A mathematical model for ketosis-prone diabetes suggests the existence of multiple pancreatic β-cell inactivation mechanisms

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Abstract Ketosis-prone diabetes mellitus (KPD) is a subtype of type 2 diabetes, which presents much like type 1 diabetes, with dramatic hyperglycemia and ketoacidosis. Although KPD patients are initially insulin-dependent, after a few months of insulin treatment, $\sim 70\%$ undergo near-normoglycemia remission and can maintain blood glucose without insulin, as in early type 2 diabetes or prediabetes. Here, we propose that these phenomena can be explained by the existence of a fast, reversible glucotoxicity process, which may exist in all people but be more pronounced in those susceptible to KPD. We develop a simple mathematical model of the pathogenesis of KPD, which incorporates this assumption, and show that it reproduces the phenomenology of KPD, including variations in the ability for patients to achieve and sustain remission. These results suggest that a variation of our model may be able to quantitatively describe variations in the course of remission among individuals with KPD.

Introduction

Diabetes, a disease characterized by high blood glucose levels, is one of the most common chronic diseases in the United States, affecting more than 34 million adults in 2020 (***CDC, 2020***). In healthy people, blood glucose levels are regulated by the hormone insulin through a negative feedback loop. High blood glucose promotes the secretion of insulin from the β-cells of the pancreas. Insulin, in turn, lowers blood glucose by suppressing glucose production (e.g., in the liver) and promoting glucose uptake (e.g., by the muscle). Thus, diabetes is associated with defects in this homeostatic feedback loop (***DeFronzo, 1988***). Diabetes is often divided into Type 1 diabetes (T1D) and Type 2 diabetes (T2D). In T1D, autoimmune destruction of the β-cells results in a complete lack of insulin production, and thus dependence on insulin treatment for survival (***Katsarou et al., 2017***). In T2D, such autoimmunity is not present. T2D is generally viewed as a progressive disease, in which blood glucose control gradually worsens over the course of years. In early stages of T2D pathogenesis, the body produces insulin, but its ability to reduce blood glucose levels is inadequate (*insulin resistance*). In later stages of T2D, insulin production declines, eventually leading to dependence on insulin treatment (***DeFronzo et al., 2015***).

Mathematical modeling of diabetes has focused on two widely separated timescales. Short-

timescale models describe the dynamics of insulin and glucose over minutes or hours (***Bergman et al., 1979***; ***Cobelli et al., 2014***; ***Toffolo et al., 1995***, ***2001***; ***Stefanovski et al., 2020***). These models describe the negative feedback loop, where glucose promotes insulin secretion and insulin promotes glucose disposal. Such models have been used extensively in the interpretation of physiological measurements, e. g., to infer insulin sensitivity on the basis of glucose tolerance tests (***Bergman et al., 1979***; ***Della Man et al., 2002***). A second class of models integrate simple short-timescale models with processes that occur on longer timescales of months to years, with the goal of describing T2D pathogenesis (***Topp et al., 2000***; ***Ha et al., 2016***; ***Ha and Sherman, 2020***; ***Karin et al., 2016***; ***De Gaetano and Hardy, 2019***). These models generally include an *adaptive* process, where either slightly elevated glucose or per-β-cell insulin secretion prompts increases in β-cell activity or mass, and a *glucotoxicity* process, where severely elevated glucose causes death or deactivation of β-cells. Adaptation may involve increases in mass or secretory function of individual cells, or it may include cell division that can eventually produce recovery from death of cells (***Topp et al., 2000***; ***Ha et al., 2016***), but evidence suggests that β-cells do not proliferate appreciably in adults (***Cnop et al., 2009***; ***Saisho et al., 2013***). Whether or not some amount of proliferation can occur, it is empirically true that T2D of short duration can generally be reversed by interventions which improve insulin resistance and secretion, while T2D of longer duration which has advanced to severe hyperglycemia cannot be reversed (***UK Prospective Diabetes Study Group, 1995***; ***Turner et al., 1999***), a fact which is explained by existing models since they connect severe hyperglycemia to severe losses of β-cells (***Ha et al., 2016***).

The focus of this work is on *Ketosis-prone type 2 diabetes* (KPD), a subtype of T2D, common in particular in patients of African descent (***Vellanki and Umpierrez, 2017***; ***Umpierrez et al., 1995***; ***McFarlane et al., 2001***; ***Mauvais-Jarvis et al., 2004b***). KPD presents with ketosis or diabetic ketoacidosis (DKA), an episode of extremely high blood glucose and low blood pH due to excess ketone bodies. Such an episode is associated with a lack of insulin secretion and action and thus, in the absence of a known precipitating cause, is classically thought of as a symptom of T1D rather than T2D. Unlike in T1D, however, β-cell autoimmunity is not present in KPD. Further, KPD patients can often achieve partial remission: after a few weeks or months of treatment with insulin, they are no longer dependent on insulin and can control blood sugar with diet or oral antidiabetic agents (***Mauvais-Jarvis et al., 2004b***; ***McFarlane et al., 2001***; ***Vellanki et al., 2016***; ***Umpierrez et al., 1997***; ***Vellanki et al., 2020***). There is substantial heterogeneity in response to insulin treatment, with some patients unable to achieve remission, and the duration of the remission varying from 6 months to 10 years (***Mauvais-Jarvis et al., 2004b***). Although no study has systematically characterized the duration of high blood sugar preceding the acute DKA event, patients generally report less than 4 weeks of diabetes-associated symptoms (polyuria, polydipsia, and weight loss) prior to the emergency (***Vellanki and Umpierrez, 2017***). In Table 1, we list these and other known features associated with KPD, which any mathematical model of KPD should be able to explain.

Existing models of diabetes pathogenesis, in which β-cell deactivation occurs slowly over months and is often thought to be irreversible, cannot account for these phenomena. Instead, the possibility of rapid onset of severe hyperglycemia and rapid remission of KPD suggest the existence of a faster pathogenic mechanism, operating on timescales of days or weeks. Indeed, in an experiment where a KPD patient was given a 20-hour infusion of glucose, it was observed that their level of insulin secretion (but not that of a control) dropped by about a factor of two over the course of the infusion[2] (***Umpierrez et al., 2007***). This intermediate-time-scale process is not in current mathematical models of T2D. We thus propose that KPD differs from conventional T2D through the presence of a second type of glucotoxicity, which is fast but reversible. This mechanism may also be present, but merely less pronounced, in T2D patients who do not show features of KPD.

[1]This is a common observation in our (PV) clinic, but it is difficult to test its statistical significance because antecedent data for new-onset diabetes is usually unavailable.

[2]Note that quantitative interpretation of this experiment is hard since there was just one patient and since the experiment measured the ratio of C-peptide to glucose, and not directly the amount of secreted insulin at fixed glucose.

Table 1. Features of KPD that a mathematical model should explain

1	Associated with obesity and insulin resistance (***Umpierrez et al., 1995***)
2	Potentially rapid onset of hyperglycemic crisis (***Umpierrez et al., 1995***; ***Vellanki and Umpierrez, 2017***)
3	Onset of hyperglycemic crisis associated with period of high sugar consumption[1]
4	Ketotic relapses are preceded by a period of hyperglycemia (***Mauvais-Jarvis et al., 2004b***)
5	Poor β-cell function at presentation (***Umpierrez et al., 1995***)
6	Improvement of β-cell function with weeks or months of insulin treatment (***Umpierrez et al., 1995***; ***McFarlane et al., 2001***)
7	Worsening of β-cell function after many hours of glucose infusion. (***Umpierrez et al., 2007***)
8	Patient-to-patient variation in ability to achieve and sustain remission (***Mauvais-Jarvis et al., 2004b***; ***McFarlane et al., 2001***; ***Vellanki et al., 2016***; ***Umpierrez et al., 1997***; ***Vellanki et al., 2020***)
9	Duration of remission is improved by (non-insulin) blood glucose management, due to greater β-cell function (***Vellanki et al., 2016***; ***Umpierrez et al., 1997***; ***Vellanki et al., 2020***)
10	Long-term declines in insulin sensitivity and secretion are similar to "conventional" T2D (***Mauvais-Jarvis et al., 2004b***; ***Banerji et al., 1996***)
11	Patients with less insulin resistance have lower glucose in remission, although it is unclear if this predicts long-term prognosis (***Vellanki et al., 2020***)

Adding this mechanism to the existing view of diabetes pathogenesis, we arrive at a mathematical model depicted in Fig. 1 and described by Eqs. (1–4) (*Materials and methods*).

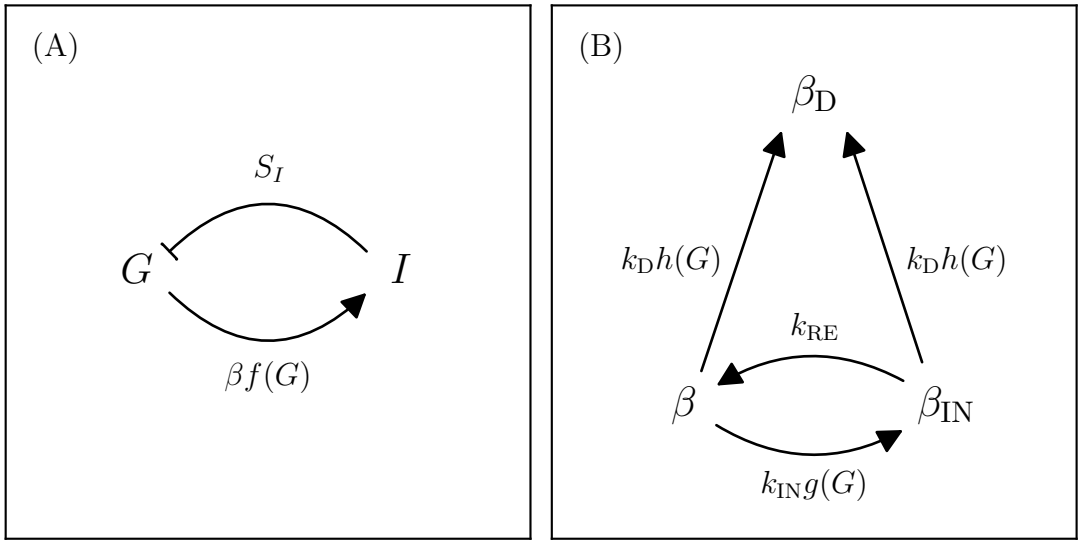

Figure 1. A model of KPD incorporating the hypothesis of reversible β-cell deactivation. Here we illustrate schematically the model described by Eqs. (1–4) (*Materials and methods*). A: Glucose promotes insulin secretion, and insulin lowers glucose, in a negative feedback loop. The effect of insulin on glucose disposal is mediated by the insulin sensitivity S_I, and the amount of insulin secreted is proportional to the mass of active beta cells β. This couples these fast dynamics to the slower dynamics in panel B. B: Longer timescale dynamics incorporate two distinct types of glucotoxicity. An intermediate scale, reversible glucotoxicity with rate $k_{\mathrm{IN}}g(G)$ produces an inactive pheonotype β_{IN}, which recovers at rate k_{RE}. Simultaneously, a slower process causes permanent β-cell deactivation or death at rate $k_{\mathrm{D}}h(G)$. The dependence of these rates on G couples these processes to those in panel A.

In addition to the processes described in Fig. 1 and Eqs. (1–4), we assume the existence of a slow

adaptation process where β-cells can increase their secretory capacity when G is above some set point value (which we take to be $80\ \mathrm{mg/dL}$). However, below we only simulate patients in advanced prediabetes, where we presume that β-cells have already maximized their secretory capacity, so that no increase in β due to further adaptation is modeled. Further details are provided in the Methods.

Results

Numerical simulations of this model reproduce the phenomenology of KPD

We begin by simulating our model, Eqs. (1–4), for different parameter choices, representing different possible patient phenotypes. Since the glycemic emergency or DKA in KPD is often preceded by a period of high sugar consumption (table 1, criterion 3), and in past experiments such patients show reductions in β-cell function during a period of glucose infusion (***Umpierrez et al., 2007***), we simulate a period of a month of increased sugar consumption. The outcome of this simulation is shown for four different choices of model parameters in Fig. 2. All four sets of parameter values are chosen to result in a similar level of fasting hyperglycemia ($G \approx 110\ \mathrm{mg/dL}$) by adjusting the values of k_{IN}, k_{RE}, k_{D} and β_{TOT} with all other parameters held fixed.

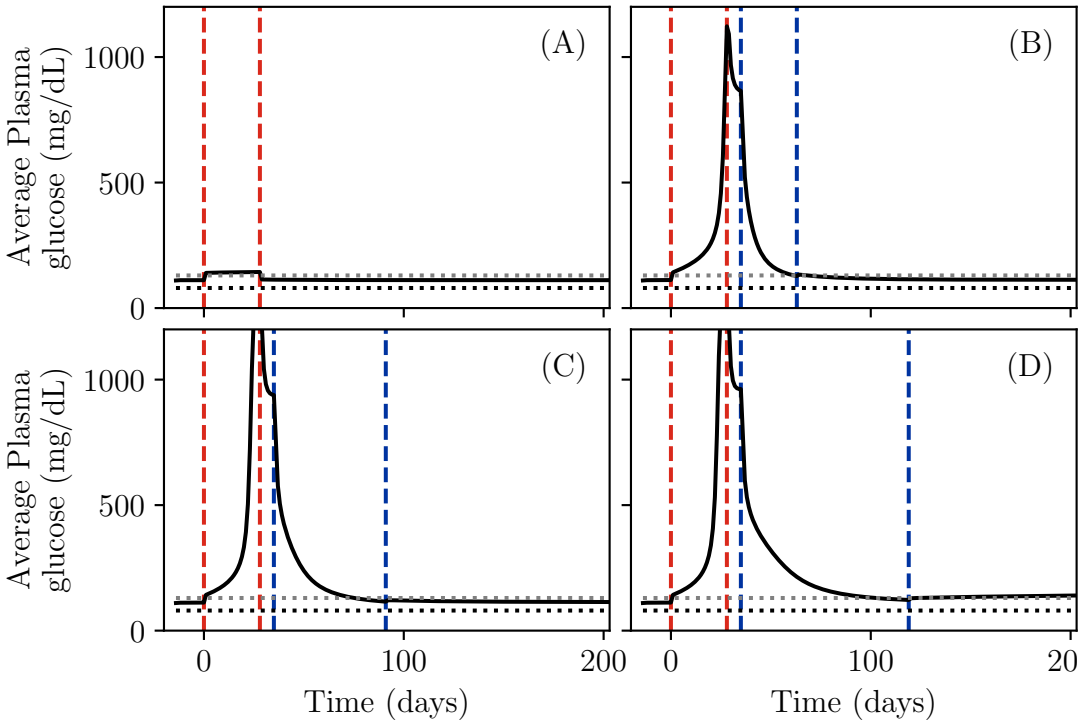

Figure 2. Simulations showing the onset and remission of KPD in our model. Solid black lines show daily blood glucose averages. Red dashed lines demarcate a period of increased sugar consumption, while blue dashed lines demarcate a period of insulin treatment, if present. Horizontal dotted lines indicate 80 mg / dL (black, typical normoglycemia) and 130 mg / dL (gray, diabetes control threshold per American Diabetes Association). A: With a low rate k_{IN} of reversible β-cell inactivation, blood glucose returns to normal after the period of high sugar consumption. B: With a high rate k_{IN} of reversible β-cell inactivation, the same period of high sugar consumption produces a sharp rise in the blood glucose level, associated with a sharp drop in β-cell function, which persists after the period of sugar consumption ends. A sufficiently long period of insulin treatment can produce an insulin-free remission. C: A lower rate k_{RE} of β-cell reactivation, compared to B, increases the time required to produce remission with the same insulin treatment. D: A higher rate k_{D} of permanent β-cell death, compared to C, results in a failure to achieve insulin-free remission.

Figure 2(A) shows the daily average of the plasma glucose for a low value of the reversible β-cell inactivation rate k_{IN}. For this set of parameters, although blood glucose rises during the period of

high sugar consumption, it returns to its previous value when the period of high sugar consumption ends. In contrast, when k_{IN} is large, Fig. 2(B), the same period of increased sugar consumption results in a dramatic rise of blood glucose which persists after the sugar consumption is stopped (between the second red and first blue lines). Insulin treatment, carried out until blood glucose is well controlled (between the blue lines), produces a remission of this dramatic hyperglycemia, returning the glucose to its value before the period of high sugar consumption. The character of this remission is affected by the parameters of the model. Figure 2(C) shows a simulation with a slower reactivation rate k_{RE}. In this case, a longer period of insulin treatment is necessary in order to produce remission. Finally, Fig. 2(D) shows a simulation with this lower reactivation rate, and furthermore a higher rate of β-cell death k_D. As a result, the total β-cell population, β_{TOT}, declines enough during the period of high blood sugar that insulin-free remission cannot be maintained.

We thus see that our model reproduces the qualitative features associated with KPD. Starting from a period of mild hyperglycemia, a period of increased sugar consumption can produce a rapid progression to reduced β-cell function and severe hyperglycemia (Table 1, criteria 2–5). Treatment with insulin for weeks or months can produce a partial remission, in which a state of mild hyperglycemia is maintained without further insulin treatment (Table 1, criterion 6). Further, the model can produce heterogeneous patient outcomes: the time required to achieve remission and the possibility of relapse are different for different parameter values (Table 1, criterion 8). Since a failure to maintain remission emerges from glucotoxicity in this model, it is also consistent with the observation that better blood sugar management increases the duration of remission (Table 1, criterion 9). Since long-term prognosis, in the absence of further crises, is governed by the same slow glucotoxicity process as progresion of conventional T2D, criterion 10 is also satisfied. Criteria 1 and 11 will be discussed below. Finally, recall that criterion 7 has been directly included as an assumption in the model. Thus, the model reproduces the desired features of KPD, described in Table 1.

We will now perform more detailed analysis of the properties of our model, to understand why it produces this phenomenon of rapid onset and remission, and which biological parameters are expected to be most relevant to the KPD phenotype.

Rapid onset and remission of severe hyperglycemia result from bistability of fasting glucose

The onset and remission seen in our simulations are reminiscent of bistability in dynamical systems: the blood glucose in the KPD patients in this model seems to have two stable values, with transition between the two triggered by intense glucose consumption or insulin treatment. Indeed, since bistability is often associated with positive feedback loops (***Alon, 2019***), and the reversible inactivation of β-cells by glucose creates such a loop, it is natural to expect such a behaviour. We now make this intuition more precise.

We begin by analyzing the model in the absence of exogenous glucose intake. The fixed point of the fast dynamics in this case is the fasting glucose. If a high-glucose fixed point is present in the reversible β-cell deactivation dynamics even in the absence of glucose intake, we expect it to persist in the presence of glucose intake. Since the glucose/insulin dynamics are fast at fixed β, we assume that they reach their fixed point, and since the β-cell death is slow, we neglect it entirely (for our form of death dynamics, the only true fixed point is at $\beta = 0$).

Figure 3 shows the result of this analysis for the parameters shown in Fig 2. In panel A, corresponding to a set of parameters that do not give KPD-like behaviour, there is a single stable fixed point. Thus, when glucose intake is low, the active β-cell population will always return to a healthy level, and the glucose will always return to its original, moderate elevation. On the other hand, in panel B, there is a second stable fixed point of the β-cell dynamics, corresponding to low β and high G. Since this fixed point is stable even in the absence of glucose intake, the state of β-cell dysfunction and high glucose persists even in the absence of continued sugar intake, as seen between the second red and first blue dashed lines in Fig 2B.

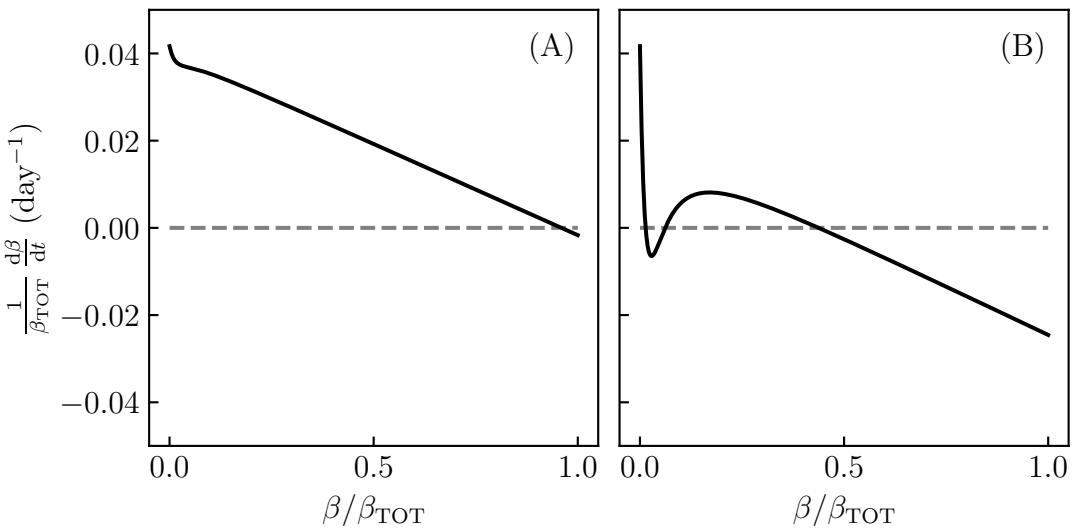

Figure 3. The reversible β-cell dynamics have two fixed points for parameters which produce KPD-like behavior. After assuming that the fast-timescale glucose/insulin dynamics relax to their fixed-point at a given value of β, we compute $\mathrm{d}\beta/\mathrm{d}t$ for the intermediate-timescale, reversible dynamics as a function of β for the parameter values shown in Fig. 2(A,B). Fixed points are given by values of β where the curve crosses the dashed line an thus $\mathrm{d}\beta/\mathrm{d}t = 0$. A: For model parameters where simulations do not show KPD-like behavior, there is a single stable fixed point of the intermediate-timescale dynamics. B: For model parameters where simulations show KPD-like behavior, there are two stable fixed points, corresponding to a high β / moderate G state and a low β / high G state.

Moving from the high-β fixed point to the ketosis fixed point, however, requires a period of high glucose intake. Thus, to understand fully the dynamics seen in our simulations (Fig. 2), we must extend our analysis to include glucose intake. We have assumed, as is natural, that glucose intake is concentrated at a few meals rather than being constant. Thus, in this case we cannot assume that G and I sit at a fixed point. We may still, however, make use of the rough separation of timescales between the fast and intermediate-timescale dynamics. At each fixed value of β, we simulate a single day of glucose/insulin dynamics, as in Fig. 2. From the trace of $G(t)$ over a single day and the current values of β and β_{IN}, we then compute the current rates of β-cell activation and deactivation. We continue to neglect the slower, permanent β-cell death.

Figure 4 shows how the fixed points change as a result of glucose intake. At moderate glucose intake (black curves), the fixed points of the β-cell dynamics are shifted slightly, but remain qualitatively unchanged from the case without sugar intake (Fig. 3). At high glucose intake (red curves), however, the difference between the "conventional" T2D patient and the KPD patient is revealed. In the former case (A), the single fixed point is again only shifted by the increased sugar intake. In the latter case (B), however, the high-β fixed point vanishes. Thus, as seen in our simulations, the period of high sugar intake results in a flow toward the low-β fixed point, regardless of the initial conditions. Finally, when a sufficiently high amount of exogenous insulin is delivered (B, blue curve), the ketosis fixed point vanishes, resulting in a flow toward the high-β fixed point, regardless of the initial conditions.

As in Fig. 2(D), it is possible for the irreversible β-cell death during a period of high glucose to move the fixed points, or perhaps even destroy the high-β fixed point, resulting in permanent insulin dependency. Furthermore, improvements in the insulin sensitivity S_I, associated with lifestyle modifications, may be able to destroy the low-β fixed point, or increase the degree of sugar intake required to destabilize the high-β fixed point. To study these possibilities, we adjust S_I and the total β-cell population $\beta_{\mathrm{TOT}} = \beta + \beta_{\mathrm{IN}}$, with all other parameters of the model held fixed to the values from Fig. 2(A,B). For each value of $(S_I, \beta_{\mathrm{TOT}})$, we classify the resulting state based on the fixed points

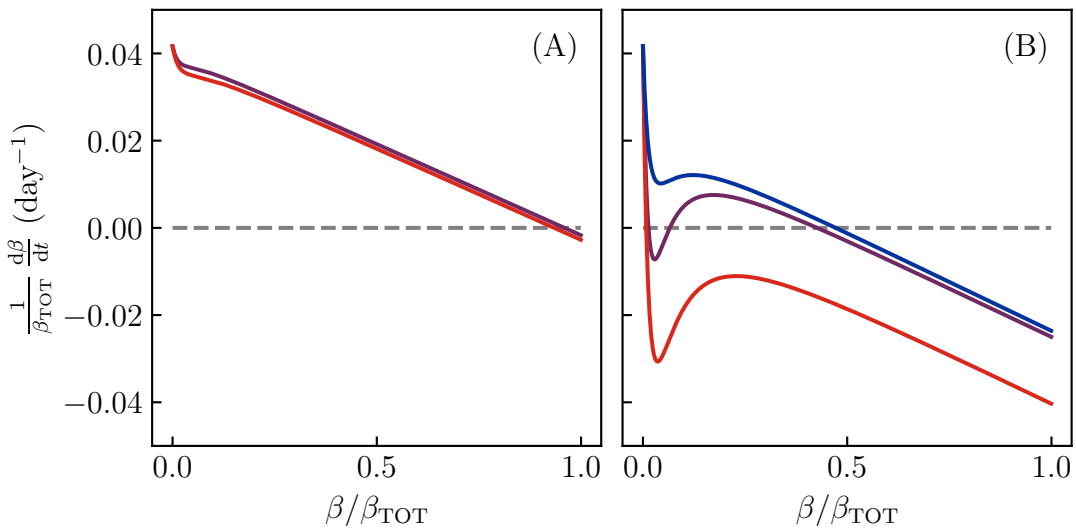

Figure 4. Glucose or insulin intake can push the β-cell dynamics between the fixed points. We compute $\mathrm{d}\beta/\mathrm{d}t$ for the intermediate-timescale, reversible dynamics, averaged over a day. We use the parameter values shown in Fig 2A,B. Purple curves correspond to the low daily sugar intake (region outside the blue and red dashed lines in Fig. 2; note that the curves are only slightly different from the black curves in Fig. 3), red curves to the high sugar consumption between the red dashed lines in Fig. 2, and blue to a gradual release insulin treatment, as between the blue dashed lines in Fig. 2). A: For model parameters where simulations do not show KPD-like behavior, there is a single stable fixed point of the intermediate-timescale dynamics, which is qualitatively unchanged by the high-glucose-consumption condition. Thus, as in Fig. 2A, β-cell function remains healthy. B: For model parameters where simulations show KPD-like behavior, there are two stable fixed points. The high-β fixed point is not present in the high-sugar-consumption condition (red), and thus this condition produces a flow from the high-β fixed point to the low-β fixed point, as seen between the red lines in Fig. 2B–D. The insulin-treatment condition (blue) instead destroys the low-β fixed point, and thus produces a flow from the low-β fixed point to the high-β fixed point, allowing for remission as seen in Fig. 2B,C.

of fasting glucose, analyzed as in Fig. 3. The result of this classification is shown in Fig. 5. The color indicates the lowest value of fasting glucose at a given pair $(S_I, \beta_{\mathrm{TOT}})$, with blue indicating normal blood glucose, red indicating glucose above the ADA fasting glucose criterion for diabetes, and a gradient for values in between. The hatching indicates the presence of β-cell deactivation, with single hatching indicating the bistability that allows for entry into a reversible state of ketosis, and double hatching indicating that the high-β fixed point has disappeared and β-cell function cannot be restored by insulin treatment (unless treatment also improves insulin sensitivity).

We see in Fig. 5 that the boundaries of the hatched regions roughly follow the contours of fasting glucose. Thus, even when the rate of irreversible inactivation is high enough to predispose to KPD, if the total β-cell population or S_I is high enough to result in normal fasting glucose, this protects against the β-inactive state. Note, however, that the boundary of the bistable region is at higher fasting glucose for larger S_I. This is likely because, even at fixed fasting glucose, better glucose tolerance (i. e., smaller glucose excursions) will result in a lower average rate of reversible glucotoxicity.

At fixed β_{TOT}, greater insulin resistance both predisposes to KPD in this model and will result in higher glucose levels after treatment, consistent with clinical data (Table 1, criteria 1, 11). However, note that the observed association of insulin sensitivity with remission is without controlling for β-cell function and thus may be confounded.

Discussion

Our model predicts that the primary difference between individuals predisposed to KPD and those who are predisposed to "conventional" T2D are the rates associated with the reversible glucotoxi-

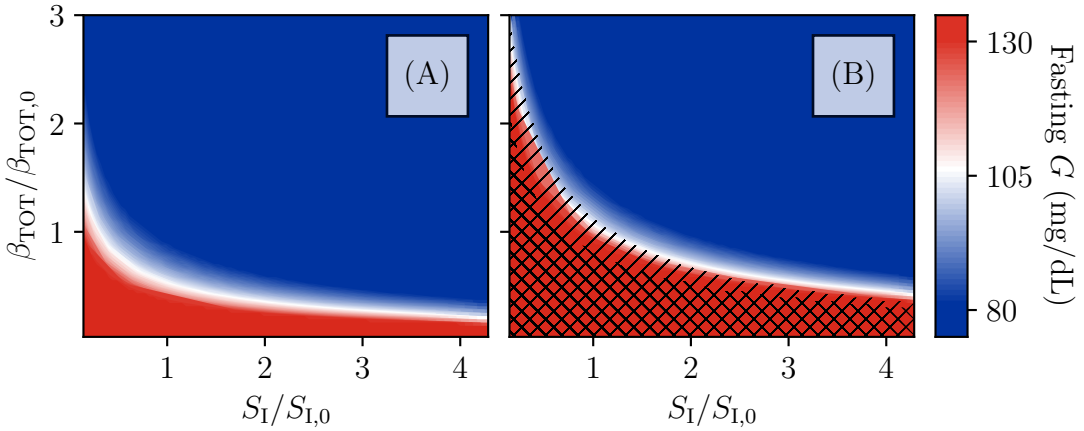

Figure 5. Phase diagram of the model Fixed-point structure of the model (fixed points of black curves in Fig. 3) as a function of total β-cell population and insulin sensitivity S_I, relative to the values used in Fig 2B. Color indicates fasting glucose (with all values of G above $130\ \mathrm{mg/dL}$ the same red), while hatching indicates the number of fixed points. No hatching indicates existence of just one stable fixed point at high β and intermediate or normal fasting glucose. Single-hatched regions have two fixed points, allowing for transient loss of β-cell function and remission, while double-hatched regions have only the low-β fixed point (i. e., total insulin dependence). A: For the β-cell inactivation rate as in Fig. 2A, the bistability which produces KPD-like presentation and remission is not seen, even for β-cell populations and S_I values which produce fasting hyperglycemia consistent with T2D. B: For the β-cell inactivation rate as in Fig 2B, mild fasting hyperglycemia tends to correspond with a susceptibility to KPD. Reduction of β-cell populations (e.g., due to the slower, permanent glucotoxicity as in 2D) can produce greater hyperglycemia and even total insulin dependence. Improvements in insulin sensitivity, in contrast, contribute to maintenance of remission.

city process (both the inactivation rate k_{IN} and the reactivation rate k_{RE}). Other parameters, such as the total β-cell population and insulin resistance, are predicted to be associated with both KPD and "conventional" T2D. In particular, since a lower total β-cell reserve is associated with both the appearance of KPD and difficulty in achieving remission, a period of uncontrolled T2D, even conventional T2D, during which the slow glucotoxicity will reduce the number of β-cells, can lead to the onset of KPD, and is predicted to make recovery less likely.

Although KPD is more prevalent in specific ethnic groups, very little is known about specific genetic factors which predispose individuals to KPD. An *pax4* allele specific to West African populations, seems to be associated with KPD, with a small number of monozygous individuals found in a sample of KPD patients and none in control individuals or those with conventional T2D (***Mauvais-Jarvis et al., 2004a***). Since PAX4 is expressed during development of pancreatic islets, where β-cells are located, it was hypothesized that this variant acts either through an effect on the total number of β-cells formed or through the formation of defective β-cells (***Mauvais-Jarvis et al., 2004a***). Since, in our model, a decrease in the total number of β-cells should predispose to either KPD or "ordinary" T2D equally well, depending on the rate of the reversible inactivation process k_{IN}, our results would suggest that this allele might predispose to KPD through a β-cell phenotype that is more susceptible to reversible inactivation. Other work has found that KPD is associated with deficiency in glucose-6-phosphate dehydrogenase, an enzyme which plays role in reducing oxidative stress, which is consistent with a mechanism where this reversible glucotoxicity is mediated by oxidative stress (***Sobngwi et al., 2005***). The fact that KPD patients tend to have a family history of diabetes (***Umpierrez et al., 1995***) is also consistent with genetic variation in the rate of reversible inactivation of β-cells.

If, as we hypothesize, the reversible activation process is present in all individuals, with a heterogeneous rate, then it is possible that "conventional" T2D always involves some degree of reversible inactivation, with KPD representing only the extreme end of a continuum. This may explain obser-

vations of partial remission after insulin treatment in populations with more conventional forms of T2D (***Ryan et al., 2004***; ***Weng et al., 2008***; ***Retnakaran et al., 2010***, ***2014***; ***Kramer et al., 2013a***,b; ***Chon et al., 2018***).

Our preliminary model is lacking many details that may play an important role in analyzing real patient data. Our description of glucose intake in meals has been simplistic. We have neglected the well-known time delay of insulin action present in the commonly-used minimal model of glucose kinetics (***Bergman et al., 1979***), or a realistic description of kidney clearance of glucose which should be relevant to the specific degree of hyperglycemia in the ketotic state (***De Gaetano et al., 2014***). Our simple model of β-cell adaptation also neglects the known hyperglycemia-induced leftward shift in the insulin secretion curve ($f(G)$ in Eq. (2)) (***Ha et al., 2016***; ***Glynn et al., 2016***; ***Leahy et al., 1993***). Other details included in recent models of pathogenesis may need to be included as well (***Ha et al., 2016***; ***De Gaetano and Hardy, 2019***; ***Ha and Sherman, 2020***).

A period of extreme hyperglycemia and low insulin secretion does not guarantee the presence of ketoacidosis. Thus, our model is consistent with the observation that a similar remission is seen in insulin treatment of patients with similar demographics to KPD patients who present with severe hyperglycemia, but not ketoacidosis (***Umpierrez et al., 1995***).

How could this model of KPD be more fundamentally incorrect? Broadly, there are two possible classes of alternative. Firstly, the pathology of KPD may not actually reflect bistability. Secondly, bistability could be generated by a different mechanism.

The first type of alternative would be one in which the decline in β-cell function preceding presentation is not actually that rapid, and instead some other change prompts the apparently rapid clinical presentation. For example, chronically high glucose could drive dehydration, worsening kidney function and thus leading to both further increases in glucose and inability to clear ketones.

What other mechanisms could generate bistability on a suitable timescale? There are some reversible processes which may be suitable for this role. The adaptive change in the shape of $f(G)$ is believed to occur over the scale of weeks (***Ha et al., 2016***), and in animal models, changes in diet can produce insulin resistance on timescales of weeks (***Mittelman et al., 2000***). It has been proposed in the past that insulin resistance may adaptively change in response to levels of insulin or glucose (***Rossetti et al., 1987***; ***DeFronzo, 1988***; ***Ader et al., 2014***). Furthermore, insulin resistance and the shape of $f(G)$ can both be seen to improve during the remission of KPD (***Umpierrez et al., 1995***). Thus, a feedback loop with a suitable timescale could exist between changes in insulin secretion and insulin resistance or glucose effectiveness. On the other hand, these changes are generally though to be adaptive, and thus it is unclear how they would form a positive feedback loop rather than a negative feedback loop.

One final possibility is that insulin *per se* acts to produce remission. Although insulin treatment is associated with reductions in insulin resistance (***Umpierrez et al., 1995***; ***Scarlett et al., 1982***), this effect is likely downstream of glucose levels: insulin itself has been proposed to promote insulin resistance (***Ader et al., 2014***; ***DeFronzo, 1988***). Thus, if remission is produced by insulin *per se* rather than normoglycemia, it would likely be mediated by insulin acting directly on β-cells to promote insulin secretion, as suggested, e. g., by experiments where β-cell specific insulin receptor knockouts show a reduction in glucose-stimulated insulin secretion (***Kulkarni et al., 1999***). On the other hand, due to the much lower relative concentration of insulin produced in the islets by exogeneous insulin administration rather than endogenous insulin (***Unger and Cherrington, 2012***), this seems unlikely.

The qualitative success of our model suggests that multiple distinct types of glucotoxicity may operate in the pathogenesis of T2D and KPD: a slower, irreversible death of β-cells which is responsible for slow, irreversible decline in T2D and failure to maintain or achieve remission in KPD, and a faster, reversible process associated with rapid onset and remission of KPD. The clearest test of our model would be a cellular or systems-biology-based identification and characterization of multiple β-cell states and inactivation mechanisms, all dependent on glucose level. Some pioneering studies along these lines have been done already, showing diversity of β-cell secretory

phenotypes and transition between phenotypes in a glucose-dependent way (***Miranda et al., 2021***; ***Laybutt et al., 2002***; ***Jonas et al., 1999***; ***Laybutt et al., 2003***; ***Wang et al., 2014***; ***Dahan et al., 2017***), though mostly in rodent models. Such experiments show that $\sim 2-4$ weeks of hyperglycemia can change gene expression and secretory phenotypes in β-cells, and then normoglycemia can restore normal function on similar scales (***Laybutt et al., 2002***; ***Jonas et al., 1999***; ***Laybutt et al., 2003***). However, lab-based cellular-level characterization of similar phenomena in human β-cells and in pancreatic islets, or analysis of human physiological data still must be done. Crucially, it remains to be seen if the rates of β-cell activation and deactivation in such experiments in humans would correlate with the predisposition to KPD.

As mentioned previously, ***Umpierrez et al.*** (***2007***) found that a 20-hour infusion of glucose produced a roughly 50% decline of β-cell function in a KPD patient. During this infusion, G fluctuated around 150 mg/dL. The functional form of $g(G)$ and rate constant k_{IN} used as the rate of the reversible reactivation rate give a roughly 10% decline of β per day at 150 mg/dL; given the nonlinearity of $g(G)$ this is an underestimate of the decline produced by G which fluctuates substantially around 150 mg/dL as in the experiment. Thus, our rate of reversible inactivation is roughly consistent with the limited existing data in KPD patients. However, given that this data comes from a single patient and that we expect the rate to vary substantially from patient-to-patient, many more such *in vivo* measurements are needed to understand the reversible deactivation process in a whole body. If G can be well controlled in a clamp, such measurements could also shed light on the functional form of $g(G)$.

This general class of models, even if the functional form of $g(G)$ that we have assumed is not accurate, makes several predictions about the natural history of KPD which can be tested. As seen in Fig. 5, our model generally produces bistability only when glucose is already at least slightly elevated. In other words, within our model, onset of KPD crucially depends on the β-cell adaption mechanisms having reached nearly maximum adaptation, and then the patient undergoing a period of high carbohydrate consumption. While this is anecdotally true in our practice (Table 1, criterion 3), there is no strong quantitative data yet to support this requirement of the model. Thus possibly the easiest way of validating or disproving our model is through focusing on careful collection of quantitative antecedent data at presentation on the recent food intake history and HbA1c (as a proxy for hyperglycemia over the preceding few months), as well as HbA1c at previous routine screenings, where available.

One clear prediction of the model, at least with the form of $g(G)$ we have considered, is that recovery of glucose control is gradual. This should be testable using more frequent measurements of glucose, as well as tracking of the needed insulin doses, during the process of remission.

Further, in order to constrain the functional form of $g(G)$ in models of this type, more clinical data will be necessary. Most past work has not analyzed remission with this frequency, instead tracking clinical progress every few weeks or months (***Mauvais-Jarvis et al., 2004b***; ***Umpierrez et al., 1995***; ***Vellanki et al., 2016***). The form of $g(G)$, however, cannot be well constrained by low-frequency measurements such as these. As seen in Fig. 2(B-C), in this model, patients with different values of the reversible inactivation rate k_{IN} and reactivation rate k_{RE} can still present with similar levels of hyperglycemia and achieve similar final states upon remission. This suggests that new, higher frequency data, should be collected in order to better distinguish possible mechanisms of KPD pathogenesis using models of this type. In particular, continuous glucose monitoring would allow the dynamics of remission to be studied, which would provide a much more stringent test on the form of $g(G)$.

While simple models of the type that we developed here are certainly wrong in that they do not account for the full complexity of the underlying physiology, they can be useful both for basic biomedical science and in the clinic. Specifically, they predict new β-cell states and activation/deactivation processes, and hence tell us to look for diversity of β-cell phenotypes. They also suggest that clinical practice should be modified to include more frequent followups (or continuous monitoring) to generate data on temporal scales that match the dynamics of the model. And they

propose key mechanisms (rates of secretory phenotype switching) that might determine predisposition to KPD, which also can be accessed experimentally or even clinically. Finally, the simplicity of such models makes it plausible that the proposed additional feedback loops in the glucose control circuitry may be general enough to contribute to explanation of other observations that involve rapid onset or remission of diabetes-like phenomena, such as during pregnancy or for patients on very low calorie diets.

Materials and methods

Model

We model the short timescale of dynamics of glucose and insulin as

$$\frac{\mathrm{d}G}{\mathrm{d}t} = M(t) + \frac{m_0}{I_0 + I} - (S_E + S_I I)G, \tag{1}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta c f(G) - \gamma I, \tag{2}$$

$M(t)$ represents the intake of glucose in meals, while $\frac{m_0}{I_0+I}$ represents the endogenous production of glucose, mainly in the liver. The final terms represent both insulin-independent and insulin-dependent clearance of glucose. ***Ha and Sherman*** (***2020***) uses a similar model of HGP suppression by insulin, while this glucose production term is instead a constant R_0 in ***Topp et al.*** (***2000***); ***Karin et al.*** (***2016***); ***Ha et al.*** (***2016***).

Here $f(G)$ is the β-cell insulin secretion rate (normalized by the blood volume), which we take to be $f(G) = G^2/(G^2 + K_f^2)$, as in ***Topp et al.*** (***2000***) and ***Karin et al.*** (***2016***). c is a measure of the mass or secretory activity of an individual β-cell, which we assumed to adapt to produce a target fasting glucose as described below. Insulin is assumed to be cleared from the blood by the liver at a constant rate γ.

We model β-cell dynamics using

$$\frac{\mathrm{d}\beta}{\mathrm{d}t} = -\left(k_{\mathrm{IN}} g(G) + k_{\mathrm{D}} h(G)\right)\beta + k_{\mathrm{RE}}\beta_{\mathrm{IN}} \tag{3}$$

$$\frac{\mathrm{d}\beta_{\mathrm{IN}}}{\mathrm{d}t} = -\left(k_{\mathrm{RE}} + k_{\mathrm{D}} h(G)\right)\beta_{\mathrm{IN}} + k_{\mathrm{IN}} g(G)\beta. \tag{4}$$

Here $k_{\mathrm{D}} h(G)$ is the β-cell death rate, k_{RE} is the (glucose-independent) β-cell reactivation rate, and $k_{\mathrm{IN}} g(G)$ is the rate of reversible β-cell inactivation. In all simulations we take $h(G) = G^2/(G^2 + K_h^2)$ and $g(G) = G^2/(G^2 + K_g^2)$ with K_g chosen to be very large, since generating bistability requires a substantial drop in steady-state insulin secretion at high steady-state glucose, and thus requires $K_g \gg K_f$.

We also assume that β-cell mass, through c, adapts to produce a target fasting glucose (***Topp et al., 2000***; ***Karin et al., 2016***; ***Ha et al., 2016***), which we take to be 80 mg/dL. We assume that this adaptation has a maximum capacity (i. e., a maximum value of c) (***Woller et al., 2024***), and in analysis in the main text we assume that this maximum capacity has already been reached, as should be the case in chronic hyperglycemia. Thus, we do not need to specify explicit dynamics for c, and in Figures 2–4, c does not change. In the analysis of Fig. 5, c remains at its maximum value whenever $G > 80\,\mathrm{mg/dL}$. If, however, S_I or β_{TOT} is large enough to allow $G < 80\,\mathrm{mg/dL}$, then c is assumed to decrease in order to produce $G = 80\,\mathrm{mg/dL}$

Simulations

The parameters γ, S_E, and S_I are taken from ***Topp et al.*** (***2000***). ***Topp et al.*** (***2000***); ***Karin et al.*** (***2016***); ***Ha et al.*** (***2016***) take the rate of hepatic glucose production (HGP) to be a constant while we allow it to decrease when insulin increases, similarly to ***Ha and Sherman*** (***2020***). We chose $I_0 = 5\mu\mathrm{U\,mL}^{-1}$, which is on the scale of observed fasting insulin values, and chose m_0 so that our rate of HGP matches the constant R_0 used in ***Topp et al.*** (***2000***); ***Karin et al.*** (***2016***); ***Ha et al.*** (***2016***) when $I = I_0$. For the chosen level of hyperglycemia and other parameters, this produces a fasting

insulin of roughly $7\mu\mathrm{U\,mL}^{-1}$ and a fasting HGP roughly 15% lower than the constant R_0 used by ***Topp et al.*** (***2000***); ***Karin et al.*** (***2016***); ***Ha et al.*** (***2016***).

During "normal" periods the sugar consumption from the three "meals" adds up to roughly 3% of the daily hepatic glucose production, while during the high sugar consumption period it adds up to roughly 70% of the daily hepatic glucose production. In humans, 2 mg / (kg min) is a typical glucose flux (***DeFronzo, 1988***). Assuming a body weight of 70 kg, this amounts to 201 grams of glucose per day, so that 70% of this would correspond to 3–4 cans of soda per day, a plausible "high sugar consumption" condition. However, note that the rate of glucose appearance from ***Topp et al.*** (***2000***), interpreted in recent works as the rate of glucose production (***Ha and Sherman, 2020***; ***Karin et al., 2016***), is actually about $1/7$ of this estimate (assuming a plasma volume of 3.5 L). Indeed, ***Topp et al.*** (***2000***) originally interpreted this term as the difference of the rate of glucose production and a glucose-independent component of the rate of glucose disposal. Thus, while the scale of sugar consumption relative to HGP required to produce the onset of DKA in our model is reasonable, the parameters will likely need some adjustment when fitting to patient data.

The rates of the hypothesized reversible glucotoxicity processes were then chosen by trial and error to reproduce the desired variation of possible patient phenotypes.

All numerical simulations are done using the differential equations package Diffrax (***Kidger, 2021***). We used a 5th-order implicit Runge–Kutta method due to Kværnø (***Kværnø, 2004***), adjusting the timestep with a PID controller (***Hairer and Wanner, 1991***; ***Söderlind, 2002***).

Dynamical systems analysis

To analyze the possible stable equilibria of fasting glucose with $M(t) = 0$ (Fig. 3), we assume equilibration of the fast dynamical equations, Eqs. (1, 2). The steady-state glucose G then solves the equation

$$\frac{m_0}{\beta c f(G)/\gamma + I_0} = G\left(S_E + \frac{S_I \beta c f(G)}{\gamma}\right). \tag{5}$$

Multiplying by $\beta c f(G)/\gamma + I_0$, and then subsequently by the denominator of the Hill function $f(G)$, yields a polynomial equation for G, which we solve using the companion matrix (***Horn and Johnson, 1985***; ***Harris et al., 2020***). The steady state insulin is then $\beta c f(G)/\gamma$.

To extend the analysis to include meals and insulin (Fig. 4), we first determine the fasting G by assuming equilibration of the fast-timescale dynamics. Equations (2, 5) must be modified in the presence of an external insulin flux F_I, giving

$$\frac{m_0}{(\beta c f(G) + F_I)/\gamma + I_0} = G\left(S_E + \frac{S_I(\beta c f(G) + F_I)}{\gamma}\right). \tag{6}$$

This equation is solved by the same method as above, and the fasting insulin is then $(\beta c f(G) + F_I)/\gamma$. From the fasting (G, I), we integrate the fast equations over a single day containing 3 meals, each modeled as a constant glucose flux $M(t) = M$ for 30 minutes. We then compute the mean value $\overline{g(G)}$ over the day using the trapezoidal rule, and plot the approximation

$$\frac{\mathrm{d}\beta}{\mathrm{d}t} \approx -k_{\mathrm{IN}}\overline{g(G)}\beta + k_{\mathrm{RE}}\beta_{\mathrm{IN}} = -k_{\mathrm{IN}}\overline{g(G)}\beta + k_{\mathrm{RE}}(\beta_{\mathrm{TOT}} - \beta). \tag{7}$$

Since in all considered cases, $(1/\beta_{\mathrm{TOT}})\,\mathrm{d}\beta/\mathrm{d}t$ is small (Fig. 4), we expect this approximation to be good. Furthermore, in the vicinity of a fixed point, $\mathrm{d}\beta/\mathrm{d}t \approx 0$, so the approximation is particularly accurate near fixed points, protecting our qualitative conclusions about the presence and the stability of fixed points.

All simulation and analysis code used to produce all data in this article, as well as code used to produce all figures in this article, is available at https://zenodo.org/records/11373235 (DOI: 10.5281/zenodo.11373235).

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