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Chronic Antigen Exposure and Immune Tolerance Dynamics: A Unified Treg–Tpex Phase Transition Framework

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Research Article

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Abstract

Chronic antigen exposure underpins persistent viral infection, cancer, pregnancy, transplantation, and autoimmunity. The unifying dynamical principles governing immune fate across these diverse scenarios remain unclear. We demonstrate that immune tolerance and effector transitions can be reduced to a single governing index—the antigen-specific tolerance stability index S_i = F_Treg^i / N_Tpex^i. This index captures the balance between Treg suppressive capacity and Tpex reservoir load.

Antigen entry into this framework is governed by the host immune state at exposure, which we conceptualize as a dynamic "immune tide" —the systemic immune setpoint shaped by superimposed circadian, developmental, and physiological rhythms. In plain terms, the immune tide is the global immunological "weather" that determines whether a new antigen is attacked or tolerated. This tide, together with the local tissue microenvironment, strongly biases the antigen toward one of two primary entry routes: Route A (failed active clearance) or Route B (direct tolerance entry). In addition, a special boundary case exists—Route C (immune executive structure destruction) —in which the antigen directly damages the immune system's own clearance capacity.

When S_i crosses a critical bifurcation boundary S*, the immune system undergoes an abrupt immune state transition between tolerance- and effector-dominant regimes. Disease heterogeneity arises from differences in antigen kinetics—persistence, diversity, and programmed withdrawal—modulated by the immune tide at the moment of encounter. Systems approaching S exhibit critical slowing down (delayed recovery, increased variance, elevated autocorrelation), serving as a universal early-warning signal. This framework provides a unified phase-space theory for chronic antigen-driven immune homeostasis across diverse clinical settings.

Introduction

Persistent antigen exposure is a defining feature of chronic viral infection [1], tumor progression [2], maternal–fetal tolerance [3], allogeneic transplantation [4], and systemic autoimmunity [5, 6, 17]. These contexts are typically conceptualized through distinct paradigms—T cell exhaustion [7], immune escape [2], physiological tolerance [3], and immune dysregulation [4]. A unified description of immune fate under continuous stimulation has been lacking.

We propose that immune responses to chronic antigen exposure are governed by a single governing index, S_i. This index captures the balance between antigen-specific Treg suppressive capacity and Tpex reservoir load [8]. The route by which an antigen enters this dynamical system is dictated by the immune tide—the systemic immune setpoint at the time of first encounter. This tide fluctuates across circadian, developmental, and physiological time scales.

Antigens enter primarily through two routes: Route A (failed active clearance) and Route B (direct tolerance entry). In addition, a special boundary case —Route C (immune executive structure destruction) —is discussed in the Framework Admission Criteria. Once chronicity is established, all routes converge onto the same phase space. Disease phenotypes are determined by antigen kinetics operating within this shared space. Systems approaching the bifurcation boundary exhibit critical slowing down [10, 11], providing a universal dynamical signature of impending transitions.

Framework Admission Criteria

An antigen enters the S_i dynamical system only when two core constraints are simultaneously satisfied:

(1) TCR Recognition Constraint: The host TCR repertoire contains at least one clone capable of recognizing an epitope of the antigen. If all specific TCR clones have been deleted through central tolerance, N_Tpex^i = 0, S_i is undefined.

(2) Kinetic Failure of Antigen Elimination: The antigen fails to be completely cleared within a finite acute response window (~ 6 months). This window corresponds to the timescale required for the adaptive immune system to complete the "initiation → expansion → contraction → memory" cycle [1].

Prerequisite: The Immune Tide and Microenvironmental Context. The entry route is strongly biased by the superimposed effect of the systemic immune tide and the local tissue microenvironment at the moment of antigen encounter.

The immune tide refers to the global immune setpoint. In simpler terms, it is the immunological "weather" that determines whether a newly encountered antigen is attacked or tolerated. This tide oscillates across three interconnected time scales:

Circadian/Ultradian Rhythms: Cortisol, melatonin, and autonomic nervous system oscillations impose ~ 24-hour cycles on T cell trafficking, APC function, and cytokine production. Antigens encountered during pro-inflammatory peaks are more likely to trigger Route A. Those encountered during anti-inflammatory troughs are predisposed to Route B.

Developmental/Aging Rhythms: Early childhood (typically before age 5–7) constitutes a high-plasticity, iTreg-skewed phase favoring Route B1. The adult immunocompetent phase favors Route A. The elderly phase—marked by inflammaging and reduced T cell diversity—tends toward regulatory and exhaustion pathways.

Physiological/Reproductive Cycles: Estrogen, progesterone, and testosterone fluctuations across the menstrual cycle and pregnancy systematically alter the Treg/Th17 balance. These fluctuations create transient suppressive tides (e.g., mid-luteal phase, pregnancy) that bias new antigen encounters toward Route B2.

Of note, the immune tide does not absolutely determine the entry route in every single antigen encounter. Rather, it biases the system's default response. A pro-inflammatory tide strongly favors Route A. A suppressive tide strongly favors Route B. This probabilistic gating accounts for stochastic variation in individual immune responses.

The outcome of any antigen encounter is thus determined by the phase of the immune tide at the precise moment of first presentation. This phase is superimposed on the local tissue microenvironment. This spatiotemporal framework explains why the same antigen yields divergent outcomes depending on the time of day, developmental age, and physiological cycle phase.

Entry Routes

Path Classification Summary

To facilitate orientation, the three entry routes are summarized below before detailed description. The entry route is determined by the immune tide (the systemic immune setpoint at exposure) superimposed on the local tissue microenvironment.

Route	Immune Tide Context	Local Microenvironment	Initial T Cell Differentiation Bias	Representative Scenarios
Route A	Pro-inflammatory tide	Normal, non-inflamed niche	Effector T cell	Adult chronic infections (HCV, EBV); tumor founding clone
Route B1	Developmental suppressive tide (age < 5–7)	Normal niche	iTreg	Early-childhood infections (HBV); developmental self-antigens
Route B2	Suppressive tide (circadian trough, physiological, post-inflammatory) or pharmacologic suppression	Immunosuppressive niche (e.g., TGF-β/IL-10-dominated)	iTreg (skewed)	Infections under immunosuppression; pregnancy; tumor subclonal variants; transplant tolerance induction
Route C*	Variable (immune structures damaged)	Variable (immune tissue destroyed)	Impaired/absent (due to immune destruction)	HIV; congenital immunodeficiencies

*Route C represents a boundary case of the framework; see "Special Note" below for details.

Route A—Failed Active Clearance: The immune system encounters the antigen during a pro-inflammatory tide in a normal tissue niche. It mounts an effector T cell-mediated clearance attempt. If this attempt fails to eliminate the antigen within the acute window, the antigen becomes chronic. This applies to adult acute infections that become chronic. It also applies to founding tumor clones emerging in immunocompetent, non-inflamed tissues. For tumors, Route A manifests as a progressive failure. Each newly emerged neoantigen triggers an effector T cell response. However, continuous emergence prevents fulfillment of the 6-month clearance window.

Route B—Direct Tolerance Entry: The immune system encounters the antigen during a suppressive tide (developmental, circadian trough, or physiological). Alternatively, it may encounter the antigen within an immunosuppressive local microenvironment (e.g., TGF-β/IL-10-dominated niche). Under these conditions, APC-mediated priming skews naïve T cells toward iTreg/Treg differentiation rather than effector T cell activation.

A critical nuance: subclonal neoantigens arising in chronically inflamed tissues (e.g., HBV-driven hepatitis, inflammatory bowel disease) are often encountered within a post-inflammatory suppressive tide. They thus enter via Route B2. This explains why recurrently inflamed tissues are prone to immune escape. Similarly, fetal antigens during pregnancy encounter a systemic suppressive tide combined with a locally suppressed decidual niche. They enter via Route B2. Route B is subclassified into B1 (developmental window, age < 5–7) and B2 (passive/physiological suppression) .

Special Note—Route C: Immune Executive Structure Destruction

For certain antigens, chronicity arises neither from failed clearance within a functioning immune system, nor from direct tolerance induction, but from destruction of the immune executive structures themselves that are required for clearance.

Typical scenario: HIV infection. The virus directly infects and depletes $CD4^+$ T cells, progressively dismantling the very apparatus required for antigen-specific immune responses. In this context, the antigen does not simply "fail to be cleared" (Route A) or "enter via suppression" (Route B)—it cripples the system that would otherwise clear it.

Framework placement:

If destruction is irreversible (e.g., advanced HIV with $CD4^+$ T cell count < 200/μL, no immune reconstitution): the framework does not apply, as N_Tpex^i cannot be meaningfully defined when the T cell compartment is globally depleted.

If destruction is reversible (e.g., HIV with successful antiretroviral therapy and immune reconstitution): the framework can become applicable again—the reconstituted immune system can then be assessed via the immune tide framework (often entering a post-inflammatory or pharmacologically modulated state, functionally aligning with Route B2).

This distinction places immune-executive-destruction pathogens at the boundary of the framework, rather than strictly within Route A or Route B. This nuance is essential for correctly interpreting chronic infections that combine direct immune injury with persistent antigenemia.

Once chronicity is established, all routes converge onto the same S_i phase space. We term this path-independent convergence. In other words, once an antigen persists beyond the acute window, the system behaves the same way regardless of how it got there.

Scope of Application

This framework applies to persistent antigen exposure satisfying the above constraints. It does not apply to acute responses with rapid clearance, antigens lacking TCR recognition clones, or scenarios with irreversibly destroyed immune executive structures (e.g., advanced HIV with $CD4^+$ T cell depletion). If immune executive structures are reversible (e.g., immune reconstitution following antiretroviral therapy), the framework can become applicable again after reconstitution.

Results

1. Immune Stability Is Governed by a Minimal Governing Index

We define:

S_i = F_Treg^i / N_Tpex^i

where F_Treg^i represents the suppressive capacity of antigen-specific Treg cells, and N_Tpex^i represents the reservoir load of progenitor-exhausted T cells (Tpex: $PD\text{-}1^+TCF\text{-}1^+TOX^+$) specific for antigen i. Tpex possess dual capacity for self-renewal and differentiation into terminal effectors [8].

Higher S_i indicates stable tolerance. Lower S_i indicates a tendency toward effector immune state transition. S* represents a critical bifurcation boundary within a given local dynamical system. Its absolute value may shift across tissue microenvironments due to variations in IL-2 availability, TGF-β concentration, and metabolic constraints. Within each defined system, however, a clear threshold exists.

2. Treg–Tpex Antagonism Constitutes the Core Regulatory Axis

Under persistent antigen exposure, Treg and Tpex constitute a core antagonistic pair. Treg suppress effector T cells through three mechanisms: IL-10/TGF-β secretion, IL-2 competition, and CTLA-4-mediated trans-endocytosis [6, 9]. Tpex continuously generate terminally differentiated effector cells [8]. Perturbations transmit through this antagonistic axis, manifesting as S_i evolution.

3. Immune State Transitions and Critical Slowing Down

When S_i crosses S*, the system undergoes an abrupt immune state transition. This transition is characterized by three features: threshold behavior, irreversibility (or low reversibility), and critical slowing down. Critical slowing down manifests as slowed recovery, increased fluctuation variance, and elevated autocorrelation following perturbation [10, 11].

A critical distinction—tumor immune escape is not an immune state transition across S*. Rather, it is a stalling phenomenon. Continuous neoantigen emergence drives competitive consumption of limited immune resources. This prevents any single antigen-specific Tpex pool from accumulating sufficiently to drive S_i below S*. This stalling state is reversible. By relieving resource limitation or modulating the Treg/Tpex balance, the system can regain the capacity to cross S*.

4. Disease Heterogeneity Arises from Immune Tide, Microenvironment, and Antigen Kinetics

Disease-specific trajectories arise from the superimposed effects of three factors: the immune tide phase at entry, the local microenvironment, and antigen kinetics (persistence, diversity, programmed withdrawal). Table 1 summarizes key parameters for each scenario.

Table 1
Immune tide context, entry route, antigen kinetics, and S_i trajectories across scenarios

Scenario	Immune Tide at Exposure	Local Microenvironment	Initial T cell differentiation	Entry Route	Antigen Kinetics	S_i trajectory	Phase-space type
Adult acute infection → chronic	Pro-inflammatory (adult baseline)	Normal	Effector T cell	Route A	Single burst, failed clearance	Fluctuation → high-level maintenance	Failed clearance
Early-childhood infection (age < 5–7)	Developmental (iTreg-skewed)	Normal	iTreg	Route B1	Persistent, no withdrawal	High-level maintenance	Direct tolerance
Infection under immunosuppression	Suppressed (pharmacologic)	Suppressed	Impaired effector/iTreg	Route B2	Persistent, no withdrawal	High-level maintenance	Direct tolerance
Tumor—founding clone	Pro-inflammatory (adult baseline)	Normal (non-inflamed)	Effector T cell	Route A (progressive)	Low diversity, continuous emergence	Fluctuating decline → crosses S*	Crossing (immune control)
Tumor—subclonal variants in inflamed tissue	Post-inflammatory suppressive tide	Inflamed, TGF-β/IL-10-rich	iTreg (skewed)	Route B2	High diversity, continuous emergence	Cannot decline → stalls above S*	Stalling (immune escape)
Pregnancy (fetal antigens)	Suppressed (physiological, post-implantation)	Decidual (IDO/IL-10)	iTreg/Th2	Route B2	Programmed withdrawal (parturition)	Rise → crosses S* → rebounds	Programmed withdrawal
Transplantation—standard	Pro-inflammatory (adult baseline)	Graft (inflamed)	Effector T cell	Route A	Persistent, no withdrawal	Monotonic decline → crosses S*	Progressive decay (rejection)
Transplantation—tolerance induction	Modulated (Treg-enhanced)	Graft with mixed chimerism	iTreg/anergy	Route B2	Persistent with regulatory boost	Initial decline → U-shaped recovery → stable above S*	Recovery (operational tolerance)
Autoimmunity—developmental self-antigens	Developmental (age < 5–7)	Normal	iTreg (needs unlocking)	Route B1	Persistent self, intermittent flares	Slow decline → oscillation around S*	Oscillatory (flare-remission)
Autoimmunity—adult neo-self-antigens (limited)	Pro-inflammatory	Normal/inflamed	Effector T cell	Route A (progressive)	Limited variant emergence	Rapid decline → crosses S*	Crossing (flare)
Autoimmunity—adult neo-self-antigens (high-frequency)	Post-inflammatory suppressive tide	Inflamed	iTreg (skewed)	Route B2	High-frequency variant emergence	Cannot decline → stalls above S*	Stalling

Table 1 footnote (Tumor): For tumors, the table distinguishes between the founding clone (emerging in a non-inflamed, immunocompetent niche) and subclonal variants (emerging within an inflamed, post-inflammatory suppressive microenvironment). At the whole-tumor level, S_i evolution represents a weighted composite of these coexisting trajectories. The dominant trajectory determines the overall phenotype (crossing vs. stalling).

Table 1 footnote (Route C): Pathogens such as HIV that cause chronicity through direct destruction of immune executive structures do not fall into the typical Route A or Route B categories. If destruction is irreversible, the framework does not apply (N_Tpex^i is undefined); if immune reconstitution is achieved through treatment, the framework can become applicable again, with the reconstituted state functionally aligning with Route B2. This boundary case does not affect the classification of the typical scenarios listed in the table.

Clinical Prediction Framework

It is critical to distinguish two uses of S_i in this framework:

(1) Dynamic $S_i(t)$ — the actual time-varying state variable within an individual patient, which evolves as Treg/Tpex balance changes over time.

(2) Cross-sectional proxy S_i — an inferred approximation based on static biomarker measurements (e.g., HBsAg level), used for population-level stratification.

All predictions regarding immune state transitions and critical slowing down refer to dynamic $S_i(t)$. Cross-sectional proxies serve only as heuristic guides for clinical trial design and patient enrichment. They are not substitutes for longitudinal monitoring.

Prediction 1: Cross-Scenario Dynamic Monitoring

The direction of S_i evolution can be approximated through proxy indicators (Table 2). Cross-sectional high antigen load correlates with high S_i. Longitudinal antigen decline signals S_i movement toward S*, creating a therapeutic window.

Table 2
Cross-scenario monitoring framework

Scenario	Key Monitoring Indicators	Predicted Outcome	Critical Time Window
Chronic HBV	Treg/HBV-specific Tpex; HBsAg trend	Clearance vs. chronicity	3–6 months post-infection; during ASO/siRNA
Tumor	Treg subtypes; Tpex clonal diversity	Control vs. escape	Entire equilibrium phase
Pregnancy	Treg/fetal-specific T cells	Parturition timing	Late pregnancy to 3 months postpartum
Transplantation	Treg/donor-reactive Tpex; iBOX [15, 16]	Rejection vs. tolerance	1–5 years post-surgery
Autoimmunity	Treg/self-Tpex; autoantibody fluctuations	Remission vs. flare	Preclinical phase

Prediction 2: Critical Slowing Down as Universal Early-Warning Signal

Increased variance, prolonged recovery, and elevated autocorrelation precede immune state transitions across all scenarios [10, 11]. Detection requires sufficiently high-frequency longitudinal sampling to capture statistical changes in indicator fluctuations.

Prediction 3: Cross-Scenario Therapeutic Logic

Two fundamentally different therapeutic strategies emerge from this framework:

Enhancing F_Treg (Treg transfer, low-dose IL-2): increases S_i, strengthens tolerance.

Enhancing N_Tpex output (immune checkpoint blockade): decreases S_i, promotes effector responses. This is beneficial in tumors but potentially harmful in transplantation and autoimmunity.

Prediction 4: HBV Immunotherapy Stratification

Low HBsAg patients have S_i closer to S*. They require only moderate antigen reduction to trigger clearance. High HBsAg patients require more profound reduction.

Prediction 5: Chrono-Immunotherapy Windows

Vaccination and immunotherapy outcomes depend on the phase of the host's endogenous immune tide at administration. This phase can be approximated by circadian markers (e.g., cortisol awakening response, lymphocyte subset diurnal variation). Pro-inflammatory tide phases favor Route A and strong effector responses. Suppressive phases favor Route B and tolerance induction. Timing interventions to the individual's pro-inflammatory peak—rather than a fixed clock time—may enhance efficacy. This principle extends to developmental windows (e.g., pediatric vaccination scheduling) and physiological cycles (e.g., menstrual cycle phase for female patients).

Discussion

We demonstrate that immune tolerance under chronic antigen exposure is governed by a minimal phase-space structure determined by a single governing index, S_i.

Core contributions:

First, incorporation of the immune tide as the spatiotemporal entry determinant. We formally distinguish between pro-inflammatory and suppressive immune tides across circadian, developmental, and physiological time scales. This distinction resolves why the same antigen yields divergent outcomes depending on the time of day, developmental age, and physiological cycle phase at first encounter.

Of note, the founding clone of a tumor (emerging in an immunocompetent, non-inflamed tissue) enters via Route A. By contrast, subclonal neoantigens arising in chronically inflamed tissues are encountered within a post-inflammatory suppressive tide. They directly enter via Route B2. This explains why recurrent inflammation promotes immune escape. This same logic unifies pregnancy tolerance. Post-implantation inflammation rapidly triggers a systemic suppressive tide, channeling fetal antigens into Route B2.

Second, path-independent convergence. Two distinct entry routes converge onto the same S_i phase space once chronicity is established. Disease heterogeneity arises from antigen kinetics (persistence, diversity, programmed withdrawal) rather than from different immune mechanisms. In other words, once chronicity is established, the system's behavior depends on how the antigen behaves over time—not on how it initially entered.

Third, dynamical distinction between immune state transition and stalling. Crossing S* induces an abrupt immune state transition. Stalling above S* due to resource limitation represents reversible immune escape, not a fixed endpoint. Resource limitation refers to competitive consumption of limited antigen-presenting and Tpex expansion resources by diverse antigen clones. Importantly, while S* is defined as a fixed bifurcation threshold within a given local system, its absolute value may shift across tissue microenvironments. This nuance does not undermine the framework's predictive power, as each defined system retains its own clear threshold.

Fourth, trajectory diversity across clinical settings, summarized in Table 1. Transplantation under standard immunosuppression follows a monotonic decline → crossing trajectory (Route A, progressive decay). Tolerance-inducing protocols (mixed chimerism, Treg infusion) exhibit a U-shaped recovery trajectory (Route B2, recovery type). Similarly, developmental self-antigens follow an oscillatory trajectory (Route B1). Adult-onset neo-self-antigens follow either crossing or stalling trajectories (Route A or B2, depending on the immune tide at emergence).

Framework boundaries: This framework applies to persistent antigen exposure satisfying admission criteria. It does not apply to acute responses with rapid clearance, antigens lacking TCR recognition clones, or scenarios with irreversibly destroyed immune executive structures (e.g., advanced HIV). If immune executive structures are reversibly restored through treatment (e.g., immune reconstitution following antiretroviral therapy), the framework can become applicable again after reconstitution—the reconstituted immune system functionally aligns with Route B2. By explicitly defining this boundary case, the framework not only clarifies its scope of applicability but also enhances its credibility as a scientific model.

Falsifiability: The framework predicts that across all chronic antigen-driven systems, immune state transitions are universally preceded by critical slowing down under sufficiently high-frequency longitudinal monitoring. Failure to detect these signals would falsify the framework.

Conclusion

The tolerance–effector transition under persistent antigen exposure is governed by S_i = F_Treg^i/N_Tpex^i. Antigen entry requires both TCR recognition constraint and kinetic failure of elimination. The entry route is biased by the immune tide—the systemic immune setpoint shaped by circadian, developmental, and physiological rhythms—superimposed on the local tissue microenvironment at the moment of first encounter. Once chronicity is established, all routes follow identical dynamical rules. When S_i crosses S*, an immune state transition occurs. When S_i stalls above S* due to resource limitation (competitive consumption of limited antigen-presenting and Tpex expansion resources by diverse antigen clones), immune escape ensues. This framework provides a unified spatiotemporal theory of chronic antigen-driven immune homeostasis, offering a generalizable paradigm for cross-disease immune tolerance research.

Declarations

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Figures

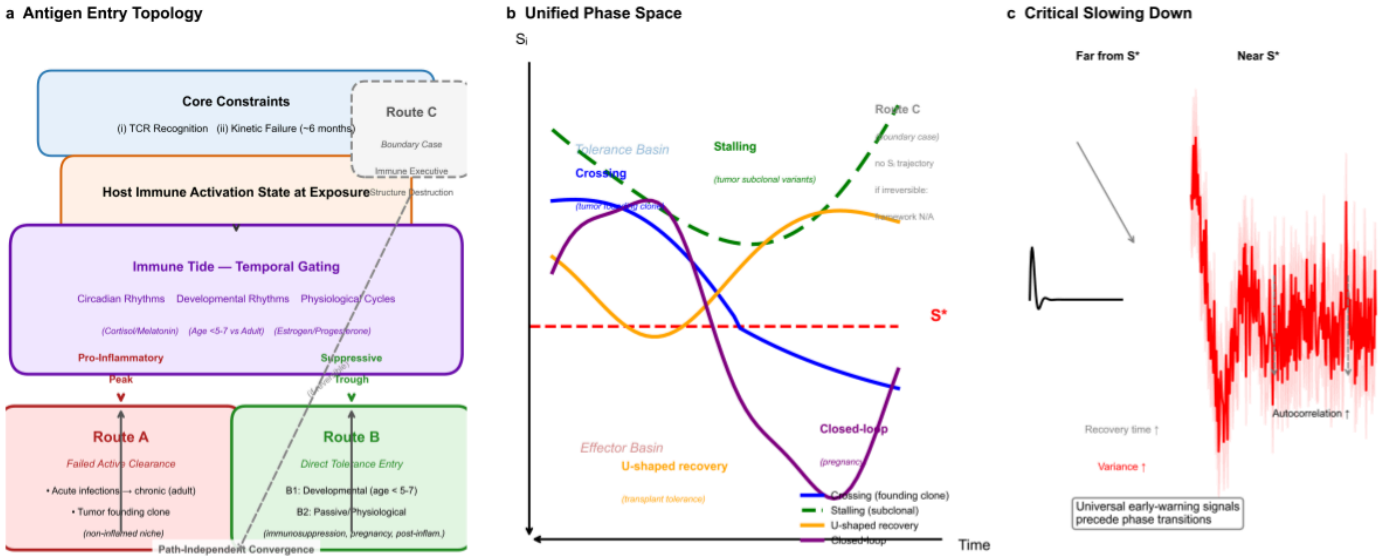


Figure 1

A unified phase-space framework for chronic antigen-driven immune state transitions

a, Antigen entry topology. Antigen entry requires two core constraints: TCR recognition and kinetic failure of elimination. Entry is gated by the immune tide—the systemic immune setpoint at exposure, fluctuating across circadian, developmental, and physiological rhythms—superimposed on the local microenvironment. A pro-inflammatory tide in a normal niche yields Route A (failed active clearance) . A suppressive tide (developmental, circadian trough, physiological, or post-inflammatory) yields Route B (direct tolerance entry) , subclassified into B1 (developmental, age < 5–7) and B2 (passive/physiological suppression). Route C (immune executive structure destruction) represents a boundary case: when an antigen directly destroys the immune system's own clearance capacity (e.g., HIV), the framework does not apply if destruction is irreversible; if immune reconstitution is achieved through treatment, the framework can become applicable again. Once chronicity is established, all routes exhibit path-independent convergence onto the shared S𝒊 phase space. In plain terms, once an antigen persists, the system's subsequent dynamics are independent of its entry route.

b, Unified phase space defined by S𝒊 = F_Treg/N_Tpex. S* partitions the space into tolerance (S𝒊 > S*) and effector (S𝒊 < S*) basins. Representative trajectories include: crossing (Route A, limited antigens—tumor founding clone, immune control); stalling (Route B2, high-diversity antigens—tumor

subclonal variants, immune escape); U-shaped recovery (Route B2, tolerance induction); and closed-loop (Route B2, programmed withdrawal). S* may vary across tissue microenvironments but remains a clear threshold within each defined system.

c, Critical slowing down as universal early-warning signal. Systems far from S* recover rapidly. Systems near S* exhibit prolonged recovery, amplified fluctuations, and elevated autocorrelation. These are model-independent signals preceding immune state transitions. Detection requires sufficiently high-frequency longitudinal monitoring.

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