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# A comparison of models of the glucose-insulin regulatory system for applications in circadian research

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Circadian clocks control 24-hour rhythms in the human body, including glucose and insulin dynamics. Glucose tolerance changes depending on the time of day and misalignment between environmental stimuli such as light and food and internal circadian clocks, e.g., as observed in shiftwork, is associated with metabolic disturbances and diabetes. The mechanisms of these are poorly understood. A number of mathematical models of circadian clocks and those of glucose-insulin dynamics have been developed. However, no model accounts for the interaction between the two systems. Here we examine and compare key existing models of glucose-insulin regulatory system with the aim to select the most appropriate model for incorporation of circadian rhythms.

A large number of mathematical models designed to study glucose-insulin dynamics have been developed over the past few decades and account for such key features as (i) ultradian oscillations, (ii) response to glucose infusion, and (iii) glucose homeostasis. The seminal model able to reproduce these oscillations was developed by Sturis *et al.* (1991) utilising a system of 6 ODEs. Since then, a number of other models have been adapted from this model, aiming to either reformulate the Sturis model—often as a system of DDEs—or to extend the model to allow other applications, for example in the Intravenous Glucose Tolerance Test. However, comparisons of the models with physiological experimental studies have been relatively limited in scope.

In this work, we compare the qualitative and quantitative predictions of the Sturis *et al.* (1991), Tolić *et al.* (2000), and Li *et al.* (2006) models and two other models with experimental results, under constant glucose infusion. We show the different parameter ranges in which the models display sustained ultradian oscillations and how this corresponds to the expected behaviour in published physiological studies. We also test the mean values, amplitudes, and frequencies of the simulated glucose and insulin concentrations against experimental studies. This sophisticated comparison of the models allows us to select the most appropriate model to incorporate circadian rhythms.

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