MODELING AND ANALYSIS OF RECURRENT AUTOIMMUNE DISEASE*

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Abstract. Many autoimmune diseases are characterized by a pattern of recurrence and remission, in which periods of apparent self-tolerance are punctuated by intervals of recurring autoimmunity. We introduce a newly discovered class of terminally differentiated regulatory T cells, HLA-DR⁺ T_{Reg} cells, into an existing autoimmune disease model. Our newly developed 4-dimensional model exhibits recurrent dynamics, which are preserved in a reduced and rescaled 3-dimensional model as well. Applying dynamical systems theory, we analyze the dynamics underlying this behavior in both the 4-dimensional and 3-dimensional models and further prove that the recurrent behavior (or oscillation) arises due to a Hopf bifurcation or a persistent oscillation rather than from homoclinic orbits. Numerical simulations are conducted to verify the analytical results and identify the recurrent parameter region.

 ${\bf Key}$ words. autoimmunity, modeling, recurrent infection, dynamical system, stability, bifurcation

AMS subject classifications. 92D30, 37L10, 37N25

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1. Introduction. The adaptive immune system consists of a set of highly specialized cells and processes that can limit or eradicate the growth of foreign pathogens. Normally, the immune system must be able to mount responses against pathogens that invade the host, but avoid attacking the organism's own tissues; when this discrimination fails, the result is autoimmunity. Autoimmune diseases are often chronic and debilitating. They affect 50 million (or one in five) Americans, but are more common in women (75 percent of cases), according to the American Autoimmune Related Diseases Association [2]. In fact, autoimmune diseases, such as systemic sclerosis and rheumatoid arthritis, are among the main causes of death of young and middle-aged women in developed countries [9]. Evidence is also mounting that the prevalence of autoimmune disease is increasing: for example, a 3% global increase in type 1 diabetes per year has been reported [30]. Although health care costs related to autoimmune diseases amount to over a billion dollars each year in the United States alone, patients are still suffering from misdiagnosis and delayed diagnosis due to a lack of understanding of autoimmune disease. These facts illustrate the vital need to focus further research on all autoimmune diseases.

To address autoimmune disease in a mathematical model, we first outline in brief the normal function of the immune system. The cells of the adaptive immune system are T- and B lymphocytes: B cells are involved in "humoral immune responses," while T cells play a large role in the cell-mediated immune responses. Here, in order to investigate T cell-mediated autoimmune disease, we focus on the latter response. Initiation of an adaptive immune response starts when immature dendritic cells (DCs), which are the most important professional antigen presenting cells (pAPCs), settle

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at a site of infection or inflammation, become activated, and undergo maturation. Simultaneously, naive conventional T cells, each bearing a specific antigen receptor, constantly circulate through the peripheral lymphoid tissues, browsing many DCs as they carry out brief contacts, and receiving two signals: discrimination of the antigen presented by DCs and interplay with co-stimulatory molecules on the same DCs. After making a stable interaction with DCs presenting their cognate antigen, naive T cells can be activated and proliferate into effector T cells. The proliferation phase is significant and driven by the cytokine interleukin-2 (IL-2), which can be produced by active conventional T cells themselves and from other sources as well.

Central tolerance is the main mechanism which allows the immune system to avoid mounting a response against the organism's own tissues. In this process, autoreactive T cells, which have antigen receptors specific to self-antigens, are deleted during lymphocyte development in the thymus. Nevertheless, the T cells that leave the thymus are relatively but not absolutely safe. A large body of research has demonstrated that some auto-reactive T cells are present in the periphery under normal conditions [43]. In this case, peripheral tolerance is established after T cells mature and migrate into the periphery, which prevents auto-reactive T cells from directing an immune response toward self-antigens. One mechanism of peripheral tolerance is the population of regulatory T (T_{Reg}) cells.

Regulatory T cells are a subpopulation of CD4^+ T cells that modulate the immune system, preventing the expansion of auto-reactive T cells and subsequent autoimmune disease [34]. Evidence [33, 4, 20] has shown that human T_{Reg} cells are phenotypically heterogeneous. Most thymus-derived T_{Reg} cells found in the periphery are naive T_{Reg} cells [20, 25, 15], which have not experienced T cell receptor (TCR) stimulationmediated maturation and are in a quiescent stage, resistant to apoptosis. Like naive conventional T cells, in order to participate in an immune response, naive T_{Reg} cells require activation by antigen on pAPCs and possible co-stimulation [1, 23]. IL-2 seems to be a necessary factor [10, 37, 35] for T_{Reg} cell proliferation. Activated conventional T cells are believed to be the main source of IL-2 [12, 45], although there also exist other IL-2 sources, such as DCs. Following activation, naive T_{Reg} cells become effector natural T_{Reg} (n T_{Reg}) cells, which have potent suppressive activity. T_{Reg} cells can also develop from mature conventional T cells outside the thymus; however, the distinction between these "induced" T_{Reg} cells and natural T_{Reg} cells is immaterial to our model.

Recently, a new subset of effector nT_{Reg} cells has been discovered experimentally [5, 31]. This subset of cells have further matured to become terminally differentiated suppressors, which show more efficient suppression, but have a shorter lifespan, than nT_{Reg} cells. Phenotypic analysis has demonstrated that the expression of the cell surface receptor denoted HLA-DR in nT_{Reg} cells is heterogeneous [32] and distinguishes this terminally differentiated subpopulation; in particular, HLA-DR⁺ T_{Reg} cells suppress proliferation of conventional T cells more rapidly than do HLA-DR⁻ T_{Reg} cells. It is believed that activation and expansion of HLA-DR⁻ effector nT_{Reg} cells provoke the generation of this subset of HLA-DR⁺ T_{Reg} cells [5].

Despite these multilayer barriers, self-tolerance mechanisms fail occasionally. Although the activity of auto-reactive T cells in humans is not understood completely, research in nonhuman primates has indicated that these cells in the periphery can be activated and may provoke a T cell-mediated attack against self-determinants [41], causing autoimmune disorders. For example, when auto-reactive T cells attack the central nervous system [41], acute focal inflammation may cause a relapse of symptoms in multiple sclerosis [42]. T_{Reg} cells are capable of limiting these attacks, and their deficiency can lead to fatal autoimmune disease which affects multiple organs in mice [6, 14] and human beings [38, 29].

Autoimmune diseases are often chronic, requiring lifelong care and monitoring, despite the fact that symptoms may disappear occasionally. Many autoimmune diseases are characterized by recurrence, that is, disease relapses (return of symptoms) followed by remittance (absence of symptoms, possibly for a long period). In several autoimmune diseases, this relapse-remission behavior occurs even in the absence of treatment, for example in multifocal osteomyelitis [16, 21], eczema [13], subacute discoid lupus erythematosus [27], and psoriasis [11]. In fact, the subtypes of some diseases are clinically classified based on the patterns of this recurrent behavior [42]. Therefore, an improved understanding of recurrent dynamics in autoimmune disease is crucial to promoting correct diagnosis, patient management, and treatment decisions.

Recently, the relapse-remission behavior of multiple sclerosis was studied using a stochastic differential equation model developed by Velez de Mendizabal et al. [40]. The authors investigated cross-regulation interactions, modeled as Hill functions, between regulatory and auto-reactive effector T cells. A predator-prey system was adopted in that paper, in which auto-reactive effector T cells act as prey and T_{Reg} cells as predators. The deterministic system derived in this model does not display recurrent dynamics. However, when the resting auto-reactive effector T cell and resting T_{Reg} cell populations are introduced to the deterministic model using stochastic pulse trains [44], modeling the probabilistic influx of resting cells, the characteristic relapse-remission behavior of multiple sclerosis is observed. The paper concludes that weakness in the negative feedback between effector and regulatory T cells may allow the immune system to generate the typical recurrent dynamics of autoimmune disease. This work is similar to recent models of recurrent dynamics in HIV, in which stochastic inputs or forcing functions are typically necessary to generate recurrent behavior [49, 50].

Recent models introduced by Alexander and Wahl [1] capture the intrinsic feedback cycle of autoimmunity, in which pAPCs present self-antigen, eliciting self-reactive effector T cells, which in turn attack host tissues. The damage to host tissue results in increased concentrations of self-antigen, activating further pAPCs. This cycle is kept in check by the actions of T_{Reg} cells, which limit the self-reactive immune response via several putative mechanisms. These models exhibit equilibria corresponding to tolerance and autoimmunity, but bistability is not observed. Instead, a branching process was used to demonstrate that, from identical starting conditions, states of immune tolerance or intolerance could be reached probabilistically. Although this set of related models offers a general approach to autoimmunity and the role of T_{Reg} cells, it does not capture the recurrent behavior which characterizes many autoimmune diseases.

Following the recent experimental discovery of the HLA-DR⁺ T_{Reg} cells described above, we have chosen to expand the model of Wahl and Alexander to include this new class of potently suppressive cells. In some parameter regimes, we observe numerically that the expanded model exhibits long periods of self-tolerance, punctuated by brief episodes of disease recurrence, deterministic dynamics reminiscent of our recent investigations of viral blips in in-host infection models [49]. In these infection models, relapse-remission behavior may in some cases arise simply from the nonlinear dynamics of the underlying dynamical system, in the absence of stochasticity, therapy, or other trigger mechanisms [46, 39]. By taking advantage of dynamical systems theory, we recently proposed four conditions which guarantee recurrent behavior in deterministic viral infection models [49]. Given the importance of recurrence to autoimmune disease, here we apply a similar approach to gain an analytical understanding of the dynamical features underlying recurrence in the autoimmune model.

The rest of the paper is organized as follows. In section 2, we introduce two established models [1] describing autoimmune disease. We demonstrate that these two models do not have Hopf bifurcations, and so cannot exhibit the oscillatory behavior which underlies recurrence. Based on recent experimental findings, we introduce the new T_{Reg} subtype and establish a new model. In section 3, we first prove that the new model is well-posed, and then perform mathematical analysis to find equilibrium solutions and determine their local and global stability. By choosing proper bifurcation parameters, we also identify the transcritical and Hopf bifurcation critical points, showing that the new model should display the recurrent dynamics characteristic of many autoimmune diseases. Further, by applying center manifold theory and normal form theory, we find approximate solutions of the limit cycles and determine their stability. Then, in section 4, we use numerical simulation to verify the analytical predictions obtained in section 4. Moreover, a comparison between the analytical and numerical results for the Hopf bifurcation is given in this section. In order to identify key factors in the mechanism of recurrence, in section 5 we perform model reduction under a quasi-steady state assumption. This is achieved by reducing the number of state variables and parameters, and also by a rescaling of the time variable. Then, we prove that the original and reduced models exhibit the same dynamical behavior as long as the parameter values are chosen properly. Based on the reduced model, three bifurcation parameters are used to classify the parameter ranges for which recurrence exists. Furthermore, we show that there do not exist homoclinic orbits in either the original or the reduced models, and so the recurrence phenomenon either comes from Hopf bifurcation or is due to persistent oscillations. We conclude with a brief discussion of these results in section 6.

2. Model development. Following recent experimental findings, we sought to introduce terminally differentiated regulatory T cells as an explicit variable into models established by Alexander and Wahl [1]. Their models consider two suppressive mechanisms enacted by T_{Reg} cells. Since pAPCs are primarily DCs, which are targets of nT_{Reg} cell suppressive action [26], the first of the suppressive mechanisms is the direct suppression of pAPCs by T_{Reg} cells, effectively removing pAPCs from the system [18]. The corresponding model is given by

(2.1)
$$\begin{aligned} A &= f\tilde{v}G - (\sigma_1 R_n + b_1)A - \mu_A A, \\ \dot{R}_n &= (\pi_1 E + \beta)A - \mu_n R_n, \\ \dot{E} &= \lambda_E A - \mu_E E, \\ \dot{G} &= \gamma E - \tilde{v}G - \mu_G G, \end{aligned}$$

where the variables A, R_n , E, G represent the populations of mature pAPCs, active nT_{Reg} cells, active auto-reactive effector T cells, and the particular self-antigen of interest, respectively. All cell populations are specific for a given self-antigen. Parameter definitions and their numerical values are listed in Table 1; meaningful numerical values were carefully chosen in [1] with extended reference to the primary literature. Model (2.1) assumes that pAPCs undergo maturation at a rate of $f \tilde{v} G$, while during this process the antigen uptake rate is $\tilde{v} G$. The activated auto-reactive effector T cells (E) are produced at a rate of $\lambda_E A$ by resting T cells through an interaction with mature pAPCs (A). After activation, auto-reactive effector T cells (E) can produce IL-2, which is required for T_{Reg} cell proliferation, while other IL-2 sources also exist. Thus nT_{Reg} cells are activated at a rate of ($\pi_1 E + \beta A$, where $\pi_1 E$ represents IL-2

TABLE 1

Parameter definitions and values used in previous models.

Para.	Definition	Values
ũ	Per capita rate at which free antigen (G) is taken up by immature pAPCs	0.0025 /day
f	Proportion of antigen molecules that, upon uptake, lead to maturation of the pAPC to enter population A	$1 \times 10^{-4} \ [A]/[G]$
π_1	Rate (per A , per E) at which active nT_{Reg} cells are generated from the pool of "naive" T_{Reg} cells, due to encounter with mature pAPCs (A) and influence of IL-2 from specific effector T cells	$0.0160 \ [R_n]/(\operatorname{day} \cdot [E] \cdot [A])$
π_3	Rate (per A, per E) at which active nT_{Reg} cells are generated from the pool of "naive" T_{Reg} cells, due to encounter with mature pAPCs (A) and influence of IL-2 from specific effector T cells	$0.0256 \ [R_n]/(\operatorname{day} \cdot [E] \cdot [A])$
β	Rate (per A) at which active nT_{Reg} cells are generated from the resting pool, due to encounter with mature pAPCs (A) and influence of IL-2 from other sources	$200 \ [R_n]/(\mathrm{day} \cdot [A])$
λ_E	Rate (per A) at which effector T cells (E) are gen- erated from the resting pool, due to encounter with mature pAPCs (A)	$1000 \ [E]/(\mathrm{day} \cdot [A])$
γ	Rate (per E) at which self-antigen (G) is released due to the actions of effector T cells (E)	2000 $[G]/(\text{day} \cdot [E])$
$\sigma_{1,3}$	Rate (per capita, R_n) at which mature pAPCs (A) and effective T cells are effectively eliminated due to suppression by specific active nT _{Reg} cells (R_n)	$3 \times 10^{-6} / (\operatorname{day} \cdot [R_n])$
b_1	Rate (per capita) at which mature pAPCs (A) are effectively eliminated due to suppression by T_{Reg} cells of other specificities or by therapy	0.25 /day
b_3	Rate (per capita) at which effective T cells (E) are effectively eliminated due to suppression by T_{Reg} cells of other specificities or by therapy	0.25 /day
μ_A	Per capita death rate of mature pAPCs	0.2 /day
μ_E μ_G	Per capita death rate of effector T cells (E) Per capita rate at which free antigen (G) is cleared, for example due to degradation	5 /day
μ_n	Per capita death rate of active nT_{Reg} cells (R_n)	0.1 /day
μ_d	Per capita death rate of terminal T_{Reg} cells (R_d)	0.2 /day
ξ	Proportion of activated nT_{Reg} cells	0.025/day
α	Rate (per E) at which immature pAPCs become mature	$1 \times 10^{-4} [A]/(\text{day} \cdot [E])$
d	Ratio of suppressive effectiveness of nT_{Reg} cells to that of terminal T_{Reg} cells	$2 \ [R_n]/[R_d]$
С	Factor by which matured $nT_{\rm Reg}$ cells expand and proliferate to terminal $T_{\rm Reg}$ cells	$2^3 = 8 \left[R_d \right] / R_n]$

produced by active auto-reactive effector T cells (E) and β represents background sources of IL-2. nT_{Reg} cells (R_n) then suppress pAPCs (A) at a rate of $\sigma_1 R_n A$, while b_1 represents a level of nonspecific background suppression. Auto-reactive effector T cells (E) attack the host tissues, causing the release of self-antigen at a rate of γE , which in turn triggers the maturation of pAPCs and thus initiates a new cycle of autoimmunity. Here, the death/clearance rates of the populations A, R_n , E, and Gare μ_A , μ_n , μ_E , and μ_G , respectively.

By down-regulating IL-2 transcription, Treg cells could suppress effector T cells [43],

or even kill them [17, 18]. Therefore, another suppressive mechanism is considered in isolation in [1]; that is, nT_{Reg} cells may directly reduce the auto-reactive effector T cell population. This model is described by

(2.2)
$$\begin{aligned} A &= f\tilde{v}G - \mu_A A, \\ \dot{R}_n &= (\pi_3 E + \beta)A - \mu_n R_n, \\ \dot{E} &= \lambda_E A - (\sigma_3 R_n + b_3)E - \mu_E E, \\ \dot{G} &= \gamma E - \tilde{v}G - \mu_G G, \end{aligned}$$

where the auto-reactive effector T cells are suppressed by nT_{Reg} cells and background suppression at a rate of $(\sigma_3 R_n + b_3) E$. Other terms have the same meanings as their counterparts in model (2.1).

2.1. No recurrence in models (2.1) and (2.2). Since the main purpose of this paper is to study recurrence in autoimmune models, we first want to ask whether the above two models (2.1) and (2.2) can exhibit this behavior. According to the hypothesis given in [49], a Hopf bifurcation is a necessary condition for recurrence. In this section, we will show that the two models (2.1) and (2.2) do not have a Hopf bifurcation. For simplicity, we briefly outline the proof only for model (2.1). One can prove this for model (2.2) similarly.

First, as usual, we can show that the solutions of model (2.1) are nonnegative if the initial conditions are nonnegative, and all solutions are bounded. Further, we show that model (2.1) has two equilibrium solutions: one of them is the trivial equilibrium,

$$\mathbf{E}_0: \ A_0 = R_{n0} = E_0 = G_0 = 0,$$

and the other is the nontrivial equilibrium,

$$E_1: R_{n1} = \frac{f\tilde{v}\gamma\lambda_E - \mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G)}{\sigma_1\mu_E(\tilde{v} + \mu_G)}, \quad E_1 = \frac{\lambda_E}{\mu_E}A_1, \quad G_1 = \frac{\gamma\lambda_E}{\mu_E(\tilde{v} + \mu_G)}A_1,$$

where

(2.3)
$$A_1 = -\frac{\beta\mu_E}{2\pi_1\lambda_E} + \sqrt{\left(\frac{\beta\mu_E}{2\pi_1\lambda_E}\right)^2 + \frac{f\tilde{v}\gamma\lambda_E - \mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G)}{\sigma_1\pi_1\lambda_E}},$$

for $f\tilde{v}\gamma\lambda_E - (b_1 + \mu_A)\mu_E(\tilde{v} + \mu_G) > 0$, and thus $A_1 > 0$.

Then, the stability of E_0 and E_1 can be determined from the linearized system of (2.1) and its characteristic polynomials, associated with these two equilibria. The characteristic polynomial for E_0 is obtained as $P_0(L) = (L + \mu_n)(L^3 + a_{01}L^2 + a_{02}L + a_{03})$, where

$$a_{01} = b_1 + \mu_A + \mu_E + \tilde{v} + \mu_G, a_{02} = \mu_E(b_1 + \mu_A + \tilde{v} + \mu_G) + (b_1 + \mu_A + \tilde{v} + \mu_G), a_{03} = \mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G) - f\tilde{v}\gamma\lambda_E.$$

Further, it is easy to show that

$$\Delta_{02} = a_{01} a_{02} - a_{03}$$

= $(b_1 + \mu_A)(\mu_E + \tilde{v} + \mu_G)^2 + (\mu_E + \tilde{v} + \mu_G) [\mu_E (\tilde{v} + \mu_G) + (b_1 + \mu_A)^2] + f \tilde{v} \gamma \lambda_E > 0$

Thus, according to the Routh–Hurwitz criterion, we can conclude that the equilibrium E_0 is stable (unstable) if $\mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G) - f\tilde{v}\gamma\lambda_E$ is > 0 (< 0). The only

possible bifurcation from E₀ is a static bifurcation which occurs at the critical point, determined by $f\tilde{v}\gamma\lambda_E = \mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G)$. Note that when $\mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G) - f\tilde{v}\gamma\lambda_E > 0$, the equilibrium E₁ does not exist.

Next, similarly we can discuss the stability of E₁. The characteristic polynomial associated with E₁ is given by $P_1(L) = L^4 + a_{11}L^3 + a_{12}L^2 + a_{13}L + a_{14}$, where

$$\begin{aligned} a_{11} &= \frac{1}{\mu_E(\tilde{v} + \mu_G)} \Big[f \tilde{v} \gamma \lambda_E + \mu_E(\tilde{v} + \mu_G)(\mu_u + \mu_E + \tilde{v} + \mu_G) \Big], \\ a_{12} &= \frac{1}{\mu_E(\tilde{v} + \mu_G)} \Big\{ \sigma_1(\tilde{v} + \mu_G)(\pi_1 \lambda_E A_1 + \beta \mu_E) A_1 + f \tilde{v} \gamma \lambda_E(\mu_n + \mu_E + \tilde{v} + \mu_G) \\ &\quad + \mu_E(\tilde{v} + \mu_G) \Big[\mu_E \mu_n + (\mu_n + \mu_E)(\tilde{v} + \mu_G) \Big] \Big\}, \\ a_{13} &= \frac{1}{\mu_E(\tilde{v} + \mu_G)} \Big\{ \sigma_1(\tilde{v} + \mu_G) \Big[\lambda_E \pi_1(\tilde{v} + \mu_G + 2\mu_E) A_1 + \beta \mu_E(\mu_E + \tilde{v} + \mu_G) \Big] A_1 \\ &\quad + \mu_n \Big[\mu_E^2(\tilde{v} + \mu_G)^2 + (\mu_E + \tilde{v} + \mu_G) f \tilde{v} \gamma \lambda_E \Big] \Big\}, \\ a_{14} &= \sigma_1(\tilde{v} + \mu_G) (2\pi_1 \lambda_E A_1 + \beta \mu_E) A_1, \end{aligned}$$

where A_1 is given in (2.3). It is easy to see that $a_{1i} > 0$, i = 1, 2, 3, 4. Moreover, we can show that

$$\begin{aligned} \Delta_{12} &= a_{11} a_{12} - a_{13} \\ &= \frac{1}{\mu_E^2 (\tilde{v} + \mu_G)^2} \left\{ \mu_E^3 (\tilde{v} + \mu_G)^2 \sigma_1 \beta A_1 \\ &+ \mu_E^2 (\tilde{v} + \mu_G)^2 \left[\mu_n (\mu_E + \tilde{v} + \mu_G)^2 + (\tilde{v} + \mu_G) \left(\mu_E^2 + \mu_n^2 + \mu_E (\tilde{v} + \mu_G) \right) \right. \\ &+ \mu_E \mu_n (\mu_n + b_1 + \mu_A) \right] \\ &+ f \tilde{v} \gamma \mu_E (\tilde{v} + \mu_G) \lambda_E \left[(\mu_n + \tilde{v} + \mu_G)^2 + \mu_E \left(3 (\tilde{v} + \mu_G) + \mu_E + \mu_n \right) \right] \\ &+ (f \tilde{v} \gamma \lambda_E)^2 (\mu_n + \mu_E + \tilde{v} + \mu_G) \\ &+ \mu_n \left[f \tilde{v} \gamma \lambda_E + \mu_n \mu_E (\tilde{v} + \mu_G) \right] \left[f \tilde{v} \gamma \lambda_E - \mu_E (b_1 + \mu_A) (\tilde{v} + \mu_G) \right] \right\} \\ \geq 0. \end{aligned}$$

due to $f\tilde{v}\gamma\lambda_E > \mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G)$, as well as $\Delta_{13} = (a_{11}a_{12} - a_{13})a_{13} - a_{14}a_{11}^2 > 0$. Here the lengthy expression of Δ_{13} is omitted for brevity. Therefore, E_1 is stable if $f\tilde{v}\gamma\lambda_E - \mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G) > 0$. Noticing the stability condition for E_0 , we can see that E_0 and E_1 exchange their stability at the critical point, determined by $f\tilde{v}\gamma\lambda_E = \mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G)$, and only a transcritical bifurcation exists at this critical point. This implies that there is also no Hopf bifurcation that can occur from the equilibrium E_1 .

Further, we can show that the trivial equilibrium of model (2.1) is globally asymptotically stable. This can be achieved by first considering the first, third, and last equations of (2.1), and ignoring the nonlinear term $-\sigma_1 R_n A$ in the first equation, yielding a linear system which has the characteristic polynomial $P_0(L)$. Thus, by using comparison theory and this linear system (obtained by ignoring the nonlinear term) [24], we can easily prove that the equilibrium E_0 is globally asymptotically stable. Although we have not proved the global stability of the nontrivial equilibrium, we have tried a number of numerical simulations, which show that all solutions converge to E_1 regardless of the initial conditions, as long as the condition $f\tilde{v}\gamma\lambda_E > \mu_E(b_1 + \mu_A)(\tilde{v} + \mu_G)$ is satisfied. Hence, we conjecture that the two models (2.1) and (2.2) do not have any persistent solutions, except the two equilibrium solutions E_0 and E_1 . This motivates the development of new models for studying relapse-remission dynamics in autoimmune disease.

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2.2. Developing new models. Now, based on the two models (2.1) and (2.2), we develop new models. First, instead of considering the two immunosuppressive mechanisms in isolation, we combine them to obtain the following 4-dimensional ODE model:

(2.4)
$$\begin{aligned} A &= f\tilde{v}G - (\sigma_1 R_n + b_1)A - \mu_A A, \\ \dot{R}_n &= (\pi_3 E + \beta)A - \mu_n R_n, \\ \dot{E} &= \lambda_E A - (\sigma_3 R_n + b_3)E - \mu_E E, \\ \dot{G} &= \gamma E - \tilde{v}G - \mu_G G, \end{aligned}$$

where the π_1 is replaced by π_3 . Note that the numerical value of either π_1 or π_3 from [1] could be used; the difference is immaterial to our analysis.

As mentioned in the introduction, phenotypic analysis indicates that the effector T_{Reg} cell subset is heterogeneous in the expression of HLA-DR [33], which identifies a terminally differentiated subpopulation of effector T_{Reg} cells, the HLA-DR+ T_{Regs} . Therefore, we introduce these short-lived but potently suppressive T_{Reg} cells into our model (2.4), denoted by R_d . Then, we get a 5-dimensional model as follows:

(2.5)

$$A = f\tilde{v}G - \sigma_1(R_n + dR_d)A - b_1A - \mu_AA,$$

$$\dot{R}_n = (\pi_3E + \beta)A - \mu_nR_n - \xi R_n,$$

$$\dot{R}_d = c\,\xi R_n - \mu_d R_d,$$

$$\dot{E} = \lambda_E A - \sigma_3(R_n + dR_d)E - b_3E - \mu_E E,$$

$$\dot{G} = \gamma E - \tilde{v}G - \mu_G G.$$

For the above model, the possibility remains that HLA-DR⁻ nT_{Reg} cells may be activated to become terminal HLA- DR^+ T_{Reg} cells [33]. Therefore, we indicate the part of $HLA-DR^ nT_{Reg}$ cells which undergo activation as an output term from R_n population, with the activation rate ξR_n . The activated HLA-DR⁻ nT_{Reg} cells may further experience expansion and proliferation, say three divisions, and thus $c = 2^3 = 8[R_d]/[R_n]$, which contributes an input source of HLA-DR⁺ T_{Reg} cells, denoted by $c \xi R_n$. From the functional point of view, compared to HLA-DR⁻ T_{Reg} cells, $HLA-DR^+$ T_{Reg} cells show more effective suppression of effector conventional T cells and pAPCs and secrete cytokines more rapidly [5]. Therefore, we assume the suppression rate to pAPCs and effector T cells to be $\sigma_1 dR_d A$ and $\sigma_3 dR_d E$, respectively, and set $d = 2 [R_n]/[R_d]$. In healthy adults, HLA-DR is expressed by approximately one third of effector T_{Reg} cells in peripheral blood [3], so here we assume in autoimmune disease patients that the ratio is one half, implying that the ratio $\frac{R_d}{R_n}$ is one. We can use this fact to approximate ξ in the quasi-steady state of the R_d population, that is, $c\xi R_n - \mu_d R_d = 0$, yielding $\xi = 0.025/\text{day}$. The death and clearance rates μ_E and μ_A are based on the references given in [1] and are much the same here. Effector T cell lifetimes are approximately 4–5 days [28], so we set $\mu_E = 0.2 \text{ day}^{-1}$. The death rate of mature pAPCs is less certain [22]; we assume that the lifetime of a mature pAPC is of the same order as that of a mature effector T cell and take $\mu_A = 0.2 \text{ day}^{-1}$ as well [1]. We likewise assume a similar death rate between the effector T cells and T_{Reg} cells, set terminal T_{Reg} 's death rate as $\mu_d = 0.2 \text{ day}^{-1}$, and set $\mu_n = 0.1 \text{ day}^{-1}$ due to the rapid death rate of terminally differentiated effector HLA- DR^+ T_{Reg} cells.

To simplify this model, for which the parameter values are shown in Table 1, we impose a quasi-steady state assumption on the free antigen concentration. In particular, we know that the decay rate of the free antigen molecules (μ_G) is much faster than the dynamics of the effector T cells (E), and we can thus assume that the free antigen is in quasi-steady state with (and proportional to) the effector T cell population. Therefore, in the following, we shall eliminate G from system (2.5) by setting $\gamma E - \tilde{v}G - \mu_G G = 0$ to obtain $G = \frac{\gamma}{\mu_G + \tilde{v}} E$, to reduce system (2.5) by one dimension. Further, letting $\alpha = \frac{f\tilde{v}\gamma}{\mu_G + \tilde{v}} = 1 \times 10^{-4} [A]/(\text{day} \cdot [E])$, we obtain a new model, given by

(2.6a)
$$\dot{A} = \alpha E - \sigma_1 (R_n + dR_d) A - b_1 A - \mu_A A,$$

(2.6b) $\dot{R}_n = (\pi_3 E + \beta)A - \mu_n R_n - \xi R_n,$

(2.6c)
$$R_d = c \xi R_n - \mu_d R_d,$$

(2.6d)
$$E = \lambda_E A - \sigma_3 (R_n + dR_d) E - b_3 E - \mu_E E.$$

The parameter definitions and their values are given in Table 1. For readability, in the sections to follow, we will consistently use the units provided in Table 1 and will not repeat unit values for each parameter. The state variables in (2.6) are defined as follows [1]:

- A: Number of mature pAPCs (professional antigen presenting cells), primarily mature dendritic cells, which present a particular self-antigen of interest and express sufficiently high levels of co-stimulatory molecules so as to be capable of activating T cells.
- R_n : Number of activated T_{Reg} cells, HLA-DR⁻, specific for the antigen of interest, capable of exerting their suppressor function.
- R_d : Number of terminally differentiated T_{Reg} cells, HLA-DR⁺, with hypersuppressive ability.
- E: Number of active auto-reactive effector T cells that are specific for the antigen of interest. These may be either CD4⁺ or CD8⁺ T cells, or even a combination of these two; the distinction is not important, given the other simplifications we employ.

In the following sections, we study the new model (2.6) in detail, with particular interest in stability and bifurcation behaviors, and show that the model can exhibit cycles of relapse, separated by relatively long periods of remission, which are characteristic of several autoimmune diseases.

3. Well-posedness, equilibrium solutions, and stability of model (2.6). First, we investigate the well-posedness of the solutions of model (2.6).

3.1. Well-posedness. Due to physical meaning of this autoimmune disease model, only nonnegative initial conditions are considered, and negative solutions are not allowed. Likewise the parameters in (2.6) are all positive due to their biological meaning. More precisely, we have the following result.

THEOREM 3.1. All solutions of system (2.6) are nonnegative if the initial conditions are nonnegative. Furthermore, they are bounded.

Proof. Write (2.6a) and (2.6d) as a nonautonomous system:

(3.1)
$$\dot{A} = -\left[\sigma_1 \left(R_n(t) + dR_d(t)\right) + b_1 + \mu_A\right] A + \alpha E, \\ \dot{E} = -\left[\sigma_3 \left(R_n(t) + dR_d(t)\right) + b_3 + \mu_E\right] E + \lambda_E A.$$

Thus, according to Theorem 2.1 in [36, p. 81], we know that $A(t) \ge 0$ and $E(t) \ge 0$ for t > 0, provided that $A(0) \ge 0$ and $E(0) \ge 0$. Then, $R_n(t) = R_n(0) \exp\left[-(\mu_n + \xi)t\right] + \int_0^t [\pi_3 E(\tau) + \beta] A(\tau) \exp\left[-(\mu_n + \xi)(t - \tau)\right] d\tau \ge 0$ for $A(t) \ge 0$, $E(t) \ge 0$, and $R_n(0) \ge 0$. Further $R_d(t) = R_d(0) \exp\left(-\mu_d t\right) + \int_0^t c \xi R_n(\tau) \exp\left[-\mu_d(t - \tau)\right] d\tau \ge 0$ for $R_n(t) \ge 0$ and $R_d(0) \ge 0$.

Next, we prove that all solutions of system (2.6) are bounded. We first consider two equations, (2.6a) and (2.6d). Let

(3.2)
$$w_1(t) = \sigma_1[R_n(t) + dR_d(t)] + (b_1 + \mu_A), w_2(t) = \sigma_3[R_n(t) + dR_d(t)] + (b_3 + \mu_E).$$

With nonnegative initial conditions, we have $w_1(t) > 0$ and $w_2(t) > 0 \forall t > 0$. We construct a Lyapunov-candidate-function of the form $V_1(A, E) = \frac{1}{2}(A^2 + E^2) \forall A, E \geq$ 0. It is easy to see that $V_1(A, E) > 0 \forall A, E > 0$ and $V_1(0, 0) = 0$. Taking the time derivative of V_1 along the trajectory governed by the differential equation (2.6a) and (2.6d) yields

$$\left. \frac{\mathrm{d}\mathbf{V}_1}{\mathrm{d}t} \right|_{(2.6\mathrm{a}),\,(2.6\mathrm{d})} = A\,\dot{A} + E\,\dot{E} = A\left(-w_1A + \alpha E\right) + E\left(\lambda_E A - w_2 E\right)$$

$$(3.3) = -\left(A, E\right)Q(t)\left(\begin{array}{c}A\\E\end{array}\right),$$

where

(3.4)
$$Q(t) = \begin{bmatrix} w_1(t) & -\frac{1}{2}(\alpha + \lambda_E) \\ -\frac{1}{2}(\alpha + \lambda_E) & w_2(t) \end{bmatrix}.$$

To consider the positive definiteness of Q(t), first note that $w_1(t) > 0$ and $w_2(t) > 0$ $0 \ \forall t \geq 0$. For the sign of det(Q(t)), if we assume that $R_n(t)$ is unbounded, i.e., $\lim_{t\to+\infty} \sup R_n(t) = +\infty$, then we will arrive at a contradiction. Due to the positivity of $R_d(t)$, σ_1 , σ_3 , d, b_1 , b_3 , μ_A , and μ_E , it follows from (3.2) that $\lim_{t\to+\infty} \sup w_1(t) =$ $\lim_{t\to+\infty} \sup w_2(t) = +\infty$, and so $\lim_{t\to+\infty} \sup \det(Q(t)) = +\infty$, which implies that $\lim_{t\to+\infty} \sup A(t) = \lim_{t\to+\infty} \sup E(t) = 0$. Then, from (2.6b) we have

$$\lim_{t \to +\infty} \sup \dot{R}_n(t) \leq \lim_{t \to +\infty} \sup \left[(\pi_3 E(t) + \beta) A(t) - (\mu_n + \xi) R_n(t) \right]$$

$$\leq \lim_{t \to +\infty} \sup (\pi_3 E(t) + \beta) A(t) + (\mu_n + \xi) \lim_{t \to +\infty} \sup \left(-R_n(t) \right)$$

(3.5)
$$\leq 0 - \lim_{t \to +\infty} \inf R_n(t)$$

$$\leq 0,$$

leading to $\lim_{t\to+\infty} R_n(t) = 0$, which is a contradiction with our assumption. Thus, $R_n(t)$ is bounded, and we define $M_{R_n} = \max\{R_n(t), t \ge 0\}$.

For the remainder of the proof, we give a general claim first. Suppose that we have the differential inequality $T \leq \lambda - dT(\lambda, d > 0, T(0) > 0)$. Then, for T = $\lambda - dT$, we have the solution $T(t) = T(0) e^{-dt} + \frac{\lambda}{d} (1 - e^{-dt})$, which implies that $\lim_{t\to+\infty} \sup T(t) = \frac{\lambda}{d}$. Thus, from (2.6c), we have $\dot{R}_d \leq c \xi M_{R_n} - \mu_d R_d$, which yields $\lim_{t\to+\infty} \sup R_d(t) = \frac{c \xi M_{R_n}}{\mu_d}$, and so R_d is bounded. Since $R_n(t)$ is bounded, it follows from (2.6b) that A(t) must be bounded. Oth-

erwise, suppose $\lim_{t\to+\infty} \sup A(t) = +\infty$. Then, (2.6b) yields $\lim_{t\to+\infty} \sup R_n(t) =$ $+\infty$, implying that $R_n(t)$ is unbounded, giving a contradiction. Hence A(t) is bounded. Write $M_A = \max\{A(t), t \ge 0\}.$

Finally, from (2.6d) we obtain that $\dot{E} \leq \lambda_E M_A - (b_3 + \mu_E) E$, which yields $\lim_{t \to +\infty} \sup E(t) = \frac{\lambda_E M_A}{b_3 + \mu_E}$, indicating that E(t) is bounded.

The proof is now complete.

Next, we will consider the equilibrium solutions of system (2.6) and determine their stability by using the Routh–Hurwitz criterion [19]. When we consider a Hopf bifurcation, we will use the result given in [48] to determine the Hopf critical condition.



FIG. 1. (a) Complete bifurcation diagram for model (2.6) projected on the α -A plane, with the red and blue lines denoting E_0 and E_1 , respectively. (b) Bifurcation diagram in (a), restricted to the first quadrant. (c) Bifurcation diagram for model (2.6) projected on the α -A-R_n space, with the red, green, and blue lines denoting E_0 , the inner branch of E_1 , and the outer branch of E_1 , which is biologically meaningless since R_n takes negative values. Here, the dotted and solid lines indicate unstable and stable equilibria, respectively.

3.2. Equilibrium solutions. By setting $\dot{A} = \dot{R}_n = \dot{R}_d = \dot{E} = 0$ in model (2.6), we get two equilibrium solutions: the tolerance equilibrium $E_0 : (\bar{A}_0, \bar{R}_{n0}, \bar{R}_{d0}, \bar{E}_0) = (0, 0, 0, 0)$, and the autoimmune disease equilibrium $E_1 : (\bar{A}, \bar{R}_n, \bar{R}_d, \bar{E})$, where

(3.6)

$$\bar{R}_{n} = \frac{\left[\pi_{3}(b_{1}+\mu_{A})\bar{A}+\beta\alpha\right]\mu_{d}\bar{A}}{\mu_{d}\alpha(\mu_{n}+\xi)-\pi_{3}\sigma_{1}(\mu_{d}+d\,c\,\xi)\bar{A}^{2}},$$

$$\bar{R}_{d} = \frac{c\,\xi\bar{R}_{n}}{\mu_{d}},$$

$$\bar{E} = \frac{\left[\sigma_{1}\bar{R}_{n}(\mu_{d}+d\,c\,\xi)+\mu_{d}(b_{1}+\mu_{A})\right]\bar{A}}{\mu_{d}\alpha},$$

and \overline{A} is a function in terms of the system parameters, particularly α , and determined by the following fourth-degree equation, in which the parameter values given in Table 1 have been used. Note that the rational numbers given below are obtained using symbolic computation in which all the parameter values given in digital format (see Table 1) have been transformed into rational numbers for convenience in computation. (3.7)

$$F_1(A, \alpha) = \frac{81}{38146972656250} A^4 - \frac{1521\,\alpha}{625000000} A^2 - \frac{81\,\alpha}{10000000} A + \frac{5}{8}\alpha^2 - \frac{81\,\alpha}{640000} = 0.$$

It should be noted that the existence condition of the disease equilibrium E_1 depends upon the existence condition of A determined by the fourth-degree polynomial (3.7), which has already been simplified by substituting the parameter values (except the bifurcation parameter α) into the equation. This fourth-degree polynomial with all nonfixed parameters is too involved to determine the existence condition of A.

The graphs of A = 0 and $F_1(A, \alpha) = 0$ as given in (3.7) are shown in Figure 1, where Figure 1(a) shows the complete bifurcation diagram, while Figure 1(b) depicts only the part which is biologically meaningful. Figure 1(c) shows a 3-dimensional plot, indicating why the branch in Figure 1(a) is biologically meaningless.

3.3. Stability of the disease-free equilibrium, E_0. For the stability of E_0 , we have the following result.

THEOREM 3.2. When $\alpha < \alpha_t = \frac{1}{\lambda_E}(b_1 + \mu_A)(b_3 + \mu_E)$, the disease-free equilibrium E_0 of the model (2.6) is globally asymptotically stable.

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Proof. In order to examine the stability of equilibria for system (2.6), we compute the Jacobian matrix of system (2.6), given by (3.8)

 $J = \begin{bmatrix} -\sigma_1(R_n + dR_d) - (b_1 + \mu_A) & -\sigma_1 A & -\sigma_1 dA & \alpha \\ \pi_3 E + \beta & -(\mu_n + \xi) & 0 & \pi_3 A \\ 0 & c \xi & -\mu_d & 0 \\ \lambda_E & -\sigma_3 E & -\sigma_3 dE & -\sigma_3 (R_n + dR_d) - (b_3 + \mu_E) \end{bmatrix}.$

Evaluating the Jacobian (3.8) at E_0 : $(\bar{A}_0, \bar{R}_{n0}, \bar{R}_{d0}, \bar{E}_0) = (0, 0, 0, 0)$ yields $J|_{E_0}$, and then setting det $(L I - J|_{E_0})$ to zero results in a fourth-degree characteristic equation, which can be factorized as

(3.9)

$$P_0(L,\alpha) = (L+\mu_d)(L+\mu_n+\xi) \left[L^2 + (b_3+\mu_E+b_1+\mu_A)L + (b_1+\mu_A)(b_3+\mu_E) - \lambda_E \alpha \right] = 0.$$

The asymptotic stability of E_0 is determined by the sign of the real part of the roots of (3.9): if all roots of (3.9) have negative real part, then E_0 is asymptotically stable; if at least one root has positive real part, then E_0 is unstable. In fact, $P_0(L, \alpha)$ contains three factors: the first two are linear polynomials in L, with positive parameter values from Table 1, both of them stable (i.e., their roots (eigenvalues) have negative real part); thus the stability of E_0 depends only upon the third factor, which gives a quadratic equation,

(3.10)
$$L^{2} + (b_{3} + \mu_{E} + b_{1} + \mu_{A})L + (b_{1} + \mu_{A})(b_{3} + \mu_{E}) - \lambda_{E} \alpha = 0.$$

Using the general formula for solutions of the quadratic equation, we know that whether the two roots of (3.10) have negative real part is determined by the sign of $(b_3 + \mu_E)(b_1 + \mu_A) - \lambda_E \alpha$: the negativity (positivity) of the real part of the two roots of (3.10) is equivalent to $(b_3 + \mu_E)(b_1 + \mu_A) - \lambda_E \alpha > 0$ (< 0); that is, (3.10) has stable (unstable) roots if $(b_3 + \mu_E)(b_1 + \mu_A) - \lambda_E \alpha > 0$ (< 0), and a zero eigenvalue root comes out at

(3.11)
$$\alpha_t = \frac{(b_1 + \mu_A)(b_3 + \mu_E)}{\lambda_E}.$$

Here and hereafter, we will use the subscript "t" for transcritical bifurcation; using the parameter values from Table 1, the transcritical bifurcation point is obtained as $(\alpha_t, A_t) = (2.025 \times 10^{-4}, 0)$. The equilibrium solution E₀ is locally asymptotically stable (unstable), when $\alpha < \alpha_t$ ($\alpha > \alpha_t$).

Next, we want to prove that E_0 is also globally asymptotically stable for $\alpha < \alpha_t$. To achieve this, we construct a Lyapunov function of the form

(3.12)
$$V_2(A, E) = \frac{1}{2} \left(\lambda_E A^2 + \alpha E^2 \right),$$

which is positive-definite and continuously differentiable for all positive bounded values of A and E; i.e., $V_2(0, 0) = 0$ and $V_2(A, E) > 0 \forall A, E > 0$. Moreover, the time

derivative of the Lyapunov function V_2 satisfies

$$\dot{V}_2 = \lambda_E A \dot{A} + \alpha E \dot{E}$$

$$= \lambda_E A [\alpha E - \sigma_1 (R_n + dR_d)A - (b_1 + \mu_A)A]$$

$$+ \alpha E [\lambda_E A - \sigma_3 (R_n + dR_d)E - (b_3 + \mu_E)E]$$

$$= -\lambda_E (b_1 + \mu_A) A^2 - \alpha (b_3 + \mu_E) E^2 + 2 \alpha \lambda_E A E$$

$$- (\lambda_E \sigma_1 A^2 + \alpha \sigma_3 E^2)(R_n + dR_d)$$

$$\leq -\lambda_E (b_1 + \mu_A) A^2 - \alpha (b_3 + \mu_E) E^2 + 2 \alpha \lambda_E A E$$

$$= - (A E) Q (A E)^T,$$

which is a quadratic form, with

(3.13)
$$Q = \begin{bmatrix} \lambda_E(b_1 + \mu_A) & -\alpha \lambda_E \\ -\alpha \lambda_E & \alpha(b_3 + \mu_E) \end{bmatrix}$$

being positive definite for $(b_1+\mu_A)(b_3+\mu_E) > \alpha\lambda_E$. Hence, $\dot{V}_2 \leq 0$ and $\dot{V}_2 = 0$ if and only if (A, E) = (0, 0). This yields $A(t), E(t) \to 0$ as $t \to +\infty$ for any positive initial conditions. It follows that (2.6b) becomes an asymptotically autonomous equation with the limiting equation $\dot{R}_n = -(\mu_n + \xi)R_n$. By the theory of asymptotically autonomous systems [7], we know that the solution $R_n(t) \to 0$ as $t \to +\infty$. Finally, using the same theory on (2.6c), we get $R_d(t) \to 0$ as $t \to +\infty$. Therefore, under the condition $\alpha < \alpha_t$, the local stability and the global attractivity of E_0 established above give the global asymptotic stability of E_0 . \square

3.4. Stability of the autoimmune disease equilibrium, E₁. In order to examine the stability of E₁, we evaluate the Jacobian matrix (3.8) of system (2.6) at E₁, to obtain the characteristic equation $det(LI - J|_{E_1}) = 0$. By straightforward but tedious computations, the characteristic polynomial of J at E₁ is obtained as the following fourth-degree polynomial:

(3.14)
$$P_1(L, A, \alpha) = L^4 + a_1(A, \alpha)L^3 + a_2(A, \alpha)L^2 + a_3(A, \alpha)L + a_4(A, \alpha) = 0,$$

where the coefficients, $a_i(A, \alpha)$, i = 1, 2, 3, 4, are expressed in terms of A and α , with other parameter values taken from Table 1, and A satisfies $F_1(A, \alpha) = 0$ (see (3.7)).

The static bifurcation happens at equilibrium E_1 , when the characteristic polynomial $P_1(L, A, \alpha) = 0$ in (3.14) has zero root (zero eigenvalue). That means $a_4(A, \alpha) = 0$, and A should satisfy $F_1(A, \alpha) = 0$. Thus, we obtain

$$(3.15) A_s(\alpha_s) = -\frac{2133359375000000\,\alpha_s^3 + 26617447265625\,\alpha_s^2 - 49464843750\,\alpha_s + 8748000}{3525388312500\,\alpha_s^2 - 4572342000\,\alpha_s + 979776}$$

where α_s is the root of $F_2(\alpha_s) = \alpha_s(13530125\alpha_s - 2592) \times (400000 \alpha_s - 81) = 0$. Solving $F_2(\alpha_s) = 0$, and then substituting the solutions into $A_s(\alpha_s)$ using (3.15), we get three points. The first is a transcritical bifurcation point, $(\alpha_t, A_t) = (2.025 \times 10^{-4}, 0)$, which is exactly the same as the one we obtained from the tolerance equilibrium E₀. Moreover, at this point, all other Hurwitz arrangements are positive; that is, $\Delta_1 = \frac{49}{40}$, $\Delta_2 = \frac{5863}{16000}$, and $\Delta_3 = \frac{52767}{6400000}$. The two equilibrium solutions E₀ and E₁ intersect and exchange their stability at this critical point. E₁ is stable when $\alpha > \alpha_t$ (E₁ does not exist for $\alpha < \alpha_t$), as shown in Figure 1. Here, the subscript "t" stands for transcritical bifurcation. The second point is a turning point ($\alpha_{\text{Turning}}, A_{\text{Turning}}$) =

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 $(1.9157 \times 10^{-4}, -1.7097)$, which has a negative value for A and so is not biologically interesting (see Figure 1(a)). The third is $(\alpha_s, A_s) = (0, 0)$, which is not allowed since the parameter α cannot take the value zero.

To check whether a Hopf bifurcation exists from the infected equilibrium E_1 of system (2.6), we apply the theorem given in [48] to E_1 defined by (3.6), where A satisfies equation $F_1(A, \alpha) = 0$ in (3.7). Based on the fourth-degree characteristic polynomial $a_3^2 - a_1^2 a_4 = 0$. Solving $\Delta_3(A, \alpha) = 0$ and $F_1(A, \alpha) = 0$, together with the parameter values given in Table 1, we get two Hopf bifurcation points: $(\alpha_{H1}, A_{H1}) = (7.8666 \times$ 10^{-4} , 11.4436) and $(\alpha_{H2}, A_{H2}) = (5.0387 \times 10^{-4}, -13.1534)$, as shown in Figure 1(a). We consider only the biologically meaningful point with two positive entries to obtain a unique Hopf bifurcation point: $(\alpha_H, A_H) = (7.8666 \times 10^{-4}, 11.4436)$. Here, the subscript "H" stands for Hopf bifurcation. At the critical point (α_H, A_H) , other conditions are satisfied: $a_1 = 2.0989$, $a_2 = 0.6311$, $a_3 = 0.1145$, $a_4 = 0.0314$, $\Delta_2 = 1.2100$, $\Delta_3 = -0.1 \times 10^{-18} \approx 0$. Indeed, with these given parameter values, one can numerically calculate the Jacobian matrix of system (2.6) at E_1 , which contains a purely imaginary pair and two negative real eigenvalues: $\pm 0.2335 i, -1.7739$, and -0.325. Thus, as α is varied across the point $\alpha = \alpha_H$, the equilibrium solution E₁ becomes unstable and a Hopf bifurcation occurs, leading to a family of limit cycles. Summarizing the above results gives the following theorem.

THEOREM 3.3. When $\alpha_t < \alpha < \alpha_H$, the disease equilibrium E_1 of model (2.6) is asymptotically stable.

Now we apply normal form theory and the Maple program developed in [47] to system (2.6) to analyze the Hopf bifurcation which occurs at the critical point $(\alpha_H, A_H) = (7.8666 \times 10^{-4}, 11.4436)$ (with other parameters given in Table 1). Using a series of linear and nonlinear transformations and the Maple program [47], we obtain the normal form associated with this Hopf bifurcation up to third order, given by

(3.16)
$$\dot{r} = r (v_0 \mu + v_1 r^2), \qquad \dot{\theta} = \omega_c + \tau_0 \mu + \tau_1 r^2,$$

where $v_0 = 34.2048$, $v_1 = -2.0161 \times 10^{-12}$, $\omega_c = 0.2335$, $\tau_0 = 132.8998$, $\tau_1 = -1.3186 \times 10^{-11}$. Note that $\mu = \alpha - \alpha_H$, representing a perturbation of the parameter α from the critical point $\alpha = \alpha_H$. The steady-state solutions of (3.16) are determined by $\dot{r} = \dot{\theta} = 0$, resulting in $\bar{r}_1 = 0$ and $\bar{r}_2^2 = 0.1697 \times 10^{14} \mu$. The equilibrium solution $\bar{r}_1 = 0$ actually represents the autoimmune equilibrium E₁ of model (2.6). A linear analysis on the first differential equation of (3.16) shows that $\frac{d}{dr}(\dot{r})|_{\bar{r}=\bar{r}_1} = v_0 \mu$, and thus $\bar{r}_1 = 0$ (E₁) is stable (unstable) for $\mu < 0$ (> 0), as expected. When μ is increasing from negative values to cross zero, a Hopf bifurcation occurs, and the amplitude of the bifurcating limit cycles is given by the nonzero steady state solution,

(3.17)
$$\bar{r}(\mu) = 0.4119 \times 10^7 \sqrt{\mu} \quad (\mu > 0)$$

Since $\frac{d}{dr}(\dot{r})|_{(3.17)} = 2v_1 r^2$, the negative V_1 indicates that the bifurcating limit cycles are stable for $\mu > 0$. We can get the same stability conclusion from $v_1 < 0$, implying that the Hopf bifurcation is supercritical and so the bifurcating limit cycles are stable. Equation (3.17) gives the approximate amplitude of the bifurcating limit cycles, while the phase of the motion is determined by $\theta = \omega t$, where ω is given by $\omega = \dot{\theta}|_{(3.17)} = 0.2335 - 90.8185 \mu$. We summarize the above results, yielding the following theorem.

THEOREM 3.4. At the critical point $\alpha = \alpha_H$, a supercritical Hopf bifurcation occurs, leading to a family of stable limit cycles.

4. Numerical simulation. In this section, we present some simulation results to verify the analytical predictions obtained in the previous section. In particular, we will show the comparison between the analytical and numerical results obtained for the Hopf bifurcation. For convenience in the simulation, we will fix all parameter values, except for α (or μ). We will vary α to demonstrate the stable equilibrium solutions E_0 and E_1 and the stable limit cycles. Finally, we will also choose a large positive value of μ , which means that this value is far away from the Hopf critical point α_H , to show the relapse-remission phenomenon. Note that the mechanism of generating recurrence in this paper is slightly different from that defined by the conditions in Hypothesis 1 of [49], in which recurrence is guaranteed to appear near a transcritical point. In this paper, recurrent oscillations are generated far from the transcritical point $\alpha_t = 2.025 \times 10^{-4}$. In other words, the oscillations described in this paper are determined by more global properties of the system.

Suppose that all parameter values, except for α , are taken from Table 1. Then, it follows from (3.11) that the equilibrium solution E_0 is asymptotically stable for $0 < \alpha < \alpha_t = 2.025 \times 10^{-4}$. E_0 becomes unstable when α is increased to pass through α_t , and bifurcates into the equilibrium solution E_1 , which is asymptotically stable for $\alpha_t < \alpha < \alpha_H = 7.8666 \times 10^{-4}$. E_1 becomes unstable at $\alpha = \alpha_H$, and a family of limit cycles bifurcates from this Hopf critical point. The normal form for the Hopf bifurcation is given by (3.16). Since $v_1 = -2.0161 \times 10^{-12}$, the Hopf bifurcation is supercritical, and the bifurcating limit cycles are stable.

Now, we first take $\alpha = 1.50 \times 10^{-4} < \alpha_t$. The simulation result is shown in Figure 2(a), which clearly indicates that E_0 is asymptotically stable, in agreement with the analytical prediction. Next, choose $\alpha_t < \alpha = 4.0 \times 10^{-4} < \alpha_H$, for which the simulation result is depicted in Figure 2(b), showing that E_1 is asymptotically stable, which again agrees with the analytical prediction. Further, we select a value of $\mu = 3.0 \times 10^{-12}$, which implies that we take a postcritical value of α near the Hopf critical point. This is a perfect Hopf bifurcation, as shown in Figure 3.



FIG. 2. Simulated time history for system (2.6) with the initial condition A(0) = 17, $R_n(0) = R_d(0) = 48000$, E(0) = 12700 for (a) $\alpha = 1.50 \times 10^{-4} < \alpha_t$, converging to E_0 , and (b) $\alpha = 4.0 \times 10^{-4}$, converging to E_1 .

The simulations are compared with the analytical predictions in Figure 3, showing excellent agreement between the two, particularly for smaller values of μ , as expected. Note that the analytical predictions are obtained through a series of linear and non-linear transformations, available from the output of the Maple programs [47]. The details are omitted here for brevity. Finally, we take $\alpha = 3.0 \times 10^{-3} > \alpha_H$, which is



FIG. 3. Comparison between the simulated time history and analytical prediction for system (2.6) with $\mu = 3 \times 10^{-12}$: the red solid line denotes the simulation results, while the black dash-dot line indicates the analytical predictions, showing stable limit cycles.

not close to α_H . For this case, normal form theory is not applicable, since this value of α is not near α_H . In other words, if we apply the above procedure to obtain an approximation, it would have a very large error. The simulation result is given in Figure 4, indeed showing the recurrence phenomenon. It should be noted that the vertical axes in Figure 4(c) and (d) have a logarithmic scale so that the minimum level of effector T cells (E) can be clearly seen. The reason for this behavior can be seen from Figure 4(a) and (b) to be that the E population grows very quickly in the absence of R_n and R_d , and then R_n responds very quickly (EA term) and suppresses E, but R_n does not last long. This pattern describes, of course, how the adaptive and innate immune responses work against pathogens, as well. But why is E not eliminated like a pathogen would be? We speculate that the system is now "torn between two equilibria," as described later in the discussion.

5. Model reduction and parameter identification for autoimmune recurrence. In the previous sections, we have studied the 4-dimensional (4-d) model (2.6) in detail and found recurrence. Now, we are interested in finding the key factors which play the most important roles in generating this phenomenon. To achieve this, a common approach is first to reduce the dimension of the system under a quasi-steady state assumption, and then identify the main system parameters (usually treated as bifurcation parameters) which may effectively influence recurrence so that we may find the mechanism of generating relapse and remission. For model reduction (in particular, the reduction from the 5-d model (2.5) to (2.6) and a further reduction from the 4-d model (2.6) to a 3-d model, which will be considered below in detail), we need to answer a fundamental question: does model reduction alter the dynamical behavior of the system? We have carefully studied this problem and have shown that, when proper parameter values are chosen, both the original 5-d and 4-d models as well



FIG. 4. Simulated time history for system (2.6) when $\alpha = 3 \times 10^{-3}$, showing recurrence.

as the reduced 4-d and 3-d models exhibit the same dynamical behavior: recurrence. (Details will be given in a forthcoming paper.) Therefore, in the following, we will not consider the 5-d model (2.5) but the 4-d model and its reduction.

5.1. Model reduction. For the model described by (2.6), we assume that at the site of the autoimmune reaction the influence of IL-2 from other sources, such as dendritic cells [1], is negligible compared to that of the IL-2 generated by activated effector T cells. Therefore, we can set $\beta = 0$, and the model becomes

(5.1)
$$A = \alpha E - \sigma_1 (R_n + dR_d) A - (b_1 + \mu_A) A, \\ \dot{R}_n = \pi_3 E A - (\mu_n + \xi) R_n, \\ \dot{R}_d = c \xi R_n - \mu_d R_d, \\ \dot{E} = \lambda_E A - \sigma_3 (R_n + dR_d) E - (b_3 + \mu_E) E.$$

It can be shown that model (5.1) still has two equilibrium solutions. One is the tolerance equilibrium, E_0 : $(A, R_n, R_d, E) = (0, 0, 0, 0)$, and the other is the autoimmune equilibrium, $E_1 = (\bar{A}, \bar{R}_n(\bar{A}), \bar{R}_d(\bar{A}), \bar{E}(\bar{A}))$. We again choose α as the bifurcation parameter and find that the two equilibrium solutions exchange their stability at the transcritical bifurcation point $(\alpha_s, A_s) = (2.025 \times 10^{-4}, 0)$. That is, as α increases from $\alpha < \alpha_s$ to cross the critical point $\alpha = \alpha_s$, the stable E_0 becomes unstable, while E_1 emerges from this critical point and is stable. As α continues to increase, a Hopf bifurcation occurs from E_1 at the critical point $(\alpha_H, A_H) = (6.4729 \times 10^{-4}, 12.4401)$. The simulated time history for $\alpha = 3 \times 10^{-3}$ shown in Figure 4 displays recurrent autoimmunity, as expected.

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FIG. 5. Simulated time history for system (5.1) with the initial conditions A(0) = E(0) = 1, $R_n(0) = R_d(0) = 0$, for the bifurcation parameter $\alpha = 3 \times 10^{-3}$: (a) for the transient period and (b) over a longer interval showing periodic behavior. The rates of change of cell populations, \dot{A} , $\dot{R_n}$, $\dot{R_d}$, and \dot{E} , are represented by the red solid, black dotted, blue dotted, and green solid curves, respectively.

In order to further simplify the analysis on model (5.1), here we will adopt a quasisteady state assumption, which is often used in the study of biochemical and biological systems. The basic idea of the quasi-steady state assumption can be described using the following system [8]:

(5.2)
$$\begin{aligned} \dot{x} &= \epsilon^{-1} f(x, y), \qquad x \in \mathbb{R}^m, \\ \dot{y} &= g(x, y), \qquad y \in \mathbb{R}^n, \end{aligned}$$

where $0 < \epsilon \ll 1$, f and g are nonlinear functions, and x and y represent "fast" and "slow" variables, respectively. We consider the evolution of the system from an arbitrary initial condition, including a transient period. For the fast variable x, we may rewrite the first equation of (5.2) as $\epsilon \dot{x} = f(x, y)$. Thus, for small ϵ , setting $\epsilon = 0$ results in f(x, y) = 0, from which we obtain an algebraic expression for x in terms of the slow variables, x = x(y); $\dot{x} \neq 0$ (see [8] for more details on this topic). This leads to a differential equation for the slow variable y in the form $\dot{y} = g(x(y), y)$. Intuitively, although the slow variable y is changing, the fast variable "catches up" so quickly that f(x, y) remains close to zero at all times.

Now, we return to consider system (5.1) and carefully compare the coefficients in the system, finding that the parameter $\lambda_E = 1000$ is greater than all other parameters, which are on the order of $10^{-6} \sim 1$. Thus, we may write the fourth equation of (5.1) as

$$\dot{E} = \lambda_E \left(A - \frac{\sigma_3}{\lambda_E} (R_n + dR_d) E - \frac{b_3 + \mu_E}{\lambda_E} E \right) = \epsilon^{-1} \left(A - \frac{\sigma_3}{\epsilon} (R_n + dR_d) E - \frac{b_3 + \mu_E}{\epsilon} E \right),$$

where $\epsilon = 10^{-3}$. Then, according to the general formula (5.2), we observe that E is a fast variable, while A, R_n , and R_d are slow variables, all of the same order. This is also reflected in the simulated time history for the transient period shown in Figure 5(a), which shows the rapid rate of change in E relative to the other populations; simulation over a longer interval is illustrated in Figure 5(b). Therefore, we can make a quasi-steady state assumption on the fast variable E, yielding

(5.3)
$$E = \frac{\lambda_E A}{\sigma_3(R_n + dR_d) + b_3 + \mu_E},$$

and so the reduced system is given by

(5.4)

$$\dot{A} = \frac{\alpha \lambda_E A}{\sigma_3 (R_n + dR_d) + b_3 + \mu_E} - \sigma_1 (R_n + dR_d) A - (b_1 + \mu_A) A$$

$$\dot{R}_n = \frac{\pi_3 \lambda_E A^2}{\sigma_3 (R_n + dR_d) + b_3 + \mu_E} - (\mu_n + \xi) R_n,$$

$$\dot{R}_d = c \, \xi R_n - \mu_d R_d.$$

5.2. Rescaling on system (5.4). In order to reduce the number of parameters for convenience in analysis, we further attempt to rescale system (5.4) by scaling the state and time variables as

(5.5)
$$R_n = e_1 x, \quad R_d = e_2 y, \quad A = e_3 z, \quad t = e_4 \tau.$$

Then, with $\frac{d\tau}{dt} = \frac{1}{e_4}$, the left-hand side of system (5.4) becomes

(5.6)
$$\frac{\mathrm{d}R_n}{\mathrm{d}t} = \frac{e_1}{e_4}\frac{\mathrm{d}x}{\mathrm{d}\tau}, \quad \frac{\mathrm{d}R_d}{\mathrm{d}t} = \frac{e_2}{e_4}\frac{\mathrm{d}y}{\mathrm{d}\tau}, \quad \frac{\mathrm{d}A}{\mathrm{d}t} = \frac{e_3}{e_4}\frac{\mathrm{d}z}{\mathrm{d}\tau}$$

Next, we substitute (5.5) and (5.6) into system (5.4) to yield (5.7) $dx \qquad e_2^2 e_4 \lambda_E \pi_2$

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}\tau} &= \frac{e_3 \, e_4 \, x_E \, \pi_3}{e_1^2 \, \sigma_3 \, x + e_1 \, e_2 \, \sigma_3 \, dy + e_1 \, (b_3 + \mu_E)} \, z^2 - e_4 \, (\mu_n + \xi) \, x, \\ \frac{\mathrm{d}y}{\mathrm{d}\tau} &= \frac{e_1 \, e_4 \, c\xi}{e_2} \, x - e_4 \, \mu_d \, y, \\ \frac{\mathrm{d}z}{\mathrm{d}\tau} &= \frac{e_4 \, \alpha \, \lambda_E}{e_1 \, \sigma_3 \, x + e_2 \, \sigma_3 \, dy + (b_3 + \mu_E)} \, z - e_1 \, e_4 \, \sigma_1 \, x \, z - e_2 \, e_4 \, \sigma_1 \, dy \, z - e_4 \, (b_1 + \mu_A) \, z \end{aligned}$$

Further, we set $e_1 e_4 \sigma_1 = 1$, $e_2 e_4 \sigma_1 d = 1$, $e_3^2 e_4 \lambda_E \pi_3 = 1$, and $e_4 \mu_d = 1$ to obtain

(5.8)
$$e_1 = \frac{\mu_d}{\sigma_1}, \quad e_2 = \frac{\mu_d}{\sigma_1 d}, \quad e_3 = \left(\frac{\mu_d}{\lambda_E \pi_3}\right)^{\frac{1}{2}}, \quad e_4 = \frac{1}{\mu_d}$$

Finally, system (5.4) becomes

(5.9)
$$\frac{\mathrm{d}x}{\mathrm{d}\tau} = \frac{z^2}{\mathcal{A}(x+y) + \mathcal{B}} - \mathcal{C} x,$$
$$\frac{\mathrm{d}y}{\mathrm{d}\tau} = \mathcal{D} x - y,$$
$$\frac{\mathrm{d}z}{\mathrm{d}\tau} = \frac{\mathcal{E}}{\mathcal{F}(x+y) + \mathcal{G}} z - x z - y z - \mathcal{H} z$$

where the new parameters are defined as follows: $\mathcal{A} = \frac{\sigma_3 \mu_d^2}{\sigma_1^2} [R_n] \cdot \text{day}^{-1}$, $\mathcal{B} = \frac{\mu_d}{\sigma_1} (b_3 + \mu_E) \text{day}^{-1} [R_n]^{-1}$, $\mathcal{C} = \frac{\mu_n + \xi}{\mu_d}$, $\mathcal{D} = \frac{c \xi d}{\mu_d} \text{day}^{-2}$, $\mathcal{E} = \frac{\alpha \lambda_E}{\mu_d} \text{day}^{-3}$, $\mathcal{F} = \frac{c \xi d}{\mu_d} \text{day}^{-1}$

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 $\frac{\sigma_3 \mu_d}{\sigma_1} \operatorname{day}^{-1}, \ \mathcal{G} = b_3 + \mu_E \operatorname{day}^{-1}, \ \mathcal{H} = \frac{b_1 + \mu_A}{\mu_d} \operatorname{day}^{-1}.$ Here, we set \mathcal{E} as the bifurcation parameter, since α is used as the bifurcation parameter for the original system (2.6). We then use the parameter values from Table 1 to obtain new parameter values for system (5.9) as $\mathcal{A} = \frac{40000}{3} [R_n] \cdot \operatorname{day}^{-1}, \ \mathcal{B} = 30000 \operatorname{day}^{-1}[R_n]^{-1}, \ \mathcal{C} = \frac{5}{8}, \ \mathcal{D} = 2 \operatorname{day}^{-2}, \ \mathcal{F} = \frac{1}{5} \operatorname{day}^{-1}, \ \mathcal{G} = \frac{9}{20} \operatorname{day}^{-1}, \ \mathcal{H} = \frac{9}{4} \operatorname{day}^{-1}.$ Moreover, it follows from (5.8) that $e_1 = \frac{200000}{3}, \ e_2 = \frac{100000}{3}, \ e_3 = \frac{\sqrt{2}}{16}, \ \text{and} \ e_4 = 5.$ The bifurcation patterns of the scaled system (5.9) are the same as that of the

The bifurcation patterns of the scaled system (5.9) are the same as that of the original system (2.6), namely, there exist two equilibrium solutions, \overline{E}_0 : $(x_0, y_0, z_0) = (0, 0, 0)$ and \overline{E}_1 : (x_1, y_1, z_1) , where $y_1 = \mathcal{D} x_1$, $z_1 = \sqrt{\mathcal{C} x_1 [\mathcal{A} (1 + \mathcal{D}) x_1 + \mathcal{B}]}$, and x_1 is determined from the equation $(1 + \mathcal{D})^2 \mathcal{F} x^2 + [(\mathcal{G} + \mathcal{H} \mathcal{F}) (1 + \mathcal{D})] x - \mathcal{E} + \mathcal{H} \mathcal{G} = 0$.

THEOREM 5.1. The solutions of system (5.9) are nonnegative and bounded, provided that the initial conditions are nonnegative.

Proof. For the nonnegativeness, we write the solutions for z and y of system (5.9) by using the method of constant variations as

(5.10)
$$z(\tau) = z(0) \exp\left[\int_0^\tau \left(\frac{\mathcal{E}}{\mathcal{F}[x(s) + y(s)] + \mathcal{G}} - x(s) - y(s) - \mathcal{H}\right) \mathrm{d}s\right]$$

and

(5.11)
$$y(\tau) = y(0)e^{-\tau} + \mathcal{D}\int_0^\tau e^{-(\tau-s)} x(s) \,\mathrm{d}s.$$

There are two cases.

- **Case 1.** z(0) = 0. Then, it follows from (5.10) that $z(\tau) \equiv 0 \ \forall \tau \geq 0$. Thus, the first equation of system (5.9) is reduced to $\frac{dx}{d\tau} = -\mathcal{C}x$, which yields the solution $x(\tau) = x(0)e^{-\mathcal{C}\tau}$. Therefore, $x(\tau) \geq 0 \ \forall \tau \geq 0$ if $x(0) \geq 0$. Then, we use (5.11) to obtain $y(\tau) \geq 0 \ \forall \tau \geq 0$ if $y(0) \geq 0$.
- **Case 2.** z(0) > 0. It is easy to see from (5.10) that $z(\tau) > 0 \ \forall \tau \ge 0$. We need to discuss four subcases.
 - **Case 2.1.** x(0) > 0 and y(0) > 0. To prove $y(\tau) > 0 \ \forall \tau > 0$, we adopt the argument of contradiction. Since y(0) > 0, we assume that the first time at which $y(\tau)$ becomes negative is τ_1 ; i.e., $y(\tau) > 0 \ \forall \tau \in [0, \tau_1)$, $y(\tau_1) = 0$, and $y(\tau) < 0 \ \forall \tau \in (\tau_1, \tau_2)$. Then, since $y(0)e^{-\tau} > 0$, (5.11) implies that there should exist an interval $(\tau_3, \tau_4) \subset [0, \tau_1)$ such that $x(\tau) < 0 \ \forall \tau \in (\tau_3, \tau_4) \ (\tau_1 \text{ may equal } \tau_4)$. With x(0) > 0, we may, without loss of generality, assume τ_3 is the first time $x(\tau)$ become zero; that is, $x(\tau_3) = 0$ and $x(\tau)$, $y(\tau) > 0 \ \forall \tau \in (0, \tau_3)$. On the other hand,

(5.12)
$$\frac{\mathrm{d}x}{\mathrm{d}\tau} = \frac{z^2}{\mathcal{A}(x+y) + \mathcal{B}} - \mathcal{C} x > -\mathcal{C} x \quad \text{for } \tau \in [0, \tau_3]$$

By the comparison principle, we have $x(\tau_3) > x(0)e^{-\mathcal{C}\tau_3} > 0$ for x(0) > 0, which contradicts that $x(\tau_3) = 0$. Therefore, there is no time for $y(\tau)$ to be zero and then become negative; that is, $y(\tau) > 0 \ \forall \tau \ge 0$. Then, using a similar argument on (5.12), we can prove that $x(\tau) > 0 \ \forall \tau \ge 0$. **Case 2.2.** x(0) = y(0) = 0. Due to the continuity of the solutions and the conditions $\mathcal{A} > 0$ and $\mathcal{B} > 0$, for the term $\frac{z^2}{\mathcal{A}(x+y)+\mathcal{B}}$, there exists $\tau_5 > 0$ such that, for $\tau \in [0, \tau_5]$, $\frac{z(\tau)^2}{\mathcal{A}[x(\tau)+y(\tau)]+\mathcal{B}} > 0$. Then, $\frac{dx}{d\tau} = \frac{z^2}{\mathcal{A}(x+y)+\mathcal{B}} - \mathcal{C}x > -\mathcal{C}x \ \forall \tau \in (0, \tau_5]$. Therefore, $x(\tau) > x(0)e^{-\mathcal{C}\tau} = 0$ for $\tau \in [0, \tau_5]$. Moreover, the solution of $y(\tau) = \mathcal{D} \int_0^{\tau} e^{-(\tau-s)} x(s) ds$ indicates that $y(\tau) > 0$ for $\tau \in [0, \tau_5]$. Hence, we obtain $x(\tau_5) > 0$ and $y(\tau_5) > 0$. So we can take τ_5 as the initial point and use the conclusion obtained in Case 2.1 to show that $x(\tau) > 0$ and $y(\tau) > 0$ for $\tau \ge \tau_5$. Combining the above two steps proves that $x(\tau) > 0$ and $y(\tau) > 0$ for $\tau \ge \tau_5$.

Case 2.3. x(0) = 0 and y(0) > 0.

Case 2.4. x(0) > 0 and y(0) = 0.

For Cases 2.3 and 2.4, we can apply arguments similar to those used for proving Cases 2.1 and 2.2 to prove that the solutions of system (5.9) with these initial conditions are nonnegative.

The remainder of the proof is devoted to the boundedness of solutions. Suppose that $y(\tau)$ is unbounded; that is, $\lim_{\tau \to +\infty} \sup y(\tau) = +\infty$. Then, according to the second equation in (5.9), we have $\lim_{\tau \to +\infty} \sup x(\tau) = +\infty$ and further obtain $\lim_{\tau \to +\infty} z(\tau) = 0$ by using the third equation in (5.9), and then obtain $\lim_{\tau \to +\infty} x(\tau) = 0$ from the first equation in (5.9). This leads to a contradiction, and so $y(\tau)$ is bounded. Now applying the boundedness of $y(\tau)$ to the second equation in (5.9) yields the boundedness of $x(\tau)$. Finally, with bounded $x(\tau)$ and $y(\tau)$, the first equation in (5.9) are bounded. The proof is complete.

The characteristic polynomial for \overline{E}_0 is $P_0(L) = (L+1) (L+C) (L\mathcal{G}-\mathcal{E}+\mathcal{H}\mathcal{G})/\mathcal{G}$, from which it is easy to show that \overline{E}_0 is asymptotically stable for $\mathcal{E} < \mathcal{E}_s = \mathcal{H}\mathcal{G}$ and becomes unstable at the critical point $\mathcal{E}_s = \mathcal{H}\mathcal{G}$, from which \overline{E}_1 appears. Further, we can use the characteristic polynomial for \overline{E}_1 to show that the two equilibrium solutions exchange their stability at the transcritical bifurcation point $\mathcal{E}_s = \mathcal{H}\mathcal{G}$. Further, we have the following result for \overline{E}_0 .

THEOREM 5.2. The trivial equilibrium E_0 : $(x_0, y_0, z_0) = (0, 0, 0)$ is globally asymptotically stable for $\mathcal{E} < \mathcal{E}_s = \mathcal{H}\mathcal{G}$.

Proof. We construct the Lyapunov function, $V(x, y, z) = \frac{1}{2}(x^2 + \rho_1 y^2 + \rho_2 z^2)$ for system (5.9), where $\rho_1 = \frac{3C}{D^2}$, and $\rho_2 = \frac{1}{B}$. V is continuously differentiable for all positive bounded values of each variable and positive definite with positive parameter values; i.e., V(0, 0, 0) = 0 and $V(x, y, z) > 0 \forall x, y, z > 0$. Then, the derivative of the Lyapunov function V with respect to time, along the solution trajectory of system (5.9), yields

$$\frac{\mathrm{d}V}{\mathrm{d}\tau}\Big|_{(5.9)} = x\frac{\mathrm{d}x}{\mathrm{d}\tau} + \rho_1 y\frac{\mathrm{d}y}{\mathrm{d}\tau} + \rho_2 z\frac{\mathrm{d}z}{\mathrm{d}\tau}
= x\left[\frac{z^2}{\mathcal{A}(x+y) + \mathcal{B}} - \mathcal{C}x\right] + \rho_1 y\left[\mathcal{D}x - y\right]
+ \rho_2 z^2 \left[\frac{\mathcal{E}}{\mathcal{F}(x+y) + \mathcal{G}} - x - y - \mathcal{H}\right]
= \left[\frac{1}{\mathcal{A}(x+y) + \mathcal{B}} - \rho_2\right] xz^2 - \mathcal{C}\left(x - \frac{\rho_1 \mathcal{D}}{2\mathcal{C}}y\right)^2 - \rho_1\left(1 - \frac{\rho_1 \mathcal{D}^2}{4\mathcal{C}}\right) y^2
+ \rho_2 z^2 \left[\frac{\mathcal{E}}{\mathcal{F}(x+y) + \mathcal{G}} - \mathcal{H}\right] - \rho_2 xz^2 - \rho_2 yz^2,$$

which implies that $\frac{dV}{d\tau} < 0 \ \forall x, y, z > 0$ due to $\mathcal{E} < \mathcal{H}\mathcal{G}$. The proof is complete. The characteristic polynomial for \overline{E}_1 is $P_1(L) = L^3 + a_1(x_1) L^2 + a_2(x_1) L + a_3(x_1)$.

 $a_3(x_1) = 0$ defines the transcritical point $\mathcal{E} = \mathcal{E}_s$. The Hopf bifurcation point can



FIG. 6. Bifurcation diagrams for the scaled system (5.9) in 2-d $C - \mathcal{E}$ and $\mathcal{D} - \mathcal{E}$ parameter spaces, where (a) $\mathcal{D} = 2$ and (b) $C = \frac{5}{8}$: red lines and blue curves denote the transcritical and Hopf bifurcations, respectively. Points (1)–(9) in (a) and (b) show parameter value pairs chosen for simulation. The simulated time histories are displayed in Figures 7 and 8.

be determined from the Hurwitz arrangement $\Delta_2 = a_1(x_1) a_2(x_1) - a_3(x_1) = 0$. In general, we may take three parameters, say, \mathcal{C} , \mathcal{D} , and \mathcal{E} , as the bifurcation parameters. Therefore, the stability boundary, based in particular on the Hopf critical condition, can be displayed in the 3-d parameter space as a surface. We then try to identify the region in the 3-d parameter space where recurrence may occur. For a clear view of the stability boundary, we use $\mathcal{C} = \text{constant}$ or $\mathcal{D} = \text{constant}$ to intersect the surface to obtain planes, as shown in Figure 6. The curves shown in Figure 6 are the stability boundary determined by the Hopf critical condition. The graphs of $\Delta_2(\mathcal{C}, \mathcal{E}) = 0$ and $\Delta_2(\mathcal{D}, \mathcal{E}) = 0$ are plotted in the 2-d $\mathcal{C} - \mathcal{E}$ and $\mathcal{D} - \mathcal{E}$ parameter planes in Figure 6. Recurrence may occur on the right side (stable side for bifurcating limit cycles) of the Hopf critical curves. Moreover, in these planes, we select several fixed values for \mathcal{C} or \mathcal{D} to obtain the horizontal lines, as shown in Figure 6. Then, we choose the points (according to the values of \mathcal{E}) on these lines to perform simulation. Two sets of nine simulated results are presented in Figures 7 and 8, corresponding to the nine points marked on the five solid lines in each panel of Figure 6. It is seen from Figure 7 that recurrence becomes more visible when the notation number of the points increases. That is, as \mathcal{D} is fixed, reducing the value of \mathcal{C} (see Figure 6(a)) causes more dramatic recurrence, while changing \mathcal{E} in this case does not change the pattern. Figure 8, on the other hand, shows that when \mathcal{C} is fixed at an appropriate value, the changes of \mathcal{D} and \mathcal{E} (see Figure 6(b)) do not play a significant role in determining recurrence. These parameter studies provide us with information regarding which parameters play an important role in generating recurrence: while some parameters mainly change the frequency of the motion, others only affect amplitude.

Finally, we would like to ask a question: since the recurrent pattern (or periodic solution) occurs at parameter values which are far away from the Hopf critical point, is there any factor other than the Hopf bifurcation contributing to the oscillation? More specifically, do homoclinic orbits exist? The answer is negative, given in the following theorem.

THEOREM 5.3. There exist no homoclinic orbits in the 3-d scaled system (5.9) or the 4-d system (2.6). Thus, the stable limit cycles either come from Hopf bifurcation or are due to persistent oscillations.

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FIG. 7. Numerical simulation for the parameter values $(\mathcal{E}, \mathcal{C})$ taken as (1) (13, 1.0), (2) (8.5, 0.8), (3) (10, 0.8), (4) (5, 0.625), (5) (6, 0.625), (6) (3, 0.4), (7) (4, 0.4), (8) (2, 0.2), and (9) (3, 0.2).

Proof. First, for the 3-d scaled system (5.9), note that existence of homoclinic orbits needs a saddle or a saddle-focus point, which requires $\mathcal{E} > \mathcal{HG}$. Evaluating the characteristic polynomial at \overline{E}_0 : (0, 0, 0) yields three eigenvalues: $\lambda_1 = -\mathcal{C}$, $\lambda_2 = -1$, and $\lambda_3 = \frac{\mathcal{E} - \mathcal{H}\mathcal{G}}{\mathcal{G}}$. Their corresponding eigenvectors are $V_1 = (\frac{1-\mathcal{C}}{\mathcal{D}}, 1, 0)^{\top}$, $V_2 = (0, 1, 0)^{\top}$, and $V_3 = (0, 0, 1)^{\top}$, starting from \bar{E}_0 . Then, since for \bar{E}_0 the eigenvalue λ_3 is positive, while the other two eigenvalues λ_1 and λ_2 are negative, E_0 is a saddle point. If a homoclinic orbit exists, it must connect the saddle point to itself, leaving in the direction tangent to V_3 at \overline{E}_0 and coming back along a convergent trajectory to \overline{E}_0 , which is located in the stable manifold of system (5.9). It is easy to show that the two eigenvectors V_1 and V_2 actually construct the stable manifold, which is the first quadrant of the x-y plane, denoted by S_1 . The solution on the stable manifold can be expressed as $v = T_1v_1 + T_2v_2$ for $T_1, T_2 \in \mathbb{R}^+$, where $v_1 = (\frac{1-\mathcal{C}}{\mathcal{D}}e^{-\mathcal{C}\tau}, e^{-\mathcal{C}\tau}, 0)^\top$ and $v_2 = (0, e^{-\tau}, 0)^\top$. Then it is obvious that S_1 is invariant if we verify that the solution v satisfies system (5.9). The complementary space of S_1 is the z-axis, which is tangent to the unstable manifold. Thus if a homoclinic orbit exists, it must connect the unstable and stable manifolds. However, this is impossible since there is no singular point on S_1 (expect for \bar{E}_0), and so the homoclinic orbit cannot intersect S_1 due to the uniqueness of solutions. Therefore, no homoclinic orbits



FIG. 8. Numerical simulation for the parameter values $(\mathcal{E}, \mathcal{D})$ taken as (1) (8, 1.5), (2) (10, 1.5), (3) (5, 2), (4) (7, 2), (5) (4, 3), (6) (6, 3), (7) (3, 4), (8) (5, 4), and (9) (2.5, 5).

exist in system (5.9), and thus the stable limit cycles in system (5.9) either come from Hopf bifurcation or are due to persistent oscillations.

Next, we consider the 4-d system (2.6). Note that system (2.6) also has two equilibrium solutions, E_0 : $(\bar{A}_0, \bar{R}_{n0}, \bar{R}_{d0}, \bar{E}_0) = (0, 0, 0, 0)$ and E_1 : $(\bar{A}, \bar{R}_n, \bar{R}_d, \bar{E})$, where \bar{A} is determined by (3.7) and the other three components are given in (3.6). E_0 and E_1 exchange their stability at a transcritical bifurcation point $\alpha = \alpha_t$, defined in (3.11). When $0 < \alpha < \alpha_t$, E_0 is globally asymptotically stable and E_1 does not exist; when $\alpha_t < \alpha < \alpha_H$, E_0 becomes unstable while E_1 is asymptotically stable, where α_H is a Hopf bifurcation point at which limit cycles bifurcate from E_1 . When $\alpha > \alpha_H$, E_1 also becomes unstable.

The existence of homoclinic orbits requires the existence of a saddle or a saddlefocus point, yielding the condition $\alpha > \alpha_t = \frac{1}{\lambda_E}(b_1 + \mu_A)(b_3 + \mu_E)$. The characteristic polynomial for E₀ is given by (3.9), from which we obtain four eigenvalues:

$$L_{1} = -(\mu_{n} + \xi), L_{2} = -\mu_{d}, (5.14) L_{3} = \frac{1}{2} \left\{ -(b_{1} + b_{3} + \mu_{A} + \mu_{E}) - \sqrt{(b_{1} + b_{3} + \mu_{A} + \mu_{E})^{2} + 4\lambda_{E}(\alpha - \alpha_{t})} \right\}, L_{4} = \frac{1}{2} \left\{ -(b_{1} + b_{3} + \mu_{A} + \mu_{E}) + \sqrt{(b_{1} + b_{3} + \mu_{A} + \mu_{E})^{2} + 4\lambda_{E}(\alpha - \alpha_{t})} \right\}.$$

Since $\alpha > \alpha_t$ and we have $L_3 < 0$ and $L_4 > 0$, we conclude that E_0 is a saddle point when $\alpha > \alpha_t$. The eigenvectors corresponding to the two negative eigenvalues L_1 and L_2 are $V_1 = (0, \frac{\mu_d - \mu_n - \xi}{c\xi}, 1, 0)^{\top}$ and $V_2 = (0, 0, 1, 0)^{\top}$, respectively. It is easy to verify that the solutions $v_1 = V_1 e^{-(\mu_n + \xi)t}$ and $v_2 = V_2 e^{-\mu_d t}$ satisfy system (2.6). Further, it can be shown that the general solution, $(A, R_n, R_d, E)^{\top} = T_1 v_1 +$ T_2v_2 , also satisfies system (2.6), where $T_1, T_2 \in \mathbb{R}^+$. This implies that the subspace determined by A = E = 0, i.e., the first quadrant of the R_n - R_d plane, is a 2-d invariant stable submanifold, denoted by S_2 . Hence, if a homoclinic orbit exists in system (2.6), it cannot return to E₀ via S_2 ; otherwise, it would contradict the uniqueness of solutions. So, the remaining possibility for a homoclinic orbit to appear is in the complementary space of S_2 , which is the first quadrant of the A-E plane, denoted by $C: \{(A, R_n, R_d, E) | A, E \ge 0, R_n = R_d = 0\},$ on which the dynamics are described by $\dot{A} = \alpha E - (b_1 + \mu_A)A$, $\dot{E} = \lambda_E A - (b_3 + \mu_E)E$. However, this system is linear. So no homoclinic orbits can exist in system (2.6), and thus the stable limit cycles in system (2.6) either come from Hopf bifurcation or are due to persistent oscillations. The proof is complete.

In this section, we have made two reductions, one based on a quasi-steady state assumption and the other based on rescaling. It should be noted that these two reductions have a fundamental difference. The latter actually generates an equivalent system, i.e., system (5.9) is equivalent to system (5.4), while the former yields system (5.4), which is different from system (5.1). However, system (5.4) still keeps the basic interesting dynamic behavior (recurrency) of the original system (5.1) under the quasi-steady state assumption.

6. Conclusion and discussion. Adaptive immunity in vertebrates comprises an extremely complex dynamical system, and much remains to be elucidated, particularly with respect to the role and action of regulatory T cells. In this contribution, we have demonstrated that the addition of a newly discovered subclass of T_{Reg} cells, the terminally differentiated HLA-DR⁺ class [5, 31], alters the dynamical behavior of a general model of autoimmune disease [1]. In particular, rather than being restricted to stable equilibria corresponding to self-tolerance and autoimmunity, the system now displays long periods of quiescence, punctuated by brief bursts of autoimmune activity. These cycles of relapse and remission, characteristic of many autoimmune diseases, arise naturally from the dynamical behavior of the system, without the need for stochastic input or exogenous environmental triggers.

As an intuitive explanation for this phenomenon, we argue that the dynamical system is "torn between two equilibria," one of which is the trivial equilibrium corresponding to immune tolerance (self-reactive populations at zero), the other corresponding to a full-blown autoimmune reaction. As a result, after the Hopf bifurcation the model populations remain close to the tolerance equilibrium for long intervals, during which immune regulation (the T_{Reg} population) gradually wanes. When regulatory populations are sufficiently small, the autoreactive effector population escapes immune regulation, and a brief episode of autoimmune disease, a relapse, occurs.

Although the cycles of relapse and remission observed in this system occur at regular intervals, we note that even slight fluctuations in the parameter values, or deterministic changes in parameters over time, can result in highly variable intervals between relapse episodes, as demonstrated in [49]. We also note that in any organism, self-antigen is likely to be continually present at low levels. Thus, even if the relevant populations reach extremely low densities during the cycles of remission predicted here, pAPCs specific for self-antigen are likely to be periodically generated, renewing the relapse-remission cycle if they are activated when the T_{Reg} populations have waned. This could be a further factor contributing to variable intervals between relapse episodes.

The bifurcation parameter α reflects the number of activated pAPCs generated per day through damage and subsequent antigen release caused by a single autoreactive T cell. The best available numerical value for this parameter is about $\alpha = 1 \times 10^{-4} \ [A]/\text{day}/[E]$ for a normal adult [1]. Keeping other parameters constant, we find that recurrence emerges at $\alpha = 3 \times 10^{-3}$. While it is difficult to estimate whether this difference is within the range of natural variation in this parameter, we note that α itself is a compound parameter reflecting the product of a number of process. Also, smaller changes in α will presumably produce recurrence if other parameter values change simultaneously.

Previous work has suggested that the cause of recurrence, at least in multiple sclerosis, may be a weakness in the negative feedback loop between effector and regulatory T cells [40]. In contrast, our work suggests that increases to α , either through increasing the activation rate of pAPCs or increasing the damage induced by autoreactive T cells, will make recurrence more likely. Increases to the parameter λ_E , the rate at which effector T cells are activated by pAPCs, will have a similar effect. Of the compound parameters in our reduced model, C, D, and E had the greatest impact on recurrence: these parameters reflect both α and λ_E , as well as the production and elimination rates of terminally differentiated T_{Reg} cells. Thus, in general our model points towards factors that increase the positive feedback loop between antigen presenting cells and auto-reactive effector T cells as a pathway to recurrence.

Clearly, the models we analyze are extreme simplifications of the mechanisms of immune regulation. As the precise mechanisms of action of regulatory T cells are further elucidated, more accurate and predictive models should be possible. Nonetheless we hope that the main insight of this paper, that recurrence in autoimmune diseases can arise naturally from the complex interplay of dynamic populations, will serve as a starting point for further research both in dynamical systems theory and in theoretical immunology.

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