173b Dynamic Modeling of Fatty Acid, Glucose, and Insulin Interactions

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The pancreas is a very important organ in the human body. The β-cells present in the pancreas secrete insulin in order to facilitate glucose uptake by the body tissues as a substrate for energy. Malfunctioning of these β-cells is the cause of diabetes. There are two types of diabetes: insulin dependent (Type I) and insulin independent (Type II). In Type I diabetes, the pancreas is incapable of secreting any insulin, whereas in Type II diabetes the body either becomes resistant to insulin or the pancreas does not produce sufficient insulin to control glucose concentration. One of the major long term effects of diabetes is hyperglycemia, where the plasma glucose concentration exceeds 120 mg/dl due to a lack of pancreatic insulin secretion. Prolonged hyperglycemia causes kidney disease, blindness, loss of limb, etc. Of more immediate concern in diabetes is hypoglycemia, where the plasma glucose concentration drops below the normal level (< 70 mg/dl). This starving of the cells for fuel can lead to dizziness, unconsciousness or even death. Present clinical approaches to glucose regulation for diabetic patients do not do a satisfactory job in maintaining the plasma glucose level within the normoglycemic range (70 - 120 mg/dl). For this reason there is a focus on model-based approaches to insulin delivery. The current mathematical models of diabetic patients are predominantly glucocentric (glucose-based); hence, these do not consider the effects of free fatty acid (FFA) metabolism in the body. However, approximately 90% of the muscle energy is derived from fatty acid metabolism when the body is at rest. Further more, significant interactions exist between fatty acid, glucose, and insulin. For instance, recent *in vitro* studies have shown that continuous hyperglycemia acts as a lipolytic agent thus enhancing the release of stored free fatty acid from adipose tissue into the plasma [1]. On the other hand, insulin acts as an anti-lipolytic agent by promoting the uptake of FFA from the plasma into the adipose tissue for storage as triglycerides [2]. High plasma FFA concentrations reduce insulin-mediated glucose uptake into the liver and periphery [3]. These interactions highlight the importance of fatty acids as metabolites and the necessity for their inclusion in mathematical models of metabolism.

In this work, the 'Bergman Minimal Model' [4] is extended to include fatty acid dynamics. The model assumes that all the required insulin is infused exogenously, such that the body itself is incapable of producing insulin. Modifications were made to the original model structure by adding a fourth and fifth state. The fourth state represents circulating fatty acid dynamics, including the FFA-glucose and FFA-insulin interactions. The fifth state represents a remote FFA concentration which effects the insulin mediated glucose uptake by the body tissues (akin to the "remote insulin" compartment in the original model). Terms representing FFA-glucose-insulin interaction effects were added on to the original Bergman differential equation for glucose dynamics. Parameters representing the FFA effect were estimated from published literature data.

A glucose-FFA meal model was also developed. The main purpose of the meal model was to quantitate the absorption of fed glucose, protein and FFA from gut into the circulatory system [5]. The model assumed that 90% of the fed protein yielded glucose. The outputs of the meal model (glucose and FFA absorption rate) are exogenous inputs for the extended patient model. The result shows that the modified minimal model including fatty acid dynamics fits the existing literature data well.

References

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