**Development and validation of a model of the fructose metabolism across the liver sinusoid.**

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**Highlights**

* Novel use of Process Systems Engineering techniques.
* A model of reaction mechanisms for fructose metabolism in the human liver.
* The model predicts the effects of novel therapeutic interventions.

**1. Introduction**

The liver is one of the most complicated processing organs in human body. It performs a broad range of biochemical functions for maintaining metabolic and energetic homeostasis of the whole body. Fructose, a daily dietary ingredient metabolised in the liver, had been proposed as a beneficial sweetener and recommended as a desired replacement for glucose for the obese and for diabetics. Yet both clinical and experimental studies recently have suggested a causal relationship between fructose over-consumption and damaged metabolism inducing hepatic steatosis [1-3]. However, neither animal models nor immortalised (HepG2) cell line studies have provided biologically accurate information relevant to human subjects due to species differences and the lipid build-up characteristics of HepG2 cells, respectively. Further, little is known on the effects of fructose on differential metabolic zones across the sinusoid. Therefore, a computational model based upon a systems biology approach is an attractive option to acquire a more comprehensive insight into the potential pathophysiological mechanisms of high fructose intake.

**2. Methods**

A kinetic model of hepatic fructose (± glucose/sucrose) metabolism was developed in MATLAB (Mathworks, MA, USA) based on modified Michaelis-Menten and Hill equations. The model includes literature identified biochemical components and reactions within distinct pathways, e.g. gluconeogenesis, *de novo* lipogenesis, beta-oxidation and triglyceride synthesis. The model parameters were determined and refined by comparison to literature values and also *in vitro* and *in vivo* studies (including a range of samples from healthy and diseased cases).

**3. Results and discussion**

In our *in silico* model, eight graded compartments including the fructose metabolism were constructed to represent hepatic heterogeneity along the periportal to perivenous axis. The simulations predicted increasing production of pyruvate, fatty acid and triglycerides on a 12-hour periodic basis after fructose feeding, showing good association with published values [4,5]. The model also shows sensitivity at a number of control loci that may represent therapeutic intervention points such as fructokinase and peroxisome proliferator-activated receptors (PPARs).

**4. Conclusions**

We have adopted a systems engineering approach to investigate the fructose metabolism across the liver sinusoid and to determine the rate of pathophysiological consequences that develop as a result of an affected metabolism. The results suggest that the model is robust and reliably predicts the behaviour of the fructose metabolism, showing an accumulation of lipid within the hepatocyte as a direct consequence of fructose feeding. The model is further expected to predict the effects of novel therapeutic interventions based upon identified regulatory points which can then be corroborated by experimental studies.

We believe that organ modelling *in silico* model systems will have numerous applications in developing future therapeutic strategies and are a future growth area for Process Systems Engineers in collaboration with clinical colleagues.

**References**

1. T. Jensen, et al. "Fructose and sugar: a major mediator of nonalcoholic fatty liver disease." *Journal of hepatology*, 2018.
2. X. Ouyang, et al. "Fructose consumption as a risk factor for non-alcoholic fatty liver disease." *Journal of hepatology,* 48(6), 2008, pp. 993-999.
3. L. G. Sánchez-Lozada, et al. "Comparison of free fructose and glucose to sucrose in the ability to cause fatty liver." *European journal of nutrition,* 49(1), 2010, pp. 1-9.
4. A. Asipu, et al. "Properties of normal and mutant recombinant human ketohexokinases and implications for the pathogenesis of essential fructosuria." *Diabetes*, 52(9), 2003, pp. 2426-2432.
5. K. L. Stanhope, et al. "Twenty-four-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup-, sucrose-, fructose-, and glucose-sweetened beverages with meals–." *The American journal of clinical nutrition*, 87(5), 2008, PP. 1194-1203.