Research Plan

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Question

How does treating the level of beta cells as a *continuously* varying slow parameter affect the qualitative behavior of the scaled reduced immune model developed by Mahaffy and Edelstein-Keshet [1], and how can those findings be applied to understanding and predicting type 1 diabetes?

Goals and Hypothesis

Background Information

Autoimmune diabetes, or type 1 diabetes, is a disease in which the immune system attacks insulin-producing pancreatic beta cells, leading to high blood glucose levels and other symptoms [2]. Furthermore, no screening test exists for this disease, which can only be diagnosed after symptoms appear [2]. Research with NOD (non-obese diabetic) mice has demonstrated that the onset of diabetes follows an elevated level of autoreactive T cells in the blood (which destroy beta cells); furthermore, the level of these cells followed a cyclic pattern over time [3]. To better understand the mechanism underlying these oscillations, Mahaffy and Keshet constructed a mathematical model that explained the phenomenon as caused by a gradual decrease in beta cell level [1].

Mathematical analysis of such models can reveal bifurcations, or qualitative changes in behavior; such findings can be applied to predict similar changes in real-world systems. One type, termed a Hopf bifurcation, is of particular note because when the model parameter is continuously slowly varying, the oscillations this bifurcation normally causes will be delayed and will occur later than expected [4]. Mahaffy's model has a Hopf bifurcation, which is responsible for the oscillating T cell levels, but the researchers *did not analyze it with a continuously varying parameter*, though they explicitly stated the parameter should behave this way.

Goals

This experiment aims to complete the analysis by looking into the behavior of the model when the level of pancreatic beta cells is treated as a continuously varying parameter. In particular, the analysis will focus on the behavior of the model with this modification compared to the behavior described in the original paper and the behavior of actual the biological system in NOD mice.

Hypothesis

If the model for the level of immune cells in the weeks before the onset of type 1 diabetes is analyzed with both a continuously varying and a static peptide clearance rate δ_p, then in the former analysis, the oscillations present in the original model will begin at a later time because research has shown this behavior is delayed in other models when analyzed with a continuously varying parameter.

Procedures

See the attached procedures.

Risk and Safety

As the experiment solely involves numerical computations, no safety risks are anticipated.

Data Analysis

After simulation, the experiment will result in a set of bifurcation diagrams as well as model-over-time diagrams. The bifurcation diagram shows the maximum and minimum values of A over time for

a trial run of the model with the particular parameter level indicated on the x-axis. Thus, the bifurcation diagram shows at what *static* parameter levels diabetes can occur. For this experiment, a third diagram will be generated overlaying the model-over-time diagram for the *continuous* system onto the bifurcation diagram. Since the parameter will continuously and linearly vary over time, a correspondence between the points of the two graphs exists (i.e. for the model-vs-time graph, at a certain time, the parameter will be at a unique particular value in the X-range of the bifurcation diagram), and therefore the two modes of simulation can be compared – the goal of this experiment.

Bibliography

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