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Optimal control of a two-species bioproducing microbial consortium

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Abstract

We study the optimal control of a system of nonlinear ordinary differential equations modeling microbial populations with light-inducible genetic differentiation that generates a two-species microbial consortium relevant for bioproduction. Appealing to Pontryagin’s maximum principle, we find different optimal control structures within different regions of the parameter space. Explicit solutions are obtained in a subset of parameter space, while, for the remainder of parameter space, closed-form solutions are obtained that depend on a scalar value that solves a particular transcendental equation. We show that a unique solution of the scalar equation exists and lies in a known compact interval, making its numerical approximation particularly easy. The analytical results are verified against direct numerical calculations.

1 Introduction

Microbial consortia are colonies of two or more interacting microorganisms living together. Such colonies offer increased application potential over cultures of single strains since each organism can be specialised for different tasks, allowing a diverse set of mechanisms that need not coexist in a single organism. This promises improvements in bioproduction, bioremediation, and other areas [3, 6, 8, 13]. A primary focus of recent work has been the modeling and control of such consortia [1, 9, 12].

In this work, we consider the optimal control of a model of a bioproducing microbial consortium. The model is of particular interest because it is an approximation of a wide array of more detailed heterogeneous models [7]. We apply Pontryagin’s maximum principle to solve the optimal control problem explicitly, modulo a single scalar value that must be calculated numerically in some regions of parameter space. When this numerical value is required, we show that it is the unique solution of an equation that lies in a known compact interval, making its computation eminently tractable.

The rest of the paper is organised as follows. We detail the model and its biological basis in section 2. We solve the optimal control problem in section 3. Since the solution involves partitioning the parameter space several times, we provide a summary in flowchart form in section 4 before making final remarks.

2 Problem formulation

We consider an initial population of cells constitutively producing a photoreceptive transcription factor. Upon light induction, the transcription factor is recruited in the production of recombinase which leads to genetic recombination and a rewiring of a cell’s DNA. Cells that undergo this process have been (irreversibly) differentiated: regions of the genotype not previously used are now available, thereby creating a genetically distinct subpopulation. Only in the differentiated cell construct is the protein of interest produced (to place the burden of production only on the differentiated subpopulation).

We assume that the undifferentiated cells grow at some exponential rate A , while the differentiated cells have an inhibited growth rate $0 \leq a < A$, as a result of the protein production. We thus call the undifferentiated cells the “growers” and the differentiated cells the “producers”. We denote their respective population masses by $G(t)$ and $P(t)$. We further assume that the transcription factor recruitment and cell recombination is faster than the other transient timescales of the process and may thus be neglected. Moreover, we assume that the colony

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is housed in a bioreactor that is run in turbidostat mode, whereby the optical density of the contents (which we assume an accurate proxy for the population density) is kept constant by means of dilution. Finally, we assume that the media is maintained such that nutrients are present in abundance and the culture is well stirred.

Ultimately, we model these dynamics by the governing equations

$$\dot{G}(t) = AG(t) - \Lambda(t)G(t) - Fu(t)G(t), \quad G(0) = g_0, \quad (1a)$$

$$\dot{P}(t) = aP(t) - \Lambda(t)P(t) + Fu(t)G(t), \quad P(0) = p_0, \quad (1b)$$

where $\Lambda(t)$ is the turbidostat dilution rate, $u(t) \in [0, 1]$ is the (dimensionless) light signal that induces differentiation, and $F > 0$ is the differentiation rate for the maximal light signal. We take arbitrary initial conditions. In practice, the culture is typically grown in darkness so that the initial population is of known composition, however, we consider the more general problem of arbitrary initial conditions. This is because we are also interested in using the solution with Model–Predictive Control (MPC), where state updates can be made throughout the bioproduction process, and the optimal control recalculated from the intermediate state.

We may determine the turbidostat dilution rate by fixing $\Lambda(t)$ such that the total population mass remains constant. Adding (1a) and (1b) and taking $\dot{G}(t) + \dot{P}(t) = 0$ we find that

$$\Lambda(t) = \frac{AG(t) + aP(t)}{G(t) + P(t)} = \frac{AG(t) + aP(t)}{g_0 + p_0}. \quad (1c)$$

We seek to maximise the protein yield J , which we take to be proportional to the producer population mass from both the diluted media and what remains in the bioreactor at the terminal time $t = T$. The objective function takes the form

$$J = P(T) + \int_0^T \Lambda(t)P(t) dt. \quad (1d)$$

We can, without loss of generality, take $g_0 + p_0 = 1$, since this amounts to rescaling $G(t)$ and $P(t)$ by the denominator $g_0 + p_0$, whereby the dilution rate is then given by $\Lambda(t) = AG(t) + aP(t)$. We thus obtain the unit conservation property

$$G(t) + P(t) = 1, \quad (2)$$

from which we reduce the optimal control problem (1) to a single dimension. The problem then reads: maximise

$$J = -G(T) + \int_0^T (A - 2a)G(t) - (A - a)G(t)^2 dt, \quad (3a)$$

for $0 \leq u(t) \leq 1$, where we have neglected terms that are constant for all controls, subject to the dynamics

$$\dot{G}(t) = (A - a - Fu(t))G(t) - (A - a)G(t)^2, \quad G(0) = g_0 \in [0, 1]. \quad (3b)$$

Equipped with the optimal control problem (3), we proceed to briefly discuss the nonlinear dynamics (3b) and then study the optimal control problem (3).

At the outset, we may make predictions of the optimal control under certain assumptions based on the turnpike property. Since the running component of the objective is a quadratic (thus convex) function of the state, we expect the optimal control to be of turnpike form [10] assuming the time horizon is long enough and the system is controllable. That is, for most of the time horizon, the optimal control should be that which guarantees the state is maximising the quadratic form of the running pay-off. The only deviations from this may be an initial transient where this steady state is established, and a terminal transient where the terminal component of the objective is maximised.

The subsequent analysis agrees with this characterisation, however, it refines and extends it in important ways. First, we deal with the case of weak induction where the system is not controllable and thus the steady state maximising the running pay-off is not guaranteed to be reachable. Second, we deal with arbitrary time horizons, in particular, those that are insufficiently long for the turnpike structure to form. Finally, in all cases we are able to pin down the optimal control structure quantitatively. For example, in the case of strong induction, we have an explicit expression for the critical time horizon at which the turnpike structure manifests.

3 Results

We begin with a useful result regarding the state $G(t)$.

Proposition 1. *The sets $\{0\}$ and $(0, 1]$ are invariant sets of the dynamics of $G(t)$.*

Proof. If $G(t) = 0$, then $\dot{G}(t) = 0$. If $G(t) = 1$, then $\dot{G}(t) \leq 0$. It thus suffices to prove that zero cannot be reached if $0 < G(t) \leq 1$. Since $G(t) \in [0, 1]$, the dynamics (3b) may be written as $\dot{G}(t) = -\gamma(t)G(t)$ where $\gamma(t) \leq F$. An application of Grönwall's inequality suffices to show that the solution is bounded from below by an exponentially decreasing function and thus must remain positive for all time. \square

We conclude from Proposition 1 that, for $g_0 > 0$, $G(t) > 0$ for all time t . Moreover, the case of $g_0 = 0$ is trivial, and is not subsequently considered.

We now consider the dynamics (3b) for a constant control $u(t) = u$. In this case, the dynamics are homogeneous, and the quadratic form on the right-hand side of (3b) reveals two equilibria, $G(t) = G_0$ and $G(t) = G_1(u)$, given by

$$G_0 = 0, \quad G_1(u) = 1 - \frac{Fu}{A-a}. \quad (4)$$

The stability of these equilibria is governed by the sign of $\dot{G}(t)$ in their vicinity. The quadratic form (3b) dictates that, when these two roots are distinct, the lesser is unstable while the greater is stable. The roots coincide for

$$u = \frac{A-a}{F} =: u_0. \quad (5)$$

When $u > u_0$, $G_1(u) < G_0$ and the stable root is G_0 , while when $u < u_0$ the sign of $G_1(u)$ switches and it becomes the stable root. When G_0 is a stable equilibrium, the grower population $G(t)$ cannot vanish in finite time (Proposition 1).

For the degenerate control value $u = u_0$ the roots coincide and the unique equilibrium $G(t) = G_0 = G_1(u_0) = 0$ is unstable to arbitrary perturbations. Nevertheless, being a population mass, $G(t)$ and its perturbations must be non-negative, and the zero equilibrium is stable to positive perturbations.

It is helpful to develop a physical interpretation of these conditions to complement the analysis. We found a critical control value u_0 at (and beyond) which the grower population tends to zero (whereby the population comprises exclusively producers) as the differentiation, which depletes the grower population, surpasses the influence of the growth. For subcritical controls $u < u_0$, the population tends to a strictly positive equilibrium $G(t) = G_1(u)$ where the differentiation and growth balance to maintain a steady growers population.

We finish studying the dynamics with a result for any time-varying control input.

Proposition 2. *When $G_1(1) > 0$, the state $G(t)$ increases monotonically in $(0, G_1(1))$, while the interval $[G_1(1), 1]$ is an invariant set of the dynamics of $G(t)$ for any $u(t) \in [0, 1]$.*

Proof. If $G(t) \in (0, G_1(1))$ then $\dot{G}(t) \geq (A-a-F)G(t) - (A-a)G(t)^2 > 0$, where the final inequality comes from minimising the quadratic over the domain $(0, G_1(1))$.

If $G(t) = G_1(1)$, then $\dot{G}(t) \geq 0$, and the claim follows from Proposition 1. \square

We now study the optimal control of problem (3) via Pontryagin's maximum principle. We introduce the Hamiltonian (with the convention of minimising $-J$),

$$H = \lambda(t) [(A-a-Fu(t))G(t) - (A-a)G(t)^2] - (A-2a)G(t) + (A-a)G(t)^2, \quad (6)$$

from which we determine that the costate equation is given by

$$\dot{\lambda}(t) = -\lambda(t)[A-a-Fu(t) - 2(A-a)G(t)] + (A-2a) - 2(A-a)G(t), \quad \lambda(T) = 1. \quad (7)$$

The Hamiltonian is linear with respect to the control, and therefore the optimal control is given by the bang-bang form when the switching function is nonzero [5]. The switching function is given by

$$\frac{\partial H}{\partial u} = -F\lambda(t)G(t), \quad (8)$$

and since $F > 0$ and $G(t) > 0$ for all time, the optimal control takes the bang-bang form

$$u(t) = \begin{cases} 1, & \lambda(t) > 0, \\ 0, & \lambda(t) < 0. \end{cases} \quad (9)$$

It remains to determine the optimal control on singular arcs, where $\lambda(t) = 0$. We denote the bang-bang arcs of control (9) by \mathcal{B}_- and \mathcal{B}_+ arcs, for $u(t) = 0$ and $u(t) = 1$, respectively, while we denote a singular arc by \mathcal{S} .

Further analysis of the adjoint equation (7) allows us to determine the structure of the optimal control.

Proposition 3. *There can be at most one \mathcal{B}_- arc. This arc, if it exists, must be adjacent to $t = 0$, that is, it must be the time interval $[0, t_0)$ for some $t_0 > 0$.*

Proof. Assume that there exists a nontrivial arc (t_0, t_1) , where $0 < t_0 < t_1 < T$, on which $\lambda(t) < 0$ and $\lambda(t_0) = \lambda(t_1) = 0$. It must be that $\dot{\lambda}(t_0) \leq 0 \leq \dot{\lambda}(t_1)$, and it follows from the costate equation (7) that $\dot{\lambda}(t_i) = 2(A - a)(G_s - G(t_i))$ for both $i = 0, 1$ where

$$G_s := \frac{A - 2a}{2(A - a)} < 1. \quad (10)$$

Therefore, $G(t_0) \geq G(t_1)$. However, the state must be monotonically non-decreasing over the interval since $\dot{G}(t) \geq 0$ when $u(t) = 0$ with equality only for $G(t) = 1$ (since we are not interested in the $G(t) = 0$ case). It follows that $G(t) = 1$ over this entire interval, and thus $\dot{\lambda}(t_1) = 2(A - a)(G_s - 1) < 0$, which is a contradiction.

This demonstrates that there cannot exist such an arc for $0 < t_0 < t_1 < T$. We cannot set $t_1 = T$, since the terminal condition in (7) will not be satisfied. Thus, the only way an arc of $\lambda(t) > 0$ can exist is if $t_0 = 0$. This arc, if it exists, must therefore be unique. \square

It is instructive to characterise the singular arcs, as in the following result.

Proposition 4. *On singular arcs, the optimal control is given by $u(t) = A/(2F)$, and satisfies the strengthened Generalised Legendre-Clebsch (GLC) condition.*

Proof. Assume that the switching function (8) vanishes on some interval. This can occur when either $G(t) = 0$ or $\lambda(t) = 0$. We proved in Proposition 1 that the former cannot happen in finite time (since $g_0 > 0$), and thus focus on the latter. On such intervals, it must hold that $\dot{\lambda}(t) = 0$ and thus from (7) we find that $G(t) = G_s$ defined in (10). Differentiating, $\dot{G}(t) = 0$, from which it follows via (3b) that the singular optimal control is given by

$$u(t) = \frac{A}{2F} =: u_s. \quad (11)$$

This allows us to calculate the GLC criterion

$$-\frac{\partial}{\partial u} \left(\frac{d^2}{dt^2} \frac{\partial H}{\partial u} \right) = \frac{F^2(A - 2a)^2}{2(A - a)} \geq 0. \quad (12)$$

Since the state $G(t)$ is positive for all time (Proposition 1), a singular arc, where $G(t) = G_s$, can only exist if $G_s > 0$, that is, $A > 2a$, in which case the right-hand side of (12) will be strictly positive. This is none other than the strengthened GLC condition, also known as the Kelley condition. \square

We have ascertained that there is a unique initial (possibly empty) \mathcal{B}_- arc, on $[0, t_0)$, say. There is also a terminal \mathcal{B}_+ arc due to the bang–bang form (9) and the terminal condition (7), on $(T - T_s, T]$, say. By continuity of the costate we may assume that this final arc is maximal. When $T - T_s > t_0$, we are interested in pinning down the optimal control structure in the intervening time. We now prove that there can be no additional \mathcal{B}_+ arc spanning (t', t'') , for some $t_0 < t' < t'' \leq T - T_s$. This demonstrates that, between these initial \mathcal{B}_- and terminal \mathcal{B}_+ arcs, there can only be another \mathcal{B}_+ arc if it is adjacent to the initial \mathcal{B}_- arc, that is, $t' = t_0$. Since there can be no more than the initial \mathcal{B}_- arc, and no more than these two potential \mathcal{B}_+ arcs, the optimal control must of the form $(\mathcal{B}_-)(\mathcal{B}_+)(\mathcal{S})\mathcal{B}_+$, where parentheses enclose arc forms that may be empty. It follows that the singular arc, if it exists, is unique.

Proposition 5. *Considering the initial \mathcal{B}_- arc to span $[0, t_0)$ for some $t_0 \geq 0$, and the terminal \mathcal{B}_+ arc to maximally span $(T - T_s, T]$ for some $T_s > 0$, there can be no \mathcal{B}_+ arc maximally spanning (t', t'') , for any $t_0 < t' < t'' \leq T - T_s$.*

Proof. By way of contradiction, consider such a \mathcal{B}_+ arc. The maximality of the arc guarantees that the times t' and t'' are critical times, that is, $\lambda(t') = \lambda(t'') = 0$. Moreover, since $t' > t_0$ by assumption, and there cannot be additional \mathcal{B}_- arcs, it must also hold, by (9), that $\dot{\lambda}(t') = \dot{\lambda}(t'') = 0$. It then follows from the costate equation (7) that $G(t') = G(t'') = G_s$.

On a \mathcal{B}_+ arc the control is maximal $u(t) = 1$. In this case, the state evolves strictly monotonically towards the stable equilibrium, G_0 or $G_1(1)$ defined in (4), unless the state $G(t') = G_s$ coincides with one of the equilibria. Since $G(t') = G(t'')$, it must be the latter case, whereby $G(t) = G_s$ on $t \in [t', t'']$. It follows from (7) and (10) that the costate remains zero throughout $[t', t'']$, which contradicts the assumption that the arc is \mathcal{B}_+ . \square

We formulate the final argument in the proof of Proposition 4 as a separate result forming a condition for the existence of singular arcs.

Proposition 6. *If $A \leq 2a$, there are no singular arcs.*

In the absence of singular arcs, the optimal control is of the form $(\mathcal{B}_-)\mathcal{B}_+$. In this case of $A \leq 2a$, the singular state is negative, and thus unreachable. Intuitively, the \mathcal{B}_+ arc will steer the state to a smaller value than a \mathcal{B}_- arc, which, in this case, is advantageous for both the running and terminal pay-offs. Therefore, we expect the optimal control to be a \mathcal{B}_+ arc, which we prove in the following result.

Proposition 7. *If $A \leq 2a$, the optimal control is a \mathcal{B}_+ arc.*

Proof. If $\lambda(t) = 0$ at any t , it follows from the costate equation (7) that $\dot{\lambda}(t) = (A - 2a) - 2(A - a)G(t) \leq -2(A - a)G(t) < 0$ when $A \leq 2a$ and thus $\lambda(t)$ must remain strictly negative for all time after t . Since $\lambda(T) = 1$, we deduce that $\lambda(t)$ never vanishes, and must remain positive for all t . The claim then follows from (9). \square

Having determined the optimal control when $A \leq 2a$, we now turn our attention to the case when $A > 2a$, where there may be singular arcs. We begin by highlighting some useful inequalities that may be verified directly from the definitions in (5), (10) and (11)

$$A > 2F \quad \iff \quad u_s > 1 \quad \iff \quad G_1(1) > G_s, \quad (13a)$$

$$A > 2a \quad \iff \quad u_s < u_0 \quad \iff \quad G_s > 0. \quad (13b)$$

This reveals a useful dichotomy in parameter space and we split the analysis based on the case of weak induction $A \geq 2F$, in which case the singular control u_s is no less than the maximal control, and strong induction $A < 2F$, where the singular control is strictly less than the maximal control.

3.1 The case of weak induction $A \geq 2F$

In addition to Proposition 6, another necessary condition for the existence of singular arcs is that the singular control (11) respects the control bounds: $u_s \leq 1$. If $u_s > 1$, the grower mass $G(t)$ will never reach the level (10) that characterises a singular arc.

Proposition 8. *If $A \geq 2F$, there are no singular arcs.*

Proof. If $A \leq 2a$, there are no singular arcs (Proposition 6), therefore, we focus on the case of $A > 2a$. In the case where $A > 2F$, we see from (13) that $G_1(1) > G_s > 0$. Therefore, from Proposition 2, the state cannot remain constant at G_s , and the claim follows.

When $A = 2F$, we look to the optimal control structure. Since every singular arc must be followed by a \mathcal{B}_+ arc, it suffices to prove that the arc combination $\mathcal{S}\mathcal{B}_+$ cannot form. The argument is identical to that in the proof of Proposition 5: the singular control is the maximal control $u_s = 1$ when $A = 2F$, therefore, the state remains constant on a $\mathcal{S}\mathcal{B}_+$ arc combination $G(t) = G_s$, and thus so too does the costate (7), contradicting the fact that the second arc is \mathcal{B}_+ . \square

We deduce, in the case of weak induction, by combining the discussion before Proposition 5, with Propositions 6 to 8, that the optimal control is of the form $(\mathcal{B}_-)\mathcal{B}_+$. We now proceed to narrow down the control structure more concretely. Intuitively, for weak induction, the maximal control does not suffice to maintain the singular state (see (13)), but will drive the state as close as possible to maximising both the running and terminal pay-offs. Therefore, we expect the optimal to be a \mathcal{B}_+ arc, as long as the initial state g_0 is not too much smaller than the singular state G_s , as we establish below.

Proposition 9. *If $A \geq 2F$ and $g_0 \geq G_s$, the optimal control is a \mathcal{B}_+ arc.*

Proof. Assume, by way of contradiction, that the optimal control is of the form $\mathcal{B}_-\mathcal{B}_+$, where the \mathcal{B}_- arc is on $t \in [0, t_0]$ for some $t_0 > 0$. On this interval $\dot{G}(t) = (A - a)G(t)(1 - G(t)) \geq 0$ with equality only for $G(t) = 1$. Therefore, $G(t) > G_s$ for all $t > 0$. By assumption, $\lambda(t_0) = 0 \leq \dot{\lambda}(t_0)$, but $\dot{\lambda}(t_0) = 2(A - a)(G_s - G(t_0)) < 0$, which is a contradiction. \square

Only when $A > 2a$, $A \geq 2F$ and $g_0 < G_s$, can there exist a \mathcal{B}_- arc. When such an arc exists, we may characterise the state and costate as functions of the switching time $t_0 > 0$ when the costate changes sign and the control switches. Equation (3b) is separable with constant coefficients when the control is constant. For constant control $u(t) = u$ and initial condition g_0 the solution is found to be

$$G(t; u, g_0) = \Sigma(u) \left[1 + \left(\frac{\Sigma(u)}{g_0} - 1 \right) e^{-(A-a-Fu)t} \right]^{-1}, \quad \Sigma(u) = \frac{A - a - Fu}{A - a}. \quad (14)$$

It follows that the state $G(t)$ is given by

$$G(t) = \begin{cases} G(t; 0, g_0), & t \in [0, t_0), \\ G(t - t_0; 1, g_1(t_0)), & t \in [t_0, T], \end{cases} \quad (15)$$

where

$$g_1(t_0) := G(t_0; 0, g_0) = \left[1 + \left(\frac{1}{g_0} - 1 \right) e^{-(A-a)t_0} \right]^{-1}. \quad (16)$$

This calculation allows us to bound the switching time by observing that $g_1(t_0) < G_s$, otherwise it follows from Proposition 9 that the control is not optimal. Requiring $g_1(t_0) \leq G_s$ yields the bound

$$t_0 < \frac{1}{A-a} \log \left[\left(1 - \frac{2a}{A} \right) \left(\frac{1}{g_0} - 1 \right) \right]. \quad (17)$$

The bound (17) is not tight, and we seek a more exact characterisation of t_0 by resolving the optimality conditions. The costate may be obtained on $[t_0, T]$, where $u(t) = 1$, by using the integrating factor

$$\begin{aligned} \Lambda(t) &:= \exp \left(\int^t A - a - F - 2(A-a)G(t-t_0; 1, g_1(t_0)) dt \right) \\ &= e^{(A-a-F)(t-t_0)} \left(e^{(A-a-F)(t-t_0)} + \frac{\Sigma(1)}{g_1(t_0)} - 1 \right)^{-2}, \end{aligned} \quad (18)$$

up to a positive multiplicative constant, which may be neglected without loss of generality. We thus find that, on $t \in [t_0, T]$, the costate is given by

$$\lambda(t) = \frac{\Lambda(T)}{\Lambda(t)} + \int_T^t [A - 2a - 2(A-a)G(s)] \frac{\Lambda(s)}{\Lambda(t)} ds. \quad (19a)$$

Using the shorthands $c := A - a - F$, $d(t_0) := -1 + \Sigma(1)/g_1(t_0)$, and $z(t; t_0) := e^{c(t-t_0)}$, we may rewrite the costate explicitly via

$$\begin{aligned} \Lambda(t) &= \frac{z(t; t_0)}{(z(t; t_0) + d(t_0))^2}, \\ \int^t \Lambda(t) dt &= -\frac{1}{c} \frac{1}{z(t; t_0) + d(t_0)}, \\ -\int^t 2(A-a)G(t)\Lambda(t) dt &= \frac{z(t; t_0)}{(z(t; t_0) + d(t_0))^2} + \frac{1}{z(t; t_0) + d(t_0)}. \end{aligned} \quad (19b)$$

Note that, since $A > 2a$, $A \geq 2F$, and $g_1(t_0) \leq G_s$, it follows that $c \neq 0$, $d(t_0) \geq 0$ and thus $z(t; t_0) + d(t_0) \neq 0$ for all $t > t_0$. Substituting (19b) into (19a), we find that the costate takes the form

$$\lambda(t) = 1 + \frac{z(t; t_0) + d(t_0)}{z(t; t_0)} \frac{a - F}{A - a - F} \left(1 - \frac{z(t; t_0) + d(t_0)}{z(T; t_0) + d(t_0)} \right). \quad (19c)$$

Therefore, the costate vanishes at the switching point, $\lambda(t_0) = 0$, if and only if

$$R(t_0) := \frac{e^{(A-a-F)(T-t_0)} - 1}{A - a - F} [(F - a) - (A - a)g_1(t_0)] - 1 = 0. \quad (20)$$

The switching time t_0 must satisfy equation (20). This equation does not appear to admit a closed-form solution, in general. Consider, for instance, any $F > a = 0$, and $A = F + \epsilon$, for a vanishingly small $\epsilon \ll 1$. Upon the change of variables $x = F(T - t_0) - 1$, the leading-order contributions give rise to the equation

$$xe^x = y, \quad \text{where} \quad y = \frac{e^{FT} - 1}{-1 + 1/g_0} \in (0, \infty), \quad (21)$$

which is transcendental [4].

Nevertheless, we may still say a great deal about solutions. The state $g_1(t_0)$ is a positive and strictly increasing function of t_0 , and so the residual $R(t_0)$ is a strictly decreasing function in t_0 that is free from singularities. The

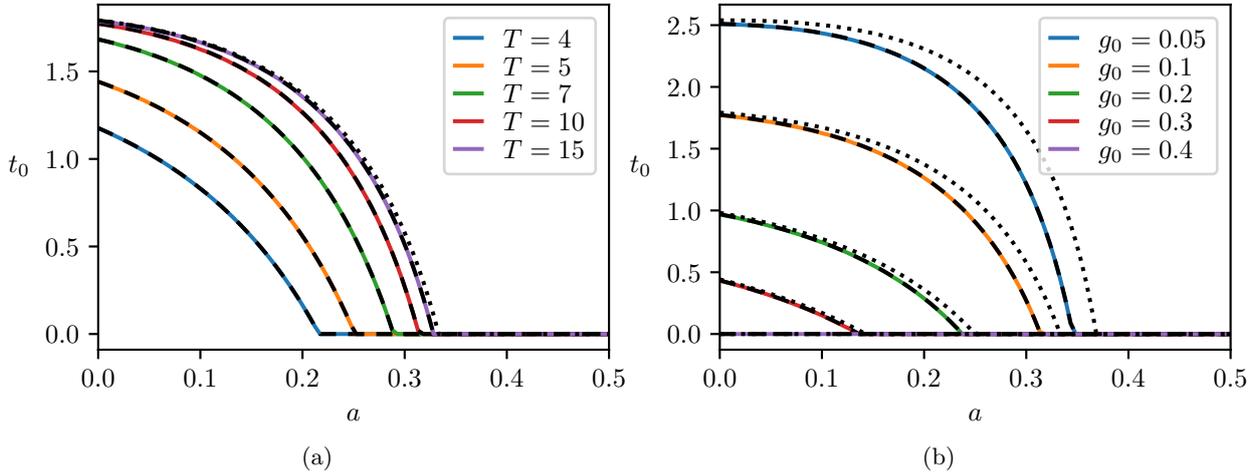


Figure 1: $A \geq 2F$. Switching times t_0 of the optimal control for various parameter values found using optimisation of the full ODE problem (coloured curves), numerical solution of equation (20) $R(t_0) = 0$ (dashed curves), and the approximate solution (23) (dotted curves). Parameters, when not specified, are $A = 1$, $F = 0.4$, $g_0 = 0.1$, and $T = 10$.

residual satisfies $R(T) = -1 < 0$ and thus there is an admissible solution $t_0 \in (0, T)$ if and only if $R(0) > 0$. A necessary condition for $R(0) > 0$ to hold is that the term in square brackets in (20) be positive, namely,

$$g_0 < \frac{F - a}{A - a}. \quad (22)$$

In particular, since $g_0 \in (0, 1]$ it must be that $F > a$. Physically, the condition (22) requires the initial condition to be sufficiently small (note that $(F - a)/(A - a) \leq G_s$) to make the $\mathcal{B}_-\mathcal{B}_+$ strategy worthwhile. When the condition (22) is satisfied, the time horizon T must be sufficiently large so that $R(0)$ can be positive. Ultimately, we arrive at the following result.

Proposition 10. *If $A \geq 2F$, the optimal control is a \mathcal{B}_+ arc unless $R(0) > 0$, in which case there is exactly one admissible solution of equation (20) characterising the switching time of the $\mathcal{B}_-\mathcal{B}_+$ control.*

We may also consider approximate solutions. Bearing in mind that we have found an upper bound (17) on t_0 and a lower bound on T , it is reasonable to consider the case of moderately large $T - t_0$ (assuming $g_0 = \mathcal{O}(1)$). In this case we see from (20) that the exponentially large term (multiplying the square brackets) must be balanced by the term in square brackets, which has to be exponentially small. Therefore, up to exponentially small corrections, we expect the solution to be given by t_0 that makes the term in square brackets vanish, namely,

$$t_0 = \frac{1}{A - a} \log \left[\frac{F - a}{A - F} \left(\frac{1}{g_0} - 1 \right) \right] \quad \text{when} \quad F > a, \quad (23)$$

while $t_0 = 0$ when $F \leq a$, that is, the optimal control is a \mathcal{B}_+ arc.

To verify the analytical solution, we implement a backward-Euler multiple-shooting direct numerical approach encoded in CasADi [2], a framework that performs automatic differentiation to produce a nonlinear program equipped with gradient information and solved by the IPOPT solver [11].

In fig. 1 we illustrate the switching times t_0 for the optimal control with weak induction $A \geq 2F$. We see perfect agreement between the full ODE problem (coloured curves) and the numerical solution of equation (20) $R(t_0) = 0$ (dashed curves). For $T \gtrsim 10$, the switching times are in close agreement with the large- T approximation (23) (dotted curves) to which they converge (fig. 1a). As the initial condition g_0 is decreased (fewer growers initially) the optimal switching time increases (fig. 1b), as more time is required to establish an optimal balance between the two population masses. In both cases, we plot results for parameter values of a up to $A/2 = 0.5$, and observe how $t_0 = 0$ for $a \geq F$ (and even before), as there is no solution to equation (20).

When $t_0 > 0$, the switching time is monotonically decreasing with a up until a critical value of a beyond which the switching time remains $t_0 = 0$ as the optimal control is just a \mathcal{B}_+ arc. We can find an implicit expression for the critical value of a at which this bifurcation occurs by noting that $R(0) = 0$, therefore,

$$\frac{e^{(A-a-F)T} - 1}{A - a - F} [(F - a) - (A - a)g_0] = 1. \quad (24)$$

Equation (24) is transcendental with respect to a but may be solved explicitly for g_0 .

We have found *necessary* conditions for the existence of a $\mathcal{B}_-\mathcal{B}_+$ extremal: when these conditions are not met the optimal control must be a \mathcal{B}_+ arc. When these conditions are met we have an extremal control but we have not ruled out the possibility that the \mathcal{B}_+ control is also extremal (though, in practice, we did not encounter a case where the \mathcal{B}_+ arc was optimal when a $\mathcal{B}_-\mathcal{B}_+$ extremal exists). Explicit formulae for the objective function are available for these solutions (though not reproduced here) and thus this too reduces to checking explicit formulae. Alternatively, sufficiency conditions or a uniqueness argument might rule out one of the extremals, although we do not pursue this here. Thus, when $A \geq 2F$, the entire solution is given in closed form, modulo one numerical root-finding procedure relevant in a subset of cases.

3.2 The case of strong induction $A < 2F$

In the case of strong induction, $A < 2F$, the control is capable of steering the state to G_s for any initial condition (given enough time and assuming that $A > 2a$ so that $G_s > 0$). Therefore, as opposed to the case of weak induction, a singular arc may arise.

Recall that the optimal control is of the form $(\mathcal{B}_-)(\mathcal{B}_+)(\mathcal{S})\mathcal{B}_+$. We proceed to refine this by proving that also the combination $\mathcal{B}_-\mathcal{B}_+\mathcal{S}$ cannot appear. Enumerating all remaining possible optimal control forms, we then find that the optimal control must be of one of the forms $\mathcal{B}_-\mathcal{S}\mathcal{B}_+$, $\mathcal{B}_+\mathcal{S}\mathcal{B}_+$, $\mathcal{S}\mathcal{B}_+$, $\mathcal{B}_-\mathcal{B}_+$, or \mathcal{B}_+ . As we will show, all of these formations are obtainable: the first three pertain to situations where there is sufficient time to optimally establish a singular arc (that is, while also optimally accounting for the terminal pay-off), and differ based on the initial conditions, $g_0 < G_s$, $g_0 > G_s$, and $g_0 = G_s$, respectively. The final two formations pertain to situations where there is insufficient time to optimally establish a singular arc, and again distinguished based on the initial condition, $g_0 < G_s$ and $g_0 \geq G_s$, respectively.

Proposition 11. *If $2a < A < 2F$, the optimal control cannot contain the arc combination $\mathcal{B}_-\mathcal{B}_+\mathcal{S}$.*

Proof. Assume by contradiction that such an arc form exists, where the \mathcal{B}_+ arc spans the interval (t_0, t_1) for $0 < t_0 < t_1 < T$. It follows that $\lambda(t) > 0$ on $t \in (t_0, t_1)$ and $\lambda(t_0) = \lambda(t_1) = 0$. It must also hold that $\dot{\lambda}(t_0) \geq 0 \geq \dot{\lambda}(t_1)$, and thus it follows from the costate equation (7) that $\dot{\lambda}(t_i) = 2(A - a)(G_s - G(t_i))$ for both $i = 0, 1$. Therefore, $G(t_0) \leq G(t_1)$.

From the state equation (3b) we see that, on a \mathcal{B}_+ arc, the state satisfies

$$\dot{G}(t) = (A - a)G(t) \left(1 - \frac{F}{A - a} - G(t) \right) = (A - a)G(t)(G_1(1) - G(t)). \quad (25)$$

Therefore, $G(t)$ is monotonically increasing on the \mathcal{B}_+ arc if $G(t_0) < G_1(1)$, monotonically decreasing on the \mathcal{B}_+ arc if $G(t_0) > G_1(1)$, and constant on the \mathcal{B}_+ arc if $G(t_0) = G_1(1)$. Since the arc following \mathcal{B}_+ is the singular arc, we know that $G(t_1) = G_s$. It follows from $2a < A < 2F$ that $G_1(1) < G_s$, and, therefore, the state cannot be increasing or constant on the \mathcal{B}_+ arc, since these trajectories will not reach G_s . We deduce that $G(t)$ must be monotonically decreasing along the \mathcal{B}_+ arc, in contradiction to earlier. \square

We now determine the critical time T_{crit} required to optimally establish a singular arc (and give the optimal control the turnpike structure discussed in section 2). For $T \leq T_{\text{crit}}$, no singular arc exists, and we are in a similar situation to the case of weak induction where the optimal control is of the form $(\mathcal{B}_-)\mathcal{B}_+$. For $T > T_{\text{crit}}$, one singular arc is established. The duration T_{crit} comprises the time it takes for $G(t)$ to evolve from $G(0) = g_0$ to $G(t) = G_s$, which we denote t_s , and the time it takes to evolve from $\lambda(t) = 0$ with $G(t) = G_s$ to $\lambda(t) = 1$ with $u(t) = 1$, which we denote T_s .

If $g_0 = G_s$ then $t_s = 0$. If $g_0 < G_s$ then the initial arc will be a \mathcal{B}_- arc and to calculate t_s we take the constant control $u(t) = 0$. Using the solution (15), we obtain t_s by solving $G(t_s; 0, g_0) = G_s$ to find that

$$t_s = \frac{1}{A - a} \log \left[\left(1 - \frac{2a}{A} \right) \left(\frac{1}{g_0} - 1 \right) \right] \quad \text{when} \quad g_0 \leq G_s. \quad (26a)$$

This is none other than the bound derived in (17). Similarly, for $g_0 > G_s$, solving $G(t_s; 1, g_0) = G_s$ yields

$$t_s = \frac{1}{A - a - F} \log \left\{ \left[1 - \frac{1}{g_0} \left(1 - \frac{F}{A - a} \right) \right] \frac{A - 2a}{2F - A} \right\} \quad \text{when} \quad g_0 > G_s \quad \text{and} \quad A - a - F \neq 0. \quad (26b)$$

When $c = A - a - F = 0$, the solution (26b) is to be understood in the limit of $c \rightarrow 0$, in which case

$$t_s = \frac{2}{F - a} - \frac{1}{g_0 F} \quad \text{when} \quad g_0 > G_s \quad \text{and} \quad A - a - F = 0. \quad (26c)$$

The terminal nonsingular arc, on $[T - T_s, T]$, of duration T_s , is characterised by the costate evolving from $\lambda(T - T_s) = 0$ to $\lambda(T) = 1$. Since the problem is homogeneous in time, it will be convenient to translate the time

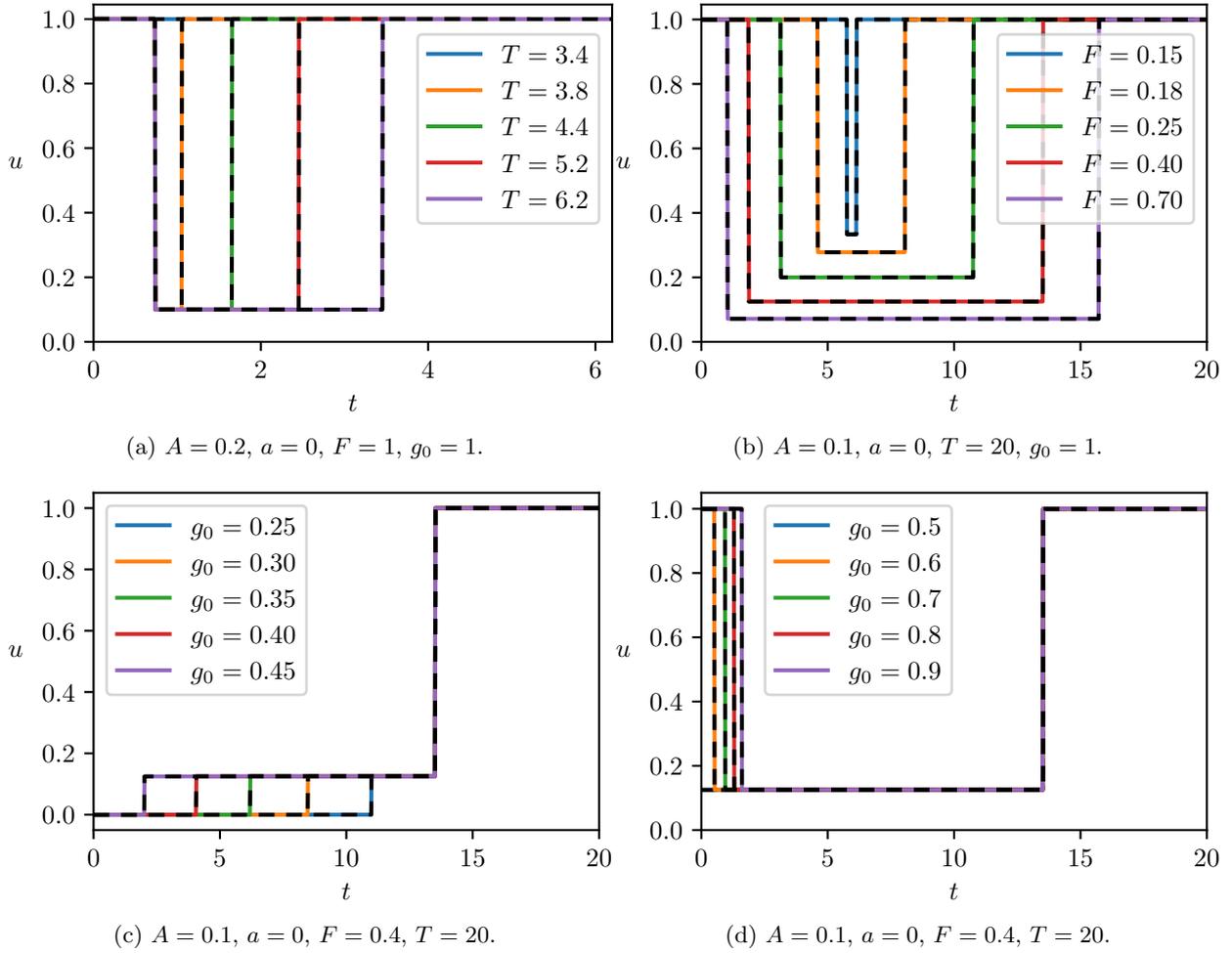


Figure 2: $A < 2F$. Optimal controls for various parameters A , a , F , and time horizons T . Coloured lines show numerical solutions (for 5000 discrete control points), black dotted lines show analytical solutions.

interval to $[0, T_s]$, and consider the state to solve (3b) subject to the initial condition $G(0) = G_s$ and the costate to solve (7) with the conditions $\lambda(0) = 0$ and $\lambda(T_s) = 1$, where $u(t) = 1$ throughout the interval. This solution may be expressed via (19) with $t_0 = 0$, $g_0 = G_s$, and $T = T_s$. Upon enforcing the initial condition $\lambda(0) = 0$, we obtain an equation for the terminal duration T_s , which may be expressed as $R(0)|_{g_0=G_s, T=T_s} = 0$:

$$e^{(A-a-F)T_s} - \frac{A-2a}{2F-A} = 0. \quad (27)$$

When $2a < A < 2F$, there exists a unique solution $T_s > 0$ to equation (27), namely,

$$T_s = \frac{1}{A-a-F} \log\left(\frac{A-2a}{2F-A}\right), \quad \text{when} \quad A-a-F \neq 0. \quad (28a)$$

When $c = A - a - F = 0$, the duration T_s may be found by considering the expression (28a) in the limit $c \rightarrow 0$, to obtain

$$T_s = \frac{2}{F-a}, \quad \text{when} \quad A-a-F = 0. \quad (28b)$$

We consolidate the calculations in the following result.

Proposition 12. *If $2a < A < 2F$ and $T \leq T_{\text{crit}} := t_s + T_s$, there is no singular arc.*

In fig. 2 we show optimal controls for the case of strong induction ($A < 2F$) with singular arcs of the forms $\mathcal{B}_+ \mathcal{S} \mathcal{B}_+$, $\mathcal{B}_- \mathcal{S} \mathcal{B}_+$, and $\mathcal{S} \mathcal{B}_+$. The agreement between the numerical and analytical results remains perfect. We see how the singular arc emerges as T increases from subcritical $T < T_{\text{crit}}$ to supercritical $T > T_{\text{crit}}$ (fig. 2a where $T_{\text{crit}} \approx 3.5$). As the induction becomes stronger with increasing F , the singular arc increases in duration (fig. 2b): the induction is able to faster establish the state $G(t) = G_s$, optimal for the running pay-off, and requires less

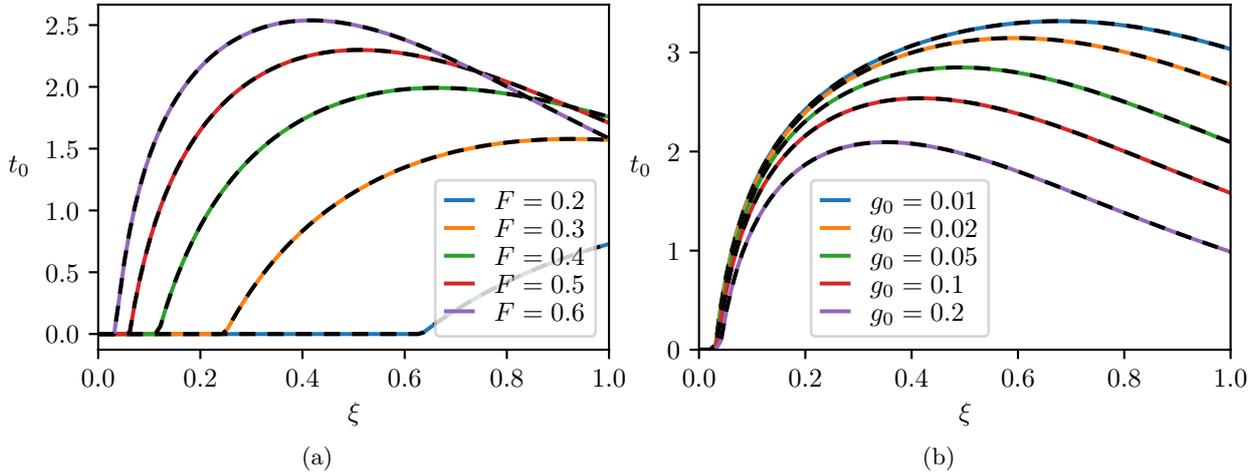


Figure 3: $A < 2F$ and $T \leq T_{\text{crit}}$. Switching times t_0 of the optimal control for various parameter values found using optimisation of the full ODE problem (coloured curves) and numerical solution of equation (20) $R(t_0) = 0$ (dashed curves). The horizontal axis shows the parameter ξ , by which we set $A = 2a + \xi(2F - 2a)$ to interpolate between $2a$ and $2F$. Parameters, when not specified, were $a = 0$, $F = 0.4$, $g_0 = 0.1$, and $T = 5$.

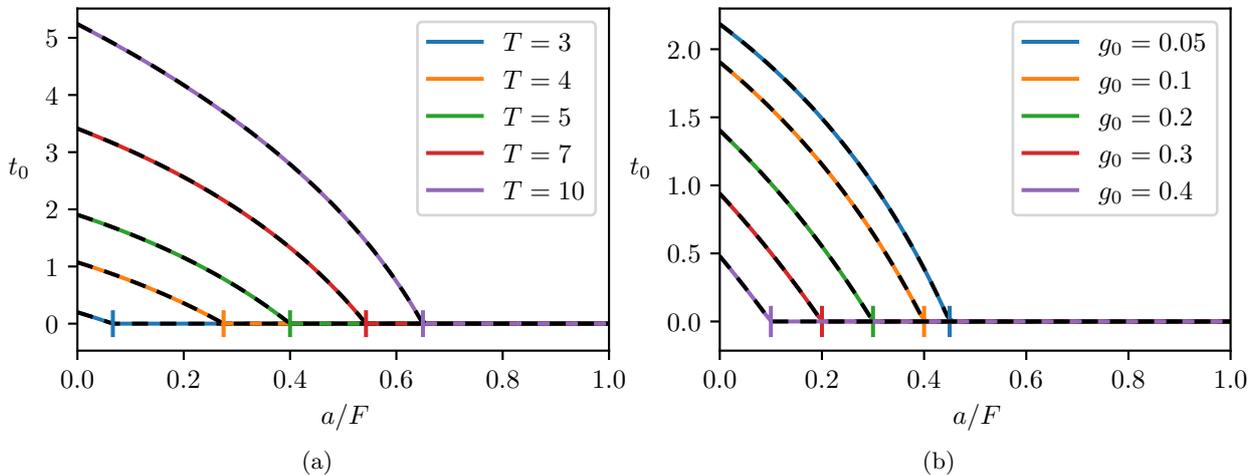


Figure 4: $A - a - F = 0$ and $T \leq T_{\text{crit}}$. Switching times t_0 of the optimal control for various parameter values found using optimisation of the full ODE problem (coloured curves) and numerical solution of equation (29) $S(t_0) = 0$ (dashed curves). The horizontal axis shows the parameter $a \in (0, F)$. Parameters, when not specified, were $A = a + F$, $F = 0.4$, $g_0 = 0.1$, and $T = 5$. Vertical lines show the bifurcation point a given in (30) beyond which the optimal control is simply a \mathcal{B}_+ arc, that is, $t_0 = 0$.

time of maximum induction for the terminal pay-off near the terminal time $t = T$. In figs. 2c and 2d, we explore the impact of initial conditions $G(0) = g_0$ where all other parameters are kept fixed. When $a = 0$, the optimal running pay-off state is an even split between growers and producers: $G_s = 1/2$. For initial conditions below the singular level, $g_0 < G_s$, the optimal control arc first has a \mathcal{B}_- arc with minimal induction (fig. 2c). This is sustained for longer as the initial grower mass g_0 decreases (reminiscent of fig. 1b). When $g_0 = G_s$ the initial arc is singular \mathcal{S} , while for $g_0 > G_s$, the initial arc is maximal induction \mathcal{B}_+ (fig. 2d). For all of the controls in figs. 2c and 2d the terminal phase is identical: once the singular arc is established, the discrepancy due to different initial conditions is eliminated.

When $T \leq T_{\text{crit}}$, no singular arc is present and the control is of the form $(\mathcal{B}_-)\mathcal{B}_+$. We may again leverage the solutions (15) and (19) for a constant control $u(t) = u$ and apply the same approach of seeking an admissible solution to the equation $R(t_0) = 0$ for the residual $R(t_0)$ defined in (20). The only difference is that, in this case, the value $c = A - a - F$ is not necessarily positive, but can also be negative or zero. When $c < 0$ it suffices to note that $R(t_0)$ remains a monotonically decreasing function of t_0 with no singularities, and, therefore, the previous condition is preserved: an admissible solution $t_0 \in (0, T)$ exists if and only if $R(0) > 0$.

Some care is required in the case of $c = 0$, which is removably singular (for example, see the solution (14) for $u = 1$) and must be tackled in the limit as $c \rightarrow 0$ as $R(t_0)$ is not strictly defined at $c = 0$. We find that a costate

solution vanishing at t_0 exists if and only if

$$S(t_0) := \lim_{c \rightarrow 0} R(t_0) = (T - t_0) [(F - a) - Fh_1(t_0)] - 1 = 0, \quad (29a)$$

where

$$h_1(t_0) := \lim_{c \rightarrow 0} g_1(t_0) = \left[1 + \left(\frac{1}{g_0} - 1 \right) e^{-Ft_0} \right]^{-1}. \quad (29b)$$

The function $S(t_0)$ is monotonic decreasing in t_0 and $S(T) = -1 < 0$, therefore, an admissible solution $t_0 \in (0, T)$ exists if and only if $S(0) > 0$, which may be written as $a < F(1 - g_0) - 1/T$. The condition (22) is necessary here too, and thus similarly $F > a$ must hold and T must be sufficiently large in order for an admissible solution to exist. We recap the case with no singular arc in the following result.

Proposition 13. *If $2a < A < 2F$ and no singular arc is formed, there is an extremal $\mathcal{B}_-\mathcal{B}_+$ control if and only if: $R(0) > 0$ when $A - a - F \neq 0$, $S(0) > 0$ when $A - a - F = 0$.*

In fig. 3 we illustrate switching times t_0 for the subcritical case of strong induction ($A < 2F$ and $T \leq T_{\text{crit}}$). The analytical and numerical results remain indistinguishable. In this case, the absence of sufficient time to establish the singular arc requires a switching time t_0 that balances between an initial arc approaching (but not reaching) the optimal running pay-off state G_s and a final arc increasing the terminal yield. This trade-off gives rise to a fascinating non-monotonicity exhibited by the switching time t_0 as the growth rate A varies. For increasing induction strength F the switching time t_0 increases (for fixed A), reflecting the fact that a longer time can be spent approaching G_s with minimal induction before inducing to increase the terminal yield (fig. 4a). As in fig. 1b, a smaller initial grower population justifies a longer arc of minimal induction (fig. 4b).

In fig. 4 we plot the results for the removably singular subcritical case ($A - a - F = 0$ and $T < T_{\text{crit}}$). The analytical and numerical results are identical. Just as for the case of weak induction, we could consider the case of asymptotically large $T - t_0$ and $g_0 = \mathcal{O}(1)$. However, subcriticality imposes an upper bound on T , while the value t_s in (26) serves as an upper bound on t_0 , therefore the assumption is severely limited. Nevertheless, we may determine bifurcation points, where the solution passes through $t_0 = 0$, satisfying (24). While the equation remains transcendental (except with respect to g_0), in the limiting case of $c \rightarrow 0$ it takes the simpler form $S(0) = 0$, which we write as

$$F(1 - g_0) - a = \frac{1}{T}. \quad (30)$$

Equation (30) admits explicit solutions with respect to a , F , g_0 , and T . Solutions for a are illustrated as coloured vertical lines in fig. 4.

4 Conclusions

The analysis in section 3 involves partitioning the parameter space into several regions and subregions. Combining these cases serves the dual purpose of summarising the results and concretely demonstrating that the entire parameter space is covered, as illustrated by the flowchart in fig. 5.

In this work, we study the optimal control problem of maximising protein yield from a microbial consortium generated via light-inducible differentiation. The model finds important application in bioproduction, and its analysis allows for the fast computation of open-loop optimal controls that may be periodically updated via MPC to close the loop [7].

In applying Pontryagin's maximum principle, we partition the parameter space into several regions. One collection of regions admit explicit optimal controls, while in the remainder of parameter space the optimal control is of known structure where the control switching time is given as the solution of a transcendental equation. We prove that, in these latter cases, the solution of the equation exists on a known compact interval and is unique, and thus amenable to standard numerical root-finding methods. We verify our analytical results via direct numerical solution of the optimal control problem, finding excellent agreement between the two approaches. We hope that these results prove useful in bioproduction processes, as well as providing a useful starting point for the optimal control of related models.

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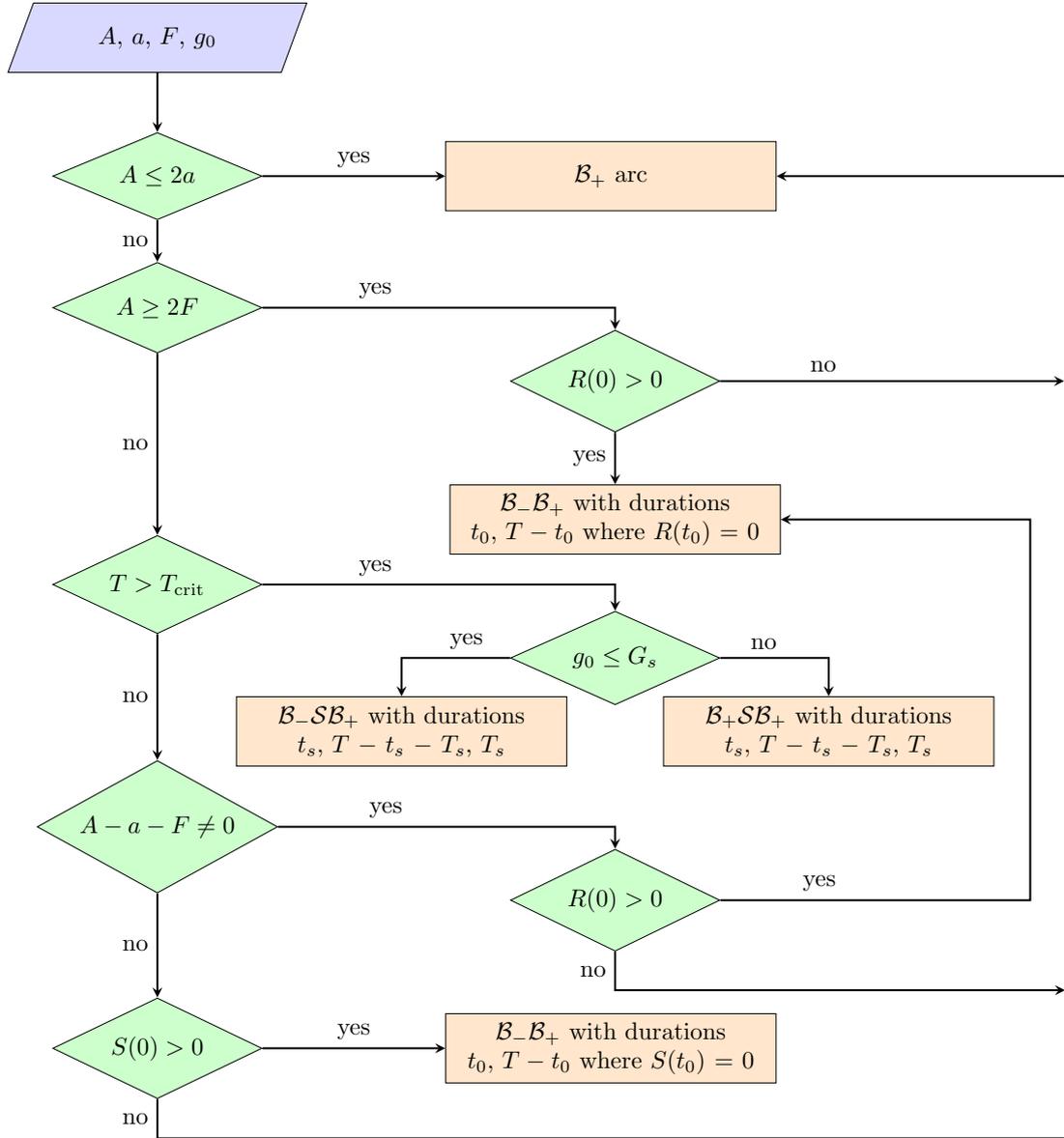


Figure 5: Flowchart summarising the optimal control synthesis for the ODE problem (3). Quantities G_s , $R(t_0)$, $S(t_0)$, t_s , and T_s are defined in (10), (20), (29), (26), (28), respectively, and are all functions of the input parameters A , a , F , and g_0 , with $T_{\text{crit}} = t_s + T_s$.

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