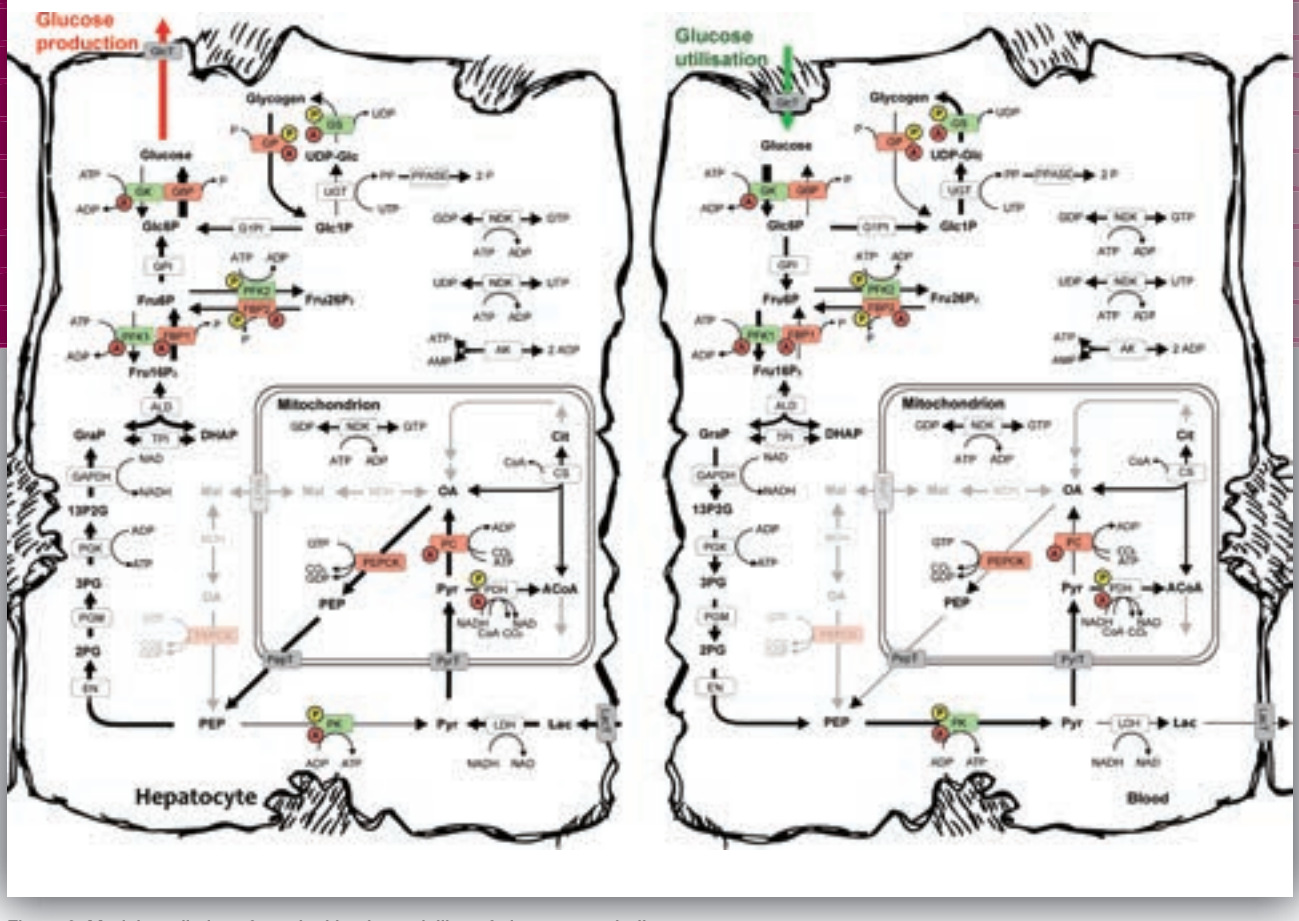

Figure 3: Model predictions from the kinetic modelling of glucose metabolism
Left: the liver works as a glucose producer when glucose concentrations are low. Part of the glucose released into the blood comes from glycogen stores, the remainder from glucose synthesis (gluconeogenesis). Right: the liver functions as a glucose consumer. Part of the utilised glucose is stored in the form of glycogen, the remainder enters glycolysis (Graphics: M. König, from König *et al.*, 2012).

The contributions of the liver are essential to the understanding glucose metabolism in the body. The developed model provides a module that can be used to model whole body glucose metabolism, thereby giving insights in disorders of glucose homeostasis such as diabetes (Ajmera *et al.*, 2013).

Application of the model to type 2 diabetes

Glucose homeostasis is impaired in type 2 diabetes mellitus (T2DM) because the hormonal signals do not match existing glucose concentrations in the blood and consequently lead to significantly increased blood glucose levels. Both the increase in insulin (relative insulin deficiency) and the decrease in glucagon as a consequence of increasing glucose concentration are reduced, resulting in higher glucagon concentrations. As a result of these wrong signals the liver produces too much glucose, which contributes additionally to the increased blood glucose level in diabetes. The administration of insulin to patients with T2DM becomes necessary if alternative therapies such as changes in lifestyle or treatment with the drug metformin fail to normalise blood glucose concentrations. One side effect of insulin therapy is an increased risk of hypoglycaemic episodes that, if untreated, can lead to confusion, loss of consciousness, and in serious cases to cramps, coma or even death.

The detailed kinetic model of glucose metabolism was used to examine the contribution of the liver to hypoglycaemia in T2DM (Koenig *et al.*, 2012). Our model predicts that the hepatic capacity to react to a falling blood glucose levels by increasing glucose production will be impaired because of changed enzymatic activities in gluconeogenesis as a result of incorrect hormonal signals. That could explain the increased number of hypoglycaemic episodes during strict insulin treatment. Furthermore, the model predictions regarding the normalization of the altered hormonal signals showed the great potential for normalising raised glucagon profiles in the treatment of T2DM.

Mathematical modelling over spatial and temporal scales

Mayor challenges in modelling the liver are the bridging of spatial and temporal scales from single hepatocytes to whole-liver in the range from seconds to days, as well as the integration of heterogeneous qualitative and quantitative data from clinical studies to animal experiments, from studies of the entire organism over isolated liver to experiments in cell cultures or on isolated proteins. Our research team is currently developing a multi-scale model of this kind.

The research project in brief:

The Computational Systems Biochemistry research group at the Charité Berlin is involved in developing computer models that simulate and predict complex biological processes. The modelling of glucose metabolism in the liver is a sub-project of the Virtual Liver Network funded by the BMBF, the German Federal Ministry for Education and Research (funding code 0315741).

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Contact:

Matthias König
Computational Systems Biochemistry
Charité – Universitätsmedizin Berlin
matthias.koenig@charite.de

Prof. Hermann-Georg Holzhütter
Computational Systems Biochemistry
Charité – Universitätsmedizin Berlin
hergo@charite.de

www.charite.de/sysbio