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The turnpike property in maximization of microbial metabolite production ⋆

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Abstract: We consider the problem of maximization of metabolite production in bacterial cells. Numerical methods showed that the major phase of the solutions for different initial states and final times is the singular regime which exhibits a special structure reminiscent of the turnpike phenomenon. We prove that singular trajectories indeed have the turnpike property by providing an estimate both on singular trajectories and on the associated controls. This result can be further used for construction of simple realistic suboptimal control strategies.

Keywords: Bacterial growth, resource allocation, optimal control, turnpike, singular flow.

1. INTRODUCTION

The recent advances in bio-engineering made it possible to reengineer gene machinery in living cells and implement feedback controllers on the molecular level. This permitted to address important problems for biotechnological applications, in particular, the problem of maximization of microbial metabolite production. We study an extended self-replicator model of resource allocation in bacterial cells. It was proposed in [Yegorov et al., 2018] and includes a pathway for the production of some metabolite of interest. The maximization of the metabolite can be then formulated as an optimal control problem (OCP). In the sequence of works [Giordano et al., 2016], [Yegorov et al., 2017], [Yegorov et al., 2018], [Yabo et al., to appear] this and related models were studied in case of bacterial growth and in case of metabolite production. Here we will concentrate on a particular issue in the case of the metabolite production. The corresponding OCP is treated by Pontryagin Maximum Principle (PMP). The resulting problem is difficult to treat due to nonlinearity of equations and complexity in the structure of the optimal solutions. The preliminary analysis of solutions of PMP applied to the problem of metabolite production was performed in [Yegorov et al., 2018] using numerical calculations via direct methods of bocop software [Team Commands, 2017]. The numerical results for different initial conditions and final times showed that each obtained solution was of the structure bang-singular-bang, where the concatenations between singular and bang arcs are achieved by chattering and the singular regime constitutes the major part of the trajectory. It was also shown that the generalized Legendre-Clebsch condition is verified along the singular arc which is necessary for its optimality. It is clear, that the singular arcs play a crucial role in optimal solutions and at the same time are difficult for calculations. Thus, understanding the singular regime is important for construction of suboptimal realistic control strategies. The numerical results performed in [Yegorov et al., 2018] showed the special property of singular arcs to approach in small time a neighborhood of the steady state which is a solution of the stationary optimal control problem and stay there for a long time. The asymptotic property of optimal trajectories to stay most of the time near a steady state when the final time is large enough is well known in control theory and refers to the turnpike phenomenon [Porretta and Zuazua, 2013], [Trélat and Zuazua, 2015], [Sakamoto et al., to appear]. The turnpike property can be also defined as a property of an extremal solution of PMP to stay close to the hyperbolic stationary point of the corresponding Hamiltonian system. More precisely, a trajectory or an extremal satisfying the turnpike property consists of 3 pieces. At the first piece the trajectory passes from the initial point to some neighborhood of the stationary point. The second middle phase consists in staying in some small neighborhood of the stationary point. At the third piece the trajectory passes from the neighborhood of the second phase to the final point. The first and the third phases are transient and the second phase lasts most of the time when the final time is large enough.

This property is especially important in applications to microbial metabolite production. Stability properties of the dynamical system together with the estimates on the turnpike property permit to deduce the suboptimality of the constant control associated with the stationary optimal control problem which is more simple to implement.

In this paper we show the local turnpike property for the singular flow associated with optimal control problem of metabolite production maximization. Our approach can

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be applied for a general hyperbolic singular flow. More technical details are contained in the next sections.

2. MODEL

The extended self-replicator model that we consider is a coarse-grained model of resource allocation in bacteria. The cell dynamics comprises the gene expression machinery and the metabolic machinery including production of some metabolite of interest. It also includes an external control which determines the proportion of resources allocated between the gene expression machinery and the metabolic machinery. The key elements in the reactions of the considered model are external substrate S, precursor metabolites P, gene expression machinery R, metabolic machinery M, metabolite of interest X, volume $\mathcal{V} = \beta(M + R)$, where β represents the inverse of the cytoplasmic density. For the sake of simplicity, quantities of the system are expressed as concentrations,

$$p = \frac{P}{\mathcal{V}}, \quad r = \frac{R}{\mathcal{V}}, \quad m = \frac{M}{\mathcal{V}}, \quad s = \frac{S}{\mathcal{V}_{ext}}, \quad x = \frac{X}{\mathcal{V}},$$

where p, r and m are intracellular concentrations of precursor metabolites, ribosomes and metabolic enzymes respectively, s is the extracellular concentration of substrate with respect to a constant external volume $\mathcal{V}_{ext}$. The dynamics of m can be expressed in terms of r and therefore is excluded from the analysis.

The general form of the dynamics equations can be found in [Yegorov et al., 2018]. Following the modeling steps in [Yegorov et al., 2018], the synthesis rates in the dynamics are further taken as Michaelis-Menten kinetics. This leads to different models for different cases of environment. In our case we restrict our attention to the constant environmental conditions. Thus, s is constant. We are led to the following control system with $u \in [0, 1]$ the control function representing the proportion of resources allocated to gene expression (r) while $1 - u$ is allocated to metabolism (m) which is excluded from the system.

$$\begin{cases} \dot{p} = E_M(1-r) - k_1 \dfrac{p(1-r)}{K_1 + p} - (p+1)\dfrac{pr}{K+p}, \\ \dot{r} = (u - r)\dfrac{pr}{K+p}, \\ \dot{x} = k_1 \dfrac{p(1-r)}{K_1+p} - \dfrac{pr}{K+p}x, \\ \dot{\mathcal{V}} = \dfrac{pr}{K+p}\mathcal{V}, \end{cases} \tag{1}$$

with constant parameters E_M, K, K_1, k_1 and $p, r, x, \mathcal{V}$ satisfying $0 < p,\ 0 < x,\ 0 < \mathcal{V},\ 0 \le r \le 1$.

3. OPTIMAL CONTROL PROBLEM

3.1 Dynamical product maximization

We are interested in maximization of the total quantity of the metabolite of interest X produced during time T using the resource allocation control u. For this, we introduce the cost function defined by

$$J_X(u) = X(T) - X_0.$$

with $X_0 = X(0)$ given. Using the dynamics of $x, \mathcal{V}$ in (1), the cost can be expressed in variables (p, r, x) as follows

$$J_X(u) = \int_0^T \frac{k_1}{x(t)} \frac{p(t)(1 - r(t))}{K_1 + p(t)} \mathrm{d}t, \tag{2}$$

where $(p(t), r(t), x(t))$ satisfy (1) for any $t \in [0, T]$. We are led to the following optimal control problem. Find a control $u(\cdot) \in L^\infty([0, T], [0, 1])$ which maximizes $J_X(u)$ for given final time T and (p, r, x) satisfying (1) with given initial point (p_0, r_0, x_0) and free final point at time T. To allow some simplifications in calculations we make a change of variables $y = \ln x$. The new cost writes as

$$J_X = \int_0^T k_1 e^{-y} \frac{p(1-r)}{K_1+p} \mathrm{d}t$$

and dynamics of (p, r, y) as

$$\begin{cases} \dot{p} = E_M(1-r) - k_1 \dfrac{p(1-r)}{K_1+p} - (p+1)\dfrac{pr}{K+p}, \\ \dot{r} = (u-r)\dfrac{pr}{K+p}, \\ \dot{y} = k_1 e^{-y} \dfrac{p(1-r)}{K_1+p} - \dfrac{pr}{K+p}. \end{cases} \tag{3}$$

The existence of an optimal solution has already been shown in [Yegorov et al., 2018], so the next step is to understand the structure of optimal solutions. To treat the OCP we use the Pontryagin Maximum Principle. It gives the first order optimality condition and describes the trajectories which are candidates to be optimal solutions.

Let us denote by $z = (p, r, y)$ the state, by $\lambda = (\lambda_p, \lambda_r, \lambda_y) \in \mathbb{R}^3$ the adjoint state and let $\lambda_0 \le 0$. We can write the cost compactly $J_X = \int_0^T f^0(z, u)$ and denote by $\mathcal{H}$ the following function called pseudo-Hamiltonian

$$\mathcal{H}(z, \lambda, \lambda_0, u) = -\lambda_0 f_0 + \lambda_p \dot{p} + \lambda_r \dot{r} + \lambda_y \dot{y}.$$

By PMP, each optimal z satisfies the generalized Hamiltonian system

$$\begin{cases} \dot{z} = \dfrac{\partial}{\partial \lambda}\mathcal{H}(z, \lambda, \lambda_0, \tilde{u}), \\ \dot{\lambda} = -\dfrac{\partial}{\partial z}\mathcal{H}(z, \lambda, \lambda_0, \tilde{u}), \\ \mathcal{H}(z, \lambda, \lambda_0, \tilde{u}) = \max\limits_{u \in [0,1]} \mathcal{H}(z, \lambda, \lambda_0, u). \end{cases} \tag{4}$$

The pseudo-Hamiltonian can be written alternatively as an affine function of the control u

$$\mathcal{H}(z, \lambda, \lambda_0, u) = H_0(z, \lambda, \lambda_0) + u\, H_1(z, \lambda, \lambda_0),$$

It is well known (see [Bonnard and Chyba, 2003]) that each solution is a concatenation of bang arcs and singular arcs. A bang arc is a solution of (4) defined for some time interval $[t_1, t_2] \subseteq [0, T]$, corresponding to $u = 0$ when $H_1 < 0$ or $u = 1$ when $H_1 > 0$. A singular arc is a solution corresponding to the case $H_1 = 0$ and is more tricky to compute.

A better understanding of real biological and mathematical properties of solutions of (4) can be achieved by a fine analysis for some fixed realistic parameters E_M, K, K_1, k_1. Thus, we take parameters as in [Yegorov et al., 2018].

$$E_M = 1, \quad K = K_1 = 0.003, \quad k_1 = \frac{0.5}{3.6}. \tag{5}$$

3.2 Singular flow

First note, that only the case $\lambda_0 \ne 0$ can occur, see [Yegorov et al., 2018] for the proof. Moreover, it is standard that λ_0 can be normalized to $\lambda_0 = -1$, this permits to define $H(z, \lambda, u) = \mathcal{H}(z, \lambda, -1, u)$. Let us denote

$H_{01} = \{H_0, H_1\}$ and by induction $H_{0i} = \{H_0, H_i\}$ and $H_{1i} = \{H_1, H_i\}$, where i is any sequence of 0s and 1s. Differentiating the condition $H_1 \equiv 0$, one gets the expression of the singular control

$$u_s = -\frac{H_{00001}}{H_{10001}} \tag{6}$$

with $H_{10001} < 0$. The associated trajectory is called singular and belongs to the singular surface

$$\Sigma = \left\{(z,\lambda) \in \mathbb{R}^6 \,|\, H_1 = 0,\ H_{01} = 0,\ H_{001} = 0,\ H_{0001} = 0\right\}.$$

To simplify notations we define

$$F(z,\lambda) = (H_1(z,\lambda), H_{01}(z,\lambda), H_{001}(z,\lambda), H_{0001}(z,\lambda)),$$

so that $F(z,\lambda) = 0$ for $(z,\lambda) \in \Sigma$. In case of singular control (4) becomes

$$\begin{cases} \dot{z} = \dfrac{\partial H}{\partial \lambda}(z,\lambda,u_s(z,\lambda)), \\ \dot{\lambda} = -\dfrac{\partial H}{\partial z}(z,\lambda,u_s(z,\lambda)). \end{cases} \tag{7}$$

The corresponding solution (z,λ) is called singular extremal. For any $(z,\lambda) \in \Sigma$, singular Hamiltonian is defined by $H_s(z,\lambda) = H(z,\lambda,u_s(z,\lambda))$. A singular extremal (z,λ) satisfies the following Hamiltonian system equivalent to (7) on Σ

$$\begin{cases} \dot{z} = \dfrac{\partial H_s}{\partial \lambda}(z,\lambda), \\ \dot{\lambda} = -\dfrac{\partial H_s}{\partial z}(z,\lambda). \end{cases} \tag{8}$$

By [Bonnard and Chyba, 2003], H_s restricted to the singular surface Σ defines an independent Hamiltonian system on Σ. Therefore, there exist coordinates (z_s, λ_s) on Σ canonical with respect to the symplectic form which is the restriction of the canonical symplectic form defined on T^*M to $T^*\Sigma$. In these coordinates (8) writes as 2-dimensional Hamiltonian system

$$\begin{cases} \dot{z}_s = \dfrac{\partial h_s}{\partial \lambda_s}(z_s,\lambda_s), \\ \dot{\lambda}_s = -\dfrac{\partial h_s}{\partial z_s}(z_s,\lambda_s), \end{cases} \tag{9}$$

where $h_s(z_s,\lambda_s) = H_s(z(z_s,\lambda_s), \lambda(z_s,\lambda_s))$. Singular flow is the Hamiltonian flow of (9) on Σ. The numerical solutions obtained in [Yegorov et al., 2018] showed that singular arcs have a special property to spend most of the time near the solution of the stationary problem which we define in the next section.

4. STATIONARY PROBLEM

Let us denote the dynamics (3) of z by $\dot{z} = f(z,u)$. The stationary problem associated with maximization of $J_X = \int_0^T f^0(z,u)$ under the dynamics constraint $\dot{z} = f(z,u)$ is defined as follows.

$$\begin{aligned} &\mathit{maximize} && f^0(z,u) \\ &\mathit{subject\ to} && f(z,u) = 0. \end{aligned} \tag{10}$$

In our case we have moreover the condition that

$$(z,u) \in \{(p,r,y,u) \mid 0 \le p,\ 0 \le r \le 1,\ 0 \le u \le 1\}.$$

We denote by $(\bar{z},\bar{u})$ solutions of the stationary problem. To separate the equality constraints from the inequality constraints we denote

$$\begin{aligned} G_E &= \{(z,u) \mid f(z,u) = 0\}, \\ G_I &= \{(p,r,y,u) \mid 0 \le p,\ 0 \le r \le 1,\ 0 \le u \le 1\}. \end{aligned} \tag{11}$$

One can actually prove that the inequality constraints are not active, so we can discard them.

4.1 Solution of the stationary problem

Let us consider (11). The constraint $f(z,u) = 0$ defines a curve in G_I and can be parameterised by p. Therefore, the maximization problem is reduced to

$$\mathit{maximize} \quad f^0(z(p),u(p)). \tag{12}$$

A simple analysis of the first order optimality condition permits to conclude that f^0 has 4 extremal points with only one corresponding to $(\bar{z},\bar{u}) = (\bar{p}, \bar{r}(\bar{p}), \bar{y}(\bar{p}), \bar{u}(\bar{p}))$ in G_I which is moreover a local maximum by second order optimality condition. This value belongs to the interior of G_I and therefore do not activate the inequality constraints.

Proposition 1. There exists a unique $(\bar{p},\bar{r},\bar{y},\bar{u})$ solution of (10).

4.2 Relation with the Hamiltonian system

Let us establish a connection between the solution of the stationary problem and the equilibrium of the singular Hamiltonian system. First we introduce the Lagrange multiplier formalism for optimization with constraints (see [Gilbert, 2008]).

Definition 2. Equality constraint $f(z,u) = 0$ is said to be qualified at $(\bar{z},\bar{u})$ for set G_E if Jacobian $D_{(z,u)}f(\bar{z},\bar{u})$ is surjective.

The surjectivity of $D_{(z,u)}f(\bar{z},\bar{u})$ holds in our case. For the next step we need the well known theorem.

Theorem 3. (Lagrange necessary condition). Let $(\bar{z},\bar{u})$ be the solution of (10). Assume that the constraint $f(z,u) = 0$ is qualified at $(\bar{z},\bar{u})$. There exists unique $\bar{\lambda} \in \mathbb{R}^3$ which satisfies

$$\nabla_{(z,u)} f^0(\bar{z},\bar{u}) + D_{(z,u)}f(\bar{z},\bar{u})^\top \bar{\lambda} = 0. \tag{13}$$

Corollary 4. Let $(\bar{z},\bar{u})$ be the solution of (10). Then there exists a unique $\bar{\lambda} \in \mathbb{R}^3$ which satisfies (13).

Theorem 5. Assume that $\bar{u} \in (0,1)$, then $(\bar{z},\bar{\lambda})$ is an equilibrium of the singular Hamiltonian system (7) if and only if $(\bar{z},\bar{u})$ is an extremal value of the static problem (10).

Proof. First, assume $(\bar{z},\bar{\lambda})$ to be an equilibrium of the Hamiltonian system. Then $\bar{u} = u(z,\lambda)$ is the singular control satisfying (6). By definition, we have $DH(\bar{z},\bar{\lambda},\bar{u}) = 0$ where $DH(\bar{z},\bar{\lambda},\bar{u})$ is the Jacobian of H at $(\bar{z},\bar{\lambda},\bar{u})$. It is straightforward that $(\bar{z},\bar{\lambda},\bar{u})$ satisfies (13). Assume now that $(\bar{z},\bar{u})$ is an extremal value of the static problem. By assumption, $\bar{u} \in (0,1)$, which is true for our choice of parameters (5). Then by Theorem 3 there exists unique $\bar{\lambda}$ satisfying (13). Set $\bar{\lambda}(t) = \bar{\lambda}$, $\bar{z}(t) = \bar{z}$, $\bar{u}(t) = \bar{u}$ for $t \in [0,T]$. By definition $(\bar{\lambda}(t), \bar{z}(t))$ satisfies (7). We are left to check that $\bar{u}$ satisfies (6). Along the trajectory $(\bar{\lambda}(t), \bar{z}(t))$ we have

$$0 = \frac{d^i}{dt^i}\left(\frac{\partial H}{\partial u}\right)(\bar{z},\bar{\lambda}) \quad i = 1,2,\ldots$$

This shows that $(\bar{z},\bar{\lambda}) \in \Sigma$ and $\bar{u}$ satisfies (6), which finishes the proof.

5. TURNPIKE PROPERTY

The asymptotic property of optimal trajectories to stay the most of the time near a steady state when the final time is large enough is well known in control theory and it refers to the turnpike phenomenon, the property of an extremal $(z(\cdot), \lambda(\cdot))$ to stay close to the hyperbolic stationary point $(\bar{z}, \bar{\lambda})$. Mathematically, turnpike can be described in different terms, here we prefer to use the approach of [Trélat and Zuazua, 2015] where it is characterized via an estimate of the norm of the extremal and the associated control at each time $t \in [0, T]$ of the following form

$$\|u(t)-\bar{u}\|+\|z(t)-\bar{z}\|+\|\lambda(t)-\bar{\lambda}\| \leq C\left(e^{-\mu t}+e^{-\mu(T-t)}\right),$$

for some parameters μ, C and for time T large enough. The turnpike property is closely related to the hyperbolicity of the Hamiltonian system underline the extremal trajectories. In our case this is the property of the singular flow, as we show further.

5.1 Properties of linearized system

Let $(\bar{z}, \bar{\lambda})$ be the stationary point of (8), it belongs to Σ and the corresponding point in canonical coordinates $(\bar{z}_s, \bar{\lambda}_s)$ is the stationary point of (9). Let us denote $\delta z(\cdot) = z(\cdot) - \bar{z}, \delta\lambda(\cdot) = \lambda(\cdot) - \bar{\lambda}, \delta u(\cdot) = u_s(\cdot) - \bar{u}$. The corresponding perturbation in canonical coordinates on Σ gives $\delta z_s(\cdot) = z_s(\cdot) - \bar{z}_s, \delta\lambda_s(\cdot) = \lambda_s(\cdot) - \bar{\lambda}_s$. The dynamics of $(\delta z_s, \delta\lambda_s)$ can be written as follows using the Taylor expansion at $(\bar{z}_s, \bar{\lambda}_s)$.

$$\frac{d}{dt}\begin{pmatrix}\delta z_s\\ \delta\lambda_s\end{pmatrix} = \mathcal{H}\begin{pmatrix}\delta z_s\\ \delta\lambda_s\end{pmatrix} + \mathrm{o}(\delta z_s, \delta\lambda_s), \tag{14}$$

where $\mathcal{H}$ is (2×2) matrix of the form

$$\mathcal{H} = \begin{pmatrix} \dfrac{\partial^2 h_s}{\partial\lambda_s \partial z_s}(\bar{z}_s, \bar{\lambda}_s) & \dfrac{\partial^2 h_s}{\partial\lambda_s^2}(\bar{z}_s, \bar{\lambda}_s) \\ \dfrac{\partial^2 h_s}{\partial z_s^2}(\bar{z}_s, \bar{\lambda}_s) & -\dfrac{\partial^2 h_s}{\partial\lambda_s \partial z_s}(\bar{z}_s, \bar{\lambda}_s) \end{pmatrix}.$$

The matrix $\mathcal{H}$ is traceless by construction and therefore has opposite eigenvalues, $\pm\alpha$. As both $(z(\cdot), \lambda(\cdot))$ and $(\bar{z}, \bar{\lambda})$ belong to Σ, $(\delta z, \delta\lambda)$ satisfy

$$0 = D_z F(\bar{z}, \bar{\lambda})\,\delta z + D_\lambda F(\bar{z}, \bar{\lambda})\,\delta\lambda + \mathrm{o}(\delta z, \delta\lambda). \tag{15}$$

These equations give a constructive way to define local coordinates on the surface Σ near $(\bar{z}, \bar{\lambda})$. In our case, (r, y) can be chosen as such coordinates and in these coordinates (14) takes the following form.

$$\frac{d}{dt}\begin{pmatrix}\delta p\\ \delta y\end{pmatrix} = \overline{\mathcal{H}}\begin{pmatrix}\delta p\\ \delta y\end{pmatrix} + \mathrm{o}(\delta p, \delta y). \tag{16}$$

Theorem 6. The matrix $\mathcal{H}$ is hyperbolic with opposite eigenvalues.

Proof. It was already shown that $\mathcal{H}$ has opposite eigenvalues. It is clear that $\overline{\mathcal{H}}$ has the same eigenvalues as $\mathcal{H}$. Eigenvalues of $\overline{\mathcal{H}}$ can be obtained by a simple numerical calculation. The obtained eigenvalues are real and different from zero and therefore, $\mathcal{H}$ is hyperbolic.

5.2 Turnpike of the singular flow

Each extremal (z, λ) of our OCP is a concatenation of bang arcs and singular arcs. Let us restrict our attention to the singular arcs. Each singular arc belongs to the singular manifold Σ and is a solution of the singular Hamiltonian system. We assume that by some means, by numerical calculations for instance, we can deduce the point $(z(t_1), \lambda(t_1))$ of entering the singular arc at time t_1 and $(z(t_2), \lambda(t_2))$ the point at which the trajectory leaves the singular arc at time t_2. Let us denote by α the positive eigenvalue of $\mathcal{H}$.

Theorem 7. For any $0 < \mu < \alpha$, there exist positive constants ϵ, T_0 such that, if $t_2 - t_1 > T_0$ and

$$|z(t_1) - \bar{z}| + \left|\lambda(t_1) - \bar{\lambda}\right| + |z(t_2) - \bar{z}| + \left|\lambda(t_2) - \bar{\lambda}\right| \leq \epsilon$$

then there exists $C > 0$ such that for any $t \in [t_1, t_2]$ there holds

$$|z(t) - \bar{z}| + \left|\lambda(t) - \bar{\lambda}\right| + |u_s(t) - \bar{u}| \leq C\left(e^{\mu(t_1-t)} + e^{\mu(t-t_2)}\right)$$

The idea of the proof relies completely on the same strategy as introduced in the proof of the main theorem in [Trélat and Zuazua, 2015], applied in our case to the singular flow. Again, the main point is to use the hyperbolicity of $\mathcal{H}$.

Stability properties of (3) with the control set to $u = \bar{u}$ around the equilibrium $(p, r, y) = \bar{z}$ implies the local exponential convergence of the solution to $\bar{z}$. Taking into account Theorem 7, this suggests a sub-optimal simple control strategy $u = \bar{u}$ along the singular arc.

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