Optimization Control Approach to sequential Activation of Metabolic pathways.

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Declaration

This is to certify that this thesis is my own work, that due reference has been made in the text to all other material used, that it is less than 20,000 words in length, exclusive list of figures, tables and bibliographies, and that it has not been previously submitted for any comparable academic award.

Student's names :Angelique DUKUNDE Date : February 2016

Dedication

To my family this work is dedicated to.

Acknowledgment

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abstract

The objective of this thesis is a study of sequential activation of metabolic pathways using optimal control theory. In particular, we study the statements made in [10] and give an alternative proof of the main results proposed in that paper. In our study we give a precise description of numbers of switching times, provide an optimization problem formulation to determine optimal switching time, which were not presented in [10]. In addition to the Pontryagin Minimum Principle, we also study the Lagrange duality theory, and apply them to the unbranched metabolic pathways. We give a self-contained presentation of mathematics necessary for this thesis to describe the results.

Acronyms

UR: University of Rwanda
SU: Stockholm University
LiU: Linköping University
MMC: Mathematically Controlled Comparison
FBA: Flux Balanced Analysis
LP: Linear Programming
PMP: Pontryangin Minimum Principle.

Contents

Chapter 1

Introduction

Metabolism is the set of chemical reactions that occur in a cell, which enable it to keep living, growing and dividing. A cell's metabolism is the network of enzyme-catalysed reactions in which sources of energy and materials are broken down and cellular components (e.g. amino acids, lipids) are produced. The reactants and products in metabolic reactions are referred to as metabolites; they are typically small molecules.

A cell's complete metabolic network is organized roughly in a "bow-tie" structure, in which a wide range of substrates are broken down into a much smaller number of intermediates, from which a large number of distinct biomolecules are formed.

The structure of metabolic networks varies from species to species, but there are many aspects of "core" metabolism that are conserved across all organisms.

Reactions that break down sources of energy and materials are called *catabolic*. Well-studied catabolic pathways include glycolysis, which converts glucose to pyruvate, and the tricarboxylic acid cycle (also called the citric acid cycle or the Krebs cycle), which consumes pyruvate and produces substrates for biosynthetic and energy-producing pathways. Metabolic reactions that build up cellular components are called *anabolic*. Standard examples of anabolism include the branched pathways leading to amino acid production and the pathways responsible for generating lipids and nucleic acids. See [6].

So metabolic processes are usually classified as:

- *catabolism*: obtaining energy and reducing power from nutrients.
- *anabolism*: production of new cell components, usually through processes that require energy and reducing power obtained from nutrient catabolism.

The biochemical reactions in the individual organism under consideration are governed by ordinary differential equations. Network structure and the kinetics of the enzymes for catalyzing the individual interaction are depended on Metabolic pathways and produce required molecules directing to different dynamic behavior such that the organism have the stability. Most cellular processes need a particular support on the particular operation of some set of pathways, so their behavior give a basic structure functional requirement for cellular operation. The metabolic dynamics that plays a significant role in cell fitness and together with the metabolic design alternatively has been optimized through evolutionary process [9].

The simplest metabolic network is an unbranched (so-called 'linear') chain of reactions. Truly unbranched metabolic pathways are rare, and they typically consist of only a few reactions. Nevertheless, by neglecting side reactions and reaction co-factors, models of metabolism frequently make use of this unbranched structure – it is the simplest way to describe a path from substrate to product. Below is an unbranched metabolic chain: the substrate S_0 and the product P are held at fixed concentrations where we only explain the irreversible reactions, since this is relevant to our study.

$$S_0 \xrightarrow{r_1} S_1 \xrightarrow{r_3} S_2 \xrightarrow{r_3} P$$

In an unbranched pathway, all reactions rates must be equal at steady state, and so the pathway flux is the steady-state rate of every reaction. Chains consisting of irreversible reactions display a simple behaviour: the first reaction has a fixed rate and so dictates the pathway flux. In this case, all of the reactions except the first have flux control coefficients of zero, while the first reaction – which exerts total control over the pathway flux – has a coefficient of one.

We can think of an unbranched pathway as an assembly line that generates a product. In many cases, cellular activities require a steady rate of production – the pathway flux should be robust to perturbations. In other cases, pathways need to be responsive – to generate product when it is called for, and otherwise keep the production rate low. Sensitivity analysis can be used to address these aspects of pathway performance: robustness corresponds to insensitivity to perturbations, while responsiveness is characterized by high sensitivity with respect to the appropriate input signals.

Earlier work on behavior of metabolic pathways are under static enzyme concentrations. Here are two methods: The method of Mathematically Controlled Comparisons (MMC) and an optimization technique called Flux Balanced Analysis (FBA). The former allows the comparison of alternative metabolic designs with respect to specific quantitive criteria with applications e.g. in effective study of optimal regulatory structures in metabolic pathways. In FBA the reaction fluxes of a stoichiometric model are chosen to optimize a linear objective function. It provides useful predictions of

metabolic responses in a number of different organisms under diverse conditions. Dynamic enzyme optimization for activation of biosynthetic pathways has been studied before [10]: The problem was posed under a constraint on the total enzyme abundance, which reflects the fact that fells have limited biosynthetic capability.

In the article [10], the authors extend these studies on temporal distribution of enzymatic concentrations using framework of linear programming. They consider an unbranched pathway and provided a theoretical framework originated from the Pontryagin Minimal Principle (PMP). For a more detailed historical development we refer to [10]. Although the author considered their presentation rigorous we found some unsatisfactory facts, for example, the existence of the switching times and how they are obtained seems missing in the article. Moreover we make use the (Lagrange) dual to recast the linear programming problem obtained from the PMP in discussion of the switching time, from which an alternative proof of the main result in [10] is given.

The **significance** of this research is *to increase the understanding of the phenomena and contribute to improvement of mathematical model that can be used to predict the optimal pathway of metabolism.*

The rest of this thesis is organized as follows: In Section 2, we provide mathematical preliminaries necessary for our study. They are basically two main topics: (i) mathematical theory of linear programming and its duality, and (ii) optimal control theory focusing on PMP with a more general boundary conditions for the state variables to cope with the control problem derived from the [10]. We are also going to provide a proof of this general form of PMP because it is normally not included in textbooks. In Section 3, some background material from (bio)chemical reactions and metabolic pathways will be presented. In Section 4, we shall present our problem formulation and set up the mathematical model for analysis. Section 5 constitutes the solution of the problem and its complete proof, the main results of this thesis. In Section 6, we give a numerical example on an unbranched pathway with three reactions exhibiting Michalis-Menten kinetics by our proposed method. Finally we conclude the thesis by some further remarks and reflections.

Chapter 2

Mathematical Preliminaries

We shall in this section provide necessary mathematical theories on linear programming (LP) and optimal control. First we review some results from convex analysis, linear programming. Then we turn to general results of the Pontryagin Minimal Principle (PMP). A complete proof will be included for optimal control from initial state to a fixed end point in optimal time since it benefits our argument to derive the PMP for controlling initial state to a manifold which we need in our analysis of the metabolic pathway model. The material presented here can be found in e.g. [1] and [12]. Most of them are taken from the lecture notes for the courses on these subjects at Stockholm University, [15, 16]. We use the standard notation $\mathbb{R}^n$ for n-dimensional Euclidean space with inner product $\langle x, y\rangle = y^\top x$ for $x, y \in \mathbb{R}^n$, where $\bullet^\top$ stands for transpose of the matrix $\bullet$.

2.1 Basics in convex analysis

Convex analysis is a theoretical foundation for optimization theory. Here we collect some definitions and theorems necessary in this thesis.

A subset $C \subset \mathbb{R}^n$ is said to be *convex* if for any two points $x, y \in C$ it holds that $(1-\alpha)x + \alpha y \in C$ for all $\alpha \in [0, 1]$. Such a combination of x and y is called *convex combination*. In general , vector sum ,$\lambda_1 x_1 + \cdots + \lambda_m x_m$ is called *convex combination* of $x_1, \ldots, x_m$ if the coefficients λ_i are all non-negative and $\lambda_1 + \cdots + \lambda_m = 1$. The unit ball in $\mathbb{R}^n$, $\mathbb{B} = \{x \in \mathbb{R}^n \ : \ \|x\| \leq 1\}$ is a convex set, where $\|x\| = \sqrt{x_1^2 + \cdots x_n^2}$. Half-spaces are important examples of convex sets. They are defined as follows: For any non-zero $b \in \mathbb{R}^n$, and any $\beta \in \mathbb{R}$, the sets

$$\{x : \langle x, b\rangle \leq \beta\}, \quad \{x | \langle x, b\rangle \geq \beta\}$$

are called *closed half-spaces*. The sets

$$\{x : \langle x, b\rangle < \beta\}, \quad \{x | \langle x, b\rangle > \beta\}$$

are called *open half-spaces*. All four sets are non-empty and convex. Notice that the same quartet of half-spaces would appear if b and β are replaced by λb and $\lambda\beta$ for some $\lambda \neq 0$. Thus these half-spaces depend only on the hyperplane $H = \{x : \langle x, b\rangle = \beta\}$.

There are some elementary properties of convex sets:

Theorem 1 *The intersection of an arbitrary collection of convex sets is convex.*

Theorem 2 *Convex sets are preserved under many algebraic operations: Let $C_1, C_2 \in \mathbb{R}^n$ be convex sets, $\alpha \in \mathbb{R}$. Then, the following sets are convex*

1. $\alpha C_1 = \{\alpha x | x \in C_1\}$.
2. $C_1 + C_2 = \{x + y | x \in C_1, y \in C_2\}$.

Immediately we have the following corollary; *Let $b_i \in \mathbb{R}^n$ and $\beta_i \in \mathbb{R}$ for $i \in I$, where I is an arbitrary index set. Then the set*

$$C = \{x \in \mathbb{R}^n : \langle x, b_i\rangle \leq \beta_i, \forall i \in I\}$$

is convex. [16]

This is the main object in linear programming problems. Note that the conclusion of the corollary would still be valid, of course, if some of the inequalities $\leq$ were replaced by $\geq$, $>$, $<$ or $=$. Thus, given any system of simultaneous linear inequalities and equations in n variables, the set C of solution is a convex set in $\mathbb{R}^n$. This is a significant fact both in theory and applications. In matrix form we can write

$$C = \{x : Ax \leq b\}$$

where A is an $n \times m$ matrix and b is an m-vector. This is the main ingredient in LP problem.

A set which can be expressed as the intersection of *finitely* many closed half spaces of $\mathbb{R}^n$ is called a *polyhedral* convex set. A bounded polyhedral set is called *polytope*.

A subset C is a convex cone if $\alpha x + \beta y \in C$, for any positive scalars α, β, and any $x, y \in C$. (Convexity is followed by the theorem above.)

Theorem 3 *A subset of $\mathbb{R}^n$ is convex if and only if it contains all the convex combinations of its elements.*

Since the set of all convex combinations of its elements appears we call such set a convex hull. We can show that the intersection of all the convex sets

containing a given subset X of $\mathbb{R}^n$ is called the convex hull of X and is denoted by $\text{conv}(X)$.

We say that two sets C_1 and C_2 are *separated by a hyperplane* $H = \{x : a^\top x = b\}$ if each lies in a different closed halfspace associated with H, i.e., either $a^\top x_1 \leq b \leq a^\top x_2, \forall x_1 \in C_1, \forall x_2 \in C_2$ or $a^\top x_2 \leq b \leq a^\top x_1, \forall x_1 \in C_1, \forall x_2 \in C_2$.

Theorem 4 (Supporting Hyperplane Theorem) *Let C be a nonempty convex set in $\mathbb{R}^n$, and let $\bar{x} \in \partial C$. Then, there exists a hyperplane that supports C at $\bar{x}$; that is, there exists a nonzero vector a such that $a^\top(\bar{x}-x) \leq 0$ for each $x \in cl(C)$ [1]*

The following theorem is the key in the proof of the PMP and in derivation of the so-called *transversality condition* for the adjoint vector.

Theorem 5 (Separating Hyperplane Theorem) *Let C_1 and C_2 be nonempty convex sets in $\mathbb{R}^n$ and suppose that $C_1 \cap C_2 = \emptyset$. Then there exists a hyperplane that separates C_1 and C_2, that is, there is a nonzero vector a such that $a^\top x_1 \leq a^\top x_2$ for all $x_1 \in C_1$ and all $x_2 \in C_2$ [1].*

Two more very important concepts are in order:

1. *Extreme points:* A vector x is an *extreme point* of a convex set C if $x \in C$ and x cannot be expressed as a convex combination of two vectors of C, both of which are different from x.
2. *Extreme directions*: Let $\emptyset \neq C \subset \mathbb{R}^n$ be closed convex. A nonzero vector $d \in \mathbb{R}^n$ is said to be a *direction* of C if for each $x \in C$, $x + \lambda d \in C$, $\forall \lambda \geq 0$. Two directions are distinct if they are not positively dependent. A direction d of C is said to be an *extreme direction* if it cannot be written as a positive linear conbination of two distinct directions, i.e., if $d = \lambda_1 d_1 + \lambda_2 d_2$ for $\lambda_1, \lambda_2 > 0$ then $d_1 = \alpha d_2$ for some $\alpha > 0$ [16] .

Clearly, extreme points of a polyhedral set are the "corners" of this set, and a polytope does not have any extreme direction since it is bounded.

2.2 Linear programming (LP) problems

2.2.1 Algebraic and geometric treatments of LP

Consider an LP problem in the standard form

$$\begin{aligned} \min \quad & c^\top x \\ \text{s.t.} \quad & Ax = b \\ & x \geq 0, \end{aligned} \tag{P}$$

where $x \in \mathbb{R}^n$ is a vector of decision variables, and $c \in \mathbb{R}^n$ and $b \in \mathbb{R}^m$ are known. Assume that the matrix A is an $m \times n$ matrix of full rank of A, $(n \geq m)$. Geometrically, the feasible set, i.e., all solutions to the system of linear equations

$$Ax = b, \quad x \geq 0, \tag{2.1}$$

corresponds to an hypersurface in $\mathbb{R}^n$ and the positivity requirement $x \geq 0$. Since A is of full rank, the hyperplane $\{x : Ax = b\}$ has dimension $n - m$. We shall assume the full rank in the sequel.

Now if you are at a feasible point, you perhaps would like to go in the negative gradient direction, that is, $-c$, for minimizing the objective function. However, this direction normally lies outside the hypersurface $\{x|Ax = b\}$. Naturally, there are two ways to deal with the problem.

- To project the direction $-c$ onto the hyperplane $\{x : Ax = b\}$ and go along this projected direction
- To solve the m variables by (2.1) and express them in terms of the rest of $n - m$ variables.

In this thesis we take the second alternative. We first investigate the geometry of the feasible solutions and the feasible set.

***Characterization of extreme points for polyhedral* sets**

Consider $P = \{x|Ax = b, x \geq 0\}$, where A is an $m \times n$ matrix of rank $m \leq n$ and b is an m-vector. Without loss of generality we assume that $b \geq 0$, for otherwise we can simply multiply the equation $Ax = b$ by -1. Rearrange the columns of A so that $A = [A_B, A_N]$ with A_B being $m \times m$ matrix of full rank, and A_N an $m \times (n - m)$ matrix. Let x_B and x_N be the vectors corresponding to A_B and A_N, respectively, and they are called *basic variables* and *nonbasic variables*. In this way we view the indecis N and B as sets for indices for basic and non-basic variables. Now $Ax = b$ and $x \geq 0$ can be rewritten as

$$A_B x_B + A_N x_N = b \text{ and } x_B \geq 0, x_N \geq 0.$$

Theorem 6 *A point x is an extreme point of $P \Leftrightarrow A$ can be decomposed into $[A_B, A_N]$ such that*

$$x = \begin{bmatrix} x_B \\ x_N \end{bmatrix} = \begin{bmatrix} A_B^{-1} b \\ 0 \end{bmatrix} \text{ (\textit{basic feasible solution})}$$

This theorem tells us that corners of a polyhydral set can be found by finding basic solutions of $Ax = b$ [1].

Theorem 7 (Existence of extreme points) *Let P be nonempty. Then there is at least one extreme point of P.*
Furthermore, the number of extreme points is bounded by $\binom{n}{m}$ [1].

Characterization of extreme points for polyhedral sets

Theorem 8 *A vector $\bar{d}$ is an extreme direction of $P \Leftrightarrow A$ can be decomposed into $[A_B, A_N]$ s.t. $A_B^{-1}a_j \leq 0$ for some column a_j of A_N and $\bar{d}$ is a positive multiple of*

$$d = \begin{bmatrix} -A_B^{-1}a_j \\ e_j \end{bmatrix}$$

where e_j is an $n-m$ vector of zeros except for a 1 in position j.
Moreover, the number of extreme direction is bounded by $(n-m)\binom{n}{m}$.
Furthermore, if P has at least one extreme direction P is unbounded.

Finally we have

Theorem 9 (Representation Theorem) *Let $x_1, ..., x_k$ be extreme points of P and $d_1, ..., d_l$ be the extreme directions of P. Then $x \in P$ if and only if*

$$x = \sum_{j=1}^{k} \lambda_j x_j + \sum_{j=1}^{l} \mu_j d_j,$$

$$\sum_{j=1}^{k} \lambda_j = 1, \lambda_j \geq 0, \quad j = 1, ..., k, \mu_j \geq 0, j = 1, ...l.$$

In particular, if P is a polytope then every $x \in P$ can be written in the form

$$x = \sum_{j=1}^{k} \lambda_j x_j, \quad \sum_{j=1}^{k} \lambda_j = 1, \lambda_j \geq 0, j = 1, ..., k \text{ [1]}$$

Theorem 10 (The fundamental theorem of LP) *Consider the LP problem in standard form (P). Let A be a $m \times n$ matrix of rank $m \leq n$. Then*

(i) *if there is a feasible solution, there is a basic feasible solution.*

(ii) *if there is an optimal solution, there is an optimal basic feasible solution [1].*

Note that solutions may not be unique. If there are two basic optimal solutions then any points on the line segment between these two points are optimal because the feasible set is convex.

2.2.2 Duality theory of linear programming

We derive the LP problem (called primal problems too) in the same spirit as in [1]. First we describe how a dual problem can be determined for a mathematical programming problem, i.e.,

$$\begin{cases} \min\limits_{x} & f(x) \\ \text{s.t.} & g(x) \leq 0, \quad x \in X \end{cases} \tag{P}$$

where $X \subseteq \mathbb{R}^n$, $f : X \to \mathbb{R}$ and $g : X \to \mathbb{R}^m$ are C^1-function.

Lagrange relaxation

First we study Lagrange relaxation for the optimization problem with inequality constraints described by (P). That is, for $\lambda \in \mathbb{R}^m$ we construct the problem

$$(P_\lambda) \quad \begin{cases} \min\limits_{x} & f(x) + \sum\limits_{i=1}^{m} \lambda_i g_i(x) \\ \text{s.t.} & x \in X. \end{cases} \tag{2.2}$$

The λ_i are called *Lagrangians* or *Lagrange multipliers*. Note that Lagrangians are not variables but parameters. For every λ we have an optimization problem (P_λ) in the variables x.

The function $f_\lambda(x) := f(x) + \lambda^\top g(x) = f(x) + \sum \lambda_i g_i(x)$ is called the *Lagrange function* to (P). It is often denoted by $L(x, \lambda)$.

According to general relaxation theory we can show that

Theorem 11 *1. If $\lambda \geq 0$ then (P_λ) is a relaxation of (P).*

2. Assume that $\bar{x}_\lambda$ is optimal to (P_λ). Then $\bar{x}_\lambda$ is optimal to (P) if

(i) $g(\bar{x}_\lambda) \leq 0$

(ii) $\lambda_i g_i(\bar{x}_\lambda) = 0, i = 1, ..., m$

(iii) $\lambda \geq 0$.

Remark:

1. Condition (ii) is called *complementary condition* because it requires *either* $\lambda_i = 0$ *or* $g_i(x_\lambda) = 0$, for $i = 1, ..., m$.
2. Note that there is no sign constraint on λ if the constraints are replaced by $g(x) = 0$.
3. The idea of Lagrange relaxation is a common way to derive the necessary conditions for optimal control problems leading to the Pontryagin Minimum Principle [1].

2.2.3 Formulation of Lagrange dual problems

Consider the problem described by (P), called *primal problem* and its Lagrange relaxation (P_λ). Let p denote the optimal value of (P) and $\phi(\lambda)$ optimal value of (P_λ):

$$\begin{aligned} p &= \min\{f(x)|g(x) \leq 0, x \in X\} \\ \phi(\lambda) &= \min\{f(x) + \lambda^t g(x)|x \in X\} \end{aligned}$$

(In fact, it should be infimum here. However we will ignore all technicalities in our discussion.) Then if $\lambda \geq 0$, (P_λ) is a relaxation of (M), and hence, $\phi(\lambda) \leq p$. It is natural to choose the strongest relaxation, that is, choose $\lambda \geq 0$ such that $\phi(\lambda)$ becomes maximum. This gives us the dual prolem:

$$\begin{cases} \max & \phi(\lambda) \\ \text{s.t.} & \lambda \geq 0 \end{cases} \tag{D}$$

If we consider equality constrained problem, then we do not have the positivity requirement in the dual problem. The theorems below hold even in this case, for they only make use of $\phi(\lambda) \leq p$ for those λ which gives relaxation.

Let d be the optimal value of (D). Then we can easily prove that

$$d \leq p.$$

Observe that we cannot always have $d = p$. We call $\delta := p - d$ the *duality gap*. Moreover, $\delta \geq 0$.

2.2.4 Duality theorems

By the definition we have following theorem:

Theorem 12 (Weak duality theorem) *Let x be a feasible solution to Problem (P), that is $x \in X$ and $g(x) \leq 0$. Also let λ be a feasible solution to problem (D), that is, $\lambda \geq 0$. Then $f(x) \geq \phi(\lambda)$.*

Consequently,

Corollary. *Assume that $\bar{x}$ and $\bar{\lambda}$ are feasible solutions to (P) and (D), respectively. If $\phi(\bar{\lambda}) = f(\bar{x})$, then $\bar{\lambda}$ and $\bar{x}$ are optimal solutions to (D) and (P), respectively.*

This corollary shows a new way to look at Theorem 11. Under the assumptions in the theorem it holds that $\bar{x}_\lambda$ and λ are feasible to (P) and (D) respectively, and that $\phi(\lambda) = f(\bar{x}_\lambda) + \sum \lambda_i g_i(\bar{x}_\lambda) = f(\bar{x}_\lambda)$. The optimality follows also from this corollary [1].

The Lagrange dual problem has some nicer features than the primal problem. Here we give some of them.

(i) It has nice objective function, (concave)

(ii) It has nice constraints (positivity requirements),

(iii) It has few variables (= number of primal constraints).

For those problems where we can explicitly (analytically) determine the dual objective function ϕ it is often worthwhile solving the dual problem instead and thereafter find the primal solution using the following theorem. The gradient of ϕ can be obtained by the following theorem, [1].

Theorem 13 *Assume that X is closed and bounded and (P_λ) has a unique optimal solution $\bar{x}(\lambda)$. Then $\nabla\phi(\lambda) = g(\bar{x}(\lambda))^t$.*

Remark. Given a nonlinear programming problem, several Lagrange dual problems can be derived, depending on which constraints are handled as inequality constraints and equality constraints and which constraints are treated by the set X. This choice can affect both the optimal value of (D) (as in nonconvex situations) and the effort expended in evaluating and updating the dual function $\phi(\lambda)$ during the course of solving the dual problem. Hence, an appropriate selection of the set X must be made, depending on the structure of the problem and the purpose for solving (D). However for LP problems the dual problem is unique. Thus the dual of the dual problem is the primal problem. This can be seen from the discussion below.

Example. (LP problem) Now we consider the LP problem in standard form (P). Let $X = \{x : x \geq 0\}$, the Lagrange dual of this problem is to maximize $\phi(\lambda)$ where

$$\phi(\lambda) = \min\{c^\top x + \lambda^\top(b - Ax); x \geq 0\} = \lambda^\top b + \min\{c^\top - \lambda^\top A)x : x \geq 0\}.$$

Clearly

$$\phi(\lambda) = \begin{cases} \lambda^\top b, & \text{if } (c^\top - \lambda^\top A) \geq 0 \\ -\infty, & \text{otherwise.} \end{cases}$$

The second case is not interesting since we maximize the function. Therefore the dual problem is

$$\begin{aligned} \max \quad & b^\top \lambda \\ \text{s.t.} \quad & A^\top b \leq c. \end{aligned} \tag{D}$$

Note that the problem is not sign constrained on the variable λ. We can actually show that all linear programming problems can be converted to the standard form. We will demonstrate one case in a later section where we deal with the metabolic pathway model.

If the primal problem has a feasible solution and an unbounded objective value $-\infty$, which could never be larger than the objective value of the dual problem according to the Weak Duality Theorem. So the dual problem is infeasible. Similarly if the primal problem admits a feasible solution and an unbounded objective value, ∞, which could never be smaller than the objective value of the primal problem. If both problems have feasible solutions, then if the objective values at these solutions are equal then they are optimal by the corollary to the Weak Duality Theorem. In fact we can show the **Strong Duality Theorem**: *If both (P) and (D) are feasible, then they both have optimal solutions with the same objective value, [1].* We summarize the arguments as a theorem:

Theorem 14 (Duality Theorem of LP) *Consider the primal and dual LP problems described above. One of the following mutually exclusive cases will occur:*

(i) The primal problem has a feasible solution and an unbounded objective value, in which case the dual problem is infeasible.

(ii) The dual problem has a feasible solution and an unbounded objective value, in which case the primal problem is infeasible.

(iii) Both problems are feasible, in which case both problems have optimal solutions $\bar{x}$ and $\bar{\lambda}$ such that $c^\top \bar{x} = \bar{\lambda}^\top b$ and $(c^\top - \bar{\lambda}^\top A)\bar{x} = 0$

(iv) Both problems are infeasible [1].

2.3 Pontryagin's Minimimum Principle

Optimal control theory is a mathematical branch which deals with problems of finding a law that can control a system such that the optimality condition is satisfied [14].

It has many applications in science and engineering. An optimal control problem in continuous time is a type of a mathematical optimization problem aiming to find a control law which minimizes or maximizes some payoff or performance index or cost function (sometimes the objective functional) subject to certain dynamics and other admissible condition for control and state variables. A problem without constraints is called unconstrained problem; in the opposite case we have constrained problem [14].

The optimal control problem can be solved by using Pontryagin's maximum principal which is the necessary condition or by solving the Hamilton-Jacobi-Bellman equation which is necessary and sufficient condition.

A variable is considered as a control variable if: (i) it is subject to the optimizer's choice and (ii) it will have an impact on the value of the state variable of interest [4].

We will discuss the Pontryagin Minimum Principle in several cases. The derivation and proofs will follow the book "Mathematical Theory of Optimal Processes" by Pontryagin *et al* [12]. We start with their simplest case for autonomous systems controlling the initial to a fixed final state.

2.3.1 Autonomous systems with fixed initial and final states

Consider the optimization problem

$$\begin{cases} J^* = \quad \min \displaystyle\int_0^{t_f} f_0(x(t), u(t))dt \\ \qquad \text{s.t.} \begin{cases} \dot{x}(t) = f(x(t), u(t)) \\ x(0) = x_{\text{i}},\ x(t_f) = x_f \\ u(t) \in U,\ t_f > 0 \end{cases} \end{cases} \tag{2.3}$$

where we assume that

- $f_0 : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}$ and $f : \mathbb{R}^n \times \mathbb{R}^m \to \mathbb{R}^n$ are C^1-functions (i.e. continuous and continuously differentiable) with respect to x.
- The final time t_f is free. This means that it is a variable that must be optimized.

It is important to note that there is no restriction to assume that the initial time is $t_0 = 0$. The reason is that an autonomous system allows arbitrary time shift of its solutions. In other words, if $u(t) \in U$ transfers $x(0) = x_{\text{i}}$ to $x(t_f) = x_f$, then $\tilde{u}(t) = u(t - t_0)$ transfers $\tilde{x}(t_0) = x_{\text{i}}$ to $\tilde{x}(t_0 + t_f) = x_f$, and the trajectories are related to $\tilde{x}(t) = x(t - t_0)$. See [13]. Moreover, for the objective functional we have the following relation:

$$\int_{t_0}^{t_f + t_0} f_0(\tilde{x}(t), \tilde{u}(t))dt = \int_0^{t_f} f_0(x(t), u(t))dt.$$

Following Pontryagin we reformulate our problem (2.3) by introducing a new variable

$$x_0(t) = \int_0^t f_0(x(s), u(s))ds.$$

This yields

$$\dot{x}_0(t) = f_0(x(t), u(t)) \text{ and } x_0(0) = 0.$$

Next we define the extended state vector and the extended vector field as

$$\tilde{x} = \begin{pmatrix} x_0 & x_1 & \cdots & x_n \end{pmatrix}^\top,\ \tilde{f} = \begin{pmatrix} f_0 & f_1 & \cdots & f_n \end{pmatrix}^\top.$$

Consequently the initial extended state is $\tilde{x}_{\mathrm{i}} = (0 \ x_{\mathrm{i}}^{\top})^{\top}$, and the final extended state belongs to the line $\pi := \mathbb{R} \times \{x_f\}$. This gives us an equivalent formulation of (2.3) [5]

$$\begin{cases} J^* = \min \quad x_0(t_f) \\ \text{s.t.} \begin{cases} \dot{\tilde{x}}(t) = \tilde{f}(\tilde{x}(t), \tilde{u}(t)) \\ \tilde{x}(0) = \tilde{x}_{\mathrm{i}}, \ \tilde{x}(t_f) \in \pi \\ u(t) \in U, \ t_f > 0 \end{cases} \end{cases}.$$

This is illustrated by Figure 1.

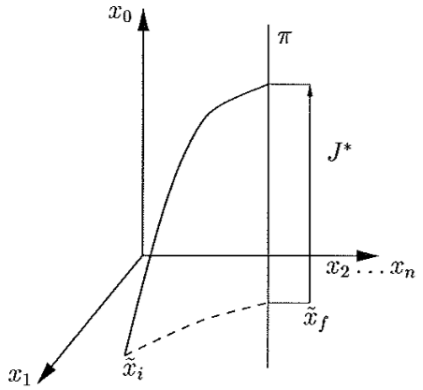

Figure 2.1: The dashed line corresponding to the state trajectory $x(t)$ and the solid line corresponds to the extended state trajectory $\tilde{x}(t)$.

Introduce now the extended vector $\tilde{\lambda} = \begin{pmatrix} \lambda_0 & \lambda_1 & \cdots & \lambda_n \end{pmatrix}^{\top}$ to this reformulated optimization problem we get from the PMP in for free final state we have the adjoint system

$$\dot{\lambda}_j(t) = -\sum_{k=0}^{n} \frac{\partial f_k(x(t), u(t))}{\partial x_j} \lambda_k(t), \quad j = 0, 1, ..., n.$$

In particular, we have

$$\dot{\lambda}_0 = 0 \quad \Longrightarrow \quad \lambda_0 = \text{const.}$$

The Hamiltonian function the extended problem can be defined as follows:

$$H(x, u, \tilde{\lambda}) := \tilde{\lambda}^{\top} \tilde{f}(x, u) = \lambda_0 f_0(x, u) + \lambda^{\top} f(x, u)$$

where $\lambda = \begin{pmatrix} \lambda_1 & \cdots & \lambda_n \end{pmatrix}^{\top}$. Using the Hamiltonian we have the state and adjoint equations as follows

$$\dot{\tilde{x}}(t) = H_{\tilde{\lambda}}(x(t), u(t), \tilde{\lambda}(t)) = \tilde{f}(x(t), u(t))$$
$$\dot{\tilde{\lambda}}(t) = -H_{\tilde{x}}(x(t), u(t), \tilde{\lambda}(t)) = -\tilde{f}_{\tilde{x}}(x(t), u(t))^{\top} \tilde{\lambda}(t)$$

Theorem 15 (PMP control to a fixed point) *Assume that* $(x^*(t), u^*(t), t_f^*)$ *is an optimal solution of* (2.3)*, i.e., it transfers* x_i *to* x_f *by minimal cost at the optimal transition time* t_f^**. Then there exists a nonzero extended adjoint function* $\tilde{\lambda}(\cdot)$ *such that*

(i) $\dot{\tilde{\lambda}}(t) = -H_{\tilde{x}}(x^*(t), u^*(t), \tilde{\lambda}(t))$*;*

(ii) $H(x^*(t), u^*(t), \tilde{\lambda}(t)) = \min_{v \in U} H(x^*(t), v, \tilde{\lambda}(t)) = 0$ *for all* $t \in [0, t_f^*]$*;*

(iii) $\lambda_0(t) =$ *const.* ≥ 0

Before processing the proof we make the following remarks.

Remark 1. The theorem can be transformed to a maximization problem but the sign of λ_0 is negative.

Remark 2. Note that (i) the Hamiltonian function does not depend on x_0, and (ii) the adjoint equation is a system of linear differential equations.

Remark 3. If the final time t_f is fixed then theorem remains the same except the second statement (ii) is replaced by
(ii) $H(x^*(t), u^*(t), \tilde{\lambda}(t)) = \min_{v \in U} H(x^*(t), v, \tilde{\lambda}(t)) =$ const. for all $t \in [0, t_f^*]$;
This will be made clear in the proof of the theorem.

Remark 4. Since we know that λ_0 is a constant, we often replace the extended adjoint equation in (i) by

$$\dot{\lambda}(t) = -H_x(x^*(t), u^*(t), \tilde{\lambda}(t)) = -\frac{\partial f_0}{\partial x}(x^*(t), u^*(t))\lambda_0 - \frac{\partial f}{\partial x}(x^*(t), u^*(t))^\top \lambda(t).$$

In many situations we simply assume $\lambda_0 = 1$.

Remark 5. The λ_0 does not appear in PMP for free final state. In most situations we will have it positive and then there is no restriction to let it be 1. This follows because the adjoint equation is linear so we can multiply it by any positive number. The cases where $\lambda_0 = 0$ are pathological. It is often due to lack of controllability or other related problems. We give an example to show this in a little while. Note that $\lambda_0 = 0$ means that the cost integral does not affect the criterion. For the most parts of literature one simply ignores the case $\lambda_0 = 0$.

Now we consider an example.

Example: (LQ control). Minimize

$$J = \int_0^{t_f} u(t)^2 dt \quad \text{subject to} \quad \begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ x(0) = x_0, x(t_f) = 0 \end{cases}$$

Assume that the system is completely controllable. We start by minimizing the Hamiltonian

$$H(x,u,\tilde{\lambda}) = \lambda_0 u^2 + \lambda^\top (Ax + Bu).$$

There are two cases.

Case 1: $\lambda_0 = 0$. If this is the case, we have

$$\arg\min_u H(x,u,\tilde{\lambda}) = \arg\min_u [\lambda^\top (Ax + Bu)] = \pm\infty$$

unless $\lambda^\top B = 0$. It is however, impossible to have $u = \pm\infty$ on a nonzero time interval since then the cost would be infinite, which clearly cannot be the minimum since we know that the system can be driven to origin with finite energy expenditure. The other alternative $\lambda(t)^\top B = 0$ for $t \in [0, t_f]$ is also impossible. To see this we note that the adjoint equation

$$\dot{\lambda}(t) = -A^\top p(t)$$

has the solution $\lambda(t) = e^{-A^\top t}\lambda(0)$. Hence, in order for $\lambda(t)^\top B = 0$ for $t \in [0, t_f]$ we need

$$\begin{cases} \lambda(0)^\top B = 0 \\ \dot{\lambda}(0)^\top B = 0 \\ \vdots \\ \lambda^{(n-1)}(0)^\top B = 0 \end{cases} \Leftrightarrow \begin{cases} \lambda(0)^\top B = 0 \\ \lambda(0)^\top AB = 0 \\ \vdots \\ \lambda(0)^\top A^{n-1} B = 0 \end{cases} \Leftrightarrow \quad \lambda(0)^\top [B, AB, ..., A^{n-1}B] = 0.$$

If the system is controllable, then the matrix $[B, AB, A^{n-1}B]$ has full rank, which implies that $\lambda(0) = 0$. However, then $\lambda(t) = 0$ and $\tilde{\lambda}(t) = 0$ which contradicts the theorem. This leads to the conclusion that $\lambda_0 = 0$ is impossible for a controllable system.

The above arguments explains why we can skip this case without any serious loss.

Case 2: $\lambda_0 = 1$. We have $u(t) = -\frac{1}{2}B^\top \lambda$ minimizing the Hamiltonian. The adjoint equation is

$$\dot{\lambda}(t) = -A^\top \lambda(t)$$

which has the solution $\lambda(t) = e^{-A^\top t}\lambda(0), x(0) = x_0$. By the variation of constants formula we obtain

$$\begin{aligned} x(t_f) &= e^{At_f}x_0 - \frac{1}{2}\int_0^{t_f} e^{A(t_f - s)} BB^\top e^{-A^\top s} ds \lambda(0) \\ &= e^{At_f}x_0 - \frac{1}{2}W(t_f, 0)e^{-A^\top t_f}\lambda(0) \end{aligned}$$

where the reachability Grammian is

$$W(t_f, 0) = \int_0^{t_f} e^{A(t_f - s)} B B^\top e^{A^\top (t_f - s)} ds$$

In our case the system is controllable and therefore $W(t_f, 0)$ is positive definite and thus invertible. We can solve for $p(0)$, which gives

$$p(0) = 2e^{A^\top t_f} W(t_f, 0)^{-1} e^{A t_f} x_0$$

This gives the optimal control

$$u(t) = -\frac{1}{2} B^\top e^{-A^\top t} p(0) = -B^\top e^{A^\top (t_f - t)} W(t_f, 0)^{-1} e^{A t_f} x_0$$

and the optimal cost becomes (after some calculations)

$$J^* = x_0^\top e^{A^\top t_f} W(t_f, 0)^{-1} e^{A t_f} x_0.$$

Remark 6. The conditions are necessary for stationary "points" and we can use them to find the candidates for optimality. A professional way to address optimal control problems is to start with investigation of the vector field and the objective functional to determine if

- it is possible to conclude that there must exist an optimal solution,
- if the optimal solution is unique.

The existence and uniqueness questions are rarely discussed in elementary course and addressed in more advanced books e.g. the Pontryagin's book mentioned above. The next step is to apply the PMP, (here we take $\lambda_0 = 1$)

1. Define the Hamiltonian: $H(x, u, \lambda) = f_0(x, u) + \lambda^\top f(x, u)$.
2. Perform pointwise minimization: $\tilde{\mu}(x, \lambda) = \arg\min_{u \in U} H(x, u, \lambda)$.
3. Solve the two-point boundary value problems (TPBVP)

$$\dot{x}(t) = H_\lambda(x(t), \tilde{\mu}(x(t), \lambda(t)))$$
$$\dot{\lambda}(t) = -H_x(x(t), \tilde{\mu}(x(t), \lambda(t)))$$

   with some boundary conditions, which will be discussed later.

4. Compare the candidate solutions obtained using PMP.

Note that the state and adjoint equations are two-point boundary value problems. One of the difficulties in using PMP lies in solving TPBVP, which needs to find appropriate boundary conditions for x and λ. They are often solved numerically, using e.g. shooting method.

2.3.2 Proof of Theorem 15

Now we turn to the proof of Theorem 15. Looking at the proof in Pontryagin's book at first time one may get an impression that it is very complicated. However, the idea behind the proof are pretty easy to understand. The complicated part in the proof is that $u(\cdot)$ is allowed to be discontinuous since we only require it piecewise continuous. To make the idea clear, we do not discuss the problem with discontinuity in the control u. The proof is divided into several steps.

Step 1. Perturbation of optimal control and transition time

Assume that $(x^*(\cdot), u^*(\cdot), t_f^*)$ is an optimal solution. The main idea is to investigate what happens to the value of the cost functional if there is a small change at the optimal control $u^*(\cdot)$ and the optimal transfer time t_f^*. *Basic perturbation of control*: Let us consider a small perturbation in time at some time τ, where $u^*(\cdot)$ is continuous.

$$u(t) = \begin{cases} u^*(t), & t \le \tau - \Delta\tau \\ v, & \tau - \Delta\tau \le t \le \tau \\ u^*(t), & t \ge \tau \end{cases} \tag{2.4}$$

where $v \in U$. Note that only $\Delta\tau$ is assumed to be small and v may be very different from $u^*(\tau)$. The question is how much such a change will affect the cost $x_0(t_f)$. Now we study the local effect of the perturbation. As usual we use first order approximation. It gives

$$\begin{aligned} \delta\tilde{x}(\tau) = \tilde{x}(\tau) - \tilde{x}^*(\tau) &= \int_{\tau-\Delta\tau}^{\tau} \left(\tilde{f}(x(t), v) - \tilde{f}(x^*(t), u^*(t)) \right) dt \\ &= \left(\tilde{f}(x^*(\tau), v) - \tilde{f}(x^*(\tau), u^*(\tau)) \right) \Delta\tau + o(\Delta\tau) \end{aligned}$$

Next we shall demonstrate how this change can be transported to the optimal end point $x^*(t_f)$ using the linearized dynamics.

Transportation of the basic perturbation: We have seen that a perturbation of the optimal control in the form (2.4) to the first order corresponds to a change $\tilde{x}(\tau) = \tilde{x}^*(\tau) + \delta\tilde{x}(\tau)$ of the state vector at time τ, where

$$\delta\tilde{x}(\tau) = (\tilde{f}(x^*(\tau), v) - \tilde{f}(x^*(\tau)))\Delta\tau.$$

Now we want to show how this perturbation is transported to the optimal final time t_f^*. Note that we can view $\delta\tilde{x}(\tau)$ as a perturbation in the initial condition at time τ. Then it follows, by the theorem on continuous dependence on the iniitial conditions and right hand side of ordinary differential equations, that

$$\delta\tilde{x}(t_f^*) = \tilde{x}(t_f^*) - \tilde{x}^*(t_f^*) = O(\delta\tilde{x}(\tau)).$$

This is a motivation for considering the linearized dynamics. Processing by Taylor expansion we obtain

$$\begin{aligned}\frac{d}{dt}\delta\tilde{x}(t) =&\dot{\tilde{x}}(t) - \dot{\tilde{x}}^*(t) = \tilde{f}(x(t), u^*(t)) - \tilde{f}(x^*(t), u^*(t)) \\ =&\tilde{f}_x(x^*(t), u^*(t))\delta\tilde{x}(t) + o(\delta\tilde{x}(t)), t \in [\tau, t_f^*].\end{aligned}$$

Hence we have proved that the perturbation to first order approximation is transported by the linear system

$$\frac{d}{dt}\delta\tilde{x}(t) = A(t)\delta\tilde{x}(t),\ \delta\tilde{x}(\tau) = (\tilde{f}(x^*(\tau), v) - \tilde{f}(x^*(\tau), u^*(\tau)))\Delta\tau$$

where $A(t) = \tilde{f}_{\tilde{x}}(x^*(t), u^*(t))$. Hence, we have

$$\delta\tilde{x}(t_f^*) = \Phi(t_f^*, \tau)\delta\tilde{x}(\tau)$$

with Φ being the transition matrix corresponding to $A(t)$. Figure 2 shows how the perturbation $\delta\tilde{x}(\tau)$ is moved to a perturbation $\Phi(t_f^*, \tau)\delta\tilde{x}(\tau)$, which has its vertex at the optimal point $x^*(t_f^*)$.

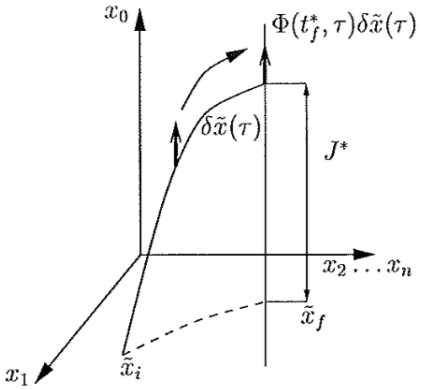

Figure 2.2: Transportation of the perturbation: $\delta\tilde{x}(\tau)$ to the end point by the linearized dynamics. The perturbation is illustrated by thick arrows.

Perturbation of the final time: We can perturb the final time either by extending the optimal control to time $t_f^* + \Delta t$ (if $\Delta t \geq 0$)

$$u(t) = \begin{cases} u^*(t), & t \in [0, t_f^*] \\ u^*(t_f^*), & t \in [t_f^*, t_f^* + \Delta t] \end{cases}$$

or by stopping earlier (if $\Delta t \leq 0$)

$$u(t) = u^*(t_f^* + \Delta t), \quad t \in [0, t_f^* + \Delta t].$$

Therefore, a perturbation of the final time to $t_f^* + \Delta t$ yields the following change of the end point

$$\delta\tilde{x}(t_f^*) = \tilde{x}(t_f^*+\Delta t) - \tilde{x}^*(t_f^*) = \int_{t_f^*}^{t_f^*+\Delta t} \tilde{f}(x(t), u(t))dt = \tilde{f}(x^*(t_f^*), u^*(t_f^*))\Delta t + o(\Delta t).$$

Note that Δt here may be positive or negative.

Combined perturbation: Let us now combine perturbations discussed above, see Figure 3.

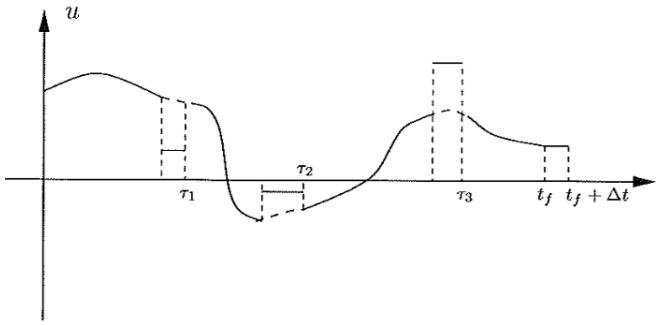

Figure 2.3: A more general perturbation of $u^*(\cdot)$ drawn in dashed lines and the perturbed control in solid line.

Each of the individual perturbations will contribute to the perturbation at the end point in the way described above. The first order contribution at the end point can then be obtained by adding up the individual contributions.

Assume that the control is perturbed at times $0 < \tau_1 \leq \tau_2 \leq \cdots \leq \tau_{p-1} \leq \tau_p < t_f^*$ and that the control value at each perturbation point is $v_k \in U$. If we choose the intervals of perturbation to be $I_k := [\tau_k - \alpha_k\Delta\tau, \tau_k]$, where the $\alpha_k \geq 0$ are such that the intervals are disjoint. Then we have the perturbed control

$$u(t) = \begin{cases} v_k, & t \in I_k, v_k \in U \\ u^*(t), & t \notin I_K \cup [t_f^*, t_f^* + \Delta t] \\ u^*(t_f^*), & t \in [t_f^*, t_f^* + \Delta t] \end{cases}$$

and similar if $\Delta < 0$. It can be shown that all possible perturbed controls of this type gives rise the following set of end point perturbations, which follows from the superposition of the individual perturbations at point τ_k and at the end point t_f^*:

$$\mathcal{K}(t_f^*) := \{\tilde{f}(x^*(t_f^*), u^*(t_f^*))\Delta t + \sum_{k=1}^{p} \alpha_k \Phi(t_f^*, \tau_k)\delta\tilde{x}_k : \Delta t \in \mathbb{R}; \alpha_k \geq 0; \tau_k \in (0, t_f^*),$$
$$p \text{ is an integer, } \delta\tilde{x}_k = (\tilde{f}(x^*(\tau_k), v_k) - \tilde{f}(x^*(\tau_k), u^*(\tau_k)))\Delta\tau, v_k \in U\}$$

Clearly this set is a convex cone.

Step 2. Separating hyperfine at the endpoint Now we know that the set of end point perturbations is a cover cone $\mathcal{K}(t_f^*)$ with vertex at $\tilde{x}^*(t_f^*)$, that is we consider the set $\mathcal{K}(t_f^*) + \tilde{x}^*(t_f^*)$. Next we consider the ray

$$r := \{x_0 : x_0 \leq x_0^*(t_f^*)\} \times \{x_f\}.$$

This consists of all points below the optimal end point. Intuitively it is clear that this ray cannot contain any points of $\mathcal{K}(t_f^*)+\tilde{x}^*(t_f^*)$, because that would contradict optimality. It is possible to give a mathematical justification of this but we just give a picture to illustrate this fact in Figure 4: Note that

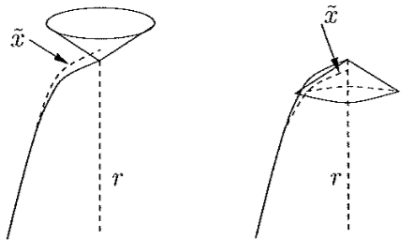

Figure 2.4: Left: The ray r does not contain any points of the cone $\mathcal{K}(t_f^*)$. Then every admissible perturbation of the control and/or transition time will give a trajectory $\tilde{x}(\cdot)$ with end point above the optimal point. Right: The cone $\mathcal{K}(t_f^*)$ intersects the ray r and then it is possible to perturb the the control and/or transition time such that the corresponding trajectory $\tilde{x}(\cdot)$ intersects the ray below $\tilde{x}^*(t_f^*)$, contradicting the optimality of $\tilde{x}^*(\cdot)$. So this case is impossible.

we draw the cones as "icecream cones" but it should be understood that they can have very different appearance in reality. We also point out that the separating hyperplane is not necessarily unique.

Since the ray r and the cone $\mathcal{K}(t_f^*)$ are both convex and with no common points it follows that there exists a separating hyperplane. In other words, there exists a nonzero vector a such that

$$\begin{aligned} &a^\top y \geq 0, \ \forall y \in \mathcal{K}(t_f^*) \\ &a^\top y \leq 0, \ \forall y \in r - x^*(t_f^*) = \{(y_0, 0, ..., 0) : y_y \leq 0\}. \end{aligned} \tag{2.5}$$

It is pictured Figure 5. It is important to note that the first coordinate of a must be positive, that is $a_0 \geq 0$. Otherwise the second condition above cannot hold.

Step 3. Minimizing the Hamiltonian.

Now we will prove that

$$H(\tilde{x}^*(t), u^*(t), \tilde{\lambda}(t)) = \min_{v \in U} H(\tilde{x}^*(t), v, \tilde{\lambda}(t)).$$

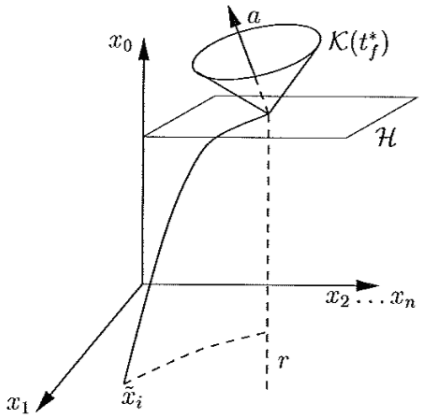

Figure 2.5: The perturbation cone $\mathcal{K}(t_f^*)$ has its vertex at the optimal $x^*(t_f^*)$. The vector a is the normal of the corresponding hyperplane.

Let the end condition for the adjoint differential equation be $\tilde{\lambda}(t_f^*) = a$. That is,

$$\dot{\tilde{\lambda}}(t) = -A(t)^\top \tilde{\lambda}(t), \quad \tilde{\lambda}(t_f^*) = a$$

where $A(t) = \tilde{f}_{\tilde{x}}(x^*(t), u^*(t))$. Then we can easily show that $\tilde{\lambda}(t) = \Phi(t_f^*, t)^\top a$. With this $\tilde{\lambda}$ we obtain

$$\begin{aligned}
&H(x^*(\tau_k), v_k, \tilde{\lambda}(\tau_k)) - H(x^*(\tau_k), u^*(\tau_k), \tilde{\lambda}(\tau_k)) \\
=&\tilde{\lambda}(\tau_k)^\top \left(\tilde{f}(x^*(\tau_k), v_k) - \tilde{f}(x^*(\tau_k), u^*(\tau_k)) \right) \\
=&a^\top \Phi(t_f^*, \tau_k) \left(\tilde{f}(x^*(\tau_k), v_k) - \tilde{f}(x^*(\tau_k), u^*(\tau_k)) \right) = a^\top y \geq 0
\end{aligned}$$

since $y = \Phi(t_f^*, \tau_k) \left(\tilde{f}(x^*(\tau_k), v_k) - \tilde{f}(x^*(\tau_k), u^*(\tau_k)) \right) \in \mathcal{K}(t_f^*)$. This show the optimality condition as desired for $v_k \in U$ and $\tau_k \in (0, t_f^*)$ are arbitrary. Note also that the condition $\lambda_0 \geq 0$ also holds since we have already concluded that $a_0 \geq 0$.

Step 4. The value of Hamiltonian

Now we turn to proof of $H(x^*(t), u^*(t), \tilde{\lambda}(t)) = 0$ for all $t \in [0, t_f^*]$.
The first step is to show that th condition holds at the endpoint, i.e.,

$$H(x^*(t_f^*), u^*(t_f^*), \tilde{\lambda}(t_f^*)) = 0.$$

To this end we note that

$$y = \tilde{f}(x^*(t_f^*), u^*(t_f^*))\Delta t \in \mathcal{K}(t_f^*), \ \forall \Delta t,$$

Thus, in order for the separating hyperplane condition

$$a^\top y = a^\top \tilde{f}(x^*(t_f^*), u^*(t_f^*))\Delta t \geq 0.$$

to hold for all Δt, we need

$$a^\top y = a^\top \tilde{f}(x^*(t_f^*), u^*(t_f^*)) = 0.$$

In other words, the normal to the hyperplane in the above Figure 5 must be perpendicular to $\tilde{f}(x^*(t_f^*), u^*(t_f^*))$, yielding

$$H(x^*(t_f^*), u^*(t_f^*), \tilde{\lambda}(t_f^*)) = \tilde{\lambda}(t_f^*)^\top \tilde{f}(x^*(t_f^*), u^*(t_f^*)) = a^\top \tilde{f}(x^*(t_f^*), u^*(t_f^*)) = 0.$$

Our next step is to show that $H(x^*(t), u^*(t), \tilde{\lambda}(t))$ must be a constant function and this constant is zero due to the fact that it takes value zero at the final time we just proved. To make the idea transparent we only show a special case when (i) $u^*(\cdot)$ is continuously differentiable in a neighborhood about t and lies in the interior of U, and (ii) f_0 and f are C^1 also with respect to u. For a more general situation we refer to Pontryagin's book [12]. for details.

In this special case we have, using the state and adjoint equations (or simply the Hamiltonian system) and the pointwise minimization

$$H_u(x^*(t), u^*(t), \tilde{\lambda}(t)) = 0.$$

Then

$$\frac{d}{dt} H(x^*(t), u^*(t), \tilde{\lambda}(t)) = \frac{\partial H^\top}{\partial \tilde{x}} \dot{\tilde{x}}^* + \frac{\partial H^\top}{\partial \tilde{\lambda}} \dot{\tilde{\lambda}}^* + \frac{\partial H^\top}{\partial u} \dot{u} = -(\dot{\tilde{\lambda}})^\top \dot{\tilde{x}} + (\dot{\tilde{x}})^\top \dot{\tilde{\lambda}} = 0$$

This shows that the Hamiltonian $H(x^*(t), u^*(t), \tilde{\lambda}(t))$ is constant along the optimal trajectory.

2.3.3 Optimal control to a manifold

In this section we show what happens with the optimality conditions in Theorem 15 if the terminal state is required to belong to a manifold S_f. First we give a short description on what kind of manifolds we will work on. An $(n-p)$-dimensional smooth manifold in $\mathbb{R}^n$ is an intersection of p hypersurfaces (each described by a set $S_k := \{x \in \mathbb{R}^n : g_k(x) = 0\}$):

$$S_f := \{x \in \mathbb{R}^n : G(x) = 0\}$$

with $G(x) = (g_1(x)\ g_2(x)\ \cdots\ g_p(x))^\top$, where $\nabla g_k(x)$ are linearly independent for all points on the manifold. (in fact it is enough to assume linear independence in a neighborhood of the final point). This is equivalent to ask the matrix

$$G_x(x) = \begin{pmatrix} \dfrac{\partial g_1(x)}{\partial x_1} & \cdots & \dfrac{\partial g_1(x)}{\partial x_n} \\ \vdots & & \vdots \\ \dfrac{\partial g_p(x)}{\partial x_1} & \cdots & \dfrac{\partial g_p(x)}{\partial x_n} \end{pmatrix}$$

has rank p for all $x \in S_f$.
Now formulate the optimal control problem:

$$\begin{cases} J^* = \min \int_0^{t_f} f_0(x(t), u(t))dt \\ \quad \text{s.t.} \begin{cases} \dot{x}(t) = f(x(t), u(t)) \\ x(0) = x_{\text{i}},\ x(t_f) \in S_f \\ u(t) \in U,\ t_f > 0 \end{cases} \end{cases} \tag{2.6}$$

where everything is defined as in the previous section. This new problem is different from the old one (2.3) only in that we now need to determine the optimal position at the terminal manifold S_f. It turns out that the only change to the optimality condition in Theorem 15 is that the boundary value of the adjoint vector must be perpendicular to the manifold S_f. To prove this statement we take the same approach as before and introduce the extended state vector $\tilde{x}$ and the extended vector field $\tilde{f}$. We also introduce an extended terminal state manifold

$$\tilde{S}_f := \mathbb{R} \times S_f = \{\tilde{x} \in \mathbb{R}^n : G(x) = 0\}.$$

Then the optimal control problem can be reformulated as follows: Find an admissible control such that the extended state vector is transferred from $\tilde{x}_{\text{i}} = (0, x_{\text{i}}^\top)^\top$ to a point on the extended manifold $\tilde{S}_f$ with as low x_0 coordinate as possible, see Figure 6.

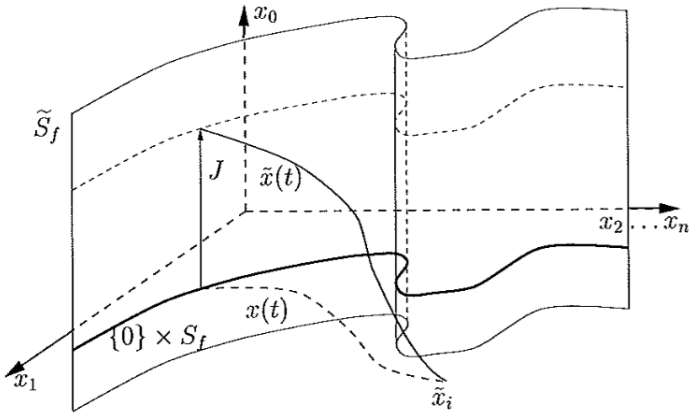

Figure 2.6: The state trajectory $x(t)$ is the dashed curve. The corresponding extended state trajectory $\tilde{x}(t)$ is the solid curve.

Let us repeat the key idea behind the proof of Theorem 15 to derive the PMP for driving the trajectory to final state onto a manifold: The optimal control and the optimal transition time t_f^* where perturbed, which contributes to a

perturbation cone $\mathcal{K}(t_f^*)$ at the optimal end point $\tilde{x}^*(t_f^*)$. Then we proved that there must be a hyperplane that separates the perturbation cone $\mathcal{K}(t_f^*)$ from the terminal points with smaller values of the x_0-coordinate than the the optimal. The final value of extended vector $\tilde{\lambda}(t_f^*)$ was the normal vector to the hyperplane (as pointed out before it's not necessary that it be unique). Transportation of the hyperplane to points corresponding to times in the interval $[0, t_f^*]$ was then used to derive the conditions on the Hamiltonian function.

Now the situation is similar, but the hyperplane must be tangent to the "curve" $\{x_0^*(t_f^*)\} \times S_f$ at the optimal point, depicted as in Figure 7. An

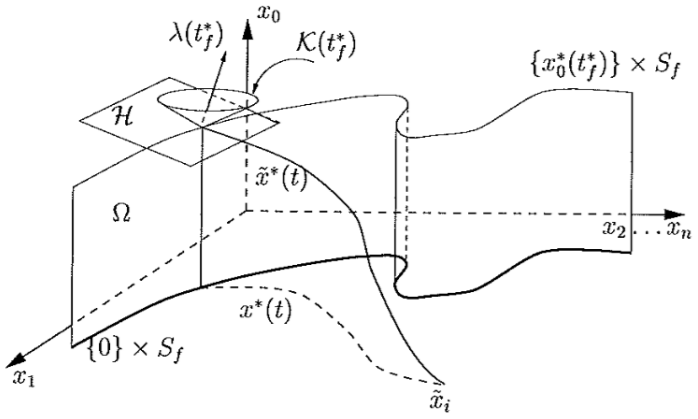

Figure 2.7: Let the surface $\Omega := \{x_0 : x_0 \leq x_0^*(t_f^*)\} \times S_f$ of points on the extended terminal manifold with smaller x_0 coordinate than the optimal point $x^*(t_f^*)$. In order for $\tilde{x}^*(t_f^*)$ to be the optimal terminal point, it is necessary that the perturbation cone $\mathcal{K}(t_f^*)$ do intersect the interior of Ω (locally about the optimal point). We can show that this implies the existence of a separating hyperplane tangential to the boundary of Ω, i.e., tangential to the "curve" $\{x_0^*(t_f^*)\} \times S_f$.

arbitrary tangent vector of $\{x_0^*(t_f^*)\} \times S_f$ at $\tilde{x}^*(t_f^*)$ has the form $\tilde{v} := (0\ v^\top)$ where $v \in \mathbb{R}^n$ is perpendicular to all gradients $\nabla g_k(x^*(t_f^*))$, that is,

$$G_x(x^*(t_f^*))v = 0,$$

or explicitly,

$$\begin{pmatrix} \dfrac{\partial g_1(x^*(t_f^*))}{\partial x_1} & \cdots & \dfrac{\partial g_1(x^*(t_f^*))}{\partial x_n} \\ \vdots & & \vdots \\ \dfrac{\partial g_p(x^*(t_f^*))}{\partial x_1} & \cdots & \dfrac{\partial g_p(x^*(t_f^*))}{\partial x_n} \end{pmatrix} v = 0.$$

Therefore, for a hyperplane to be tangential to the "curve" $\{x_0^*(t_f^*)\} \times S_f$

we require that its normal be perpendicular to $\tilde{v}$,

$$\tilde{v}^\top \tilde{\lambda}(t_f^*) = 0,$$

implying the following *transversality condition*

$$\lambda(t_f^*)^\top v = 0 \text{ for all } v \text{ such that } \begin{pmatrix} \frac{\partial g_1(x^*(t_f^*))}{\partial x_1} & \cdots & \frac{\partial g_1(x^*(t_f^*))}{\partial x_n} \\ \vdots & & \vdots \\ \frac{\partial g_p(x^*(t_f^*))}{\partial x_1} & \cdots & \frac{\partial g_p(x^*(t_f^*))}{\partial x_n} \end{pmatrix} v = 0, \tag{2.7}$$

or equivalently,

$$\lambda(t_f^*) = G_x(x^*(t_f^*))^\top \nu = \sum_{k=1}^{p} \nu_k \nabla g_k(x^*(t_f^*)), \text{ for some appopriate vector } \nu \in \mathbb{R}^p.$$

This transversality condition is often written as

$$\lambda(t_f^*) \perp S_f.$$

The above argument is an outline of a proof to the following theorem of PMP.

Theorem 16 (PMP: control to a manifold) *Assume that $(x^*(t), u^*(t), t_f^*)$ is an optimal solution of (2.6), i.e., it transfers x_i to S_f by minimal cost at the optimal transition time t_f^*. Then there exists a nonzero extended adjoint function $\tilde{\lambda}(\cdot)$ such that*

(i) $\dot{\tilde{\lambda}}(t) = -H_{\tilde{x}}(x^*(t), u^*(t), \tilde{\lambda}(t))$;

(ii) $H(x^*(t), u^*(t), \tilde{\lambda}(t)) = \min_{v \in U} H(x^*(t), v, \tilde{\lambda}(t)) = 0$ *for all* $t \in [0, t_f^*]$;

(iii) $\lambda_0(t) = const. \geq 0$;

(iv) $\lambda(t_f^*) \perp S_f$.

For the complete details of proof we refer to Pontryagin's book [12].

2.3.4 Optimal control from a manifold to a manifold

In this section we apply the previous results to the following cases:

- The initial point lies on a smooth manifold;
- There is a terminal cost term.

So we consider the optimization problem

$$\begin{cases} \min \quad \displaystyle\int_0^{t_f} f_0(x(t),u(t))dt + \phi(x(t_f)) \\ \quad \text{s.t.} \begin{cases} \dot{x}(t) = f(x(t),u(t)) \\ x(0) \in S_0,\ x(t_f) \in S_f \\ u(t) \in U,\ t_f \geq 0 \end{cases} \end{cases} \tag{2.8}$$

where ϕ is assumed to be a C^1-function, S_0 is a smooth manifold, and everything is defined as in the previous sections.

To derive necessary optimality conditions we rewrite the problem so that the precious results can be applied. Introduce new control and state variables u_{m+1} and x_{n+1}, respectively. Then we have the following equivalent optimization problem

$$\begin{cases} \min \quad \displaystyle\int_0^{t_f} \left(f_0(x(t),u(t)) + u_{m+1}(t)\right) dt \\ \quad \text{s.t.} \begin{cases} \dot{x}(t) = f(x(t),u(t)) \\ \dot{x}_{n+1}(t) = u_{m+1} \\ x(0) \in S_0,\ x(t_f) \in S_f \\ x_{n+1}(0) = 0, x_{n+1}(t_f) = \phi(x(t_f)) \\ u(t) \in U,\ t_f \geq 0 \end{cases} \end{cases}$$

since

$$\int_0^{t_f} u_{m+1}(f)dt = x_{n+1}(t_f) = \phi(x(t_f)).$$

Now it is almost in the framework we have set up earlier. Apart from that we have an initial transversality condition on the adjoint variable due to the initial point on the manifold S_0, $\lambda(0) \perp S_0$ (which can be argued as that for the final transversality condition on the adjoint variable in Theorem 16), we can apply Theorem 16 to get the optimality conditions. After straightforward computation we will see that the terminal transversality condition is changed to

$$(\lambda(t_f^*) - \nabla\phi(x^*(t_f^*)))^\top v = 0 \text{ for all } v \text{ s.t. } \begin{pmatrix} \dfrac{\partial g_1(x^*(t_f^*))}{\partial x_1} & \cdots & \dfrac{\partial g_1(x^*(t_f^*))}{\partial x_n} \\ \vdots & & \vdots \\ \dfrac{\partial g_p(x^*(t_f^*))}{\partial x_1} & \cdots & \dfrac{\partial g_p(x^*(t_f^*))}{\partial x_n} \end{pmatrix} v = 0,$$

which can be written as $\lambda(t_f^*) - \lambda_0\nabla\phi(x^*(t_f^*)) \perp S_f$. Or equivalently,

$$\lambda(t_f^*) = \lambda_0\nabla\phi(x^*(t_f^*)) + G_x(x^*(t_f^*))^\top\nu = \lambda_0\nabla\phi(x^*(t_f^*)) + \sum_{k=1}^{p}\nu_k\nabla g_k(x^*(t_f^*))$$

for some vector $\nu \in \mathbb{R}^p$.

Now we are in the position to formulate the PMP where we ignore the pathological case and normalize $\lambda_0 = 1$.

Theorem 17 (PMP: control from a manifold to a manifold) *Define the Hamiltonian*

$$H(x, u, \lambda) = f_0(x, u) + \lambda^\top f(x, u).$$

Assume that $(x^*(t), u^*(t), t_f^*)$ *is an optimal solution of* (2.8)*, i.e., it transfers* $x(0) \in S_0$ *to* S_f *by minimal cost at the optimal transition time* t_f^**. Then there exists a nonzero adjoint function* $\lambda(\cdot)$ *such that*

(i) $\dot{\lambda}(t) = -H_x(x^*(t), u^*(t), \tilde{\lambda}(t))$;

(ii) $H(x^*(t), u^*(t), \tilde{\lambda}(t)) = \min_{v \in U} H(x^*(t), v, \tilde{\lambda}(t)) = 0$ *for all* $t \in [0, t_f^*]$;

(iii) $\lambda(0) \perp S_0$;

(iv) $\lambda(t_f^*) - \nabla\phi(x^*(t_f^*)) \perp S_f$.

For the complete details of proof and discussions we refer to [12].

Before we close this section we summarize some special cases.

- It is reasonable to assume that the terminal cost and the terminal manifold involve two disjoint set of states. For example $\phi(x) = (\phi(x_{p+1}, ..., x_n))$ and $g_k(x) = g_k(x_1, ..., x_p)$, $k = 1, ..., p$. Then the transversality condition will be reduced to

$$\begin{pmatrix} \lambda_{p+1}(t_f^*) \\ \vdots \\ \lambda_{p+n}(t_f^*) \end{pmatrix} = \begin{pmatrix} \frac{\partial\phi(x(t_f^*))}{\partial x_{p+1}} \\ \vdots \\ \frac{\partial\phi(x(t_f^*))}{\partial x_n} \end{pmatrix}$$

  and the remaining variables $(\lambda_1(t_f^*), ..., \lambda_p(t_f^*))$ remain undetermined.

- If $S_0 = \{x_{\mathrm{i}}\}$ (a given point) then there is no constraint on $\lambda(0)$.
- If $S_f = \mathbb{R}^n$ then $\lambda(t_f^*) = \nabla\phi(t_f^*)$.
- If $S_f = \mathbb{R}^n$ and $\phi = 0$ then $\lambda(t_f^*) = 0$.
- If $S_f = \{x_f\}$ (a given point) and $\phi = 0$ then there is no constraint on $\lambda(t_f)$.
- If the final time is fixed then (i) is replaced by

$$H(x^*(t), u^*(t), \lambda(t)) = \min_{v \in U} H(x(t), v, \lambda(t)) = \text{const.}$$

  for all $t \in [0, t_f]$.

Chapter 3

Basic biological/chemical concepts

In this section we provide some different theories related to this thesis.

3.1 Commonly used terminologies

In this thesis we shall use the following from biology in [3].

- *A cell* is the simplest fundamental unit to the living system.
- *Metabolism* is a set of all chemical reactions inside a living organism involving catabolic and anabolic reactions. Metabolism relates to various processes within the body that convert food and other substances into energy and other metabolic biproducts used by the body. [8] In metabolism we may have two categories:
- *Anabolic* reactions are reactions that syntheses complex molecules from simplex ones.
- *Catabolic* reaction refers to breaking down complex to simple molecules.
- *Metabolic pathways* is a successor of enzymatically catalyzed reaction occurring within a cell. It has been discovered that enzymes determine the metabolic pathways of a cell.
- *Chemical reaction* is a process by which atoms of the same or different elements rearrange to form a new substance.

3.2 Dynamic behaviour of reaction network

- *A dynamic equilibrium* is a steady state that engage a steady stream in the network [6].
- *Steady state* is the state in which the concentration of every metabolite does not change [8].
- *Reaction rate* is the amount of chemical substrate that is consumed and the amount of product that is formed by that reaction [8].

The rate of reaction depends on the concentration of the reactants and the physico-chemical reaction such as temperature, PH etc; and it will help us to predict the time varying changes in species concentration. Reaction rates are described by two assumptions: Spatial homogeneity (the reactants and the volume are equally distributed) and continuum hypothesis says that "in a given species there are a great number of molecules". A simple description under these assumptions is provided by the law of the mass that says:" The rate of chemical reaction is proportional to the product of the concentration of the reactants" [6].

Let $[\cdot]$ be the concentration of, then the rate of reaction $X \to Y$ is $k_1[X]$ the rate of reaction $R + T \to S$ is $k_2[R][T]$ because we have two reactants and the rate of $E + E \to D$ is $k_3[E]^2$ because we have two identical reactants.

Recall that *Kinetic order is an exponent raised to each reactant in the rate law* [7].

3.3 The law of mass action

The mass action law describes the rate at which chemicals interact in a reaction. It is assumed that different chemical molecules come into contact by collision before reacting, and that the collision rate is directly proportional to the number of molecules of each reacting species [7].
Suppose that two chemicals A and B form a product chemical C, this can be written as

$$A + B \xrightarrow{k} C$$

The law of mass action says that $\frac{dC}{dt}$ is proportion to the product of concentration A and B with proportionality constant k, where k is the rate constant of the reaction [7].
That is:

$$\frac{dC}{dt} = kAB. \tag{3.1}$$

The mass action law enable us to write an equation for the time derivative of the reactant concentration A and B

$$\frac{dA}{dt} = -kAB \tag{3.2}$$

and

$$\frac{dB}{dt} = -kAB \tag{3.3}$$

see [7]. When using the law of mass to find the rate of change of a concentration the chemical that the arrow points toward is increasing in concentration and have positive sign, the chemical that the arrow point away from is decreasing in concentration and have negative sign. The product of concentration on the right-hand-side is always that of the reactants from which that arrow points away, multiplied by the rate constant that is on top of the arrow. Equation (3.1) can be solved using law of conservation analytically. Each reactant original and converted, is conserved since one molecule of each reactant gets converted into one molecule of products [7]. Mathematically,

$$\frac{d(A+C)}{dt} = 0 \Leftrightarrow A + C = A_0$$

$$\frac{d(B+C)}{dt} = 0 \Leftrightarrow B + C = B_0$$

by (3.1), (3.2) and (3.3) where A_0 and B_0 are the initial concentrations of the reactants, and no product is initially present. Using the law of conservation, (3.1) becomes

$$\frac{dC}{dt} = k(A_0 - C)(B_0 - C)$$

with

$$C(0) = 0$$

using separation of variable to integrate, the solution to the above equation is

$$C(t) = A_0 B_0 \frac{e^{(B_0 - A_0)kt} - 1}{B_0 e^{(B_0 - A_0)kt} - A_0}$$

Further when $t \to \infty$ we get

$$\lim_{t\to\infty} C(t) = \begin{cases} A_0 & \text{if } A_0 < B_0 \\ B_0 & \text{if } B_0 < A_0. \end{cases}$$

The reaction stops after one of the reactants is washed-out; and the final concentration of the product is equal to the initial concentration of the washed-out reactant [7].

Now let us consider the case where all reactions are reversible; consider the reverse reaction,

$$A + B \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C.$$

As before we obtain the equation

$$\frac{dC}{dt} = k_+ AB - k_- C$$

where k_+ and k_- are reaction rate constants.
At the equilibrium

$$\frac{dC}{dt} = 0.$$

Using conservation law of mass we get

$$(A_0 - C)(B_0 - C) - \frac{k_-}{k_+} C = 0$$

where $\frac{k_-}{k_+}$ is called *equilibrium constant* denoted as K_{eq} and has unit of concentration [7]. At the equilibrium, the concentration of the products is given by the solution of the quadratic equation

$$C^2 - (A_0 + B_0 + K_{eq})C + A_0 B_0 = 0$$

Assume $A_0 = B_0 \equiv R_0$. Then the solution of the above equation is either

$$C = R_0 + \frac{K_{eq}}{2} + \frac{K_{eq}}{2}\sqrt{1 + \frac{4R_0}{K_{eq}}},$$

or

$$C = R_0 + \frac{K_{eq}}{2} - \frac{K_{eq}}{2}\sqrt{1 + \frac{4R_0}{K_{eq}}}.$$

Since $A + C = R_0$, C must be less than R_0. Thus we have a unique solution $C = R_0 - \frac{K_{eq}}{2}\sqrt{1 + \frac{4R_0}{K_{eq}}}$, which is called the *Michaelis-Menten constant* [7].
A mathematical model of chemical reaction network has the form of ordinary differential equation and its construction needs the law of mass action [6].

3.4 Enzimes kinetiks

Enzymes are proteins which are produced by living cells [3]. Enzyme is also a molecule which catalyses a biochemical reaction in living organism [14].

Each enzyme has a high particularity for active at least one reaction, and it can accelerate this reaction by million of times. Without enzymes most reactions are so slow for life to be possible. So enzymes are so important

to our life. Enzymes do not follow the law of mass action directly; with A substrate, P product, and E enzyme the reaction

$$S + E \overset{k}{\rightarrow} P + E$$

is a poor model since the reaction velocity $\frac{dP}{dt}$ is known to attain a finite limit when we increase the concentation of the substrate. The complete model presents the intermediate molecule and is proposed by Michaelis and Menten [7]. That model is:

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} P + E$$

The intermediate molecule explain that there is an increases of concentration because of the enzyme E.

3.5 Biochemical kinetics

- *Chemical kinetics* is the study of the rates of chemical reaction.

  In contrast to chemical reaction, in biochemical process we will use the law of rates instead of law of mass action [6].

- *Biochemical reaction* is a reaction within a cell [6].

  Elementary reaction is a single chemical reaction event. Individual biochemical reaction engage small network of elementary reaction. To develop rate laws for biochemical reaction we will divide these network into single reaction event using separation of time-scale method, [6].

- *Biochemical kinetics is the rate of laws that illustrate reaction event* [6]

One example of a rate law that describes an enzyme catalysed reaction is called Michaelis-Menten Kinetics. The individual chemical event involved in a single substrate enzyme catalysed reaction can be written as

$$S + E \rightleftharpoons C_1 \rightleftharpoons C_2 \rightleftharpoons P + E.$$

Putting C_1 and C_2 together by assuming that the time-scale of the conversion $C_1 \rightleftharpoons C_2$ is first time compered to scale of association and disassociation event and suppose that product P never joins free enzyme E. This makes the analysis simple and is motivated by the fact that laboratory measurements of reaction rates are typically carried out in the absence of product. Finally the above network can generalized as

$$S + E \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \overset{k_2}{\rightarrow} P + E.$$

The reaction rate k_2 is called the *enzyme's catalytic* constant.

Chapter 4

Mathematical modeling of metabolic path way

Consider the unbranched metabolic pathway below

$$x_0 \xrightarrow{r_0} x_1 \xrightarrow{r_1} x_2 \xrightarrow{r_2} x_3 \longrightarrow \cdots x_n \xrightarrow{r_n}$$

where x_0 is the concentration of atomic provided by the pathway. Assume x_0 is a constant, and $x_i(t)$ is the concentration of the i^{th} intermediate metabolite at time t and r_i the rate of chemical characterizing the i^{th} reaction. Assume further that the chemical rate is a function of the concentration of the i^{th} intermediate metabolite and the concentration of the enzyme catalyzing that reaction. We can denote:

$$r_i(t) = r_i(x_i(t), e_i(t)) \geq 0,$$

where $e_i(t)$ is the enzyme concentration. The kinetic property of one of the enzymes catalyzing the reaction in the pathway is characterized by rate r_i.

4.1 Derivation of ODE model for the metabolic pathway

In the sequel we will use two assumptions to derive an ODE system for the unbranched metabolic pathway following [10]:

A1. Each rate law is linear in the enzyme concentration, i.e.

$$r_i(x_i(t), e_i(t)) = w_i(x_i(t))e_i(t),\ i = 0, 1, ..., n$$

The function $w_i(x_i(t))$ is independent of $e_i(t)$. This assumption is satisfied by many class of enzyme dynamics.

A2.

$$w_i(0) = 0 \ \text{ for all } \ i = 0, 1, ..., n$$

$$\frac{dw_i}{dx_i} > 0 \ \ \forall x_i \in \mathbb{R}_+, \ \text{for all } i = 0, 1, ..., n. \tag{4.1}$$

As pointed out in [10] **A2** is trivial since a nonzero concentration in atom x_i is required for the i^{th} reaction to occur, and (4.1) means an increase in x_i yields an increase in the reaction rate which can be saturated when x_i grows unbounded.

Note that (4.1) is satisfied in a class of enzyme dynamics, for example the following kinetic models:

(i) Mass action:
$$\frac{dw_i}{dx_i} = k_i x_i;$$

(ii) Michaelic-Menten:
$$\frac{dw_i}{dx_i} = \frac{k_i x_i}{K_i + x_i};$$

(iii) Hill:
$$\frac{dw_i}{dx_i} = \frac{k_i x_i^n}{K_i + x_i^n};$$

(iv) Power-law:
$$\frac{dw_i}{dx_i} = k_i x_i^c,$$

where $k_i > 0$, $K_i > 0$.

The ODE model for the pathway is given by conservation of mass as

$$\dot{x_i}(t) = r_{i-1}(x_{i-1}(t), e_{i-1}(t)) - r_i(x_i(t), e_i(t)), \quad \text{for all } \ i = 1, 2, ..., n. \tag{4.2}$$

In the reaction, the enzyme concentration must be positive and limited, so $e_0, e_1, ..., e_n$ satisfy

$$\begin{cases} \sum_{i=0}^{n} e_i \le E_T \\ e_i \ge 0 \ \text{ for all } \ i = 0, 1, ..., n. \end{cases}$$

Let

$$x(t) := \begin{pmatrix} x_1(t) & x_1(t) & \cdots & x_n(t) \end{pmatrix}^\top,$$

$$e(t) := \begin{pmatrix} e_0(t) & e_1(t) & \cdots & e_n(t) \end{pmatrix}^\top,$$

$$v(t) := \begin{pmatrix} v_0(t) & v_1(t) & \cdots & v_n(t) \end{pmatrix}^\top$$

be the state, control, and flux vectors, respectively.

Assume that the pathway is initially at rest, that is,

$$x(0) = 0 \text{ and } e(0) = 0.$$

We have to find the enzyme temporal profiles that in the time interval $[0, t_f]$ drive the pathway to a steady state characterized by constant flux

$$V \in \mathbb{R}_+,$$

$$r_i(t) = V \text{ for all } t \geq t_f \text{ for all } i = 0, 1, ..., n,$$

where t_f is the duration of the activation process whose value is left unspecified and regarded as an outcome of the optimization. This means that after the final time r_i is a constant which is equal to the flux [9].

4.2 Objective function for optimization

If the pathway to be activated has a critical impact on cellular fitness, then the metabolic product has to be built rapidly and with efficient enzyme usage. To quantitatively express this principle, the control $e(t)$ (as our control variable) should minimize a cost functional of the form

$$J = \int_0^{t_f} (1 + \alpha^\top e(t))\, dt \tag{4.3}$$

with a weighting vector

$$\alpha \in \mathbb{R}^n_{\geq 0}.$$

The minimization of J implies a combined optimization of: (i) the time taken to reach the new steady state, and (ii) a measure of the enzyme usage.

4.3 Input constraints

The cell can expend only a limited set of resources on the activation of any given pathway. A simple and convenient way of taking those limitations into account is to consider an upper bound on the total enzyme abundance [9]. For that purpose, we consider a control that is constrained as $e(t) \in U$ for all $t \in [0, t_f]$, where U is the polytope defined as

$$U = \left\{ e \in \mathbb{R}^n_{\geq 0} : \sum_{i=0}^{n} e_i \leq E_T \right\}.$$

The constant $E_T > 0$ is the upper bound on the total enzymatic concentration that can be allocated for the pathway activation. The positivity of

$e(t)$ implies that the minimization of J implies the time taken to arrive at the new steady state and a measure of the energy demanded by the enzyme usage [9]. Then the steady state flux V is attained for $t \leq t_f$. And from the lineality of r_i and the formula

$$r_i(t) = V \quad \text{for all } t \geq t_f \text{ for all } \quad i = 0, 1, ..., n.$$

So we have

$$e_i(t) = \frac{V}{w_i(x_i(t_f))} \quad \text{for all } t \geq t_f \text{ for all } i = 0, 1, ..., n. \tag{4.4}$$

This shows the constant enzyme level needed after $t = t_f$ for having the target steady state flux V. The optimization is achieved over the interval $[0, t_f]$ so that the enzyme level in the equation above are not significant to the optimization [9]. This implies that the terminal state for the optimization problem is defined by equation

$$x(t_f) = \lim_{\delta \to 0} x(t_f - \delta), \delta > 0$$

the value $x(t_f)$ must be consistant with the steady state flux because of the continuity of $x(t)$.

Input constraint and (4.4) allow us to say that the final state must belong to the set

$$S_f = \left\{ x > 0 \ : \ \sum_{i=0}^{n} \frac{V}{w_i(x_i)} \leq E_T \right\}.$$

4.4 Mathematical model

We summarize our discussion by the mathematical model:

$$\begin{cases} \min J = \displaystyle\int_0^{t_f} (1 + \alpha^\top e(t))\, dt \\ \text{s.t.} \begin{cases} \dot{x}(t) = N(x(t))e(t) \\ x(0) = 0 \\ x(t_f) \in S_f := \left\{ x > 0 \ : \ \displaystyle\sum_{i=0}^{n} \frac{V}{w_i(x_i)} \leq E_T \right\} \\ e \in U := \left\{ e \in \mathbb{R}^{n+1}_{\geq 0} \ : \ \displaystyle\sum_{i=0}^{n} e_i \leq E_T \right\} \\ t_f \geq 0 \end{cases} \end{cases} \tag{4.5}$$

where N is an $n \times (n+1)$ matrix of the form

$$\begin{pmatrix} w_0(x_0) & -w_1(x_1) & 0 & \dots & 0 & 0 \\ 0 & w_1(x_1) & -w_2(x_2) & & \dots & 0 \\ 0 & \dots & \dots & \dots & \dots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & w_{n-1}(x_{n-1}) & -w_n(x_n) \end{pmatrix}$$

Note that this optimal control has fixed terminal state on a given set S_f and we remind that t_f is to be minimized.

Chapter 5

Solution of the problem

In this section we will discuss how to solve the problem (4.5) using the PMP discussed earlier. We write the Hamiltonian function as

$$H(x, e, \lambda) = \lambda_0 f_0(x, e) + \lambda^\top f(x, e) \tag{5.1}$$

where $\lambda \in \mathbb{R}^n$ is the co-state vector, λ_0 is a constant. Note that in this section we use e (standing for enzyme) instead of u for control variable. The Pontraygin Minimum Principle says that: If an optimal e^* exists, then there exist nontrivial x^* and λ^* such that

1. They satisfy two point boundary value problem:

$$\dot{x^*} = \frac{\partial H(x^*, e^*, \lambda^*)}{\partial \lambda}$$
$$\dot{\lambda^*} = -\frac{\partial H(x^*, e^*, \lambda^*)}{\partial x}$$

   where $\frac{\partial H}{\partial \lambda}$ denote, the partial derivative of H with respect to $\lambda_1, \lambda_2, ..., \lambda_n$ and $\frac{\partial H}{\partial x}$ denote the partial derivatives of H with respect to $x_1, x_2, ..., x_n$ with $x^*(0) = 0$,and $x^*(t_f) \in S_f$.

2. The Hamiltonian is minimized over $v \in U$ and for all $t \in [t_0, t_f]$. This means that

$$H(x^*(t), e^*(t), \lambda(t)) = \min_{v \in U} H(x^*(t), v, \lambda(t)) \tag{5.2}$$

3. The co-state is transversal to S_f in the final time; meaning

$$(\lambda^*)^T(t_f)(q - x^*(t_f)) = 0, \forall q \in M(x^*(t_f)) \tag{5.3}$$

   where $M(x^*(t_f))$ is the tangent plane to S_f at $x^*(t_f)$.

4. The Hamilitonian evaluated at the optimal trajectory is constant for all $t \in [0, t_f]$ i.e

$$H(x^*(t), e^*(t), \lambda^*(t)) = 0, \quad \forall t \in [0, t_f] \tag{5.4}$$

Now, we apply Pontryagin's Minimum Principle to the mathematical model derived before. Using $\lambda_0 = 1$ our Hamiltonian is defined as

$$H(x, e, \lambda) = 1 + \alpha^\top e(t) + (\lambda^*)^\top Ne \tag{5.5}$$

$$\begin{aligned} H(x, e, \lambda) =& 1 + \alpha^\top e + \lambda^\top Ne & (5.6)\\ =& 1 + \sum_{i=0}^{n} \alpha_i e_i + \sum_{i=1}^{n} \lambda_i (w_{i-1}(x_{i-1})e_{i-1} - w_i(x_i)e_i) \\ =& 1 + \sum_{i=0}^{n} [\alpha_i + (\lambda_{i+1} p_{i+1} - \lambda_i) w_i(x_i)] e_i. & (5.7) \end{aligned}$$

with $\lambda_0(t) = 0$ and $\lambda_{n+1}(t) = 0$.
Let

$$h_i(t) := \alpha_i + (\lambda_{i+1} - \lambda_i) w_i(x_i) \tag{5.8}$$

Then we have

$$H(x(t), e(t), \lambda) = 1 + \sum_{i=0}^{n} h_i(t) e_i(t). \tag{5.9}$$

By the PMP at the optimum x^*, λ^*, e^* we have the following condition:
a) state equation

$$\dot{x}(t) = N(x)e, \quad x(0) = 0, \ x(t_f) \in S_f$$

b) adjoint equation

$$\dot{\lambda}_i(t) = (\lambda_i(t) - \lambda_{i+1}(t)) \frac{\partial w_i}{\partial x_i} e_i(t), \quad i = 1, 2, ..., n, \tag{5.10}$$

since $\frac{\partial H}{\partial x_i} = (\lambda_{i+1} - \lambda_i) \frac{\partial w_i}{\partial x_i} e_i, i = 1, 2, ..., n$.
Our aim is to minimize $H(x, e, \lambda)$ over $e \in U$, a polytope. Since $H(x, e, \lambda)$ is linear in $e_1, e_2, ..., e_n$, we expect the so-called *bang-bang control*. Note that 1 is not essential in the optimization procedure , so we have a pointwise linear programming problem (for fixed t);

$$\begin{cases} \min & \displaystyle\sum_{i=0}^{n} h_i e_i \\ \text{s.t.} & \displaystyle\sum_{i=0}^{n} e_i \le E_T, e_i \ge 0 \end{cases} \tag{5.11}$$

or

$$\begin{cases} \min & \sum_{i=0}^{n} h_i e_i \\ \text{s.t.} & e \in U \end{cases} \tag{LP}$$

Clearly (LP) is feasible since the origin is a point in U.
To determine where on S_f, $x(t_f)$ hits in optimal time t_f we need the transversality condition

$$(\lambda^*)^\top(t_f)(q - x^*(t_f)) = 0, q \in M(x^*(t_f)) \tag{5.12}$$

where $M(x^*(t_f))$ is the tangent plane to S_f at $x^*(t_f)$ and finally

$$H(x(t), e(t), \lambda(t)) = 0, \quad t \in [0, t_f].$$

5.1 Main theorem

The following theorem is a main part of the solution to our problem.

Theorem 18 *There exists a set of switching times* $\{t_0, t_1, ..., t_{n-1}\}$ *with the property that* $0 < t_0 < t_1 < ... < t_{n-1} \leq t_f$, *and*

$$[0, t_f) = [0, t_0) \cup [t_0, t_1) \cup \cdots \cup [t_{n-2}, t_{n-1}) \tag{5.13}$$

such that the optimal solution $e^*(t)$ *to the problem satisfies*

$$e_i^*(t) = \begin{cases} E_T, & t \in [t_{i-1}, t_i) \\ 0, & t \notin [t_{i-1}, t_i) \end{cases}$$

for $(i = 0, ..., n-1)$, *where* $[t_{-1}, t_0) := [0, t_0)$.

In terms of the physical model this theorem states that the optimal enzyme concentration e for the problem formulated above

(a) has only one enzyme active (non zero concentration) at a time in $[0, t_f)$, and

(b) attains maximum concentration.

Moreover, enzyme is active over a single time (resulted from the switching curves) and the order of enzyme activation matches the order of the reaction in the pathways.

5.2 Proof of Theorem 18

We shall make use of duality theory to solve the problem. Recall that minimization of $H(x, e, \lambda)$ over $e \in U$ is equivalent to solving (LP) described in the beginning of this section, i.e., pointwise

$$\text{minimizing } \sum_{i=0}^{n} h_i e_i, \text{ over } U = \{e : \sum_{i=0}^{n} e_i \leq E_T, e \geq 0\}.$$

Existence of solutions and optimal value to (LP)

It is easy to see that the feasible set U is a polytope since this is a positive orthant covered by a hyperplane $\sum_{i=0}^{n} e_i = E_T$, and it has exactly $n+1$ extreme points (or corners), since the matrix $A = (\underbrace{1 \quad \cdots \quad 1}_{n+1}) = I_{n+1}$ has $n+1$ non-zero entries in all positions, which means all $e_0, ..., e_n$ can be the basic feasible variables. Moreover, they are $(\underbrace{0 \quad \cdots \quad 0}_{n+1})^\top$, $E_i = \begin{pmatrix} 0 & \cdots & E_T & 0 & \cdots & 0 \end{pmatrix}^\top$is a basic feasible solution, where E_T is in the i-th position, $i = 0, 1, ..., n$. Hence the problem is feasible. By the Fundamental Theorem for LP, (LP) has an optimal solution and at least one of these extreme points must be optimal.

On the other hand an optimal solution must be nonzero due to (5.4) which is

$$1 + \sum_{i=0}^{n} h_i(t) e_i^*(t) = 0 \Longleftrightarrow \sum_{i=0}^{n} h_i(t) e_i^*(t) = -1 \neq 0$$

Therefore the value of the objective function to (LP) is

$$E_T \min(h_0, h_1, ..., h_n).$$

If the optimal solution is not unique then there must exist optimal basic solutions. So we can find all optimal basic feasible solutions say $E_{i_1}, ..., E_{i_k}$ for some k. Thus any point in the convex hull, $\text{conv}(\{E_{i_1}, ..., E_{i_k}\})$ is an optimal solution.

The dual problem of (LP)

Next we study the dual problem of (LP). Writing (LP) in matrix form we have

$$\begin{cases} \min & h^\top e \\ \text{s.t.} & Ae \leq E_T, e \geq 0. \end{cases}$$

where $h = (h_0, ..., h_n)^\top$. Introducing now $y \geq 0$, following Lagrange duality we form a new LP problem

$$\begin{cases} \min & h^\top e + y(Ae - E_T) \\ \text{s.t.} & e \geq 0. \end{cases}$$

$\Longleftrightarrow$

$$\begin{cases} \min & (h^\top + yA)e - \lambda E_T \\ \text{s.t.} & e \geq 0. \end{cases}$$

Let $f_y(e) = (h^\top + yA)e - \lambda E_T$. If $(h^\top + yA) \geq 0$ then $e = 0$ gives the minimal value of f_y which is $-\lambda E_T$. If there is a component of $(h^\top + yA)$ negative, say i_k for some k then we choose $e_{i_k} = \infty$. So $f_y = \infty$. In other words

$$\min f_y = \begin{cases} -yE_T & \text{if } h^\top + yA \geq 0 \\ -\infty & \text{otherwise.} \end{cases}$$

According to Langrange duality we have the dual problem

$$\begin{cases} \max & -E_T y \\ \text{s.t.} & h^\top + yA \geq 0 \\ & y \geq 0. \end{cases}$$

or, equivalently

$$\begin{cases} \max & -E_T y \\ \text{s.t.} & yA \geq -h^\top \\ & y \geq 0 \end{cases} \tag{5.14}$$

Remark. We can, in fact, derive the dual problem through the example shown in Section 2. Having introduced a slack variable $s \geq 0$ in the case at hand, we obtain an LP problem in the form

$$\begin{cases} \min & h^\top e \\ \text{s.t.} & Ae + s = E_T \\ & e \geq 0, s \geq 0. \end{cases}$$

Or

$$\begin{cases} \min & \begin{pmatrix} h^\top & 0 \end{pmatrix} \begin{pmatrix} e \\ s \end{pmatrix} \\ \text{s.t.} & \begin{pmatrix} A & 1 \end{pmatrix} \begin{pmatrix} e \\ s \end{pmatrix} = E_T, \quad \begin{pmatrix} e \\ s \end{pmatrix} \geq 0. \end{cases}$$

It is now in standard form. Recall that the dual problem for minimizing $c^\top x$ subject to $Ax = b$, $x \geq 0$ is maximizing $b^\top y$ subject to $A^\top y \leq c$. Using this result for the currently derived LP problem we get the dual problem

$$\begin{cases} \max & E_T y \\ \text{s.t.} & y \begin{pmatrix} A^\top \\ 1 \end{pmatrix} \leq \begin{pmatrix} h \\ 0 \end{pmatrix} \end{cases}$$

The constraints are now equivalent to $yA^\top \leq h$ and $y \leq 0$. Replace y by $-\tilde{y}$ we have $-\tilde{y} \geq 0$. Call $\tilde{y}$ y again we recover the same dual problem (5.14) as derived earlier.

By the duality theorem, there is an optimal solution y^* to (5.14) and

$$-E_T y^* = \sum_{i=0}^{n} h_i e_i^* = E_T \min(h_0, h_2, ..., h_n).$$

Consequently,

$$y^* = \max(-h_0, ..., -h_n). \tag{5.15}$$

Since we have argued above that the right hand side (the value of primal problem) is nonzero, $-y^* E_T \neq 0$. We get $y^* > 0$.

Moreover we have the following equivalence: (LP) has optimal solution e^* and (5.14) has optimal solution y^* if and only if

$$\begin{cases} e_i^*(y^* + h_i) = 0, \quad i = 0, 1, ..., n \\ y^*(\sum_{i=0}^{n} e_i^* - E_T) = 0. \end{cases} \tag{5.16}$$

Remember that these are complementary slackness conditions. The second equation holds always because $y^* > 0$, and the optimal value is attained at an extreme point, as shown above. The first equation states that either $e_i^* = 0$ or $y^* + h_i = 0$, $i = 0, 1, ..., n$. This brings us to the situation where e has jumps since e is a function of t and t varies from 0 to t_f. We come back to this discussion later.

Relation between the switching curves and the optimum of (LP)

Now we discuss how optimal value of (LP) is related to the switching curve. In particular, we show that the switching function corresponding to each nonzero enzyme, say $h_j(t)$, is negative and equal to $-1/E_T$ for some t.

- Assume there is a unique optimal solution to (LP) at $e^*(t) = E_j$ for some j. Then the optimal value is $\sum_{i=0}^{n} h_i(t) e_i^*(t) = h_j(t) E_T = -1$, for some t, where the last equality followed by (5.4). Hence for some t

$$h_j(t) = -\frac{1}{E_T} < 0.$$

- If there are more than one optimal solutions, then they must include some extreme points of U. Let them be $E_{i_1}, ..., E_{i_k}$ for some k (no more other extreme points are optimal) and $\{i_1, ..., i_k\}$ is a subset of $\{0, 1, ..., n\}$, Then the optimal value is

$$\sum_{i=0}^{n} h_i(t) e_i^*(t) = h_{i_l}(t) E_T = -1 \quad l = 1, ..., k.$$

Hence

$$h_{i_l}(t) = -\frac{1}{E_T} < 0, \quad l = 1, ..., k.$$

That is, all corresponding switching functions $h_{i_l}(t)$ are equal for $l = 1, ..., k$. For a non-extreme optimal solution we know that it is a convex combination of some of the extreme solutions. Thus we get the same results.

Existence and number of switching times: Intuitive discussion

Now we turn to the discussion of existence of switching times. From the complementary slackness conditions we have two possibilities. If $e_i^* = 0$ then $y^* + h_i \neq 0$ for $i = 0, 1, ..., n$. If $e_i^* \neq 0$ (it must be $e_i^* = E_T$) then $y^* + h_i = 0 \Longleftrightarrow \lambda^* = -h_i > 0$ for a fixed $i = 0, 1, ..., n$.

In a while, it will be shown that it is not possible to have one component of $e(t)$, say $e_i^*(t) = E_T$ for all $t \in [0, t_f]$, so at some time t_s (switching time) the control must be changed to $e_k^*(t) = E_T$, $k \neq i$. Then the second alternative takes place. Thus condition $y^* + h_i = 0$ will not hold for all t after t_s. Then we will have next switch.

Intuitively we have the following hypothesis:

We start with choosing $e_0^* = E_T$ for $t \in [0, t_0)$ where t_0 is such that $y^* + h_0 \neq 0$. Thus $t = t_0$ is the first time $y^* + h_0 \neq 0$. If this is the case we choose $e_1^* = E_T$ for $t \in [t_0, t_1)$ where t_1 is such that until $y^* + h_1 \neq 0$. We will do it inductively until then switch to $e_n^* = E_T$. Thus we will have at most $n + 1$ switching times. However $e_n(t)$ must be zero during the whole optimization period because otherwise we would have $\dot{x}_n(t) = -w_n(x_n)E_T < 0$. This means that $x_n(t)$ is a decreasing function for $t \geq t_{n-1}$. If t is sufficiently large $x_n(t)$ will be zero, but the final point x must be positive, violating the condition that $x(t_f) \in S_f$. So we can conclude that there are exactly n switching times.

So we obtain an order of enzyme regulation regime. Our next task is to show that this is indeed the case.

Order of switching times

Our strategy of proving the previous hypothesis is to study the dynamics of the metabolic pathway along time. Unfortunately, it seems necessary to do some lengthy (and sometimes seemingly repeated) computations to reach our goal.

The initial control $e^* = E_0$ ***.***

We start with $t = 0$. Then $x(0) = 0$ as assumed. We simply prove that it is not possible to start with an optimal choice $e_0^* = 0$. Assume by contradiction

$e_0^* = 0$ then $e_{i_0}^* = E_T$ for some i_0 and $0 < i_0 \leq n$ then

$$\begin{aligned}\dot{x}_1(t) &= w_0(x_0(t))e_0^*(t) - w_1(x_1(t))e_1^*(t) \\ &= 0 - w_1(x_1(t))e_1^*(t) \\ &= -w_1(x_1(t))e_1^*(t)\end{aligned}$$

If $e_1^* = E_T$ then

$$\dot{x}_2(t) = w_1(x_1(t))e_1^*(t) - w_2(x_2(t))e_2^*(t) = w_1(x_1(t))e_1^*(t),$$

and

$$\dot{x}_i(t) = 0, \quad \text{for } 3 \leq i \leq n.$$

Thus $x_i(t)$ is a constant for $3 \leq i \leq n$. Since $x_i(0) = 0$ we must have $x_i(t) = 0$, for $3 \leq i \leq n$, $\forall t \geq 0$.

Clearly from dynamics of x_1, x_2 described above, $\dot{x}_1(t) + \dot{x}_2(t) = 0$ which is equivalent to $x_{1(t)} + x_2(t)$ is a constant for all t. By $x_1(0) = x_2(0) = 0, x_1(t) + x_2(t) = 0$ for all t. Since $x_i(t) \geq 0$ we have $x_1(t) = x_2(t) = 0 \forall t \geq 0$. Hence $x(t) = 0, \forall t \geq 0$.

However $x(t)$ can not be zero in whole interval $[0, t_f]$ because $x(t_f) \neq 0$. So there is some t_0 such that $x(t) = 0$, $\forall t \in [0, t_0)$. This together with the condition $w_i(0) = 0$ implies that

$$h_i(t) = \alpha_i + (\lambda_{i+1}(t) - \lambda_i(t))w_i(x_i(t)) = \alpha_i \geq 0, \quad \forall i = 1, ..., n$$

But $h_1(t) < 0$ as shown in the previous section. Hence $e^* = E_1$ is not a solution to our problem.

Similar computation and argument can be used to show that for the case $e^* = E_i$, $i = 2, ..., n$ are not a solution. This can be done as follows:

$$\begin{aligned}\dot{x}_j(t) &= 0, \quad i \neq j, j+1 \\ \dot{x}_j(t) &= -w_j(x_j(t))e_j(t), \\ \dot{x}_{j+1}(t) &= w_j(x_j(t))e_j(t).\end{aligned}$$

That implies $x(t) = 0, \forall t \geq 0$ because $x(0) = 0$. Since $x(t)$ cannot be zero on the whole time interval, there is a $t_0 > 0$ where we have to change the control. So up to this time $x(t) = 0, \forall t \in [0, t_0)$. This implies that $h_i(t) = \alpha_i \geq 0$, $i = 1, 2, ..., n$ but $h_j(t) = -\frac{1}{E_T} < 0$. Thus we obtain a contradiction if $e^* = E_i$, $i = 1, ..., n$.

Now we see that there is a t_0 such that $0 < t_0 < t_f$, $e_0^* = E_T$, i.e., $e^* = (E_T, 0, ..., 0)$ is a solution for $0 \leq t < t_0$ since the optimal solution exists as shown earlier.

Existence of $t_0 > 0$**.**

The choice of e^* $(t \geq 0)$ implies that $e_0^*(t)(y^*(t) + h_0(t)) = 0$ (see (5.16)), that is, $y^*(t) = -h_0(t)$. As time t varies $y^*(t) + h_0(t) = 0$ violates (for otherwise we will get $x(t) = 0$ for all t). So there must be $t_0 > 0$, the first time $y^*(t) + h_0(t) = 0$ violates, at which we have to change the control.

Determination of the initial condition $x(t_0)$ ***for dynamics of*** $x(t)$***.***

Now from t_0, $e^* = E_0$ cannot be optimal due to (5.16). Hence we have to choose $e_0^* = 0$ from t_0 onwards.

To continue, we have to find the initial conditions for $\dot{x}$-system for $t \geq t_0$. These are final value of $x_i(t)$ in $[0, t_0)$ by continuity of $x(t)$. To repeat, for $e^* = (E_T, 0, ..., 0)^\top$, $\forall t \in [0, t_0)$ we have

$$\begin{aligned} \dot{x}_1(t) &= w_0(x_0(t))E_T, \\ \dot{x}_i(t) &= 0, \quad 2 \leq i \leq n. \end{aligned}$$

And $x(0) = 0$ implies that $x_i(t) = 0$, $\forall t \in [0, t_0)$. Hence $x_i(t_0) = 0$, $2 \leq i \leq n$. Obviously with this control e^* the adjoint variables $\dot{\lambda}_i(t) = 0$, $(i = 1, ..., n)$, by (5.10).

Before proceeding further we conclude:

▷ **Claim 0**: *There is a* $t_0 > 0$ *such that for* $t \in [0, t_0)$*, the optimum is* $e^* = (E_T, 0, ..., 0)^\top$*. In particular,* $x_i^*(t_0) = 0$*,* $2 \leq i \leq n$*, and* $\lambda_i^*(t)$ $(i = 1, ..., n)$ *are constants.*

Next we shall inductively find optimal control e^*. We shall prove the following claim:

▷ **Claim 1**: *There is a* $t_1 > t_0$ *such that for* $t \in [t_0, t_1)$*,* $e^* = (0, E_T, 0, ..., 0)^\top$ *is optimal, and* $x_i(t_1) = 0$*,* $i = 3, ..., n$*.*

(i) First we show that $e_{i_0}^* = E_T$, $2 \leq i_0 \leq n$, $e_i^* = 0$, $i \neq i_0$ is not optimal.

Let us assume that $e_{i_0}^* = E_T$, for some i_0 where $2 \leq i_0 \leq n$, and $e_i = 0$ for $i = 0, 1, ..., n$ but $i \neq i_0$. By this choice

$$\begin{aligned} \dot{x}_1(t) &= 0 \\ \dot{x}_2(t) &= 0 \\ &\vdots \\ \dot{x}_{i_0}(t) &= -w_{i_0}(x_{i_0}(t))e_{i_0}^*(t) \\ \dot{x}_{i_0+1} &= w_{i_0}(x_{i_0}(t))e_{i_0}^*(t) \\ &\vdots \\ \dot{x}_n(t) &= 0 \end{aligned}$$

By the same argument provided in the proof of Claim 0, we obtain the solution $x_i(t)$ being constant for all $t \geq t_0$. Now $x_i(t_0) = 0$, implying $x_i(t) = 0$ for $2 \leq i \leq n$ and $\forall t \geq t_0$. Since $x(t_f) \neq 0$ we expect another

jump t_1. Moreover, for all $2 \leq i \leq n$

$$h_i(t) = \alpha_i + (\lambda_{i+1}(t) - \lambda_i(t)) w_i(x_i(t)) = \alpha_i + (\lambda_{i+1}(t) - \lambda_i(t)) w_i(x_i(0)) = \alpha_i \geq 0,$$

because $w_i(0) = 0$. But $h_{i_0}(t) = -\frac{1}{E_T} < 0$, a contradiction, meaning that

$$e_i^* = \begin{cases} E_T & \text{for } i = i_0,\ i_0 \in [2, n] \\ 0 & i \neq i_0 \end{cases}$$

is not a sloution for $t \geq t_0$.

(ii) Next we show that $(E_T, 0, ..., 0)^\top$ and $(0, E_T, 0, ..., 0^\top)$ can not be optimal simultaneously.

If this were the case, we would have, by (5.16) $y^*(t) + h_0(t) = 0$ and $y^*(t) + h_1(t) = 0$, i.e., $h_0 = h_1$. We know further that $h_0(t) = -\frac{1}{E_T} < 0, \forall t \in [t_0, t_1)$, where t_1 is the switching time to be determined if any. Thus

$$\dot{h}_0 = \dot{h}_1 = 0 \quad \forall t \in [t_0, t_1).$$

On the other hand,

$$\begin{aligned} h_0(t) &= \alpha_0 + \lambda_1(t) w_0(x_0(t)) \\ h_1(t) &= \alpha_1 + (\lambda_2(t) - \lambda_1(t)) w_1(x_1(t)). \end{aligned}$$

Using state and adjoint equations, noting that $x_0(t)$ is a constant, we obtain

$$\begin{aligned} \dot{h}_0(t) &= \dot{\lambda}_1(t) w_0(x_0(t)) + \lambda_1(t) \frac{\partial w_0}{\partial x_0} \frac{dx_0}{dt} \\ &= (\lambda_1(t) - \lambda_2(t)) \frac{\partial w_1}{\partial x_1} e_1(t) w_0(x_0) \end{aligned}$$

$$\begin{aligned} \dot{h}_1(t) &= (\dot{\lambda}_2(t) - \dot{\lambda}_1(t)) w_1(x_1(t)) + (\lambda_2(t) - \lambda_1(t)) \frac{\partial w_1}{\partial x_1} \frac{dx_1}{dt} \\ &= (\lambda_2(t) - \lambda_3(t)) \frac{\partial w_2}{\partial x_2} \frac{dx_2}{dt} - (\lambda_1(t) - \lambda_2(t)) \frac{\partial w_1}{\partial x_1} e_1(t) + (\lambda_2(t) - \lambda_1(t)) \frac{\partial w_1}{\partial x_1} \frac{dx_1}{dt} \\ &= (\lambda_2(t) - \lambda_3(t)) \frac{\partial w_2}{\partial x_2} (w_1(x_1(t)) e_1(t) - w_2(x_2(t)) e_2(t)) - (\lambda_1(t) - \lambda_2(t)) \frac{\partial w_1}{\partial x_1} e_1 \\ &\quad + (\lambda_2(t) - \lambda_1(t)) \frac{\partial w_1}{\partial x_1} (w_0(x_0(t)) e_0(t) - w_1(x_1(t)) e_1(t)) \\ &= (\lambda_2(t) - \lambda_1(t)) \frac{\partial w_1}{\partial x_1} w_0(x_0(t)) e_0(t). \end{aligned}$$

Substituting $\lambda_2(t) - \lambda_1(t)$ by $\dfrac{h_1(t) - \alpha_1}{w_1(x_1(t))}$ yields (note that this is well defined since $w_1(x_1(t)) \neq 0$, $\forall t \geq t_0$, otherwise $h_1(t) = \alpha_1 \geq 0$ for some $t \geq t_0$,

contradicting $h_1(t) < 0$)

$$\dot{h}_0(t) = -\frac{\partial w_1}{\partial x_1} w_0(x_0(t)) e_1(t) \left(\frac{h_1(t) - \alpha_1}{w_1(x_1(t))} \right)$$
$$\dot{h}_1(t) = \frac{\partial w_1}{\partial x_1} w_0(x_0(t)) e_0(t) \left(\frac{h_1(t) - \alpha_1}{w_1(x_1(t))} \right)$$

By the assumption $\frac{\partial w_1}{\partial x_1} > 0$ for $x_1 > 0$ and $w_0(x_0(t)) \neq 0$, (otherwise $h_0(t) = h_1(t) \geq 0$, contradicting $h_0(t) < 0$, $\forall t \geq t_0$) and $h_1(t) \neq \alpha_1$ we see that $\dot{h}_0 = \dot{h}_1 = 0$ only if $e_1(t) = 0$ and $e_0(t) = 0$, which contradicts the feasibility condition $\sum_{i=0}^{n} = E_T$. This completes the proof.

(iii) The only case left is for $t \geq t_0$, $e^* = (0, E_T, 0, ..., 0)^\top$. Because there must be a solution to (LP), this $e^*(t)$ is the optimal solution and this control law is applied until the condition $h_1(t) + y^*(t) = 0$ violates. Then we get $t_1 > t_0$.

In the similar way as done in proving Claim 0, we can show that $x_i(t_1) = 0$ for $i = 3, ..., n$.

Description of switching curves

Assume now there are $t_0, ..., t_k$ so that $\{T_0, ..., T_k\}$ is a partition of $[0, t_f)$ where $T_0 = [0, t_0)$, $T_i = [t_{i-1}, t_i)$, $i = 1, ..., k$. Consider now the interval T_l, $l \geq 2$. Assume $x_i(t_l) = 0$ $\forall i > l + 1$, and

$$e_j^* = \begin{cases} E_T, & t \in [t_{j-1}, t_j) \\ 0, & \text{elsewhere} \end{cases}, \quad j \leq l.$$

Now we will describe the switching curves $h_j(t)$. Note that it is given that $x(0) = 0$, then the e^* given above implies

$$x_j(t) = 0, \quad t \in T_0 \cup \cdots \cup T_{j-2}, \forall 2 \leq j \leq l.$$

(This can be shown in detail in the same way as done before.) By definition of $h_j(t)$ we have

$$h_j(t) = \alpha_j, \quad t \in T_0 \cup \cdots \cup T_{j-2}, \forall\ 2 \leq j \leq l.$$

Using the state and adjoint equations the derivative of $h_j(t)$ is

$$\begin{aligned} \dot{h}_j(t) &= (\dot{\lambda}_{j+1}(t) - \dot{\lambda}_j(t)) w_j(x_j(t)) + (\lambda_{j+1}(t) - \lambda_j(t)) \frac{\partial w_j}{\partial x_j} \dot{x}_j(t) \\ &= (\lambda_{j+1}(t) - \lambda_{j+2}(t)) \frac{\partial w_{j+1}}{\partial x_{j+1}} w_j(x_j(t)) e_{j+1}(t) \\ &\quad - (\lambda_j(t) - \lambda_{j+1}(t)) \frac{\partial w_j}{\partial x_j} w_{j-1}(x_{j-1}(t)) e_{j-1}(t) \end{aligned} \tag{5.17}$$

where we set $w_{-1} = 0$. Since $e_j(t) = 0 \ \forall j \neq l$, $t \in T_l$, the above equation gives rise

$$\dot{h}_j(t) = 0, \text{ for all } j \text{ except } j = l-1, l+1.$$

For $j = l-1$, $e_{j+1}(t) = e_l(t) = E_T$, $t \in T_l$, and $e_{j-1}(t) = e_{l-2}(t) = 0$. Substituting these values in (5.17) yields

$$\dot{h}_{l-1}(t) = (\lambda_l(t) - \lambda_{l+1}(t))\frac{\partial w_l}{\partial x_l}(x_{l-1}(t))E_T, \quad t \in T_l.$$

By definition of $h_l(t)$ we can rewrite

$$\lambda_l(t) - \lambda_{l+1}(t) = \frac{\alpha_l - h_l(t)}{w_l(x_l(t))}$$

Hence

$$\dot{h}_{l-1}(t) = \frac{\alpha_l - h_l(t)}{w_l(x_l(t))}\frac{\partial w_l}{\partial x_l}w_{l-1}(x_{l-1}(t))E_T, \quad t \in T_l.$$

As in the proof of Claim 1 part (ii) we can argue that $\dot{h}_{l-1}(t)$ is well defined on there interval T_l. Similarly, $e_j^*(T)$ as assumed implies that $w_{l-1}(x_{l-1}(t)) > 9$ on T_{l-1}, since otherwise $h_{l-1}(t) = \alpha_{l-1} \geq 0$ for some $t \in T_{l-1}$, contradicting $h_{l-1}(t) = -1/E_T < 0$ by the choice of $e(t)$. Furthermore we can show in the same manner as before that $\dot{x}_{l-1}(t) = 0$, for all $t \in T_l$. Then $w_{l-1}(x_{l-1}(t)) > 0$, for all $t \in T_l$. Hence, together with $h_l(t) = -1/E_T$ and A2,

$$\dot{h}_{l-1}(t) = \frac{\alpha_l - h_l(t)}{w_l(x_l(t))}\frac{\partial w_l}{\partial x_l}w_{l-1}(x_{l-1}(t))E_T > 0, \quad t \in T_l.$$

Summarize above discussion we have the following description for the switching curves $h_j(t)$:

- $$h_j(t) = \begin{cases} \alpha_j, & \forall\ 2 \leq j \leq l,\ \forall\ t \in \bigcup_{i=0}^{j-2} T_i \\ -\frac{1}{E_T}, & \forall\ j \leq l,\ \forall\ t \in T_j \end{cases};$$
- $\dot{h}_j(t) > 0, \ \forall\ j < l, \ \forall\ t \in T_{j+1}$;
- $\dot{h}_j(t) = 0, \ \forall\ j < l, \ \forall\ t \in \bigcup_{i=j+1}^{l} T_i$.

Finally we show

▷ **Claim** l ($l \geq 2$). Assume that we have found optimal solution on the interval $[0, t_l) = [0, t_0) \cup [t_0, t_1) \cup ... \cup [t_{l-1}, t_l)$,

$$e_j^* = \begin{cases} E_T, & t \in [t_{j-1}, t_j) \\ 0, & \text{elsewhere} \end{cases}, \quad j = 0, 1, ..., l$$

with $t_{-1} = 0$, and the optimal trajectory $x_i(t_l) = 0$ for $i > l+1$, where t_j (the switching time), $j = 0, 1, ..., l$, are the first time t that violates the condition $y^* + h_j(t) = 0$, and $y^* = \max(-h_0(t), -h_1(t), ..., -h_n(t))$ for $t_{j-1} \leq t < t_j$, $j = 0, 1, ..., l$. Then the optimal solution on $[0, t_{l+1}) = [0, t_0) \cup [t_0, t_1) \cup ... \cup [t_{l-1}, t_l) \cup [t_l, t_{l+1})$ is

$$e_j^* = \begin{cases} E_T, & t \in [t_{j-1}, t_j) \\ 0, & \text{elsewhere} \end{cases}, \quad j = 0, 1, ..., l+1$$

where t_{l+1} is the first time so that $y^*(t)+h_l(t) \neq 0$ and $y^* = \max(-h_0(t), -h_1(t), ..., -h_n(t))$ for $t_l \leq t < t_{l+1}$.

▷ ***Case*** $j < l$:

Let $e_j(t) = E_T$ for $t \in T_{l+1}$ for some $j < l$. Then $h_j(t) = -1/E_T$ for $t \in T_{l+1}$. In particular, $\dot{h}_j(t_l) = 0$. But $h_j(t_l) = \alpha_j$ according to the description of $h_j(t)$. So this case is impossible.

▷ ***Case*** $j > l + 1$:

If for some $j > l + 1$, $e_j(t) = E_T$ for $t \in T_{l+1}$, thus $h_j(t) = -1/E_T$. Then from the condition that $x_i(t_l) = 0$ for all $i > l + 1$ $x_i(t) = 0$ for all $i > l + 1$, all $t \in T_{l+1}$, then $w_i(x_i(t)) = w_i(0) = 0$, and hence $h_i(t) = \alpha_i \geq 0$, for all $i > l + 1$. But $h_j(t) < 0$. So this case is also impossible.

▷ ***Case*** $j = l$***, and*** $j = l + 1$:

We have to show that $(0, 0, ..., E_T, 0, ...0)$ and $(0, 0, ..., 0, E_T, 0, ...0)$ where E_T is at j^{th} and $(j+1)^{th}$ position respectively can not be optimal simultaneously.

$$\dot{h}_l(t) = (\lambda_{l+1}(t) - \lambda_{l+2}(t)) \frac{\partial w_{l+1}}{\partial x_{l+1}} w_l(x_l(t)) e_{l+1}$$

$$\dot{h}_{l+1}(t) = -(\lambda_{l+1}(t) - \lambda_{l+2}(t)) \frac{\partial w_{l+1}}{\partial x_{l+1}} w_l(x_l(t)) e_l$$

we have also that

$$h_j(t) = \alpha_j + (\lambda_{j+1}(t) - \lambda_j(t)) h_j(t) w_j(x_j(t))$$

we can deduce that $\lambda_{j+1}(t) - \lambda_j(t) = \frac{h_j(t) - \alpha_j}{w_j(x_j(t))}$

• for $j = l$

$$\dot{h}_l(t) = \left(\frac{h_j(t) - \alpha_j}{w_j(x_j(t))} \right) \frac{\partial w_{l+1}}{\partial x_{l+1}} w_l(x_l(t)) e_{l+1}$$

and for $j = l + 1$

$$\dot{h}_{l+1}(t) = -\left(\frac{h_j(t) - \alpha_j}{w_j(x_j(t))} \right) \frac{\partial w_{l+1}}{\partial x_{l+1}} w_l(x_l(t)) e_l$$

We will have $\dot{h}_i = \dot{h}_{l+1} = 0$ if and only if $e_l(t) = 0$, and $e_{l+1}(t) = 0$ which contradict the feasibility condition $\sum_{i=0}^{n} e_i(t) = E_T$. This implies the relation $e_l^*(t)$ can not be optimal in interval $[t_l, t_{l+1})$ and therefore is $e_{l+1}^* = E_T$ in that interval.

5.3 The complete solution and numerical computation

In the previous section we show that there are n switching times $0 < t_0 < ... < t_{n-1}$ so that the optimal control $e^*(t)$ is in the form that $e_i^*(t) = E_T$ and $e_j^*(t) = 0$ if $j \neq i$ for all $t \in T_i = [t_{i-1}, t_i)$, where $i = 0, 1, ..., n-1$ and the optimal value of $e_n(t)$ is zero for the whole period of $[0, t_f]$. However, we did not discuss how to find the optimal switching times. We will in this section give a complete solution to our pathway network control.

Problem reformation: derivation of a static optimization problem As done before in proving PMP we reformulate the optimal control problem by introducing a new variable $x_{n+1}(t) = \int_0^t (1+\alpha^\top e(s))ds$. Then $x_{n+1}(0) = 0$ and $x_{n+1}(t_f)$ is to be minimized. The problem becomes

$$\begin{cases} \min & x_{n+1}(t_f) \\ \text{s.t} & \dot{\tilde{x}}(t) = \tilde{f}(x(t), e(t)) \\ & \tilde{x}(0) = 0,\ x(t_f) \in S_f \\ & e \in U, t_f \geq 0 \end{cases} \tag{5.18}$$

where $\tilde{x} = (x^\top\ x_{n+1})^\top$ and $\tilde{f}(x, e) = ((N(x)e)^\top\ 1 + \alpha^\top e)^\top$. Since this problem is equivalent to our original optimal control problem, the solution derived in previous section applies to this problem. Let t_i's $(i = 0, ..., n-1)$ be switching times and $\xi_i = t_i - t_{i-1}$, $\xi_0 = t_0$ and $\xi_n = t_f - t_{n-1}$. The dynamics of $\tilde{x}$ is for $t \in T_0 = [0, t_0) = [0, \xi_0)$,

$$\begin{cases} \dot{x}_1 = E_T w_0(x_0) \\ \dot{x}_j = 0, \quad j = 2, ..., n, \end{cases} \tag{5.19}$$

and $x(0) = 0$, for $t \in T_i = [t_{i-1}, t_i) = [t_{i-1}, t_{i-1} + \xi_i), i > 0$,

$$\begin{cases} \dot{x}_i = -E_T w_i(x_i) \\ \dot{x}_{i+1} = E_T w_i(x_i) \\ \dot{x}_j = 0, \quad j \neq i \wedge j \neq i+1 \end{cases} \tag{5.20}$$

with initial conditions

$$\begin{cases} x_j(t_{i-1}) = x_j(t_{i-1}^-), j = 1, ..., i \\ x_j(t_{i-1}) = 0, \quad j = i+1, ..., n \end{cases}$$

and

$$x_{n+1}(t) = \int_0^t (1 + \alpha^\top e^*(s))ds.$$

In particular

$$x_{n+1}(t_f) = \sum_{i=0}^{n-1}(1+\alpha_i e_i(t))(t_i - t_{i-1}) = \sum_{i=0}^{n-1}(1+\alpha_i E_T)\xi_i,$$

is going to be minimized.

Now we parameterize the solution $x(t)$ on the interval T_l by $x(t_{l-1}+\delta)$, where $\delta \in [0, \xi_l)$, $l = 0, 1, ..., n$. Denote $x(t_{l-1}+\delta) := x(\delta; \xi_{l-1}, ..., \xi_0)$. For the final point in the last interval we write $x(\xi) := x(\xi_n; \xi_{n-1}, ..., \xi_0)$. So the optimal control problem (5.18) is reduced to the following optimization problem

$$\begin{cases} \min & c^\top \xi \\ \text{s.t.} & x(\xi) \in S_f,\ \xi \geq 0, \end{cases} \tag{5.21}$$

where c is an n-vector with components $1 + \alpha_i E_T$, and $x(\xi)$ is obtained by solving the sequence of above initial value problems. Next we show that this can be avoided. The first alternative is to use the special structure of our system, while the second can be applied to more general systems.

Further simplification

Integrating the equations in (5.19) from 0 to t_0

$$\xi_0 = \frac{x_1(t_0)}{E_T w_0(x_0)}. \tag{5.22}$$

Integrating the equation (5.20) for $i = 1$ gives

$$\xi_1 = \int_{x_1(t_0)}^{x_1(t_1)} -\frac{ds}{E_T w_1(s)}.$$

By inspecting (5.20) $x_1(t)$ is a constant for all $t \geq t_1$ Then, $x_1(t) = x_1(t_1)$ which implies

$$x_1(t_1) = x_1(t_f) = x_1^f.$$

Hence

$$\xi_1 = \int_{x_1(t_0)}^{x_1^f} -\frac{ds}{E_T w_1(s)}.$$

Similarly, We will have

$$\xi_i = \int_{x_i(t_{i-1})}^{x_i^f} -\frac{ds}{E_T w_i(s)}, \quad i = 1, ..., n-1. \tag{5.23}$$

where

$$x_i(t_{i-1}) = \sum_{j=i}^{n} x_j^f,\ i = 1, ..., n.$$

This follows from the facts that $x_j = -x_{j-1}$ and $x_j(t_{i-1}) = 0$, implying $x_j(t_i) - x_j(t_{i-1}) = -(x_{j-1}(t_i) - x_{j-1}(t_{i-1}))$.
Substituting (5.22) and (5.23) into (5.21) we have the following new and simpler, but equivalent optimization problem, depending only on the final state without solving the sequential ODEs:

$$\begin{cases} \min & c^\top \xi \\ \text{s.t.} & x^f \in S_f, \end{cases} \tag{5.24}$$

where

$$\xi_0 = \frac{x_1^f + \cdots + x_n^f}{E_T w_0(x_0)}, \quad \xi_i = \int_{x_i^f}^{x_i^f + \cdots + x_n^f} \frac{ds}{E_T w_i(s)}, \ i = 1, ..., n-1.$$

Clearly $\xi_i \geq 0$.

5.3.1 An example

Numerical methods for the solution of dynamic optimization problems can be classified into two groups: direct and indirect methods. Indirect methods solve the optimization problem using the Pontryagin Minimum Principle. This method is based on the transformation of the original problem using the necessary optimality conditions of Pontryagin. This results in a two or multi-point boundary value problem, in the presence of constraints, to be solved for state and co-state variables. In this work we consider the objective functional of minimization of the time needed to reach a certain amount of product when the substrate remains unalterable as represented in matrix N.

$$r_i = \frac{K_i x_i}{K_M + x_i} e_i(t), i = 0, 1, 2, 3 \tag{5.25}$$

The limitation of the amount of enzyme and their rates are imposed by constraint $0 \leq r_i \leq 1mMs^{-1}$ and $0 \leq e_i \leq E_T$ with $E_T = 1mM$. Taking $k_0 = 1s^{-1}$, $k_1 = 2s^{-1}$, $k_2 = 4s^{-1}$, $k_3 = 3s^{-1}$, $K_M = 1s^{-1}$, $V = 0.2mM/s$, $x_0 = 5mM$, and $\alpha_i = 1mM$.
We find solution of (5.25) by solving the static optimization problem described in the previous section. Using Mathematica `FindMinimum` or using Lagrange relaxation followed by Mathematica function `FindRoot` to solve the resulting nonlinear system we get approximate values of optimal final states (with unit mM)

$$x_1^f \approx 0.646751, \quad x_2^f \approx 0.316699, \quad x_3^f \approx 0.288806,$$

the optimal objective value 2.37006 which is, in fact, the optimal final time $t_f(= t_2)$, and the optimal time increments

$$\xi_0 \approx 1.50271, \quad \xi_1 \approx 0.633123, \quad \xi_2 \approx 0.234229.$$

In conclusion we have optimal switching times at (with unit seconds)

$$t_0 \approx 1.50271, \quad t_1 \approx 2.13583, \quad t_2 \approx 2.37006.$$

Now we can plot the optimal control e^* (enzyme profiles) and the optimal trajectories (metabolites) for the state equations using program Mathematica.

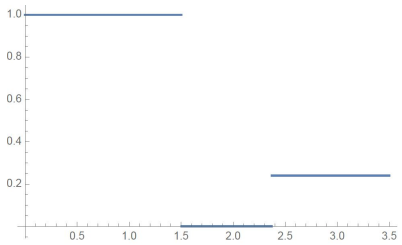

Figure 5.1: enzyme profile

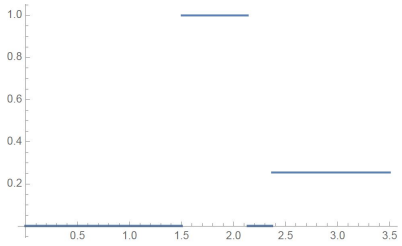

Figure 5.2: enzyme profile

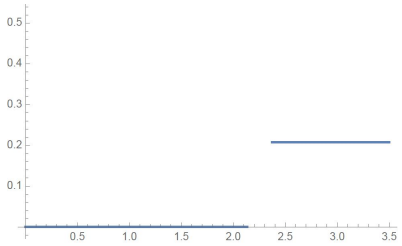

Figure 5.3: enzyme profile

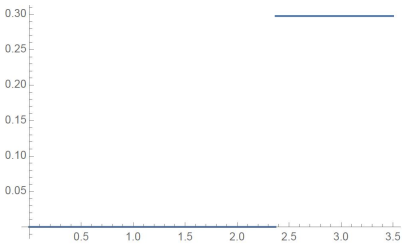

Figure 5.4: enzyme profile

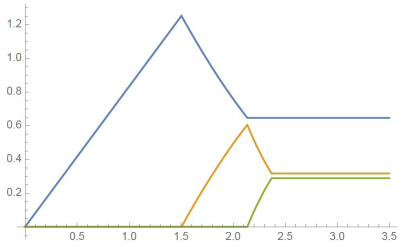

Figure 5.5: Optimal activation for pathway of length $n = 3$ with Michaelis-Menten kinetics.

Note that we do not have to solve the adjoint equations explicitly here, which is very efficient since the adjoint equations are boundary value problems. They are not as easy as the initial value problems to solve numerically.

Remark. In a real application there might be more switching times and working load will be much higher. Then we can solve its dual problem instead because the dual problem has much less variables.

Chapter 6

Conclusions and recommendation

In this thesis we studied a metabolic pathway model proposed in [10]. We derived the mathematical model for an unbranched metabolic pathway. The model is described by an optimal control problem. Then we proved that there is a series of switching time that solve the problem optimally. The arguments are based on mathematical optimal control theory and Lagrange duality theory, more precisely the Pontryagin Minimum Principle controlling trajectory from a given initial state on to a manifold and Linear programming problem and its dual. Our approach is different from the arguments provided in [10]. Moreover, we described how to determine the optimal switching times. A description for how to get a complete solution was provided. To make the thesis accessible for students with the author's background, we provided an almost complete proof of the version of PMP with our personal understanding. Finally we illustrated our solution method by an example for dynamics of Michaelis-Menten. Nevertheless there are still things needed investigating. Two of those are worth mentioning. We did not give a mathematical proof of the existence of optimal control to our model due to lack of time and we expected to continue the research in the future. Although it can be argued true by practical reasoning, say from experiments shown in [10] it would be nice to give a rigorous mathematical proof. The second is that it is desirable to have sensitivity robust analysis.

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