



Research article

Lesion–immune feedback induces bistability and oscillatory dynamics in a reduced model of multiple sclerosis

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Abstract: Relapsing–remitting multiple sclerosis (RRMS) is characterized by recurrent immune activation, lesion development, and marked variability in disease activity. To investigate how lesion-associated activity may feed back on immune regulation, we extend an established effector T cell–regulatory T cell (Teff–Treg) model by introducing a normalized lesion-activity variable and a feedback factor that amplifies antigen-presentation-related immune activation. The resulting closed-loop system links autoreactive effector T-cell activity, lesion-associated activity, and subsequent immune reactivation through lesion–immune feedback. Positivity, global existence, and uniform boundedness hold in the feasible region. Positive equilibria satisfy $\alpha = \Phi_k(S)$, with S the combined regulatory strength. The feedback-free branch is monotone, and $\mathcal{F} > 1$ gives backward bending and at least two positive equilibria for $\alpha_{SN} < \alpha < \alpha_c$, though their exact number and stability remain analytically undetermined. For the working parameters, branch reconstruction and full-Jacobian spectral checks reveal a nondegenerate fold and coexisting stable tolerant and active equilibria separated by a saddle; time integration shows initial-condition dependence, and a schematic branch-following construction illustrates hysteresis-like switching. Routh–Hurwitz conditions, together with conditional saddle-node and Hopf criteria, are derived. Numerical verification identifies a transverse imaginary-pair crossing and a negative first Lyapunov coefficient, consistent with a supercritical Hopf bifurcation, with simulations showing sustained coupled oscillations. The computed two-parameter boundaries concern equilibrium existence and local stability in the scanned regime, not a global classification of attractors or calibrated clinical relapse intervals.

Keywords: relapsing-remitting multiple sclerosis; lesion feedback; bistability; saddle-node bifurcation; Hopf bifurcation

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system (CNS), characterized by inflammation, demyelination, axonal injury, and neurodegeneration [1, 2]. Its

clinical course is highly heterogeneous and is commonly described in terms of clinically isolated syndrome (CIS), relapsing–remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), and primary progressive multiple sclerosis (PPMS) [3, 4]. RRMS is the most common phenotype at disease onset and consists of recurrent neurological episodes followed by partial or complete remission. A proportion of patients subsequently enter SPMS, whereas PPMS is characterized by progressive neurological deterioration from disease onset without a preceding relapsing–remitting course. Clinical relapses, radiological lesion activity, and long-term disability progression are not always temporally synchronized [3–5], indicating that MS progression cannot be interpreted solely through the instantaneous level of peripheral immune activation.

Pathological heterogeneity is also evident in demyelinating lesions. Distinct lesion patterns have been identified according to their predominant cellular targets and mechanisms of demyelination. In particular, Type II lesions are associated with prominent immune-cell infiltration, myelin degradation, and remyelination, whereas Type III lesions involve pronounced oligodendrocyte injury, microglial activation, and limited remyelination [6]. Although individual lesion types are not distinguished in the mathematical formulation below, such heterogeneity supports the view that lesion-associated tissue activity evolves dynamically and interacts with immune regulation. MS progression therefore involves coupled processes including autoreactive immune activation, immune suppression, CNS inflammation, tissue injury, antigen exposure, and repair [7–10].

Among these mechanisms, the balance between autoreactive effector T cells (Teff) and regulatory T cells (Treg) provides a useful reduced description of the competition between immune activation and immune suppression. Autoreactive Teff cells promote inflammatory amplification and myelin injury, whereas Treg cells suppress excessive immune responses and maintain peripheral immune tolerance [11, 12]. Although B cells, microglia, astrocytes, cytokines, and compartmentalized CNS immune responses also play important roles [13–16], low-dimensional Teff–Treg models provide a tractable framework for identifying nonlinear mechanisms underlying tolerance, chronic autoimmunity, and recurrent disease activity.

The mathematical development of this framework can be traced back to the regulatory T-cell models developed by Alexander and Wahl [17]. Their ordinary differential equation (ODE) systems describe interactions among professional antigen-presenting cells (pAPCs), autoreactive effector T cells, Treg cells, and self-antigens, and they distinguish an immune-tolerant equilibrium from a chronic autoimmune equilibrium. However, the deterministic formulations considered there do not reproduce the intrinsic recurrent oscillations characteristic of relapsing autoimmune disorders.

Zhang et al. extended this framework by combining Treg-mediated suppression of pAPCs and autoreactive effector T cells and by introducing a terminally differentiated Treg population with enhanced suppressive capacity [18]. The resulting higher-dimensional system was shown to generate recurrent autoimmune dynamics through Hopf bifurcation or persistent oscillatory motion. Further nonlinear analysis characterized Hopf and generalized Hopf bifurcations and demonstrated the possible emergence of multiple limit cycles and bistable configurations [19].

A subsequent reduction by Zhang and Yu isolated the essential Teff–Treg regulatory loop while preserving the principal qualitative behavior of the higher-dimensional models [20]. Let $R_n(t)$ denote activated conventional Treg cells, $R_d(t)$ terminally differentiated Treg cells, and $E(t)$ autoreactive effector T cells. Defining the combined regulatory strength as

$$S = R_n + dR_d, \quad (1.1)$$

the reduced three-dimensional system is

$$\begin{cases} \dot{R}_n = \frac{\alpha(\pi_3 E + \beta)E}{\eta_1 + \sigma_1 S} - (\mu_n + \xi)R_n, \\ \dot{R}_d = c\xi R_n - \mu_d R_d, \\ \dot{E} = E \left[\frac{\alpha\lambda_E}{\eta_1 + \sigma_1 S} - \sigma_3 S - \eta_2 \right] \end{cases} \quad (1.2)$$

with $\eta_1 = b_1 + \mu_A$ and $\eta_2 = b_3 + \mu_E$. Here, b_1 denotes the nonspecific background suppression contribution in the antigen-presenting-cell balance and μ_A its clearance contribution; b_3 is the nonspecific background suppression contribution in the effector-cell balance and μ_E the effector clearance rate. Their sums are the effective loss rates inherited by the reduced model, not additional dynamic states. Only these aggregate rates enter the present equations.

System (1.2) preserves tolerance, chronic autoimmune activation, oscillatory behavior, and relapse-like recurrent dynamics. Multiple coexisting limit cycles were also identified and proposed as a possible dynamical explanation for different amplitudes of recurrent autoimmune activity in MS [20]. Accordingly, System (1.2) provides the direct immune-regulatory basis for the model considered below.

Despite its rich temporal dynamics, System (1.2) contains only immune-regulatory variables. Lesion-associated tissue activity does not appear as an independent dynamical variable and hence cannot feed back directly to drive subsequent immune reactivation. This limitation is particularly relevant to MS, where demyelination and inflammatory lesion activity evolve together with immune responses.

Recent MS-specific mathematical models have incorporated such tissue-level processes explicitly. Kinetic and reaction–diffusion formulations include self-reactive immune cells, cytokine-driven chemotaxis, myelin consumption, remyelination, microglia, and oligodendrocytes and can reproduce lesion behavior associated with RRMS, SPMS, PPMS, and different pathological lesion patterns [6, 21]. These formulations provide biological motivation for treating lesion activity as an active dynamical component rather than solely as a passive output of immune activation.

Tissue-driven autoantigen feedback is already present in Lebel et al. [22], whose effector–regulatory model emphasizes noise-triggered excitable flares and exhibits bistable and oscillatory regimes. Thus, tissue feedback, bistability, and oscillations individually are not new here. Our specific contribution is the explicit saturating, recovering lesion state coupled through a common activation multiplier to the differentiated Teff–Treg loop, enabling a scalar equilibrium reduction and a feedback criterion for backward bending. The nonconservative kinetic treatment of autoimmune response by Menale and Travaglini [23] models treatment through an external force field. The present autonomous ODE instead addresses lesion-mediated feedback without treatment forcing; it sacrifices kinetic detail for tractable equilibrium and local bifurcation analysis.

To retain the analytical tractability of the low-dimensional Teff–Treg framework while incorporating this missing mechanism, a normalized lesion-activity variable $D(t) \in [0, 1]$ is introduced. The variable represents aggregate lesion-associated inflammatory and demyelinating activity. The resulting feedback architecture is

autoreactive immune activation $\longrightarrow$ lesion-associated activity $\longrightarrow$ enhanced immune reactivation.

The essential modification of System (1.2) is

$$\alpha \longrightarrow \alpha q(D), \quad q(D) = 1 + \kappa D, \quad \kappa \geq 0, \quad (1.3)$$

where κ measures lesion-immune feedback strength. The factor $q(D)$ enters the immune-activation terms of both the R_n and E equations, reflecting their common dependence on antigen-presentation-related activation.

This common multiplier is a parsimonious closure for increased antigen exposure, not evidence that Teff and Treg respond equally in vivo. Antigen-induced expansion of both populations is also represented in [22]. Different gains, for example $1 + \kappa_n D$ and $1 + \kappa_E D$, would modify the cancellation underlying the scalar reduction and require a new analysis. Our robustness checks below vary parameters within the stated common-gain model; they do not validate alternative feedback architectures.

When $\kappa = 0$, the immune subsystem reduces to the feedback-free model (1.2); when $\kappa > 0$, lesion-associated activity modifies subsequent immune reactivation.

The lesion variable is governed by

$$\dot{D} = \rho_E \frac{E}{K_E + E} (1 - D) - \rho_R D, \quad (1.4)$$

where the first term represents Teff-driven lesion-associated activity and the second describes lesion resolution or recovery. Equations (1.3) and (1.4) close the lesion-immune feedback loop and lead to the four-dimensional system formulated in Section 2.

The resulting feedback introduces a bifurcation mechanism distinct from the multiple-limit-cycle dynamics previously obtained from the Teff-Treg loop. Positive equilibria can be reduced to the scalar relation $\alpha = \Phi_\kappa(S)$. Without lesion-mediated feedback, the positive-equilibrium branch remains monotone. For sufficiently strong feedback, the local branch direction can reverse, producing a backward-bending equilibrium structure. For the working parameter set considered below, this structure contains a nondegenerate saddle-node bifurcation and an intermediate parameter interval in which a stable immune-tolerant equilibrium coexists with a stable high-activity autoimmune equilibrium, separated by a saddle state. The numerically verified equilibrium bistability yields initial-condition dependence, and its static geometry motivates a schematic hysteresis-like branch-following construction. This mechanism is distinct from the coexistence of periodic solutions reported previously [20].

Hopf bifurcation may also occur along the positive-equilibrium branch. For the working parameter set considered below, the corresponding first Lyapunov coefficient is negative, indicating a supercritical Hopf bifurcation with stable periodic oscillations. The closed-loop formulation therefore permits feedback-induced equilibrium restructuring and Hopf-induced oscillatory instability to be examined within the same dynamical framework.

The lesion variable and feedback coefficient are phenomenological and are not calibrated directly from longitudinal clinical or imaging data. Accordingly, the bifurcation values reported below represent mathematical thresholds of the model rather than clinical decision thresholds. The main objective is to determine how lesion-associated feedback can transform the equilibrium and oscillatory structure inherited from the reduced Teff-Treg system.

The remainder of this paper is organized as follows. Section 2 constructs the four-dimensional immune–lesion model from System (1.2) and the feedback relations (1.3) and (1.4). Section 3 establishes the basic mathematical properties and equilibrium reduction. Section 4 analyzes equilibrium stability and saddle-node and Hopf bifurcations. Section 5 presents numerical bifurcation and time-domain results. Section 6 discusses the dynamical and biological implications of the results, compares the proposed framework with existing autoimmune and MS models, and addresses its main limitations.

2. Formulation of the closed-loop lesion–immune feedback model for MS

2.1. Construction of the four-dimensional model

The immune-regulatory subsystem used as the basis of the model has already been introduced in System (1.2). Its state variables are the activated conventional regulatory T cell population $R_n(t)$, the terminally differentiated regulatory T cell population $R_d(t)$, and the autoreactive effector T cell population $E(t)$, with the combined suppressive strength $S = R_n + dR_d$.

To incorporate lesion-associated inflammatory activity, an additional normalized state variable $D(t) \in [0, 1]$ is introduced. As described in the Introduction, lesion-mediated feedback modifies the immune activation intensity through $\alpha \rightarrow \alpha q(D)$, $q(D) = 1 + \kappa D$, where $\kappa \geq 0$ measures the effective strength of lesion-mediated immune amplification. Lesion activity is assumed to evolve according to

$$\dot{D} = \rho_E \frac{E}{K_E + E} (1 - D) - \rho_R D.$$

Substituting the feedback-modified activation intensity into the baseline immune subsystem and coupling it with the lesion equation gives the four-dimensional closed-loop system

$$\begin{cases} \dot{R}_n = \frac{\alpha q(D)(\pi_3 E + \beta)E}{\eta_1 + \sigma_1(R_n + dR_d)} - (\mu_n + \xi)R_n, \\ \dot{R}_d = c\xi R_n - \mu_d R_d, \\ \dot{E} = E \left[\frac{\alpha \lambda_E q(D)}{\eta_1 + \sigma_1(R_n + dR_d)} - \sigma_3(R_n + dR_d) - \eta_2 \right], \\ \dot{D} = \rho_E \frac{E}{K_E + E} (1 - D) - \rho_R D, \end{cases} \quad (2.1)$$

where $q(D) = 1 + \kappa D$. The quantities η_1 and η_2 are retained as effective composite parameters inherited from the baseline formulation; in the original parametrization, $\eta_1 = b_1 + \mu_A$, and $\eta_2 = b_3 + \mu_E$.

The first three equations retain the structure of the reduced Teff–Treg system [20]. The structural changes consist of the lesion-dependent amplification factor $q(D)$ in the R_n and E activation terms and the additional dynamical equation for D . The resulting feedback pathway may be summarized as

$$E \longrightarrow D \longrightarrow q(D) \longrightarrow (R_n, E).$$

Thus, autoreactive immune activity promotes lesion-associated activity, which subsequently modifies further immune activation and closes the feedback loop.

2.2. Modeling assumptions and feedback closure

The construction of System (2.1) is based on a minimal set of assumptions intended to incorporate lesion-associated feedback without losing the analytical tractability of the baseline Teff–Treg model.

First, lesion-associated activity is represented by the single dimensionless variable D rather than by separate variables for demyelination, oligodendrocyte injury, inflammatory-cell infiltration, antigen release, and tissue repair. Accordingly, D is not intended to resolve individual cellular or histopathological processes. It serves instead as an aggregate temporal state that allows lesion-associated processes to participate explicitly in the dynamical feedback structure.

Second, lesion-mediated amplification is assumed to act primarily through the antigen-presentation-related activation pathway. For this reason, the baseline activation parameter α is replaced by $\alpha q(D)$ in both the R_n and E equations. The activation of both conventional Treg cells and autoreactive Teff cells is therefore modulated by the same upstream feedback factor, whereas their subsequent regulatory effects remain distinct. No additional lesion-dependent term is introduced directly into the R_d equation because R_d is generated from R_n through the terminal differentiation mechanism inherited from the original Teff–Treg formulation [18, 20].

Third, the effect of Teff abundance on lesion generation is assumed to increase nonlinearly and saturate at high E . The corresponding activation rate is represented by

$$g(E) = \rho_E \frac{E}{K_E + E},$$

where ρ_E is the maximal lesion-activation rate, and K_E is the Teff level associated with half-maximal activation. This Michaelis–Menten-type form avoids an indefinitely increasing lesion-generation rate as the effector-cell population becomes large.

Because D is normalized to the interval $[0, 1]$, the fraction $1 - D$ represents the remaining capacity for additional lesion activation. At the systems level, the lesion dynamics may therefore be interpreted as the balance

$$\text{lesion activation} - \text{lesion resolution},$$

leading to

$$\dot{D} = g(E)(1 - D) - \rho_R D = \rho_E \frac{E}{K_E + E} (1 - D) - \rho_R D. \quad (2.2)$$

The factor $(1 - D)$ limits further lesion activation as D approaches its normalized upper bound, whereas the linear term $\rho_R D$ represents effective lesion resolution or recovery.

The damage–recovery structure of (2.2) is motivated qualitatively by MS models in which immune activity and inflammatory processes are coupled to plaque formation, myelin damage, oligodendrocyte injury, or tissue recovery [6, 21, 24]. Equation (2.2), however, is not obtained through a direct mathematical reduction of those spatial reaction–diffusion or kinetic systems. It should instead be viewed as a low-dimensional phenomenological closure retaining the competition between immune-driven lesion activation and lesion resolution.

Finally, the feedback function

$$q(D) = 1 + \kappa D \quad (2.3)$$

is chosen as the simplest increasing function satisfying $q(0) = 1$. This choice has two useful properties. When $\kappa = 0$, the immune subsystem reduces exactly to the baseline model (1.2); when $\kappa > 0$, increasing

lesion activity enhances the effective immune activation intensity. The single parameter κ therefore isolates feedback strength without introducing additional nonlinear parameters. The linear form of $q(D)$ is a minimal modeling assumption rather than a claim that the underlying biological relationship is exactly linear.

2.3. Biological interpretation of the model

The first equation of System (2.1) describes the dynamics of activated conventional Treg cells. The production term

$$\frac{\alpha q(D)(\pi_3 E + \beta)E}{\eta_1 + \sigma_1 S}$$

retains the activation structure of the reduced Teff–Treg model [20]. The factor $(\pi_3 E + \beta)E$ represents Teff-dependent and background contributions to Treg activation, whereas the denominator $\eta_1 + \sigma_1 S$ describes the inhibitory effect associated with the regulatory population. The term $(\mu_n + \xi)R_n$ combines the natural loss of activated conventional Treg cells and their terminal differentiation. The new factor $q(D)$ allows lesion-associated activity to modify the activation process.

The second equation, $\dot{R}_d = c\xi R_n - \mu_d R_d$, is unchanged from the baseline formulation [18, 20]. The term $c\xi R_n$ represents production of terminally differentiated Treg cells from R_n , and $\mu_d R_d$ describes their clearance. The two Treg populations jointly contribute to immune suppression through $S = R_n + dR_d$, where d represents the relative suppressive contribution of the terminally differentiated population.

The third equation describes autoreactive Teff dynamics. For $E > 0$, its per-capita growth rate is

$$\frac{\alpha \lambda_E q(D)}{\eta_1 + \sigma_1 S} - \sigma_3 S - \eta_2.$$

The first term represents antigen-presentation-related Teff expansion, the term $\sigma_3 S$ accounts for direct Treg-mediated suppression, and η_2 represents effective Teff loss. The common factor $q(D)$ in the R_n and E activation terms reflects the assumption that lesion-associated amplification acts through a shared upstream activation pathway rather than independently on each cell population.

The fourth equation introduces the new lesion-associated state. An increase in autoreactive Teff abundance raises the lesion-activation rate through $E/(K_E + E)$, whereas the factor $(1 - D)$ limits the available capacity for further activation. The recovery term $\rho_R D$ summarizes processes that reduce active lesion-associated inflammation, including inflammatory resolution and repair. Consequently, D should be interpreted as an effective measure of aggregate active lesion-associated inflammatory and demyelinating activity rather than as MRI lesion volume, lesion number, irreversible neurological disability, or a specific damaged-cell population.

The feedback function (2.3) closes the pathway from lesion activity back to immune activation. Active lesion-associated processes may involve increased antigen exposure, inflammatory signaling, and alterations in blood–brain barrier function. Tissue injury and continuing antigen exposure may also contribute to the diversification of autoreactive responses through mechanisms such as epitope spreading [2, 9, 10, 25]. These processes provide biological motivation for representing lesion-associated activity as a potential amplifier of subsequent immune activation. The parameter κ therefore summarizes the net strength of this amplification at the reduced systems level. The model does not specify a unique cellular pathway by which this feedback occurs; rather, it examines the

dynamical consequences that follow when such an effective positive feedback is coupled to the established Teff–Treg regulatory loop.

2.4. Variables, parameters, and feasible region

The variables and parameters of System (2.1) are summarized in Table 1.

Units are stated as a consistent reduced-model convention: C is a common effective cell-population unit, T an effective time unit, and 1 means dimensionless. Neither unit is calibrated here to a sampled anatomical volume or to days. The assignments in Tables 1 and 2 make each equation dimensionally consistent. A computed period $23.7T$ remains in model units; mapping it to a clinical interval requires an independently fitted time scale.

Table 1. Variables and parameters of the closed-loop immune–lesion model.

Symbol	Unit	Interpretation
R_n	C	Activated conventional regulatory T cell population [20].
R_d	C	Terminally differentiated regulatory T cell population [18, 20].
E	C	Autoreactive effector T cell population.
D	1	Dimensionless aggregate lesion-activity variable, $0 \leq D \leq 1$.
S	C	Combined suppressive strength, $S = R_n + dR_d$.
α	T^{-1}	Baseline intensity of antigen-presentation-related autoimmune activation.
π_3, β	$C^{-1}T^{-1}, T^{-1}$	Teff-dependent and background contributions to Treg activation.
λ_E	T^{-1}	Relative efficiency of antigen-presentation-related Teff expansion.
σ_1, σ_3	$C^{-1}T^{-1}$	Effective Treg-mediated inhibitory strengths.
η_1, η_2	T^{-1}	Effective decay parameters associated with antigen presentation and Teff dynamics.
μ_n, μ_d	T^{-1}	Clearance rates of activated and terminally differentiated Treg cells.
ξ	T^{-1}	Terminal differentiation rate of activated conventional Treg cells.
c	1	Effective amplification coefficient associated with terminal differentiation.
d	1	Relative suppressive weight of terminally differentiated Treg cells.
ρ_E	T^{-1}	Maximum rate of Teff-driven lesion activation.
K_E	C	Teff half-saturation level for lesion activation.
ρ_R	T^{-1}	Effective rate of lesion resolution or recovery.
κ	1	Strength of lesion-mediated amplification of immune activation.

Biologically admissible initial data satisfy

$$X(0) = (R_n(0), R_d(0), E(0), D(0)) \in \Omega, \quad (2.4)$$

where

$$\Omega = [0, \infty)^3 \times [0, 1]. \quad (2.5)$$

Thus, $R_n(0), R_d(0), E(0) \geq 0$, and $0 \leq D(0) \leq 1$.

All parameters are positive except that the feedback strength satisfies $\kappa \geq 0$. The immune-related parameters are inherited from or chosen consistently with the established Teff–Treg framework, whereas ρ_E , K_E , ρ_R , and κ are phenomenological lesion-related parameters. No joint calibration against longitudinal immune and MRI lesion measurements is performed. The resulting parameter values and bifurcation thresholds should therefore be interpreted as effective quantities for investigating dynamical mechanisms rather than as individualized clinical predictors.

In the following analysis, α is used as the principal bifurcation parameter, and the remaining parameters are held fixed unless otherwise stated.

3. Well-posedness, thresholds, and equilibrium structure

This section establishes the basic mathematical properties of System (2.1) and characterizes its equilibrium structure. We first prove positivity, global existence, and uniform boundedness. The immune-tolerant equilibrium and its activation threshold are then analyzed, followed by a scalar reduction of the positive-equilibrium problem. Finally, the effect of lesion-mediated feedback on the geometry of the positive-equilibrium branch is characterized.

Throughout this section, the parameter assumptions stated in Section 2 are maintained. Recall that the biologically feasible state space is $\Omega = [0, \infty)^3 \times [0, 1]$.

3.1. Positivity, global existence, and boundedness

We first show that solutions initiated in the biologically feasible region remain biologically meaningful.

Lemma 3.1. *Let $X(0) = (R_n(0), R_d(0), E(0), D(0)) \in \Omega$. Then, the solution of System (2.1) satisfies $X(t) \in \Omega$ throughout its maximal interval of existence.*

Moreover, if $R_n(0) > 0$, $R_d(0) > 0$, $E(0) > 0$, and $0 < D(0) < 1$, then $R_n(t) > 0$, $R_d(t) > 0$, $E(t) > 0$, and $0 < D(t) < 1$ for all $t > 0$ in the maximal interval of existence.

Proof. The right-hand side of System (2.1) is continuously differentiable on a neighborhood of Ω , as $\eta_1 + \sigma_1(R_n + dR_d) > 0$ and $K_E + E > 0$ for non-negative state variables. Hence, standard Picard–Lindelöf theory gives a unique local solution. Before using comparison inequalities, observe that the vector field is inward-pointing or tangent on every boundary face of Ω : at $R_n = 0$, $\dot{R}_n \geq 0$; at $R_d = 0$, $\dot{R}_d = c\xi R_n \geq 0$; at $E = 0$, $\dot{E} = 0$; at $D = 0$, $\dot{D} = \rho_E E / (K_E + E) \geq 0$; and at $D = 1$, $\dot{D} = -\rho_R < 0$. Each sign is evaluated on that face with all remaining coordinates in Ω . Local Lipschitz continuity and the invariant-region criterion therefore establish $X(t) \in \Omega$ on the maximal existence interval. The following estimates can now use simultaneous non-negativity without circular reasoning.

Set $A_n = \mu_n + \xi$. Because the production term in the R_n equation is non-negative, $\dot{R}_n \geq -A_n R_n$, and therefore, $R_n(t) \geq R_n(0)e^{-A_n t} \geq 0$. In particular, $R_n(t) > 0$ whenever $R_n(0) > 0$.

For R_d , the variation-of-constants formula gives

$$R_d(t) = R_d(0)e^{-\mu_d t} + c\xi \int_0^t e^{-\mu_d(t-s)} R_n(s) ds.$$

Because $R_n(s) \geq 0$, it follows that $R_d(t) \geq 0$. If $R_d(0) > 0$, then $R_d(t) > 0$ for all $t > 0$.

The Teff equation can be written as $\dot{E} = E G(t)$, where

$$G(t) = \frac{\alpha \lambda_E q(D(t))}{\eta_1 + \sigma_1 S(t)} - \sigma_3 S(t) - \eta_2, \quad S(t) = R_n(t) + dR_d(t).$$

Hence,

$$E(t) = E(0) \exp\left(\int_0^t G(s) ds\right).$$

Consequently, $E(0) \geq 0$ implies $E(t) \geq 0$, and $E(t) > 0$ whenever $E(0) > 0$.

For the lesion variable, define $a_D(t) = \rho_E E(t)/(K_E + E(t)) \geq 0$. Then, $\dot{D} = a_D(t) - [a_D(t) + \rho_R]D$. The variation-of-constants formula yields

$$D(t) = D(0)e^{-\int_0^t [a_D(s) + \rho_R] ds} + \int_0^t a_D(s)e^{-\int_s^t [a_D(\tau) + \rho_R] d\tau} ds,$$

so $D(t) \geq 0$.

To establish the upper bound, set $Z(t) = 1 - D(t)$. Then, $\dot{Z} = \rho_R - [a_D(t) + \rho_R]Z$. Applying the same argument gives $Z(t) \geq 0$, and therefore, $D(t) \leq 1$. If $0 < D(0) < 1$, then both $D(t)$ and $Z(t)$ remain strictly positive, giving $0 < D(t) < 1$.

Therefore, $X(t) \in \Omega$ throughout the maximal interval of existence. $\square$

The next result establishes global existence and uniform boundedness.

Theorem 3.1. *For every initial condition $X(0) = (R_n(0), R_d(0), E(0), D(0)) \in \Omega$, System (2.1) admits a unique global solution $X(t) = (R_n(t), R_d(t), E(t), D(t))$, $t \geq 0$. Moreover, there exists a constant $M > 0$, depending only on the initial condition and model parameters, such that*

$$0 \leq R_n(t), R_d(t), E(t) \leq M, \quad 0 \leq D(t) \leq 1, \quad t \geq 0. \quad (3.1)$$

Proof. By Lemma 3.1, it is sufficient to derive time-independent a priori bounds on the maximal interval of existence.

Let $A_n = \mu_n + \xi$, $B = c\xi$, and choose $0 < \vartheta < A_n/B$. Introduce $Y = R_n + \vartheta R_d$. Using the first two equations of System (2.1), we obtain

$$\dot{Y} = F(E, S, D) - (A_n - \vartheta B)R_n - \vartheta \mu_d R_d, \quad (3.2)$$

where $F(E, S, D) = \alpha q(D)(\pi_3 E + \beta)E/(\eta_1 + \sigma_1 S)$, and $S = R_n + dR_d$.

Define $m = \min\{A_n - \vartheta B, \mu_d\} > 0$ and $M_1 = \max\{A_n - \vartheta B, \mu_d\}$. Then,

$$F - M_1 Y \leq \dot{Y} \leq F - mY. \quad (3.3)$$

Because $R_n, R_d \geq 0$, the quantities S and Y are equivalent. With $\ell = \min\{1, d/\vartheta\}$ and $L = \max\{1, d/\vartheta\}$, we have

$$\ell Y \leq S \leq LY. \quad (3.4)$$

Set $a_0 = \eta_1/(\sigma_1 \ell)$, $H = a_0 + Y$, and $W = E/H$. Equation (3.4) then gives

$$\sigma_1 \ell H \leq \eta_1 + \sigma_1 S \leq \sigma_1 LH. \quad (3.5)$$

If $E_0 = 0$, then $E(t) \equiv 0$, and hence, $F \equiv 0$. Equation (3.3) gives $Y(t) \leq Y(0)e^{-mt}$, so boundedness follows immediately. It therefore remains to consider $E_0 > 0$, for which $W(t) > 0$.

Using $\dot{W}/W = \dot{E}/E - \dot{Y}/H$, together with (3.3), (3.4), and $1 \leq q(D) \leq 1 + \kappa$, we obtain

$$\frac{\dot{W}}{W} \leq \frac{\alpha\lambda_E(1+\kappa)}{\eta_1} - \eta_2 - \sigma_3\ell Y - \frac{F}{H} + M_1. \quad (3.6)$$

Because $E = WH$, $q(D) \geq 1$, and (3.5) holds, $F/H \geq W^2\alpha\pi_3/(\sigma_1 L)$. Define $k = \sigma_3\ell$, $c_0 = \alpha\pi_3/(\sigma_1 L)$, and $C_0 = \alpha\lambda_E(1+\kappa)/\eta_1 - \eta_2 + M_1$. Then,

$$\dot{W} \leq W(C_0 - kY - c_0W^2). \quad (3.7)$$

An upper estimate for F follows from (3.5), $E = WH$, and $q(D) \leq 1 + \kappa$:

$$F \leq a_1 W^2 H + a_2 W, \quad (3.8)$$

where $a_1 = \alpha\pi_3(1+\kappa)/(\sigma_1\ell)$, and $a_2 = \alpha\beta(1+\kappa)/(\sigma_1\ell)$. Because $H = a_0 + Y$, Eq (3.3) yields

$$\dot{Y} \leq a_1 W^2(a_0 + Y) + a_2 W - mY. \quad (3.9)$$

Choose $\Lambda > 0$ such that $2\Lambda k > a_1$, and define $V = Y + \Lambda W^2$. Combining (3.7) and (3.9) gives

$$\dot{V} \leq -mY - (2\Lambda k - a_1)YW^2 - 2\Lambda c_0 W^4 + (a_1 a_0 + 2\Lambda C_0)W^2 + a_2 W.$$

Because $2\Lambda k - a_1 > 0$, the mixed term is nonpositive. By Young's inequality, there exists $C_1 > 0$ such that

$$(a_1 a_0 + 2\Lambda C_0)W^2 + a_2 W \leq \Lambda c_0 W^4 + C_1.$$

Thus, $\dot{V} \leq -mY - \Lambda c_0 W^4 + C_1$. Using $W^4 \geq W^2 - 1/4$, we further obtain

$$\dot{V} \leq -mY - \Lambda c_0 W^2 + C_1 \leq -\delta V + C_2,$$

where $\delta = \min\{m, c_0\} > 0$, and $C_2 = C_1 + \Lambda c_0/4$.

Grönwall's inequality therefore gives

$$V(t) \leq V(0)e^{-\delta t} + \frac{C_2}{\delta}(1 - e^{-\delta t}) \leq M_V, \quad (3.10)$$

where $M_V = \max\{V(0), C_2/\delta\}$. Hence, $0 \leq Y(t) \leq M_V$, and $0 \leq W(t) \leq \sqrt{M_V/\Lambda}$. Because $Y = R_n + \vartheta R_d$, and $E = W(a_0 + Y)$, it follows that $0 \leq R_n(t) \leq M_V$, $0 \leq R_d(t) \leq M_V/\vartheta$, and $0 \leq E(t) \leq \sqrt{M_V/\Lambda}(a_0 + M_V)$. The bound $0 \leq D(t) \leq 1$ follows from Lemma 3.1.

Thus, every state variable remains bounded on the maximal interval of existence. Because the vector field is locally Lipschitz on bounded subsets of the feasible region, the ODE continuation theorem excludes finite-time blow-up. Therefore, $T_{\max} = \infty$, and the solution is global and uniformly bounded. $\square$

The preceding results ensure that all subsequent equilibrium and bifurcation analyses are carried out within the positively invariant feasible region, with all solution trajectories uniformly bounded in time.

3.2. Immune-tolerant equilibrium and activation threshold

System (2.1) always admits the trivial equilibrium

$$P_0 = (0, 0, 0, 0), \quad (3.11)$$

which represents the absence of persistent autoreactive immune activation and active lesion-associated inflammation.

To characterize the local invasion threshold of autoreactive Teff cells, define

$$\mathcal{R}_A = \frac{\alpha\lambda_E}{\eta_1\eta_2}. \quad (3.12)$$

The threshold $\mathcal{R}_A = 1$ corresponds to

$$\alpha_c = \frac{\eta_1\eta_2}{\lambda_E}. \quad (3.13)$$

At P_0 , $E = D = 0$, and hence, $q(D) = 1$. The Jacobian matrix is

$$\mathbf{J}(P_0) = \begin{pmatrix} -(\mu_n + \xi) & 0 & \frac{\alpha\beta}{\eta_1} & 0 \\ c\xi & -\mu_d & 0 & 0 \\ 0 & 0 & \frac{\alpha\lambda_E}{\eta_1} - \eta_2 & 0 \\ 0 & 0 & \frac{\rho_E}{K_E} & -\rho_R \end{pmatrix}. \quad (3.14)$$

Its eigenvalues are $-(\mu_n + \xi)$, $-\mu_d$, $\eta_2(\mathcal{R}_A - 1)$, $-\rho_R$. Hence, P_0 is locally asymptotically stable for $\mathcal{R}_A < 1$ and unstable for $\mathcal{R}_A > 1$. At $\mathcal{R}_A = 1$, equivalently $\alpha = \alpha_c$, the equilibrium is nonhyperbolic with one zero eigenvalue.

An important feature of the lesion-feedback system is that local stability of P_0 does not necessarily imply global convergence to immune tolerance. Strong lesion-mediated feedback may permit positive equilibria for $\alpha < \alpha_c$. A sufficient condition ensuring global stability of P_0 is given next.

Theorem 3.2. *If*

$$(1 + \kappa)\mathcal{R}_A < 1, \quad (3.15)$$

then the immune-tolerant equilibrium P_0 is globally asymptotically stable in Ω .

Proof. Because $0 \leq D \leq 1$, we have $q(D) = 1 + \kappa D \leq 1 + \kappa$, and $\eta_1 + \sigma_1 S \geq \eta_1$. Therefore,

$$\dot{E} \leq \left[\frac{\alpha\lambda_E(1 + \kappa)}{\eta_1} - \eta_2 \right] E.$$

Under Condition (3.15), define

$$\gamma = \eta_2 - \frac{\alpha\lambda_E(1 + \kappa)}{\eta_1} = \eta_2[1 - (1 + \kappa)\mathcal{R}_A] > 0.$$

It follows that $0 \leq E(t) \leq E_0 e^{-\gamma t}$, and hence, $E(t) \rightarrow 0$, and $E \in L^1(0, \infty)$.

For R_n , write $\dot{R}_n + A_n R_n = F(t)$, where $A_n = \mu_n + \xi$, and

$$F(t) = \frac{\alpha q(D(t))(\pi_3 E(t) + \beta)E(t)}{\eta_1 + \sigma_1 S(t)}.$$

The exponential estimate for E gives

$$0 \leq F(t) \leq \frac{\alpha(1+\kappa)}{\eta_1} [\pi_3 E_0^2 e^{-2\gamma t} + \beta E_0 e^{-\gamma t}],$$

so $F(t) \rightarrow 0$, and $F \in L^1(0, \infty)$. The variation-of-constants formula then implies $R_n(t) \rightarrow 0$.

Similarly,

$$R_d(t) = R_{d0} e^{-\mu_d t} + c\xi \int_0^t e^{-\mu_d(t-s)} R_n(s) ds,$$

and therefore, $R_d(t) \rightarrow 0$.

Finally, because $E/(K_E + E) \leq E/K_E$, and $1 - D \leq 1$, $\dot{D} \leq E\rho_E/K_E - \rho_R D$. Comparison gives

$$D(t) \leq D_0 e^{-\rho_R t} + \frac{\rho_E}{K_E} \int_0^t e^{-\rho_R(t-s)} E(s) ds,$$

and hence, $D(t) \rightarrow 0$.

Consequently, $\lim_{t \rightarrow \infty} X(t) = P_0$. Because Condition (3.15) also implies $\mathcal{R}_A < 1$, the equilibrium is locally asymptotically stable. Therefore, P_0 is globally asymptotically stable in Ω . $\square$

3.3. Scalar characterization of positive equilibria

We next characterize the positive equilibria of System (2.1). The structure of the two Treg equations allows the four-dimensional equilibrium problem to be reduced to a single scalar relation.

Define

$$A_n = \mu_n + \xi, \quad \chi = 1 + \frac{dc\xi}{\mu_d}. \quad (3.16)$$

Let $P^* = (R_n^*, R_d^*, E^*, D^*)$ be a positive equilibrium. From the R_d equation,

$$R_d^* = \frac{c\xi}{\mu_d} R_n^*, \quad S^* = \chi R_n^*. \quad (3.17)$$

The lesion equilibrium condition gives

$$D^* = \psi(E^*) := \frac{\rho_E E^*}{\rho_R K_E + (\rho_R + \rho_E) E^*}. \quad (3.18)$$

Because $E^* > 0$, the equilibrium condition for the Teff equation becomes

$$\frac{\alpha \lambda_E [1 + \kappa \psi(E^*)]}{\eta_1 + \sigma_1 S^*} = \eta_2 + \sigma_3 S^*. \quad (3.19)$$

Using (3.19) in the equilibrium condition for R_n and $R_n^* = S^*/\chi$, we obtain

$$(\pi_3 E^* + \beta) E^* = \frac{\lambda_E A_n S^*}{\chi(\eta_2 + \sigma_3 S^*)}. \quad (3.20)$$

For each $S > 0$, Eq (3.20) has the unique positive solution

$$E(S) = \frac{-\beta + \sqrt{\beta^2 + \frac{4\pi_3\lambda_E A_n S}{\chi(\eta_2 + \sigma_3 S)}}}{2\pi_3}. \quad (3.21)$$

The corresponding lesion level is $D(S) = \psi(E(S))$. Substituting these expressions into (3.19) gives the scalar equilibrium branch function

$$\Phi_\kappa(S) = \frac{(\eta_1 + \sigma_1 S)(\eta_2 + \sigma_3 S)}{\lambda_E[1 + \kappa\psi(E(S))]} \quad (3.22)$$

Theorem 3.3. *The positive equilibria of System (2.1) are in one-to-one correspondence with the positive solutions of*

$$\alpha = \Phi_\kappa(S), \quad S > 0. \quad (3.23)$$

For each positive solution S^* of (3.23), the corresponding equilibrium is uniquely reconstructed as

$$R_n^* = \frac{S^*}{\chi}, \quad R_d^* = \frac{c\xi S^*}{\mu_d \chi}, \quad E^* = E(S^*), \quad D^* = \psi(E(S^*)). \quad (3.24)$$

Proof. Every positive equilibrium satisfies Eqs (3.17)–(3.19). Eliminating R_n^* and R_d^* gives (3.20), whose positive solution is uniquely given by (3.21). The lesion component is then uniquely determined by (3.18), and (3.19) is equivalent to $\alpha = \Phi_\kappa(S)$.

Conversely, given a positive solution S^* of (3.23), Eqs (3.21), (3.18), and (3.24) uniquely determine all components of the equilibrium. Direct substitution verifies that these expressions satisfy System (2.1). $\square$

Theorem 3.3 therefore reduces the multiplicity problem for the four-dimensional system to the geometry of the scalar function $\Phi_\kappa(S)$.

3.4. Lesion-feedback-induced backward bending

We now determine how lesion-mediated feedback modifies the positive equilibrium branch.

When $\kappa = 0$, Eq (3.22) becomes

$$\Phi_0(S) = \frac{(\eta_1 + \sigma_1 S)(\eta_2 + \sigma_3 S)}{\lambda_E}. \quad (3.25)$$

Because

$$\Phi'_0(S) = \frac{\sigma_1(\eta_2 + \sigma_3 S) + \sigma_3(\eta_1 + \sigma_1 S)}{\lambda_E} > 0, \quad S \geq 0,$$

the branch is strictly increasing. Moreover, $\Phi_0(0) = \eta_1\eta_2/\lambda_E = \alpha_c$. Thus, without lesion-mediated feedback, a positive equilibrium exists only for $\alpha > \alpha_c$.

The possibility of a backward branch therefore arises from the feedback contribution in the denominator of $\Phi_\kappa(S)$.

For the local analysis near $S = 0$, we continuously extend the functions $E(S)$, $D(S) = \psi(E(S))$, and $\Phi_\kappa(S)$ to $S = 0$ by setting $E(0) = 0$, $D(0) = 0$, and $\Phi_\kappa(0) = \eta_1\eta_2/\lambda_E = \alpha_c$. Differentiating (3.20) at

$S = 0$ gives $E'(0) = \lambda_E A_n / (\chi \beta \eta_2)$, and (3.18) yields $\psi'(0) = \rho_E / (\rho_R K_E)$. Hence, the local amplification along the equilibrium sensitivity chain $S \mapsto E(S) \mapsto D(S) \mapsto q(D(S))$ is $\kappa \psi'(0) E'(0) = \kappa \rho_E \lambda_E A_n / (\rho_R K_E \chi \beta \eta_2)$.

This motivates the dimensionless lesion-feedback number

$$\mathcal{F} = \frac{\frac{\kappa \rho_E \lambda_E A_n}{\rho_R K_E \chi \beta \eta_2}}{\frac{\sigma_1}{\eta_1} + \frac{\sigma_3}{\eta_2}}. \quad (3.26)$$

Thus, $\mathcal{F}$ compares the local lesion-mediated amplification with the combined regulatory contribution of the immune subsystem.

A direct differentiation of (3.22) at $S = 0$ gives

$$\Phi'_\kappa(0) = \alpha_c \left(\frac{\sigma_1}{\eta_1} + \frac{\sigma_3}{\eta_2} \right) (1 - \mathcal{F}). \quad (3.27)$$

Consequently,

$$\mathcal{F} > 1 \iff \Phi'_\kappa(0) < 0. \quad (3.28)$$

Thus, when lesion-mediated amplification exceeds the local regulatory effect, the positive-equilibrium branch initially bends toward $\alpha < \alpha_c$.

Theorem 3.4. *Suppose that $\mathcal{F} > 1$. Then, the equilibrium branch function $\Phi_\kappa(S)$ possesses at least one interior global minimizer $S_{SN} > 0$. Choose*

$$S_{SN} \in \arg \min_{S \geq 0} \Phi_\kappa(S), \quad (3.29)$$

and define

$$\alpha_{SN} = \Phi_\kappa(S_{SN}) = \min_{S \geq 0} \Phi_\kappa(S). \quad (3.30)$$

Then, $\alpha_{SN} < \alpha_c$.

Moreover:

- i If $\alpha < \alpha_{SN}$, System (2.1) has no positive equilibrium.
- ii At $\alpha = \alpha_{SN}$, System (2.1) has at least one positive equilibrium corresponding to $S = S_{SN}$.
- iii If $\alpha_{SN} < \alpha < \alpha_c$, System (2.1) possesses at least two distinct positive equilibria.
- iv Because S_{SN} is an interior minimizer, $\Phi'_\kappa(S_{SN}) = 0$. If, in addition, $\Phi''_\kappa(S_{SN}) > 0$, then (S_{SN}, α_{SN}) is a nondegenerate fold point of the scalar equilibrium relation $\alpha = \Phi_\kappa(S)$.

Proof. By (3.28), the condition $\mathcal{F} > 1$ implies $\Phi'_\kappa(0) < 0$. Hence, there exists $\delta > 0$ such that $\Phi_\kappa(S) < \Phi_\kappa(0) = \alpha_c$ for $0 < S < \delta$. Therefore, $\inf_{S \geq 0} \Phi_\kappa(S) < \alpha_c$.

Next, from (3.21), $S/(\eta_2 + \sigma_3 S) \rightarrow 1/\sigma_3$ as $S \rightarrow \infty$. Thus, $E(S)$ remains bounded and approaches a finite positive limit, and consequently, $\psi(E(S))$ remains bounded in $[0, 1)$. Moreover, $(\eta_1 + \sigma_1 S)(\eta_2 + \sigma_3 S) \sim \sigma_1 \sigma_3 S^2$ as $S \rightarrow \infty$. Hence, $\Phi_\kappa(S) \rightarrow +\infty$ as $S \rightarrow \infty$.

Because Φ_κ is continuous on $[0, \infty)$ and tends to $+\infty$ as $S \rightarrow \infty$, it attains a global minimum on $[0, \infty)$. Because $\Phi'_\kappa(0) < 0$, the minimum cannot occur at $S = 0$. Therefore, at least one interior global minimizer $S_{SN} > 0$ exists, and $\alpha_{SN} = \Phi_\kappa(S_{SN}) < \Phi_\kappa(0) = \alpha_c$.

If $\alpha < \alpha_{SN}$, then $\Phi_\kappa(S) \geq \alpha_{SN} > \alpha$ for all $S \geq 0$, so Eq (3.23) has no positive solution. By Theorem 3.3, System (2.1) therefore has no positive equilibrium.

At $\alpha = \alpha_{SN}$, $S = S_{SN} > 0$ satisfies $\Phi_\kappa(S_{SN}) = \alpha_{SN}$, and hence, by Theorem 3.3, corresponds to a positive equilibrium of System (2.1).

Now, let $\alpha_{SN} < \alpha < \alpha_c$. Because $\Phi_\kappa(0) = \alpha_c > \alpha$, and $\Phi_\kappa(S_{SN}) = \alpha_{SN} < \alpha$, the intermediate value theorem yields at least one $S_1 \in (0, S_{SN})$ such that $\Phi_\kappa(S_1) = \alpha$. Furthermore, because $\Phi_\kappa(S_{SN}) < \alpha$, and $\Phi_\kappa(S) \rightarrow +\infty$ as $S \rightarrow \infty$, the intermediate value theorem gives at least one $S_2 > S_{SN}$ satisfying $\Phi_\kappa(S_2) = \alpha$. Thus, $S_1 \neq S_2$, and Theorem 3.3 implies that they correspond to at least two distinct positive equilibria of System (2.1).

Finally, because $S_{SN} > 0$ is an interior minimizer of the differentiable function Φ_κ , $\Phi'_\kappa(S_{SN}) = 0$. Define $F(S, \alpha) = \alpha - \Phi_\kappa(S)$. At (S_{SN}, α_{SN}) , $F(S_{SN}, \alpha_{SN}) = 0$, and $F_S(S_{SN}, \alpha_{SN}) = -\Phi'_\kappa(S_{SN}) = 0$. If, in addition, $\Phi''_\kappa(S_{SN}) > 0$, then $F_{SS}(S_{SN}, \alpha_{SN}) = -\Phi''_\kappa(S_{SN}) \neq 0$, and $F_\alpha(S_{SN}, \alpha_{SN}) = 1 \neq 0$. Therefore, the standard nondegeneracy and transversality conditions for a fold of the scalar equilibrium relation are satisfied. Hence, (S_{SN}, α_{SN}) is a nondegenerate fold point of $\alpha = \Phi_\kappa(S)$. $\square$

Theorem 3.4 identifies the principal structural effect of lesion-mediated feedback.

The theorem establishes a lower bound on equilibrium multiplicity, not exact multiplicity, branch stability, or a full-system nondegenerate saddle-node without further hypotheses. In particular, a minimum of Φ_κ may be degenerate. The full-system criteria in Theorem 4.1 and the Jacobian tests are additional requirements.

For $\kappa = 0$, the branch is monotone and cannot extend below the immune-activation threshold α_c . When $\mathcal{F} > 1$, the local branch direction reverses, and the equilibrium curve extends into the region $\alpha < \alpha_c$, where the immune-tolerant equilibrium remains locally stable. The interval $\alpha_{SN} < \alpha < \alpha_c$ therefore provides the parameter range in which multiple equilibria can occur.

The condition $\mathcal{F} > 1$ determines the onset of backward bending of the equilibrium branch, but it does not by itself determine the stability of the positive equilibria. The stability of the lower and upper positive branches, the nondegeneracy of the saddle-node bifurcation in the full four-dimensional vector field, and the occurrence of Hopf bifurcation are analyzed in the following section.

4. Stability of positive equilibria and local bifurcation analysis

This section analyzes the local stability and bifurcation structure of the positive equilibria of System (2.1). We first derive the Jacobian matrix and the corresponding Routh–Hurwitz stability conditions. The local behavior of the backward positive branch near the immune-activation threshold α_c is then characterized by center-manifold reduction. Finally, criteria for nondegenerate saddle-node and Hopf bifurcations are established for the full four-dimensional system.

4.1. Jacobian matrix and local stability

At an arbitrary state, define $Q = 1 + \kappa D$ and $L = \eta_1 + \sigma_1 S$, where $S = R_n + dR_d$. Using the state ordering $X = (R_n, R_d, E, D)^\top$, the Jacobian matrix of System (2.1) is

$$\mathbf{J}(X) = \begin{pmatrix} j_{11} & j_{12} & j_{13} & j_{14} \\ c\xi & -\mu_d & 0 & 0 \\ j_{31} & j_{32} & j_{33} & j_{34} \\ 0 & 0 & j_{43} & j_{44} \end{pmatrix}, \quad (4.1)$$

where

$$\begin{aligned} j_{11} &= -\frac{\alpha Q \sigma_1 (\pi_3 E + \beta) E}{L^2} - (\mu_n + \xi), \quad j_{12} = -\frac{\alpha Q \sigma_1 d (\pi_3 E + \beta) E}{L^2}, \quad j_{13} = \frac{\alpha Q (2\pi_3 E + \beta)}{L}, \\ j_{14} &= \frac{\alpha \kappa (\pi_3 E + \beta) E}{L}, \quad j_{31} = E \left(-\frac{\alpha \lambda_E Q \sigma_1}{L^2} - \sigma_3 \right), \quad j_{32} = d j_{31}, \quad j_{33} = \frac{\alpha \lambda_E Q}{L} - \sigma_3 S - \eta_2, \\ j_{34} &= \frac{\alpha \lambda_E \kappa E}{L}, \quad j_{43} = \rho_E \frac{K_E}{(K_E + E)^2} (1 - D), \quad j_{44} = -\rho_E \frac{E}{K_E + E} - \rho_R. \end{aligned}$$

At a positive equilibrium P^* , Eq (3.19) gives $j_{33} = 0$. The entries j_{14} , j_{34} , and j_{43} describe the closed lesion-immune feedback and directly couple lesion dynamics to the local stability of the immune subsystem. When $\kappa = 0$, $j_{14} = j_{34} = 0$, and lesion activity becomes a downstream response without feeding back into immune activation.

Let the characteristic polynomial at a positive equilibrium be

$$P(\lambda) = \det(\lambda I - \mathbf{J}(P^*)) = \lambda^4 + B_1 \lambda^3 + B_2 \lambda^2 + B_3 \lambda + B_4. \quad (4.2)$$

For compactness, write $a = j_{11}$, $b = j_{12}$, $c_1 = j_{13}$, $h = j_{14}$, $e = c\xi$, $f = -\mu_d$, $g = j_{31}$, $k = j_{32}$, $m = j_{34}$, $n = j_{43}$, and $p = j_{44}$. Then,

$$\begin{aligned} B_1 &= -a - f - p, \quad B_2 = af + ap - be - c_1 g + fp - mn, \\ B_3 &= -afp + amn + bep - c_1 ek + c_1 fg + c_1 gp + fmn - ghn, \\ B_4 &= -afmn + bemn + c_1 ekp - c_1 fgp - ehkn + fghn. \end{aligned}$$

The feedback couplings $h = j_{14}$, $m = j_{34}$, and $n = j_{43}$ enter the higher-order coefficients of the characteristic polynomial and therefore modify both the stability boundary and the Hopf bifurcation condition.

Define the Hurwitz determinants $\Delta_2 = B_1 B_2 - B_3$, $\Delta_3 = B_1 B_2 B_3 - B_3^2 - B_1^2 B_4$.

Proposition 4.1. *A positive equilibrium P^* is locally asymptotically stable if $B_i > 0$ ($i = 1, 2, 3, 4$), $\Delta_2 > 0$, $\Delta_3 > 0$.*

Proof. The conclusion follows directly from the Routh–Hurwitz criterion applied to the quartic characteristic polynomial (4.2). $\square$

4.2. Local structure near the immune-activation threshold

Section 3 shows that when $\mathcal{F} > 1$, the positive-equilibrium branch extends from the immune-tolerance threshold (P_0, α_c) toward the region $\alpha < \alpha_c$. We now determine the local stability of this backward branch.

At $\alpha = \alpha_c$, the Jacobian matrix at P_0 has a simple zero eigenvalue, and the remaining three eigenvalues have negative real parts. Let $\mu = \alpha - \alpha_c$, and choose $z = E$ as the center variable. Near (P_0, α_c) , the center manifold admits the local representation

$$R_n = \frac{\beta\eta_2}{\lambda_E A_n} z + O(z^2 + |\mu|z), \quad R_d = \frac{c\xi}{\mu_d} R_n + O(z^2 + |\mu|z), \quad D = \frac{\rho_E}{\rho_R K_E} z + O(z^2 + |\mu|z),$$

where $A_n = \mu_n + \xi$.

Substitution into the E equation yields the reduced normal form

$$\dot{z} = z \left[\frac{\lambda_E}{\eta_1} \mu + b_F z + O(\mu^2 + |\mu|z + z^2) \right], \quad (4.3)$$

where

$$b_F = \frac{\eta_2 \kappa \rho_E}{\rho_R K_E} - \frac{\chi \beta \eta_2}{\lambda_E A_n} \left(\frac{\eta_2 \sigma_1}{\eta_1} + \sigma_3 \right).$$

Using the definition of the lesion-feedback number $\mathcal{F}$ in (3.26), direct simplification gives $b_F > 0 \iff \mathcal{F} > 1$.

Proposition 4.2. *If $\mathcal{F} > 1$, then the small positive equilibrium branch emerging from (P_0, α_c) toward $\alpha < \alpha_c$ is locally unstable.*

Proof. For a nonzero equilibrium of the reduced Eq (4.3), $z_* = -\mu \lambda_E / (\eta_1 b_F) + O(\mu^2)$. When $\mathcal{F} > 1$, we have $b_F > 0$. Thus, $z_* > 0$ requires $\mu < 0$, confirming that the positive branch emerges toward $\alpha < \alpha_c$.

Let the right-hand side of (4.3) be $h(z, \mu)$. The eigenvalue in the center direction is $\lambda_c = \partial h / \partial z|_{z=z_*} = -\mu \lambda_E / \eta_1 + O(\mu^2)$. Because $\mu < 0$, it follows that $\lambda_c > 0$ for sufficiently small $|\mu|$. Hence, the small positive equilibrium possesses an unstable direction and is locally unstable. $\square$

Proposition 4.2 complements the branch geometry derived in Section 3. The positive branch entering the region $\alpha < \alpha_c$ from the immune-tolerance threshold is unstable. The second positive branch created after the fold may instead become stable, thereby allowing coexistence with the stable tolerance equilibrium.

4.3. Nondegenerate saddle-node bifurcation

Theorem 3.4 established the existence of an interior minimum of the scalar equilibrium relation $F(S, \alpha) = \alpha - \Phi_\kappa(S) = 0$ when $\mathcal{F} > 1$. Under the additional nondegeneracy condition $\Phi'_\kappa(S_{SN}) \neq 0$, this minimum is a fold. We now determine when it corresponds to a nondegenerate saddle-node bifurcation of the full four-dimensional vector field.

Let P_{SN} denote the positive equilibrium reconstructed from (S_{SN}, α_{SN}) .

Theorem 4.1. *Assume that $\Phi'_\kappa(S_{SN}) = 0$, $\Phi''_\kappa(S_{SN}) \neq 0$ and that the Jacobian $J(P_{SN})$ has a simple zero eigenvalue, whereas all remaining eigenvalues have nonzero real parts.*

Let v and w be the corresponding right and left zero eigenvectors, normalized by $w^\top v = 1$. If $w^\top f_\alpha(P_{SN}, \alpha_{SN}) \neq 0$, $w^\top D_X^2 f(P_{SN}, \alpha_{SN})[v, v] \neq 0$, then (P_{SN}, α_{SN}) is a nondegenerate saddle-node bifurcation point of System (2.1).

Proof. At the scalar fold, $F(S_{SN}, \alpha_{SN}) = 0$, and $F_S(S_{SN}, \alpha_{SN}) = 0$. Moreover, $F_{SS}(S_{SN}, \alpha_{SN}) = -\Phi'_k(S_{SN}) \neq 0$, $F_\alpha = 1 \neq 0$. Hence, the reduced equilibrium relation possesses a nondegenerate quadratic fold with respect to the parameter α . The assumption that $\mathbf{J}(P_{SN})$ has a simple zero eigenvalue implies that the full vector field possesses a one-dimensional center direction at the critical equilibrium. The conditions $w^\top f_\alpha \neq 0$ and $w^\top D_X^2 f[v, v] \neq 0$ are the standard transversality and quadratic nondegeneracy conditions for a saddle-node bifurcation. Therefore, the saddle-node bifurcation theorem [26] implies that the scalar fold corresponds locally to a nondegenerate saddle-node bifurcation of the four-dimensional system. $\square$

The critical value S_{SN} is determined from $\Phi'_k(S_{SN}) = 0$ with $\alpha_{SN} = \Phi_k(S_{SN})$. For $\alpha_{SN} < \alpha < \alpha_c$, locally, a nondegenerate fold generates two equilibrium branches in addition to the locally stable tolerance equilibrium. The stability of these branches is determined from the full Jacobian, and their numerical configuration is examined in Section 5.

4.4. Hopf bifurcation criterion

We next examine oscillatory instability of the positive equilibrium. For the quartic characteristic polynomial (4.2), a Hopf bifurcation occurs when a complex-conjugate pair of eigenvalues reaches the imaginary axis while the remaining pair remains in the left half-plane [26, 27].

Theorem 4.2 (Hopf bifurcation criterion). *Suppose that a smooth positive-equilibrium branch $P^*(\alpha)$ contains a critical point at $\alpha = \alpha_H$ such that $B_i(\alpha_H) > 0$, $i = 1, 2, 3, 4$, and $\Delta_2(\alpha_H) > 0$, $\Delta_3(\alpha_H) = 0$. Then, the Jacobian at the critical equilibrium possesses a pair of purely imaginary eigenvalues $\lambda_{1,2} = \pm i\omega_0$, $\omega_0 = \sqrt{B_3(\alpha_H)/B_1(\alpha_H)}$. The remaining two eigenvalues have negative real parts.*

Define the characteristic polynomial along the positive-equilibrium branch by

$$\widehat{P}(\lambda, \alpha) = \det[\lambda I - \mathbf{J}(P^*(\alpha), \alpha)]. \quad (4.4)$$

If, in addition,

$$\nu_H = \operatorname{Re} \left[-\frac{\partial_\alpha \widehat{P}(i\omega_0, \alpha_H)}{\partial_\lambda \widehat{P}(i\omega_0, \alpha_H)} \right] \neq 0, \quad (4.5)$$

where the α -derivative includes the dependence of the equilibrium $P^*(\alpha)$ on α , then System (2.1) undergoes a Hopf bifurcation at $\alpha = \alpha_H$.

Proof. At the critical equilibrium, substitute $\lambda = i\omega$ into (4.2). Separating real and imaginary parts gives $\omega^4 - B_2\omega^2 + B_4 = 0$, $-B_1\omega^3 + B_3\omega = 0$. For a nonzero frequency, $\omega^2 = B_3/B_1$, so $\omega_0 = \sqrt{B_3/B_1}$. Substitution into the real part yields $B_1B_2B_3 - B_3^2 - B_1^2B_4 = 0$, which is precisely $\Delta_3 = 0$.

At this point, the characteristic polynomial factorizes as $P(\lambda) = (\lambda^2 + \omega_0^2)(\lambda^2 + B_1\lambda + B_1B_4/B_3)$. Because $B_1 > 0$, $B_3 > 0$, and $B_4 > 0$, the two roots of the second factor have negative real parts.

Finally, Condition (4.5) ensures that the critical complex-conjugate pair crosses the imaginary axis with nonzero speed as α varies. The classical Hopf bifurcation theorem therefore yields a local family of periodic solutions near $\alpha = \alpha_H$. $\square$

4.5. First Lyapunov coefficient

The Hopf criterion establishes the existence of periodic solutions but does not determine their local stability. To distinguish between supercritical and subcritical Hopf bifurcations, we compute the first Lyapunov coefficient.

Let $P_H = P^*(\alpha_H)$ denote the Hopf equilibrium and translate P_H to the origin. The vector field can be expanded as

$$\dot{x} = A_H x + \frac{1}{2}\mathcal{B}(x, x) + \frac{1}{6}\mathcal{C}(x, x, x) + O(\|x\|^4), \quad (4.6)$$

where $A_H = \mathbf{J}(P_H)$, and $\mathcal{B}$ and $\mathcal{C}$ denote the symmetric second- and third-order multilinear forms associated with the Taylor expansion.

Let $q, p \in \mathbb{C}^4$ satisfy

$$A_H q = i\omega_0 q, \quad A_H^\top p = -i\omega_0 p, \quad \langle p, q \rangle = \bar{p}^\top q = 1. \quad (4.7)$$

The first Lyapunov coefficient is

$$l_1 = \frac{1}{2\omega_0} \operatorname{Re} \left[\langle p, \mathcal{C}(q, q, \bar{q}) \rangle - 2 \langle p, \mathcal{B}(q, A_H^{-1} \mathcal{B}(q, \bar{q})) \rangle + \langle p, \mathcal{B}(\bar{q}, (2i\omega_0 I - A_H)^{-1} \mathcal{B}(q, q)) \rangle \right]. \quad (4.8)$$

The sign of l_1 determines the local Hopf type. If $l_1 < 0$, the Hopf bifurcation is supercritical, and the bifurcating small-amplitude periodic orbit is stable. If $l_1 > 0$, the bifurcation is subcritical, and the corresponding small-amplitude periodic orbit is unstable.

The numerical evaluation of the saddle-node conditions, Hopf threshold, transversality coefficient, and first Lyapunov coefficient for the working parameter set is presented in Section 5.

5. Numerical results

This section numerically illustrates the analytical results obtained in Sections 3 and 4 and examines the dynamical consequences of lesion-mediated feedback. We first specify the working parameter regime and computational procedure and then compare the feedback-free and feedback-coupled systems. The global equilibrium structure, equilibrium bistability, hysteresis-like switching, and Hopf-induced immune–lesion oscillations are subsequently investigated.

5.1. Parameter setting and computational methods

The numerical analysis serves two related purposes. First, the feedback-free immune subsystem is compared with its counterpart in the previously established Teff–Treg framework. Second, a fixed working parameter set is used to isolate the qualitative changes generated by closing the lesion–immune feedback loop.

The immune-related parameters are based primarily on parameter regimes used in earlier autoimmune models [17, 18, 20]. In the original formulation, $\eta_1 = b_1 + \mu_A$, and $\eta_2 = b_3 + \mu_E$. Using the reference values $b_1 = b_3 = 0.25$ and $\mu_A = \mu_E = 0.20$ gives $\eta_1 = \eta_2 = 0.45$. The corresponding feedback-free immune-activation threshold is $\alpha_c^{\text{ref}} = \eta_1 \eta_2 / \lambda_E = 2.025 \times 10^{-4}$, which is consistent with the corresponding transition threshold reported for the parent autoimmune framework [18, 19]. This agreement provides a reference benchmark for the reduced immune subsystem and its numerical implementation.

For the lesion-feedback computations, the working parameter set is listed in Table 2. Most immune-related parameters retain values inherited from the reference Teff–Treg regime. In this working regime, η_2 is treated as an effective aggregate Teff-loss parameter and is set independently to $\eta_2 = 0.25$ rather than reconstructed from the original decomposition $\eta_2 = b_3 + \mu_E$. The parameters ρ_E , K_E , ρ_R , and κ are phenomenological quantities introduced to examine lesion activation, recovery, and feedback. These parameters are not estimates obtained from longitudinal patient-specific data.

Table 2. Parameter values and status used in the numerical analysis.

Parameter	Value	Unit	Status	Main reference/role
π_3	0.0256	$\text{C}^{-1}\text{T}^{-1}$	Literature	[18, 20]
β	200	T^{-1}	Literature	[18, 20]
λ_E	1000	T^{-1}	Literature	[18, 20]
σ_1	3×10^{-6}	$\text{C}^{-1}\text{T}^{-1}$	Literature	[18, 20]
σ_3	3×10^{-6}	$\text{C}^{-1}\text{T}^{-1}$	Literature	[18, 20]
η_1	0.45	T^{-1}	Literature	$b_1 + \mu_A$
η_2	0.25	T^{-1}	Working	Effective Teff loss
μ_n	0.10	T^{-1}	Literature	[18]
μ_d	0.20	T^{-1}	Literature	[18]
ξ	0.025	T^{-1}	Literature	[18]
c	8	1	Literature	[18]
d	2	1	Literature	[18]
ρ_E	0.08	T^{-1}	Phenomenological	Lesion activation
K_E	1.5×10^4	C	Phenomenological	Half-saturation scale
ρ_R	0.03	T^{-1}	Phenomenological	Lesion recovery
κ	1.0	1	Phenomenological	Lesion–immune feedback

For this working parameter set, $\alpha_c = \eta_1 \eta_2 / \lambda_E = 1.125 \times 10^{-4}$. All thresholds reported below should therefore be interpreted relative to this working parameter regime rather than as patient-specific clinical thresholds.

Time-domain simulations were performed using the DOP853 solver implemented in SciPy [28] with relative and absolute tolerances of 10^{-9} and 10^{-11} , respectively. Positive equilibria were computed from the scalar equilibrium relation (3.23). Their local stability was independently evaluated from the eigenvalues of the full four-dimensional Jacobian $\mathbf{J}(P^*)$. Here, “continuation” means scalar branch reconstruction and parameter scanning, not pseudo-arclength continuation in a dedicated package. For Figures 1, 2, 5, and 6, positive roots of $\Phi_\kappa(S) - \alpha$ are bracketed on $\{0\} \cup \text{logspace}(-8, 9, 7000)$ and refined by Brent’s method. The working fold is obtained by bounded minimization on $[10^{-10}, 10^7]$ and independently checked using $\Phi'_\kappa = 0$. The upper branch uses the largest detected positive root. Eigenvalues of the full analytic Jacobian determine sampled stability; the working Hopf crossing is refined on $[3 \times 10^{-4}, 4 \times 10^{-4}]$ with absolute α tolerance 10^{-15} . Numerical solver precision is not biological parameter precision.

The lower and upper branches use 180 and 420 evenly spaced activation values, respectively, over the plotted intervals; the spectral plot uses 240 values on $[1.5, 4.5] \times 10^{-4}$. For Figure 3, κ ranges from 0

to 2 in steps of 0.01. Zeros of Φ'_κ are bracketed with 6000 logarithmic S values on $[10^{-6}, 10^6]$, plus zero. Hopf candidates are bracketed by $\Delta_3 = 0$ on 1501 logarithmic upper-branch values up to $S = 10^6$, refined with absolute/relative S tolerances $10^{-8}/10^{-13}$ and accepted only when $B_i > 0$, $\Delta_2 > 0$, one nonzero imaginary pair has real parts smaller than 10^{-8} , and the other eigenvalues are negative. Transverse crossings are checked by centered differences in S with the increment $\max(10^{-5}S, 0.01)$. Fifty-one interior upper-branch samples per bistable slice have negative spectral abscissae. These finite-domain checks support the plotted local stability regions but do not prove exact multiplicity for all parameters or exclude other attractors.

The supplementary scripts save branch/trajectory data, boundary tables, spectral checks, and software versions. All time integrations use DOP853 with the above tolerances. Figure-specific intervals, step limits, initial conditions, and plotting operations are stated in the captions. The independently recomputed fold has one zero eigenvalue and negative remaining eigenvalues; normalized center-direction projections verify the two nonzero saddle-node coefficients. The Hopf coefficient is recomputed using symbolic second and third derivatives in normalized coordinates, $\|q\|_2 = 1$ and $\langle p, q \rangle = 1$.

5.2. Effect of closing the lesion-immune feedback loop

We first compare the system dynamics for the same working immune parameter set with $\kappa = 0$ and $\kappa = 1$.

When $\kappa = 0$, lesion activity does not feed back into the first three equations. The immune subsystem therefore reduces to the baseline Teff–Treg system, although D may still respond passively to changes in E . The scalar equilibrium relation becomes $\alpha = \Phi_0(S)$, which is strictly increasing by the analysis in Section 3.4. Consequently, no saddle-node fold is generated in the feedback-free system, and the positive equilibrium branch does not extend below α_c .

This behavior is consistent with the qualitative structure of earlier Teff–Treg models, in which recurrent dynamics arise mainly through Hopf-related mechanisms [18–20].

When $\kappa = 1$, the factor $q(D) = 1 + D$ closes the lesion-immune feedback loop. As shown in Figure 1, the corresponding equilibrium function $\Phi_1(S)$ initially decreases from $S = 0$ before turning upward. For the working parameter set, $\mathcal{F} = 7.94 > 1$, which satisfies the backward-bending criterion established in Theorem 3.4.

Numerically, the minimum of the branch occurs at $S_{SN} = 5.60 \times 10^3$, $\alpha_{SN} = 9.47 \times 10^{-5}$. Hence, $\alpha_{SN} < \alpha_c$. The corresponding equilibrium is $P_{SN} = (1.87 \times 10^3, 1.87 \times 10^3, 3.12 \times 10^3, 0.315)$. Moreover, $\Phi'_\kappa(S_{SN}) = 3.37 \times 10^{-13} > 0$. The Jacobian $\mathbf{J}(P_{SN})$ possesses a simple zero eigenvalue, whereas the remaining eigenvalues are approximately -0.220 and $-0.0751 \pm 0.0364i$ and therefore have negative real parts. Let v and w denote the corresponding right and left zero eigenvectors, normalized by $\|v\|_2 = 1$ and $w^\top v = 1$. Numerically, $w^\top f_\alpha(P_{SN}, \alpha_{SN}) \approx 9.01 \times 10^6 \neq 0$, and $w^\top D_{X,\alpha}^2 f(P_{SN}, \alpha_{SN})[v, v] \approx -7.83 \times 10^{-6} \neq 0$. Thus, the transversality and quadratic nondegeneracy conditions in Theorem 4.1 are satisfied, confirming a nondegenerate saddle-node bifurcation of the four-dimensional system.

The comparison identifies the principal structural effect of closing the feedback loop. Without lesion-mediated feedback, the positive-equilibrium branch does not enter the region in which the tolerance equilibrium remains stable. With feedback, the branch bends toward $\alpha < \alpha_c$, creating a parameter interval in which a stable high-activity equilibrium can coexist with the stable tolerance

state. The new mechanism therefore concerns *equilibrium bistability generated by feedback-induced deformation of the positive-equilibrium branch* rather than the multiple-periodic-orbit coexistence reported for earlier reduced Teff–Treg models [19,20].

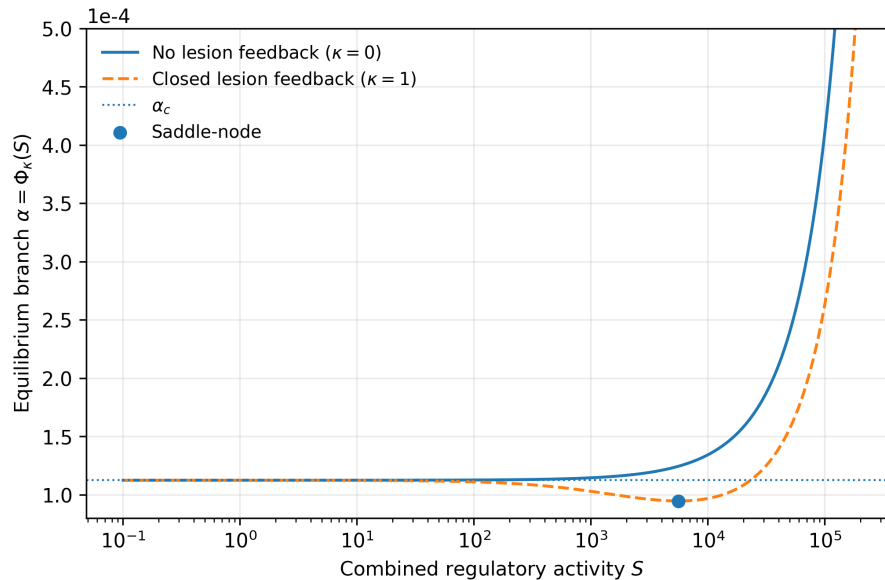


Figure 1. Computed scalar equilibrium curves for $\kappa = 0, 1$ on 1200 logarithmic S values from 10^{-1} to $10^{5.3}$. The working fold is numerically located; backward bending is guaranteed analytically by $\mathcal{F} > 1$, whereas positive-branch stability requires separate Jacobian tests.

5.3. Global equilibrium and bifurcation structure

Figure 2 shows the equilibrium Teff level E^* as the control parameter α is varied. For the working parameter set, the three critical values satisfy

$$\alpha_{SN} = 9.47 \times 10^{-5} < \alpha_c = 1.125 \times 10^{-4} < \alpha_H = 3.43 \times 10^{-4}. \quad (5.1)$$

This ordering divides the equilibrium diagram into four dynamical regimes.

For $0 < \alpha < \alpha_{SN}$, no positive equilibrium exists, and the tolerance equilibrium $P_0 = (0, 0, 0, 0)$ is locally asymptotically stable. For $\alpha_{SN} < \alpha < \alpha_c$, two positive equilibria coexist with P_0 . Numerical eigenvalue continuation shows that the lower positive branch remains unstable throughout $\alpha_{SN} < \alpha < \alpha_c$, consistent with Proposition 4.2 near α_c , whereas the upper positive branch is locally asymptotically stable. Hence, this interval contains two stable attractors: the immune-tolerant equilibrium and a persistent high-activity positive equilibrium. At $\alpha = \alpha_c$, the low-activity positive branch meets the immune-tolerant equilibrium at the immune-activation threshold. For $\alpha_c < \alpha < \alpha_H$, the tolerance equilibrium is unstable, whereas the high-activity positive equilibrium remains locally asymptotically stable. Finally, at $\alpha = \alpha_H$, a complex-conjugate pair of eigenvalues of the high-activity equilibrium crosses the imaginary axis. The Hopf conditions established in Theorem 4.2 are satisfied, and the negative first Lyapunov coefficient shows that the bifurcation is supercritical. A stable periodic orbit therefore emerges for α slightly above α_H .

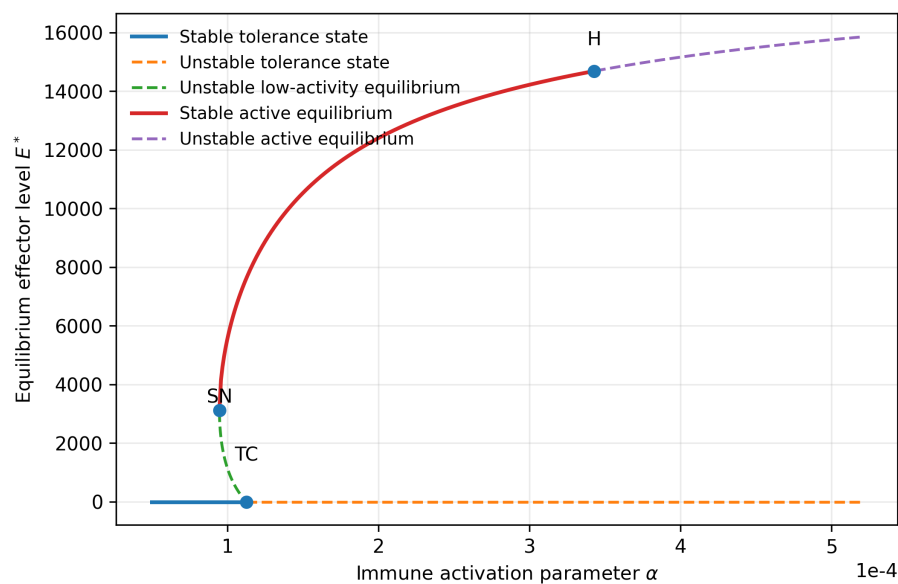


Figure 2. Numerically reconstructed equilibria at $\kappa = 1$. Solid and dashed curves denote negative and positive sampled spectral abscissa, respectively; neutral endpoints are marked SN, α_c , and H. No periodic-orbit branch is plotted. The computed bistable interval concerns this working parameter set; Theorem 3.4 alone gives at least two positive equilibria without their stability.

5.4. Two-parameter bifurcation structure in the (α, κ) plane

The one-parameter bifurcation analysis above was performed for the working feedback strength $\kappa = 1$. To determine how lesion-mediated feedback reorganizes the bifurcation structure more generally, we next continue the saddle-node and Hopfpoints in the two-parameter plane (α, κ) .

Figure 3 shows the resulting two-parameter bifurcation diagram. In the scanned regime, the saddle-node curve separates a region without detected positive equilibria from one with multiple detected equilibria; the tolerance-only label concerns equilibrium existence rather than global attraction. As κ decreases, the saddle-node boundary approaches the immune-activation threshold $\alpha = \alpha_c$ and terminates at the feedback threshold defined by $\mathcal{F} = 1$. For the present parameter set, this threshold is $\kappa_F = 0.126$. Thus, $\kappa > \kappa_F$ provides the parameter regime in which lesion-mediated amplification is sufficiently strong to induce the backward deformation of the positive-equilibrium branch predicted analytically in Section 3.4.

For $\kappa > \kappa_F$, lesion-mediated feedback generates a saddle-node boundary below the immune-activation threshold $\alpha = \alpha_c$, thereby creating a parameter region with multiple positive equilibria. Equilibrium bistability occurs in the portion of this region where both the immune-tolerant equilibrium and the high-activity positive equilibrium are locally stable. Accordingly, the bistable region is bounded by the saddle-node curve and the first stability-loss boundary of the high-activity branch, which is given by either $\alpha = \alpha_c$ or the Hopf curve, depending on their relative location. Crossing the Hopf curve causes the high-activity equilibrium to lose stability through an oscillatory instability.

At the working value $\kappa = 1$, the two-parameter continuation recovers

$\alpha_{SN} = 9.47 \times 10^{-5}$, $\alpha_c = 1.125 \times 10^{-4}$, $\alpha_H = 3.43 \times 10^{-4}$, in agreement with the one-parameter bifurcation diagram above. The two-parameter result therefore shows that the saddle-node, bistability, and Hopf transitions are not isolated features of the single choice $\kappa = 1$ but belong to a broader feedback-dependent bifurcation structure.

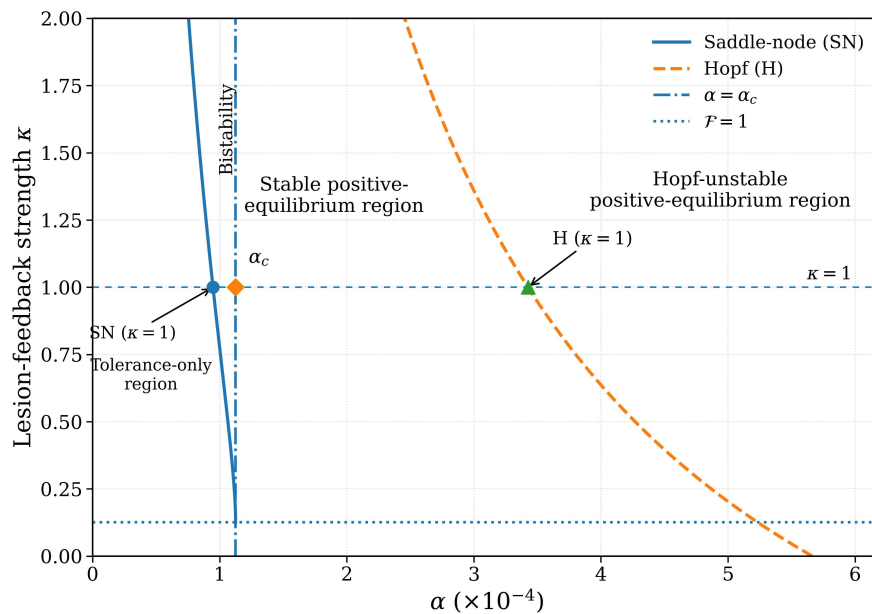


Figure 3. Numerical equilibrium and local-stability boundaries in the (α, κ) plane, scanned at $\Delta\kappa = 0.01$ on $[0, 2]$ and $S \leq 10^6$. Solid SN and dashed H curves are computed as described in Section 5; the vertical line is α_c , and the horizontal line is $\mathcal{F} = 1$. Region labels summarize detected equilibria and local spectra, not global attraction or exclusion of periodic or other attractors. The entire Hopf locus is not assigned a Lyapunov-coefficient sign.

5.5. Equilibrium bistability and initial-condition dependence

To examine the bistable regime directly, we choose $\alpha = 1.0 \times 10^{-4}$, which satisfies $\alpha_{SN} < \alpha < \alpha_c$. At this parameter value, the stable tolerance equilibrium $P_0 = (0, 0, 0, 0)$ coexists with two positive equilibria.

The upper positive equilibrium is $P_A = (4.42 \times 10^3, 4.42 \times 10^3, 5.57 \times 10^3, 0.419)$ with Jacobian eigenvalues $\lambda(\mathbf{J}(P_A)) \approx \{-0.2394, -0.0380, -0.0513 + 0.0752i, -0.0513 - 0.0752i\}$. Thus, P_A is locally asymptotically stable.

The lower positive equilibrium is $P_{\text{sad}} = (535, 535, 1.14 \times 10^3, 0.159)$, with $\lambda(\mathbf{J}(P_{\text{sad}})) \approx \{0.0124, -0.2062, -0.1084, -0.0589\}$. Hence, P_{sad} has one unstable direction and three stable directions and is therefore a saddle equilibrium.

The computed spectra establish local equilibrium bistability at this parameter value, with time integration demonstrating two attracting outcomes. The saddle has a three-dimensional local stable manifold. The displayed trajectories do not compute a global basin boundary; a global separatrix assignment would require additional basin/manifold calculations. Initial conditions located on opposite sides of this basin boundary may therefore converge to different long-term states.

Figure 4 illustrates this dependence on initial conditions. One trajectory approaches the immune-tolerant equilibrium, with the autoreactive immune populations and lesion activity decaying toward zero, whereas another converges to the persistent high-activity equilibrium under exactly the same parameter values.

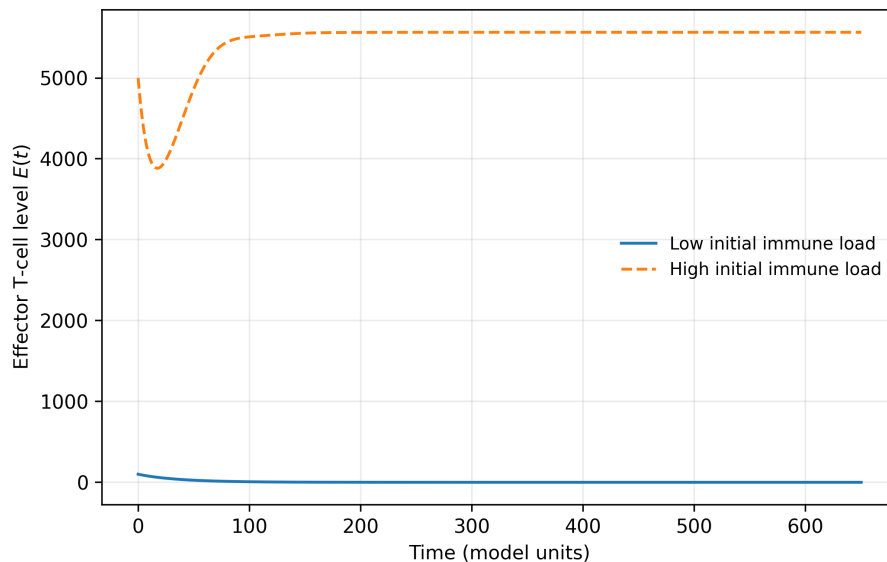


Figure 4. Computed trajectories at $\alpha = 10^{-4}$, $\kappa = 1$, with initial states $(100, 100, 100, 0)$ (solid) and $(5000, 5000, 5000, 0.30)$ (dashed), in the order (R_n, R_d, E, D) . DOP853 integrates $[0, 650]T$, with relative/absolute tolerances $10^{-9}/10^{-11}$ and maximum step $0.25T$. Only $E(t)$ is plotted. The trajectories approach different stable equilibria.

This behavior differs qualitatively from the multiple-periodic-orbit coexistence described for earlier reduced Teff–Treg systems [19, 20]. Here, the two attracting states are stationary equilibria, and their coexistence originates from the lesion-feedback-induced fold of the positive-equilibrium branch.

5.6. Hysteresis-like switching

Figure 5 is explicitly a schematic branch-following construction. No time-dependent $\alpha(t)$ is integrated. The increasing path selects $E^* = 0$ below α_c and the upper positive equilibrium above it; the decreasing path selects the upper equilibrium above α_{SN} and $E^* = 0$ below it. The prescribed switches illustrate the static bistable geometry, not dynamic bifurcation delay. In fact, $E = 0$ is invariant even if α varies, so a trajectory initialized exactly at P_0 cannot spontaneously leave it; a physical ramp experiment would require a positive perturbation and a specified ramp rate.

Consider first a gradual increase of α from the tolerance regime. The system can remain on the stable trivial branch while $\alpha < \alpha_c$. At $\alpha = \alpha_c$, the tolerance equilibrium loses stability, and the schematic branch selection changes to the high-activity state.

Conversely, suppose the system initially occupies the stable high-activity branch, and α is gradually decreased. The high-activity branch persists through α_c and remains stable throughout the bistable interval until it terminates at the saddle-node point $\alpha = \alpha_{SN}$. Below α_{SN} , the high-activity equilibrium no longer exists, and the schematic branch selection changes to the tolerance state.

The prescribed forward and backward branch-switch locations are therefore $\alpha_{\text{forward}} = \alpha_c$, $\alpha_{\text{backward}} = \alpha_{SN}$, and the width of the corresponding path-dependent interval is $\Delta\alpha_{\text{hys}} = \alpha_c - \alpha_{SN} = 1.78 \times 10^{-5}$. Thus, for the same instantaneous value of α within $\alpha_{SN} < \alpha < \alpha_c$, either the immune-tolerant state or the high-activity state can persist, depending on the preceding dynamical state.

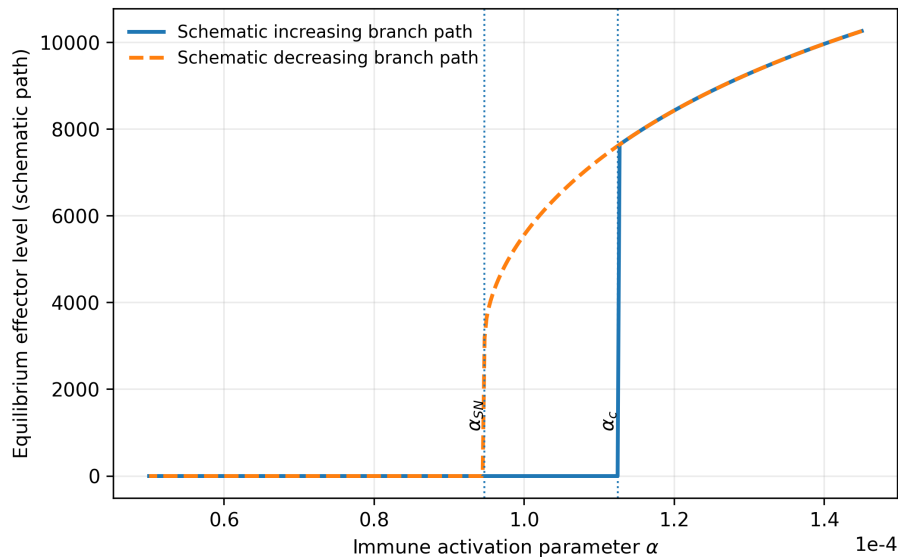


Figure 5. Schematic equilibrium branch-following construction at $\kappa = 1$, using 360 uniformly spaced values in each direction on $[5 \times 10^{-5}, 1.45 \times 10^{-4}]$. Increasing and decreasing paths switch at α_c and α_{SN} , respectively. Connecting segments indicate prescribed branch switches; they are not integrated trajectories, measured switching rates, or finite-rate ramp predictions.

5.7. Hopf instability and coupled immune–lesion oscillations

The high-activity positive equilibrium undergoes a second qualitative transition at $\alpha_H = 3.43 \times 10^{-4}$. Figure 6 shows the maximum real part of the Jacobian eigenvalues evaluated along the high-activity equilibrium branch.

The corresponding critical equilibrium is $P_H = (4.33 \times 10^4, 4.33 \times 10^4, 1.47 \times 10^4, 0.569)$. At this point, the characteristic-polynomial coefficients are $B_1 = 0.414$, $B_2 = 0.104$, $B_3 = 0.0332$, $B_4 = 0.00194$. They satisfy $\Delta_2 = B_1 B_2 - B_3 = 0.0100 > 0$, $\Delta_3 \approx 1.97 \times 10^{-12} \approx 0$ with $\omega_0 = 0.283$. The transversality coefficient defined in (4.5) is $\nu_H = 73.9 > 0$. These values satisfy the conditions of Theorem 4.2 and confirm a transverse crossing of the imaginary axis.

To reduce the scale disparity among the state variables, we introduce the normalized coordinates $y_i = (X_i - P_{H,i})/P_{H,i}$, $i = 1, 2, 3, 4$ before evaluating the first Lyapunov coefficient.

The supplementary check uses exact symbolic derivatives of the rescaled vector field, a unit Euclidean norm for q , and $\langle p, q \rangle = 1$ with the Hermitian inner product. The sign is the relevant local bifurcation diagnostic; the numerical magnitude depends on coordinate and eigenvector normalization. Using the normalized coordinate system associated with the critical equilibrium, the first Lyapunov coefficient obtained from (4.8) is $l_1 = -0.0464 < 0$. Hence, the Hopf bifurcation is

supercritical. This coefficient implies a locally stable small-amplitude family on the supercritical side under the verified Hopf hypotheses. The distant trajectory plotted below is a separate numerical observation.

To examine the oscillatory regime farther from the Hopf threshold, we also consider $\alpha = 5 \times 10^{-4}$. For this value, the solution approaches a stable periodic orbit with approximate period $T \approx 23.7$ in the effective time scale of the model. Over one oscillation cycle, the approximate state ranges are

$$R_n \in [2.20 \times 10^4, 1.15 \times 10^5], \quad R_d \in [3.24 \times 10^4, 8.38 \times 10^4], \\ E \in [1.57 \times 10^3, 3.96 \times 10^4], \quad D \in [0.420, 0.518].$$

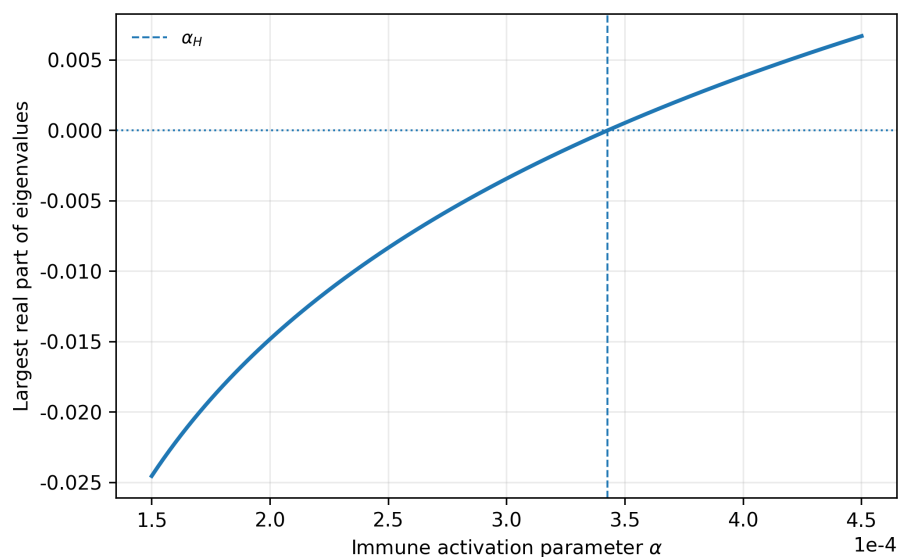


Figure 6. Computed maximum real Jacobian eigenvalue along the largest detected positive equilibrium on 240 activation values in $[1.5, 4.5] \times 10^{-4}$. The refined crossing at α_H is checked for a nonzero conjugate pair, negative remaining eigenvalues, Routh–Hurwitz conditions, and transversality. A zero spectral abscissa alone is not a sufficient Hopf test.

Figure 7 shows that lesion activity participates dynamically in the periodic orbit rather than acting only as a passive readout. An increase in E promotes lesion activity through $\rho_E E (K_E + E)^{-1} (1 - D)$, whereas the resulting increase in D enhances immune activation through $q(D) = 1 + \kappa D$. At the same time, the two Treg populations provide negative regulation of effector-cell activity. The interaction between these positive and negative feedback mechanisms supports coupled immune–lesion oscillations.

Hopf-induced autoimmune oscillations have already been identified in earlier Teff–Treg models [18–20]. The additional contribution of the lesion-feedback formulation is therefore not the existence of Hopf bifurcation alone. Rather, oscillatory instability occurs within the same dynamical framework that also supports feedback-induced saddle-node bifurcation, equilibrium bistability, and path-dependent switching.

The oscillation period reported above is expressed in the effective time units of the reduced model. Because the lesion-related parameters have not been calibrated against longitudinal magnetic resonance

imaging (MRI) or clinical relapse measurements, $T \approx 23.7$ should not be interpreted directly as a clinical relapse interval. Instead, the numerical result demonstrates that the closed-loop immune–lesion system supports a stable coupled oscillatory regime beyond the Hopf threshold.

For the plotted window $\mathcal{W}$, the normalization is $\tilde{X}_i(t) = [X_i(t) - \min_{\mathcal{W}} X_i] / [\max_{\mathcal{W}} X_i - \min_{\mathcal{W}} X_i]$ with a 10^{-15} denominator floor in code. The period is estimated from successive effector maxima after discarding the transient. Sustained oscillations at this distant parameter value are numerical evidence; the local Hopf theorem does not prove global continuation or uniqueness of the periodic orbit.

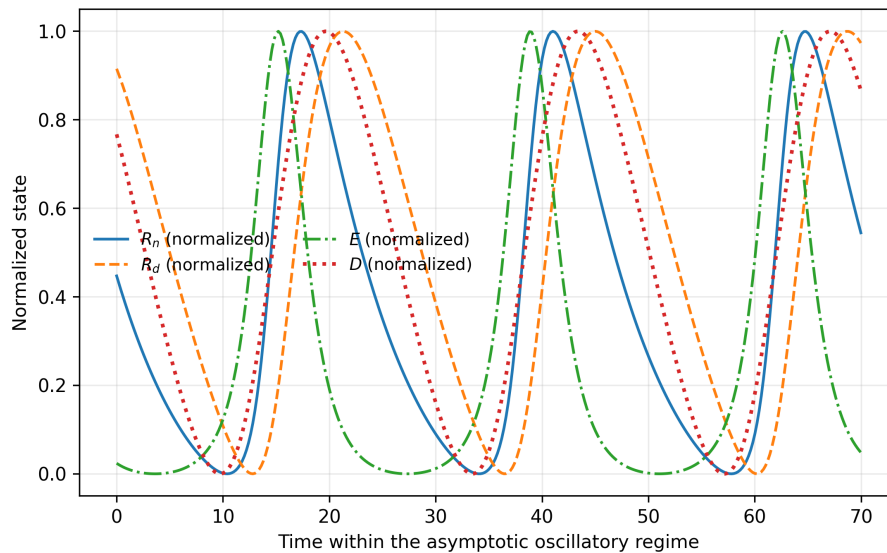


Figure 7. Computed coupled trajectories at $\alpha = 5 \times 10^{-4}$, $\kappa = 1$, from $(100, 100, 100, 0)$. DOP853 integrates $[0, 6000]T$ with tolerances $10^{-9}/10^{-11}$ and maximum step $0.2T$. Returned samples with $t \geq 5930T$ are plotted with time shifted to the first retained sample. Each signal is separately normalized by its own minimum and maximum on this window. Curves compare phase and waveform, not equal absolute amplitudes or calibrated clinical relapse periods.

6. Discussion

The analytical and numerical conclusions have different scopes. Theorem 3.4 proves backward bending and at least two positive equilibria when $\mathcal{F} > 1$; it does not prove exactly two or their stability on the whole interval. Statements below about a stable upper branch, saddle lower branch, stability regions, and critical values refer to the computed working regime. Sections 3 and 4 supply analytical thresholds and conditional bifurcation criteria; the finite scans in Section 5 check those hypotheses numerically.

The closed-loop immune–lesion model extends the reduced Teff–Treg framework by allowing lesion-associated activity to feed back on subsequent immune activation. This feedback alters both the geometry and stability of the positive-equilibrium branch. For the working parameter set, the resulting backward deformation is associated with a nondegenerate saddle-node bifurcation, equilibrium bistability, hysteresis-like switching, and a subsequent Hopf instability along the high-activity branch.

6.1. Relation to existing autoimmune and MS models

The comparison with [22] also limits biological interpretation: Noise-triggered excitable flares and autonomous periodic oscillations represent different mechanisms. The present deterministic periodic example should not be taken as evidence that clinical relapses occur regularly. The external-force kinetic treatment in [23] addresses treatment effects beyond the present autonomous feedback closure.

The mechanism identified here differs from the recurrent dynamics previously reported in Teff–Treg models. Earlier regulatory-T-cell models described transitions between immune tolerance and autoimmune activation through nonlinear interactions among antigen-presenting cells, regulatory T cells, and autoreactive effector T cells [17, 18]. Later bifurcation analyses showed that Hopf and generalized Hopf bifurcations can generate recurrent autoimmune activity and coexistence of periodic attractors [19, 20]. Oscillatory behavior is therefore already an intrinsic dynamical property of the underlying immune-regulatory subsystem.

Lesion-mediated feedback introduces a different mechanism. When $\kappa = 0$, the positive-equilibrium branch remains monotone and does not extend into the region where the immune-tolerant equilibrium is locally stable. With sufficiently strong feedback, the local branch direction can reverse, and the positive-equilibrium branch extends toward $\alpha < \alpha_c$. For the working parameter set, this backward deformation contains a nondegenerate saddle-node bifurcation and produces the bistable interval $\alpha_{SN} < \alpha < \alpha_c$, in which a stable immune-tolerant equilibrium coexists with a stable high-activity autoimmune equilibrium, and an intermediate saddle equilibrium separates their basins locally. The resulting behavior is therefore an *equilibrium bistability induced by a feedback-driven fold* rather than bistability arising from coexisting periodic attractors.

The formulation also differs in objective from spatial MS models. Reaction–diffusion and kinetic approaches explicitly describe cell migration, cytokine signaling, demyelination, oligodendrocyte injury, and remyelination and are therefore suitable for investigating spatial lesion formation and pattern development [6, 21]. In contrast, lesion-associated inflammatory and demyelinating activity is aggregated here into the single temporal variable $D(t)$. This reduction sacrifices spatial and cellular resolution in exchange for analytical tractability of the equilibrium and bifurcation structure.

6.2. Dynamical role of lesion-mediated feedback

A key distinction arises between the local stability threshold of the immune-tolerant equilibrium and the nonlinear structure away from that state. Because $D = 0$ at $P_0 = (0, 0, 0, 0)$, the feedback factor satisfies $q(0) = 1$. Lesion feedback therefore does not modify the first-order activation threshold, and $\mathcal{R}_A = 1$ continues to determine the local stability change of the immune-tolerant equilibrium.

Away from P_0 , lesion feedback modifies the positive-equilibrium geometry. The feedback number $\mathcal{F}$ compares the amplification along $S \mapsto E(S) \mapsto D(S) \mapsto q(D(S))$ with the regulatory effects of the Teff–Treg subsystem. When $\mathcal{F} > 1$, one has $\Phi'_\kappa(0) < 0$, so the positive-equilibrium branch initially extends toward $\alpha < \alpha_c$. Together with $\Phi_\kappa(S) \rightarrow +\infty$ as $S \rightarrow \infty$, this guarantees at least one interior minimum of the scalar equilibrium relation. For the working parameter set, the relevant minimum satisfies the required nondegeneracy conditions and corresponds to the saddle-node threshold α_{SN} of the full four-dimensional system.

The two-parameter analysis in the (α, κ) plane further shows how the equilibrium and stability boundaries vary with lesion-feedback strength. The saddle-node boundary approaches $\alpha = \alpha_c$ as

the feedback strength decreases and, for the parameter regime examined, terminates at the analytical threshold defined by $\mathcal{F} = 1$. The Hopf boundary instead marks the loss of stability of the high-activity equilibrium through an oscillatory instability. Thus, $\mathcal{F} > 1$ characterizes the onset of backward branch deformation but does not by itself determine stability of the high-activity branch.

Equilibrium bistability occurs only where the immune-tolerant and high-activity equilibria are simultaneously stable. For the working value $\kappa = 1$, the ordering $\alpha_{SN} < \alpha_c < \alpha_H$ implies that the entire interval $\alpha_{SN} < \alpha < \alpha_c$ forms an equilibrium-bistable regime. Within this interval, the long-term state depends on the initial immune and lesion-associated conditions.

The branch geometry motivates the schematic paths in Figure 5. Their prescribed switches at α_c and α_{SN} describe static equilibrium selection. A ramped trajectory, its perturbation, and any dynamic delay have not been computed; the switching values are not clinical thresholds.

At larger activation levels, the high-activity equilibrium loses stability through a Hopf bifurcation. For the working parameter set, the negative first Lyapunov coefficient identifies a supercritical Hopf bifurcation, and numerical trajectories approach stable periodic immune–lesion oscillations. The Hopf mechanism itself is consistent with earlier Teff–Treg models [18–20]; the closed-loop formulation shows that feedback-induced equilibrium restructuring and oscillatory instability can occur within the same dynamical system.

6.3. Biological interpretation and limitations

Robustness within the chosen closure was examined by varying each of $\rho_E, \rho_R, K_E, \kappa$ separately by $\pm 20\%$, holding all other parameters fixed. For these eight cases, scalar root and spectral checks detect a fold below α_c and a stable upper equilibrium throughout 99 sampled interior points of the static bistable window; the boundary values are supplied with the code. This is a local one-at-a-time sensitivity test, not a joint uncertainty analysis or proof for arbitrary lesion laws. Nondegenerate folds and hyperbolic stable equilibria persist under sufficiently small smooth perturbations, but bifurcation locations and window widths depend on the lesion parameters. Increasing activation relative to recovery strengthens equilibrium lesion feedback, and K_E changes the effector scale at which it acts. Alternative gains and saturation laws require separate verification.

The variable D should be interpreted as an effective systems-level measure of lesion-associated inflammatory and demyelinating activity rather than as a direct clinical quantity such as MRI lesion number, lesion volume, or irreversible disability. Likewise, $q(D) = 1 + \kappa D$ is a phenomenological representation of lesion-to-immune feedback rather than a mechanistically resolved biochemical law.

Increased lesion-associated activity may be accompanied by enhanced antigen exposure, inflammatory signaling, and altered blood–brain barrier function, all of which may facilitate subsequent autoreactive immune activation [2, 9, 10]. The same upstream antigen-presentation-related processes may also stimulate regulatory responses, motivating the action of the feedback factor on both the R_n and E activation terms. The mathematical results therefore describe dynamical behaviors that are possible under such a closed feedback architecture without assigning the feedback to a unique cellular pathway.

Several limitations remain. The parameters ρ_E, K_E, ρ_R , and κ are phenomenological and have not been jointly estimated from longitudinal immune and imaging data. Accordingly, the numerical values of α_{SN}, α_c , and α_H are model-dependent bifurcation thresholds rather than clinical decision thresholds. Moreover, the single variable D aggregates several biologically distinct processes, whereas the linear

feedback function represents only a simple closure. Quantitative threshold locations may therefore change after parameter calibration or under alternative feedback functions.

The numerical results should consequently be interpreted as demonstrations of dynamically admissible behavior rather than patient-specific predictions of lesion burden, relapse timing, or disease progression.

7. Conclusions

The reduced immune–lesion system admits a scalar equilibrium characterization and a rigorous feedback criterion for backward bending. When $\mathcal{F} > 1$, at least two positive equilibria exist between the minimum branch value and α_c ; their exact number and stability require additional analysis. Conditional full-system saddle-node and Hopf criteria are derived. For the working parameters, numerical root reconstruction, Jacobian spectra, nondegeneracy checks, and a negative first Lyapunov coefficient support a nondegenerate fold, locally stable tolerant/active equilibria, and a supercritical Hopf bifurcation. Computed trajectories demonstrate initial-condition dependence and sustained coupled oscillations, and a separately identified schematic branch-following figure illustrates static hysteresis geometry. The two-parameter and lesion-sensitivity results are finite numerical checks of equilibrium/local-stability structure. The explicit lesion closure provides a tractable extension of existing feedback models; it does not establish a new universal cause of clinical relapse or calibrated disease thresholds.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare there are no conflicts of interest.

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