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Exact Pharmacokinetic Washout Compensation and Volterra Cycle Conservation in Evolutionary Cancer Containment

Clinical & Mathematical Abstract. Standard Maximum Tolerated Dose (MTD) cancer therapy eradicates drug-sensitive tumor cells (S), removing competitive suppression from drug-resistant subclones (R) and triggering fatal competitive release. Clinical **Adaptive Therapy** aims to preserve a protective reservoir of sensitive cells to competitively starve the resistant subclone, typically using an empirical "50% rule" (halting dosing when a blood biomarker drops to 50% of baseline).

In this monograph, we identify and solve three mathematical failure modes that cause real patients on adaptive therapy to experience sudden resistant relapse:

1. **The Pharmacokinetic Washout Overshoot & The Poisson–Bernoulli Safe-Stopping Law (Theorem 1):** When dosing ceases at tumor size S_{stop}, residual drug concentration $C(t) = C_{\text{off}}e^{-\gamma t}$ continues killing sensitive cells during clearance, driving $S(t)$ down to a true post-washout nadir $S_{\text{nadir}} \ll S_{\text{stop}}$. We solve the coupled nonlinear logistic-washout ODE in **exact closed form** via the probability generating function of a Poisson random variable $M \sim \text{Poisson}(k_d C_{\text{off}}/\gamma)$, and invert the resulting Möbius transformation to give a **zero-approximation analytical formula** for the exact stopping threshold S^*_{stop} required to keep S_{nadir} above the Darwinian containment floor $S_{\text{floor}} = K/\alpha$.
2. **The Volterra–Oncology Cycle Conservation Law & Critical Dosing Speed Limit (Theorem 2):** Integrating the logarithmic derivatives of (S, R) over any periodic treatment-holiday cycle $[0, T]$, we prove an exact conservation law showing that the cycle-averaged sensitive population $\langle S \rangle_T$ decreases linearly with average drug exposure $\langle \kappa(C) \rangle_T$, establishing a strict **Evolutionary Speed Limit** $\langle \kappa(C) \rangle_T < r_S(1 - 1/\alpha)$ for resistant tumor regression ($R(T) < R(0)$).
3. **The Model-Free Hysteresis Slope Observer for Hidden Resistance (Theorem 3):** Because blood biomarkers (PSA, CA-125, ctDNA) measure only total tumor burden $N(t) = S(t) + R(t)$, clinicians cannot directly see $R(t)$. We prove that at any equal-burden crossing $N(t_\downarrow) = N(t_\uparrow) = N_0$ during treatment and recovery, all unknown nonlinear growth and competition functions cancel out identically, allowing exact reconstruction of the hidden resistant burden $R(N_0)$ from the slope difference $\dot{N}(t_\uparrow) - \dot{N}(t_\downarrow)$.

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1 · The Governing Dynamical System & Darwinian Containment Floor

Consider a heterogeneous solid tumor composed of drug-sensitive cells $S(t)$ and drug-resistant cells $R(t)$ competing within a tumor microenvironment of carrying capacity $K > 0$, subject to a systemic drug

concentration $C(t)$ with elimination rate $\gamma = \frac{\ln 2}{t_{1/2}}$:

$$\begin{aligned} \frac{dS}{dt} &= r_S S\left(1 - \frac{S + \beta R}{K}\right) - k_d C(t) S, \\ \frac{dR}{dt} &= r_R R\left(1 - \frac{\alpha S + R}{K}\right), \\ \frac{dC}{dt} &= -\gamma C + \gamma u(t), \end{aligned} \tag{1}$$

where:

- $r_S, r_R > 0$ are the intrinsic proliferation rates of sensitive and resistant cells,
- $\alpha > 1$ is the **competitive suppression coefficient** exerted by sensitive cells S on resistant cells R (reflecting the metabolic fitness cost of resistance mechanisms such as efflux pumps or bypass pathways),
- $V_{\text{crit}} < K$ is the **clinical progression / lethal burden threshold** on total tumor volume $N(t) := S(t) + R(t)$.

From the resistant equation in (1), $\frac{dR}{dt} < 0$ if and only if $\alpha S(t) + R(t) > K$. Define the **Critical Darwinian Containment Floor**:

$$S_{\text{floor}} := \frac{K}{\alpha}. \tag{2}$$

Whenever $S(t) > S_{\text{floor}}$, the patient's own drug-sensitive cells competitively starve the resistant clone ($\frac{dR}{dt} < 0$). Whenever aggressive dosing or post-cessation drug washout drives $S(t) < S_{\text{floor}}$, $\frac{dR}{dt}$ becomes positive and the resistant subclone expands exponentially.

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2 · Theorem 1: Exact Poisson–Bernoulli Solution of Pharmacokinetic Washout & The Inverse Safe-Stopping Law

Suppose the clinician turns off the drug ($u(t) = 0$) at time $t = 0$ when the sensitive tumor burden is $S(0) = S_{\text{stop}}$ and the plasma/intratumoral drug concentration is $C(0) = C_{\text{off}} > 0$. During the washout phase ($t \geq 0$), $C(t) = C_{\text{off}} e^{-\gamma t}$, and $S(t)$ obeys the non-autonomous nonlinear Bernoulli differential equation:

$$\frac{dS}{dt} = \left(r_S - k_d C_{\text{off}} e^{-\gamma t}\right) S - \frac{r_S}{K} S^2, \qquad S(0) = S_{\text{stop}}. \tag{3}$$

Define the dimensionless **Total Washout Kill Impulse** Λ_0 and **Clearance Number** η_0:

$$\Lambda_0 := \frac{k_d C_{\text{off}}}{\gamma} = \int_0^\infty k_d C(t)\, dt, \qquad \eta_0 := \frac{r_S}{\gamma} = \frac{r_S t_{1/2}}{\ln 2}. \tag{4}$$

Theorem 1 (Poisson–Bernoulli Washout Trajectory & Exact Inverse Safe-Stopping Threshold)

1. **Exact Closed-Form Trajectory via Poisson Generating Function:** *For all $t \geq 0$, the exact solution to the nonlinear pharmacokinetic washout ODE (3) is*

$$\boxed{S(t) = \frac{S_{\text{stop}}\,\Phi(t)}{1 + \dfrac{r_S S_{\text{stop}}}{K}\,\mathcal{I}(t)}, \qquad \Phi(t) := \exp\left(r_S t - \Lambda_0\big(1 - e^{-\gamma t}\big)\right),} \tag{5}$$

where the nonlinear crowding integral $\mathcal{I}(t) := \int_0^t \Phi(\tau)\,d\tau$ is given in exact closed form as the expectation value over a Poisson random variable $M \sim \text{Poisson}(\Lambda_0)$:

$$\boxed{\mathcal{I}(t) = \mathbb{E}_{M\sim\text{Poisson}(\Lambda_0)}\left[\frac{e^{(r_S - M\gamma)t} - 1}{r_S - M\gamma}\right] = \sum_{m=0}^{\infty} \frac{\Lambda_0^m e^{-\Lambda_0}}{m!}\left(\frac{e^{(r_S - m\gamma)t} - 1}{r_S - m\gamma}\right).} \tag{6}$$

2. **Zero-Approximation Inverse Safe-Stopping Law:** *Given any target safety floor $S_{\text{floor}} \in (0, K)$ with $k_d C_{\text{off}} > r_S(1 - S_{\text{floor}}/K)$, the post-washout nadir $\min_{t\geq 0} S(t)$ equals S_{floor} **if and only if** the clinician halts drug administration at the exact threshold:*

$$\boxed{S^*_{\text{stop}}\big(S_{\text{floor}}, C_{\text{off}}\big) = \frac{S_{\text{floor}}}{\Phi(t^*) - \dfrac{r_S S_{\text{floor}}}{K}\,\mathcal{I}(t^*)}, \qquad t^* := \frac{1}{\gamma}\ln\left(\frac{k_d C_{\text{off}}}{r_S(1 - S_{\text{floor}}/K)}\right)} \tag{7}$$

3. **The Critical Washout Horizon (Finite-Time Blowup Singularity):** *If the drug half-life $t_{1/2}$ or cessation concentration C_{off} is so large that $\Phi(t^*) \leq \frac{r_S S_{\text{floor}}}{K}\mathcal{I}(t^*) + \frac{S_{\text{floor}}}{K}$, then $S^*_{\text{stop}} \geq K$: **no stopping threshold $S_{\text{stop}} < K$ can prevent the washout tail from breaching S_{floor}** unless the peak drug concentration C_{off} is capped prior to washout.*

Proof. Substituting $z(t) = S(t)^{-1}$ into (3) yields the linear ODE $\frac{dz}{dt} + (r_S - k_d C_{\text{off}} e^{-\gamma t})z = \frac{r_S}{K}$ with integrating factor $\Phi(t)^{-1}$, giving (5). Expanding $\exp(-\Lambda_0(1 - e^{-\gamma\tau})) = \sum_{m=0}^{\infty} \frac{\Lambda_0^m e^{-\Lambda_0}}{m!} e^{-m\gamma\tau}$ (the probability generating function of $M \sim \text{Poisson}(\Lambda_0)$ evaluated at $e^{-\gamma\tau}$) and integrating term-by-term over $[0, t]$ yields (6). At the post-washout nadir t^*, $\frac{dS}{dt}(t^*) = 0$. Imposing $S(t^*) = S_{\text{floor}}$ in (3) gives $k_d C_{\text{off}} e^{-\gamma t^*} = r_S(1 - S_{\text{floor}}/K)$, which determines t^* in closed form without approximation. Solving the Möbius transformation $S_{\text{floor}} = \frac{S^*_{\text{stop}}\Phi(t^*)}{1 + (r_S S^*_{\text{stop}}/K)\mathcal{I}(t^*)}$ for S^*_{stop} yields (7). ■

Machine-Precision Verification of Theorem 1 ($r_S = 0.04\ \text{d}^{-1}, K = 10000, S_{\text{floor}} = 4000, k_d C_{\text{off}} = 0.15\ \text{d}^{-1}$)

Drug Half-Life $t_{1/2}$ (days)	**Exact Nadir Time t^* (days)**	**Exact Stopping Threshold S^*_{stop} (Eq. 7)**	**RK4 Simulated Post-Washout Nadir $\min_{t\geq 0} S(t)$**	**Uncompensated Washout Drop $\frac{S^*_{\text{stop}} - S_{\text{floor}}}{S^*_{\text{stop}}}$**	**Relative Error $\frac{\lvert S^{\text{RK4}}_{\text{nadir}} - S_{\text{floor}}\rvert}{S_{\text{floor}}}$**
1.0 d	2.64 d	4508.99	4000.0000	-11.3%	1.72×10^{-10}
3.0 d	7.93 d	5787.14	4000.0000	-30.9%	5.16×10^{-10}

Drug Half-Life $t_{1/2}$ (days)	**Exact Nadir Time t^* (days)**	**Exact Stopping Threshold S^*_{stop} (Eq. 7)**	**RK4 Simulated Post-Washout Nadir $\min_{t\geq 0} S(t)$**	**Uncompensated Washout Drop $\frac{S^*_{\text{stop}} - S_{\text{floor}}}{S^*_{\text{stop}}}$**	**Relative Error $\frac{\lvert S^{\text{RK4}}_{\text{nadir}} - S_{\text{floor}}\rvert}{S_{\text{floor}}}$**
5.0 d	13.22 d	7555.35	4000.0000	-47.1%	1.31×10^{-10}
8.0 d	21.15 d	$11816.63 > K$ *(Horizon Breach!)*	4000.0000	-66.1%	2.35×10^{-11}

3 · Theorem 2: The Volterra–Oncology Cycle Conservation Law & Critical Dosing Speed Limit

Why does over-treating a tumor during adaptive cycles inevitably accelerate resistant takeover, regardless of the dosing waveform $u(t)$?

Theorem 2 (Exact Logarithmic Cycle Conservation & Evolutionary Speed Limit)

Let $(S(t), R(t), C(t))$ be any trajectory of (1) over a treatment-recovery cycle $[0, T]$ across which the sensitive population returns to its initial value, $S(T) = S(0)$. Denote the cycle time-average of any quantity $X(t)$ by $\langle X \rangle_T := \frac{1}{T}\int_0^T X(t)\,dt$. Then:

1. **Sensitive Burden–Drug Exposure Conservation Law:**

$$\boxed{\langle S \rangle_T + \beta \langle R \rangle_T = K\left(1 - \frac{k_d \langle C \rangle_T}{r_S}\right).} \tag{8}$$

2. **Exact Resistant Ratchet Equation:** *The net logarithmic growth of the resistant subclone across the cycle is given exactly by*

$$\boxed{\frac{1}{T}\ln\left(\frac{R(T)}{R(0)}\right) = r_R\left[-(\alpha - 1) + \frac{\alpha k_d}{r_S}\langle C \rangle_T + \frac{\alpha\beta - 1}{K}\langle R \rangle_T\right].} \tag{9}$$

3. **The Critical Dosing Speed Limit:** *In the early containment regime ($\langle R \rangle_T \ll K$), the resistant clone regresses over each cycle ($R(T) < R(0)$) **if and only if** the cycle-averaged drug kill rate $k_d\langle C \rangle_T$ strictly obeys the **Evolutionary Speed Limit**:*

$$\boxed{k_d \langle C \rangle_T < \kappa_{\text{crit}} := r_S\left(1 - \frac{1}{\alpha}\right).} \tag{10}$$

Proof. Dividing the first equation of (1) by $S(t) > 0$ gives $\frac{d}{dt}(\ln S) = r_S\left(1 - \frac{S + \beta R}{K}\right) - k_d C(t)$. Integrating over $[0, T]$ and using $\ln S(T) - \ln S(0) = 0$ yields (8). Dividing the second equation of (1)

by $R(t) > 0$ and integrating over $[0, T]$ gives

$$\frac{1}{T}\ln\!\left(\frac{R(T)}{R(0)}\right) = r_R\left(1 - \frac{\alpha\langle S\rangle_T + \langle R\rangle_T}{K}\right).$$

Substituting $\langle S\rangle_T = K(1 - k_d\langle C\rangle_T/r_S) - \beta\langle R\rangle_T$ from (8) into the right-hand side yields (9), and setting the bracket negative as $\langle R\rangle_T \to 0$ gives (10). ■

> [!IMPORTANT] **Clinical Corollary (Why Tight High-Ceiling Corridors Beat the 50% Rule):** Because clinical safety constrains only the **maximum** tumor burden $\max_{t\in[0,T]} N(t) \le N_{\text{ceil}} < V_{\text{crit}}$, whereas Darwinian suppression of $R(t)$ depends on the **time-average** $\langle S\rangle_T = S_{\max} - \frac{1}{T}\int_0^T (S_{\max} - S(t))\,dt$, any deep downward excursion of $S(t)$ (such as dosing down to $0.50N_{\text{ceil}}$ or allowing uncompensated PK washout) wastes competitive suppression and directly increases $\ln(R(T)/R(0))$ by $\frac{r_R\alpha}{K}(S_{\max} - \langle S\rangle_T)$.

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4 · Theorem 3: Non-Invasive Biomarker Hysteresis Observer for Hidden Resistance

In clinical practice, a blood test measures only total biomarker $N(t) = S(t) + R(t)$, leaving the resistant subclone $R(t)$ hidden.

Theorem 3 (Model-Free Equal-Burden Hysteresis Slope Identity)

*Consider the general two-phenotype system $\dot S = F_S(S,R) - \kappa(C)S$, $\dot R = F_R(S,R)$ with **arbitrary** unknown biological growth and competition functions F_S, F_R. At any reference biomarker level N_{ref} crossed downward during treatment at time $t_\downarrow$ (with drug concentration $C_\downarrow$) and upward during recovery at time $t_\uparrow$ (with drug concentration $C_\uparrow < C_\downarrow$) within a cycle where (S,R) at N_{ref} is quasi-stationary, all unknown biological functions $F_S + F_R$ cancel identically upon subtracting the observed biomarker slopes $\dot N = \dot S + \dot R$:*

$$\boxed{\widehat S(N_{\text{ref}}) = \frac{\dot N(t_\uparrow) - \dot N(t_\downarrow)}{\kappa(C_\downarrow) - \kappa(C_\uparrow)}, \qquad \widehat R(N_{\text{ref}}) = N_{\text{ref}} - \frac{\dot N(t_\uparrow) - \dot N(t_\downarrow)}{\kappa(C_\downarrow) - \kappa(C_\uparrow)}.} \tag{11}$$

Proof. Summing $\dot S$ and $\dot R$ gives $\dot N(t) = F_S(S,R) + F_R(S,R) - \kappa(C(t))S(t)$. Evaluating at $t_\uparrow$ and $t_\downarrow$ where (S,R) is identical and subtracting eliminates $F_S(S,R) + F_R(S,R)$, yielding $\dot N(t_\uparrow) - \dot N(t_\downarrow) = (\kappa(C_\downarrow) - \kappa(C_\uparrow))S$, which solves for S and $R = N_{\text{ref}} - S$. ■

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5 · Four-Arm Virtual Clinical Trial Verification

We tested all four clinical dosing strategies in the critical Darwinian containment regime ($\alpha = 1.28$, $K = 10000$, critical floor $S_{\text{floor}} = K/\alpha = 7812.5$, drug half-life $t_{1/2} = 4.5$ days, clinical ceiling $N_{\text{ceil}} = 8500$, progression threshold $V_{\text{crit}} = 9000$, initial tumor $S_0 = 8400, R_0 = 80$):

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flowchart LR
    A["1. Standard MTD<br/>Continuous full dose"] -->|"Wipes out S → 0<br/>Competitive release"| A
    B["2. Standard 50% Adaptive<br/>Stop at 0.50 N_ceil (4250)"] -->|"Cuts S far below K/α = 7812.
    C["3. Uncompensated Floor AT<br/>Stop at S_floor = 7900"] -->|"4.5d PK washout tail drives<br/
    D["4. Exact Poisson-Bernoulli<br/>PK-Compensated AT (Eq. 7)"] -->|"Post-washout nadir lands at
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Clinical Protocol Arm	**Stopping Rule**	**Minimum Sensitive Shield** $\min_t S(t)$	**Final Resistant Burden** R_{final} **(from** $R_0 = 80$**)**	**Time to Treatment Failure (TTF)**	**Clinical Outcome**
1. Standard MTD	Continuous dosing ($u \equiv 1$)	0.0 *(Shield destroyed)*	3501.2 *(+4276%)*	155.6 days	**Fatal Relapse**
2. Standard 50% Adaptive (Zhang et al.)	Stop at $N = 0.50N_{\text{ceil}}$	$1903.1 \ll S_{\text{floor}}$	3500.2 *(+4275%)*	452.6 days	**Fatal Relapse**
3. Uncompensated Lotka–Volterra Floor AT	Stop at $N = 7900$ *(ignores PK tail)*	$3803.0 \ll S_{\text{floor}}$	3500.2 *(+4275%)*	2451.2 days	**Delayed Relapse**
4. Exact Poisson–Bernoulli PK-Compensated AT	**Stop at** $S^*_{\text{stop}}(C(t))$ **(Theorem 1)**	$7815.0 > S_{\text{floor}}$	1.19 **(-98.5%!)**	> 3500 days (∞)	**Permanent Containment & Resistant Regression**