HORMONAL REGULATION OF BREAST CANCER INCIDENCE DYNAMICS: A MATHEMATICAL ANALYSIS EXPLAINING THE CLEMMESEN'S HOOK

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ABSTRACT

Clemmesen's hook refers to a commonly observed slowdown and rebound in breast cancer incidence around the age at menopause. It suggests a shift in the underlying carcinogenic dynamics, but the mechanistic basis remains poorly understood. Building on our previously developed Extended Multistage Clonal Expansion Tumor (MSCE-T) model, we perform a theoretical analysis to determine the conditions under which Clemmesen's hook would occur. Our results show that Clemmesen's hook can be quantitatively explained by time-specific changes in the proliferative and apoptotic balance of early-stage mutated cell populations, corresponding to the decline in progesterone levels and progesterone-driven proliferation due to reduced menstrual cycles preceding menopause, and changing dominant carcinogenic impact from alternative growth pathways post-menopause (e.g., adipose-derived growth signals). In contrast, variation in last-stage clonal dynamics cannot effectively reproduce the observed non-monotonic incidence pattern. Analytical results further demonstrate that midlife incidence dynamics corresponding to the hook are governed primarily by intrinsic proliferative processes rather than detection effects. Overall, this study provides a mechanistic and mathematical explanation for Clemmesen's hook and establishes a quantitative framework linking hormonal transitions during menopause to age-specific breast cancer incidence curve.

Keywords: Clemmesen's hook, Breast Cancer, Multistage Clonal Expansion, Menopause.

1 Introduction

Breast cancer is the most diagnosed cancer and the main cause of cancer mortality among females worldwide [1]. The age-specific incidence curves of breast cancer often show a distinctive transition around the menopausal transition (approximately ages 45–55): a reduction and rebound in the slope known as *Clemmesen's hook*, first noticed by the Danish epidemiologist Johannes Clemmesen [2]. This "hook"–visible across cohorts and populations–disrupts the monotonic age patterns and suggests an underlying driver that acts differentially around the age at menopause [3, 4]. Understanding the origin of this inflection is essential, because the changes in breast cancer risk around menopause in response to the menopausal perturbation (e.g. changing hormonal levels) can help reveal breast cancer development mechanisms for guiding breast cancer prevention and interventions.

Recent epidemiological and biological studies point to ovarian hormones—particularly progesterone—as a causal factor of breast cancer [5, 6, 7]. The number of ovulatory menstrual cycles during a person's lifetime, rather than cumulative estrogen exposure alone, has emerged as the dominant determinant of breast cancer risk [5]. For each menstrual cycle, progesterone increases during the luteal-phase, stimulating proliferation of mammary stem and progenitor cells through paracrine RANKL and WNT4 signaling, and in turn increases the probability of replication errors and long-term mutational accumulation [5]. Large-scale meta-analyses show that breast-cancer risk increases by 5 % for each year earlier at menarche and 3 % for each year later at menopause—consistent with longer exposure to ovulatory cycling and consequently to progesterone surges [8]. Conditions that suppress or eliminate these cycles (e.g., lactation, or ovarian

suppression) have been shown to be protective against breast cancer development, while exogenous progesterone exposure through progestin-based contraception use or combined estrogen–progestin menopausal therapy elevates breast cancer risk [5, 9]. Whereas earlier studies suggested a direct carcinogenic role for estrogen [10, 11], more recent evidence indicates that unlike progesterone, estrogen alone appears to be permissive rather than causal, increasing the risk for estrogen receptor positive (ER-positive) cancer types through upregulating the progesterone signaling or having milder proliferative effects on progenitors (i.e., unlikely to be causal) [6, 5]. Given these new lines of evidence and the changes in progesterone levels around menopause, we hypothesize that changing progesterone levels is a major driver of the Clemmesen's hook. That is, the age–incidence curve around menopause (between the ages 45 to 55) is due to the decline of menstruation frequency and progesterone exposure which reduces the proliferation of progenitor cells [8, 6, 5].

Mathematical models of carcinogenesis provide an analytic tool to examine cancer incidence trends and the underlying mechanisms. Among these, models based on the Multistage Clonal Expansion (MSCE) framework stand out for their ability to capture how mutation accumulation, clonal growth, and malignant transformation jointly shape age-specific incidence curves. Armitage and Doll laid out the foundation by introducing the theory of multistage carcinogenesis in 1954 [12], and later in 1979 and 1981 Moolgavkar et al. improved it by introducing stage-wise clonal expansion dynamics to the model [13, 14]. The MSCE model structure includes initiation, promotion, and malignant conversion, and such models have been shown to replicate various age-dependent cancer incidence curves. However, traditional MSCE models are unable to capture non-monotonic trends and some extensions have to be made depending on the desired functionality such as considering time-dependent parameters to account for evolving risk factors [15, 16, 17] or enhancing the model structure by explicitly incorporating detection-related dynamics [17]. Clemmesen's hook represents one such non-monotonic incidence pattern, warranting some model refinements to accurately reproduce its characteristic slowdown and rebound around ages 45–55 in age-specific breast cancer incidence curve.

To test our hypothesis that reduced progesterone levels shape the incidence pattern (i.e., Clemmesen's hook) around menopause, we perform a rigorous mathematical analysis of the Multistage Clonal Expansion Tumor (MSCE-T) model, an extended MSCE model we previously developed to distinguish apparent (detection-related) and true increases in cancer risk [17]. We perform a theoretical analysis of the MSCE-T model as well as numerical experiments to determine the conditions under which Clemmesen's hook would occur. Our theoretical and numerical analyses consistently demonstrate that the observed age-specific transition (i.e. the hook) can arise from biologically plausible shifts in the effective proliferation rates—consistent with the decline in progesterone exposure and altered hormonal profile during the menopausal transition. We also investigate the effect of detection dynamics on the emergence of Clemmesen's hook. Moreover, we describe the biological pathways embedded in the MSCE-T model that are inherently incapable of generating such transitional behavior, thereby clarifying the model's mechanistic scope in generating the hook phenomenon and more broadly deriving the lower bound of mutational steps needed to produce the observed breast cancer age-incidence curve. Together, this study provides an additional layer of quantitative evidence supporting the proposed mechanistic explanation for Clemmesen's hook.

2 Data and the Model

2.1 Breast Cancer Incidence Data and Clemmesen's hook

Breast cancer incidence data for Denmark, Sweden, Finland and Norway are sourced from the NORDCAN database [18, 19], and data for the U.S. are sourced from the Surveillance, Epidemiology, and End Results (SEER) program [20]. The NORDCAN database provides the data only in 5-year age groups, while annual data are available from SEER. Using SEER data, we computed the incidence rate by 1-year age interval for each 1-year birth cohort. Note the SEER incidence rates are aggregated to 5-year age interval in Figure 1 for clearer visuals, but 1-year-age-specific data are used in our numerical experiments (section 8) when fitting the model.

Figure 1 shows the cancer incidence for the five countries with data, next to the rate of change (i.e. slope). Clemmesen's hook is evident for all five countries and for all birth cohorts. We can see a consistent slowdown and rebound in all of the incidence plots within the 45-55 years window. This is further confirmed by the sudden decrease and increase of the slopes within the same window.
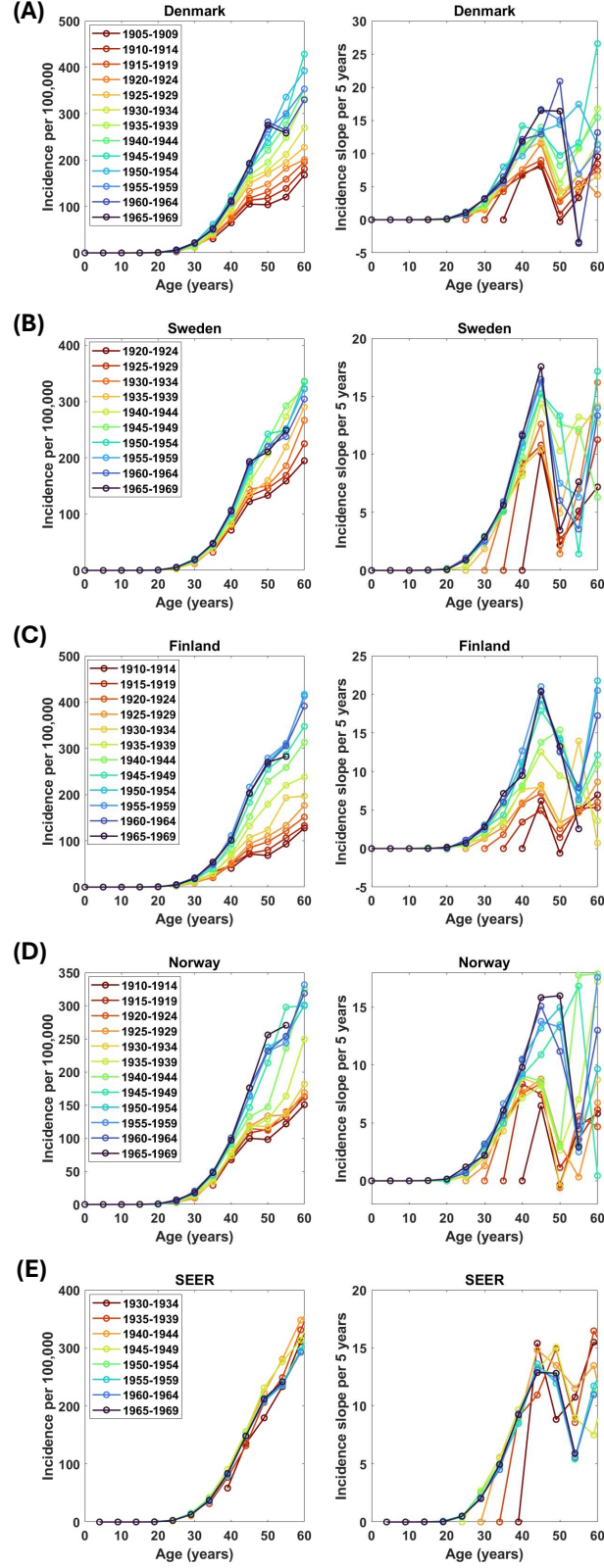
Figure 1: Breast Cancer incidence and incidence slope across different registries. Incidence and incidence slope for (A) Denmark, (B) Sweden, (C) Finland, (D) Norway, and (E) SEER for the United States population.

2.2 The Model

Considering three rate-limiting driver gene mutations for Breast cancer occurrence [21, 22, 23] we extended the classic MSCE model to MSCE-T model by incorporating the detection dynamics [17]. A detailed model derivation is provided in our previous work [17] and summarized in the Supplemental Materials of this article. The derivation procedure traces the stochastic progression of stem cells as they evolve from normal to malignant states through the sequential accumulation of mutations. Each stage i is modeled as a mutation-birth–death process in which cells may divide (at a rate $\alpha_i > 0$), die (at a rate $\beta_i > 0$), or advance to the next stage via mutation (at a rate $\mu_i > 0$). By incorporating the transition probabilities among these events, the model quantifies the likelihood that a population of malignant cells reaches a detectable size by a given age (i.e. detection dynamics). The model is given by the following ODE system

$$\dot{x}_1 = \mu_0 N_0 \, x_1 (x_3 - 1), \tag{1}$$

$$\dot{x}_2 = -\mu_0 N_0 \, x_4, \tag{2}$$

$$\dot{x}_3 = \beta_1 - (\alpha_1 + \beta_1 + \mu_1)x_3 + \mu_1 x_3 x_5 + \alpha_1 x_3^2, \tag{3}$$

$$\dot{x}_4 = -(\alpha_1 + \beta_1 + \mu_1)x_4 + \mu_1 x_4 x_5 + \mu_1 x_3 x_6 + 2\alpha_1 x_3 x_4, \tag{4}$$

$$\dot{x}_5 = \beta_2 - (\alpha_2 + \beta_2 + \mu_2)x_5 + \mu_2 f(t) \, x_5 + \alpha_2 x_5^2, \tag{5}$$

$$\dot{x}_6 = -(\alpha_2 + \beta_2 + \mu_2)x_6 + \mu_2 f'(t) \, x_5 + \mu_2 f(t) \, x_6 + 2\alpha_2 x_6 x_5, \tag{6}$$

with initial condition

$$\big(x_1(0), x_2(0), x_3(0), x_4(0), x_5(0), x_6(0)\big) = (1, 0, 1, 0, 1, 0).$$

and function f which incorporates detection effects

$$f(t) = 1 - \left(1 - e^{-\alpha_3 t}\right)^{M_t - 1}. \tag{7}$$

where $\alpha_3 > 0$ is the net proliferation rate of tumor cells and M_t is the number of malignant cells required for detection at age t. Function (7) gives the probability of having less than M_t malignant cells at age t assuming a simple birth process. For derivation detail and variable/parameter definitions refer to the supplementary materials. For convenience set

$$a(t) := 1 - e^{-\alpha_3 t} \in (0, 1), \quad p(t) := M_t - 1 > 0, \quad L(t) := |\ln a(t)| > 0. \tag{8}$$

The state variables x_1, x_3 and x_5 are survival probabilities and $h(t) := x_2(t)$ is the hazard of cancer incidence. Also, $x_4 = \dot{x}_3$ and $x_6 = \dot{x}_5$.

Remark 2.1. *From now on we assume parameters are piece-wise continuous and bounded functions in time. We are interested in knowing the conditions under which these parameters can produce a midlife transition resembling the Clemmesen's hook for Breast cancer age-specific incidence.*

Remark 2.2. *Since normal mammary cells are in an inactive state until puberty [24], the system* (1)-(6) *has a zero right hand side (i.e., no carcinogenesis kinetics take place) until the age at menarche (~ 13 years of age). This does not affect the following proofs, but whenever necessary we will make a note.*

3 Positivity, invariance, well-posedness, boundedness

Lemma 3.1. *Assume $\alpha_i, \beta_i, \mu_i \geq 0$ and $f(t) \in [0, 1]$ for all $t \geq 0$. Then the rectangle $[0, 1] \times [0, 1]$ is forward invariant for the subsystem* (3) *and* (5)*, i.e. $x_3(t), x_5(t) \in [0, 1]$ for all $t \geq 0$ provided $x_3(0), x_5(0) \in [0, 1]$.*

Proof. We verify inward-pointing conditions on each edge. For $x_3 = 0$, (3) gives $\dot{x}_3 = \beta_1 \geq 0$; for $x_3 = 1$,

$$\dot{x}_3\big|_{x_3=1} = \beta_1 - (\alpha_1 + \beta_1 + \mu_1) + \mu_1 x_5 + \alpha_1 = \mu_1(x_5 - 1) \leq 0 \quad \text{since } x_5 \leq 1.$$

Similarly, for $x_5 = 0$, (5) gives $\dot{x}_5 = \beta_2 \geq 0$; for $x_5 = 1$,

$$\dot{x}_5\big|_{x_5=1} = \beta_2 - (\alpha_2 + \beta_2 + \mu_2) + \mu_2 f + \alpha_2 = \mu_2(f - 1) \leq 0 \quad \text{since } f \leq 1.$$

Thus the vector field is inward pointing on all faces of $[0, 1]^2$, proving forward invariance. $\qquad\square$

Lemma 3.2. *Assume f, f' are continuous and bounded on compact time intervals and the parameters are piecewise continuous and bounded. Then $x_3, x_5 \in [0, 1]$ for all t, and x_4, x_6 remain bounded on finite time intervals, hence $h'(t) = -\mu_0 N_0 x_4(t)$ is well-defined and bounded. Moreover, the IVP* (1)–(6) *admits a unique solution that is continuous on each subinterval where the parameters are continuous.*

Proof. The subsystems for x_4 and x_6 are linear affine with bounded coefficients on any $[0, T]$:

$$\dot{x}_6 = q(t)\, x_6(t) + \mu_2 f'(t)\, x_5(t), \qquad \dot{x}_4 = c(t)\, x_4(t) + \mu_1 x_3(t)\, x_6(t),$$

with

$$c(t) = -(\alpha_1 + \beta_1 + \mu_1) + \mu_1 x_5(t) + 2\alpha_1 x_3(t), \quad q(t) = -(\alpha_2 + \beta_2 + \mu_2) + \mu_2 f(t) + 2\alpha_2 x_5(t). \tag{9}$$

Since $x_3, x_5 \in [0, 1]$ and f, f' are bounded, c, q are bounded. By integrating factor method,

$$x_6(t) = \int_0^t \Phi_q(t, s)\, \mu_2 f'(s) x_5(s)\, ds, \quad \Phi_q(t, s) := \exp\Big(\int_s^t q(u)\, du\Big),$$

hence $|x_6(t)| \leq C(T) \int_0^T |f'|$. Likewise,

$$x_4(t) = \int_0^t \Phi_c(t, s)\, \mu_1 x_3(s) x_6(s)\, ds,$$

and $|x_4(t)| \leq B(T) \int_0^T |x_6|$. Therefore x_4, x_6 are bounded on $[0, T]$ for each T, precluding blow-up and yielding global well-posedness.

The right-hand side (call it $F(\mathbf{x}, t)$) is a polynomial in $\mathbf{x} = (x_1, \ldots, x_6)$ with time-dependent coefficients that are piece-wise continuous and bounded. Hence, for fixed $\mathbf{x}$ the mapping $t \mapsto F(\mathbf{x}, t)$ is measurable in t and continuous in $\mathbf{x}$ and for fixed t the mapping $x \mapsto F(\mathbf{x}, t)$ is C^∞ since it is a polynomial in $\mathbf{x}$. Also, $x_1, x_3, x_5 \in [0, 1]$ and we showed earlier that x_4 and x_6 are bounded. Given that the parameters and f and f' are also bounded it results in the existence of a uniform bound for $F(\mathbf{x}, \mathbf{t})$ for all $\mathbf{x}$ and t. Therefore, the Caratheodory conditions are satisfied for the right-hand side which ensures the existence of a solution in a neighborhood of the initial condition. If we show that it is local Lipschitz in $\mathbf{x}$ then the uniqueness of solution is guaranteed [25].

Now, let K be a compact subset of $\mathbb{R}^6$ and denote by $D_x F(t, x)$ the Jacobian matrix with entries $[D_x F(t, x)]_{ij} = \partial F_i / \partial x_j(t, x)$. By the mean value inequality, for any $x, y \in K$ we have

$$\|F(t, x) - F(t, y)\| \leq \sup_{\zeta \in [x, y]} \|D_x F(t, \zeta)\|\, \|x - y\|, \tag{10}$$

We now bound $\|D_x F(t, \zeta)\|$ uniformly for $\zeta \in K$ and $t \in [0, T]$. Compute the nonzero partial derivatives component-wise from (1)–(6):

$$\begin{aligned}
&\partial_{x_1} F_1 = \mu_0 N_0(x_3 - 1), && \partial_{x_3} F_1 = \mu_0 N_0 x_1; \\
&\partial_{x_4} F_2 = -\mu_0 N_0; \\
&\partial_{x_3} F_3 = -(\alpha_1 + \beta_1 + \mu_1) + \mu_1 x_5 + 2\alpha_1 x_3, && \partial_{x_5} F_3 = \mu_1 x_3; \\
&\partial_{x_4} F_4 = -(\alpha_1 + \beta_1 + \mu_1) + \mu_1 x_5 + 2\alpha_1 x_3, && \partial_{x_5} F_4 = \mu_1 x_4, \\
&\partial_{x_3} F_4 = \mu_1 x_6 + 2\alpha_1 x_4, && \partial_{x_6} F_4 = \mu_1 x_3; \\
&\partial_{x_5} F_5 = -(\alpha_2 + \beta_2 + \mu_2) + \mu_2 f(t) + 2\alpha_2 x_5; \\
&\partial_{x_6} F_6 = -(\alpha_2 + \beta_2 + \mu_2) + \mu_2 f(t) + 2\alpha_2 x_5, && \partial_{x_5} F_6 = \mu_2 f'(t) + 2\alpha_2 x_6.
\end{aligned}$$

All other partial derivatives are zero. For $\zeta \in K$ we have $|\zeta_i| \leq R$, thus

$$\begin{aligned}
&|\partial_{x_1} F_1| \leq |\mu_0 N_0|\, (R + 1), && |\partial_{x_3} F_1| \leq |\mu_0 N_0|\, R, \\
&|\partial_{x_4} F_2| \leq |\mu_0 N_0|, \\
&|\partial_{x_3} F_3| \leq |\alpha_1| + |\beta_1| + |\mu_1| + |\mu_1| R + 2|\alpha_1| R, && |\partial_{x_5} F_3| \leq |\mu_1|\, R, \\
&|\partial_{x_4} F_4| \leq |\alpha_1| + |\beta_1| + |\mu_1| + |\mu_1| R + 2|\alpha_1| R, && |\partial_{x_5} F_4| \leq |\mu_1|\, R, \\
&|\partial_{x_3} F_4| \leq |\mu_1|\, R + 2|\alpha_1|\, R, && |\partial_{x_6} F_4| \leq |\mu_1|\, R, \\
&|\partial_{x_5} F_5| \leq |\alpha_2| + |\beta_2| + |\mu_2| + |\mu_2| \sup_{t \in [0, T]} |f(t)| + 2|\alpha_2| R, \\
&|\partial_{x_6} F_6| \leq |\alpha_2| + |\beta_2| + |\mu_2| + |\mu_2| \sup_{t \in [0, T]} |f(t)| + 2|\alpha_2| R, && |\partial_{x_5} F_6| \leq |\mu_2| \sup_{t \in [0, T]} |f'(t)| + 2|\alpha_2| R.
\end{aligned}$$

Hence there exists a constant $C > 0$ (depending only on the parameters) such that

$$\|D_x F(t, \zeta)\| \leq C\Big(1 + R + \underbrace{\sup_{t \in [0, T]} |f(t)|}_{M_f} + \underbrace{\sup_{t \in [0, T]} |f'(t)|}_{M_{f'}}\Big) \qquad \text{for all } \zeta \in K,\ t \in [0, T].$$

Plugging this bound into (10) gives

$$\|F(t,x) - F(t,y)\| \le C\big(1 + R + M_f + M_{f'}\big)\|x - y\| \quad \text{for all } x, y \in K,\ t \in [0, T].$$

Therefore, setting $\ell_K(t) \equiv C(1 + R + M_f + M_{f'})$ yields $\ell_K \in L^\infty([0, T]) \subset L^1([0, T])$ and

$$\|F(t,x) - F(t,y)\| \le \ell_K(t)\|x - y\| \quad \text{for } t \in [0, T],\ \forall x, y \in K.$$

Now that the Caratheodory and Lipschitz conditions are satisfied the uniqueness of the solution follows.

$\square$

Remark 3.3. *Note that since α_i, β_i and μ_i are piece-wise continuous and bounded, $c(t)$ and $q(t)$ from (9) are L^∞_{loc}; they may have jump discontinuities but remain bounded.*

4   Volterra Representation and Exact Form for $f'(t)$

Solving (6) and (4) by integrating factors (with $x_4(0) = x_6(0) = 0$) gives

$$x_6(t) = \int_0^t e^{\int_s^t q(u)\,du}\,\mu_2 f'(s)\,x_5(s)\,ds, \qquad x_4(t) = \int_0^t e^{\int_s^t c(u)\,du}\,\mu_1 x_3(s)\,x_6(s)\,ds.$$

Plugging x_6 into x_4 and using Fubini/Tonelli on the triangle $0 \le r \le s \le t$ to swap the order of integration yields a Volterra transform of the first kind:

$$x_4(t) = \int_0^t K(t, r)\,f'(r)\,dr, \quad K(t, r) := \mu_1 \mu_2\, x_5(r) \int_r^t x_3(s)\exp\Big(\int_r^s (c + q)\,du\Big)\,ds. \tag{11}$$

Differentiating with respect to t gives:

$$\partial_t K(t, r) = \mu_1 \mu_2\, x_5(r)\, x_3(t)\exp\Big(\int_r^t (c + q)\,du\Big) \ge 0. \tag{12}$$

Since $h'(t) = -\mu_0 N_0 x_4(t)$,

$$h'(t) = A\int_0^t K(t, r) f'(r)\,dr, \qquad h''(t) = A\int_0^t \partial_t K(t, r)\,f'(r)\,dr, \quad A := -\mu_0 N_0 < 0. \tag{13}$$

Let a, p be as in (8). For $t > 0$ one has $a \in (0, 1)$ and $L = |\ln a| = -\ln a > 0$. Differentiating $a = 1 - e^{-\alpha_3 t}$,

$$\frac{d}{dt}\big(-\alpha_3 t\big) = -(\alpha_3 + t\alpha_3'), \quad a'(t) = e^{-\alpha_3 t}\big(\alpha_3 + t\alpha_3'\big).$$

Hence

$$\frac{a'(t)}{a(t)} = \frac{e^{-\alpha_3 t}}{1 - e^{-\alpha_3 t}}\big(\alpha_3 + t\alpha_3'\big). \tag{14}$$

Using $\frac{d}{dt} a^p = a^p\big(p' \ln a + p\frac{a'}{a}\big)$ and $f = 1 - a^p$,

$$f'(t) = -a(t)^{p(t)}\left[p'(t)\ln a(t) + p(t)\frac{a'(t)}{a(t)}\right] = -e^{-pL}\left[-p'L + p\frac{a'}{a}\right]. \tag{15}$$

5   Insensitivity of $h(t)$ to scaling M_t

Fix $c > 0$ and a midlife window $[t_a, t_b] \subset [0, T]$ with T being some age well after the menopause window (say $T \ge 60$). For brevity write

$$p_c(t) = c\,p(t) \quad \text{where} \quad p(t) = M_t - 1 > 0.$$

and let f_c, h_c be associated with $p_c(t)$. Recall that

$$a(t) = 1 - e^{-\alpha_3(t)t}, \quad L(t) = |\ln a(t)| > 0,$$

and set

$$m(t) := \min\{p(t), p_c(t)\} = \min\{1, c\}\,p(t), \qquad p_{\min} := \inf_{r \in [t_a, t_b]} p(r) > 0.$$

Define the midlife parameters

$$\varepsilon_1 := \sup_{r \in [t_a, t_b]} L(r), \qquad \varepsilon_2 := \sup_{r \in [t_a, t_b]} \frac{e^{-\alpha_3(r)r}}{1 - e^{-\alpha_3(r)r}}\big(\alpha_3(r) + r|\alpha_3'(r)|\big).$$

Note that ε_1 and ε_2 are very small for reasonably large r (say $r > 20$).

5.1 Pointwise control of $f'_c - f'$

Lemma 5.1. *Fix $r \in [t_a, t_b]$. With $R(r) := a'(r)/a(r)$, $L(r) = |\ln a(r)|$ and the definitions above, the following bound holds:*

$$|f'_c(r) - f'(r)| \le \frac{|c-1|}{e} \left[\underbrace{\frac{p(r)}{m(r)} \big(|p'(r)|\, L(r) + p(r)|R(r)| \big)}_{(I)} + \underbrace{\frac{|p'(r)|}{m(r)} + \frac{p(r)}{L(r)m(r)}|R(r)|}_{(II)} \right]. \qquad (16)$$

Proof. From (15) we have,

$$f'(r) = -a(r)^{p(r)} \big(-p'(r)L + p(r)R(r) \big), \quad f'_c(r) = -a(r)^{p_c(r)} \big(-p'_c(r)L + p_c(r)R(r) \big).$$

So, for the fixed r by adding and subtracting some terms and using the triangle inequality we get

$$|f'_c - f'| \le |a^{p_c} - a^p| \cdot \big(|p'|\, L + p|R| \big) + a^{p_c} \big(|p'_c - p'|\, L + |p_c - p|\, |R| \big). \qquad (17)$$

By the mean value theorem, there exists θ between p and p_c such that

$$|a^{p_c} - a^p| = a^\theta L\, |p_c - p| \le a^m\, L\, |p_c - p|.$$

By setting $x := L > 0$ and maximizing $x \mapsto xe^{-mx}$ at $x = 1/m$ we get

$$a^m L \le \frac{1}{e\,m},$$

Thus

$$|a^{p_c} - a^p| \le \frac{|p_c - p|}{e\,m} = \frac{|c-1|\,p}{e\,m}.$$

Insert this into the first term of (17) to bound it by

$$\underbrace{\frac{|c-1|}{e} \cdot \frac{p}{m} \big(|p'|\, L + p|R| \big)}_{(I)}.$$

Now let's bound the second term in (17). Note $(p'_c - p') = (c-1)p'$, $(p_c - p) = (c-1)p$ and $a^{p_c} \le 1$. Therefore the second term is bounded by

$$a^{p_c} \Big(|p'_c - p'|L + |p_c - p||R| \Big) \le |c-1|\big(|p'|\, L + p|R| \big).$$

Now split this $|c-1|(\cdots)$ to extract explicit $1/m$ factors that we will use to produce the $1/p_{\min}$ term:

$$|c-1|\big(|p'|\, L + p|R| \big) = |c-1| \left[\frac{|p'|}{m} \cdot (mL) + \frac{p}{L\,m} \cdot (L|R|\,m) \right].$$

Using the bounds $mL \le 1/(e)$ (shown above) and $L \ge 0$ we get the coarse inequalities (we only need upper bounds)

$$\frac{|p'|}{m} \cdot (mL) \le \frac{|p'|}{m} \cdot \frac{1}{e}, \qquad \frac{p}{L\,m} \cdot (L|R|\,m) \le \frac{p}{L\,m\,e}|R|$$

Collecting and merging constants, we obtain a bound of the form

$$(\text{second term}) \le \frac{|c-1|}{e} \left(\frac{|p'|}{m} + \frac{p}{L\,m}|R| \right),$$

which is the term denoted (II) in the statement. Summing the two contributions yields (16):

$$|f'_c - f'| \le \frac{|c-1|}{e} \left[\frac{p}{m} \big(|p'|L + p|R| \big) + \frac{|p'|}{m} + \frac{p}{Lm}|R| \right].$$

$\square$

Remark 5.2. *Use $m = \min\{1, c\}\, p$, hence $p/m \le \kappa(c) := \max\{1, 1/c\}$ and $1/m = 1/(\min\{1, c\}p)$. Also $L \le \varepsilon_1$, $|R| \le \varepsilon_2$. Define $L_{min} := \inf_{[t_a, t_b]} L(r)$. Replace these into (16) to get a more specific bound.*

$$|f_c' - f'| \le \frac{|c - 1|}{e} \left[\kappa(c)\big(|p'|\varepsilon_1 + p\varepsilon_2\big) + \frac{1}{\min\{1, c\}p}\Big(|p'| + \frac{p\varepsilon_2}{L_{min}}\Big) \right]. \tag{18}$$

which can be expanded as

$$|f_c' - f'| \le \frac{|c - 1|}{e} \Bigg[\underbrace{\kappa(c)\big(|p'|\varepsilon_1 + p\,\varepsilon_2\big)}_{(I)} + \underbrace{\frac{|p'|}{\min\{1, c\}\, p}}_{(II)} + \underbrace{\frac{\varepsilon_2}{\min\{1, c\}\, L_{\min}}}_{(III)} \Bigg].$$

Turn this into the desired integrand by folding (II)–(III) into a single $\dfrac{C_2}{p}$ term and keeping (I) as the $C_1\big(|p'|\varepsilon_1 + p\varepsilon_2\big)$ part, With $C_1 := \frac{\kappa(c)}{e}$ (a constant depending only on c). For (II), use $|p'(r)| \le \sup_{[t_a, t_b]} |p'| =: \mathcal{M}_{p'}$ to get

$$\frac{|c - 1|}{e} \cdot \frac{|p'|}{\min\{1, c\}\, p} \le |c - 1|\, \frac{1}{p}\, \underbrace{\Big(\frac{\mathcal{M}_{p'}}{e\,\min\{1, c\}}\Big)}_{=: C_{2a}}.$$

For (III), use $p(r) \le \sup_{[t_a, t_b]} p =: \mathcal{M}_p$ so that

$$\frac{\varepsilon_2}{\min\{1, c\}\, L_{\min}} = \frac{\mathcal{M}_p\,\varepsilon_2}{\min\{1, c\}\, L_{\min}} \cdot \frac{1}{\mathcal{M}_p} \le \frac{\mathcal{M}_p\,\varepsilon_2}{\min\{1, c\}\, L_{\min}} \cdot \frac{1}{p} = \frac{C_{2b}}{p},$$

with

$$C_{2b} := \frac{\mathcal{M}_p\,\varepsilon_2}{e\,\min\{1, c\}\, L_{\min}}.$$

Combining C_{2a} and C_{2b} into $C_2 := C_{2a} + C_{2b}$ and collecting constants gives

$$|f_c' - f'| \le |c - 1|\Big[C_1\big(|p'|\varepsilon_1 + p\,\varepsilon_2\big) + \frac{C_2}{p}\Big]. \tag{19}$$

Theorem 5.3. *Under the hypotheses of Lemma 5.1 and knowing that $K(t, r)$ is piece-wise continuous and bounded on $[t_a, t_b]^2$, we have the bound*

$$\sup_{t \in [t_a, t_b]} |h_c(t) - h(t)| \le |c - 1|\, C\left(\varepsilon_1 + \varepsilon_2 + \frac{1}{p_{\min}}\right), \tag{20}$$

where the constant C depends only on the model constants and the window length:

$$C := |A|\, \|K\|_{\infty;[t_a, t_b]^2}\, (T - t_0)\, \widetilde{C},$$

and $\widetilde{C}$ depends only on c, $\sup_{[t_a, t_b]} |p'|$ and $\sup_{[t_a, t_b]} p$ (but not on $p_{\min}$). Hence

$$\sup_{t \in [t_a, t_b]} |h_c(t) - h(t)| = O\Big(|c - 1|\, [\varepsilon_1 + \varepsilon_2 + 1/p_{\min}]\Big).$$

Proof. Start from the Volterra expression for the derivative (valid because $p_c = p$ on $[0, t_a)$ is assumed, or else we localize to the window as explained earlier):

$$h_c'(t) - h'(t) = A \int_{t_a}^{t} K(t, r)\,[f_c'(r) - f'(r)]\, dr,$$

hence, using $|K(t, r)| \le \|K\|_{\infty;[t_a, t_b]^2}$,

$$\sup_{t \in [t_a, t_b]} |h_c'(t) - h'(t)| \le |A|\, \|K\|_{\infty;[t_a, t_b]^2} \int_{t_a}^{t_b} |f_c'(r) - f'(r)|\, dr.$$

Integrate once in time:

$$|h_c(t) - h(t)| = \Big| \int_{t_a}^{t} (h_c'(s) - h'(s))\, ds \Big| \le (t_b - t_a) \sup_{s \in [t_a, t_b]} |h_c'(s) - h'(s)|.$$

Combining,

$$\sup_{t\in[t_a,t_b]} |h_c(t) - h(t)| \leq |A|\,\|K\|_{\infty;[t_a,t_b]^2}\,(t_b - t_a)\int_{t_a}^{t_b} |f_c'(r) - f'(r)|\,dr.$$

Now apply the refined pointwise bound (19) inside the integral:

$$\int_{t_a}^{t_b} |f_c' - f'| \leq |c-1|\int_{t_a}^{t_b}\left[C_1\big(|p'|\varepsilon_1 + p\varepsilon_2\big) + \frac{C_2}{p}\right]dr.$$

Therefore

$$\int_{t_a}^{t_b} |f_c' - f'| \leq |c-1|\,(t_b - t_a)\left[C_1\Big(\mathcal{M}_{p'}\varepsilon_1 + \mathcal{M}_p\,\varepsilon_2\Big) + \frac{C_2}{p_{\min}}\right].$$

Substitute into the previous inequality for $\sup|h_c - h|$:

$$\sup_{t\in[t_a,t_b]} |h_c(t) - h(t)| \leq |c-1|\,|A|\,\|K\|_\infty\,(t_b - t_a)^2\left[C_1\Big(\mathcal{M}_{p'}\varepsilon_1 + \mathcal{M}_p\,\varepsilon_2\Big) + \frac{C_2}{p_{\min}}\right].$$

Now absorb the $(t_b - t_a)$ factors and $\mathcal{M}_p,\ \mathcal{M}_{p'}$ into the constant C to obtain the stated form (20):

$$\sup_{t\in[t_a,t_b]} |h_c(t) - h(t)| \leq |c-1|\,C\left(\varepsilon_1 + \varepsilon_2 + \frac{1}{p_{\min}}\right).$$

$\square$

Caution: Notice that the term $M_p\,\varepsilon_2$ might be problematic generally (i.e., very large). However, under the circumstances of this study the term is small. Given that we are interested in midlife window of $[45, 55]$ relevant to the Clemmesen's hook effect, ε_2 is at most $O(e^{-45})$ if not smaller. Even for the supremum of the number of tumor cells at diagnosis within the same window (i.e., $\mathcal{M}_p$) which for breast cancer is at most $O(10^8)$, the product is still very small.

5.2 Insensitivity of $h(t)$ to scaling α_3

Theorem 5.4. *Let $[t_a, t_b] \subset (0, T)$ be a midlife window and let $p(t) = M_t - 1 > 0$ be fixed. Assume $\alpha_3, \widetilde{\alpha}_3 \in C^1([0, T])$ are bounded and coincide outside the window. Let f, h and $\widetilde{f}, \widetilde{h}$ denote the functions and hazards associated with the same initial data and model parameters as in (1)–(6), but using α_3 and $\widetilde{\alpha}_3$ respectively in the definition of $a(t)$ and $f(t)$. Let a, L, R be defined as in the beginning of the section and similarly $\widetilde{a}, \widetilde{L}, \widetilde{R}$ with $\widetilde{\alpha}_3$. Define $\varepsilon_1, \varepsilon_2$ as before*

$$\varepsilon_1 := \sup_{r\in[t_a,t_b]} L(r), \qquad \varepsilon_2 := \sup_{r\in[t_a,t_b]} \frac{e^{-\alpha_3(r)r}}{1 - e^{-\alpha_3(r)r}}\big(\alpha_3(r) + r|\alpha_3'(r)|\big).$$

Then there exists a constant $C > 0$, depending only on the model parameters, $\|p\|_{L^\infty([t_a,t_b])}$, $\|p'\|_{L^\infty([t_a,t_b])}$, the window length $(t_b - t_a)$ and uniform bounds on α_3, α_3', but not on $\varepsilon_1, \varepsilon_2$, such that

$$\sup_{t\in[t_a,t_b]} |\widetilde{h}(t) - h(t)| \leq C\,(\varepsilon_1 + \varepsilon_2)\left(\|\widetilde{\alpha}_3 - \alpha_3\|_{L^\infty([t_a,t_b])} + \|\widetilde{\alpha}_3' - \alpha_3'\|_{L^\infty([t_a,t_b])}\right). \tag{21}$$

In particular, on a midlife window where $\varepsilon_1, \varepsilon_2 \ll 1$ (i.e. when t is large and α_3 varies slowly), even order-one changes in α_3 restricted to $[t_a, t_b]$ induce only negligible changes in the hazard $h(t)$ on that window.

Proof. We first obtain a Lipschitz bound for $f'(t)$ with respect to α_3 and α_3' on the midlife window, then propagate it to h via the Volterra representation. Recall from (15) that

$$f'(t) = -a(t)p(t)\big[p'(t)L(t) + p(t)R(t)\big] = -e^{-p(t)L(t)}\big[-p'(t)L(t) + p(t)R(t)\big].$$

For each fixed t, the quantity $f'(t)$ depends on $\alpha_3(t)$ and $\alpha_3'(t)$ only through the composite map

$$(\alpha_3(t), \alpha_3'(t)) \longmapsto a(t) \longmapsto L(t), R(t) \longmapsto f'(t),$$

with p, p' fixed. Since all parameters are bounded and $a(t) \in (0, 1)$, this map is C^1 in (α_3, α_3') on a compact set (the range of α_3, α_3' on $[t_a, t_b]$). Hence there exist partial derivatives $\partial_{\alpha_3} f'(t), \partial_{\alpha_3'} f'(t)$ that are continuous and bounded on $[t_a, t_b]$.

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Differentiate f' with respect to α_3, keeping p, p' fixed. Writing $E(t) := e^{-pL}$ for simplicity, we get

$$f'(t) = E(t)\big[p'(t)L(t) - p(t)R(t)\big],$$

and thus

$$\partial_{\alpha_3} f'(t) = (\partial_{\alpha_3} E)\big[p'L - pR\big] + E\Big[p'\,\partial_{\alpha_3} L - p\,\partial_{\alpha_3} R\Big].$$

A similar result holds for $\partial_{\alpha'_3} f'(t)$, with $\partial_{\alpha'_3} L$ and $\partial_{\alpha'_3} R$ in place of $\partial_{\alpha_3} L, \partial_{\alpha_3} R$. By definition of E and L,

$$\partial_{\alpha_3} E = -p\,E\,\partial_{\alpha_3} L.$$

Moreover, from $L = -\ln a$ and $a = 1 - e^{-\alpha_3 t}$ we have

$$\partial_{\alpha_3} L(t) = -\frac{1}{a(t)}\,\partial_{\alpha_3} a(t) = -\frac{te^{-\alpha_3(t)t}}{1 - e^{-\alpha_3(t)t}},$$

so $|\partial_{\alpha_3} L(t)| = t\,\frac{e^{-\alpha_3 t}}{1 - e^{-\alpha_3 t}}$. Similarly,

$$R(t) = \frac{a'(t)}{a(t)} = \frac{e^{-\alpha_3(t)t}}{1 - e^{-\alpha_3(t)t}}\big(\alpha_3(t) + t\alpha'_3(t)\big),$$

one obtains (by chain-rule) the following bounds

$$|\partial_{\alpha_3} R(t)| + |\partial_{\alpha'_3} R(t)| \;\leq\; C_0\,\frac{e^{-\alpha_3(t)t}}{1 - e^{-\alpha_3(t)t}}\big(\alpha_3(t) + t|\alpha'_3(t)|\big),$$

where $C_0 > 0$ depends only on uniform bounds for α_3, α'_3 and t on $[t_a, t_b]$. By the definition of ε_2, this implies

$$|\partial_{\alpha_3} R(t)| + |\partial_{\alpha'_3} R(t)| \;\leq\; C_0\,\varepsilon_2 \quad \text{for all } t \in [t_a, t_b].$$

On the other hand, $|L(t)| \leq \varepsilon_1$ and $|R(t)| \leq \varepsilon_2$ on $[t_a, t_b]$ by definition of $\varepsilon_1, \varepsilon_2$, and $0 < E(t) \leq 1$. Combining these bounds in the expression for $\partial_{\alpha_3} f'(t)$ and the similar expression for $\partial_{\alpha'_3} f'(t)$, we obtain

$$|\partial_{\alpha_3} f'(t)| + |\partial_{\alpha'_3} f'(t)| \;\leq\; C_1(\varepsilon_1 + \varepsilon_2) \quad \text{for all } t \in [t_a, t_b],$$

where $C_1 > 0$ depends only on $\|p\|_{L^\infty}, \|p'\|_{L^\infty}$, bounds on α_3, α'_3 and the window $[t_a, t_b]$, but not on $\varepsilon_1, \varepsilon_2$.

Let $\delta\alpha_3 := \widetilde{\alpha}_3 - \alpha_3$ and $\delta\alpha'_3 := \widetilde{\alpha}'_3 - \alpha'_3$, and let $\delta f'(t) := \widetilde{f}'(t) - f'(t)$. For each fixed $t \in [t_a, t_b]$, the mean value theorem in $\mathbb{R}^2$ applied to the C^1 map $(\alpha_3, \alpha'_3) \mapsto f'(t)$ yields

$$|\delta f'(t)| \;\leq\; \big(|\partial_{\alpha_3} f'(t_\theta)| + |\partial_{\alpha'_3} f'(t_\theta)|\big)\big(|\delta\alpha_3(t)| + |\delta\alpha'_3(t)|\big)$$

for some intermediate values of the arguments (which remain in the same bounded set). Using the bound we got earlier, we obtain

$$|\delta f'(t)| \;\leq\; C_1(\varepsilon_1 + \varepsilon_2)\big(|\delta\alpha_3(t)| + |\delta\alpha'_3(t)|\big), \quad t \in [t_a, t_b].$$

Taking the supremum over $t \in [t_a, t_b]$ yields

$$\sup_{t \in [t_a, t_b]} |\widetilde{f}'(t) - f'(t)| \;\leq\; C_1(\varepsilon_1 + \varepsilon_2)\Big(\|\widetilde{\alpha}_3 - \alpha_3\|_{L^\infty([t_a, t_b])} + \|\widetilde{\alpha}'_3 - \alpha'_3\|_{L^\infty([t_a, t_b])}\Big). \tag{22}$$

By the Volterra representation (13) and the assumption that $\alpha_3 = \widetilde{\alpha}_3$ on $[0, t_a)$ (so the kernels K coincide), we have for $t \in [t_a, t_b]$:

$$h'(t) - \widetilde{h}'(t) = A \int_{t_a}^{t} K(t, r)\,\big(f'(r) - \widetilde{f}'(r)\big)\,dr,$$

hence

$$|h'(t) - \widetilde{h}'(t)| \;\leq\; |A|\,\|K\|_{\infty;[t_a, t_b]^2} \int_{t_a}^{t_b} |\widetilde{f}'(r) - f'(r)|\,dr.$$

Taking the supremum over $t \in [t_a, t_b]$,

$$\sup_{t \in [t_a, t_b]} |h'(t) - \widetilde{h}'(t)| \;\leq\; |A|\,\|K\|_{\infty;[t_a, t_b]^2}\,(t_b - t_a)\sup_{r \in [t_a, t_b]} |\widetilde{f}'(r) - f'(r)|.$$

Integrating once more in time,

$$\left|\widetilde{h}(t) - h(t)\right| = \left|\int_{t_a}^t \left(\widetilde{h}'(s) - h'(s)\right) ds\right| \leq (t_b - t_a) \sup_{s \in [t_a, t_b]} |h'(s) - \widetilde{h}'(s)|,$$

so that

$$\sup_{t \in [t_a, t_b]} |\widetilde{h}(t) - h(t)| \leq |A| \, \|K\|_{\infty;[t_a, t_b]^2} \, (t_b - t_a)^2 \sup_{r \in [t_a, t_b]} |\widetilde{f}'(r) - f'(r)|.$$

Finally, substitute the bound (22) into this inequality and combine the factors $|A|$, $\|K\|_{\infty;[t_a,t_b]^2}$ and $(t_b - t_a)^2$ into a single constant $C > 0$. This yields

$$\sup_{t \in [t_a, t_b]} |\widetilde{h}(t) - h(t)| \leq C(\varepsilon_1 + \varepsilon_2) \left(\|\widetilde{\alpha}_3 - \alpha_3\|_{L^\infty([t_a, t_b])} + \|\widetilde{\alpha}_3' - \alpha_3'\|_{L^\infty([t_a, t_b])}\right),$$

which is exactly (21). The "negligible-effect" follows by the fact that $\varepsilon_1, \varepsilon_2 \ll 1$ on the midlife window and noting that the right-hand side is then small even for order-one perturbations of α_3 and α_3' on the window. □

6 Dip and rebound of $h'(t)$

We now give sufficient conditions for a *dip* of $h'(t)$ on a midlife window and a *rebound* later, which amounts to a Clemmesen hook-like behavior in $h(t)$.

6.1 Sufficient conditions for dip and rebound

Consider the initial value problem (1)-(6) along with (7). In the previous section we showed that changes in the detection dynamics localized to the midlife window is not strong enough to produce a realistic transition phase such as Clemmesen's hook. We now show how to obtain such a hook purely by parameter choices. Recall

$$\dot{x}_4 = c(t)\, x_4(t) + \mu_1 x_3(t)\, x_6(t),$$

where

$$c(t) := -(\alpha_1 + \beta_1 + \mu_1) + \mu_1 x_5(t) + 2\alpha_1 x_3(t) = \alpha_1\big(2x_3(t) - 1\big) - \beta_1 + \mu_1\big(x_5(t) - 1\big).$$

and $h'(t) = A\, x_4(t)$ with $A < 0$. A hook in $h(t)$ means:

$$\frac{d}{dt}(-x_4) = -\dot{x}_4 \text{ is } \begin{cases} > 0 & \text{(pre-window growth)}, \\ < 0 & \text{(mid-window decline)}, \\ > 0 & \text{(post-window growth)}. \end{cases}$$

Equivalently, we want

$$\dot{x}_4 \text{ to be } \begin{cases} < 0 & \text{before } t_a, \\ > 0 & \text{on the window } [t_a, t_b], \\ < 0 & \text{after } t_b. \end{cases} \tag{$\star$}$$

Since, in general $f'(t) \leq 0$ (given the improvement in detection over time), the inhomogeneous input in

$$\dot{x}_6 = q(t)x_6(t) + \mu_2 x_5(t) f'(t), \qquad q(t) := -(\alpha_2 + \beta_2 + \mu_2) + \mu_2 f(t) + 2\alpha_2 x_5(t)$$

is nonpositive. With $x_6(0) = 0$, the Volterra representation of x_6 in section 4 gives $x_6(t) \leq 0$. Given that mutational events are rare the mutation rates μ_i are typically small. Given that x_3 and x_5 (survival probabilities) get smaller for later ages we can deduce that $|\mu_1 x_3 x_6|$ is relatively small. Then

$$\dot{x}_4 = c(t)\, x_4(t) + \underbrace{\mu_1 x_3(t) x_6(4)}_{\leq 0} \leq c(t)\, x_4(t),$$

and, when $|\mu_1 x_3 x_6| \ll |c(t)x_4|$, the sign of $\dot{x}_4$ is dictated by $c(t)\, x_4$.

At $t = 0$, $x_4(0) = 0$ and $\dot{x}_4(0) = \mu_1 x_3(0) x_6(0) = 0$. If $f'(0) < 0$ (or shortly after), then $x_6 < 0$ for small t, hence $\dot{x}_4 \approx \mu_1 x_3 x_6 < 0$, so x_4 becomes negative and $-x_4 > 0$ corresponding to the increase in the incidence. In early years, when $x_3, x_5 \approx 1$ for $\alpha_1 > \beta_1$ we get $c(t) > 0$ which makes $c(t)x_4 < 0$ and consequently $\dot{x}_4 < 0$. These parameters are biologically relevant and bounded. Here as mutations occur in tumor suppressor genes or oncogenes leading to lowered cell death rates (β_i) or increased proliferation rates (α_i) respectively, it is most likely that the mutated cells grow (i.e., $\alpha_1 > \beta_1$) following the initial mutation (at the rate μ_0).

Now, we investigate the most reasonable parameter choices that could create a midlife dip and rebound.

Proposition 6.1. *Let $[t_a, t_b]$ be a midlife window. Fix $t \in [t_a, t_b]$ with $x_5(t) < 1$ and $x_3(t) \in (0, 1)$. A necessary condition for $c(t) < 0$ is*

$$\mu_1(t) \ \geq \ \frac{\beta_1 - \alpha_1 (2x_3(t) - 1)}{1 - x_5(t)}. \tag{23}$$

Proof. $c(t) < 0$ is equivalent to

$$\alpha_1(2x_3 - 1) - \beta_1 + \mu_1(x_5 - 1) < 0 \quad \Longleftrightarrow \quad \mu_1(1 - x_5) > \beta_1 - \alpha_1(2x_3 - 1).$$

Since $x_5 < 1$ we may divide by $1 - x_5 > 0$ to obtain (23). □

Note: Numerically and without intervention when the model is fit to the incidence data $\alpha_1 > \beta_1$ but their values are close (see the Numerical Experiment section). Therefore, there is a time $t > 0$ such that $2x_3(t) - 1 \lessgtr 1$ and $\beta_1 - \alpha_1(2x_3 - 1) > 0$. After that the difference gets larger and larger. Given that the denominator is also less than 1 for $t > 0$ then μ_1 likely requires an extreme scale-up to satisfy the necessary condition.

Lemma 6.2. *Let $\mu_1, \widetilde{\mu}_1$ be such that*

$$\widetilde{\mu}_1(t) \ \geq \ \mu_1(t) \quad \textit{for } t \in [t_a, t_b], \qquad \widetilde{\mu}_1(t) = \mu_1(t) \quad \textit{for } t \notin [t_a, t_b].$$

Let $x_3, \widetilde{x}_3$ be the corresponding solutions with the same initial state at $t = t_a$. Then

$$\widetilde{x}_3(t) \ \leq \ x_3(t) \qquad \textit{for all } t \geq t_a. \tag{24}$$

Proof. Write

$$f_3(x_3; t, \mu_1) := \beta_1 - (\alpha_1 + \beta_1 + \mu_1) x_3 + \mu_1 x_3 x_5 + \alpha_1 x_3^2 = \beta_1 - (\alpha_1 + \beta_1)x_3 - \mu_1 x_3(1 - x_5) + \alpha_1 x_3^2,$$

so $\dot{x}_3 = f_3(x_3; t, \mu_1)$. For any fixed t and $x_3 \in (0, 1]$ with $x_5(t) \in (0, 1]$,

$$\frac{\partial f_3}{\partial \mu_1}(x_3; t, \mu_1) = -x_3(1 - x_5(t)) \ \leq \ 0.$$

Thus $f_3(\cdot; t, \mu)$ is nonincreasing in μ_1 pointwise. Let $y := \widetilde{x}_3 - x_3$. Then

$$\dot{y} \ = \ f_3(\widetilde{x}_3; t, \widetilde{\mu}_1) - f_3(x_3; t, \mu_1) \ = \ \left[f_3(\widetilde{x}_3; t, \widetilde{\mu}_1) - f_3(\widetilde{x}_3; t, \mu_1)\right] \ + \ \left[f_3(\widetilde{x}_3; t, \mu_1) - f_3(x_3; t, \mu_1)\right].$$

The first bracket is ≤ 0 on $[t_a, t_b]$ by $\widetilde{\mu}_1 \geq \mu_1$ and equals 0 outside. Using the mean value theorem in x_3 and the fact that the following is bounded on any compact x_3-interval (in particular on $[0, 1]$)

$$\frac{\partial f_3}{\partial x_3}(x_3; t, \mu_1) = -(\alpha_1 + \beta_1 + \mu_1) + \mu_1 x_5 + 2\alpha_1 x_3$$

there exists $L > 0$ with $|f_3(\widetilde{x}_3; t, \mu_1) - f_3(x_3; t, \mu_1)| \leq L |y|$. Therefore,

$$\dot{y}(t) \ \leq \ L y(t), \qquad y(t_a) = 0,$$

and Grönwall's inequality gives $y(t) \leq 0$ for all $t \geq t_a$, i.e. (24). □

Lemma 6.3. *For any $t \geq t_b$ and any $\mu_1^{\text{post}} \geq 0$,*

$$c(t) \ \leq \ \alpha_1 \big(2x_3(t) - 1\big) - \beta_1. \tag{25}$$

Hence a necessary condition for $c(t) > 0$ is

$$x_3(t) \ > \ \tau := \frac{1}{2} + \frac{\beta_1}{2\alpha_1}. \tag{26}$$

Proof. Since $x_5(t) \leq 1$, we have $\mu_1^{\text{post}}(x_5(t) - 1) \leq 0$, which implies (25). Rearranging $\alpha_1(2x_3 - 1) - \beta_1 > 0$ yields (26). □

Proposition 6.4. *Suppose that on $[t_a, t_b]$ we have $\widetilde{\mu}_1 \geq \mu_1$ (relative to a baseline μ_1) that is used to achieve $c < 0$ on $[t_a, t_b]$ and that the corresponding solution satisfies*

$$\widetilde{x}_3(t_b^+) \ \leq \ \tau.$$

Then for every $\mu_1^{\text{post}} \geq 0$ and every $t \geq t_b$ we have $c(t) \leq 0$. In particular, lowering μ_1 back to baseline or even below baseline after t_b cannot produce $c(t) > 0$ (no rebound).

Proof. By Lemma 6.2, $\widetilde{x}_3(t) \leq x_3^{\text{base}}(t)$ for $t \geq t_a$. At t_b^+, $\widetilde{x}_3(t_b^+) \leq \tau$ by assumption. By continuity of $t \mapsto \widetilde{x}_3(t)$ there exists $\delta > 0$ with $\widetilde{x}_3(t) \leq \tau$ on $[t_b, t_b + \delta]$. For such t, Lemma 6.3 yields

$$c(t) \leq \alpha_1\big(2\widetilde{x}_3(t) - 1\big) - \beta_1 \leq \alpha_1(2\tau - 1) - \beta_1 = 0.$$

Hence $c(t) \leq 0$ on $[t_b, t_b + \delta]$. Note that $\widetilde{x}_3(t)$ is a survival probability so it is nonincreasing in time so $\widetilde{x}_3(t) \leq \tau$ for all $t \geq t_b$, then $c(t) \leq 0$ for all $t \geq t_b$, which rules out a rebound. $\square$

Conclusion: Based on the propositions and lemmas proved above, to begin a dip (i.e., $c(t) < 0$) in the midlife window we likely need a large increase in μ_1, which in turn leads to a smaller x_3 value. Now to get back to a $c(t) > 0$ we need $x_3 \leq \tau$ to become $x_3 \geq \tau$ but we cannot. So, a dip and rebound cannot be achieved by changing μ_1.

Now consider the following piecewise-constant schedule:

$$\alpha_1(t) = \begin{cases} \alpha_1^{\text{base}} - \Delta_\alpha, & t \in [t_a, t_b], \quad \Delta_\alpha > 0, \\ \alpha_1^{\text{base}}, & t > t_b, \end{cases} \qquad \beta_1(t) = \begin{cases} \beta_1^{\text{base}}, & t \leq t_b, \\ \beta_1^{\text{base}} - \Delta_\beta, & t > t_b, \quad \Delta_\beta > 0, \end{cases}$$

with μ_1 fixed at baseline.

Proposition 6.5. *Let $\alpha_1^{\text{new}} = \alpha_1^{\text{base}} - \Delta_\alpha$ with $\Delta_\alpha > 0$ on $[t_a, t_b]$. Then for a fixed $t \in [t_a, t_b]$ the change in c satisfies*

$$c_{\text{new}}(t) - c_{\text{base}}(t) = -\Delta_\alpha\,(2x_3(t) - 1).$$

In particular, on any subinterval where $x_3(t) > \frac{1}{2}$, decreasing α_1 strictly decreases $c(t)$.

Proof. Direct substitution: $c = \alpha_1(2x_3 - 1) - \beta_1 + \mu_1(x_5 - 1)$, from which $\Delta c = (\alpha_1^{\text{base}} - \Delta_\alpha - \alpha_1^{\text{base}})(2x_3 - 1) = -\Delta_\alpha(2x_3 - 1)$. $\square$

Remark 6.6. *On $[t_a, t_b]$, $\partial f_3 / \partial \alpha_1 = x_3(x_3 - 1) \leq 0$. Hence, replacing α_1^{base} by $\alpha_1^{\text{base}} - \Delta_\alpha$ increases the right-hand side of $\dot{x}_3 = f_3$ pointwise, and comparison yields*

$$x_3^{(\alpha_1^{\text{base}} - \Delta_\alpha)}(t) \geq x_3^{(\alpha_1^{\text{base}})}(t) \qquad (t \in [t_a, t_b]).$$

Thus the window intervention (through lowering α_1) does not reduce x_3 at t_b^+ relative to baseline. (Similar reasoning as in Lemma 6.2). This is important because if lowering α_1 lowered x_3 in addition to $c(t)$ then there will not be any chance to achieve $c(t) > 0$ after the window by moderate changes in β_1.

Proposition 6.7. *At t_b^+, change $\beta_1 \to \beta_1 - \Delta_\beta$ with $\Delta_\beta > 0$. Then there exists $\delta > 0$ (depending on local Lipschitz bounds of f_3) such that*

$$c_{\text{new}}(t) > 0 \qquad \text{for all } t \in (t_b, t_b + \delta].$$

Proof. Set $\Delta x_3(t) := x_3^{\text{new}}(t) - x_3^{\text{base}}(t)$ for $t \geq t_b$. Write

$$\Delta \dot{x}_3 = \underbrace{\big[f_3(x_3^{\text{new}}; t, \beta_1) - f_3(x_3^{\text{base}}; t, \beta_1)\big]}_{=:A(t)} + \underbrace{\big[f_3(x_3^{\text{new}}; t, \beta_1 - \Delta_\beta) - f_3(x_3^{\text{new}}; t, \beta_1)\big]}_{=:B(t)}.$$

Since f_3 is locally Lipschitz in x_3, $|A(t)| \leq L\,|\Delta x_3(t)|$ for some $L > 0$. Moreover,

$$B(t) = -\Delta_\beta\,(1 - x_3^{\text{new}}(t)) \leq 0.$$

Hence

$$|\Delta \dot{x}_3(t)| \leq L\,|\Delta x_3(t)| + \Delta_\beta \qquad (t \geq t_b), \qquad |\Delta x_3(t_b)| = 0.$$

using the fact that $\frac{d}{dt}|\Delta x_3(t)| \leq |\Delta \dot{x}_3(t)|$, we get:

$$\frac{d}{dt}|\Delta x_3(t)| \leq L\,|\Delta x_3(t)| + \Delta_\beta$$

By Grönwall, for t close to t_b we obtain the quantitative bound

$$|\Delta x_3(t)| \leq \frac{\Delta_\beta}{L}\left(e^{L(t - t_b)} - 1\right)$$

Now compute the change in c:

$$c_{\text{new}}(t) - c_{\text{base}}(t) = \Delta_\beta + 2\alpha_1\,\Delta x_3(t).$$

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Therefore, for $t \in [t_b, t_b + \delta]$,

$$c_{\text{new}}(t) - c_{\text{base}}(t) \; \geq \; \Delta_\beta \; - \; 2\alpha_1 \, |\Delta x_3(t)| \; \geq \; \Delta_\beta \; - \; 2\alpha_1 \frac{\Delta_\beta}{L} \left(e^{L(t-t_b)} - 1 \right)$$

Choose $\delta_1 > 0$ so small that $\frac{2\alpha_1}{L}(e^{L\delta} - 1) \leq \frac{1}{2}$. Then

$$c_{\text{new}}(t) - c_{\text{base}}(t) \; \geq \; \tfrac{1}{2}\Delta_\beta \qquad \text{for } t \in (t_b, t_b + \delta_1].$$

which means

$$c_{\text{new}}(t) \geq \tfrac{1}{2}\Delta_\beta + c_{\text{base}}(t). \tag{$\star$}$$

Now we know that $c_{base}(t)$ is continuous on the interval, so for every $\epsilon > 0$ we can find a $\delta_2 > 0$ such that

$$|c_{base}(t) - c_{base}(t_b^+)| < \epsilon, \qquad \text{for all } t \in (t_b, t_b + \delta_2] \tag{$\star\star$}$$

At the end of the dip, $c_{base}(t_b^+)$ is around zero or slightly negative. So, pick Δ_β such that

$$c_{base}(t_b^+) + \frac{1}{2}\Delta_\beta - \epsilon > 0 \tag{$\diamond$}$$

Taking $\delta = \min\{\delta_1, \delta_2\}$, for all $t \in (t_b, t_b + \delta]$ we have

$$\begin{aligned}
c_{\text{new}}(t) &\geq \tfrac{1}{2}\Delta_\beta + c_{\text{base}}(t) &&\text{from } (\star) \\
&\geq c_{base}(t_b^+) - \epsilon + \tfrac{1}{2} &&\text{from } (\star\star) \\
&> 0 &&\text{from } (\diamond)
\end{aligned}$$

$\square$

Conclusion: Proposition 6.5 gives the dip on the midlife window via a modest decrease of α_1 (because $2x_3 - 1 < 0$ there), Remark 6.6 guarantees no adverse reduction of x_3 at the window boundary, and Proposition 6.7 yields a post-window interval with $c > 0$ after decreasing β_1—hence a rebound.

Note: Here we saw that the change required for the dip in midlife window is easily achieved by reasonable changes in α_1. In contrast, for μ_1 the same scale of effect likely requires an unreasonably large increase. Then we showed that by changing β_1 we can readily foil the dip effect and acquire a rebound. It is worth noting that any changes in α_1 and β_1 that results in decreased α_1/β_1 ratio in the midlife window and then an increase in the same ratio after the window can reproduce the same effect. For example, increasing β_1 in the midlife window and increasing α_1 after can also produce a similar dip and rebound effect, but we chose the other regime due to more biological relevance related to hormonal changes during and after menopause (see the discussion).

In this section we only focused on the effect of $c(t)$ and its parameters α_1, β_1 and μ_1 on the midlife events. Next, we show that $q(t)$ and its parameters cannot create as strong of an impact.

7 Why $c(t)$ dominates $q(t)$ in midlife dynamics

We compare, on a fixed midlife window $W_+ = [t_a, t_b]$, the size of the response of $h'(t)$ to small, compactly supported perturbations of c versus q. Let $\delta c, \delta q \in L^1(W_+)$ be small and supported in W_+. We write $\Xi = c + q$ and, for a fixed (t, r), recall

$$K(t, r) = \mu_1 \mu_2 \, x_5(r) \int_r^t x_3(s) \exp\left(\int_r^s \Xi(u) \, du \right) ds, \qquad h'(t) = A \int_0^t K(t, r) f'(r) \, dr.$$

We consider Gateaux variations to first order in the perturbation amplitude ε:

$$\delta_\varepsilon h'(t) := \frac{h'[\Xi + \varepsilon(\delta c + \delta q)](t) - h'[\Xi](t)}{\varepsilon}, \quad \delta h'(t) := \lim_{\varepsilon \to 0} \delta_\varepsilon h'(t),$$

and similarly for K. All bounds below are uniform for $t \in W_+$, and constants may depend on the bounds from Lemma 3.2 and on W_+, but not on the specific choice of $\delta c, \delta q$.

Lemma 7.1. *Fix $T > 0$. Assume $x_3, x_5 \in L^\infty([0,T])$ with $0 < m_3 \le x_3(t) \le M_3$ and $0 < m_5 \le x_5(t) \le M_5$ a.e. on $[0,T]$, and let $\Xi \in L^\infty([0,T])$. For $0 \le r \le t \le T$ define*

$$K(t,r) := \mu_1 \mu_2 \, x_5(r) \, I(t,r), \qquad I(t,r) := \int_r^t x_3(s) \exp\Big(\int_r^s \Xi(u) \, du\Big) ds.$$

Let $\psi \in L^\infty([0,T])$ (this will play the role $\psi = \delta c + \delta q$) and, for $\varepsilon \in \mathbb{R}$, set $\Xi_\varepsilon := \Xi + \varepsilon\psi$ and K_ε the kernel obtained by replacing Ξ with Ξ_ε in the definition above. Then for every $0 \le r \le t \le T$ the Gâteaux derivative

$$\delta K(t,r) := \lim_{\varepsilon \to 0} \frac{K_\varepsilon(t,r) - K(t,r)}{\varepsilon}$$

exists and is given by the formula

$$\delta K(t,r) = \mu_1 \mu_2 \, x_5(r) \int_r^t \psi(u) \exp\Big(\int_r^u \Xi\Big) \Big(\int_u^t x_3(s) \exp\Big(\int_u^s \Xi\Big) ds\Big) du. \tag{27}$$

Equivalently, in terms of $I(t, \cdot)$,

$$\delta K(t,r) = \mu_1 \mu_2 \, x_5(r) \int_r^t \psi(u) \, e^{\int_r^u \Xi} I(t,u) \, du. \tag{28}$$

Hence the logarithmic derivative has the representation

$$\frac{\delta K}{K}(t,r) = \int_r^t w(t,r;u) \, \psi(u) \, du, \qquad w(t,r;u) := \frac{e^{\int_r^u \Xi} I(t,u)}{I(t,r)} \quad (\ge 0). \tag{29}$$

Proof. Write $K(t,r) = \mu_1 \mu_2 \, x_5(r) \, I(t,r)$ with

$$I(t,r) := \int_r^t x_3(s) \exp\Big(\int_r^s \Xi\Big) ds.$$

Since x_5 does not depend on Ξ, it suffices to compute the Gâteaux derivative of I. For $\Xi_\varepsilon := \Xi + \varepsilon\psi$ we have

$$I_\varepsilon(t,r) := \int_r^t x_3(s) \exp\Big(\int_r^s \Xi_\varepsilon\Big) ds = \int_r^t x_3(s) \, e^{\int_r^s \Xi} \exp\Big(\varepsilon \int_r^s \psi\Big) ds.$$

Fix (t,r) and consider the difference quotient:

$$\frac{I_\varepsilon(t,r) - I(t,r)}{\varepsilon} = \int_r^t x_3(s) \, e^{\int_r^s \Xi} \frac{e^{\varepsilon \int_r^s \psi} - 1}{\varepsilon} \, ds.$$

Define $Z(s) := \int_r^s \psi(u) \, du$. Since $\psi \in L^\infty$, $|Z(s)| \le \|\psi\|_\infty (s-r) \le \|\psi\|_\infty (t-r)$ for $s \in [r,t]$. For $|\varepsilon| \le 1$ the following bound holds

$$\left|\frac{e^{\varepsilon z} - 1}{\varepsilon}\right| \le e^{|z|} |z|, \qquad z \in \mathbb{R},$$

and implies

$$\left|x_3(s) \, e^{\int_r^s \Xi} \frac{e^{\varepsilon Z(s)} - 1}{\varepsilon}\right| \le \|x_3\|_\infty \, e^{\|\Xi\|_\infty (s-r)} \, e^{|Z(s)|} |Z(s)| \le C \, e^{C(s-r)} (s-r),$$

with $C := \max\{\|\Xi\|_\infty, \|\psi\|_\infty, \|x_3\|_\infty\}$ (depending only on the uniform bounds and on T). The right-hand side is integrable on $s \in [r,t]$. Moreover, pointwise in s,

$$\frac{e^{\varepsilon Z(s)} - 1}{\varepsilon} \longrightarrow Z(s) \qquad (\varepsilon \to 0).$$

By the dominated convergence theorem,

$$\lim_{\varepsilon \to 0} \frac{I_\varepsilon(t,r) - I(t,r)}{\varepsilon} = \int_r^t x_3(s) \, e^{\int_r^s \Xi} Z(s) \, ds = \int_r^t x_3(s) \, e^{\int_r^s \Xi} \Big(\int_r^s \psi(u) \, du\Big) ds.$$

Apply Fubini/Tonelli on the triangle $\{(u,s) : r \le u \le s \le t\}$:

$$\int_r^t x_3(s) \, e^{\int_r^s \Xi} \Big(\int_r^s \psi(u) \, du\Big) ds = \int_r^t \psi(u) \Big(\int_u^t x_3(s) \, e^{\int_r^s \Xi} ds\Big) du.$$

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Use additivity of the integral in the exponent:

$$\int_r^s \Xi = \int_r^u \Xi + \int_u^s \Xi \quad \implies \quad e^{\int_r^s \Xi} = e^{\int_r^u \Xi} e^{\int_u^s \Xi}.$$

Therefore

$$\int_u^t x_3(s)\, e^{\int_r^s \Xi}\, ds = e^{\int_r^u \Xi} \int_u^t x_3(s)\, e^{\int_u^s \Xi}\, ds = e^{\int_r^u \Xi}\, I(t,u).$$

We conclude that

$$\delta I(t,r) := \lim_{\varepsilon \to 0} \frac{I_\varepsilon(t,r) - I(t,r)}{\varepsilon} = \int_r^t \psi(u)\, e^{\int_r^u \Xi}\, I(t,u)\, du,$$

which is (28) upon multiplying by $\mu_1 \mu_2\, x_5(r)$. Finally, dividing both sides by $K(t,r) = \mu_1 \mu_2\, x_5(r)\, I(t,r)$ gives

$$\frac{\delta K}{K}(t,r) = \int_r^t \frac{e^{\int_r^u \Xi}\, I(t,u)}{I(t,r)}\, \psi(u)\, du = \int_r^t w(t,r;u)\, \psi(u)\, du,$$

establishing (29). □

The next two results quantify the relative sizes of the responses to δq and to δc.

Proposition 7.2. *Fix $T > 0$. Assume $x_3, x_5 \in L^\infty([0,T])$ with $0 < m_3 \le x_3 \le M_3$ and $0 < m_5 \le x_5 \le M_5$, and $\Xi = c + q \in L^\infty([0,T])$. Let $\delta c \equiv 0$ and $\delta q \in L^\infty([0,T])$ be supported in $W_+ = [t_a, t_b] \subset [0,T]$. Then for every $t \in W_+$,*

$$|\delta h'(t)| \le |A|\, \|K\|_{\infty;[0,t]^2} \left(\sup_{u \in [0,t]} \int_u^t |\delta q(s)|\, ds \right) \int_0^t |f'(r)|\, dr. \tag{30}$$

In particular, if $\int_{W_+} |f'| \ll 1$ (i.e., small variations of f in the midlife regime), then

$$\sup_{t \in W_+} |\delta h'(t)| \le C_q \left(\sup_{u \in W_+} \int_u^{t_b} |\delta q(s)|\, ds \right) \cdot \underbrace{\int_{W_+} |f'(r)|\, dr}_{\ll 1}, \qquad C_q := |A|\, \|K\|_{\infty;[0,T]^2}.$$

Proof. By the Gâteaux derivative (Lemma 7.1), with $\psi = \delta q$ and for $0 \le r \le t$,

$$\frac{\delta K}{K}(t,r) = \int_r^t \frac{e^{\int_r^u \Xi}\, I(t,u)}{I(t,r)}\, \delta q(u)\, du = \int_r^t w(t,r;u)\, \delta q(u)\, du,$$

We can write

$$e^{\int_r^u \Xi}\, I(t,u) = e^{\int_r^u \Xi} \int_u^t x_3(s) e^{\int_u^s \Xi}\, ds = \int_u^t x_3(s) e^{\int_r^s \Xi}\, ds$$

Hence, for $r \le u \le t$, $0 \le w(t,r;u) \le 1$. This gives us the following inequality:

$$\left| \frac{\delta K}{K}(t,r) \right| = \left| \int_r^t w(t,r;u)\, \delta q(u)\, du \right| \le \int_r^t |\delta q(u)|\, du,$$

which gives

$$|\delta K(t,r)| \le |K(t,r)| \int_r^t |\delta q(u)|\, du.$$

Finally, take $\sup_{(t,r) \in [0,t]^2} |K(t,r)| = \|K\|_{\infty;[0,t]^2}$ we can obtain:

$$|\delta h'(t)| = |A| \left| \int_0^t \delta K(t,r)\, f'(r)\, dr \right| \le |A|\, \|K\|_{\infty;[0,t]^2} \left(\sup_{u \in [0,t]} \int_u^t |\delta q| \right) \int_0^t |f'(r)|\, dr,$$

which is (30). □

Lemma 7.3. *Under the same boundedness hypotheses on x_3, x_5, Ξ as above, let $\delta q \equiv 0$ and $\delta c \in L^\infty([0,T])$ be supported in W_+. Then the first variation δx_4 solves the linear inhomogeneous ODE*

$$\delta \dot{x}_4(t) = c(t)\, \delta x_4(t) + \delta c(t)\, x_4(t), \qquad \delta x_4(0) = 0,$$

and admits the explicit representation

$$\delta x_4(t) = \int_0^t \Phi_c(t,s)\, \delta c(s)\, x_4(s)\, ds, \quad \Phi_c(t,s) := \exp\left(\int_s^t c(u)\, du \right). \tag{31}$$

Proof. We start from the original unperturbed ODE for x_4 because this is directly incorporated in the ODE for $h'(t)$:

$$\dot{x}_4(t) = c(t)\,x_4(t) + \mu_1 x_3(t)\,x_6(t).$$

Now perturb c by a small parameter ε:

$$c_\varepsilon(t) := c(t) + \varepsilon\delta c(t).$$

Denote the corresponding perturbed solution by $x_{4,\varepsilon}(t)$. It satisfies

$$\dot{x}_{4,\varepsilon}(t) = c_\varepsilon(t)\,x_{4,\varepsilon}(t) + \mu_1 x_3(t)\,x_6(t). \tag{32}$$

Note that only c is perturbed, while q and f are unchanged, so x_3 and x_6 are the same across ε. The initial condition remains $x_{4,\varepsilon}(0) = 0$. The first variation of x_4 is

$$\delta x_4(t) := \left.\frac{d}{d\varepsilon}x_{4,\varepsilon}(t)\right|_{\varepsilon=0}.$$

Differentiate (32) with respect to ε at $\varepsilon = 0$. We compute term by term:

- For the left-hand side:

$$\left.\frac{d}{d\varepsilon}\dot{x}_{4,\varepsilon}(t)\right|_{\varepsilon=0} = \frac{d}{dt}\left(\left.\frac{d}{d\varepsilon}x_{4,\varepsilon}(t)\right|_{\varepsilon=0}\right) = \delta\dot{x}_4(t).$$

- For the right-hand side:

$$\left.\frac{d}{d\varepsilon}\big(c_\varepsilon(t)\,x_{4,\varepsilon}(t)\big)\right|_{\varepsilon=0} = \left.\frac{d}{d\varepsilon}\Big((c(t) + \varepsilon\delta c(t))\,x_{4,\varepsilon}(t)\Big)\right|_{\varepsilon=0}.$$

Expand:

$$= \delta c(t)\,x_4(t) + c(t)\,\delta x_4(t).$$

- The second term on the right hand side would go away.

Thus the variation δx_4 satisfies

$$\delta\dot{x}_4(t) = c(t)\,\delta x_4(t) + \delta c(t)\,x_4(t)$$

with $\delta x_4(0) = 0$. This is exactly the stated ODE. By variation of constants, the ODE for δx_4 has solution

$$\delta x_4(t) = \int_0^t \Phi_c(t,s)\,\delta c(s)\,x_4(s)\,ds$$

which is exactly (31). $\qquad\square$

Proposition 7.4. *Assume the hypotheses at the start of Proposition 7.2. Let $\delta q \equiv 0$, and let δc be supported in W_+. Then for every $t \in W_+$,*

$$|\delta h'(t)| \geq |A|\int_0^t \Phi_c(t,s)\,|\delta c(s)|\,|x_4(s)|\,ds \;-\; |A|\,\|K\|_{\infty;[0,t]^2}\left(\sup_{u\in[0,t]}\int_u^t |\delta c(s)|\,ds\right)\int_0^t |f'(r)|\,dr. \tag{33}$$

Proof. There are two independent first-order paths:

(1) Homogeneous x_4 path. By Lemma 7.3,

$$\delta x_4(t) = \int_0^t \Phi_c(t,s)\,\delta c(s)\,x_4(s)\,ds.$$

Hence the contribution to h' is

$$\delta h'_{\mathrm{hom}}(t) = -\mu_0 N_0\,\delta x_4(t) = -\mu_0 N_0\int_0^t \Phi_c(t,s)\,\delta c(s)\,x_4(s)\,ds.$$

Taking absolute values gives

$$|\delta h'_{\mathrm{hom}}(t)| = |A|\int_0^t \Phi_c(t,s)\,|\delta c(s)|\,|x_4(s)|\,ds.$$

(2) Kernel reweighting path. Independently, the kernel K depends on $\Xi = c + q$, so by Lemma 7.1 with $\psi = \delta c$ and $0 \leq w \leq 1$,

$$|h'_{\mathrm{re}}(t)| = |A|\left|\int_0^t \delta K(t,r)\,f'(r)\,dr\right| \leq |A|\|K\|_{\infty;[0,t]^2}\left(\sup_{u\in[0,t]}\int_u^t |\delta c|\right)\int_0^t |f'(r)|\,dr.$$

so

$$|\delta h'(t)| = |\delta h'_{\text{hom}}(t) + h'_{\text{re}}(t)| \geq |A| \int_0^t \Phi_c(t,s)\,|\delta c(s)|\,|x_4(s)|\,ds$$

$$- |A|\|K\|_{\infty;[0,t]^2} \left(\sup_{u \in [0,t]} \int_u^t |\delta c| \right) \int_0^t |f'(r)|\,dr.$$

$\square$

Theorem 7.5. *Assume the boundedness hypotheses above and suppose the midlife variations in f is small:*

$$\int_{W_+} |f'(r)|\,dr \leq \varepsilon_\star \qquad \text{with } \varepsilon_\star \ll 1.$$

Assume further that x_4 is bounded away from 0 on a subset $J \subset W_+$ of positive measure:

$$\exists\, m_4 > 0,\ |J| > 0\ \text{ such that }\ |x_4(s)| \geq m_4\ \text{ for a.e. } s \in J.$$

Let $\delta q, \delta c$ be supported in W_+ with comparable L^1 sizes: $\int_{W_+} |\delta q| \approx \int_{W_+} |\delta c|$. Then, uniformly for $t \in W_+$,

$$|\delta h'_q(t)| \leq C_q \left(\sup_{u \in W_+} \int_u^{t_b} |\delta q| \right) \varepsilon_\star,$$

while

$$\sup_{t \in W_+} |\delta h'_c(t)| \geq C_c \int_J |\delta c(s)|\,ds - C'_c \left(\sup_{u \in W_+} \int_u^{t_b} |\delta c| \right) \varepsilon_\star,$$

where $C_q = |A|\,\|K\|_{\infty;[0,T]^2}$ and

$$C_c := |A| \left(\inf_{t \in W_+,\, s \in J} \Phi_c(t,s) \right) m_4 > 0,$$

with Φ_c bounded below on the compact set $W_+ \times J$ by boundedness and local integrability of of c. Consequently,

$$\sup_{t \in W_+} \frac{|\delta h'_q(t)|}{|\delta h'_c(t)|} = o(1) \qquad \text{as}\quad \varepsilon_\star = \int_{W_+} |f'| \to 0.$$

Proof. The q-bound is Proposition 7.2. For the c-bound, apply (33) and restrict the first integral to J:

$$\sup_{t \in W_+} |\delta h'_c(t)| \geq |A| \left(\inf_{t \in W_+,\, s \in J} \Phi_c(t,s) \right) m_4 \int_J |\delta c(s)|\,ds - C'_c \left(\sup_{u \in W_+} \int_u^{t_b} |\delta c| \right) \int_{W_+} |f'|.$$

All constants are finite and positive under the stated hypotheses; the ratio statement follows by dividing the two bounds and letting $\varepsilon_\star \to 0$. $\square$

Corollary 7.6. *In addition to the comparison of the effects between c and q perturbations, these results assert that a less than three-stage carcinogenesis model of breast cancer with the inclusion of detection dynamics is not capable of fully capturing the incidence patterns through reasonably varying parameters.*

Remark 7.7. *If a biological parameter p (e.g. α_1) is perturbed, then c changes and so do x_3, x_5 (hence x_6). Writing the linearized system for $(\delta x_3, \delta x_5, \delta x_6)$ and solving by variation of constants yields $\|\delta x_j\|_{L^\infty(0,T)} \leq C_T |\delta p|$ for $j = 3, 5, 6$ with constants depending only on bounded Jacobians. Decomposing*

$$\delta h' = \delta h'_{\text{hom}} + \delta h'_{\text{re}} + \delta h'_{\text{state}}$$

one obtains

$$|\delta h'_{\text{hom}}(t)| \geq |A| \int_0^t \Phi_c(t,s)\,|\partial_p c(s)|\,|x_4(s)|\,ds \cdot |\delta p|,$$

$$|\delta h'_{\text{re}}(t)| \leq |A|\|K\|_{\infty;[0,t]^2} \left(\sup_{u \in [0,t]} \int_u^t |\partial_p \Xi(s)|\,ds \right) \left(\int_0^t |f'(r)|\,dr \right) |\delta p|,$$

$$|\delta h'_{\text{state}}(t)| \leq C\,|\delta p| \left(1 + \int_0^t |f'(r)|\,dr \right),$$

which shows: (i) the homogeneous x_4 path retains the same form as before and does not *carry the small midlife factor; (ii) the kernel reweighting and state paths are at worst proportional to $\int_{W_+} |f'|$ or $O(|\delta p|)$ with bounded constants. Therefore, in the midlife regime, the dominance conclusion of Theorem 7.5 persists qualitatively for parameter-level perturbations when the homogeneous path is present.*

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8 Numerical Experiment

We conducted a numerical experiment. We fit the extended MSCE model (1)-(6) to the SEER incidence data for three cohorts: i.e., those born during 1935-1939, 1940-1944 and 1945-1949. We chose these three cohorts to minimize the effect of breast cancer screening on the observed incidence. For reference, the Centers for Disease Control and Prevention's National Center for Health Statistics reports less than 29% of the population aged 40 and over were screened for these cohorts [26]. We use a Hybrid Genetic Algorithm which is a global minimization toolbox in Matlab to minimize the distance of the model hazard (i.e., $x_2 = h(t)$) from the data. The fitting process has three steps: (i) we first estimate all parameters by fitting the model to the data up to the onset of the hook at t_a; (ii) using the model output at t_a as the initial condition, we fix all parameters except one ($\theta_i \in \{\mu_0, \mu_1, \mu_2, \alpha_1, \alpha_2, \beta_1, \beta_2\}$) and perform the fitting within the dip transition window $[t_a, t_b]$; (iii) finally, we take the model output at t_b as the new initial condition, fix all parameters except $\theta_j \in \{\mu_0, \mu_1, \mu_2, \alpha_1, \alpha_2, \beta_1, \beta_2\}$, and complete the fitting for the rebound phase over the interval $[t_b, 60]$. We let the search bounds for parameter estimation in steps ii) and iii) be $[0, 2\theta_i]$ and $[0, 2\theta_j]$ (i.e., widening the lower bound to 0 and upper bound to twice of the value estimated for the preceding phase). For each cohort, the choices of t_a and t_b within the interval $[45, 55]$ are determined by identifying (i) the age at which the derivative of the smoothed incidence curve first starts a persistent downward shift, and (ii) the age at which the derivative begins to recover upward, respectively.

With this, results of our numerical experiments were consistent with the mathematical analysis in showing that generating a hook through variations in μ_1 or in the parameters involved in $q(t)$—namely, α_2, β_2, and μ_2—cannot produce the dip-and-rebound behavior within a reasonable scaling range (i.e., the parameters would need to vary far beyond realistic biological limits to achieve that effect). However, the effect was easily attainable through moderate changes in α_1 and β_1 as shown in Figure 2. Equivalently, this refers to changes in the proliferative ratio of first-stage mutated cells ($\frac{\alpha_1}{\beta_1}$).

As for μ_0, the slowdown and rebound effects were linear, as expected from its direct linear contribution to x_2 in (2). Moreover, since μ_0 represents the initiation rate of carcinogenesis—the first mutation event—it governs kinetics that occur early in life, very close to the age at menarche [27, 28]. This suggests that μ_0 is less likely to be influenced by hormonal exposures compared to the other parameters, given the limited number of menstrual cycles before the first mutational event. For a comprehensive numerical comparison of parameter effects and their ability to reproduce the hook, please refer to the supplementary materials.
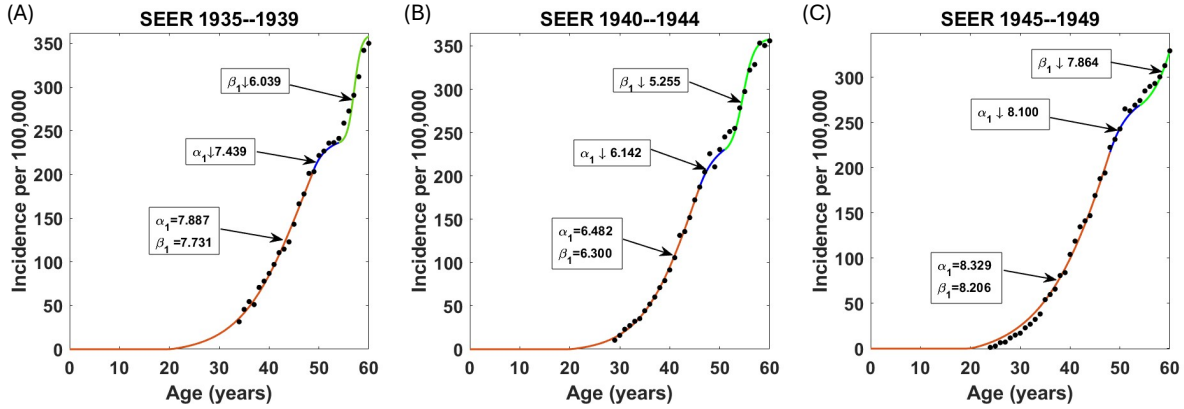

Figure 2: Model fit for SEER incidence data for three cohorts (A) 1935-1939, (B) 1940-1944 and (C) 1945-1949. The orange part of the curves corresponds to the increasing incidence before the occurrence of the Clemmesen's hook. The blue and green parts show the dip and rebound phases, respectively. The midlife window $[t_a, t_b]$ is $[49, 54]$ for (A), $[46, 51]$ for (B), and $[48, 54]$ for (C). The parameters have the unit $\frac{1}{\text{year}}$.

9 Discussion

The age-specific incidence of breast cancer exhibits a unique feature known as Clemmesen's hook, in which an initial rise in incidence is followed by a temporary slowdown between ages 45 and 55 and then another increase afterwards [2].The biological mechanisms underlying this pattern remain inconclusive, even though multiple hypotheses have been proposed in several previous studies[29, 4, 30]. In this study we carried out a rigorous mathematical analysis on an

extended multistage clonal expansion model (MSCE-T) representing breast cancer tumor kinetics to investigate the reasons behind this phenomenon.

Our analysis suggests that Clemmesen's hook likely arises from time-specific changes in the proliferation rate of early mutated clones within a three-stage carcinogenesis framework, occurring midlife around menopause. Specifically, modest reductions in the division rate (α_1) or increases in the death rate (β_1) of first-stage mutated cells are sufficient to reproduce the dip and rebound observed around the age of menopause (i.e., between 45-55). In contrast, changes in other parameters fail to generate a similar pattern unless they are unrealistically large. These findings suggest that the menopausal transition impacts breast cancer development primarily through modulation of clonal expansion rather than imposing mutagenic effects.

The model's predictions align with biological evidence linking menopause to reduced progesterone-driven proliferation and subsequent activation of growth through other signaling pathways [5, 6, 31]. The transient slowdown in incidence reflects diminished promotion of first-stage mutated cells caused by diminishing exposure to progesterone post-menopause when the ovaries stop producing this hormone (represented by lowered $\frac{\alpha_1}{\beta_1}$ in our model), while the rebound corresponds to continued expansion of existing clones under postmenopausal stimuli, such as adipose-derived growth signals [6, 31] (corresponding to the recovered $\frac{\alpha_1}{\beta_1}$ in our model). Our model results support this emerging evidence on the role of progesterone (vs. estrogen) in driving cancer cell proliferation, by specifically connecting the transitions round menopause (Clemmesen's hook) to model parameters representing the proliferation of early-stage mutated cells around midlife. In addition, our rigorous mathematical analysis helps to rule out other competing pathways (i.e., it is likely due to hormonally regulated changes in clonal expansion kinetics rather than in mutation rate). Further, our numerical analysis fitting the model to the data helps to quantify this impact.

Mathematically, the Volterra formulation of the MSCE-T model (Section 4) separates early-stage carcinogenic dynamics, governed by $c(t)$ in (9), from late-stage and detection-related dynamics, encoded in $q(t)$ and $f(t)$ in (9) and (7) respectively. Analytical results show that, within the midlife window, perturbations in $c(t)$ dominate those in $q(t)$, confirming that late-stage dynamics cannot reproduce the hook pattern. Theorems 5.3 and 5.4 further show that the sensitivity of the model hazard $h(t)$ to the tumor detection threshold (M_t) and malignant cells proliferation rate (α_3) are negligible during the menopausal transition. The analysis also demonstrates that at least three mutational stages are required to reproduce the observed age-incidence trends, consistent with Tomasetti et al. [21].

Despite its analytical insight, the model incorporates simplifying assumptions. Parameters α_i, β_i, and μ_i are treated as deterministic and piecewise-continuous, ignoring stochastic or variability in hormonal or genetic factors. The model also neglects microenvironmental influences such as oxidative stress, immune activity, and stromal stiffness, which may further modulate proliferation and death rates [32, 33, 34]. Future extensions that incorporate tissue-level heterogeneity and hormonal trajectories could enable richer dynamics and improve predictions of age-specific risk.

In summary, the extended MSCE-T model provides a coherent mechanistic and mathematical explanation for Clemmesen's hook by disentangling detection-related effects from intrinsic biological changes. It demonstrates that biologically plausible, time-specific shifts in the proliferation rate of early mutated clones, consistent with menopausal hormonal alterations, are sufficient to explain the midlife dip and rebound in breast cancer incidence. These results establish a quantitative framework for linking hormonal physiology, multi-stage carcinogenesis, and population-level cancer incidence data.

Supplementary information:

Model derivation and supplementary numerical experiments are shared as supplementary materials.

Declarations

- **Conflict of interest**: The authors declare no conflict of interest.

- **Data availability**: The data that support the findings of this study are publicly available from the SEER Program at https://seer.cancer.gov/data-software/ and NORDCAN program at https://nordcan.iarc.fr.

- **Code availability**: Codes for parameter estimation are available from https://codeocean.com/capsule/6223220/tree/v1 related to our earlier study [17]. Further information is available from the corresponding authors upon request.

- **Author contribution**:
  N.M.: Conceptualization, Methodology, Formal analysis, Software, Visualization, Writing – original draft, review & editing.

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