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Mathematical modelling of immune regulation of type 1 diabetes

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ABSTRACT

Type 1 diabetes is a disease characterized by progressive loss of β cell function due to an autoimmune reaction affecting the islets of Langerhans. Two types of T cells are involved in diabetes: turncoat auto-reactive T cells, or T cells gone bad, that kill the insulin-producing cells, and regulatory T cells that are unable to control the auto-reactive T cells. We formulate a mathematical model that incorporates the role of cytotoxic T cells and regulatory T cells in type 1 diabetes. This study shows that onset of type 1 diabetes is due to a collective, dynamical instability, rather than being caused by a single etiological factor. It is also a numbers game between regulatory T cells and auto-reactive T cells. The problem in the onset of this disease is that there are not enough of the regulatory cells that suppress the immune response against the body's insulin-producing pancreatic islet cells.

1. Introduction

Type 1 diabetes is an autoimmune disease in which the β cells of the pancreas do not produce sufficient insulin, a hormone which helps use blood sugar (glucose) for energy (Thivolet, 2002; Gillespie, 2006; Narendran et al., 2005). The cells become starved of energy and there will be excess of glucose in the blood. This is then followed by life threatening conditions of hypoglycemia, low blood sugar, and hyperglycemia, high blood sugar (Barclay, 2005; Gillespie, 2006). When hypoglycemia develops, cells do not get enough glucose and patients suffer of confusion, loss of consciousness, and coma. Even death can results when the brain is deprived of glucose for too long. Hyperglycemia and prolonged absence of insulin may lead to ketoacidosis, which is accumulation of ketones in the blood when the body uses fat for energy instead of glucose (Barclay, 2005; Narendran et al., 2005). This is because fatty acids cannot be converted into glucose at steady state (Weinman et al., 1957; de Figueiredo et al., 2009). Ketones make the blood acidic and slow down all body functions. This also leads to a coma and eventually death.

In the U.S., about 15.7 million people, or 5.9% of the population have diabetes of either type, however with about 5.4 million people that unaware of the fact that they have diabetes (Barclay, 2005; Goudy and Tisch, 2005). Type 1 diabetes is the seventh leading cause of death in U.S. and the second most chronic disease in children after Asthma. It most commonly appears in children when they are about 14 years. Also, diabetes is the leading cause of new cases of blindness in adults 20–74 years of age and the leading cause of end stage renal disease, accounting for about 40% of new cases. Other complications include (i) peripheral neuropathy, affecting about 60–70% of patients, (ii) non-traumatic lower limb amputations and the increased risk of leg amputation of 15- to 40-fold, and (iii) doubles to quadruples the risk of heart disease (Barclay, 2005; Gillespie, 2006). Most of these complications are related to changes in the microvasculture, with thickening of capillary walls resulting in local ischemia.

The immunological immune response that follows from type 1 diabetes result from the destruction of pancreatic β cells where autoreactive T cells play a critical role. The disease is primarily mediated by T cells recognizing pancreatic β cell antigens (Kanagawa et al., 2002; Dotta et al., 2005; Goudy and Tisch, 2005; Tisch and McDevitt, 1996). However, in the initial phase of the disease, macrophages, β cells, and T cells infiltrate the pancreatic islets without destroying the β cells (Kanagawa et al., 2002; Raz et al., 2005; Filippi et al., 2005). After a gradual increase in cellular infiltrate, terminal insulitis, the progressive destruction of β cells takes place, leading to a complete loss of insulin production and dysregulation of glucose metabolism. In humans, type 1 diabetes is a complex, multifactorial autoimmune disease whose full understanding is still elusive, such that much of the knowledge of its course and pathogenesis comes from studies in non-obese diabetic (NOD) mice (Lee et al., 2005). The principal effector mechanism appears to be the action of CD4+ and CD8+ T cells, where both T cell subsets are required for transfer of disease in NOD mice (Wang et al., 2004; Filippi et al., 2005; Raz et al., 2005; Chowdhury et al.,

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2002). These facts have been taken to indicate that the CD4+ T cells are the helper cells for activation of CD8+ T cells that damage islets by a direct cytotoxic attack (Nagata et al., 1989; Wang et al., 2004; Alyanakian et al., 2003). This hypothesis has two implications: (i) destruction of islet cells will be mediated by a CD8+ T cell and (ii) destruction of β cells should be restricted by major histocompatibility complex (MHC) antigens presented on the target islets (Lee et al., 2005; Wang et al., 2004; Raz et al., 2001). Also, in early diabetes, it is thought that inflammation is initiated and propagated by the effects of Th-1 secreted cytokines (e.g. interferon-γ (IFN-γ)) and suppressed by Th-2 secreted anti-inflammatory cytokines (interleukin (IL)-4, 10) (Rabinovitch, 1998). This leads to the hypothesis that diabetes can be prevented using Th-2 secreted cytokines. In animals, the disease can be induced by transferral of auto-reactive T cells. A thymic NOD mice do not develop diabetes or insulitis. As T cells specific for a number of antigens have been recognized, it is easy to surmise that the disease is initiated by polyclonal activation of T cells to multiple specificities caused by a breakdown in normal tolerance to the β cells. However, disease initiation may require T cells specific for one primary antigen; once the disease is initiated, T cells specific for a number of additional antigens may develop by epitope spreading during the effector phase and mediate β cell destruction (Krishnamurthy et al., 2006; Janeway et al., 2005). Activation of naive T cells requires not only T cell recognition of peptides, but also co-stimulation provided by accessory molecule interactions. Among accessory molecules, Lymphocyte Function Associated Antigen (LFA)-1, a member of the leukocyte integrin family, is important in cellular interactions in the immune system such as cytotoxic T cells and NK cell-mediated cytotoxicity, Th lymphocyte responses and leukocyte adhesion (Goudy and Tisch, 2005; Eldor et al., 2005; Chen et al., 2005; Bergerot et al., 1999).

Mathematical studies on diabetes type 1 have been carried out (Freiesleben De Blasio et al., 1999; Mar'ee and Kublik, 2006) to understand the earliest events on the interplay of activated macrophages, T helper (Th) lymphocytes and target cells in diabetes. The study by Freiesleben De Blasio et al. (1999) modelled the interaction of macrophages, antigens and T cells in which they demonstrated how the system can become unstable leading to the development of autoimmunity that propagate diabetes. This study (Freiesleben De Blasio et al., 1999) was modified by Mar'ee and Kublik (2006) to come up with a quantitative analysis of diabetes based on mouse parameters rather than the qualitative analysis of diabetes from the previous study (Freiesleben De Blasio et al., 1999). However, our thrust in this study is to give a qualitative analysis of diabetes in the islet using models with β cells, autolytic T cells and regulatory T cells. The earlier studies did not take into cognisence the role of β cells and the T helper cell-mediated destruction of islet β cells. We, also consider the role of regulatory T cells that can suppress pathogenic T cell trafficking.

This paper is organised as follows, in Section 2 we present a diabetes model with β cells. We add the regulatory T cells to the model in Section 3. Numerical simulations of the models and results are presented in Section 4. In Section 5 we present the concluding remarks.

2. Model Development

We build a model that is based on the assumptions of the Copenhagen model (Freiesleben De Blasio et al., 1999) together with the following assumptions: (i) Th-lymphocytes are induced to proliferate when they recognize antigens on class II MHCs situated on macrophages and this proliferation is proportional both to the population size of activated macrophages and Th-lymphocytes, (ii) the lymphocytes will decline in absence of stimulation, (iii) the effect on the death rate of the β cells and thus the amount of the antigens (A) released is proportional to the size of the lymphocyte population (T), (iv) Th-lymphocytes are able to re-stimulate macrophages to enter into effector cells, and this process, will depend on the numbers of Th-lymphocytes and (v) β cell and T cells both have a natural supply rate and a natural death rate. These assumptions are assumed since they are the basic essentials of the dynamics of diabetes and immune cells interaction. The interaction of resting macrophages (M), activated macrophages (M_A), antigen cells (A), autolytic T cells (T), and β cells (B) is modelled by the following system of equations.

$$\frac{dM(t)}{dt} = a + (b+k)M_A(t) - cM(t) - gM(t)A(t), \tag{1}$$

$$\frac{dM_A(t)}{dt} = gM(t)A(t) - kM_A(t), \tag{2}$$

$$\frac{dA(t)}{dt} = lM_A(t) + qB(t)T(t) - mA(t), \tag{3}$$

$$\frac{dT(t)}{dt} = s_T + sM_A(t)T(t) - \mu_T T(t), \tag{4}$$

$$\frac{dB(t)}{dt} = s_B - qB(t)T(t) - \mu_B B(t). \tag{5}$$

The first term in Eq. (1) represents the natural supply or recruitment rate of macrophages. The term, bM_A, represents recruitment rate of macrophages due to IL-1 and TNF-α produced by activated macrophages. The term kM_A represents the rate of addition of macrophages by deactivation back to resting macrophages awaiting activation. The third term represents the decrease in the macrophage population due to natural efflux of macrophages (Freiesleben De Blasio et al., 1999; Mar'ee and Kublik, 2006). The last term represents the rate at which macrophages become activated due to interaction with antigenic proteins, which is proportional to both the antigenic peptide and macrophage population.

Eq. (2) models the dynamics of activated macrophage population, the first term represents the increase in activated macrophages due to mass action between macrophages and antigenic proteins. The second term represents the decrease in activated macrophage population due to activated macrophages processing all the intracellular antigenic peptides and thus becoming deactivated and moving back to the pool of resting macrophages (Freiesleben De Blasio et al., 1999; Mar'ee and Kublik, 2006).

Eq. (3) models the antigenic peptide concentration, with the first term representing an increase due to antigenic peptides released by activated macrophages. The second term in Eq. (3) represents an increase in β cell antigenic peptides released in the volume by dead β cells due to cell–cell interactions of β cells and autolytic Th-lymphocytes (Kanagawa et al., 2002; Raz et al., 2005). The last term represents the rate at which antigenic proteins are cleared from the volume by extra-cellular chemical reactions and natural degradation.

The dynamics of autolytic T cells, which are a subset of helper T cells is modelled by Eq. (4). The first term in Eq. (4) represents the natural supply rate of autolytic T cells to volume while the second term represents the proliferation of T cells due to a profile of cytokines and chemokines induced by activated macrophages. The third term represents the decrease in T cell population due to lack of stimulation.

Eq. (5) models the dynamics of the β cell population. The first term represents the natural supply or replacement rate of β cells while the third term represents decrease in β cells due to natural death. The second term models the depletion/decrease in β cell population due to β cell–Th-cell interactions (Kanagawa et al., 2002; Nagata et al., 1989; Wang et al., 2004; Mauricio and Mandrup-Poulsen, 1998).

2.1. Model Analysis

The system of Eqs. (1)–(5) has an initial condition given by

$$M(0) = M_0 \geq 0, \quad M_A(0) = M_{A_0} \geq 0, \quad A(0) = A_0 \geq 0,$$
$$T(0) = T_0 \geq 0, \quad B(0) = B_0 \geq 0.$$

Since the model monitors human cell populations, all the variables and parameters of the model are non-negative. Based on biological considerations the system of Eqs. (1)–(5) will be studied in the following region,

$$D = \{(M, M_A, A, T, B) \in \Re^5_+\}. \tag{6}$$

The following theorem assures that the system of Eqs. (1)–(5) is well posed such that solutions with non-negative initial conditions remain non-negative for all $0 < t < \infty$, and therefore makes biological sense.

Theorem 1. *The region $D \subset \Re^5_+$ is positively invariant with respect to the system of Eqs. (1)–(5) and a non-negative solution exists for all time $0 < t < \infty$.*

Proof. Under the given initial conditions it can be shown that the components of solution of the system of Eqs. (1)–(5), M, M_A, A, T, and B are positive for $t > 0$, and if not, we assume for contradiction that there exist a first time t_r such that $M(t_r) = 0$, $M'(t_r) \leq 0$ and $M(t) > 0$, $M_A(t) > 0$, $A(t) > 0$, $T(t) > 0$, $B(t) > 0$ for $0 < t < t_r$ or there exist t_m such that $M_A(t_m) = 0$, $M'_A(t_m) \leq 0$ and $M_A(t) > 0$, $M(t) > 0$, $A(t) > 0$, $T(t) > 0$, $B(t) > 0$ for $0 < t < t_m$ similar to an approach in (Qiu et al., 2004). In the first case it follows from Eq. (1) that

$$\begin{aligned} \frac{dM(t_r)}{dt} &= a + (b+k)M_A(t_r) - cM(t_r) - gM(t_r)A(t_r), \\ &= a + (b+k)M_A(t_r) > 0, \end{aligned}$$

which is a contradiction. For the latter case we have

$$\begin{aligned} \frac{dM_A(t_m)}{dt} &= gM(t_m)A(t_m) - kM_A(t_m), \\ &= gM(t_m)A(t_m) \geq 0, \end{aligned}$$

this is true if for both $A(t_m) \geq 0$ and $M(t_m) = 0$, therefore it follows that if $M_A(t) \geq 0$ at any given time. These contradictions imply that $M(t)$, and $M_A(t)$ remains positive at any given time.Similarly, using the same arguments for $A(t)$, $T(t)$ and $B(t)$ it can be shown that these variables remain positive for all $t > 0$. Thus we conclude that solutions of system of Eqs. (1)–(5) remain positive for all $t > 0$.□

The disease-free steady state occurs when there are no antigenic peptides in the volume and hence no activated macrophages. Therefore the disease-free state is given by

$$\varepsilon^1_{00} = (\hat{M}, \hat{M}_A, \hat{A}, \hat{T}, \hat{B}) = \left(\frac{a}{c}, 0, 0, \frac{s_T}{\mu_T}, \frac{s_B}{q(s_T/\mu_T) + \mu_B}\right).$$

The diabetic steady state is given by

$$\varepsilon^1_{01} = (\bar{M}, \bar{M}_A, \bar{A}, \bar{T}, \bar{B}),$$

where $\bar{M}$, $\bar{M}_A$, $\bar{A}$, $\bar{T}$, and $\bar{B}$ are given by expressions (7)–(11) as follows.

The equilibrium value for resting macrophages at the diabetic state is given by

$$\bar{M} = \frac{a + (b+k)\bar{M}_A}{c - g\bar{A}}. \tag{7}$$

The numerator of (7) shows that an increase in activated macrophages results in recruitment of more resting macrophages. The denominator shows that an increase in the antigenic peptides has an impact of increasing the resting macrophage population. At the diabetic equilibrium state, the population of the activated macrophages is given by

$$\bar{M}_A = \frac{g\bar{M}\bar{A}}{k}. \tag{8}$$

This expression shows that the interaction of resting macrophage and antigenic peptides support the increase of activated macrophages. The deactivation of activated macrophages oppose the increase in population of activated macrophages. The expression for antigens at the diabetic equilibrium state is given by

$$\bar{A} = \frac{l\bar{M}_A + q\bar{B}\bar{T}}{m}. \tag{9}$$

From this expression we notice that an increase in either activated macrophage population or T-cell population promotes the increase in antigenic population. The equilibrium value for autolytic T cells is given by

$$\bar{T} = \frac{s_T}{\mu_T - s\bar{M}_A}. \tag{10}$$

An increase in activated macrophages promotes the increase in the autolytic T-cell population. At the diabetic equilibrium state the β cell population is given by

$$\bar{B} = \frac{s_B}{\mu_s + q\bar{T}}. \tag{11}$$

From expression (11), we notice that an increase in autolytic T-cell population results in a decrease in the β cell population.

To establish the local stability of the model, we evaluated the model reproduction number (R_0). The reproduction number is defined as the number of secondary infections emanating from a single primary infection. In the case of diabetes, we redefine the reproduction number as the number of autolytic T cells that arise form stimulation induced by activated macrophages as a result of the accumulation of antigenic peptides form an intial state that is non-diabetic stimulating. When the reproduction number is less than one ($R_0 < 1$), diabetes is abortive. That is, any diabetic stimulating factor will not be strong enough to set diabetes progression in motion. On the other hand if the reproduction number is greater than one ($R_0 > 1$), any stimulation of diabetes will succefully establish the on set of diabetes. The main use of this threshold parameter in to help in the control of diabetes through indentification of parameters that can be targeted to reduce R_0 to a value less than unity. For the system of Eqs. (1)–(5), we evaluated the Jacobian, J, at equilibrium state, ε^1_{00}, to be given by,

$$J(\varepsilon^1_{00}) = \begin{pmatrix} -c & (b+k) & -\frac{ga}{c} & 0 & 0 \\ 0 & -k & \frac{ga}{c} & 0 & 0 \\ 0 & l & -m & \frac{qs_B}{\mu_s} & \frac{qs_T}{\mu_T} \\ 0 & \frac{ss_T}{\mu_T} & 0 & -h & 0 \\ 0 & 0 & 0 & -\frac{qs_B}{\mu_B} & \left(-\mu_B - \frac{qs_T}{\mu_T}\right) \end{pmatrix}.$$

The eigenvalues of the Jacobian matrix J can be determined by solving the characteristic polynomial $|J - \lambda I| = 0$, which can be expanded to become

$$\begin{aligned} (-\lambda - c)(-\lambda - \mu_s)\Big[&-\lambda^3 - (m + k + \mu_T)\lambda^2 \\ &+ \left(\frac{gal}{c} - km - \mu_T m - \mu_T k\right)\lambda \\ &+ \left(\frac{gaqss_B s_T}{c\mu_B\mu_T} + \frac{gal\mu_T}{c} - \mu_T km\right)\Big] = 0. \end{aligned} \tag{12}$$

Two of the eigenvalues are $\lambda_1 = -c$, $\lambda_2 = -\mu_B$, and the characteristic polynomial is reduced to

$$\lambda^3 + (m+k+\mu_T)\lambda^2 + \left(km + \mu_T m + \mu_T k - \frac{gal}{c}\right)\lambda + \left(\mu_T km - \frac{gaqss_B s_T}{c\mu_B\mu_T} - \frac{gal\mu_T}{c}\right) = 0.$$

Using the Routh–Hurwitz criterion, stability analysis for this system can be determined using the coefficients of the characteristic equation. The system is stable if all the coefficients in the characteristic equation are all positive. That is, we require that $(km + \mu_T m + \mu_T k - (gal/c)) > 0$ and $(\mu_T km - (gaq_s s_B s s_T/c\mu_B\mu_T) - (gal\mu_T/c)) > 0$. Therefore we evaluate the reproduction number to be

$$R_0 = \frac{agl}{ckm} + \frac{agqss_T s_B}{ckm\mu_B\mu_T\mu_T}. \tag{13}$$

Theorem 2. *The disease-free equilibrium* (ε^1_{00}) *is localy asymptotically stable if* $R_0 < 1$*, otherwise it is unstable.*

The reproduction number is controlled by several factors which include the natural supply rate of both autolytic T cells and β cells (s_T, s_B) death rate of β cells (μ_B), proliferation of autolytic T-cell (s), recruitment rate of macrophages (a), uptake rate of antigenic β cells (g) and death rate of activated Th-lymphocytes. An increase in the supply rate of autolytic T cells, β cell damage or proliferation rate of autolytic T cells, or a decrease in the natural supply rate of β cells or clearance rate of free β cell proteins will result in the R_0 becoming greater than one and hence the system becomes unstable. An increase in either the proliferation rate of autolytic T lymphocytes or supply of these cells is not desirable as it results in the system becoming unstable.

Taking partial derivatives of R_0 with respect to parameters that appear in expression (13), we get the following expressions,

$$\frac{\partial R_0}{\partial a} = \frac{g}{ckm}\left(l + \frac{qss_T s_B}{\mu_B\mu_T^2}\right), \quad \frac{\partial R_0}{\partial g} = \frac{a}{ckm}\left(l + \frac{qss_T s_B}{\mu_B\mu_T^2}\right),$$
$$\frac{\partial R_0}{\partial c} = -\frac{ag}{kmc^2}\left(l + \frac{qss_T s_B}{\mu_B\mu_T^2}\right), \quad \frac{\partial R_0}{\partial l} = \frac{a}{ckm},$$
$$\frac{\partial R_0}{\partial k} = -\frac{ag}{mck^2}\left(l + \frac{qss_T s_B}{\mu_B\mu_T^2}\right), \quad \frac{\partial R_0}{\partial m} = -\frac{ag}{ckm^2}\left(l + \frac{qss_T s_B}{\mu_B\mu_T^2}\right),$$
$$\frac{\partial R_0}{\partial q} = \frac{ag}{ckm}\left(\frac{ss_T s_B}{\mu_B\mu_T^2}\right), \quad \frac{\partial R_0}{\partial \mu_B} = -\frac{ag}{ckm}\left(\frac{qss_T s_B}{\mu_B^2\mu_T^2}\right),$$
$$\frac{\partial R_0}{\partial \mu_T} = -2\frac{ag}{ckm}\left(\frac{qss_T s_B}{\mu_B\mu_T^3}\right). \tag{14}$$

This analysis shows that the partial derivatives of R_0 with respect to some of the parameters give either a positive or a negative derivative. This means that increasing all parameters which give a positive derivative result in enhanced diabetes progression, while increasing parameters that give negative derivatives will result in the reduction of the aggregate R_0, which implies reduced propagation of diabetes. From a biological point of view, targetting such parameters in the model that reduce the reproduction number, could be used as possible targets to control diabetes. Also, parameters that increase the reproduction number can be targeted in order to control diabetes in the sense that, if treatment or an form of intravention can be found that reduce such parameters, the strategy can result in positive results towards the control of diabetes. That is targetting parameters such as a, g, q, s, s_T, and s_B that give positive derivatives and it follows that increasing them increase diabetes progression, therefore decreasing them will help to control daibetes. On the other hand increasing parameters such as c, k, m, μ_B and μ_T enhance the control of diabetes. This means suppressing activation of macrophages (g) and deactivation of activated macrophages (k) can be one way to control progression of diabetes. Increasing the removal rate (m) of antigenic peptides, and decreasing (s) the multiplication of autolytic T cells and their natural supply (s_T) can help in controlling diabetes.

2.2. Global Stability Conditions for the Disease-free Equilibrium

We adopt the method of Castillo-Chavez et al. (2002) and we re-write the set of Eqs. (1)–(5) in the form:

$$\frac{dX}{dt} = F(X, Z),$$
$$\frac{dZ}{dt} = G(X, Z). \tag{15}$$

With $G(X, 0) = 0$, where $X \in \Re^3$: denotes the number of uninfected cells and $Z \in \Re^2$: denotes the number of infected cells category that mainly contribute to diabetes onset. $U_0 = (X^*, 0)$ denotes the disease-free $(X^* = (a/c, s_T/\mu_T, s_B/(q(s_T/\mu_T) + \mu_B)))$ equilibrium of the system. For the set of Eqs. (1)–(5) we set $X = (M, M_A, B)$: the set of resting macrophages, activated macrophages and β cells and $Z = (A, T)$: the antigenic peptides and the autolytic T cells.

The conditions H1 and H2 below must be met to guarantee global asymptotic stability,

H1. For $dX/dt = F(X, 0)$, X^* is globally asymptotically stable

H2. $G(X, Z) = AZ - \hat{G}(X, Z)$, $\hat{G}(X, Z) \geq 0$ for $(X, Z) \in \Omega$ where $A = D_Z G(X^*, 0)$ is an M-matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense. If the above two conditions are satisfied then the following theorem holds.

Theorem 3 (Castillo-Chavez et al., 2002). *The fixed point* $U_0 = (X^*, 0)$ *is a globally stable equilibrium of* (15) *provided that* $R_0 < 1$ *and that assumptions* H1 *and* H2 *are satisfied.*

We computed $F(X, 0)$, and $\hat{G}(X, Z)$ and are given as follows,

$$F(X, 0) = \begin{pmatrix} a - cM \\ 0 \\ s_B - \left(q\dfrac{s_T}{\mu_T} + \mu_B\right)B \end{pmatrix},$$

$$\hat{G}(X, Z) = \begin{pmatrix} (\hat{B} - B)qT - lM_A \\ -s_T - sM_A T \end{pmatrix}.$$

Global stability of the system at ε^1_{00} requires that $\hat{G}(X, Z) \geq 0$. Note, that X^* is globally asymptotically stable state of $dX/dt = F(X, 0)$, since $F(X, 0)$ is a limiting function of $dX/dt = F(X(t), Z(t))$, that is, $\lim_{t\to\infty} X(t) = X^*$ and $(-s_T - sM_A T) < 0$, therefore global stability conditions fail to hold. Therefore it follows that the disease-free equilibrium mighty not be globally asymptotically stable. This implies that, off setting the stable non-diabetic condition in a diabetic susceptible may result in the stimulation and propagation of diabetes. That is, the occurrence of diabetes is uncertain and unpredictable, this could be the reason why even change of environment is capable of stimulating diabetes (Freiesleben De Blasio et al., 1999; Goudy and Tisch, 2005).

3. Model with T Regulatory Cells

A resurgent interest in T cells with regulatory activity has prompted many recent investigations into their potential role in pathogenesis and prevention of type 1 diabetes. While some studies have suggested that regulatory T cells participate in the preservation of active tolerance to auto-antigens, findings obtained in

multiple animal models for type 1 diabetes have documented the therapeutic induction of protective regulatory T cells (Dirk and Matthias, 2004; Chen et al., 2005; Goudy and Tisch, 2005; Eldor et al., 2005). A review of the proposed mechanisms operative in regulatory T cell-mediated diabetes prevention indicates a common theme of localized regulatory T cell activation and subsequent suppression of pathogenic T cell trafficking, differentiation, and effector function (Filippi et al., 2005; Goudy and Tisch, 2005; Eldor et al., 2005). However, adaptation of experimental protocols for regulatory T cell induction to clinical applications faces several challenges. Immunization with self-antigens carries obvious risks especially in the face of multiple variables that can affect generation, trafficking, and regulatory activity of auto-antigen-specific T cells. We also emphasize that the frequent use of lymphopenic recipients of adoptively transferred pathogenic and regulatory T cells constitutes a potentially confounding variable that further complicates translation into clinical settings. The therapeutic induction of regulatory T cells in pre-diabetic individuals carries great potential but is currently limited by the risks associated with deliberate generation of autoimmune responses that may exacerbate rather than ameliorate the autoimmune process (Filippi et al., 2005; Chen et al., 2005; Goudy and Tisch, 2005; Eldor et al., 2005). However, in vitro amplification and autologous regulatory T cell therapy might soon become a clinical reality (Dirk and Matthias, 2004).

Two types of T cells are involved in diabetes – turncoat auto-reactive T cells, or T cells gone bad, that kill the insulin-producing cells, and regulatory T cells that are unable to control the auto-reactive T cells (Raz et al., 2005; Goudy and Tisch, 2005; Narendran et al., 2005). Pitt research team identified an antibody that activates regulatory T cells, and prevents rogue auto-reactive T cells from destroying insulin-producing beta cells in the pancreas of mice (Irie et al., 2007). As a result, mice are protected from diabetes. The regulatory T cells are activated through the CD137 receptor on the cells, which boosts the number and function of the cells so they can counter the auto-reactive T cells. In diabetics, Pitt research concludes that, either regulatory T cells are faulty or are lacking in numbers, which allow auto-reactive T cells to destroy islet cells that produce insulin. This can be viewed as a war between regulatory T cells and pathogenic T cells and the antibody boosts the powers of the good, regulatory cells (Irie et al., 2007). We model the possible therapeutic strategy based on the activation of regulatory T cells that stops or down-regulates the undesirable effects of autolytic T lymphocytes (Filippi et al., 2005; Goudy and Tisch, 2005; Eldor et al., 2005). The success of such an intervention strategy would be better than current ones since this aims at halting the death of insulin-producing cells and hence maintain the body's ability to produce sufficient amounts of insulin. Current treatment strategies are only aimed at providing insulin to the body from other sources but do not address the cause of the lack of or inability of the body to produce sufficient amounts of insulin.

3.1. Model Equations

Interaction of resting macrophages, activated macrophages, antigenic peptides, autolytic T cells, β cells and regulatory T cells is modelled by the following equations

$$\frac{dM(t)}{dt} = a + (b+k)M_A(t) - cM(t) - gM(t)A(t), \tag{16}$$

$$\frac{dM_A(t)}{dt} = gM(t)A(t) - kM_A(t), \tag{17}$$

$$\frac{dA(t)}{dt} = lM_A(t) + qB(t)T(t) - mA(t), \tag{18}$$

$$\frac{dT(t)}{dt} = s_T + sM_A(t)T(t) - s_2T_{\mathrm{Reg}}(t)T(t) - \mu_T T(t), \tag{19}$$

$$\frac{dB(t)}{dt} = s_B - qB(t)T(t) - \mu_B B(t), \tag{20}$$

$$\frac{dT_{\mathrm{Reg}}(t)}{dt} = s_{\mathrm{Reg}} + \gamma_c T_{\mathrm{Reg}}(t) + s_3M_A(t)T_{\mathrm{Reg}}(t) - \mu_T T_{\mathrm{Reg}}(t). \tag{21}$$

All the parameters are as explained in the previous section (Section 2). The addition of regulatory T cells result in the modification of the equation governing the autolytic T cells. Here, the third term represents the death of the autolytic Th-cells due to cell–cell interactions with the regulatory T cells and due to chemical mediators produced by regulatory T cells which down-regulate the activities of these autolytic T cells.

Eq. (21) describes the dynamics of regulatory T cells, which we present here as a possible prevention strategy. The first term represents the supply rate of regulatory T cells from the thymus into the islet. The second term is a stimulation terms of the regulatory T cells by antibody injected into the body with γ_c as the efficacy of stimulation by antibody and the efficacy γ_c lies between zero and unity. The third term represents the proliferation of regulatory T cells due to stimulation induced by activated macrophages. The last term represents the natural death or deactivation rate of the regulatory T cells.

3.2. Model Analysis

In this section, we analyse the model after incorporating the inducible regulatory T cells.

The system of Eqs. (16)–(21) has an initial condition given by

$$M(0) = M_0 \geq 0, \quad M_A(0) = M_{A_0} \geq 0, \quad A(0) = A_0 \geq 0,$$

$$T(0) = T_0 \geq 0, \quad B(0) = B_0 \geq 0, \quad T_{\mathrm{Reg}}(0) = T_{\mathrm{Reg}_0}.$$

Since the model monitors human cell populations, all the variables and parameters of the model are non-negative. Based on biological considerations the system of Eqs. (16)–(21) will be studied in the following region,

$$H = \{(M, M_A, A, T, B, T_{\mathrm{Reg}}) \in \Re^6_+\}. \tag{22}$$

The following theorem assures that the system of Eqs. (16)–(21) is well posed such that solutions with non-negative initial conditions remain non-negative for all $0 < t < \infty$, and therefore makes biological sense.

Theorem 4. *The region $H \subset \Re^6_+$ is positively invariant with respect to the system of Eqs. (16)–(21) and a non-negative solution exists for all time $0 < t < \infty$.*

The proof of this theorem follows the proof of Theorem 1 in Section 2.1.

The disease-free state of the above model is given by

$$\varepsilon^2_{00} = (\tilde{M}, \tilde{M}_A, \tilde{A}, \tilde{T}, \tilde{B}, \tilde{T}_{\mathrm{Reg}}) = \left(\frac{a}{c}, 0, 0, \frac{s_T}{\mu_T}, \frac{s_B}{q(s_T/\mu_T) + \mu_B}, \frac{s_{\mathrm{Reg}}}{\mu_T - \gamma_c}\right).$$

The diabetic steady state is given by

$$\varepsilon^2_{01} = (\breve{M}, \breve{M}_A, \breve{A}, \breve{T}, \breve{B}, \breve{T}_{\mathrm{Reg}}),$$

where $\breve{M}$, $\breve{M}_A$, $\breve{A}$, $\breve{T}$, $\breve{B}$, and $\breve{T}_{\mathrm{Reg}}$ are expressions similar to expressions (7)–(11) in Section 2.1. $\breve{T}$ and $\breve{T}_{\mathrm{Reg}}$ are given by the following expressions.

The equilibrium value for autolytic T cells is given by

$$\breve{T} = \frac{s_T}{\mu_T + s_2\breve{T}_{\mathrm{Reg}} - s\breve{M}_A}. \tag{23}$$

An increase in regulatory T-cell population opposes the increase in autolytic T cells while an increase in activated macrophages promotes the increase in the autolytic T-cell population. At the diabetic equilibrium state the regulatory T-cell population is given by

$$\breve{T}_{\mathrm{Reg}} = \frac{s_{\mathrm{Reg}}}{\mu_T - \gamma_c - s_3 \breve{M}_A}. \tag{24}$$

From expression (24), we notice that an increase in activated macrophages also promotes the increase in regulatory T-cell population.

The Jacobian of the system (16)–(21) evaluated at the equilibrium point is given by

$$J(\varepsilon_{00}^2) = \begin{pmatrix} -c & (b+k) & -\frac{ga}{c} & 0 & 0 & 0 \\ 0 & -k & \frac{gd}{c} & 0 & 0 & 0 \\ 0 & l & -m & \frac{gs_B}{\mu_s} & \frac{gs_T}{\mu_T} & 0 \\ 0 & \frac{ss_T}{\mu_T} & 0 & -h & 0 & 0 \\ 0 & 0 & 0 & -\frac{gs_B}{\mu B} & \left(-\mu_B - \frac{gs_T}{\mu_T}\right) & 0 \\ 0 & \frac{s_{\mathrm{Reg}} s_3}{\gamma_c - \mu_T} & 0 & 0 & 0 & (\gamma_c - \mu_T) \end{pmatrix}.$$

To find the eigenvalues of this system we consider its characteristic polynomial given by $|J - \lambda I| = 0$. The characteristic polynomial is expanded to

$$\begin{aligned} &(-\lambda - c)(-\lambda - \mu_T + \gamma_c) \\ &\times \left[\left(\left(-\frac{agl}{c} + (-\lambda - k)(-\lambda - m) \right) \left(-\lambda - \mu_T - \frac{s_3 s_{Reg}}{\gamma_c - \mu_T} \right) \right.\right. \\ &\left.\left. + \frac{agqss_B s_T}{c\mu_B \mu_T} \right) \left(-\lambda - \frac{qs_T}{\mu_T} - \mu_B \right) + \frac{agq^2 ss_B s_T^2}{c\mu_B \mu_T^2} \right] = 0. \end{aligned} \tag{25}$$

From which we obtain the reproduction number, R_{01} as

$$R_{01} = \left(1 + \frac{qs_T s s_B (\gamma_c - \mu_T)}{(s_3 s_{\mathrm{Reg}} + \mu_T(\gamma_c - \mu_T))(qs_T + \mu_B \mu_T) l} \right). \tag{26}$$

Note the feasibility and stability of R_{01} depends on the term

$$x = \frac{qs_T s s_B (\gamma_c - \mu_T)}{(s_3 s_{\mathrm{Reg}} + \mu_T(\gamma_c - \mu_T))(qs_T + \mu_B \mu_T) l}.$$

If $-1 < x \leq 0$, results in $R_{01} < 1$, hence the system being stable. If on the other hand $x > 0$, R_{01} will ultimately be greater than unity and hence the system becomes unstable. Any slight deviations from the health equilibrium will result in death of more β cells and hence diabetes. An understanding of the biology related to the control of the parameters contained in R_{01} could unveil possible preventive and control strategies. Taking partial derivatives of R_{01} with respect to S_{Reg} and S_3 gives negative derivatives. This means that increasing the supply of regulatory T cells and the rate of stimulation of autolytic T cells by activated macrophages has the effect of reducing diabetes progression. Looking at expressions (25) and (26), for stability to hold, μ_T should be greater than γ_c ($\mu_T > \gamma_c$) and using the parameter values in Table 1 we tested that the parameters gives a positive reproduction number. Putting the values $\gamma_c = \mu_T$ gives the value $R_{01} = 1$, which is a transtion point between the control and the onset of diabetes. This indicate that the control of diabetes require more than just inducing regulatory T cells. Further more taking the partial derivative of R_{01} with respect to γ_c gives

$$\frac{\partial R_{01}}{\partial \gamma_c} = \frac{qss_T s_B}{(qs_T + \mu_B \mu_T) l} \left(\frac{s_3 s_{Reg}}{(s_3 s_{Reg} + \mu_T(\gamma_c - \mu_T))^2} \right), \tag{27}$$

which is always positive irrespective of the values of γ_c and μ_T. This suggests that increasing γ_c increases diabetes, which does not really make sense. This is possibly because γ_c appears both in the denominator and numerator of expression (26). Also, form the stability analysis point of view, γ_c can not take a value greater than μ_T, which means increasing γ_c will result in loss of stability of the system. However, numerical simulations in Fig. 4 shows that increasing γ_c towards the values of μ_T increase the levels of β cells and regulatory T cells which is associated with the decrease of antigenic peptides and autolytic T cells which shows reduction of diabetes progression.

3.3. Global Stability Conditions for the Disease-free Equilibrium

We follow the method in Section 2.2 to determine if the system of Eqs. (16)–(21) is globally stable at the disease-free equilibrium. We expressed the set of Eqs. (16)–(21) in the form (15). Where $G(X, 0) = 0$ and $X \in \Re^4$: denotes the number of immune cells that help in the control of diabetes and $Z \in \Re^2$: denotes the cells responsible for diabetes development. $U_0 = (X^*, 0)$ denotes the diabetes-free state $(X^* = (a/c, s_T/\mu_T, s_B/(q(s_T/\mu_T) + \mu_B), s_{\mathrm{Reg}}/(\mu_T - \gamma_c)))$ of the system. For the set of Eqs. (16)–(21) we set $X = (M, M_A, B, T_{\mathrm{Reg}})$: the set of resting macrophages, activated macrophages and β cells and $Z = (A, T)$: the antigenic peptides and the autolytic T cells.

Theorem 5 (Castillo-Chavez et al., 2002). *The fixed point $U_0 = (X^*, 0)$ is a globally stable equilibrium of (15) provided that $R_{01} < 1$ and that assumptions H1 and H2 are satisfied.*

Table 1
Parameters used in the model. Est means estimated.

Name	Definition	Value	Units	References
a	Macrophage supply	50.0	$\mathrm{mm}^{-3}\,\mathrm{day}^{-1}$	Wigginton and Kischner (2001) and Mar'ee and Kublik (2006)
b	Macrophage induced supply	0.3	day^{-1}	Wigginton and Kischner (2001) and Mar'ee and Kublik (2006)
c	Macrophage death rate	0.1	$\mathrm{mm}^{-3}\,\mathrm{day}^{-1}$	Wigginton and Kischner (2001) and Mar'ee and Kublik (2006)
g	Rate of antigen uptake	0.000065	day^{-1}	Mar'ee and Kublik (2006) and Kublik (2005)
k	Macrophage deactivation	0.2	day^{-1}	Mar'ee and Kublik (2006)
l	Induced β cell damage	0.00025	day^{-1}	Est
m	Decay rate of β cell proteins	0.025	day^{-1}	Nerup et al. (1974)
q	Damage of autolytic cells on β cells	2×10^{-6}	$\mathrm{mm}^{-3}\,\mathrm{day}^{-1}$	Mar'ee and Kublik (2006)
s_T	Supply of autolytic cells	20.0	$\mathrm{mm}^{-3}\,\mathrm{day}^{-1}$	Est
s	Proliferation of autolytic T cells	2×10^{-5}	day^{-1}	Mar'ee and Kublik (2006)
μ_T	Death rate of T cells	0.02	day^{-1}	Mar'ee and Kublik (2006)
s_B	Supply of β cells	20.0	$\mathrm{mm}^{-3}\,\mathrm{day}^{-1}$	Est
μ_B	Death rate of β cells	0.02	$\mathrm{mm}^{-3}\,\mathrm{day}^{-1}$	Mar'ee and Kublik (2006)
s_2	Autolytic cells death due to T_{Reg}	0.0001	day^{-1}	Est
s_3	Proliferation of T_{Reg} cells	0.0005	day^{-1}	Est
s_{Reg}	Supply rate of T_{Reg} cells	20.0	day^{-1}	Est
μ_c	Efficacy of induced antibody	0.0075	Scalar	Est

We computed $F(X, 0)$, and $\hat{G}(X, Z)$ and are given as follows,

$$F(X,0) = \begin{pmatrix} a - cM \\ 0 \\ s_B - \left(q\frac{s_T}{\mu_T} + \mu_B\right)B \\ s_{\mathrm{Reg}} - (\mu_T - \gamma_c)T_{\mathrm{Reg}} \end{pmatrix},$$

$$\hat{G}(X,Z) = \begin{pmatrix} (\hat{B} - B)qT - lM_A \\ -s_T - sM_AT + s_2(T_{\mathrm{Reg}} - \hat{T}_{\mathrm{Reg}})T \end{pmatrix}$$

Global stability of the system at ε_{00}^2 requires that $\hat{G}(X, Z) \geq 0$. Note, that $\hat{G}(X, Z) \geq 0$ if (i) $(\hat{B} - B)qT \geq lM_A$ and (ii) $s_2(T_{\mathrm{Reg}} - \hat{T}_{\mathrm{Reg}})T \geq -s_T - sM_AT$. Also, X^* is a globally asymptotically stable state of $dX/dt = F(X, 0)$, since $F(X, 0)$ is a limiting function of $dX/dt = F(X(t), Z(t))$. Therefore ε_{00}^2 is globally asymptotically stable if $\hat{G}(X, Z) \geq 0$. In this case, the global stability of a diabetic situation becomes more stable if regulatory T cells are boosted and stimulated enough, unlike in Section 2.2, where we showed that the stability of the system is unpredictable. Therefore, injecting antibodies that improve the level of regulatory T cells can stabilise the diabetic condition.

4. Numerical Simulations

We solve the system of differential Eqs. (1)–(5) and (16)–(21) numerically using C programming language based on the Runge–Kutta method of order four. Parameter values used in the simulations are obtained from published experimental data, derived from experiments using animals or are estimated. The following initial conditions are used in the numerical simulations $M(0) = 500$, $M_A(0) = 0$, $A(0) = 5$, $T(0) = 1000$, $B(0) = 1000$. In all the simulations a step-size $h = 0.1$ is used. The parameters used in the numerical simulations are given in Table 1.

We carry simulations to determine how the antigenic peptides in the islet are affected as the population of autolytic T cells increases. The simulations were aimed to show the influence of increase of autolytic T cells on the progression of diabetes as well as to investigate how infiltration of macrophages in the islet stimulate the onset of diabetes. Also, the other aim of the simulations was to show the effect of regulatory T cells in the control of diabetes and investigate if antibodies that simulate regulatory T cells are injected in the body can significantly affect diabetes progression.

Fig. 1 shows that, increase of macrophages and autolytic T cells infiltration in the islet can cause the stimulation of diabetes. Once this occurs, activation of macrophage follows and this will in turn prompt the proliferation of autolytic T cells then will lead to the increase of the antigenic peptides. This combination of evens will result in the depletion of insulin-producing β cells hence setting a good precedence of propagation of diabetes.

Increasing the rate of autolytic T cells proliferation result in the increase of the population of these cells (Fig. 2(c)). The implications of increasing the number of autolytic T cells in the islet is the increased death of insulin-producing cells and production of more antigenic peptides. This will cascade more activation of macrophages, hence a series of more autolytic T cells and antigenic cells and further depletion of β cells in the islet. Hence, increased production of autoimmune cells that target β cells propel diabetes.

In Section 3 we extended the model in Section 2 to incorporate regulatory T cells that down-regulate the activity of auto-reactive T cells. We sort to find how regulatory T cells can be improved to control diabetes. The main short fall of regulatory T cells is that they are normally insufficient in number to fully control the activity of autolytic T cells. We explore options that include (i) enhancing their recruitment through injecting antibodies and (ii) a theoretical assessment that involve different magnitudes of their constant supply from where they are matured and created (that is if their production and maturation in the thymus is increased then their natural turn over in the islet will increase over time). The main thrust of these simulations is to determine how increased levels of regulatory T cells can be of help in alleviating the progression of diabetes.

Simulation results in Fig. 3 show that, when there are no regulatory T cells, autolytic T cells growth is uncontrolled. Autolytic T cells will push the population of β cells down, hence increasing the amount of antigenic peptides, therefore promoting diabetes. Introduction of regulation to the system of Eqs. (1)–(5) in Section 2 to the dynamics give a new picture as shown in Fig. 3. Fig. 3 shows that as the initial amount of regulatory T cells is increased or as their natural turn over is increased a corresponding decrease in autolytic T cells is noticed, which subsequently results in reduction of antigenic peptides and activated macrophages, and increase of β cells. This shows that if regulatory T cells are sufficient enough in numbers they can reduce the progression of diabetes.

Fig. 4 shows that increasing the efficacy (γ_c) of induced antibodies in stimulating regulatory T cells enhance recruitment and

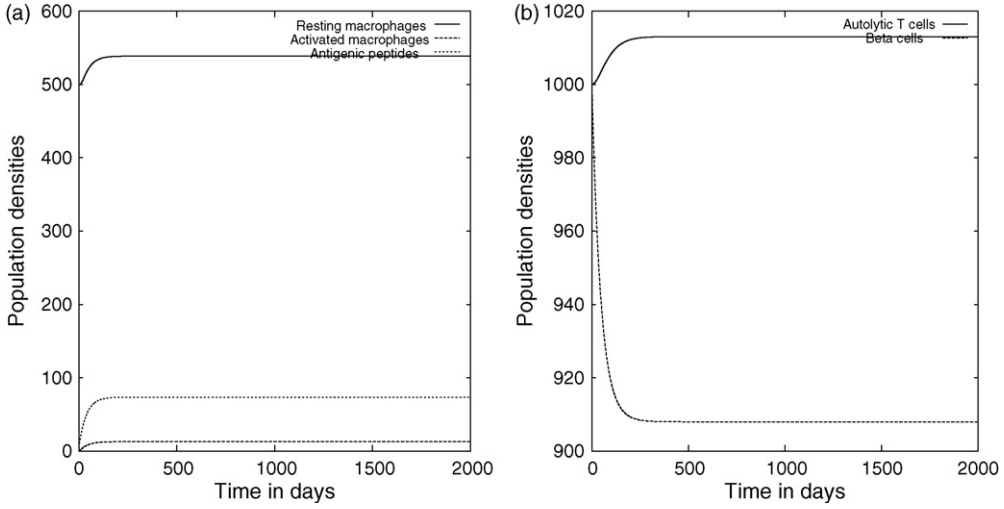

Fig. 1. Graphs of numerical solutions showing propagation of macrophages, antigenic peptides, β cells and autolytic T cells after stimulation of diabetes.

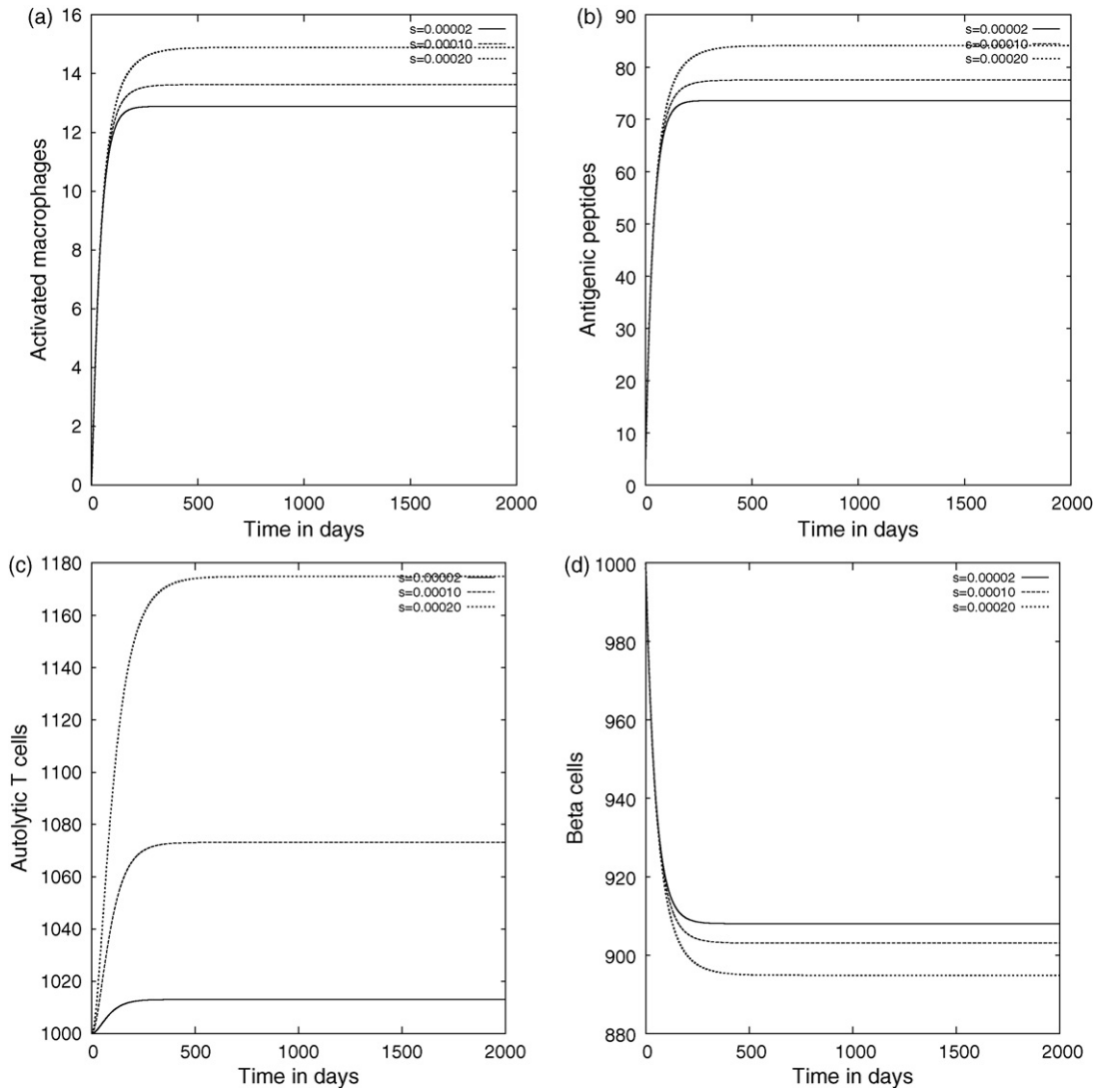

Fig. 2. Graphs of numerical simulations of (a) activated macrophages, (b) antigenic peptides, (c) autolytic T cells and (d) β cells in a diabetic person as the rate of autolytic T cells proliferation is varied.

proliferation of these cells. This helps in reducing autolytic T cells and antigenic peptides and hence control of diabetes. However, this fails to eliminate antigenic peptides and autolytic T cells completely, but achieves their suppression to a certain level (Fig. 4(a) and (b)) which is accompanied with an increase in β cells and regulatory T cells that support the control of diabetes. Suppression of autolytic T cells and antigenic peptides without total elimination suggests that, regulatory T cells and an intravention strategy that could be used to enhance their proliferation and production may only be potent enough to prevent propagation of diabetes or its progression to fatal levels without completely clearing it. Failure of total clearance of the antigenic peptides and autolytic cells imply that if there could be something else to off set the stable steady level of the autolytic T cells, the antigenic peptides and autolytic T cells will start to increase again and eventually progession of diabetes.

Generally results in Figs. 3 and 4 show that the increase in regulatory T cells is important in the control of diabetes. The more the regulatory T cells the greater the extend of suppression of autolytic cells and antigenic peptides. This is in line with the results from Pitt research (Irie et al., 2007), which concluded that in the progression of diabetes it is either that the regulatory T cells are faulty or are lacking in numbers. This study confirms that the higher the level of regulatory T cells the greater is the suppression of autolytic T cells, which implies that if the amount of regulatory T cells is high enough, they could possibily push the level of autolytic T cells down toward possible clearance of diabetes.

5. Discussion

In this paper we presented mathematical models incorporating both β cells and autolytic T lymphocytes. We determined parameters which might have a big role in the development of type 1 diabetes. The involvement of autolytic T cells in the immune system is favoured if there already exists an unstable parameter space which results in more β cell death. In this case a cascade like sequence of events propagates death of β cells which trigger an increase in the level of antigenic peptides which in turn propels activation of macrophages that fuels the growth of autolytic cells. This results in death of even more β cells until the whole islet is unable to produce any or enough amounts of insulin required for metabolic activities. The results show that the presence of autolytic T cells results in the depletion of β cells. If the level of β cells is too low, the islets and hence the pancreas will be unable to produce insulin in sufficient amounts to meet the metabolic needs of the

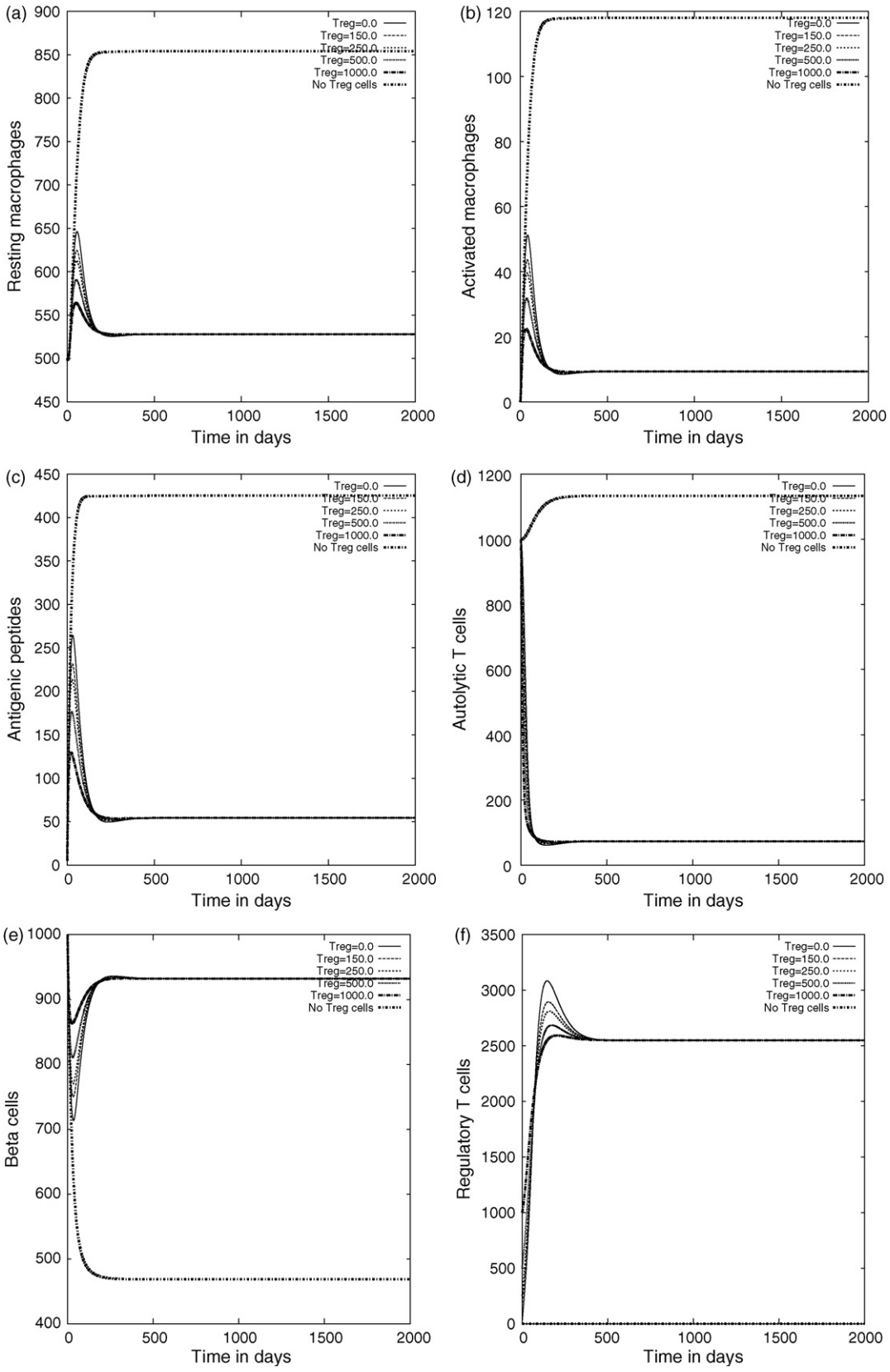

Fig. 3. Numerical simulations that show how different amounts of inflows of regulatory T cells affect the level of (a) resting macrophages, (b) activated macrophages, (c) antigenic peptides, and (d) autolytic T cells. (e) β cells and (f) regulatory T cells.

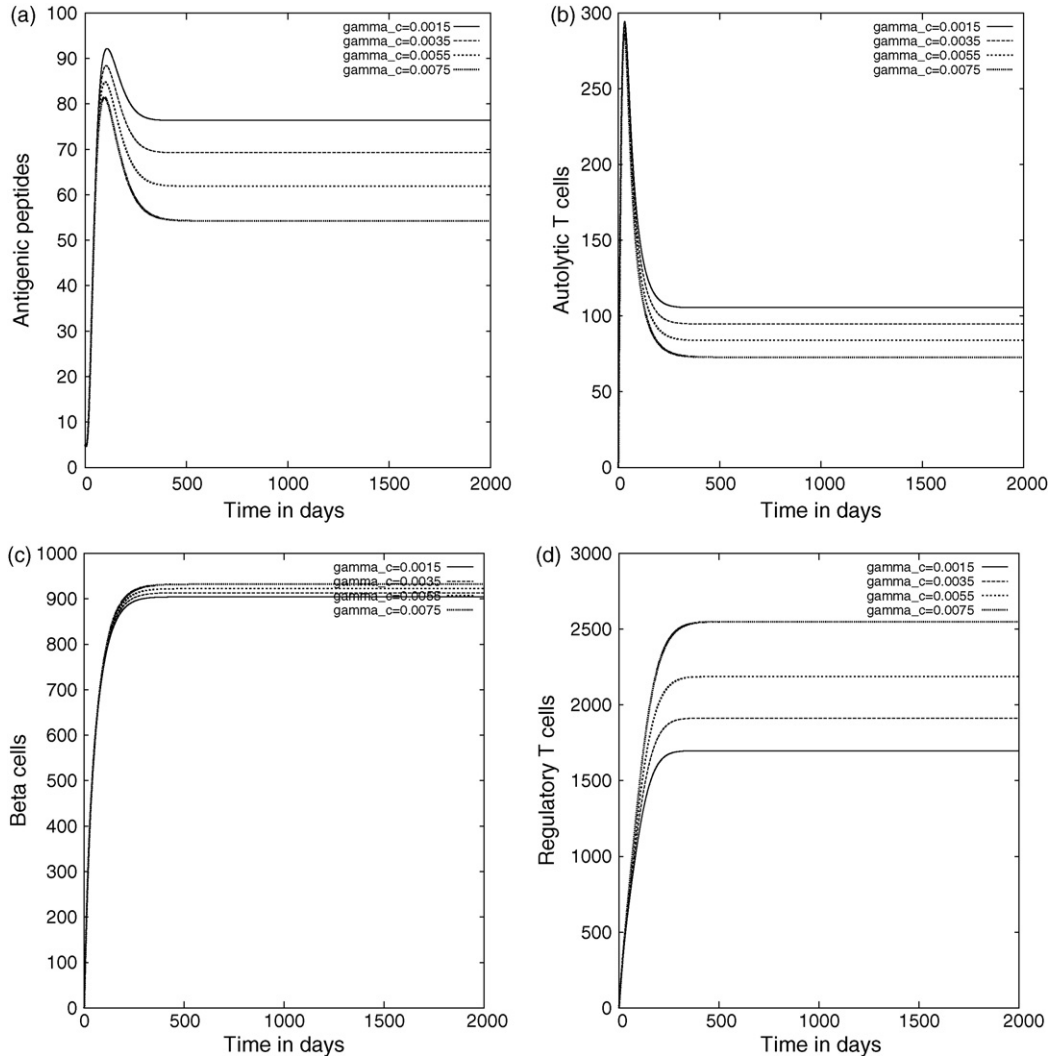

Fig. 4. Simulations showing the effect of varying the efficacy of injected antibodies in stimulating regulatory T cells on (a) antigenic peptides, (b) autolytic T cells, (c) β cells and (d) regulatory T cells.

body resulting in a need to obtain the insulin from other sources other than one's own body.

This study, shows that the stimulation and propagation of diabetes is a combination of events, and that there is no single event that is fully responsible for it. A chain of reactions are collectively responsible for diabetes disease. However, targeting regulation of autolytic T cells by regulatory T cells can pay more dividends in the control of diabetes. Our simulations suggest that if the level of regulatory T cells are sufficiently increased they can down-regulate the activity of auto-reactive T cells to a level that will enable β cells to replenish so as to enable insulin production. Our mathematical analysis showed that the diabetes-free state in a diabetic individual is unpredictable, such that slight alteration of the steady state can trigger the onset of diabetes propagation. This result is in line with known results that even environmental changes can propel diabetes (Freiesleben De Blasio et al., 1999).

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