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Optimal allocation control in microbial growth under a heat-shock*

Javier Innerarity Imizcoz¹, Agustín G. Yabo², Walid Djema³, Francis Mairet⁴ and Jean-Luc Gouzé¹

Abstract—Resource allocation models are a highly useful tool to study microbial growth in a variety of contexts. We use here a model of this kind describing the metabolism of a micro-organism subjected to a heat-shock. Under extreme temperatures, proteins have a higher tendency to unfold and lose their ability to perform their function, which is counteracted by an increase in the production of folding-assisting chaperones. The model considers a two-dimensional control, representing precursors allocation to the production of chaperones and ribosomes, with the remainder going to the metabolic machinery. We are interested in determining the control that maximizes growth rate following a temperature change. We begin with a theoretical analysis of the resulting optimal control problem (OCP) by use of Pontryagin’s Maximum Principle (PMP). We show that this control follows a bang-bang structure, and characterize and give analytical expressions for some of the singular arcs that can emerge. We use the numerical resolution package `OptimalControl.jl` to solve the OCP in fixed final time in the case of a heat-shock from 37°C to 42 °C. The resulting control presents a simple structure consisting of an arc maximizing chaperone production followed by a constant arc corresponding to the optimal equilibrium in the different internal concentrations at the new temperature, in line with biological observations. Finally, we show how the optimal response to a heat-shock follows this structure independently of the temperature prior to the shock.

I. INTRODUCTION

Studying microbial growth is of great interest in many fields of biology. The potential applications range from deepening our understanding of ecosystems, to which micro-organisms are essential, to optimizing microbial bioprocesses. Appropriate mathematical models are often found to be greatly helpful in simplifying this complex question. In particular, resource allocation models can predict and explain many well-known naturally-evolved strategies in bacterial growth like as the production of stress response proteins [1] or diauxic growth in environments with substitutable substrates [2], [3]. They are also accurate at predicting experimentally-observed growth laws, such as the linear relationship between growth rate and ribosome concentration in balanced growth [4], [5], [6].

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Most of these works have focused on the effect of substrate limitation on the resource allocation of cells. Another fundamental factor affecting the ability of micro-organisms to grow is temperature. An increase in temperature has the general effect of accelerating reaction kinetics inside the cell. However, at extreme temperature, proteins have a tendency to unfold. Since only correctly folded proteins can effectively perform their function, a response of the cell to temperature changes is needed. Many micro-organisms react to this kind of stress by increasing their production of chaperones, which can refold unfolded proteins [7], [8], [9].

We are interested in studying the immediate response of a cell when subjected to a heat-shock. This sudden increase to an extreme temperature could be caused by a physical displacement to a warmer medium, for example. In order to study this response, we use the model defined in [10], which was used to solve the associated static optimization problem (i.e. in balanced growth conditions). Here, we define a dynamic optimal control problem. We seek the resource allocation control that is able to maximize the growth rate of a cell, following the common assumption that micro-organisms have evolved according to this criteria. In particular, we study the relation between the dynamic and the static optimal resource allocation.

The paper is organized as follows. In Section II, we introduce the model that we use. We formulate the optimal control problem (OCP) in Section III. Section IV is devoted to the analysis of this problem through Pontryagin’s Maximum Principle (PMP). We numerically solve the OCP in the case of a heat-shock from 37°C to 42 °C in Section V, and we use this solution to find the general structure of the optimal control in a heat-shock to the latter temperature.

II. MODEL FORMULATION

We use the model of bacterial metabolism under temperature fluctuations proposed by [10] to represent the effect of resource allocation on bacterial growth under the influence of temperature changes. The reader can find a diagram of this model in Figure 1. It features two macroreactions. First, the metabolic machinery (m) of the cell absorbs substrate (s) from its external medium and converts it into precursors (p).

The second reaction consists of the ribosome of the cell (r) producing proteins from their precursors. Since only correctly folded proteins are able to perform their function, for each type of protein $x \in \{r, m\}$, the model introduces the variables x_f and x_u , with $x_f + x_u = x$, which represent the proportion of proteins of each type folded and unfolded, respectively.

Proteins have a tendency to unfold and thus lose their ability to perform their function, which is stronger at more extreme temperatures. To counteract this tendency, the ribosomes r of the cell also produce chaperones c , whose role is to catalyze the folding of the other macromolecules. Finally, the cell also produces a fraction, which is commonly assumed to be constant, of so-called house-keeping proteins q .

Therefore, the ribosomes of the cell produce c, m, r and q . The fraction of the biomass produced that corresponds to each type x is denoted by α_x .

The rates of the two macro reactions are given by $v_M(s, m_f)$ and $v_R(p, r_f)$, respectively.

From mass balance, the model results in the following equations.

$$\begin{cases} \frac{dp}{dt} = v_M(s, m_f) - (1+p)v_R(p, r_f), \\ \frac{dc}{dt} = (\alpha_c(t) - c)v_R(p, r_f), \\ \frac{dm}{dt} = (\alpha_m(t) - m)v_R(p, r_f), \\ \frac{dr}{dt} = (\alpha_r(t) - r)v_R(p, r_f), \\ \frac{dq}{dt} = (\alpha_q(t) - q)v_R(p, r_f), \end{cases}$$

where each variable represents the concentration of each biomolecules in mass to total mass of the cell, This total mass is assumed to be equal to the total protein mass, i.e. the mass of p is assumed to be negligible with respect to the mass of proteins. Therefore $c + m + r + q = 1$. Since the functions α_i represent fractions of the total biomass produced by the ribosomes, we also have $\alpha_c + \alpha_m + \alpha_r + \alpha_q = 1$. We can assume that the cell uses a separate regulation mechanism to maintain the concentration of house-keeping proteins constant [11], [12], that is $q(t) = \alpha_q(t) = q \forall t$, so we can remove \dot{q} . We define the constant $r_{\max} = 1 - q$. We also remove \dot{m} by using the identity $m = 1 - q - r - c = r_{\max} - r - c$.

We use the classic Michaelis-Menten kinetics

$$v_M(s, m_f, T) = k_M(T) \frac{s}{K_s + s} m_f,$$

$$v_R(p, r_f, T) = k_R(T) \frac{p}{K_p + p} r_f,$$

where T is the temperature of the medium and $k_M(T)$ and $k_R(T)$ are Arrhenius functions described in detail in [10]. We also use the slow-fast approximation stated in [10] which considers the (un)folding dynamics at quasi steady-state:

$$m_f = \frac{k_f(T)c}{k_u(T) + k_f(T)c} m, \quad r_f = \frac{k_f(T)c}{k_u(T) + k_f(T)c} r.$$

We define $F(T) = k_u(T)/k_f(T)$, which we interpret as the tendency for proteins to be unfolded. That is, if the chaperone concentration c remains constant, higher values of $F(T)$ mean a higher concentration of unfolded proteins

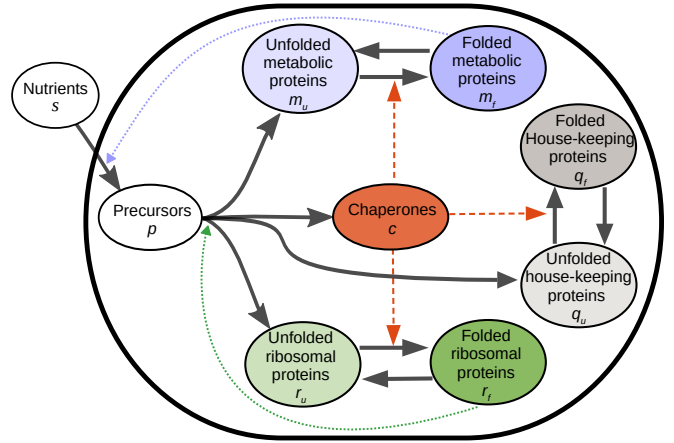


Fig. 1. Diagram of the model of resource allocation in bacteria subjected to temperature changes, as given in [10].

m_f and r_f . This finally gives:

$$\begin{cases} \frac{dp}{dt} = k_M(T) \frac{s}{K_s + s} \frac{c}{F(T) + c} (r_{\max} - r - c) \\ \quad - (1+p)k_R(T) \frac{p}{K_p + p} \frac{c}{F(T) + c} r, \\ \frac{dc}{dt} = (\alpha_c(t) - c)k_R(T) \frac{p}{K_p + p} \frac{c}{F(T) + c} r, \\ \frac{dr}{dt} = (\alpha_r(t) - r)k_R(T) \frac{p}{K_p + p} \frac{c}{F(T) + c} r, \end{cases} \quad (1)$$

for $0 \leq p, c, r$ and $r + c \leq r_{\max}$.

The functions α_c and α_r are controls the cell can exert on its internal resource allocation. We suppose that the cell can set the value of this couple at any given time $t \geq 0$ to any positive value satisfying $\alpha_r + \alpha_c \leq r_{\max}$. Notice that $\alpha_m = r_{\max} - \alpha_r - \alpha_c$.

III. OPTIMAL CONTROL PROBLEM

A. Problem Definition

We consider the maximization problem established by [10], which is based on the common assumption that evolution has led micro-organisms to optimize their growth rate. In its dynamic version, this problem can be expressed as follows. Find

$$\max_{\alpha_c, \alpha_r \in \mathcal{U}} \int_0^\tau v_R(t) dt \quad (2)$$

for a certain final time $\tau > 0$, where $v_R(t) = k_R(T) \frac{p(t)}{K_p + p(t)} \frac{c(t)}{F(T) + c(t)} r(t)$, the state variables (p, c, r) follow 1 and \mathcal{U} is the set of measurable functions $(\alpha_c, \alpha_r) : [0, \tau] \rightarrow \mathbb{R}^2$ such that

$$0 \leq \alpha_c(t), \quad 0 \leq \alpha_r(t), \quad \alpha_c(t) + \alpha_r(t) \leq r_{\max} \quad \forall t \in [0, \tau].$$

Finally, we set initial conditions $(p, c, r)(0) = (p_0, c_0, r_0)$, where all variables are initially positive and verify $c_0 + r_0 \leq r_{\max}$.

B. Static Optimal Point

As shown in [10], the static optimal, which is the point (p, c, r) given by the solution of the constrained optimization problem

$$(\alpha_c^{\text{opt}}, \alpha_r^{\text{opt}}) = \arg \max_{\alpha_c, \alpha_r \in U} v_R$$

such that $\frac{dp}{dt} = \frac{dc}{dt} = \frac{dr}{dt} = 0$,

where

$$U = \{(\alpha_c, \alpha_r) \text{ such that } 0 \leq \alpha_c \leq r_{\max}, \\ 0 \leq \alpha_r \leq r_{\max}, \alpha_c + \alpha_r \leq r_{\max}\},$$

is the set of admissible controls, is the temperature-dependent point

$$\begin{cases} p_{\text{opt}}(T) = \sqrt{\frac{s}{K_s + s} \frac{k_M^{\text{ref}} K_p}{k_R^{\text{ref}}}} \\ c_{\text{opt}}(T) = F(T) \left(-1 + \sqrt{1 + \frac{r_{\max}}{F(T)}} \right) \\ r_{\text{opt}}(T) = (r_{\max} - c_{\text{opt}}) \frac{p_{\text{opt}}(K_p + p_{\text{opt}})}{K_p + 2K_p p_{\text{opt}} + p_{\text{opt}}^2} \end{cases}$$

corresponding to the control $\alpha_c, \alpha_r = c_{\text{opt}}, r_{\text{opt}}$. Notice that p_{opt} does not depend on the temperature, and that the optimal concentrations r_{opt} and c_{opt} are, respectively, lower and higher at more extreme temperatures (i.e. with higher values of $F(T)$). This is consistent with the cell needing more chaperones when other proteins have a higher tendency to unfold, at the cost of having less metabolic machinery and fewer ribosomes.

IV. PONTRYAGIN'S MAXIMUM PRINCIPLE

A. Statement of the Principle

We are considering the case of a temperature change at $t = 0$. Since the temperature T is constant at $t > 0$, we can rewrite the system in this new form:

$$\begin{cases} \frac{dp}{dt} = \bar{w}_S w_c(c) (r_{\max} - r - c) - (p + 1) w_R(p) w_c(c) r, \\ \frac{dc}{dt} = (\alpha_c(t) - c) w_R(p) w_c(c) r, \\ \frac{dr}{dt} = (\alpha_r(t) - r) w_R(p) w_c(c) r, \end{cases}$$

where $\bar{w}_s = k_M(T) \frac{s}{K_s + s}$, $w_R(p) = k_R(T) \frac{p}{K_p + p}$ and $w_c(c) = \frac{c}{F(T) + c}$.

The Hamiltonian given by Pontryagin's Maximum Principle [13] writes

$$H = H(t, p, c, r, \lambda, \lambda_0, \alpha_c, \alpha_r) = \\ \left(\left[\bar{w}_S (r_{\max} - r - c) - (p + 1) w_R(p) r \right] \lambda_p + \right. \\ \left. (\alpha_c - c) w_R(p) r \lambda_c + (\alpha_r - r) w_R(p) r \lambda_r + w_R(p) r \right) w_c(c),$$

where adjoint state is $\lambda = (\lambda_p, \lambda_c, \lambda_r)$ and the constant $\lambda_0 = 1$ (the normal case of PMP) by the transversality conditions

$$\lambda(t_f) = (0, 0, 0),$$

and by the condition

$$(\lambda(t), \lambda_0) \neq 0 \forall t \in [0, t_f].$$

The Hamiltonian can be decomposed as

$$H = H_0 + \alpha_c H_c + \alpha_r H_r$$

with

$$H_0 = \left(\left[\bar{w}_S (r_{\max} - r - c) - (p + 1) w_R(p) r \right] \lambda_p \right. \\ \left. - c w_R(p) r \lambda_c - r w_R(p) r \lambda_r + w_R(p) r \right) w_c(c), \\ H_c = w_R(p) w_c(c) r \lambda_c, \\ H_r = w_R(p) w_c(c) r \lambda_r.$$

It is constant since the system of differential equations is autonomous.

The dynamics of the adjoint state are

$$\dot{\lambda}_p = -\frac{w'_R(p)}{w_R(p)} \left[H - \bar{w}_s (r_{\max} - r - c) w_c(c) \lambda_p \right] \\ + w_R(p) w_c(c) r \lambda_p, \\ \dot{\lambda}_c = -\frac{w'_c(c)}{w_c(c)} H + \bar{w}_s w_c(c) \lambda_p + H_c, \\ \dot{\lambda}_r = -\frac{1}{r} \left[H - \bar{w}_s (r_{\max} - c) w_c(c) \lambda_p \right] + H_r.$$

At final time, we have

$$H(t_f) = w_R(p(t_f)) w_c(c(t_f)) r(t_f) > 0.$$

Finally, we have the maximization condition

$$H(t, p, c, r, \lambda, \lambda_0, \alpha_c(t), \alpha_r(t)) = \\ \max_{u, v \in U} H(t, p, c, r, \lambda, \lambda_0, u, v) \text{ a.e. on } [0, +\infty).$$

The following lemma is immediate.

Lemma 4.1: $\lambda_p > 0$ for all $t \in [0, t_f]$.

Proof: The Hamiltonian is constant and positive at final time, therefore always positive. From the dynamics of λ_p , if this adjoint variable is zero, then its derivative is negative. Therefore, the set $\lambda_p < 0$ is forward invariant, and having $\lambda_p(t) \leq 0$ for some $t < t_f$ would contradict the transversality condition $\lambda_p(t_f) = 0$. ■

B. Characterization of the Control

Since the Hamiltonian is affine in both α_c and α_r , by the Hamiltonian maximization condition, the value of these controls is determined by the relative value of λ_c and λ_r . Indeed, since the expression $w_R(p) w_c(c) r$, which is the common factor of H_c and H_r , is always positive, the maximization condition is equivalent to

$$\lambda_c \alpha_c(t) + \lambda_r \alpha_r(t) = \max_{u, v \in U} (\lambda_c u + \lambda_r v).$$

The value of the control depends on the value of these two adjoint states. For most possible values of the latter, the

maximization condition can be solved and the control follows a bang arc (BA) in which one of its components α_c , α_r or α_m is set to the maximum r_{\max} and the other two are equal to zero:

$$(\alpha_c, \alpha_r) = \begin{cases} (0, 0) & \text{if } \lambda_c < 0, \lambda_r < 0 \quad (\alpha_m = r_{\max}) \\ (r_{\max}, 0) & \text{if } \lambda_c > \lambda_r, \lambda_c > 0 \quad (\alpha_m = 0) \\ (0, r_{\max}) & \text{if } \lambda_c < \lambda_r, \lambda_r > 0 \quad (\alpha_m = 0) \end{cases}$$

In the cases where the value of the control is not directly deductible from the maximization condition, the control is said to be in a singular arc, and further computations are needed in order to determine its value. In those cases, we can have the following singular arcs.

$$(\alpha_c, \alpha_r) = \begin{cases} (\alpha_{c,s}, 0) & \text{if } \lambda_c > \lambda_r, \lambda_c = 0 \quad (\alpha_m > 0) \\ (0, \alpha_{r,s}) & \text{if } \lambda_c < \lambda_r, \lambda_r = 0 \quad (\alpha_m > 0) \\ (\tilde{\alpha}_{c,s}, \tilde{\alpha}_{r,s}) & \text{if } \lambda_c = \lambda_r, \lambda_c > 0 \quad (\alpha_m = 0) \\ (c_{\text{opt}}, r_{\text{opt}}) & \text{if } \lambda_c = 0, \lambda_r = 0 \quad (\alpha_m > 0), \end{cases}$$

where $\tilde{\alpha}_{c,s} + \tilde{\alpha}_{r,s} = r_{\max}$. The values of these singular arcs can be deduced by differentiation of the relevant equation(s) among $\lambda_c = 0$, $\lambda_r = 0$ and $\lambda_c = \lambda_r$. In the following propositions, we study the value these arcs take in the first, second and last case. The order of a singular control $\alpha_i > 0$ is the smaller k such that

$$\frac{d^{2k} \lambda_i}{dt^{2k}} \neq 0.$$

Such an arc is said to be a feedback if it can be expressed analytically as a function of only the state variables.

Proposition 1: A singular arc on α_c when $\lambda_c = 0$ over an interval is a first-order feedback control given by the expression

$$\alpha_{c,s}(p, c, r) = c - \frac{\bar{w}_s \frac{w'_R(p)}{w_R^2(p)r} \left[r + \frac{w_c(c)}{w'_c(c)} - (r_{\max} - c) \right] - 1}{\phi(c)}. \quad (3)$$

where

$$\phi(c) = 2 \frac{w'_c(c)}{w_c(c)} - \frac{w''_c(c)}{w'_c(c)} > 0.$$

Proof: Suppose $\lambda_c = 0$ over an interval. Differentiating yields

$$-w'_c(c)H + \bar{w}_s w_c^2(c) \lambda_p = 0, \quad (4)$$

which means that

$$H = \bar{w}_s \frac{w_c^2(c)}{w'_c(c)} \lambda_p.$$

Differentiating a second time yields (3). ■

Proposition 2: A singular control $\alpha_{r,s}$ of order at least 2 appears when $\lambda_r = 0$ over an interval. Moreover, it is a feedback control.

Proof: Suppose $\lambda_r = 0$ over an interval. Differentiating yields

$$H - \bar{w}_s (r_{\max} - c) w_c(c) \lambda_p = 0, \quad (5)$$

which means that

$$H = \bar{w}_s (r_{\max} - c) w_c(c) \lambda_p.$$

Differentiating once more gives

$$\begin{aligned} \bar{w}_s \dot{c} w_c(c) \lambda_p - \bar{w}_s (r_{\max} - c) w'_c(c) \dot{c} \lambda_p \\ - \bar{w}_s (r_{\max} - c) w_c(c) \dot{\lambda}_p = 0. \end{aligned}$$

We replace derivatives and simplify common factors and we get

$$\begin{aligned} [w_c(c) - (r_{\max} - c) w'_c(c)] \lambda_p (\alpha_c - c) w_R(p) r \\ - (r_{\max} - c) \left[-\frac{w'_R(p)}{w_R(p)} (\bar{w}_s r w_c(c) \lambda_p) + w_R(p) w_c(c) r \lambda_p \right] \\ = 0. \end{aligned}$$

Simplifying factors in every term yields

$$\begin{aligned} \left[\frac{w_c(c)}{w'_c(c)} - (r_{\max} - c) \right] (\alpha_c - c) \\ - (r_{\max} - c) \left[1 - \frac{w'_R(p)}{w_R^2(p)} \bar{w}_s \right] \frac{w_c(c)}{w'_c(c)} = 0. \end{aligned} \quad (6)$$

We can observe from the latter expression that it is not possible to solve for α_r , and thus further differentiation is required to obtain an explicit expression of α_r , which proves that the singular control is of at least order 2. Additionally, since the latter expression depends only on the state (and not on the adjoint states), its successive derivatives also depend only on the state, and thus, the expression of α_r can only depend on the state. ■

Proposition 3: A singular arc on both α_c and α_r appears when $\lambda_c = \lambda_r = 0$ over an interval. The controls are then first- and at-least-second-order singular controllers, respectively, given by $(\alpha_c, \alpha_r) = (c_{\text{opt}}, r_{\text{opt}})$. Additionally, the state is on the point $(p, c, r) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T)$ defined and computed in Subsection III-B.

Proof: Suppose $\lambda_r = \lambda_c = 0$ over an interval. Combining conditions (4) and (5) imply $c = c_{\text{opt}}(T)$ is constant, and so $\alpha_c = c$, and by 6 $p = p_{\text{opt}}$. By equating the derivative of p to zero, we deduce that $r = r_{\text{opt}}(T)$, and since r is constant, we have $\alpha_r = r$. The order of the controls is given by Propositions 1 and 2. ■

These singular arcs can result in quite complicated optimal controls, such as the one shown in Figure 2, which model a temperature decrease from $T = 42^\circ\text{C}$ to $T = 37^\circ\text{C}$.

V. THE HEAT-SHOCK RESPONSE

A. Numerical Resolution of the OCP

We are interested in the case of a heat-shock, where a cell used to a normal temperature gets subjected to an extreme high temperature. For this reason, we have taken the initial condition $(p_0, c_0, r_0) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(37^\circ\text{C})$ and the temperature $T = 42^\circ\text{C}$ during the entire simulation. We have solved this problem using the numerical resolution package OptimalControl.jl [14], with a final time of $\tau = 0.4$ hours and the constants given in [10]. We have used $N = 8000$ time steps.

The numerically found solution of the OCP exhibits an exact turnpike phenomenon, where it reaches and stays at the static optimal $(p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T)$. It is also subject to

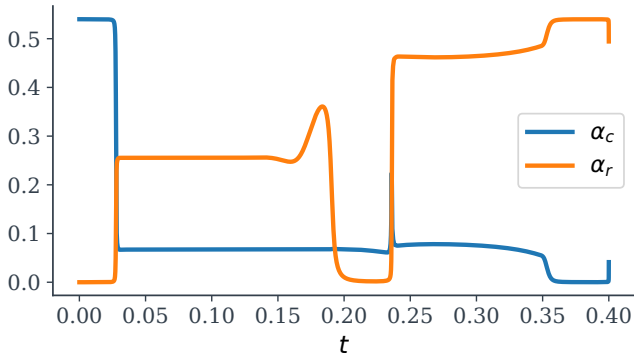


Fig. 2. Solution of the OCP with $T = 37^\circ\text{C}$ and $(p_0, c_0, r_0) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(42^\circ\text{C})$. The solution includes a few singular arcs.

boundary effects, where it depletes the cell of its precursors just before the arbitrarily set final time of the problem. This phenomenon, as observed in [15], is not relevant from a biological point of view. For these reasons, we have chosen to show the solution only until time $t = 0.15$, after the state reached its optimal equilibrium point but before the onset of these boundary effects.

Figure 3 shows the optimal control and the time plot of the state it entails. The solution starts with a bang arc on α_c to maximize its production of chaperones. This way, the cell can quickly increase its concentration of the molecules supporting protein folding to counteract the effects of heat-shock. Then, the control becomes singular and takes the value $\alpha_c, \alpha_r = (c_{\text{opt}}, r_{\text{opt}})(T)$, which corresponds to the optimal concentration at equilibrium. This can be verified by observing that the singular arc that appears in Figure 3 has $\alpha_c, \alpha_r, \alpha_m > 0$. By the analysis of the possible cases of singular arcs, this corresponds to $\lambda_c = \lambda_r = 0$, and by Proposition 3, the state must remain at the static optimal $(p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T)$.

B. Characterization of the Optimal Response to a Heat-Shock

We observe that the control follows a single bang arc on α_c before reaching the optimal equilibrium point $(p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T)$. This strategy can be applied for any change of temperature. Indeed, the following lemma is true.

Lemma 5.1: Let $(p, c, r)(t)$ be the solution of the system of ODE 1 with $(\alpha_c, \alpha_r)(t) = (r_{\text{max}}, 0) \forall t \geq 0$. Suppose $(p, c, r)(0) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T_0)$ for any temperature T_0 and that there exists a time $t_1 > 0$ and a temperature T_1 such that $c(t_1) = c_{\text{opt}}(T_1)$. Then, for any $t \in [0, t_1]$, there exists T such that $(p, c, r)(t) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T)$.

Proof: The curve defined by $(p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T)$ verifies

$$\begin{aligned} \frac{dr_{\text{opt}}(T)}{dT} &= -\frac{p_{\text{opt}}(K_p + p_{\text{opt}})}{K_p + 2K_p p_{\text{opt}} + p_{\text{opt}}^2} \frac{dc_{\text{opt}}(T)}{dT} \\ \frac{dp_{\text{opt}}(T)}{dT} &= 0. \end{aligned}$$

If we suppose that $(\alpha_c, \alpha_r)(t) = (r_{\text{max}}, 0)$, and that variables of System 1 lies on this curve, then

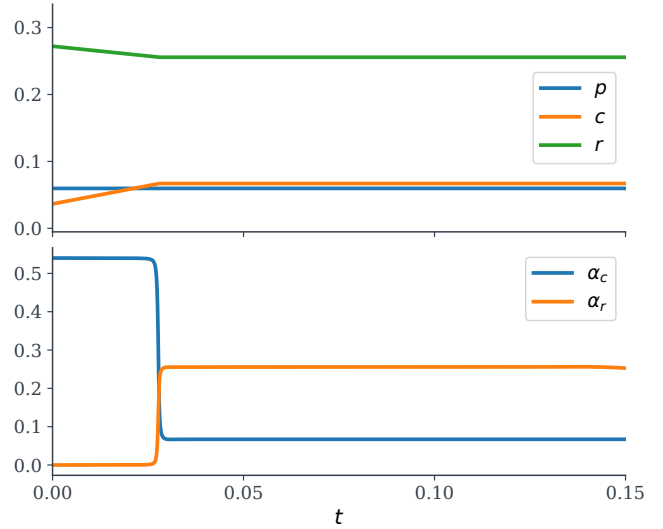


Fig. 3. Time-plot of the optimal controls for a heat-shock. On the top, the time-plot of the state variables under this control. We can observe an exact turnpike phenomenon, where after a transient phase the state stays at $(p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T)$, and the control follows the singular arc $\alpha_c, \alpha_r = (c_{\text{opt}}, r_{\text{opt}})(T)$.

$$\begin{aligned} \frac{dc}{dt} &= (r_{\text{max}} - c_{\text{opt}})w_R(p)w_c(c)r \\ \frac{dr}{dt} &= -r_{\text{opt}}w_R(p)w_c(c)r = \frac{-r_{\text{opt}}}{(r_{\text{max}} - c_{\text{opt}})} \frac{dc}{dt} \\ &= -\frac{p_{\text{opt}}(K_p + p_{\text{opt}})}{K_p + 2K_p p_{\text{opt}} + p_{\text{opt}}^2} \frac{dc}{dt} \\ \frac{dp}{dt} &= 0. \end{aligned}$$

The gradient of System 1 is parallel to the gradient of the curve, therefore the trajectory of the system follows the curve. ■

We have shown a simple control that allows the cell to reach an optimal equilibrium point for a more extreme temperature, that is, where $F(T)$ is higher and the optimal concentration of chaperones is also higher, from the equilibrium point corresponding to a less extreme temperature. Figure 4 illustrates this lemma with the example of the solution of the OCP shown in Figure 3.

We hypothesize that the solution of this optimal control problem, provided that the initial conditions are $(p, c, r)(0) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T_0)$, that the temperature T_1 fulfills $F(T_1) \geq F(T_0)$, the final time is long enough and omitting the final arcs caused by boundary effects, is given by

$$(\alpha_c, \alpha_r)(t) = \begin{cases} (r_{\text{max}}, 0) & \text{if } t < t_1 \\ (c_{\text{opt}}, r_{\text{opt}})(T_1) & \text{if } t_1 \leq t < t_2, \end{cases} \quad (7)$$

where t_1 is the first time the state reaches $(p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T_1)$ and t_2 is the time that boundary effects start occurring. Notice that t_1 is finite as long as

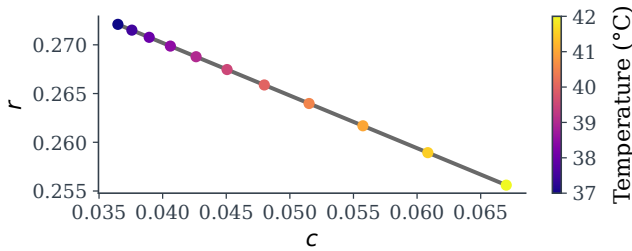


Fig. 4. Phase plot of the variables c and r from the solution of the OCP shown in Figure 1. The dots represent some points from the curve $(c, r) = (c_{\text{opt}}, r_{\text{opt}})(T)$ for $T \in [T_0, T_1]$. The curve given by the optimal controls passes through all these points.

$c_{\text{opt}}(T_1) < r_{\text{max}}$. If this is true, the optimal response of the cell to any heat-shock is to allocate all of its available resources to producing chaperones until it has reached the optimal equilibrium for the new temperature. This is similar to the behavior observed in micro-organisms subjected to a heat-shock in [16]. In the experiments described in this article, the cells quickly increase their chaperones production to a maximum and then reduce it to a new, higher constant value.

It is possible to numerically verify this hypothesis to some extent, thanks to the following lemma.

Lemma 5.2: Suppose that the optimal solution of OCP 2 for a certain temperature T_1 , final time τ and initial conditions $(p, c, r)(0) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T_0)$, with $c_{\text{opt}}(T_0) < c_{\text{opt}}(T_1)$ follows the structure defined in Equation 7, with the final arcs caused by boundary effects omitted. Then, for any \tilde{T}_0 such that $c_{\text{opt}}(T_0) < c_{\text{opt}}(\tilde{T}_0) < c_{\text{opt}}(T_1)$, there exists $\tilde{t}_1 < t_1$ such that the solution of OCP 2 for the same temperature T_1 , final time $\tau - \tilde{t}_1$ and initial conditions $(p, c, r)(0) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(\tilde{T}_0)$ is

$$(\alpha_c, \alpha_r)(t) = \begin{cases} (r_{\text{max}}, 0) & \text{if } t < t_1 - \tilde{t}_1 \\ (c_{\text{opt}}, r_{\text{opt}})(T_1) & \text{if } t_1 - \tilde{t}_1 \leq t < t_2 - \tilde{t}_1, \end{cases}$$

also with the final arcs omitted.

Proof: Since

$$c(t=0) = c_{\text{opt}}(T_0) < c_{\text{opt}}(\tilde{T}_0) < c_{\text{opt}}(T_1) = c(t=t_1),$$

there must exist a time $\tilde{t}_1 < t_1$ such that $c(\tilde{t}_1) = c_{\text{opt}}(\tilde{T}_0)$. By lemma 5.1, the state slides along the curve $(p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(T)$, therefore $(p, c, r)(\tilde{t}_1) = (p_{\text{opt}}, c_{\text{opt}}, r_{\text{opt}})(\tilde{T}_0)$. Then, the solution of the OCP with the new final time and initial condition must be the one given above, which is essentially equivalent to the solution of the OCP with the original parameters. This result is similar to Bellman's principle of optimality [17]. ■

Given the temperature $T_0 \approx 34.27^\circ\text{C}$, which results in the minimal optimal chaperones concentration $c_{\text{opt}}(T_0)$, we have numerically verified that for $T_1 = 42^\circ\text{C}$ and a long enough final time, the optimal control does indeed follow the structure given in Equation 7. We omitted the plot of this optimal control for reasons of space. This numerical solution allows us to immediately deduce that this is the structure of

the optimal control for a heat-shock to $T = 42^\circ\text{C}$ from any other temperature for which the optimal concentration of chaperones is smaller. It is interesting to note that this control is a pure feedback, i.e., its expression depends only on the current state of the system.

VI. CONCLUSION

In this work we studied a model of microbial resource allocation and its effect on cellular growth under a heat-shock. At more extreme temperature proteins inside a cell have a higher tendency to unfold, and thus lose their ability to perform their function. For this reason we are particularly interested in the production of chaperones, which assist protein folding. We reformulated the static optimization model given in [10] as an optimal control problem, where the internal resource allocation is the control, in order to better model the response to a change of temperature in the medium of a given micro-organism.

We defined the corresponding optimal control problem. Then we studied its solution using Pontryagin's Maximum Principle (PMP), which allowed us to determine that the optimal control follows a bang-bang structure, with some complicated singular arcs possibly appearing. In some of the cases where singular arcs appear, we were able to determine their value as feedback of the different internal concentrations inside of the cell.

We computed the optimal control in the case of a heat-shock, where the temperature suddenly shifts from 37°C to 42°C . In this case, the optimal control presents a simple structure consisting of a bang arc where the production of chaperones is maximal followed by a constant singular arc on which the state stays at the static optimal for the new temperature.

We proved that this structure of control drives the internal concentration of the different proteins from the optimal concentration at equilibrium for a less extreme temperature to the optimal for a more extreme temperature. We numerically proved that the optimal strategy in a heat-shock to 42°C is always to maximize the production of chaperones until the concentrations reach the new static optimal point.

In a future work, we intend to analytically verify this result for any pre- and post-heat-shock temperatures. We also intend to compare the optimal control we have found with regulation mechanisms that have been experimentally observed, such as the one mediated by the σ^{32} molecule [16]. Finally, it would be interesting to design experiments with both substrate and temperature changes, as a change in substrate means that $p_0 \neq p_{\text{opt}}(s)$ and $r_0 \neq r_{\text{opt}}(T, s)$, which could lead to a more complicated optimal control. This control could potentially cause interesting oscillations in the optimal growth rate.

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