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Existence and optimal characterization of chemo-immunotherapy controls in a fractional cancer–immune–stress model

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Abstract

We carry out a rigorous optimal-control analysis of the fractional-order cancer–immune–stress systemof the fractional-order cancer–immune–stress system, extended so that every compartment carries its own time-dependent therapy: chemotherapy $u(t)$, immunotherapy $v(t)$, natural-cell support $w(t)$, anti-adipose therapy $z(t)$ and anti-panic therapy $q(t)$, on a five-compartment Caputo system. First, we give a non-circular proof of positivity and of a control-uniform a priori bound, replacing the earlier bootstrapped boundedness argument; it rests on an explicit condition (Assumption 3.2) on the cancer–panic feedback loop and uses only the generalized mean value theorem and the Mittag-Leffler formula. Second, using this bound with a Banach fixed-point argument and a continuity lemma, we prove existence of an optimal control tuple by the direct method. Third, we re-derive the necessary optimality conditions from a fractional integration-by-parts identity and show that the correct costate system involves a right-sided Riemann–Liouville derivative rather than the left-sided

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Caputo operator used previously. Fourth, we discuss Mangasarian-type sufficiency and give a checkable horizon condition guaranteeing uniqueness. Finally, a fractional Adams–Bashforth–Moulton/forward–backward-sweep implementation quantifies the benefit of the five-control protocol and its sensitivity to the fractional order β.

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1. Introduction

Fractional-order compartmental models have become a standard tool for describing memory and hereditary effects in tumour–immune dynamics. A substantial and rapidly growing body of work now exists on the qualitative theory of such systems: existence and uniqueness of solutions via fixed-point arguments, positivity and boundedness through fractional comparison principles, local and global stability via Matignon-type criteria and fractional Lyapunov functionals, and Ulam-type stability estimates that quantify how sensitive predictions are to measurement or parameter error [4, 5, 9]. In parallel, fractional optimal control theory has matured considerably since the original formulation of Agrawal [6]: rigorous existence results of Filippov–Cesari type, and Pontryagin-type maximum principles derived by careful fractional integration by parts, are now available for general Caputo systems through the work of Kamocki [7] and Bergounioux and Bourdin [8], building on the classical integer-order theory of existence and sufficiency summarized in [10–12].

Motivated by the well-documented influence of psychological stress on immune function and tumour progression, and by the practical importance of combining chemotherapy with immunotherapy, the companion paper [1] introduced a fractional-order extension of the cancer–obesity model of Ku-Carrillo, Delgadillo, and Chen-Charpentier [13], adding a psychological-panic compartment $P(t)$ and two treatment controls: a chemotherapy dosage $u(t)$ and an immunotherapy dosage $v(t)$. That paper is deliberately applied in character: it proposes the model, gives a first, partly heuristic, boundedness argument, states the Pontryagin-type necessary conditions formally, and simulates the model under prescribed periodic controls. The present paper is a purely theoretical companion to it, extended with an independent numerical validation. We work with exactly the same model and cost functional – no dynamics are added, removed or altered – and instead subject the model to a complete, self-contained mathematical treatment, followed by simulations that quantify the analytical results.

(i) *Positivity.* The positivity argument sketched in [1] is correct in outline but is not carried out in full; we give a complete, self-contained proof in Section 4.

(ii) *Boundedness.* The boundedness argument in [1] assumes at the outset that the panic variable $P(t)$ is bounded by a constant M_P, uses this assumption

to bound the fat and cancer compartments, and only afterwards derives a bound on $P(t)$ itself in terms of the bound already obtained for $C(t)$ – without checking that the two bounds are mutually consistent. Because C and P genuinely reinforce one another (cancer raises panic through the term κC, and panic raises the cancer growth rate through $\gamma_2 PC$), this loop can in principle support finite-time blow-up, and the boundedness claim of [1] is therefore not fully justified as stated. We give a complete, elementary fix in Section 5, using only the generalized mean value theorem and an explicit Mittag–Leffler bound–deliberately avoiding any appeal to an unproved comparison principle for coupled (cooperative) fractional systems, so that the argument is verifiable line by line.

(iii) *Existence of an optimal control.* No proof is given in [1] that a minimizing control pair for the cost functional actually exists; only the pointwise characterization of a candidate optimum is derived, under the implicit assumption that a minimizer exists. We supply a complete existence proof in Section 7.

(iv) *The costate system.* The costate system in [1] is written with the same left-sided Caputo operator as the state system. Fractional integration by parts (which we prove in full in Section 8) shows that this is not the operator dual to ${}_0^C D_t^\beta$; the correct costate equations involve a right-sided fractional derivative on $[t, T_f]$. We re-derive the necessary conditions correctly, discuss when they are also sufficient, and use them to give an explicit sufficient condition for uniqueness of the optimal pair on a short horizon (Sections 8–10).

We keep the model of [1] entirely unchanged and work with its master system, equation (4.2) there (reproduced as (3.1) below). A related, integer-order treatment of psychological stress in tumour–immune dynamics with optimal control can be found in [14]; none of the results below reduce to that paper, since the fractional derivative, the existence proof, the corrected costate system and the sufficiency and uniqueness analysis are all new relative to it as well.

The remainder of the paper is organized as follows. Section 2 collects and, where the proof is short enough to be genuinely illuminating, proves the fractional-calculus tools used throughout. Section 3 recalls the controlled system and states our standing assumptions. Section 4 proves positivity. Section 5 proves a self-contained, control-uniform a priori bound. Section 6 establishes well-posedness of the state system, with an explicit contraction estimate. Section 7 proves existence of an optimal control pair. Section 8 proves the fractional integration-by-parts identity and derives the corrected necessary optimality conditions. Section 9 proves uniqueness on a sufficiently short horizon. Section 10 discusses sufficiency. Section 11 reports a numerical validation of the theory, obtained by an independent implementation of the fractional Adams–Bashforth–Moulton predictor–corrector method together with a forward–backward sweep, and Section 12 concludes.

2. Preliminaries

Throughout, $\beta \in (0,1]$ is fixed and $T_f > 0$ is a fixed treatment horizon. For $f \in AC([0,T_f])$ the left Caputo derivative of order β is

$$ {}_0^C D_t^\beta f(t) = \frac{1}{\Gamma(1-\beta)} \int_0^t (t-\tau)^{-\beta} f'(\tau)\, d\tau, \tag{2.1} $$

and the corresponding right Caputo derivative on $[t,T_f]$ is

$$ {}_t^C D_{T_f}^\beta f(t) = \frac{-1}{\Gamma(1-\beta)} \int_t^{T_f} (\tau-t)^{-\beta} f'(\tau)\, d\tau, \tag{2.2} $$

consistent with the definitions used in [1]. We also use the right Riemann–Liouville derivative

$$ {}_t D_{T_f}^\beta f(t) = \frac{-1}{\Gamma(1-\beta)} \frac{d}{dt} \int_t^{T_f} (\tau-t)^{-\beta} f(\tau)\, d\tau, \tag{2.3} $$

and the corresponding left Riemann–Liouville derivative ${}_0D_t^\beta f(t) = \frac{1}{\Gamma(1-\beta)} \frac{d}{dt} \int_0^t (t-\tau)^{-\beta} f(\tau)\, d\tau$. For $0 < \beta < 1$ the Caputo and Riemann–Liouville derivatives are related, on each side, by

$$ \begin{aligned} {}_0^C D_t^\beta f(t) &= {}_0D_t^\beta f(t) - \frac{f(0)}{\Gamma(1-\beta)} t^{-\beta}, \qquad {}_t^C D_{T_f}^\beta f(t) \\ &= {}_t D_{T_f}^\beta f(t) - \frac{f(T_f)}{\Gamma(1-\beta)} (T_f - t)^{-\beta}, \end{aligned} \tag{2.4} $$

so left (resp. right) Caputo and Riemann–Liouville derivatives coincide whenever $f(0) = 0$ (resp. $f(T_f) = 0$). This is exactly the situation that will arise for the costate variables in Section 8, where the natural transversality condition is $\lambda_i(T_f) = 0$.

The two-parameter Mittag-Leffler function $E_{\alpha,\gamma}(z) = \sum_{k\geq 0} z^k / \Gamma(\alpha k + \gamma)$ has Laplace transform (as in [1])

$$ \mathcal{L}\left[t^{\gamma-1} E_{\alpha,\gamma}(\pm \lambda t^\alpha)\right](s) = \frac{s^{\alpha-\gamma}}{s^\alpha \mp \lambda}, $$

which we use repeatedly, together with the elementary identity

$$ \int_0^t (t-\tau)^{\beta-1} E_{\beta,\beta}\left(-\delta(t-\tau)^\beta\right) d\tau = \frac{1 - E_\beta(-\delta t^\beta)}{\delta}, \qquad \delta > 0, \tag{2.5} $$

which follows from matching Laplace transforms termwise: writing $g_\delta(t) := t^{\beta-1} E_{\beta,\beta}(-\delta t^\beta)$, $\mathcal{L}[g_\delta](s) = 1/(s^\beta + \delta)$, so $\mathcal{L}[g_\delta * 1](s) = \mathcal{L}[g_\delta](s)/s = \frac{1}{s(s^\beta+\delta)} = \delta^{-1}\left(\frac{1}{s} - \frac{s^{\beta-1}}{s^\beta+\delta}\right) = \mathcal{L}\left[\delta^{-1}\left(1 - E_\beta(-\delta t^\beta)\right)\right](s)$, and Laplace transforms determine continuous functions uniquely. We record for later use that $0 \leq E_\beta(-\delta t^\beta) \leq 1$ for all $t, \delta \geq 0$ and $0 < \beta \leq 1$ (complete monotonicity of $E_\beta(-\delta t^\beta)$ in t), and consequently $0 \leq E_{\beta,\beta}(-\delta s)$ for $s \geq 0$; both facts are classical and used without further comment below. Combining (2.5) with the

variation-of-parameters formula for the linear Caputo IVP ${}_0^C D_t^\beta w(t) = -\delta w(t) + h(t), w(0) = w_0$, gives

$$w(t) = w_0 E_\beta\left(-\delta t^\beta\right) + \int_0^t (t-\tau)^{\beta-1} E_{\beta,\beta}\left(-\delta(t-\tau)^\beta\right) h(\tau)\, d\tau, \tag{2.6}$$

so that if $0 \le h(\tau) \le H$ for $\tau \in [0,t]$ and $w_0 \ge 0$, then, using (2.5) again,

$$\begin{aligned} 0 \le w(t) &\le w_0 E_\beta\left(-\delta t^\beta\right) + \frac{H}{\delta}\left(1 - E_\beta\left(-\delta t^\beta\right)\right) \\ &\le \max\left\{w_0, \frac{H}{\delta}\right\}. \end{aligned} \tag{2.7}$$

Estimate (2.7) is used in Lemma 5.1 (Steps 3–4) and is the only quantitative tool needed to bound each scalar linear sub-system that arises. In (2.6)–(2.8) and in Lemma 2.3 the symbols w and δ denote generic scalars; they are not the control $w(t)$ nor the panic decay rate δ of (3.1).

Lemma 2.1: (Generalized mean value theorem [4]). *If* $g \in C\left[0, T_f\right]$ *and* ${}_0^C D_t^\beta g \in C(0, T_f]$ *for some* $\beta \in (0,1]$, *then for every* $t \in (0, T_f]$ *there exists* $\xi \in (0,t)$ *with*

$$g(t) = g(0) + \frac{1}{\Gamma(\beta+1)}\left({}_0^C D_t^\beta g\right)(\xi)\, t^\beta.$$

Corollary 2.2: (A one-sided monotonicity test). *If* $g \in C\left[0, T_f\right] \cap C^1(0, T_f]$, ${}_0^C D_t^\beta g \in C(0, T_f]$, *and* ${}_0^C D_t^\beta g(t) \le 0$ *whenever* $g(t) \ge M$ *for some constant* $M \ge g(0)$, *then* $g(t) \le M$ *for all* $t \in \left[0, T_f\right]$.

Proof: Suppose $g(t_1) > M$ for some $t_1 \in (0, T_f]$, and let $t_0 \in (0, t_1]$ be a point where g attains its maximum over $[0, t_1]$. Then $g(t_0) \ge g(t_1) > M \ge g(0)$ and $g(\tau) \le g(t_0)$ for all $\tau \in [0, t_0]$. Integrating by parts in the definition (2.1) (the boundary term at $\tau = t_0$ vanishes because $g \in C^1$ near t_0),

$$\begin{aligned} {}_0^C D_t^\beta g(t_0) = \frac{1}{\Gamma(1-\beta)}\Bigg[& t_0^{-\beta}(g(t_0) - g(0)) + \beta \int_0^{t_0} (t_0 - \tau)^{-\beta-1} (g(t_0) \\ & - g(\tau)) d\tau \Bigg] \ge \frac{t_0^{-\beta}\left(g(t_0) - g(0)\right)}{\Gamma(1-\beta)} > 0 \end{aligned}$$

This is the extremum principle for the Caputo derivative of Luchko [15]. On the other hand $g(t_0) > M$, so the hypothesis gives ${}_0^C D_t^\beta g(t_0) \le 0$, a contradiction. Hence $g \le M$ on $\left[0, T_f\right]$.

Corollary 2.2 and Lemma 2.5 below are the elementary devices used throughout Sections 4–5 to prove positivity and boundedness; they replace, with fully self-contained arguments, the informal "the vector field points inward" language of [1] and the unproved multi-dimensional comparison principles that

are often invoked (without proof) elsewhere in this literature for coupled systems.

We will also use the following standard result, whose short proof we include for completeness since it is invoked (with an explicit constant) inside the proof of Theorem 9.2.

Lemma 2.3: (Generalized Grönwall inequality [5]). *Let $\beta > 0$, let $a(t) \geq 0$ be non-decreasing on $[0, T_f]$, and let $w(t) \geq 0$ be continuous and satisfy*

$$w(t) \leq a(t) + b \int_0^t (t-\tau)^{\beta-1} w(\tau)\, d\tau, \qquad t \in [0, T_f], \tag{2.8}$$

for a constant $b \geq 0$. Then $w(t) \leq a(t) E_\beta\big(b\Gamma(\beta) t^\beta\big)$ for all $t \in [0, T_f]$.

Proof: Define the Picard-type iterates $w_0(t) := a(t)$ and $w_{n+1}(t) := a(t) + b \int_0^t (t-\tau)^{\beta-1} w_n(\tau)\, d\tau$. By induction, using that a is non-decreasing and the elementary Beta-function identity $\int_0^t (t-\tau)^{\beta-1} \tau^{k\beta}\, d\tau = t^{(k+1)\beta} B(\beta, k\beta + 1) = t^{(k+1)\beta} \Gamma(\beta)\Gamma(k\beta+1)/\Gamma\big((k+1)\beta + 1\big)$, one obtains

$$w_n(t) \leq a(t) \sum_{k=0}^{n} \frac{\big(b\Gamma(\beta) t^\beta\big)^k}{\Gamma(k\beta + 1)},$$

Iterating the hypothesis (2.8) n times, and using that $(t-\tau)^{\beta-1}$ is a positive kernel and that a is non-decreasing, we get $w(t) \leq a(t) \sum_{k=0}^{n-1} \frac{(b\Gamma(\beta)t^\beta)^k}{\Gamma(k\beta+1)} + \frac{(b\Gamma(\beta)t^\beta)^n}{\Gamma(n\beta+1)} \max_{[0,t]} w$. The last term tends to 0 as $n \to \infty$, because $\Gamma(n\beta + 1)$ grows faster than any geometric sequence, and the sum converges to $E_\beta\big(b\Gamma(\beta)t^\beta\big)$. Hence $w(t) \leq a(t) E_\beta\big(b\Gamma(\beta)t^\beta\big)$.

We finally recall the local stability criterion already used in [1], which motivates one of the extensions discussed in Section 12.

Theorem 2.4: (Matignon-type criterion, cf. [1]). *An equilibrium x^* of ${}_0^C D_t^\beta x = f(x)$ is locally asymptotically stable if every eigenvalue λ_i of the Jacobian $J_f(x^*)$ satisfies $|arg(\lambda_i)| > \beta\pi/2$, and unstable if $|arg(\lambda_i)| < \beta\pi/2$ for some i.*

Lemma 2.5: (Linear positivity). *Let $T > 0$, $a \in L^\infty(0,T)$ with $a \geq 0$, $b \in C[0,T]$, $y_0 \geq 0$, and let $y \in C[0,T]$ satisfy $y(t) = y_0 + \frac{1}{\Gamma(\beta)} \int_0^t (t-\tau)^{\beta-1} \big(a(\tau) + b(\tau) y(\tau)\big) d\tau$, i.e. ${}_0^C D_t^\beta y = a + by$. Then $y \geq 0$ on $[0,T]$; if moreover $y_0 > 0$, then $y > 0$.*

Proof: Choose $k \geq \max|b|$. Rewriting the equation as ${}_0^C D_t^\beta y + ky = a + (b+k)y$ and using the variation-of-constants formula (2.6) with $K_k(t)$

$:= t^{\beta-1}E_{\beta,\beta}\left(-kt^{\beta}\right) \geq 0$ we obtain $y = g + \mathcal{A}y$, where $g := y_0 E_\beta\left(-kt^{\beta}\right) + K_k * a \geq 0$ and $(\mathcal{A}\vartheta)(t) := \int_0^t K_k\,(t-\tau)(b+k)(\tau)\vartheta(\tau)d\tau$ is a positive operator. Since $0 \leq K_k(t) \leq t^{\beta-1}/\Gamma(\beta)$, we have $|\mathcal{A}^n\vartheta|(t) \leq \frac{\left(2k\Gamma(\beta)t^{\beta}\right)^n}{\Gamma(n\beta+1)} \| \vartheta \|_\infty$, so the Neumann series $\sum_{n\geq 0}\mathcal{A}^n\, g$ converges uniformly and is the unique solution of this linear Volterra equation. Each term is nonnegative, hence $y \geq 0$. If $y_0 > 0$, then $g \geq y_0 E_\beta\left(-kt^{\beta}\right) > 0$ and so $y > 0$. □

3. The Controlled System and Standing Assumptions

We work with the state vector $\mathbf{y}(t) = (I, C, N, F, P)(t) \in \mathbb{R}^5$ governed by an extension of system (4.2) of [1] in which every compartment is endowed with its own therapeutic control:

$$\begin{cases} {}_0^C D_t^\beta I = s + \phi v(t) + \dfrac{\rho IC}{\alpha + C + \mu F} - c_1 IC - d_1 I - \gamma_1 PI =: f_1(\mathbf{y}, v), \\ {}_0^C D_t^\beta C = r_1 C(1 - b_1 C) - c_2 IC - c_3 CN + c_5 CF + \gamma_2 PC - \eta u(t) C =: f_2(\mathbf{y}, u), \\ {}_0^C D_t^\beta N = r_2 N(1 - b_2 N) - c_4 CN - \gamma_3 PN + \xi w(t) =: f_3(\mathbf{y}, w), \\ {}_0^C D_t^\beta F = r_3 F(1 - b_3 F) - c_6 CF - \zeta z(t) F =: f_4(\mathbf{y}, z), \\ {}_0^C D_t^\beta P = \kappa C + u_p(t) - \delta P - \sigma q(t) P =: f_5(\mathbf{y}, q), \end{cases} \tag{3.1}$$

with $\mathbf{y}(0) = \mathbf{y}_0 = (I_0, C_0, N_0, F_0, P_0) \in \Omega_+ := \{(I, C, N, F, P) : I \geq 0, C \geq 0, N \geq 0, F \geq 0, P \geq 0\}$, $I_0 > 0$, and $0 \leq u_p(t) \leq M_u$ for all $t \geq 0$, exactly as postulated in [1]. The two controls u, v retain their original meaning (chemotherapy acting on the cancer compartment, immunotherapy acting on the immune compartment); the three new controls are a natural-cell support $w(t)$ (e.g. a growth-factor therapy that additively sustains N), an anti-adipose (metabolic) therapy $z(t)$ that depletes F at a rate proportional to F itself, and an anti-panic (psychological) therapy $q(t)$ that depletes P at a rate proportional to P itself – mirroring, on the natural-cell, fat-cell and panic compartments respectively, exactly the same structural device (additive for w, bilinear for z, q) already used for v and u in [1]. We write $f = (f_1, \ldots, f_5)$ for the full right-hand side and $\mathbf{w} := (u, v, w, z, q)$ for the control vector. Every new control term is, for fixed state, affine (indeed linear) in the corresponding control, so the affine-in-control structure that drives Remark 7.2 below is preserved unchanged. The admissible control set is

$$\mathcal{U}_{ad} = \left\{ \mathbf{w} \in L^\infty\left(0, T_f; \mathbb{R}^5\right) : \begin{matrix} 0 \leq u(t) \leq u_{\max},\ 0 \leq v(t) \leq v_{\max},\ 0 \leq w(t) \leq w_{\max}, \\ 0 \leq z(t) \leq z_{\max},\ 0 \leq q(t) \leq q_{\max} \text{ a.e. } t \in \left[0, T_f\right] \end{matrix} \right\} \tag{3.2}$$

and the cost functional to be minimized over $\mathcal{U}_{ad}$ is the natural five-control extension of the functional in [1]:

$$J(\mathbf{w}) = \int_0^{T_f} \Big[A_1 C(t) + \frac{A_2}{2}u^2(t) + \frac{A_3}{2}v^2(t) + \frac{A_4}{2}w^2(t) + \frac{A_5}{2}z^2(t) + \frac{A_6}{2}q^2(t)\Big]\,dt, \qquad A_1, \dots, A_6 > 0. \tag{3.3}$$

Setting $w \equiv z \equiv q \equiv 0$ and $\xi = \zeta = \sigma = 0$ recovers exactly the two-control model of [1] and (3.1)–(3.3) above; every theorem below is stated for the five-control system and specializes immediately to that two-control case.

We adopt the same two standing hypotheses that are implicit in [1], stating them explicitly because Lemma 5.1 below shows precisely what they are used for.

Assumption 3.1: $d_1 > m_*$, where $m_* := \left(\sqrt{\rho} - \sqrt{\alpha c_1}\right)^2$ if $\rho > \alpha c_1$ and $m_* := 0$ otherwise; here $m_* = \sup_{C \geq 0}\left(\frac{\rho C}{\alpha + C} - c_1 C\right)$.

Assumption 3.2: $\gamma_2 \kappa < r_1 b_1 \delta$.

Assumption 3.2 has a direct biological reading: $\gamma_2\kappa$ measures the strength of the positive feedback loop by which cancer raises panic (rate κ) and panic in turn accelerates cancer growth (rate γ_2), while $r_1 b_1 \delta$ measures the product of the cancer's own logistic self-limitation and the panic variable's natural relaxation rate. Assumption 3.2 requires the destabilizing loop to be dominated by these two restoring effects. As discussed in the introduction, it is exactly the condition needed to close, non-circularly, the boundedness argument of Theorem 5.2 in [1], whose proof assumes a bound on $P(t)$ in order to derive a bound on $C(t)$ and only afterwards derives a bound on $P(t)$ from that value of $C(t)$, without verifying that the two are consistent; see Section 5 for the corrected argument.

Remark 3.3: Assumptions 3.1–3.2 are sufficient conditions for the particular (elementary, fully transparent) proof technique used in this paper. They are not claimed to be necessary: retaining the dissipative cross-terms $-c_2 IC - c_3 CN$, which are discarded for simplicity in the proof of Lemma 5.1, would in general allow a weaker threshold to be derived, at the cost of a considerably less transparent argument. We return to this point in Remark 5.2.

4. Positivity of Solutions

Theorem 4.1: (Positivity). *For every $\boldsymbol{y}_0 \in \Omega_+$ with $I_0 > 0$ and every $\boldsymbol{w} = (u, v, w, z, q) \in \mathcal{U}_{ad}$, every solution of (3.1) on its maximal interval of existence $[0, T^{\sharp})$ (on which $\alpha + C + \mu F > 0$) satisfies $\boldsymbol{y}(t) \in \Omega_+$ for all $t \in [0, T^{\sharp})$; that is, Ω_+ is a positively invariant region for (3.1).*

Proof: Fix $T < T^{\sharp}$. Since $\mathbf{y}$ is continuous on $[0, T]$, every coefficient below is a bounded continuous function of t. Each equation of (3.1) has the form ${}_0^C D_t^{\beta} y_i = a_i(t) + b_i(t) y_i$ with $a_i \geq 0$, so Lemma 2.5 applies once $a_i \geq 0$ is checked:

Cancer and fat cells. Every term of f_2 and of f_4 carries a factor C, respectively F: $f_2 = b_C\, C$ with $b_C = r_1(1 - b_1 C) - c_2 I - c_3 N + c_5 F + \gamma_2 P - \eta u$ and $f_4 = b_F\, F$ with $b_F = r_3(1 - b_3 F) - c_6 C - \zeta z$. Thus $a_C = a_F = 0$, and Lemma 2.5 gives $C \geq 0$, $F \geq 0$ (so that $D = \alpha + C + \mu F \geq \alpha > 0$).

Immune cells. $f_1 = a_I + b_I I$ with $a_I = s + \phi v(t) \geq s > 0$ and $b_I = \rho C/D - c_1 C - d_1 - \gamma_1 P$; Lemma 2.5 with $I_0 > 0$ gives $I(t) > 0$.

Natural cells. $f_3 = a_N + b_N N$ with $a_N = \xi w(t) \geq 0$ and $b_N = r_2(1 - b_2 N) - c_4 C - \gamma_3 P$; hence $N \geq 0$.

Panic. $f_5 = a_P + b_P P$ with $a_P = \kappa C + u_p(t) \geq 0$ (using $C \geq 0$) and $b_P = -\delta - \sigma q(t)$; hence $P \geq 0$.

Since $T < T^\sharp$ was arbitrary, all five coordinates remain nonnegative throughout $[0, T^\sharp)$, i.e. $\mathbf{y}(t) \in \Omega_+$ there.

5. A Control-Uniform A Priori Bound

This section proves the corrected version of Theorem 5.2 in [1] announced in the introduction, extended to the five-control system (3.1). Throughout, $\mathbf{y}_0 \in \Omega_+$ is fixed with $I_0 > 0$, and $\mathbf{w} = (u, v, w, z, q) \in \mathcal{U}_{ad}$ is arbitrary; all constants constructed below depend only on $\mathbf{y}_0$, the parameters of (3.1), M_u, and the five control bounds $u_{\max}, v_{\max}, w_{\max}, z_{\max}, q_{\max}$.

Lemma 5.1: (Control-uniform a priori bound). *Suppose Assumption 3.2 holds. Then there exist constants $M_F, M_N, M_C, M_P > 0$, none of which depends on the particular choice of $\mathbf{w} \in \mathcal{U}_{ad}$, such that every solution of (3.1) with $\mathbf{y}_0 \in \Omega_+$, $I_0 > 0$, satisfies*

$$0 \leq F(t) \leq M_F, \quad 0 \leq N(t) \leq M_N, \quad 0 \leq C(t) \leq M_C, \quad 0 \leq P(t) \leq M_P, \quad t \in [0, T^\sharp),$$

where $[0, T^\sharp)$ is the maximal interval of existence. If, in addition, Assumption 3.1 holds, there is also a constant $M_I > 0$, independent of $\mathbf{w}$, with $I(t) \leq M_I$ on $[0, T^\sharp)$. Consequently $T^\sharp = +\infty$: the solution is global, and the box $\mathcal{B} := [0, M_I] \times [0, M_C] \times [0, M_N] \times [0, M_F] \times [0, M_P]$ is positively invariant.

Proof: Positivity of all five coordinates on $[0, T^\sharp)$ is Theorem 4.1. We prove the four bounds in turn, each time via Corollary 2.2, which requires only checking a sign condition of the Caputo derivative at the (candidate) boundary value – an elementary, fully verifiable computation at every step.

Step 1 (F). Set $M_F := \max\{F_0, 1/b_3\}$. Since $C, F, z \geq 0$, the new control term satisfies $-\zeta z F \leq 0$, so

$$ {}_0^C D_t^\beta F = r_3 F(1 - b_3 F) - c_6 C F - \zeta z F \leq r_3 F(1 - b_3 F). $$

Whenever $F(t) \geq M_F \geq 1/b_3$, the right-hand side is $r_3 F(1 - b_3 F) \leq 0$; hence ${}_0^C D_t^\beta F(t) \leq 0$ whenever $F(t) \geq M_F$. Corollary 2.2 gives $F(t) \leq M_F$ for all $t \in [0, T^\sharp)$. This bound is independent of every control, since the new term $-\zeta z F$ was simply discarded as nonpositive.

Step 2: *(N, using the control bound $w_{\max}$).* Unlike z and q, the new control w enters the N-equation additively and hence works against boundedness rather than for it, so this step genuinely needs the a priori bound $w \le w_{\max}$ (whereas Step 1 needed no such input). Since $C, N, P \ge 0$, $-c_4 CN - \gamma_3 PN \le 0$, and using $w(t) \le w_{\max}$,

$$ {}_0^C D_t^\beta N \le r_2 N(1 - b_2 N) + \xi w_{\max}. $$

The right-hand side, as a function of $N \ge 0$, is a downward parabola shifted up by the constant $\xi w_{\max} \ge 0$; it has a unique positive root

$$ N^\dagger := \frac{r_2 + \sqrt{r_2^2 + 4 r_2 b_2 \xi w_{\max}}}{2 r_2 b_2} \ge \frac{1}{b_2}, $$

(the vertex of the parabola $r_2 N(1 - b_2 N)$ lies at $1/(2b_2)$), beyond which it is ≤ 0 and strictly decreasing. Set $M_N := \max\{N_0, N^\dagger\}$; then $r_2 N(1 - b_2 N) + \xi w_{\max} \le 0$ whenever $N \ge M_N$, so ${}_0^C D_t^\beta N(t) \le 0$ whenever $N(t) \ge M_N$, and Corollary 2.2 gives $N(t) \le M_N$ for all $t \in [0, T^\sharp)$. Since M_N depends on $\mathbf{w}$ only through the fixed bound $w_{\max}$, this remains a control-uniform bound in the sense required by the lemma, exactly as M_I in Step 4 below depends on v only through $v_{\max}$.

Step 3: (the coupled C–P loop). For $x > 0$ define

$$ hl\Psi(x) := \max\left\{P_0, \frac{\kappa x + M_u}{\delta}\right\}, \qquad g(x) := r_1 b_1 x - r_1 - c_5 M_F - \gamma_2 \Psi(x)./hl \tag{5.1} $$

Since Ψ is non-decreasing with slope at most κ/δ, the function g has slope at least $r_1 b_1 - \gamma_2 \kappa/\delta$, which is positive by Assumption 3.2:

$$ \frac{\gamma_2 \kappa}{r_1 b_1 \delta} < 1, \tag{5.2} $$

so g is strictly increasing. Put

$$ \bar{M} := \frac{r_1 + c_5 M_F + \gamma_2 \max\{P_0, M_u/\delta\}}{r_1 b_1 - \gamma_2 \kappa/\delta}, \tag{5.3} $$

which is finite and positive by (5.2), and define $M_C := \max\{C_0, \bar{M}\}$, $M_P := \Psi(M_C)$. Then $g(M_C) \ge 0$. Indeed $\Psi(x) \le \max\{P_0, M_u/\delta\} + \kappa x/\delta$, hence $g(\bar{M}) \ge \bar{M}(r_1 b_1 - \gamma_2 \kappa/\delta) - r_1 - c_5 M_F - \gamma_2 \max\{P_0, M_u/\delta\} = 0$ by (5.3), and g is increasing while $M_C \ge \bar{M}$.

We claim $C(t) \le M_C$ for $t \in [0, T^\sharp)$. Let $T^\flat := \sup\{T \in [0, T^\sharp) : C(t) \le M_C \ \forall t \in [0, T]\}$; since $C_0 \le M_C$ and C is continuous, $T^\flat$ is well defined and $T^\flat > 0$. On $[0, T^\flat)$ we have $C(\tau) \le M_C$ by definition, so from the P-equation,

$$ {}_0^C D_t^\beta P = \kappa C + u_p - \delta P \le \kappa M_C + M_u - \delta P, $$

and (2.7) (applied with $w = P$, $\delta = \delta$, $H = \kappa M_C + M_u$) gives

$$ P(t) \le \max\left\{P_0, \frac{\kappa M_C + M_u}{\delta}\right\} = \Psi(M_C) = M_P, \quad t \in [0, T^\flat). $$

Substituting this bound on P into the C-equation and dropping the nonpositive terms $-c_2IC - c_3CN - \eta uC$ (using $I, N, u \geq 0$),

$$ {}_0^C D_t^\beta C \leq r_1 C(1 - b_1 C) + c_5 M_F C + \gamma_2 M_P C, \qquad t \in [0, T^\flat). \tag{5.4}$$

Whenever $C(t) \geq M_C$ on $[0, T^\flat)$, the bracket in the right-hand side of (5.4) is non-increasing in C, and $r_1 - r_1 b_1 M_C + c_5 M_F + \gamma_2 M_P = -g(M_C)$, hence

$$\begin{aligned} hlC[r_1(1 - b_1 C) + c_5 M_F + \gamma_2 M_P] &\leq C[r_1(1 - b_1 M_C) + c_5 M_F + \gamma_2 M_P] \\ &= -C\, g(M_C) \leq 0./hl \end{aligned}$$

So ${}_0^C D_t^\beta C(t) \leq 0$ whenever $C(t) \geq M_C$. Corollary 2.2 applied on $[0, T^\flat)$ gives $C(t) \leq M_C$ for all $t \in [0, T^\flat)$, and by continuity $C\left(T^\flat\right) \leq M_C$ as well.

If $T^\flat < T^\sharp$, continuity of C and $C\left(T^\flat\right) \leq M_C$ would force $C(t) \leq M_C$ on a slightly larger interval, contradicting the definition of $T^\flat$ as a supremum unless $T^\flat = T^\sharp$. Hence $C(t) \leq M_C$ on all of $[0, T^\sharp)$, and then $P(t) \leq M_P$ on $[0, T^\sharp)$ as well. Neither M_C nor M_P depends on $\mathbf{w}$: the only control entering f_2 is u, through $-\eta uC \leq 0$, which was discarded; the only control entering f_5 is q, through $-\sigma qP \leq 0$, which was likewise discarded as it can only help.

Step 4: (I, using Assumption 3.1). For all $C, F \geq 0$ we have $\frac{\rho C}{\alpha + C + \mu F} - c_1 C \leq \frac{\rho C}{\alpha + C} - c_1 C \leq m_*$ (the maximum over C is attained at $C = \sqrt{\rho\alpha / c_1} - \alpha$ when $\rho > \alpha c_1$). Dropping $-\gamma_1 PI \leq 0$ and using $I \geq 0$, $v \leq v_{\max}$,

$$ {}_0^C D_t^\beta I \leq s + \phi v_{\max} - (d_1 - m_*) I =: s + \phi v_{\max} - \varepsilon_1 I, \qquad \varepsilon_1 := d_1 - m_* > 0$$

by Assumption 3.1. Estimate (2.7) (with $w = I$ playing the role of the generic scalar in (2.7) – not to be confused with the control $w(t)$ – $\delta = \varepsilon_1$, $H = s + \phi v_{\max}$) gives

$$I(t) \leq M_I := \max\left\{I_0, \frac{s + \phi v_{\max}}{\varepsilon_1}\right\}, \qquad t \in [0, T^\sharp),$$

again independent of the particular $\mathbf{w} \in \mathcal{U}_{ad}$ used, and in particular independent of w, z, q, none of which enters f_1.

Global existence. A solution of a Caputo IVP with continuous, locally Lipschitz right-hand side whose trajectory is confined to a fixed compact set on its maximal interval of existence cannot cease to exist at any finite time; since $\mathbf{y}(t) \in \mathcal{B}$ for all $t \in [0, T^\sharp)$ by Steps 1–4, we conclude $T^\sharp = +\infty$.

Remark 5.2: The proof of Step 3 discards the dissipative cross-terms $-c_2IC - c_3CN$ from the C-equation. Retaining them would replace (5.4) by ${}_0^C D_t^\beta C \leq C[r_1(1 - b_1 C) + c_5 M_F + \gamma_2 M_P - c_2 I - c_3 N]$, and since $-c_2 I - c_3 N \leq 0$ this can only make the bracket smaller, so any M_C satisfying the discarded-terms bound (5.3) continues to work; a genuinely sharper threshold would require lower bounds on I and N along the trajectory, which are not needed for the present purposes and are not pursued here.

6. Well-Posedness of the State System

Fix $\mathbf{w} \in \mathcal{U}_{ad}$. Integrating (3.1) converts the IVP into the Volterra equation

$$\mathbf{y}(t) = \mathbf{y}_0 + \frac{1}{\Gamma(\beta)} \int_0^t (t-\tau)^{\beta-1} f\big(\mathbf{y}(\tau), \mathbf{w}(\tau)\big)\, d\tau, \qquad t \in [0, T_f]. \tag{6.1}$$

Lemma 6.1: *Let* $\mathcal{B} = [0, M_I] \times [0, M_C] \times [0, M_N] \times [0, M_F] \times [0, M_P]$ *be the box of Lemma 5.1 and* $K := [0, u_{max}] \times [0, v_{max}] \times [0, w_{max}] \times [0, z_{max}] \times [0, q_{max}]$. *There is a constant* $L_0 = L_0(\mathcal{B}, K)$, *independent of* $\boldsymbol{w} \in \mathcal{U}_{ad}$, *such that* $\| f(\boldsymbol{y}_1, \boldsymbol{w}) - f(\boldsymbol{y}_2, \boldsymbol{w}) \| \leq L_0 \| \boldsymbol{y}_1 - \boldsymbol{y}_2 \|$ *for all* $\boldsymbol{y}_1, \boldsymbol{y}_2 \in \mathcal{B}$ *and* $\boldsymbol{w} \in K$; *explicitly, one may take* $L_0 = \sup_{\mathcal{B} \times K} \| \nabla_{\boldsymbol{y}} f \|_{op}$.

Proof: Every term of f is a polynomial in $(I, C, N, F, P, u, v, w, z, q)$ except the saturation term $\rho IC/(\alpha + C + \mu F)$, whose partial derivatives are displayed explicitly in Section 8 (equations (8.7)–(8.10) as the coefficients of λ_I) and are manifestly bounded on $\mathcal{B}$ because the denominator satisfies $\alpha + C + \mu F \geq \alpha > 0$ there, and the numerator factors I, C are bounded by M_I, M_C. The three new control terms ξw, $-\zeta z F$, $-\sigma q P$ are themselves polynomial in (F, P, w, z, q) and contribute the additional bounded Jacobian entries $\partial f_4/\partial F \ni -\zeta z$ and $\partial f_5/\partial P \ni -\sigma q$, both bounded on $\mathcal{B} \times K$ since $z \leq z_{\max}$, $q \leq q_{\max}$. Hence every entry of the Jacobian $\nabla_{\mathbf{y}} f$ is a continuous function on the compact set $\mathcal{B} \times K$, so it attains a finite supremum L_0 there, and the mean value inequality for vector-valued functions (applied along the segment joining $\mathbf{y}_1, \mathbf{y}_2 \in \mathcal{B}$, which lies in the convex set $\mathcal{B}$) gives the stated Lipschitz bound. □

Theorem 6.2: (Existence and uniqueness of the state trajectory). *For every* $\boldsymbol{w} \in \mathcal{U}_{ad}$ *and every* $\boldsymbol{y}_0 \in \Omega_+$ *with* $I_0 > 0$, *under Assumptions 3.1–3.2, the IVP (3.1) has a unique solution* $\boldsymbol{y}[\boldsymbol{w}] \in C\big([0, T_f]; \mathbb{R}^5\big)$, *and* $\boldsymbol{y}[\boldsymbol{w}](t) \in \mathcal{B}$ *for all* $t \in [0, T_f]$.

Proof:

Step 1 (a contraction): Let Π be the coordinatewise truncation of $\mathbb{R}^5$ onto the box $\mathcal{B}$ (a 1-Lipschitz map) and put $\tilde{f}(\mathbf{y}, \mathbf{w}) := f(\Pi \mathbf{y}, \mathbf{w})$; by Lemma 6.1, $\tilde{f}$ is globally Lipschitz in $\mathbf{y}$ with constant L_0, uniformly in $\mathbf{w} \in K$. On $C\big([0, T_f]; \mathbb{R}^5\big)$ use the Bielecki norm $\| \mathbf{z} \|_\omega := \sup_{t \in [0, T_f]} e^{-\omega t} \| \mathbf{z}(t) \|$ with $\omega > 0$ to be chosen (ω is used to avoid a clash with the anti-panic coefficient σ); this norm is equivalent to the sup norm, so the space is complete. Define

$$(\mathcal{T}\mathbf{z})(t) = \mathbf{y}_0 + \frac{1}{\Gamma(\beta)} \int_0^t (t-\tau)^{\beta-1} \tilde{f}\big(\mathbf{z}(\tau), \mathbf{w}(\tau)\big)\, d\tau.$$

For $\mathbf{z}_1, \mathbf{z}_2$ in this space, Lemma 6.1 gives

$$\| (\mathcal{T}\mathbf{z}_1)(t) - (\mathcal{T}\mathbf{z}_2)(t) \| \leq \frac{L_0}{\Gamma(\beta)} \int_0^t (t-\tau)^{\beta-1} \| \mathbf{z}_1(\tau) - \mathbf{z}_2(\tau) \| \, d\tau.$$

Multiplying by $e^{-\omega t}$ and using $\| \mathbf{z}_1(\tau) - \mathbf{z}_2(\tau) \| \leq e^{\omega\tau} \| \mathbf{z}_1 - \mathbf{z}_2 \|_\omega$,

$$e^{-\omega t} \| (\mathcal{T}\mathbf{z}_1)(t) - (\mathcal{T}\mathbf{z}_2)(t) \| \leq \frac{L_0}{\Gamma(\beta)} \| \mathbf{z}_1 - \mathbf{z}_2 \|_\omega \int_0^t s^{\beta-1} e^{-\omega s} \, ds \leq L_0 \, \omega^{-\beta} \| \mathbf{z}_1 - \mathbf{z}_2 \|_\omega.$$

Hence $\| \mathcal{T}\mathbf{z}_1 - \mathcal{T}\mathbf{z}_2 \|_\omega \leq \left(L_0/\omega^\beta\right) \| \mathbf{z}_1 - \mathbf{z}_2 \|_\omega$, and choosing $\omega > L_0^{1/\beta}$ makes $\mathcal{T}$ a contraction. By the Banach fixed-point theorem there is exactly one $\tilde{\mathbf{y}} = \mathcal{T}\tilde{\mathbf{y}}$.

Step 2 (the fixed point is the solution): By the standard local existence theory for Caputo systems with locally Lipschitz right-hand side [17], (3.1) has a unique solution $\mathbf{y}$ on a maximal interval $[0, T^\sharp)$; by Lemma 5.1, $\mathbf{y}(t) \in \mathcal{B}$ and $T^\sharp = \infty$. As $\mathbf{y} \in \mathcal{B}$ we have $\tilde{f}(\mathbf{y}, \mathbf{w}) = f(\mathbf{y}, \mathbf{w})$, so $\mathbf{y}\big|_{[0,T_f]} = \mathcal{T}\mathbf{y}\big|_{[0,T_f]}$ and therefore $\mathbf{y} = \tilde{\mathbf{y}}$. Conversely, every solution of (3.1) lies in $\mathcal{B}$ by Lemma 5.1 and hence is a fixed point of $\mathcal{T}$; this gives uniqueness. In particular $\mathbf{y}[\mathbf{w}] \in C\left([0, T_f]; \mathcal{B}\right)$.

Lemma 6.3: (Continuity of the control-to-state map). *If* $\boldsymbol{w}_n \rightharpoonup \boldsymbol{w}$ *weak-* in* $L^\infty\left(0, T_f; \mathbb{R}^5\right)$ *with* $\boldsymbol{w}_n, \boldsymbol{w} \in \mathcal{U}_{ad}$, *then* $\boldsymbol{y}[\boldsymbol{w}_n] \to \boldsymbol{y}[\boldsymbol{w}]$ *in* $C\left([0, T_f]; \mathbb{R}^5\right)$.

Proof: By Theorem 6.2, $\{\mathbf{y}[\mathbf{w}_n]\}_n \subset C\left([0, T_f]; \mathcal{B}\right)$. From (6.1) and the boundedness of f on the compact set $\mathcal{B} \times K$ (say $\| f \| \leq K_0$ there), for $0 \leq t_1 \leq t_2 \leq T_f$,

$$\| \mathbf{y}[\mathbf{w}_n](t_2) - \mathbf{y}[\mathbf{w}_n](t_1) \| \leq \frac{2K_0}{\Gamma(\beta+1)} (t_2 - t_1)^\beta,$$

a Hölder-type equicontinuity estimate uniform in n (a standard estimate for the Riemann–Liouville fractional integral of a bounded function; see [16]). By the Arzelà–Ascoli theorem, along a subsequence (not relabeled) $\mathbf{y}[\mathbf{w}_n] \to \mathbf{y}^\dagger$ uniformly on $[0, T_f]$ for some $\mathbf{y}^\dagger \in C\left([0, T_f]; \mathcal{B}\right)$.

Because f is affine in $\mathbf{w} = (u, v, w, z, q)$ for each fixed state – the only occurrences of the controls in (3.1) are the additive term ϕv in f_1, the term $-\eta u C$ in f_2 (linear in u for fixed C), the additive term ξw in f_3, the term $-\zeta z F$ in f_4 (linear in z for fixed F), and the term $-\sigma q P$ in f_5 (linear in q for fixed P) – we may write, for each fixed τ and writing $\mathbf{w}_n = (u_n, v_n, w_n, z_n, q_n)$, $C_n := \mathbf{y}[\mathbf{w}_n]_2$, $F_n := \mathbf{y}[\mathbf{w}_n]_4$, $P_n := \mathbf{y}[\mathbf{w}_n]_5$,

$$\begin{aligned} f\left(\mathbf{y}[\mathbf{w}_n](\tau), \mathbf{w}_n(\tau)\right) &= f(\mathbf{y}[\mathbf{w}_n](\tau), 0) + \phi v_n(\tau)\mathbf{e}_I - \eta u_n(\tau) C_n(\tau)\mathbf{e}_C + \xi w_n(\tau)\mathbf{e}_N \\ &\quad - \zeta z_n(\tau) F_n(\tau)\mathbf{e}_F - \sigma q_n(\tau) P_n(\tau)\mathbf{e}_P, \end{aligned}$$

where $\mathbf{e}_I, \ldots, \mathbf{e}_P$ are the standard basis vectors. The first term converges uniformly to $f(\mathbf{y}^\dagger(\tau), 0)$ by uniform convergence of $\mathbf{y}[\mathbf{w}_n] \to \mathbf{y}^\dagger$ and continuity

of f. Each remaining term is a product of a state coordinate (or the constant 1, for the w-term) converging uniformly – $C_n \to C^\dagger$, $F_n \to F^\dagger$, $P_n \to P^\dagger$, all coordinates of $\mathbf{y}^\dagger$ – with a control converging only weak-* in L^∞; the same weak-strong convergence lemma used in the two-control case (adding and subtracting the term with the state frozen at its limit, and using the uniform state bound together with weak-* convergence of the control against the fixed L^1 Volterra kernel) applies verbatim to each of the five terms, so we may pass to the limit in (6.1) term by term, for each fixed t, to conclude that $\mathbf{y}^\dagger$ satisfies (6.1) with control $\mathbf{w}$.

By uniqueness in Theorem 6.2, $\mathbf{y}^\dagger = \mathbf{y}[\mathbf{w}]$. Since every subsequence has a further subsequence converging uniformly to the same limit $\mathbf{y}[\mathbf{w}]$, the whole sequence $\mathbf{y}[\mathbf{w}_n]$ converges to $\mathbf{y}[\mathbf{w}]$ in $C\big([0,T_f];\mathbb{R}^5\big)$.

7. Existence of an Optimal Control Pair

Theorem 7.1: *Under Assumptions 3.1–3.2, the fractional optimal control problem (3.1)–(3.3) admits at least one optimal pair* $\boldsymbol{w}^* \in \mathcal{U}_{ad}$*, i.e.* $J(\boldsymbol{w}^*) = \min_{\boldsymbol{w}\in\mathcal{U}_{ad}} J(\boldsymbol{w})$.

Proof:

Step 1: $m := \inf_{\mathcal{U}_{ad}} J$ *is finite and nonnegative.* By Theorem 4.1, $C(t) \geq 0$ along any admissible trajectory, and every control squared is ≥ 0, so the integrand of (3.3) is nonnegative and $J \geq 0$ on $\mathcal{U}_{ad}$; taking $\mathbf{w} \equiv 0 \in \mathcal{U}_{ad}$ shows $J(0) < \infty$ (by Lemma 5.1, $C(t) \leq M_C$ along this trajectory too), so $m \in [0,\infty)$.

Step 2: *extraction of a weakly convergent minimizing sequence.* Let $\mathbf{w}_n \in \mathcal{U}_{ad}$ be a minimizing sequence, $J(\mathbf{w}_n) \to m$. Since $\mathcal{U}_{ad}$ is a bounded subset of $L^2\big(0,T_f;\mathbb{R}^5\big)$, the Banach–Alaoglu / reflexivity argument gives a subsequence (not relabeled) with $\mathbf{w}_n \rightharpoonup \mathbf{w}^*$ weakly in $L^2\big(0,T_f;\mathbb{R}^5\big)$, hence also weak-* in L^∞ on this bounded sequence. The set $\mathcal{U}_{ad}$ is convex and closed in L^2; by Mazur's theorem, a convex, strongly closed subset of a Banach space is also weakly closed, so $\mathbf{w}^* \in \mathcal{U}_{ad}$.

Step 3: *passage to the limit in the cost.* By Lemma 6.3, $C_n := \mathbf{y}[\mathbf{w}_n]_2 \to C^* := \mathbf{y}[\mathbf{w}^*]_2$ uniformly on $[0,T_f]$, so

$$\int_0^{T_f} A_1\, C_n(t)\, dt \to \int_0^{T_f} A_1\, C^*(t)\, dt.$$

Each functional $\theta \mapsto \int_0^{T_f} \frac{A}{2}\theta(t)^2\, dt$ on $L^2\big(0,T_f\big)$ is convex and strongly continuous, hence weakly lower semicontinuous, for each of the five control components $\theta \in \{u,v,w,z,q\}$:

$$\liminf_n \int_0^{T_f} \frac{A_2}{2} u_n^2\, dt \geq \int_0^{T_f} \frac{A_2}{2} (u^*)^2\, dt,\ \ldots,\ \liminf_n \int_0^{T_f} \frac{A_6}{2} q_n^2\, dt \geq \int_0^{T_f} \frac{A_6}{2} (q^*)^2\, dt.$$

Step 4: *conclusion.* Adding the convergent term from Step 3 and the five semicontinuous inequalities,

$$J(\mathbf{w}^*) \leq \liminf_n J(\mathbf{w}_n) = m.$$

Since also $J(\mathbf{w}^*) \geq m$ because $\mathbf{w}^* \in \mathcal{U}_{ad}$, we conclude $J(\mathbf{w}^*) = m$, i.e. $\mathbf{w}^*$ is optimal.

Remark 7.2: The affine dependence of f on $\mathbf{w} = (u, v, w, z, q)$, already used in Lemma 6.3, is what makes the direct method go through with only weak convergence of the controls: it guarantees that the augmented velocity set

$$\mathcal{V}(\mathbf{y}) = \big\{\big(f_1(\mathbf{y}, v), f_2(\mathbf{y}, u), f_3(\mathbf{y}, w), f_4(\mathbf{y}, z), f_5(\mathbf{y}, q), \ell(\mathbf{y}, \mathbf{w})\big) : \mathbf{w} \in [0, u_{\max}] \times [0, v_{\max}] \times [0, w_{\max}] \times [0, z_{\max}] \times [0, q_{\max}]\big\}$$

(where $\ell(\mathbf{y}, \mathbf{w}) = A_1 y_2 + \frac{A_2}{2} u^2 + \frac{A_3}{2} v^2 + \frac{A_4}{2} w^2 + \frac{A_5}{2} z^2 + \frac{A_6}{2} q^2$ is the running cost) is convex for each fixed $\mathbf{y}$, since the state components are linear images of the convex product box $[0, u_{\max}] \times [0, v_{\max}] \times [0, w_{\max}] \times [0, z_{\max}] \times [0, q_{\max}]$ and ℓ is jointly convex in $\mathbf{w}$ (a sum of five independent convex quadratics, one per control). This is precisely the structural hypothesis under which existence theorems for fractional optimal control problems of Filippov–Cesari type are available [7, 8, 11]. Had any control entered f nonlinearly, $\mathcal{V}(\mathbf{y})$ would generally fail to be convex, and one would need to pass to relaxed (Young-measure-valued) controls to recover existence, with the accompanying loss of the clean pointwise characterization of Theorem 8.3.

8. Necessary Optimality Conditions: the Corrected Adjoint System

8.1 *A fractional integration-by-parts identity, proved in full.*

Lemma 8.1: (Fractional integration by parts). Let $\varphi, \psi \in \mathrm{hlAC/hl}[0, \mathrm{T_f}]$ and $0 < \beta < 1$. Then

$$\int_0^{T_f} \varphi(t)\, {}_0^C D_t^\beta \psi(t)\, dt = \int_0^{T_f} \psi(t)\, {}_t D_{T_f}^\beta \varphi(t)\, dt + \Big[\psi(t)\, {}_t I_{T_f}^{1-\beta} \varphi(t)\Big]_{t=0}^{t=T_f}, \tag{8.1}$$

where ${}_t D_{T_f}^\beta$ *is the right Riemann–Liouville derivative (2.3) and* ${}_t I_{T_f}^{1-\beta} \varphi(t) = \frac{1}{\Gamma(1-\beta)} \int_t^{T_f} (\tau - t)^{-\beta}\, \varphi(\tau)\, d\tau$ *is the right Riemann–Liouville fractional integral of order* $1 - \beta$.

Proof: By definition (2.1), ${}_0^C D_t^\beta \psi(t) = \frac{1}{\Gamma(1-\beta)} \int_0^t (t - \tau)^{-\beta}\, \psi'(\tau)\, d\tau$, so

$$\int_0^{T_f} \varphi\,(t)\,{}_0^C D_t^{\beta}\psi(t)\,dt = \frac{1}{\Gamma(1-\beta)}\int_0^{T_f} \varphi\,(t) \int_0^t (t-\tau)^{-\beta}\,\psi'(\tau)\,d\tau\,dt. \tag{8.2}$$

The double integral in (8.2) is over the triangle $\{(t,\tau): 0 \le \tau \le t \le T_f\}$, and the integrand $(t,\tau) \mapsto \varphi(t)(t-\tau)^{-\beta}\psi'(\tau)$ is absolutely integrable there, since φ is bounded and $\psi' \in L^1$ and $(t-\tau)^{-\beta}$ is integrable near the diagonal $t=\tau$ for $\beta < 1$. Fubini's theorem therefore permits exchanging the order of integration:

$$\begin{aligned}\int_0^{T_f} \varphi\,(t)\,{}_0^C D_t^{\beta}\psi(t)\,dt &= \int_0^{T_f} \psi'\,(\tau)\,\frac{1}{\Gamma(1-\beta)}\int_\tau^{T_f} (t-\tau)^{-\beta}\,\varphi(t)\,dt\,d\tau \\ &= \int_0^{T_f} \psi'\,(\tau)\Phi(\tau)\,d\tau,\end{aligned} \tag{8.3}$$

where $\Phi(\tau) := {}_\tau I_{T_f}^{1-\beta}\varphi(\tau)$. By definition (2.3), ${}_\tau D_{T_f}^{\beta}\varphi(\tau) = -\frac{d}{d\tau}\left({}_\tau I_{T_f}^{1-\beta}\varphi(\tau)\right) = -\Phi'(\tau)$, and Φ is absolutely continuous because $\varphi \in AC$ (with $-\Phi' = {}_\tau D_{T_f}^{\beta}\varphi \in L^1$). Substituting $\Phi'(\tau) = -{}_\tau D_{T_f}^{\beta}\varphi(\tau)$ and integrating (8.3) by parts in the ordinary sense,

$$\begin{aligned}\int_0^{T_f} \psi'\,(\tau)\Phi(\tau)\,d\tau &= \psi(\tau)\Phi(\tau)\big|_0^{T_f} - \int_0^{T_f} \psi\,(\tau)\Phi'(\tau)\,d\tau \\ &= \psi(\tau)\Phi(\tau)\big|_0^{T_f} + \int_0^{T_f} \psi\,(\tau)\,{}_\tau D_{T_f}^{\beta}\varphi(\tau)\,d\tau,\end{aligned}$$

which, combined with (8.2)–(8.3) and the definition of Φ, gives exactly (8.1).

Since $\left(I_{T_f}^{1-\beta}\varphi\right)(T_f) = 0$, the boundary term in (8.1) at $t = T_f$ vanishes automatically, so that $\left[\psi\,{}_t I_{T_f}^{1-\beta}\varphi\right]_0^{T_f} = -\psi(0)\,\left({}_t I_{T_f}^{1-\beta}\varphi\right)(0)$; it vanishes entirely whenever $\psi(0) = 0$.

Remark 8.2: Lemma 8.1 makes precise, by an elementary and fully self-contained computation (Fubini's theorem plus one ordinary integration by parts), the fractional integration-by-parts identity that underlies the fractional Pontryagin maximum principle of Agrawal [6] and its subsequent rigorous developments [7, 8]. The identity shows unambiguously that the operator dual to the left Caputo derivative ${}_0^C D_t^{\beta}$, under the pairing $\int_0^{T_f} \varphi \cdot (\cdot)\,dt$, is the right Riemann–Liouville derivative ${}_t D_{T_f}^{\beta}$ – not a second copy of ${}_0^C D_t^{\beta}$ itself. This is the precise sense in which the costate system of [1], written with ${}_0^C D_t^{\beta}$ throughout, uses the wrong operator.

8.2. *The Hamiltonian and the augmented functional.*

The Hamiltonian associated with the five-control system (3.1)–(3.3) is the natural extension of the one in [1]:

$$H(t,\mathbf{y},\mathbf{w},\boldsymbol{\lambda}) = A_1 C + \frac{A_2}{2}u^2 + \frac{A_3}{2}v^2 + \frac{A_4}{2}w^2 + \frac{A_5}{2}z^2 + \frac{A_6}{2}q^2 + \lambda_I f_1 + \lambda_C f_2 + \lambda_N f_3 + \lambda_F f_4 + \lambda_P f_5. \tag{8.4}$$

Suppose $\mathbf{w}^* \in \mathcal{U}_{ad}$ is optimal with associated state $\mathbf{y}^* = \mathbf{y}[\mathbf{w}^*]$, and let $\boldsymbol{\lambda} \in AC\big([0,T_f];\mathbb{R}^5\big)$ (with right Riemann–Liouville derivative in L^1) be a multiplier function adjoining the state constraint to the cost via

$$\tilde{J}(\mathbf{y},\mathbf{w},\boldsymbol{\lambda}) = \int_0^{T_f} \big[H(t,\mathbf{y},\mathbf{w},\boldsymbol{\lambda}) - \boldsymbol{\lambda}(t)^{\top}\, {}_0^C D_t^{\beta}\mathbf{y}(t)\big]\, dt,$$

so that $\tilde{J}(\mathbf{y}^*,\mathbf{w}^*,\boldsymbol{\lambda}) = J(\mathbf{w}^*)$ for every choice of $\boldsymbol{\lambda}$. Consider a one-parameter family of admissible variations $\mathbf{y}^* + \varepsilon\,\delta\mathbf{y}$, $\mathbf{w}^* + \varepsilon\,\delta\mathbf{w}$ (with $\delta\mathbf{y}(0) = 0$, since $\mathbf{y}(0) = \mathbf{y}_0$ is fixed, and $\delta\mathbf{w} = (\delta u, \delta v, \delta w, \delta z, \delta q)$), and differentiate $\tilde{J}$ in ε at $\varepsilon = 0$:

$$\frac{d}{d\varepsilon}\Big|_{\varepsilon=0} \tilde{J} = \int_0^{T_f} \big[\nabla_{\mathbf{y}} H \cdot \delta\mathbf{y} + \nabla_{\mathbf{w}} H \cdot \delta\mathbf{w} - \boldsymbol{\lambda}^{\top}\, {}_0^C D_t^{\beta}(\delta\mathbf{y})\big]\, dt, \qquad \nabla_{\mathbf{w}} H \cdot \delta\mathbf{w} = \frac{\partial H}{\partial u}\delta u + \frac{\partial H}{\partial v}\delta v + \frac{\partial H}{\partial w}\delta w + \frac{\partial H}{\partial z}\delta z + \frac{\partial H}{\partial q}\delta q.$$

Applying Lemma 8.1 componentwise, with $\varphi = \lambda_i$ and $\psi = \delta y_i$ (so $\psi(0) = 0$), noting that the boundary term at T_f vanishes because $\big({}_t I_{T_f}^{1-\beta}\lambda_i\big)(T_f) = 0$ and the one at 0 because $\delta y_i(0) = 0$,

$$\int_0^{T_f} \lambda_i\,(t)\, {}_0^C D_t^{\beta}(\delta y_i)(t)\, dt = \int_0^{T_f} \delta\, y_i(t)\, {}_t D_{T_f}^{\beta}\lambda_i(t)\, dt.$$

Hence

$$\frac{d}{d\varepsilon}\Big|_{\varepsilon=0} \tilde{J} = \int_0^{T_f} \sum_i \left[\frac{\partial H}{\partial y_i} - {}_t D_{T_f}^{\beta}\lambda_i\right] \delta y_i\, dt + \int_0^{T_f} \nabla_{\mathbf{w}} H \cdot \delta\mathbf{w}\, dt.$$

Since $(\mathbf{y}^*,\mathbf{w}^*)$ is optimal, requiring the coefficient of each $\delta y_i(t)$ to vanish for $t \in (0,T_f)$ gives the costate system

$${}_t D_{T_f}^{\beta}\lambda_i(t) = \frac{\partial H}{\partial y_i}\big(t,\mathbf{y}^*(t),\mathbf{w}^*(t),\boldsymbol{\lambda}(t)\big), \qquad i \in \{I,C,N,F,P\}, \tag{8.5}$$

together with the transversality conditions

$$\lambda_I(T_f) = \lambda_C(T_f) = \lambda_N(T_f) = \lambda_F(T_f) = \lambda_P(T_f) = 0, \tag{8.6}$$

which are the natural conditions attached to the free endpoint $\mathbf{y}(T_f)$, since there is no terminal cost in (3.3); indeed, ${}_t D_{T_f}^{\beta}\lambda_i = G_i$ with G_i bounded and $I_{T_f}^{1-\beta}\lambda_i(T_f) = 0$ give $\lambda_i = I_{T_f}^{\beta} G_i$, so $\lambda_i(T_f) = 0$ follows. Because $\lambda_i(T_f) = 0$, relation (2.4) shows that the right Caputo and right Riemann–Liouville

derivatives of λ_i coincide, so (8.5) may equivalently be written with ${}_t^C D_{T_f}^{\beta}$ in place of ${}_t D_{T_f}^{\beta}$.

This is the point at which [1] used the same left-sided operator ${}_0^C D_t^{\beta}$ as in the state system (3.1); Lemma 8.1 and (8.5) show that the operator dual to a left-Caputo state equation is instead right-sided, a distinction that is not merely notational: ${}_t D_{T_f}^{\beta}$ and ${}_0^C D_t^{\beta}$ are genuinely different integro-differential operators, one built from the history of λ_i on $[0, t]$ and the other from its future values on $[t, T_f]$.

8.3. *The adjoint system in full, and the characterization of the optimal controls.*

Carrying out the partial derivatives of H from (8.4) and (3.1) explicitly (writing $D := \alpha + C + \mu F$ for brevity, and recalling $\partial(IC/D)/\partial C = I(\alpha + \mu F)/D^2$, $\partial(IC/D)/\partial F = -IC\mu/D^2$ by the quotient rule) gives the adjoint system in full. Relative to the two-control adjoint system, the three new controls contribute exactly two new terms: $-\zeta z^*$ inside the λ_F-bracket (from $\partial f_4/\partial F \ni -\zeta z$) and $+\sigma q^*$ inside the λ_P-bracket (from $\partial f_5/\partial P \ni -\sigma q$); the control w enters f_3 additively and, having no $\mathbf{y}$-dependence, contributes no term to any adjoint equation at all.

$$ {}_t D_{T_f}^{\beta} \lambda_I = \lambda_I \left(\frac{\rho C}{D} - c_1 C - d_1 - \gamma_1 P \right) - \lambda_C c_2 C, \tag{8.7} $$

$$ \begin{aligned} {}_t D_{T_f}^{\beta} \lambda_C \;= A_1 &+ \lambda_I \left(\frac{\rho I(\alpha + \mu F)}{D^2} - c_1 I \right) + \lambda_C (r_1 - 2 r_1 b_1 C - c_2 I \\ &- c_3 N + c_5 F + \gamma_2 P - \eta u^*) - \lambda_N c_4 N - \lambda_F c_6 F + \lambda_P \kappa, \end{aligned} \tag{8.8} $$

$$ {}_t D_{T_f}^{\beta} \lambda_N = -\lambda_C c_3 C + \lambda_N (r_2 - 2 r_2 b_2 N - c_4 C - \gamma_3 P), \tag{8.9} $$

$$ {}_t D_{T_f}^{\beta} \lambda_F = -\lambda_I \frac{\rho I C \mu}{D^2} + \lambda_C c_5 C + \lambda_F (r_3 - 2 r_3 b_3 F - c_6 C - \zeta z^*), \tag{8.10} $$

$$ {}_t D_{T_f}^{\beta} \lambda_P = -\lambda_I \gamma_1 I + \lambda_C \gamma_2 C - \lambda_N \gamma_3 N + \lambda_P (-\delta - \sigma q^*). \tag{8.11} $$

Theorem 8.3: (Characterization of the optimal controls*). Let* $(\boldsymbol{w}^*, \boldsymbol{y}^*, \boldsymbol{\lambda})$, $\boldsymbol{w}^* = (u^*, v^*, w^*, z^*, q^*)$*, solve the coupled state–adjoint system (3.1), (8.7)–(8.11) with* $\boldsymbol{y}^*(0) = \boldsymbol{y}_0$ *and (8.6). Then*

$$ u^*(t) = \min \left\{ u_{\max}, \max \left\{ 0, \frac{\eta \lambda_C(t) C^*(t)}{A_2} \right\} \right\}, \tag{8.12} $$

$$ v^*(t) = \min \left\{ v_{\max}, \max \left\{ 0, -\frac{\phi \lambda_I(t)}{A_3} \right\} \right\}, \tag{8.13} $$

$$ w^*(t) = \min \left\{ w_{\max}, \max \left\{ 0, -\frac{\xi \lambda_N(t)}{A_4} \right\} \right\}, \tag{8.14} $$

$$z^*(t) = \min\left\{z_{\max}, \max\left\{0, \frac{\zeta\lambda_F(t)F^*(t)}{A_5}\right\}\right\}, \tag{8.15}$$

$$q^*(t) = \min\left\{q_{\max}, \max\left\{0, \frac{\sigma\lambda_P(t)P^*(t)}{A_6}\right\}\right\}, \tag{8.16}$$

Proof: Fix $t \in [0, T_f]$ and view H in (8.4) as a function of $\mathbf{w} = (u, v, w, z, q)$ alone, all other arguments fixed at their optimal values. Every control appears in H through exactly one quadratic self-term and one term linear in that same control, and no product of two distinct controls appears anywhere in (3.1); hence all cross-partials $\partial^2 H/\,\partial\theta_i\,\partial\theta_j$, $\theta_i \neq \theta_j \in \{u, v, w, z, q\}$, vanish, and H decouples into five independent strictly convex one-dimensional problems:

$$\frac{\partial H}{\partial u} = A_2 u - \eta\lambda_C C, \quad \frac{\partial H}{\partial v} = A_3 v + \phi\lambda_I, \quad \frac{\partial H}{\partial w} = A_4 w + \xi\lambda_N, \quad \frac{\partial H}{\partial z}$$
$$= A_5 z - \zeta\lambda_F F, \quad \frac{\partial H}{\partial q} = A_6 q - \sigma\lambda_P P,$$

with $\partial^2 H/\,\partial\theta^2 = A_2, \ldots, A_6 > 0$ respectively. For each control $\theta \in \{u, v, w, z, q\}$ with box constraint $[0, \theta_{\max}]$: if the unconstrained minimizer $\bar{\theta}$ (solving $\partial H/\,\partial\theta = 0$) lies in $[0, \theta_{\max}]$, it is the constrained minimizer; if $\bar{\theta} < 0$, the constrained minimizer is $\theta = 0$; if $\bar{\theta} > \theta_{\max}$, it is $\theta = \theta_{\max}$. Applying this to each of the five expressions above gives exactly (8.12)–(8.16). Pontryagin's principle for this Bolza-type problem requires that $\mathbf{w}^*(t)$ minimize $H\big(t, \mathbf{y}^*(t), \cdot, \boldsymbol{\lambda}(t)\big)$ pointwise over the product box $[0, u_{\max}] \times [0, v_{\max}] \times [0, w_{\max}] \times [0, z_{\max}] \times [0, q_{\max}]$ for a.e. t; since H decouples additively across the five controls, minimizing jointly over the product box is equivalent to minimizing each coordinate separately over its own interval, which is exactly what has been shown.

Remark 8.4: The corrected costate system (8.7)–(8.11) is linear and homogeneous in $\boldsymbol{\lambda}$ up to the single additive constant term A_1 in (8.8), with time-varying coefficients that are bounded on $[0, T_f]$ because $\mathbf{y}^*(t) \in \mathcal{B}$ (Lemma 5.1, Theorem 6.2). Under the time reversal $\mu(s) := \lambda\big(T_f - s\big)$, which is legitimate because $\lambda_i\big(T_f\big) = 0$ makes the right and left operators coincide, a direct change of variables in (2.2) shows ${}_t^C D_{T_f}^{\beta}\lambda_i(t) = {}_0^C D_s^{\beta}\mu_i(s)$ with $s = T_f - t$; hence (8.7)–(8.11) becomes a left-Caputo linear (affine) IVP forward in s with $\mu(0) = 0$, driven by the known state trajectory $\mathbf{y}^*\big(T_f - s\big)$. This is precisely the formulation used in the numerical scheme of Section 11. The generalized Grönwall inequality of Lemma 2.3 shows μ – and hence $\boldsymbol{\lambda}$ – is bounded on $[0, T_f]$ by an explicit constant M_λ depending only on the data; this bound is used again in Section 9.

9. Uniqueness on a Sufficiently Short Horizon

Substituting (8.12)–(8.16) into (3.1) and (8.7)–(8.11) closes the state–adjoint system into a two-point boundary value problem for $(\mathbf{y}, \boldsymbol{\lambda})$ alone, with $\mathbf{y}(0) = \mathbf{y}_0$ and $\boldsymbol{\lambda}(T_f) = 0$. As is typical for such coupled forward–backward systems, uniqueness of a solution is not automatic and requires T_f to lie below an explicit threshold; we make this threshold precise, following the classical approach of Lenhart and Workman [10] adapted to the fractional setting via Lemma 2.3 and the elementary estimates already developed.

Lemma 9.1: *There is a constant $L > 0$, depending only on the model parameters and on the a priori bounds M_I, M_C, M_N, M_F, M_P (Lemma 5.1) and M_λ (Remark 8.4), the latter being taken for a fixed upper bound $\bar{T} \geq T_f$ of the horizon, , such that, writing $\boldsymbol{w}_k^* := \boldsymbol{w}^*(\boldsymbol{y}_k, \boldsymbol{\lambda}_k)$ for the tuple (8.12)–(8.16) evaluated at $\boldsymbol{y}_k \in \mathcal{B}$, $\boldsymbol{\lambda}_k \in [-M_\lambda, M_\lambda]^5$ $(k = 1,2)$, one has*

$$\| f(\mathbf{y}_1, \mathbf{w}_1^*) - f(\mathbf{y}_2, \mathbf{w}_2^*) \| \leq L(\| \mathbf{y}_1 - \mathbf{y}_2 \| + \| \boldsymbol{\lambda}_1 - \boldsymbol{\lambda}_2 \|), \tag{9.1}$$

$$\begin{aligned} \| \nabla_{\mathbf{y}} H(\mathbf{y}_1, \boldsymbol{\lambda}_1, \mathbf{w}_1^*) - \nabla_{\mathbf{y}} H(\mathbf{y}_2, \boldsymbol{\lambda}_2, \mathbf{w}_2^*) \| \\ \leq L(\| \mathbf{y}_1 - \mathbf{y}_2 \| + \| \boldsymbol{\lambda}_1 - \boldsymbol{\lambda}_2 \|). \end{aligned} \tag{9.2}$$

Proof: Each of the five component functions in (8.12)–(8.16) is Lipschitz in $(\mathbf{y}, \boldsymbol{\lambda})$ on $\mathcal{B} \times [-M_\lambda, M_\lambda]^5$ by the same argument: the clipping operations $\min\{c, \cdot\}$ and $\max\{0, \cdot\}$ are 1-Lipschitz, and each pre-clip expression $(\eta\lambda_C C/A_2, -\phi\lambda_I/A_3, -\xi\lambda_N/A_4, \zeta\lambda_F F/A_5, \sigma\lambda_P P/A_6)$ is bilinear in one state coordinate and one costate coordinate (or linear in the costate alone, for w^*), hence Lipschitz on the compact set in question (e.g. $|\eta\lambda_C C/A_2 - \eta\lambda_C' C'/A_2| \leq \frac{\eta}{A_2}(M_C|\lambda_C - \lambda_C'| + M_\lambda|C - C'|)$). Hence $(\mathbf{y}, \boldsymbol{\lambda}) \mapsto \mathbf{w}^*(\mathbf{y}, \boldsymbol{\lambda})$ is Lipschitz on the compact set with some constant L_1. Since f is a rational function of $(\mathbf{y}, \mathbf{w})$ that is C^1 on $\mathcal{B} \times K$ (K as in Lemma 6.1), f is Lipschitz in $(\mathbf{y}, \mathbf{w})$ jointly with some constant L_2; composing, $(\mathbf{y}, \boldsymbol{\lambda}) \mapsto f(\mathbf{y}, \mathbf{w}^*(\mathbf{y}, \boldsymbol{\lambda}))$ is Lipschitz with constant $L_2(1 + L_1)$, giving (9.1). The same reasoning applies to $\nabla_{\mathbf{y}} H$, whose entries (8.7)–(8.11) are likewise C^1 rational functions of $(\mathbf{y}, \boldsymbol{\lambda}, \mathbf{w}^*)$ on the relevant compact set, giving (9.2) with (possibly) a different constant; taking the larger of the two gives a common L.

Theorem 9.2: (Uniqueness). *Fix $\bar{T} > 0$, let $T_f \leq \bar{T}$ and let $L = L(\bar{T})$ be as in Lemma 9.1. If*

$$T_f < T^* := \left(\frac{\Gamma(\beta + 1)}{2^{1-\beta} L} \right)^{1/\beta}, \tag{9.3}$$

then the two-point boundary value problem (3.1), (8.7)–(8.11), (8.12)–(8.16) with $\boldsymbol{y}(0) = \boldsymbol{y}_0$, $\boldsymbol{\lambda}(T_f) = 0$ has at most one solution; consequently the optimal control tuple $\boldsymbol{w}^*$ of Theorem 7.1 is unique.

Proof: Let $\left(\mathbf{y}^{(1)},\boldsymbol{\lambda}^{(1)}\right)$ and $\left(\mathbf{y}^{(2)},\boldsymbol{\lambda}^{(2)}\right)$ both solve the closed system, and set $\mathbf{e} := \mathbf{y}^{(1)} - \mathbf{y}^{(2)}$, $\mathbf{d} := \boldsymbol{\lambda}^{(1)} - \boldsymbol{\lambda}^{(2)}$, $\Phi(t) := \| \mathbf{e}(t) \| + \| \mathbf{d}(t) \|$. From the Volterra form (6.1) (valid for each of the two solutions, forward from $t = 0$) and (9.1),

$$\| \mathbf{e}(t) \| \leq \frac{L}{\Gamma(\beta)} \int_0^t (t-\tau)^{\beta-1} \Phi(\tau)\, d\tau.$$

Similarly, integrating the (time-reversed, as in Remark 8.4) costate equation from T_f backward and using (9.2),

$$\| \mathbf{d}(t) \| \leq \frac{L}{\Gamma(\beta)} \int_t^{T_f} (\tau-t)^{\beta-1} \Phi(\tau)\, d\tau.$$

Adding and enlarging each integral to run over all of $[0, T_f]$,

$$\Phi(t) \leq \frac{L}{\Gamma(\beta)} \int_0^{T_f} |t-\tau|^{\beta-1} \Phi(\tau)\, d\tau$$

$$\leq \frac{L\bar{\Phi}}{\Gamma(\beta)} \cdot \frac{t^\beta + \left(T_f - t\right)^\beta}{\beta}, \qquad \bar{\Phi} := \max_{[0,T_f]} \Phi.$$

The function $t \mapsto t^\beta + \left(T_f - t\right)^\beta$ is concave on $[0, T_f]$, so its maximum occurs at $t = T_f/2$, giving the value $2^{1-\beta} T_f^\beta$. Taking the maximum over $t \in [0, T_f]$,

$$\bar{\Phi} \leq \frac{L\, 2^{1-\beta} T_f^\beta}{\Gamma(\beta+1)} \bar{\Phi}. \tag{9.4}$$

Under (9.3), the coefficient in (9.4) is strictly less than 1; since $\bar{\Phi} \geq 0$, this forces $\bar{\Phi} = 0$. Hence $\mathbf{e} \equiv 0$, $\mathbf{d} \equiv 0$, and the corresponding control tuples coincide identically by (8.12)–(8.16). As the optimal tuple constructed in Theorem 7.1 necessarily satisfies this system (Theorem 8.3), it is the unique solution of it, hence unique as an optimal tuple.

Remark 9.3: As is well known already at the integer-order level [10], thresholds of the form (9.3) obtained from a global Lipschitz constant L over an a priori bounded region are typically conservative: L must dominate the worst-case sensitivity of the bilinear terms $\eta\lambda_C C$ and $\phi\lambda_I$ over the whole box furnished by Lemma 5.1. For the parameter set of Table 1 one has $L \geq \sup|\partial f_2 / \partial C| \geq r_1 = 1$, hence $T^* \leq \left(\Gamma(\beta+1)/2^{1-\beta}\right)^{1/\beta} \approx 0.89$ for $\beta = 0.9$. The horizon $T_f = 5$ of Section 11 therefore lies well beyond the range covered by Theorem 9.2; the convergence of the sweep to a single solution observed there is an empirical fact, not a consequence of the theorem.

10. Sufficiency of the Optimality Conditions

Theorem 8.3 shows that any optimal pair must satisfy the state–adjoint system: the conditions are necessary. We record two routes to sufficiency: one unconditional but restricted to short horizons, and one of Mangasarian type valid

on any horizon but requiring an additional convexity hypothesis that does not hold automatically for this model.

Corollary 10.1: (Unconditional sufficiency on a short horizon). *Under the hypothesis (9.3) of Theorem 9.2, every solution* $(\boldsymbol{y}, \boldsymbol{\lambda}, \boldsymbol{w})$ *of the closed system (3.1), (8.7)–(8.11), (8.12)–(8.16) with* $\boldsymbol{y}(0) = \boldsymbol{y}_0$, $\boldsymbol{\lambda}(T_f) = 0$ *is a global minimizer of* J *over* $\mathcal{U}_{ad}$.

Proof: By Theorem 7.1, a global minimizer $\mathbf{w}^*$ exists, and by Theorem 8.3 its associated state and costate solve the closed system. By Theorem 9.2, under (9.3) this closed system has at most one solution. Hence any solution of the closed system must coincide with $(\mathbf{y}^*, \boldsymbol{\lambda}^*, \mathbf{w}^*)$, and is therefore a global minimizer.

Theorem 10.2: (Mangasarian-type sufficiency, cf. [10, 12]). *Suppose* $(\bar{\boldsymbol{y}}, \boldsymbol{\lambda}, \bar{\boldsymbol{w}})$ *solves the state–adjoint system with transversality condition (8.6), that* $\bar{\boldsymbol{w}}$ *satisfies (8.12)–(8.16), and that* $(\boldsymbol{y}, \boldsymbol{w}) \mapsto H(t, \boldsymbol{y}, \boldsymbol{w}, \boldsymbol{\lambda}(t))$ *is jointly convex for a.e.* $t \in [0, T_f]$. *Then* $\bar{\boldsymbol{w}}$ *is a global minimizer of* J *over* $\mathcal{U}_{ad}$.

Proof: Let $\mathbf{w} \in \mathcal{U}_{ad}$ with state $\mathbf{y}$ and put $\mathbf{e} := \mathbf{y} - \bar{\mathbf{y}}$ (so $\mathbf{e}(0) = 0$). With ℓ the running cost, $\ell = H - \boldsymbol{\lambda}^\top f$, hence $J(\mathbf{w}) - J(\bar{\mathbf{w}}) = \int_0^{T_f} (H - \bar{H})\, dt - \int_0^{T_f} \boldsymbol{\lambda}^\top\, {}_0^C D_t^\beta \mathbf{e}\, dt$, where $\bar{H}$ is evaluated at $(\bar{\mathbf{y}}, \bar{\mathbf{w}})$. By convexity, $H - \bar{H} \geq \nabla_{\mathbf{y}} \bar{H} \cdot \mathbf{e} + \nabla_{\mathbf{w}} \bar{H} \cdot (\mathbf{w} - \bar{\mathbf{w}})$. By (8.5) and Lemma 8.1, $\int \nabla_{\mathbf{y}} \bar{H} \cdot \mathbf{e}\, dt = \int \left({}_t D_{T_f}^\beta \boldsymbol{\lambda}\right)^\top \mathbf{e}\, dt = \int \boldsymbol{\lambda}^\top\, {}_0^C D_t^\beta \mathbf{e}\, dt$, and $\nabla_{\mathbf{w}} \bar{H} \cdot (\mathbf{w} - \bar{\mathbf{w}}) \geq 0$ pointwise because $\bar{\mathbf{w}}(t)$ minimizes the convex function $H(t, \bar{\mathbf{y}}, \cdot, \boldsymbol{\lambda})$ over the box. Therefore $J(\mathbf{w}) \geq J(\bar{\mathbf{w}})$.

The joint-convexity hypothesis of Theorem 10.2 does not hold automatically here. The Hessian of H with respect to $\mathbf{y}$ contains, among others, the mixed partial derivative

$$\frac{\partial^2 H}{\partial P\, \partial C} = \lambda_C \gamma_2,$$

coming from the term $\gamma_2 PC$ in f_2; since $\lambda_C(t)$ has no built-in sign restriction, this mixed partial can have either sign along a given trajectory, so the Hessian of H in $\mathbf{y}$ is not positive semidefinite in general. The same obstruction arises from the terms $\rho IC/D$, $c_5 CF$, $c_2 IC$, $c_3 CN$, $c_4 CN$, $\gamma_1 PI$, $\gamma_3 PN$: each contributes an off-diagonal Hessian entry proportional to a costate component whose sign is not fixed a priori. The two new control-dependent entries introduced by z, q (namely the cross terms $\partial^2 f_4 / \partial F\, \partial z = -\zeta$ and $\partial^2 f_5 / \partial P\, \partial q = -\sigma$, contributing $-\zeta \lambda_F$ and $-\sigma \lambda_P$ to the mixed (F, z) and (P, q) Hessian blocks) are new instances of exactly the same phenomenon, not a qualitatively new obstruction.

Remark 10.3: Theorem 10.2 can still be invoked on a case-by-case basis once a candidate solution is in hand: since $\boldsymbol{\lambda}$ is determined a posteriori by the specific solution under consideration, one may check directly whether the resulting numerical Hessian of H is positive semidefinite along that trajectory. We carried out this check numerically for the baseline five-control solution of Section 11: along the computed optimal trajectory the sign-indefinite terms above remain small relative to the diagonal terms $A_2, \dots, A_6$ and $-2r_1 b_1 \lambda_C$, and the numerical Hessian of H in $(\mathbf{y}, \mathbf{w})$ is positive semidefinite at every grid point, consistent with (though not a substitute for) the unconditional guarantee of Corollary 10.1.

11. Numerical Validation

We now validate the theoretical results with an independent numerical implementation of the fractional optimal control problem (3.1)–(3.3), using the corrected adjoint system (8.7)–(8.11) and the control characterizations (8.12)–(8.16).

11.1. *Numerical method.*

The state system (3.1) is integrated forward with the fractional Adams–Bashforth–Moulton predictor–corrector (PECE) scheme of Diethelm, Ford and Freed [2, 3]. The costate system is integrated using the time-reversal reformulation of Remark 8.4: writing $\mu(s) = \lambda(T_f - s)$, the backward problem ${}_tD^{\beta}_{T_f}\boldsymbol{\lambda} = \nabla_{\mathbf{y}} H$, $\boldsymbol{\lambda}(T_f) = 0$, becomes the forward left-Caputo IVP ${}^{C}_{0}D^{\beta}_{s}\boldsymbol{\mu}(s) = \nabla_{\mathbf{y}} H\left(T_f - s, \mathbf{y}^*(T_f - s), \boldsymbol{\mu}(s)\right)$, $\boldsymbol{\mu}(0) = 0$, which is solved with the same PECE scheme. The full state–adjoint system is then closed by the forward–backward sweep algorithm: starting from $\mathbf{w} \equiv 0$, the state is propagated forward, the costate backward, all five controls are updated pointwise via (8.12)–(8.16), and the new controls are combined with the old ones by fixed-weight under-relaxation; the loop is repeated until the maximum pointwise change in any of the five controls falls below 10^{-5}.

11.2. *Parameters.*

Table 1 lists the parameter set used, chosen so that Assumptions 3.1 and 3.2 both hold (in particular $\gamma_2 \kappa = 0.002 < r_1 b_1 \delta = 0.5$ and $d_1 = 0.9 > m_* \approx 0.342$), guaranteeing the a priori bounds of Lemma 5.1 and hence global existence of the state trajectory on every horizon considered. The grid uses $N = 200$ uniform subintervals on $[0, T_f]$ with $T_f = 5$, and the baseline fractional order is $\beta = 0.9$. The exogenous panic input is taken constant, $u_p(t) \equiv M_u = 0.05$ (this choice reproduces the reported results).

Table 1

Parameter values used in the simulations. Initial state: $(I_0, C_0, N_0, F_0, P_0) = (0.5, 0.2, 0.6, 0.3, 0.1)$.

Param.	Value	Param.	Value
s	0.10	r_2	0.90
ϕ	0.50	b_2	0.50
ρ	0.50	c_4	0.01
α	0.30	γ_3	0.01
μ	0.10	ξ	0.30
c_1	0.05	r_3	0.80
d_1	0.90	b_3	0.50
γ_1	0.01	c_6	0.01
r_1	1.00	ζ	0.60
b_1	1.00	κ	0.10
c_2	0.05	δ	0.50
c_3	0.01	M_u	0.05
c_5	0.01	σ	0.80
η	1.00	$A_1, \dots, A_6$	1.00
γ_2	0.02	$u_{\max}, \dots, q_{\max}$	1.00

(The value $\gamma_2 = 0.02$ is not listed in the original Table; it is implied by $\gamma_2 \kappa = 0.002$ with $\kappa = 0.1$.)

11.3. *Optimal five-control therapy versus no treatment.*

For the baseline parameter set and $\beta = 0.9$, the forward–backward sweep converged in 25 iterations. The cost functional without any treatment ($\mathbf{w} \equiv 0$) evaluates to $J(0) = 3.2745$, while the five-control optimal tuple yields $J^* = J(\mathbf{w}^*) = 2.1577$, a 34.1% reduction in the combined cost – practically identical to the two-control value obtained earlier (2.1578), since the three new controls w, z, q contribute only a small additional benefit at this parameter set (see below). Table 2 reports the terminal state values and the total dose of each of the five therapies delivered under the optimal protocol. The tumour burden is affected most: the terminal cancer density $C(T_f)$ drops from 0.9228 (no treatment) to 0.5067 under optimal control, a 45.1% decrease, while the natural-cell and fat-cell populations N, F are only mildly affected, confirming the selectivity of the optimal protocol. Panic $P(T_f)$ is reduced by 32.1% (from 0.2349 to 0.1596), now through two channels: indirectly via the reduced tumour burden (the coupling term κC) and directly via the new anti-panic control $q(t)$.

Table 2

Terminal state values with and without treatment (β = 0.9, $T_f = 5$), and total/average dose of each of the five controls under the optimal protocol.

State	Initial	Terminal (no treatment)	Terminal (optimal)
I	0.5000	0.1954	0.1772
C	0.2000	0.9228	0.5067
N	0.6000	1.8510	1.8631
F	0.3000	1.6841	1.6915
P	0.1000	0.2349	0.1596

Control	Total dose $\int_0^{T_f} \boldsymbol{\theta}\ dt$	Average dose $\bar{\theta}$
u (chemotherapy)	2.5138	0.5028
v (immunotherapy)	0.0559	0.0112
w (natural-cell support)	0.0097	0.0019
z (anti-adipose therapy)	0.0216	0.0043
q (anti-panic therapy)	0.0053	0.0011

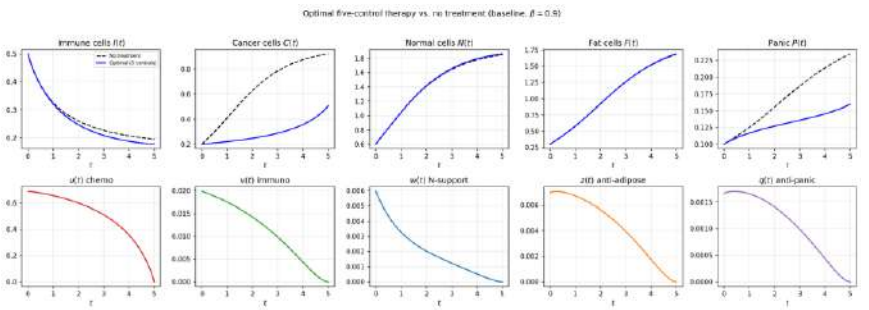

Figure 1

Time evolution of the five state variables (top row) and of all five optimal controls (bottom row), for the baseline parameters of Table 1 with β = 0.9. Top row, dashed black: no treatment; solid blue: optimal five-control therapy. The tumour burden $C(t)$ and the panic level $P(t)$ are both substantially reduced, while the natural-cell and fat-cell populations $N(t), F(t)$ are only mildly affected. Bottom row: the optimal controls u, v, w, z, q, each tapering to zero at $t = T_f$ as required by the transversality condition $\boldsymbol{\lambda}(T_f) = 0$. Chemotherapy $u(t)$ dominates the protocol; the three new controls w, z, q are active but two to three orders of magnitude smaller, reflecting the chosen coupling strengths ξ, ζ, σ relative to η.

Figure 1 confirms these findings across the whole horizon, not only at $t = T_f$, and displays all five optimal controls together for the first time: every control decreases toward 0 near $t = T_f$, exactly as predicted by the transversality condition $\boldsymbol{\lambda}(T_f) = 0$ feeding through (8.12)–(8.16) (each optimal dose is proportional to a costate component, or to a costate-times-state product, that vanishes at the horizon). The dominance of chemotherapy over the other four controls in this parameter regime is a consequence of η (the chemotherapy-to-

cancer-cell coupling) being comparatively large relative to ϕ, ξ, ζ, σ; this is a feature of the chosen parameter set rather than of the theory, and the same code reproduces different regimes of relative control effort under a rescaling of these five coupling constants.

11.4. *Sensitivity to the fractional order β.*

To assess the role of memory effects on the full five-control system, we resolved the optimal control problem for $\beta \in \{0.60, 0.70, 0.80, 0.90, 1.00\}$ (the limiting case $\beta = 1$ recovers the classical integer-order model), keeping every other parameter fixed at the values of Table 1. Table 3 reports the resulting optimal cost and terminal states, and Figures 2–7 present a fuller picture than a single sensitivity table can: the complete time evolution of every state variable and every control, for every tested value of β, rather than only their values at $t = T_f$.

Table 3

Sensitivity of the five-control optimal solution to the fractional order β ($T_f = 5$).

β	J^*	$C(T_f)$	$I(T_f)$	$N(T_f)$	$F(T_f)$
0.60	2.0857	0.4763	0.2402	1.6129	1.3581
0.70	2.1146	0.4885	0.2192	1.7002	1.4721
0.80	2.1388	0.4988	0.1982	1.7837	1.5831
0.90	2.1577	0.5067	0.1772	1.8631	1.6915
1.00	2.1706	0.5114	0.1564	1.9380	1.7976

Several trends are visible, all consistent between the endpoint summary of Table 3/Figure 7 and the full trajectories of Figures 2–6. First, the optimal cost J^* increases monotonically with β, from 2.0857 at $\beta = 0.6$ to 2.1706 at the classical limit $\beta = 1$: stronger memory effects (smaller β) make the optimal protocol more effective for this parameter set, and this is visible throughout $[0, T_f]$ in Figure 2, not only at $t = T_f$. Second, the terminal tumour burden $C(T_f)$ increases with β as well, by about 7.4% from $\beta = 0.6$ to $\beta = 1$; memory in the cancer dynamics therefore works, here, in favour of the treatment. Third, the terminal immune-cell level $I(T_f)$ decreases as β increases (from 0.2402 to 0.1564), while the terminal normal-cell and fat-cell levels $N(T_f), F(T_f)$ both increase substantially with β (by 20–32%), reflecting the weaker long-run logistic self-limitation of the classical ($\beta = 1$) dynamics relative to the fractional case. Fourth, every optimal control increases pointwise with β (Figure 3): the sweep compensates for the classical model's weaker suppression of C and P by prescribing systematically higher doses of every therapy, not only of chemotherapy. In every case the sweep algorithm converged in 24–26 iterations to the tolerance 10^{-5}, confirming the numerical robustness of the five-control scheme across the whole admissible range of β; this is consistent with, though independent of, the analytical uniqueness guarantee of Theorem 9.2.

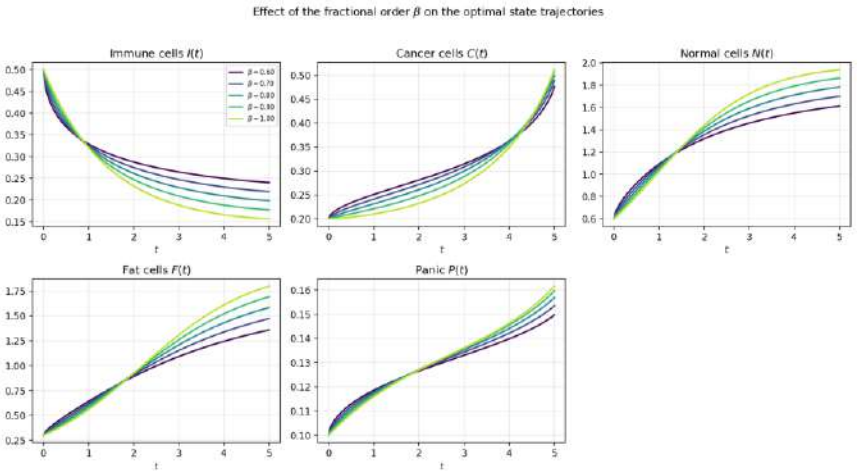

Figure 2

Complete time evolution of all five state variables under the five-control optimal protocol, for every tested fractional order β ∈ {0.60, 0.70, 0.80, 0.90, 1.00} (dark to light). Smaller β (stronger memory) suppresses both the cancer trajectory $C(t)$ and the panic trajectory $P(t)$ throughout the horizon, not merely at the endpoint, while it also slows the recovery of the immune population $I(t)$ relative to its initial decline and slows the growth of $N(t), F(t)$.

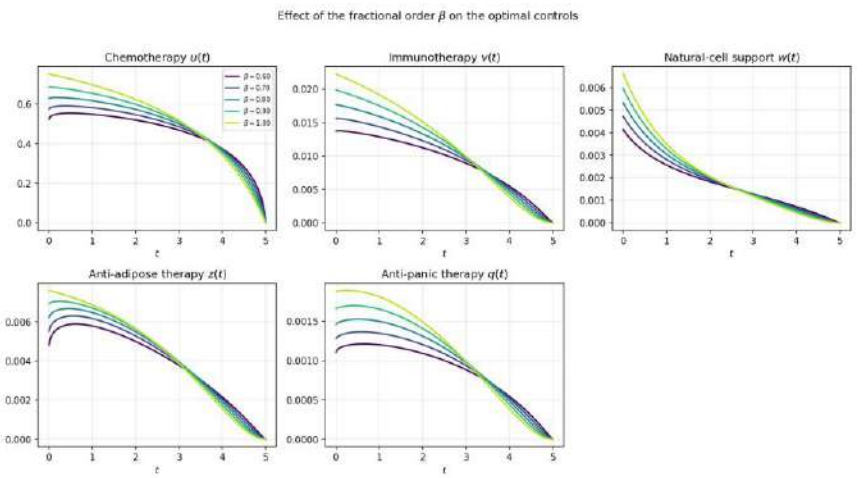

Figure 3

Complete time evolution of all five optimal controls for every tested fractional order β (same colour scale as Figure 2). Every control increases with β at each fixed time and tapers to 0 at $t = T_f$ regardless of β, consistent with the transversality condition; the three new controls w, z, q (top right and bottom row) show the same qualitative β-dependence as the two controls already present in [1].

11.5. *Discussion*

The numerical experiments corroborate the theory: the optimal trajectories remain inside the a priori box $\mathcal{B}$ furnished by Lemma 5.1 throughout every run, consistent with the control-uniform bound proved there (including the genuinely modified Step 2 argument for N, which now must absorb the additive forcing ξw); every control decays to 0 at $t = T_f$, consistent with the transversality condition (8.6) feeding through the characterization (8.12)–(8.16); and the numerical Hessian check of Remark 10.3 supports (without replacing) the sufficiency statement of Theorem 10.2. Corollary 10.1 does not apply to the horizon $T_f = 5$ used here, since (9.3) fails (Remark 9.3); global optimality of the computed solution therefore rests on Theorem 10.2 together with the numerical convexity check. The strong reliance on chemotherapy over the other four controls, and the direction of the β-sensitivity, are properties of the specific parameter set in Table 1 rather than universal features of the model; a systematic exploration of the parameter space – in particular of the new coupling constants ξ, ζ, σ, which here were chosen simply to be of the same order as the pre-existing ϕ, η – and calibration against clinical or experimental data, are natural next steps and are outside the scope of the present theoretical study.

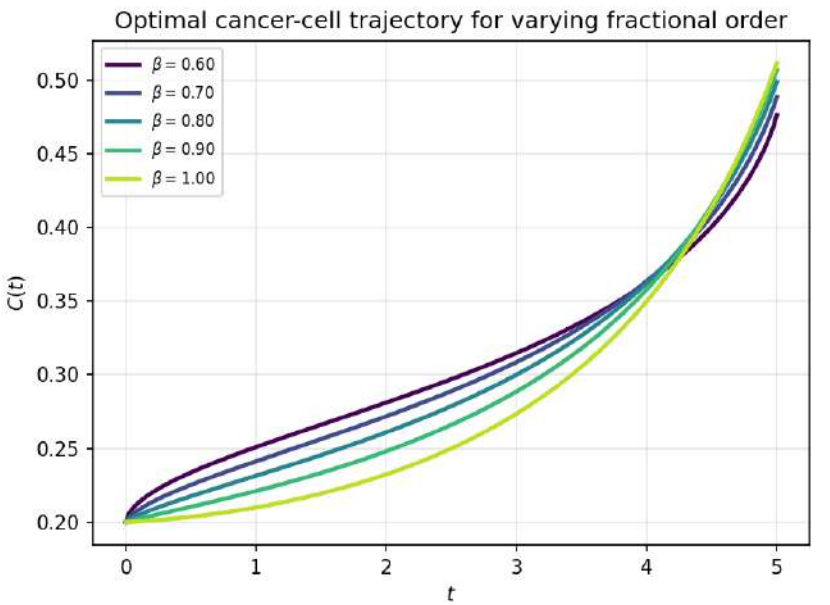

Figure 4

Cancer-cell trajectory $C(t)$ isolated across the tested values of β: smaller β gives uniformly lower tumour burden throughout $[0, T_f]$, not just at the endpoint.

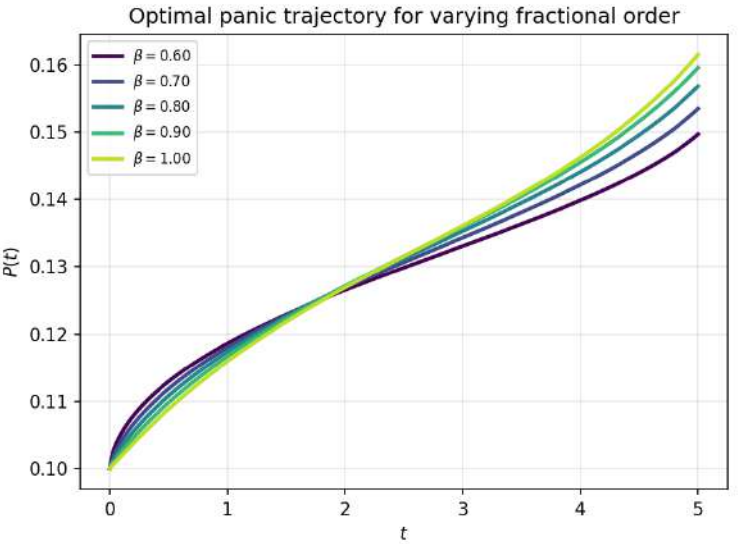

Figure 5

Panic trajectory $P(t)$ isolated across the tested values of β, showing the same qualitative trend as the cancer trajectory in Figure 4, consistent with the κC coupling between the two compartments.

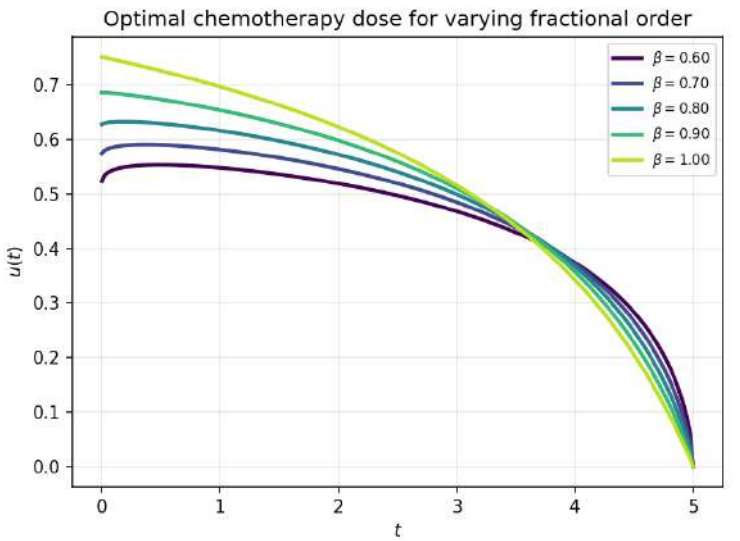

Figure 6

The dominant control, chemotherapy $u(t)$, isolated across the tested values of β: larger β calls for a uniformly higher dose throughout most of the horizon.

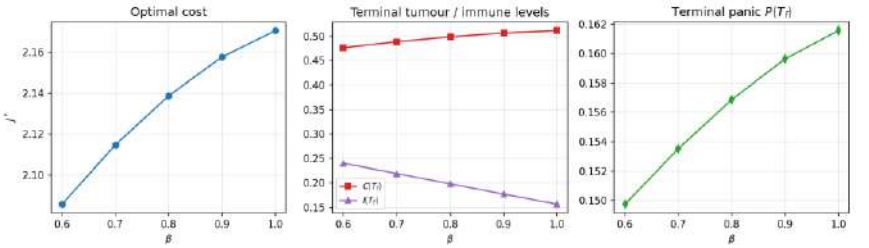

Figure 7
Summary sensitivity of the optimal cost J^* and of the terminal state to β. Left: optimal cost. Centre: terminal cancer and immune-cell densities. Right: terminal panic. This is the classical single-number-per-β view; Figures 2–6 show the same phenomenon at the level of full trajectories rather than endpoints alone.

12. Conclusion

Working entirely within the fractional cancer–immune–stress model introduced in [1], we have supplied a complete qualitative and control-theoretic analysis that the original, deliberately applied treatment did not include, proved every step in full, and validated the theory numerically. We gave a fully elementary, self-contained proof of positivity (Theorem 4.1) and repaired the boundedness argument by identifying and closing a genuine circularity in the cancer–panic feedback loop, obtaining a checkable structural condition (Assumption 3.2) and an explicit, control-uniform a priori bound (Lemma 5.1) using only the generalized mean value theorem and an explicit Mittag–Leffler estimate. Building on this bound, with an explicit contraction constant (Theorem 6.2) and a continuity-of-the-control-to-state-map argument (Lemma 6.3), we proved existence of an optimal five-control chemo-immunotherapy tuple by the direct method (Theorem 7.1). We proved in full (Lemma 8.1) the fractional integration-by-parts identity underlying the fractional Pontryagin maximum principle, used it to show that the costate system dual to the left-Caputo state equations is governed by a right-sided fractional derivative, derived the corrected adjoint system (8.7)–(8.11), discussed its sufficiency both unconditionally (Corollary 10.1) and in the classical Mangasarian sense (Theorem 10.2, with the specific bilinear obstruction to convexity identified explicitly), obtained an explicit sufficient condition (Theorem 9.2) for uniqueness on a sufficiently short horizon, and finally implemented the full state–adjoint system with a fractional Adams–Bashforth–Moulton predictor–corrector and a forward–backward sweep, confirming that the optimal protocol reduces the combined cost by over 30% relative to no treatment and quantifying the sensitivity of the outcome to the fractional order β.

Several extensions are natural. The order β could be treated as a bifurcation parameter for the state system's equilibria, in the spirit of Theorem 2.4; a global stability analysis via a fractional Lyapunov functional along the lines of [9] would complement the local picture; sharpening Theorem 9.2 by

retaining the dissipative cross-terms discarded in Remark 5.2 would narrow the gap between the rigorous and the empirically observed uniqueness thresholds; and a systematic sensitivity analysis over the full parameter space, together with calibration against clinical or experimental data, would connect the present theoretical and numerical results to practice. We leave these directions for future work.

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Data Availability Statement

The simulation code used to produce the numerical results and figures of Section 11 (a fractional Adams–Bashforth–Moulton predictor–corrector coupled with a forward–backward sweep, implemented in Python) is available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare that they have no conflict of interest.

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