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Mathematical investigation of diabetically impaired ultradian oscillations in the glucose-insulin regulation

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Abstract

We study the effect of diabetic deficiencies on the production of an oscillatory ultradian regime using a deterministic nonlinear model which incorporates two physiological delays. It is shown that insulin resistance impairs the production of oscillations by dampening the ultradian cycles. Four strategies for restoring healthy regulation are explored. Through the introduction of an instantaneous glucose-dependent insulin response, explicit conditions for the existence of periodic solutions in the linearised model are formulated, significantly reducing the complexity of identifying an oscillatory regime. The model is thus shown to be suitable for representing the effect of diabetes on the oscillatory regulation and for investigating pathways to reinstating a physiological healthy regime.

Keywords: Diabetes, Impaired ultradian rhythms, Four healthy regulation strategies, Delay differential equations, Stability analysis.

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1. Introduction

Diabetes Mellitus is an illness which impairs the regulation of glucose and insulin blood levels. There are two main types: Type 1 diabetes (T1DM), which is an autoimmune disorder where the body destroys the β-cells in the pancreas, almost completely removing the body's ability to secrete insulin [23], and type 2 diabetes (T2DM), where the muscle cells start to become insulin resistant, hindering the body's ability to utilise glucose correctly [23]. It can be the cause of many other long term problems, such as, retinopathy, cardiovascular disease, nephropathy and neuropathy [5], and is expected to be the 7th leading cause of death by the year 2030 [20].

Within this regulation, both rapid (period $\approx$ 6-15 minutes) and ultradian (period $\approx$ 80-180 minutes) oscillations of insulin have been observed [29], along with glucose oscillations (period $\approx$ 80-150 minutes) that are tightly coupled to the insulin oscillations of similar period [30]. This work solely focuses on the modelling of these ultradian oscillations, which were first discovered in [10] and have been observed during fasting, meal ingestion, continuous enteral nutrition, and under a constant glucose infusion [33]

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