

The in-host treatment window: a closed-form phagocyte-recruitment threshold separates clearance failure from immunopathology – and the window does not collapse

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Abstract

Antibiotic dosing at an infected tissue site faces a two-sided constraint: too little drug leaves bacteria to persist, while a strong host inflammatory response recruited to help clearance carries its own cost of immunopathology. Within-host models have explored this clearance–immunopathology trade-off by treatment-protocol simulation or numerical bifurcation analysis, but neither tradition provides an explicit, closed-form threshold that tells us how much immune recruitment sterility requires at a given drug dose. We analyse a minimal two-dimensional model – bacteria growing logistically under Emax-type pharmacodynamics and killed by phagocytes (mass-action or Michaelis–Menten), phagocytes receiving baseline and bacteria-triggered recruitment with autocatalytic amplification – and prove a main theorem: sterility is stable if and only if the recruitment influx λ exceeds a closed-form threshold $\lambda^\dagger(d) = \gamma_{\text{eff}}(d) \cdot \mu / \kappa$, equality marking a transcritical bifurcation at which a stable endemic equilibrium is born. Together with a pathology boundary $\lambda_P = \mu \cdot P_{\text{crit}}$, this defines three regimes – sterile window, chronic carriage, inflammatory failure – flanked by two qualitatively different failure modes: below the window, a transcritical transition to carriage; above it, not a dynamical instability but an exogenous threshold crossing into pathological phagocyte densities (or exponential runaway if autocatalysis overwhelms decay). The window is structurally robust: its two edges are governed by disjoint parameter combinations – $\lambda^\dagger$ involves only $(\gamma_{\text{eff}}, \mu, \kappa)$ and λ_P only (μ, P_{crit}) – so the relative window $\kappa P_{\text{crit}} / \gamma_{\text{eff}}(d)$ is independent of μ .

1. Introduction

The outcome of antibacterial chemotherapy is decided not by the drug alone but by a tripartite interaction between the pathogen, the drug, and the host’s recruited inflammatory cells. Within-host mathematical modelling has a long tradition of capturing this interaction (Antia et al. 1994; Nowak and May 2000; Perelson and Weisbuch 1997; Eftimie et al. 2016; Perelson 2002): bacterial load grows, the immune response is recruited, and killing proceeds through both pharmacological and immunological channels. What has received far less analytical attention is that the two channels of “killing” pull in opposite directions on the host. The same phagocyte recruitment that helps clear bacteria generates the acute-phase response (Gabay and Kushner 1999) and, when excessive, the tissue-damaging immunopathology that dominates severe infection (Long and Graham 2011; Rittirsch et al. 2008; Graham et al. 2005). Dosing a drug at an infected site therefore sits inside a *window*: enough drug must be given – or enough phagocytes recruited – to clear the bacteria, but not so much recruitment that the inflammatory response itself becomes the disease. Clinicians navigate between undertreatment and hyperinflammation at the bedside every day; the question we ask here is what this window *is*, geometrically, in a tractable model.

Two modelling traditions have approached pieces of this question, but neither delivers an explicit recruitment threshold. The first tradition simulates treatment protocols: pharmacodynamic functions are combined with host immune dynamics and different dosing or adaptation strategies are compared numerically (Gjini and Brito 2016; Reynolds et al. 2006; Herald 2010). These studies are rich in protocol

detail but leave the dependence of the outcome on the pair of control parameters (drug dose d , recruitment influx λ) unexplored as a phase diagram. The second tradition performs numerical bifurcation analysis of host–pathogen ODE systems, locating qualitative transitions in parameter space (Flores-Garza et al. 2023) with general-purpose continuation environments (Ermentrout 2002; Dhooge et al. 2003). Numerical bifurcation is powerful but returns curves and tables rather than formulas; the mechanism by which one boundary is created – which parameters it depends on, and which it ignores – can remain opaque. Meanwhile, the conceptual trade-off between bacterial clearance and immunopathology is mature in the evolutionary and immunological literature (Long and Graham 2011; Medzhitov 2010), and experiments have shown that bacterial populations can survive sub-inhibitory drug levels through collective and ecological mechanisms (Sorg et al. 2016; Yurtsev et al. 2013; Balaban et al. 2004); yet this trade-off has not been translated into an explicit dose–recruitment plane with closed-form boundaries. The gap is practical as well as conceptual: without a formula, one cannot see at a glance whether widening one constraint (say, lowering the pathology threshold) actually widens the window, or whether the two constraints are even coupled.

In this paper we close this gap with the simplest possible setting: a two-dimensional ordinary differential equation for bacteria B and phagocytes P , in which bacteria grow logistically at a drug-reduced rate $\gamma_{\text{eff}}(d) = \gamma - E_{\text{max}} d^z / (d^z + \text{EC50}^z)$. We prove a closed-form recruitment threshold $\lambda^+(d)$ for sterility, in two versions – mass-action and Michaelis–Menten killing – and show that under the natural calibration $\kappa_M = \kappa h$ the two coincide pointwise; the boundary is a transcritical bifurcation at which a stable endemic equilibrium, also available in closed form, is born. Second, we show that adding the pathology boundary $\lambda_P = \mu \cdot P_{\text{crit}}$ produces a three-regime map – a sterile window, chronic carriage, and inflammatory failure – and we prove a structural robustness result: the window’s two edges are governed by disjoint parameter combinations, $(\gamma_{\text{eff}}, \mu, \kappa)$ below and (μ, P_{crit}) above; the relative window $\kappa P_{\text{crit}} / \gamma_{\text{eff}}(d)$ is therefore independent of μ .

The main results can be previewed numerically. With illustrative parameter anchors, the recruitment needed for sterility without drug is $\lambda^+(0) = 3.0$ (in units of 10^3 phagocytes $\mu\text{L}^{-1} \text{h}^{-1}$) and the pathology boundary sits at $\lambda_P = 7.5$, giving a no-drug window of width $w(0) = 4.5$ that is monotonically non-decreasing in dose. The minimum effective dose at baseline recruitment $\lambda = 1.5$ is $d_{\text{min}} = 0.60$ for $z = 1$ (Fig. 5a).

The rest of the paper is organised as follows. Section 2 specifies the model, the dose dependence, and the parameter anchors. Section 3.1 states and proves the main theorem; Sections 3.2–3.3 construct the three-regime map and establish the structural robustness of the window; Section 3.4 contrasts the two failure modes; Section 3.5 treats killing saturation and a dimensional pitfall; Section 3.6 derives the minimum effective dose, the cost optimum, and the pulse-versus-sustained comparison; Section 3.7 summarises robustness. Section 4 discusses the relation to prior work, the clinical translation of the failure modes, and the limitations of the framework.

2. Model

2.1 State variables and baseline system

Time t is measured in hours. The bacterial load B is measured in 10^6 CFU per g of tissue. The phagocyte variable P denotes the phagocyte (neutrophil-scale) population at the infection site (Nathan 2006); we express it in blood-count units, 10^3 cells per μL , as a proxy for the tissue-infiltrate scale. This is a deliberate spatial simplification – B is per gram of tissue while the natural measurement of P is per μL of blood – which we carry as an explicit assumption throughout rather than resolve (Section 4.3). The drug dose d is normalised by its EC_{50} , so $d = 1$ means one half-maximal concentration. The baseline model is

$$\dot{B} = \gamma_{\text{eff}}(d) B \left(1 - \frac{B}{K}\right) - \kappa PB, \quad \dot{P} = \lambda + \rho B - \delta P + \sigma P \equiv \lambda + \rho B - \mu P,$$

1

where $\gamma_{\text{eff}}(d)$ is the drug-reduced growth rate defined in Eq. (4), and the net phagocyte decay rate is

$$\mu \equiv \delta - \sigma,$$

2

We require $\mu > 0$ for a regulated inflammatory response; $\sigma \geq \delta$ is itself a failure mode (Section 3.4). The sterile steady state of (1) is

$$(B^*, P^*) = \left(0, \frac{\lambda}{\mu}\right),$$

3

so the sterile phagocyte density is set by the recruitment-to-decay ratio alone – a fact that will do considerable work below. Note that autocatalysis σ enters the analysis *only* through μ : it does not appear in any threshold except via the single combination $\delta - \sigma$.

2.2 Pharmacodynamics of dosing

Drug action follows the E_{max} pharmacodynamic form (Regoes et al. 2004; Craig 1998; Andes and Craig 2002):

$$\gamma_{\text{eff}}(d) = \gamma - E_{\text{max}} \frac{d^z}{d^z + \text{EC}_{50}^z}, \quad z \in \{1, 2\},$$

4

with maximal effect $E_{\max} > \gamma$. Since γ_{eff} decreases monotonically in d and $\gamma_{\text{eff}}(d) < 0$ for large d , sufficiently high doses are bacteriostatic-to-bactericidal independent of recruitment; for $z = 1$ with our anchors $\gamma_{\text{eff}} = 0$ at $d = 3$, and for $z = 2$ at $d = \sqrt{3} \approx 1.73$. Dose therefore shifts the system along exactly one axis — the bacterial growth–killing balance — and never touches the phagocyte compartment directly. The regime $\gamma_{\text{eff}} < 0$ (beyond $d \approx 3$ for $z = 1$) lies outside the validity of the logistic framework; we make this precise in Remark 2 and confine all figures to $\gamma_{\text{eff}} \in [0, \gamma]$.

2.3 Killing saturation (Michaelis–Menten extension)

Phagocytic killing saturates at high bacterial load (Stossel 1974; Stossel 1973). The extended model replaces κPB by

$$\kappa_M \frac{PB}{h + B},$$

5

with half-saturation h (in units of B). Because this term is not linear in B , the killing rate constant κ_M is not dimensionally comparable with κ and is calibrated in Section 3.5.

2.4 Parameter anchors

Table 1 lists the protocol parameter anchors. These are illustrative values chosen to be dimensionally self-consistent and physiologically ordered (baseline sterile phagocyte density $P^* = \lambda/\mu = 5$ within the physiological range; pathology threshold $P_{\text{crit}} = 25$ in the same units).

Table 1
Protocol parameter anchors (illustrative; clinical calibration deferred).

Symbol	Meaning	Value	Unit	Anchor
γ	maximal bacterial growth rate	0.15	h^{-1}	in-host ODE literature (Antia et al. 1994)
K	tissue carrying capacity	10	10^6 CFU/g	protocol
κ	mass-action killing rate	0.015	$1/(10^3 \text{ cells} \cdot \mu\text{L}^{-1} \cdot \text{h})$	phagocytosis literature (Stossel 1974)
h	MM half-saturation in B	5	10^6 CFU/g	phagocytosis saturation (Stossel 1974)
κ_M	MM killing rate	0.075	$\text{B}/(\text{P} \cdot \text{h})$ (see § 3.5)	protocol calibration κ_M
δ	phagocyte loss rate	0.4	h^{-1}	protocol value (cycling half-life $\ln 2/\delta \approx 1.7 \text{ h}$; fast — see § 4.3)
σ	autocatalytic amplification	0.10	h^{-1}	chemokine literature (Luster 1998), $\sigma < \delta$
ρ	bacteria-triggered recruitment	0.05	$10^3 \text{ cells} \cdot \mu\text{L}^{-1} \cdot \text{h}^{-1} / (10^6 \text{ CFU/g})$	chemokine literature (Luster 1998)
λ_{base}	baseline recruitment influx	1.5	$10^3 \text{ cells} \cdot \mu\text{L}^{-1} \cdot \text{h}^{-1}$	homeostatic, $P^* = \lambda/\mu = 5$
P_{crit}	pathology threshold in P	25	$10^3 \text{ cells}/\mu\text{L}$	protocol value; chosen to order sterile baseline and pathology regime (§ 3.4.1)
E_{max}	maximal drug effect	0.20	h^{-1}	pharmacodynamics (Regoes et al. 2004), E_{max}
EC50, z	dose scale, Hill coefficient	1; {1,2}	dose; —	pharmacodynamics (Regoes et al. 2004)

3. Results

3.1 Main theorem: the closed-form recruitment threshold

Throughout, $\mu = \delta - \sigma > 0$ and $0 \leq \gamma_{\text{eff}}(d) < \gamma$ — the therapeutically relevant range in which the logistic growth term retains its sign structure; the regime $\gamma_{\text{eff}} < 0$ is excluded (Remark 2).

Theorem 1

(double closed-form recruitment threshold). Let $\mu = \delta - \sigma > 0$ and $0 \leq \gamma_{\text{eff}}(d) < \gamma$. Then:

(i) The sterile steady state (3) is locally asymptotically stable against bacterial invasion if and only if

$$\lambda > \lambda^\dagger(d), \quad \lambda_{\text{MA}}^\dagger(d) = \frac{\gamma_{\text{eff}}(d) \mu}{\kappa} \text{ (mass-action)},$$

6

$$\lambda_{\text{MM}}^\dagger(d) = \frac{\gamma_{\text{eff}}(d) \mu h}{\kappa_M} \text{ (Michaelis-Menten)}.$$

7

At $\lambda = \lambda^\dagger(d)$ the sterile state is non-hyperbolic: the invasion eigenvalue vanishes and the stability boundary is a transcritical bifurcation with transversality

$$\frac{\partial s_B}{\partial \lambda} \Big|_{\lambda^\dagger} = -\frac{\kappa}{\mu} \neq 0 \text{ (MA)}, \quad -\frac{\kappa_M}{\mu h} \neq 0 \text{ (MM)},$$

where s_B is the invasion eigenvalue at the sterile state: $s_B = \gamma_{\text{eff}} - \kappa\lambda/\mu$ (mass action) or $s_B = \gamma_{\text{eff}} - \kappa_M\lambda/(\mu h)$ (Michaelis-Menten).

1. (ii) Under the calibration $\kappa_M = \kappa h$, the two thresholds (6) and (7) coincide, so the Michaelis-Menten model inherits the mass-action result.
2. (iii) For $\lambda < \lambda^\dagger(d)$, a unique positive endemic equilibrium exists,

$$B_{\text{endo}}^* = \frac{K(\gamma_{\text{eff}}\mu - \kappa\lambda)}{\gamma_{\text{eff}}\mu + \kappa\rho K}, \quad P_{\text{endo}}^* = \frac{\gamma_{\text{eff}}(K\rho + \lambda)}{K\kappa\rho + \gamma_{\text{eff}}\mu},$$

8

and it is locally asymptotically stable throughout the endemic branch ($0 < \lambda < \lambda^\dagger(d)$), with trace

$$\text{tr} = -\mu - \frac{\gamma_{\text{eff}} B_{\text{endo}}^*}{K} < 0 \text{ and } \det = \gamma_{\text{eff}}\mu - \kappa\lambda > 0.$$

9

Proof sketch. Linearising (1) at $B = 0$, the invasion eigenvalue for bacteria is the growth rate at low load net of phagocytic removal: $s_B = \gamma_{\text{eff}} - \kappa\lambda/\mu$ for mass action, since killing contributes $-\kappa PB$ with $P \rightarrow \lambda/\mu$; for Michaelis-Menten, differentiating the killing term (5) with respect to B at $B = 0$ gives $\kappa_M P/h$, so $s_B = \gamma_{\text{eff}} - \kappa_M \lambda/(\mu h)$. Stability of the sterile state requires $s_B < 0$, which is (6)–(7) with strict inequality; at $\lambda = \lambda^\dagger(d)$, $s_B = 0$, and the sterile and endemic states exchange stability.

Remark 1

(MM endemic level). With Michaelis–Menten killing, the endemic state is no longer rational in the parameters but is available in closed form as the positive root of a quadratic. Writing the stationary equations in terms of $g = \gamma_{\text{eff}}/\kappa_M$

$$a B^{*2} + b B^* + c = 0, \quad a = \frac{\gamma_{\text{eff}}\mu}{\kappa_M K}, \quad b = \rho - \frac{\gamma_{\text{eff}}\mu}{\kappa_M} \left(1 - \frac{h}{K}\right), \quad c = \lambda - \lambda_{\text{MM}}^{\dagger},$$

10

so B_{MM} is the positive root of (10), available in closed form.

Remark 2

(outside the therapeutic range: $\gamma_{\text{eff}} < 0$). The restriction $0 \leq \gamma_{\text{eff}}(d) < \gamma$ in Theorem 1 is not cosmetic. For $\gamma_{\text{eff}} < -\kappa_p K/\mu$ (with the anchors, $d \gtrsim 7$ for $z = 1$), the denominator of (8) turns negative while the numerator is also negative: (8) yields a positive equilibrium with $\det < 0$ — a saddle, not a stable endemic state. Moreover, for $\gamma_{\text{eff}} < 0$ and $B > K$ the logistic term $\gamma_{\text{eff}} B(1 - B/K)$ is itself positive (two negative factors), and at large load it dominates: $dB/dt \approx (|\gamma_{\text{eff}}|/K)B^2$, giving finite-time divergence. A drug so strong that it reverses the sign of bacterial growth everywhere is outside what a growth-modifying logistic term can represent; a drug-only kill term would be required. All figures and quantitative statements in this paper are confined to $\gamma_{\text{eff}} \in [0, \gamma]$.

Three features of Theorem 1 deserve emphasis. First, the threshold is closed form in the two control parameters (d, λ) : sterility requires $\lambda > \lambda^{\dagger}(d)$, and since $\partial\gamma_{\text{eff}}/\partial d < 0$, raising the dose lowers the recruitment required for sterility.

3.2 Three regimes in the (d, λ) plane

The (d, λ) plane decomposes into three regimes (Fig. 1b, Fig. 2a):

- **Region I — sterile window:** $\lambda > \lambda^{\dagger}(d)$ and $P^* = \lambda/\mu \leq P_{\text{crit}}$. Bacteria are cleared and the inflammatory steady state is below the pathology threshold. In (d, λ) this is the band $\lambda^{\dagger}(d) < \lambda \leq \lambda_P$

$$\lambda_P \equiv \mu P_{\text{crit}}.$$

- **Region II — chronic carriage:** $\lambda < \lambda^{\dagger}(d)$. The endemic equilibrium (8) is positive and stable; clearance fails through the transcritical transition. At baseline recruitment $\lambda = 1.5$ and low dose, the model settles at $B^* \approx 2.9$ (10^6 CFU/g) with only mildly elevated phagocytes ($P^* \approx 5.5$).
- **Region III — inflammatory failure:** $\sigma \geq \delta$ (the phagocyte equation is self-amplifying and no steady state exists; divergence, see below) or $P^* = \lambda/\mu > P_{\text{crit}}$ (sterile but pathologically inflamed). The λ_P boundary is horizontal in (d, λ) , set by the phagocyte balance alone.

With the anchored parameters, the lower boundary is $\lambda^\dagger(d) = \gamma_{\text{eff}}(d)\mu/\kappa$ with $\lambda^\dagger(0) = \gamma\mu/\kappa = 3.0$, decreasing to $\lambda^\dagger \leq 0$ once $\gamma_{\text{eff}} \leq 0$ (at $d = 3$ for $z = 1$, where sterility needs no recruitment — Theorem 1(i) continues to hold there since $s_B < 0$ for all $\lambda \geq 0$); the upper boundary is the horizontal line $\lambda_P = \mu \cdot P_{\text{crit}} = 7.5$ with the anchors (Fig. 2a).

We cross-validated every analytic boundary numerically, independently of eigenvalue analysis: long-run simulation ($T = 8000$ h; adaptive ODE integration with SciPy (Virtanen et al. 2020)) with bisection on λ (tolerance tightened to 0.002) locates the clearance/carriage boundary to a maximum deviation of 1.22×10^{-2} from the closed form — an error budget dominated by critical slowing down at the transcritical point (finite-time resolution of order $5/(0.05 \cdot T) \approx 0.0125$) — and a randomised classification of 48 (d, λ, σ) points reproduces the analytic regimes in 44 of 44 cases once a ± 0.12 exclusion band around the boundaries is removed (Fig. 2a, open circles; validation files in the repository). The runaway branch was verified at $\sigma \in \{0.41, 0.44, 0.47\} > \delta = 0.4$, each triggering divergence (Fig. 2b).¹

¹ Exactly at $\sigma = \delta$, growth is *linear*, not exponential: $dP/dt = \lambda + pB \geq \lambda > 0$. The exponential regime requires $\sigma > \delta$ strictly.

Theorem 1

is a local result. Global attraction of the sterile state within Region I — that all initial loads $B(0) \leq K$ converge to $(0, \lambda/\mu)$ — is supported numerically (every simulated trajectory in Region I converges to the sterile state, Fig. 4) but is not proven; we flag it as open.

3.3 Why the window does not collapse — and what “does not” means

The window could in principle shrink to zero as parameters vary, which would make the dosing problem unsolvable: any dose either fails to clear or inflames. The structural content of the model is a precise statement of when this can and cannot happen (Fig. 2c).

Proposition 1

(window geometry; relative non-collapse). For $0 \leq \gamma_{\text{eff}}(d) < \gamma$ and $\mu > 0$:

(i) *The window width is*

$$w(d) = \lambda_P - \max\left(\lambda^\dagger(d), 0\right) = \mu \left(P_{\text{crit}} - \frac{\gamma_{\text{eff}}(d)}{\kappa}\right) \geq w(0) = \mu \left(P_{\text{crit}} - \frac{\gamma}{\kappa}\right),$$

11

non-decreasing in d and saturating at λ_P once $\gamma_{\text{eff}}(d) \leq 0$.

1. Collapse ($w \leq 0$) requires $\gamma_{\text{eff}}(d) \geq \kappa P_{\text{crit}}$ — phagocytic killing so inefficient that even the drug-free growth rate γ cannot be contained by a phagocyte population at the pathology threshold. With the anchors, $\gamma = 0.15 < \kappa P_{\text{crit}} = 0.375$, so collapse is excluded with the anchors.
2. (iii) *The absolute width (11) scales linearly with μ and vanishes as $\sigma \rightarrow \delta^-$ (cf. Figure 2b). The scale-free statement is the relative window*

$$\frac{\lambda_P}{\lambda^\dagger(d)} = \frac{\kappa P_{\text{crit}}}{\gamma_{\text{eff}}(d)},$$

12

which is independent of μ . Throughout the paper we therefore assume μ bounded away from zero ($\mu \geq \mu_{\text{min}}$).

The reason for robustness is parameter decoupling — the point we regard as the main theoretical insight of the paper. The lower edge $\lambda^\dagger(d)$ is determined by the bacterial growth–kill balance and contains only $(\gamma_{\text{eff}}, \mu, \kappa)$; the upper edge λ_P is determined by the pathology threshold and contains only (μ, P_{crit}) , independent of dose, and $\lambda^\dagger$ is independent of P_{crit} . Drug dosing moves only the lower edge; the pathology ceiling never moves with d . Collapse would require the pathology threshold to fall below the recruitment needed for sterility — $\gamma_{\text{eff}} \geq \kappa P_{\text{crit}} = 0.375$ with the anchors, which lies far above the admissible range.

The decoupling is also robust to perturbation. Under $\pm 30\%$ perturbation of σ (the one shared parameter), the window width at $d = 1$ takes the values $w \in \{7.15, 6.50, 5.85\}$ for $\sigma \in \{0.07, 0.10, 0.13\}$ — narrowest when amplification is strongest, but far from zero. A full $\pm 30\%$ sweep over $(\gamma, \kappa, \delta, \sigma, E_{\text{max}})$ keeps every boundary within the same $\pm 30\%$ band, and E_{max} has an identically zero effect on $\lambda^\dagger$ and hence on the window's lower edge (Section 3.7). In the anchored regime with $\mu \geq \mu_{\text{min}}$, the width remains positive.

The robustness extends one step further, to the carriage side itself:

Proposition 2

(carriage is not pathological). For $0 < \gamma_{\text{eff}}$

$$\sup_{\lambda < \lambda^\dagger} P_{\text{endo}}^* = \frac{\lambda^\dagger}{\mu} = \frac{\gamma_{\text{eff}}}{\kappa}.$$

13

Hence Region II is pathology-free ($P \leq P_{\text{crit}}$ for all $\lambda < \lambda^\dagger$) if and only if $\gamma_{\text{eff}} \leq \kappa P_{\text{crit}}$ — the same inequality as Proposition 1(ii). With the anchors ($\gamma < \kappa P_{\text{crit}} = 0.375$), the condition is satisfied throughout Region II.

One inequality thus unifies two results that could otherwise look accidental: the window exists and the carriage region carries no pathological inflammation are the same statement, $\gamma \leq \kappa P_{\text{crit}}$. Reading (13) biologically: as recruitment falls toward the transcritical boundary, the endemic inflammatory level approaches $\gamma_{\text{eff}}/\kappa$ from below — carriage never inflames beyond what sterility would have required. (Proof of (13): $dP_{\text{endo}}^*/d\lambda = \gamma_{\text{eff}}/(K\kappa\rho + \gamma_{\text{eff}}\mu) > 0$, and substituting $\lambda \rightarrow \lambda^\dagger = \gamma_{\text{eff}}\mu/\kappa$ in (8) gives $P_{\text{endo}}^* \rightarrow \gamma_{\text{eff}}/\kappa$, consistent with the bound above.

3.4 Two qualitatively different failure modes flank the window

The window's edges are not merely two sides of the same coin; they are two different kinds of transition (Fig. 4, Table 2).

Below the window (Region II): clearance failure as a transcritical bifurcation. Crossing $\lambda^\dagger$ from above, the sterile attractor is exchanged for the endemic attractor (8) in a transcritical bifurcation. The system remains near the same neighbourhood of state space: bacteria persist at moderate levels ($B^* \approx 2.9$ at $d = 0.2, \lambda = 1.5$), phagocytes rise mildly ($P^* \approx 5.5$), and the CRP proxy remains near baseline (≈ 3 mg/L; Section 3.4.1). This is chronic carriage — at the bedside, colonisation and biofilm-associated persistence — clinically quiet but epidemiologically consequential, and the setting in which collective survival mechanisms at sub-inhibitory drug levels operate (Sorg et al. 2016; Yurtsev et al. 2013).

Above the window (Region III): immunopathology as an exogenous threshold crossing. Crossing λ_p

$$P(t) = \left(P(0) + \frac{\lambda}{\sigma - \delta} \right) e^{(\sigma - \delta)t} - \frac{\lambda}{\sigma - \delta},$$

14

(the full reference solution of the linear runaway, including the constant influx; with $B \approx 0$ the ρB term is negligible). This is verified numerically: at $\sigma = 0.5 > \delta = 0.4$ with $P(0) = 5, \lambda = 1.5$, the simulated trajectory matches (14) and reaches $\approx 2.1 \times 10^{14}$ at $T = 300$ h (Fig. 4d). Biologically, real systems saturate; mathematically, however, this branch is the same explosion mechanism familiar from chemotactic aggregation models of the Keller–Segel type, where self-amplifying recruitment destroys boundedness (Segel 1984; Jäger and Luckhaus 1992; Hillen and Painter 2009); we invoke it here only as a mathematical analogy for the runaway end of the inflammatory spectrum and do not pursue a spatial model.

The contrast matters clinically. The two failure modes correspond to the two real bedside failures of anti-infective therapy — *persistence* (quiet, below the window) and *hyperinflammation* (acute, above it) — and they respond to different interventions: persistence calls for more drug or supported recruitment; hyperinflammation calls for source control of recruitment itself, since no dose change can lower P_{sterile}^*

$= \lambda/\mu$. A one-dimensional statement — “the dose is wrong” — conflates transitions of different type, direction, and remedy.

Table 2
The two failure modes flanking the window (numerical scenarios of Fig. 4).

Scenario	d	λ	σ	Terminal B (10^6 CFU/g)	Terminal P ($10^3/\mu\text{L}$)	CRP proxy	Regime
Chronic carriage	0.2	1.5	0.10	2.94	5.49	3.4 mg/L	II
Cleared (in window)	1.6	1.5	0.10	$< 10^{-6}$	5.0	1 mg/L	I
Immune pathology	1.6	9.0	0.10	$< 10^{-16}$	30.0	124.7 mg/L	III
σ -runaway	1.6	1.5	0.50	$< 10^{-23}$	2.1×10^{14} (T = 300 h)	— (diverges)	III

Phase-plane check

for the carriage scenario the B- and P-nullclines intersect at the endemic point, whose coordinates match the closed form (8); the window scenario’s trajectories instead converge to the sterile fixed point (Fig. 4c).

3.4.1 CRP proxy

To give P a bedside semantic, we use an illustrative linear mapping $\text{CRP} = 1 + 4.95 \cdot (P_{ss} - 5)$ mg/L, anchored so that the baseline sterile density $P_{ss} = 5$ maps to $\text{CRP} = 1$ mg/L.

3.5 Killing saturation: Michaelis–Menten versus mass action, and a dimensional pitfall

The main theorem is robust to the shape of the killing term. Under the calibration $\kappa_M = kh$, the two thresholds coincide exactly: $\lambda^\dagger$ is identical under mass action and Michaelis–Menten.

The calibration, however, hides a dimensional trap. κ has dimensions $1/(P \cdot h)$ (per-capita killing per phagocyte per hour), while κ_M has dimensions $B/(P \cdot h)$ (so that $\kappa_M = kh = 0.075$, and the number 0.075 cannot be compared with $\kappa = 0.015$ without the factor h).

3.6 Minimum effective dose, cost optimum, and the pulse–sustained distinction

Minimum effective dose. Solving γ_{eff}

$$d_{\min}(\lambda) = \text{EC50} \left[\frac{\gamma - \kappa \lambda / \mu}{E_{\max} - \gamma + \kappa \lambda / \mu} \right]^{1/z},$$

valid for $\lambda < \lambda^\dagger(0)$; for $\lambda \geq \lambda^\dagger(0) = 3$ no drug is needed. At baseline recruitment $\lambda = 1.5$, $d_{\min} = 0.60$ for $z = 1$ and 0.775 for $z = 2$ — a steeper Hill curve shifts the threshold right, since γ_{eff} falls more slowly at low dose (Fig. 3b, Fig. 5a). Larger λ raises the kill requirement $\kappa\lambda/\mu$ and shifts $d_{\min}$ leftward ($d_{\min} = 0.14$ at $\lambda = 2.5$; Fig. 3b).

Cost-weighted optimum. With protocol weights, the total cost

$$J(d) = T_{\text{clear}}(d) + 0.1 \int_0^{200} P dt + 60 d$$

(clearance time capped at 500 h; inflammation integral over a 200-h horizon; linear dose cost) has an interior optimum at $d^* \approx 2.3$: higher doses clear faster but only up to a plateau ($T_{\text{clear}} \approx 185$ h at high dose), while the dose cost grows linearly, so the optimum balances speed against drug expenditure (Fig. 5b). Without a dose-cost term, J decreases monotonically to the boundary $d_{\min}$, so the optimum collapses onto the minimum effective dose.

Window as a steady-state, not a pulse, property. At $\lambda = 1.5$, sustained dosing at $d = 2.2$ clears in ≈ 221 h. A 24-hour pulse at $d = 3$ followed by withdrawal relapses to the drug-free endemic level $B^* \approx 4.29$ — the $d = 0$ endemic equilibrium of (8); the 2.94 of Table 2 belongs to the $d = 0.2$ carriage scenario — despite the pulse being above $d_{\min}$ while it lasts. A pulse followed by continued maintenance at $d = 2.2$ performs slightly better than sustained dosing alone (Fig. 5c). The reason is structural: the clearance condition $\gamma_{\text{eff}}(d) < \kappa\lambda/\mu$ must hold for as long as the load stays above detection; a pulse satisfies it only transiently.

3.7 Robustness of the geometry

A $\pm 30\%$ one-at-a-time sensitivity sweep over all anchored parameters (Fig. 3a includes the independent numerical continuation; full tables in the repository) confirms the geometry's hierarchy of sensitivities:

1. $\lambda^\dagger(0)$ is first-order homogeneous in its three parameters: $\pm 30\%$ in γ or $(\delta - \sigma)$ or κ moves it $\pm 30\%$ correspondingly; $E_{\max}$ enters only through $\gamma_{\text{eff}}(d)$ and leaves λ_p untouched.
2. $d_{\min}(\lambda)$ responds to $(\gamma, \kappa, E_{\max})$ through γ_{eff} and to μ through the kill requirement $\kappa\lambda/\mu$, but not to p or K .
3. The window width $w(d = 1)$ remains within $[5.85, 8+]$ under every tested perturbation combination, and K, p have zero effect on the lower edge (verified symbolically and numerically). Combined with Propositions 1–2, the robustness is structural: disjoint parameterisation of the edges, a μ -independent relative window (12), and one inequality ($\gamma \leq \kappa_{\text{Pcrit}} = 0.375$ with the anchors).

4. Discussion

4.1 Relation to previous work

Our contribution is deliberately positioned between the two existing traditions. Treatment-protocol simulation studies, exemplified by Gjini & Brito's integration of antimicrobial therapy with host immunity (Gjini and Brito 2016), compare classical versus adaptive treatment strategies in a pharmacodynamic-immunological model; they establish that joint drug-immune action changes the optimal protocol, but they do not map the (d, λ) plane, do not provide a closed-form recruitment threshold, and do not carry an explicit immunopathology cost axis. Numerical bifurcation studies of host-pathogen systems (Flores-Garza et al. 2023; Ermentrout 2002; Dhooge et al. 2003) locate qualitative transitions accurately but report them as computed curves; the analytic form of the boundary, and hence the parameter decoupling that makes our robustness result possible, is invisible to a purely numerical workflow. The clearance-immunopathology trade-off itself is well established conceptually (Gabay and Kushner 1999; Long and Graham 2011) — immunopathology is a ubiquitous cost of the inflammatory response with public-health consequences (Long and Graham 2011) — but, to our knowledge, has not previously been embedded in an explicit dose-recruitment phase diagram with both boundaries in closed form.

An evolutionary line of work asks which direction of dosing is safe when bacteria can adapt; there, the answer is determined by the net-dose slope of the pharmacodynamic function. The present paper asks the orthogonal ecological-immunological question: *whether a safe direction exists at all*, and the answer — yes, whenever the growth-kill and pathology constraints are decoupled as in Proposition 1 and μ is bounded away from zero — is independent of evolutionary considerations. The Emax pharmacodynamic description (Regoes et al. 2004) and the optimal-control toolkit are common to both analyses; together they suggest that the geometry of the window (existence, width, orientation) and the evolution within it can be analysed in modular fashion.

4.2 Clinical translation and calibration route

The two-sided structure of the window translates into two distinct clinical failure narratives, each with its own observable. Undertreatment (Region II) manifests as persistence and carriage with near-baseline inflammatory markers (CRP proxy ≈ 3 mg/L in the carriage scenario); hyperinflammation (Region III) manifests as sterile-but-inflamed tissue with CRP proxies ≈ 125 mg/L, or, in the runaway limit, fulminant dysregulation of the type whose clinical semantics parallel the Sepsis-3 definitions (Singer et al. 2016). Because the acute-phase response tracks systemic inflammation (Sproston and Ashworth 2018), serial inflammatory markers are the natural observable for the *upper* edge, while cultures or molecular load measurements track the *lower* edge. Our CRP mapping is deliberately transparent — linear, anchored at two physiological points — so that replacing it with a calibrated $P \rightarrow \text{CRP}$ (or $P \rightarrow \text{damage}$) map is a drop-in operation that changes the upper boundary's units but not the geometry.

We are equally explicit about what is not measurable on the λ axis. The recruitment influx λ — a tissue-level phagocyte supply rate — has no direct clinical readout. Candidate proxies exist (circulating band-cell counts, G-CSF levels, tissue myeloperoxidase as a local infiltrate marker), but each is an indirect and imperfect stand-in, and intervention evidence is sobering: prophylactic recruitment support (e.g. G-CSF)

has shown mixed-to-negative results in infection prophylaxis trials (Root et al. 2003), so we do not propose λ titration as a near-term clinical lever. The honest statement is that λ is a model coordinate — the axis along which host inflammatory drive varies — and that the window’s actionable edge, with current tools, is the drug axis d . Estimating (λ, ρ, μ) at an infection site, and replacing the protocol value P_{crit} with a measured tissue density would make the regime map patient-specific.

4.3 Limitations

We list the limitations in order of how much they constrain interpretation.

1. **Illustrative parameter anchors.** Parameters are dimensionally self-consistent and literature-anchored (Antia et al. 1994; Regoes et al. 2004; Luster 1998; Stossel 1974) but not clinically fitted; all numerical effect sizes ($d_{\text{min}} = 0.6$, $d^* \approx 2.3$, clearance times) are protocol-scale statements. The theorems are parameter-free; the numbers are not. In particular $\delta = 0.4 \text{ h}^{-1}$ implies a phagocyte turnover half-life of $\approx 1.7 \text{ h}$, which is fast even for neutrophil-scale dynamics (cf. measured neutrophil kinetics in vivo (Summers et al. 2010; Tak et al. 2013)); it is a protocol choice, and μ (hence λ_p) is correspondingly protocol-scale.
2. **Spatial mismatch in P .** P is expressed in blood-count units ($10^3 \text{ cells}/\mu\text{L}$) as a proxy for the tissue infiltrate, while B is per gram of tissue; P_{crit} is correspondingly a blood-count threshold, and the conversion assumes a fixed tissue-to-blood ratio.
3. **Qualitative CRP proxy.** The mapping of Section 3.4.1 is static and linear; real CRP peaks 48–72 h after insult with a $\sim 19 \text{ h}$ half-life (Sproston and Ashworth 2018), so the proxy carries attractor semantics only, not kinetics.
4. **Simplified phagocyte dynamics.** One compartment, linear loss, linear autocatalysis; no lifespan distribution, no tissue partitioning. The $\sigma > \delta$ runaway is a true divergence (14), whereas real systems saturate; the λ_p boundary is dose-independent by construction.
5. **The $\gamma_{\text{eff}} < 0$ regime.** As Remark 2 shows, a sufficiently strong drug creates a positive saddle and finite-time divergence of the logistic term — the framework, not the biology, fails there. A drug-only kill term would extend the theory; all results here are confined to $\gamma_{\text{eff}} \in [0, \gamma)$.
6. **Finite-time continuation resolution.** The 1.22×10^{-2} deviation of simulation-based continuation from the closed form (bisection tolerance tightened to 0.002) is dominated by critical slowing down near the transcritical point (~ 0.0125 at $T = 8000 \text{ h}$); we make no assertions within a ± 0.12 band of the boundary and cover the remainder with analytic–numeric cross-validation.
7. **Scope of the robustness proof.** Propositions 1–2 hold under the specific functional forms of (1) and (4); other recruitment or growth laws could couple the two boundaries (e.g. a dose-dependent pathology threshold, or damage-mediated recruitment $\rho(d) \cdot B$). The decoupling argument identifies *which* modelling

choices protect the window; it is a diagnosis, not a universality claim. Global attraction within Region I is numerically supported but unproven (Section 3.2).

8. Single strain, single immune compartment, no evolution. Resistance emergence, within-host competition, macrophage–neutrophil interactions, and adaptive immunity are excluded by construction (Perelson and Weisbuch 1997; Eftimie et al. 2016; Mideo et al. 2008); the interface with the evolutionary treatment-direction literature is the designated next step.

4.4 Conclusion

We have shown that in a minimal host–pathogen model with drug and recruitment as the two control handles, the therapeutic window admits a complete closed-form description: a transcritical recruitment threshold $\lambda^+(d) = \gamma_{\text{eff}}(d)\mu/\kappa$ below, a pathology ceiling $\lambda_P = \mu P_{\text{crit}}$ above, and a window whose two edges are governed by disjoint parameterisations — so the relative window is independent of the inflammatory feedback and the absolute width is protected whenever μ is bounded away from zero. One inequality, $\gamma \leq \kappa_{P_{\text{crit}}} = 0.375$ with the anchors, is all that separates the window from immunopathology.

Declarations

Competing interests:

The authors declare no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used Kimi K3 (Moonshot AI) in order to assist with code development and language editing. The author reviewed and edited all AI-generated content and takes full responsibility for the integrity and accuracy of the publication.

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Author Contribution

Tian-Yu Wang: Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization.

Data Availability

The code and numerical outputs generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

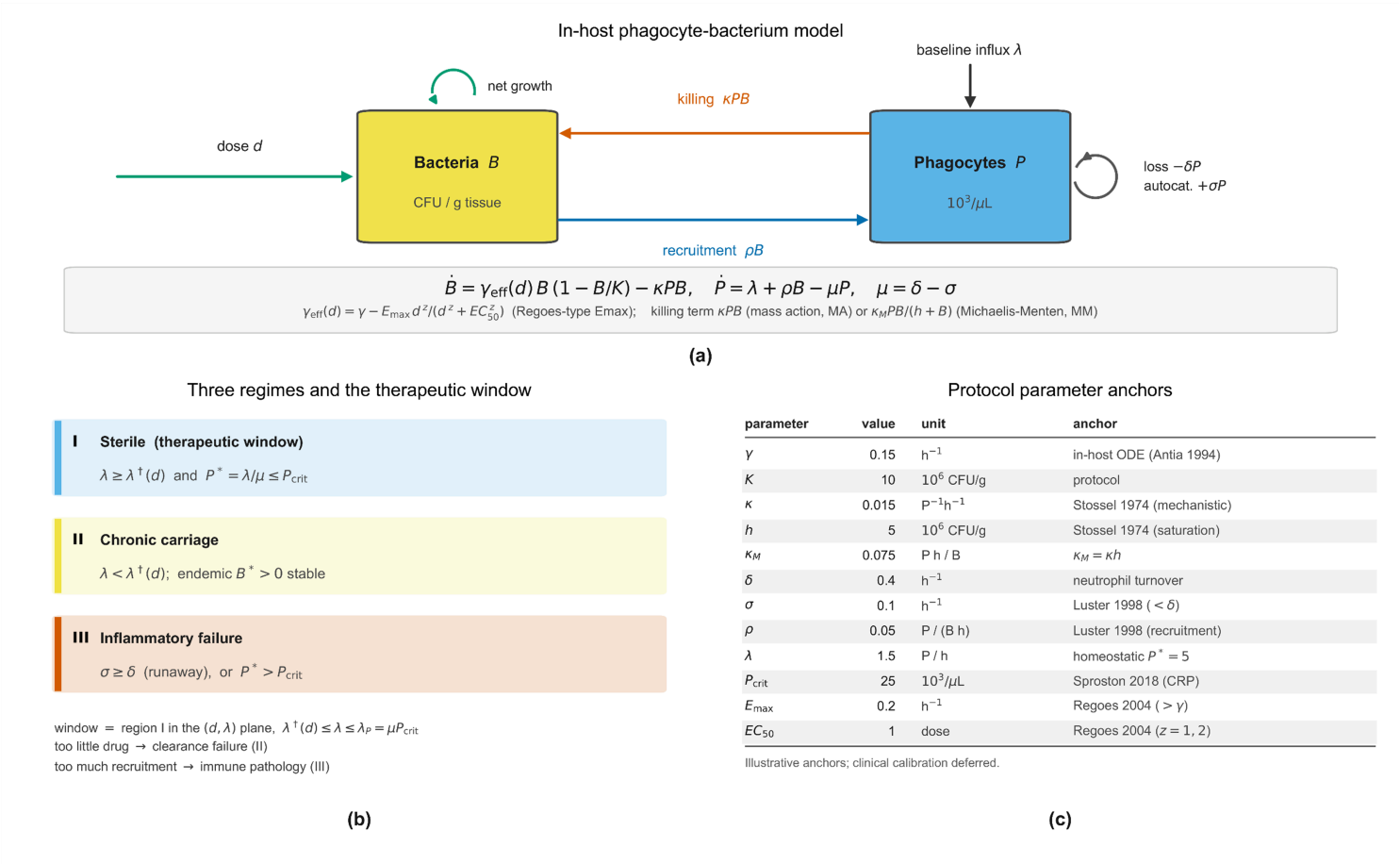


Figure 1

Model schematic, three-regime definitions, and protocol parameter anchors. (a) Phagocyte–bacterium in-host ODE. Bacteria grow logistically at a drug-reduced rate $\gamma_{\text{eff}}(d) = \gamma - E_{\text{max}} d^z / (d^z + EC_{50}^z)$ (Regoes-type Emax pharmacodynamics) and are killed by phagocytes via mass-action (κPB) or Michaelis–Menten ($\kappa_M P / (h + B)$). The sterile fixed point $(B^*, P^*) = (0, \lambda/\mu)$ exists and requires $\mu > 0$. (b) Three-regime definition in the (d, λ) plane. Region I (sterile, therapeutic window): $\lambda > \lambda^+(d)$ and $P^* = \lambda/\mu \leq P_{\text{crit}}$. Region II (chronic carriage): $\lambda < \lambda^+(d)$; the endemic equilibrium is positive and stable. Region III (inflammatory failure): $\sigma > \delta$ (exponential phagocyte runaway) or $P^* > P_{\text{crit}}$. (c) Protocol parameter anchors (illustrative values; clinical calibration deferred). Note the MM killing rate unit $B/(P \cdot \text{h})$ and $E_{\text{max}} = 0.20 \text{ h}^{-1}$.

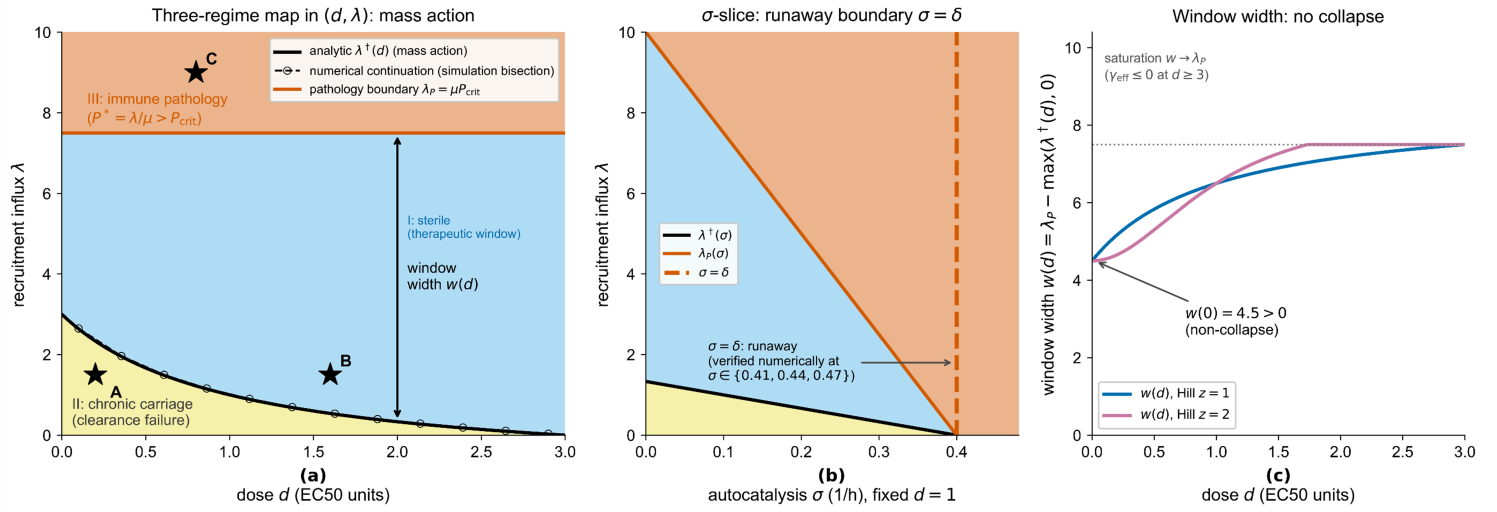


Figure 2

Three-regime map in the (d, λ) plane and structural robustness of the window. (a) Region map for the mass-action model: analytic boundary $\lambda^+(d) = \gamma_{eff}(d)\mu/\kappa$ (solid), pathology boundary $\lambda_P = \mu \cdot P_{crit} = 7.5$ (dashed horizontal). (b) Slice at fixed $d = 1$ over (σ, λ) : both boundaries $\lambda^+(\sigma)$ and $\lambda_P(\sigma)$ collapse to zero as $\sigma \rightarrow \delta$ (the absolute width $w = \mu(P_{crit} - \gamma_{eff}/\kappa) \rightarrow 0$ as well). (c) Window width $w(d) = \lambda_P - \max(\lambda^+(d), 0)$ for Hill coefficients $z = 1, 2$: $w(0) = 4.5 > 0$, w is non-decreasing, and saturates at λ_P once $\gamma_{eff} \leq 0$ (drug alone clears). The two boundaries are governed by disjoint parameter combinations — $(\gamma_{eff}, \mu, \kappa)$ for the lower and (μ, P_{crit}) for the upper — so the relative window $\kappa P_{crit}/\gamma_{eff}(d)$ is independent of μ .

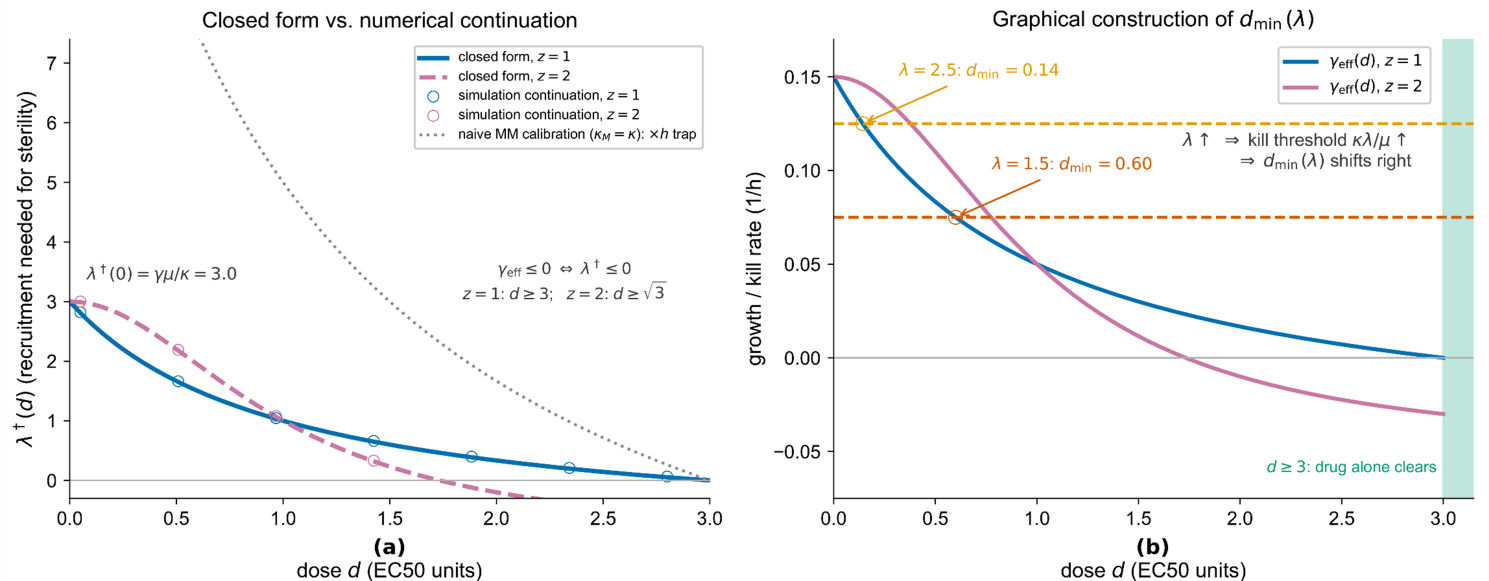


Figure 3

$\lambda^+(d)$: closed form versus numerical continuation, and the dose effect. (a) Closed-form $\lambda^+(d)$ for $z = 1$ (solid) and $z = 2$ (dashed) with independent simulation-continuation points (open circles; $\lambda^+(0) = \gamma\mu/\kappa = 3.0$). For $z = 2$, γ_{eff} crosses zero at $d = \sqrt{3}$, beyond which $\lambda^+ \leq 0$ (sterility needs no recruitment). The

dotted curve shows the dimensional pitfall of a naive Michaelis–Menten calibration (κ_M set equal to κ) against the calibrated $\lambda\tau(d)$. (b) Graphical construction of $d_{\min}(\lambda)$: clearance requires $\gamma_{\text{eff}}(d) \leq \kappa\lambda/\mu$, so the intersections of $\gamma_{\text{eff}}(d)$ with the kill-threshold lines (dashed) give $d_{\min} = 0.14$ ($\lambda = 2.5$) and 0.60 ($\lambda = 1.5$) for $z = 1$. Larger λ raises the threshold and shifts $d_{\min}$ leftward.

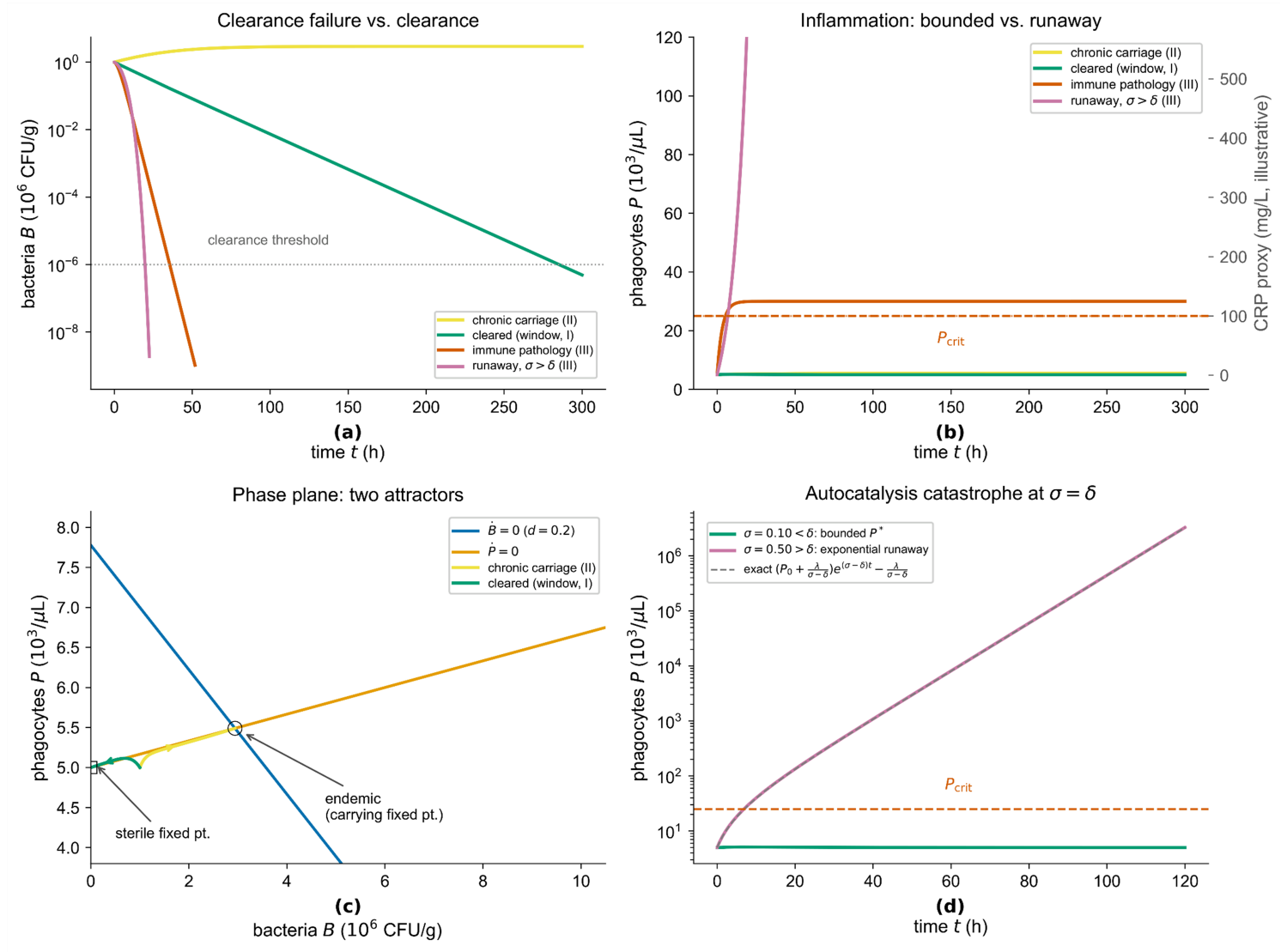


Figure 4

Two qualitatively different failure modes flanking the window. (a) Bacteria time courses (log scale) from $B(0) = 1$: chronic carriage ($d = 0.2$, $\lambda = 1.5$) converges to the endemic level $B^* \approx 2.9$ (clearance failure); within the window ($d = 1.6$) bacteria are cleared; immune pathology ($\lambda = 9$) and $\sigma > \delta$ runaway also clear bacteria. (b) Phagocyte time courses with CRP proxy (right axis, illustrative linear mapping anchored following Sproston and Ashworth 2018; $P_{\text{crit}} = 25$). (c) Phase plane for $d = 0.2$ with nullclines: the two attractors (endemic vs. sterile fixed point) correspond to clearance failure and success; the endemic point matches the closed form $B^* = K(\gamma_{\text{eff}} \mu - \kappa\lambda)/(\gamma_{\text{eff}} \mu + \kappa\rho K)$.

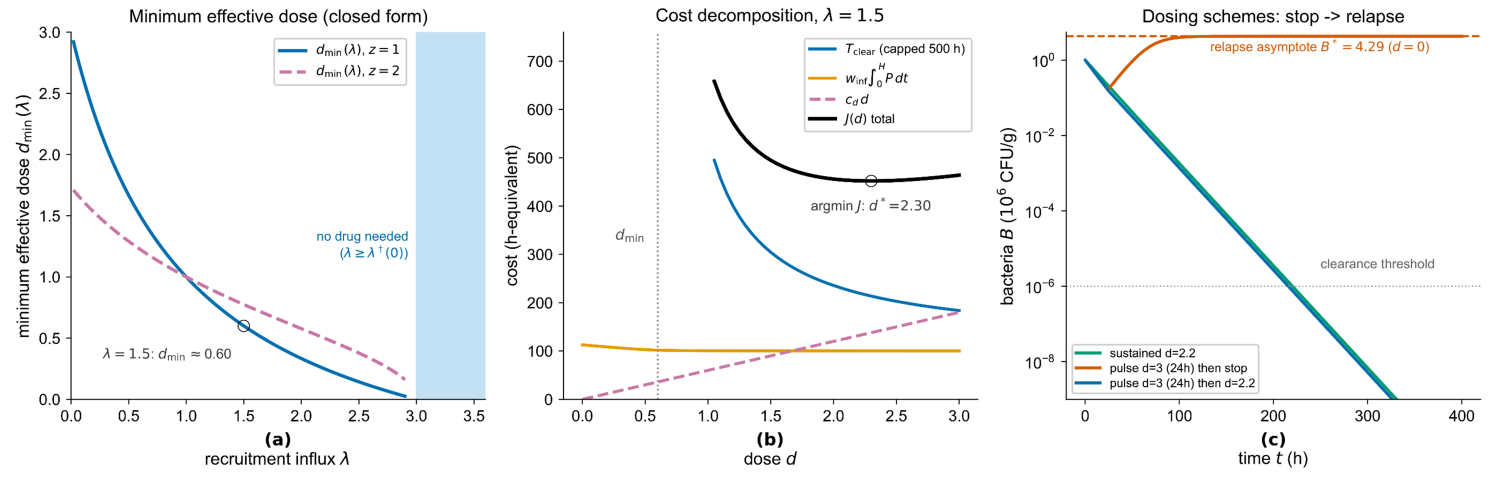


Figure 5

Minimum effective dose and dosing schemes ($\lambda = 1.5$). (a) Closed-form minimum effective dose $d_{\min}(\lambda) = EC50 \cdot [(\gamma - \kappa\lambda/\mu)/(E_{\max} - \gamma + \kappa\lambda/\mu)]^{1/z}$. (b) Cost decomposition $J(d) = T_{\text{clear}} + w_{\text{inf}} \cdot \int_0^H P dt + c_d \cdot d$ (protocol weights $w_{\text{inf}} = 0.1$, $c_d = 60$ h/unit, $H = 200$ h): the interior optimum $d^* \approx 2.3$ balances faster clearance against dose cost; $d_{\min}$ is marked. (c) Dosing schemes: sustained $d = 2.2$ clears in ≈ 221 h; a 24-h pulse ($d = 3$) followed by withdrawal relapses to the drug-free endemic state $B^* \approx 4.29$ (the $d = 0$ endemic equilibrium), showing that clearance requires the window condition $\gamma_{\text{eff}}(d) < \kappa\lambda/\mu$ to be maintained, not merely reached.