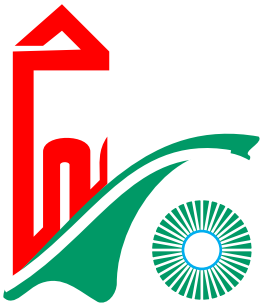
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AMEUR CHAIMA

A Numerical Method to Determine the Optimal Induction Phase of Anesthesia

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أهدي تخرجي الى من احمل اسمه بكل فخر,الى من حصد الاشواك عن دربي, إلى من كان دائمًا سندي وملهمي بابا الغالي جزاك الله عني خير الجزاء، وبارك لي في عمرك، وأمدّك بالصحة والعافية.

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إلى إخوتي الأحباء، سندي ومسندي وتِكأتي الذي لا يميل، أنتم العون في الشدة، والفرح في الرخاء، ورفاق الدرب الذين لا يخذلون.

حفظكم الله ورعاكم دائمًا. "زهرة، حميدة، هند، محمد، هشام و اسامة"

الى نعمة بيتنا "صغيري يونس" لمسة البراءة والفرح التي تملأ أيامنا بهجةً

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الطالبة: عامر شيماء

Abstract

This research paper, titled "A Numerical Method to Determine the Optimal Induction Phase of Anesthesia," explores the use of mathematical modeling and optimal control to enhance the anesthesia process. The study is based on a pharmacokinetic/pharmacodynamic (PK/PD) model for propofol and applies Pontryagin's Maximum Principle for optimal control to determine the best drug infusion rate and the minimum time required to transition from an awake to an anesthetized state. The methodology employs the shooting method alongside a novel analytical approach that avoids dependency on initial guesses. Numerical simulations in MATLAB confirmed the consistency of both methods in computing the optimal induction time and infusion rate. The study highlights the significance of these techniques in improving the safety and efficacy of anesthesia, particularly for high-risk patients, with potential applications to other PK/PD models in the future.

ملخص

يقدم هذا المذكرة البحثية بعنوان "طريقة عددية لتحديد التحكم الأمثل لمرحلة تحفيز التخدير" دراسة حول استخدام النمذجة الرياضية والتحكم الأمثل لتحسين عملية التخدير. تعتمد الدراسة على نموذج حركية دوائية/ديناميكية دوائية (PK/PD) لبروبوفول، وتطبق مبدأ بونترياجين للتحكم الأمثل لتحديد معدل ضخ الدواء الأمثل اللازم للانتقال من حالة اليقظة إلى التخدير. تتضمن المنهجية استخدام (shooting method) بالإضافة إلى طريقة عددية تتفادى مشاكل التبعية للتخمينات الأولية. تم التحقق من النتائج عبر محاكاة عددية في MATLAB، مما أظهر اتفاقًا بين الطريقتين في تحديد الوقت الأمثل ومعدل الضخ. تبرز الدراسة أهمية هذه الأساليب في تحسين سلامة وفعالية التخدير، خاصةً للمرضى المعرضين لمخاطر عالية، مع إمكانية تطبيقها على نماذج PK/PD أخرى في المستقبل.

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Introduction

Control theory focuses on the analysis of controlled systemsdynamic systems that can be influenced through control inputs. The primary objective is to steer the system from a given initial state to a desired final state, while possibly satisfying specific performance criteria [28, 29, 30, 31]. A wide variety of systems are studied, including differential systems, discrete systems, systems with noise, delays, and more. These systems arise in numerous fields such as mechanics, electrical engineering, electronics, biology, chemistry, and economics [32, 31]. Depending on the context, the goal may be to stabilize the system against disturbances (stabilization) or to determine optimal trajectories that minimize or maximize a given cost function (optimal control).

Optimal control problems for linear dynamical systems have been extensively studied in the literature [33, 31]. However, it remains challenging to develop highly efficient numerical methods that fully account for all the specific features of such problems. Optimal control aims to determine a control law for a given system such that a certain performance criterion is optimized. A typical control problem involves a cost function to be minimized (or maximized), a state equation, and one or more control variables. An optimal control problem can be divided into two main parts: first, determining whether the target state is reachable from a given initial statethis is the controllability problem. For finite-dimensional linear control systems, a simple and elegant characterization of controllability was introduced in the 1960s by R.E. Kalman. However, for nonlinear systems, the mathematical problem of controllability becomes significantly more complex. Once controllability is established, the second task is to find the optimal trajectory among all admissible ones that minimizes (or maximizes) the cost. Various methods exist to solve optimal control problems, each with its own advantages and limitations. The choice of method depends on the specific nature of the problem. Since most optimal control problems are solved numerically, solution techniques have seen considerable development in recent years.

Two main classes of methods are generally used: direct methods and indirect methods. Direct methods involve discretizing the control problemboth the state and the controlat every time point,

thereby converting it into a nonlinear optimization problem. This is typically done using discretization techniques such as Eulers method or Runge-Kutta schemes. The resulting optimization problem can then be solved using interior-point methods, sequential quadratic programming (SQP), or other nonlinear programming techniques. These methods are relatively simple to implement. In contrast, indirect methods are based on Pontryagins Maximum Principle (PMP), which provides first-order necessary conditions for optimality and leads to a boundary value problem. The goal is to find trajectories that satisfy these conditions, which, in practice, amounts to solving for the root of a so-called shooting function associated with the original problem. Indirect methods are both accurate and efficient but are highly sensitive to the choice of initial guesses. In recent years, optimal control problems have attracted increasing attention due to their applicability in engineering, biology, and economics. Numerical methods play a crucial role in finding approximate solutions to these problems, especially when analytical solutions are either too complex or impossible to obtain. The development of robust and efficient algorithms has become essential to tackle the complexity of real-world systems.

The discretization of optimal control problems transforms them into finite-dimensional optimization problems that can be solved using standard numerical techniques. Among the most widely used approaches are the Euler and Runge-Kutta methods for time discretization. These allow the translation of differential equations into algebraic systems that are more amenable to computational algorithms.

An essential part of solving control problems numerically lies in ensuring the stability and convergence of the chosen method. This requires a careful balance between the step size, computational cost, and desired accuracy. In the context of linear systems, well-established theorems provide guidance for method selection. However, in more complex systemssuch as those involving uncertainties, delays, or hybrid dynamicsthe design of numerical solvers becomes significantly more challenging.

One promising application of optimal control lies in biomedical engineering, particularly in the modeling and regulation of drug administration. This is particularly relevant in anesthesia, where the objective is to deliver the correct drug dosage over time to maintain the desired state of unconsciousness while minimizing side effects. These systems are modeled using PK/PD (Pharmacokinetics/Pharmacodynamics) equations, which describe the evolution of drug concentration and its effects on the body. We present an numerical solution for the optimal control problem in the anesthesia induction phase, demonstrating numerical agreement with conventional shooting

method results. The study builds upon the pharmacokinetic/pharmacodynamic (PK/PD) model introduced by Bailey and Haddad (2005) for propofol infusion regulation.

To validate our approach, we analyze a minimum-time anesthesia induction problem for a clinical case study. Applying the Pontryagin Minimum Principle, we first solve the problem using the shooting method. We then introduce a novel analytical method that eliminates dependency on initial adjoint variable estimatesa key limitation of shooting-based approaches.

Numerical simulations in MATLAB confirm that both methods yield consistent results for the optimal continuous infusion rate and minimum transition time from awake to anesthetized states. However, the proposed analytical method offers significant advantages by:

— Removing convergence sensitivity to initial conditions

— Providing deterministic solutions without iterative guessing

— Maintaining computational efficiency

The methodology shows potential for extension to other PK/PD models in optimal drug administration timing problems.

Guedels classification identifies the first stage of anesthesia as the induction phase, spanning from initial anesthetic administration to loss of consciousness [1]. While millions safely receive anesthesiaencompassing local, regional, general, and sedation techniques [2] potential complications persist, including anesthetic awareness, pneumothorax, malignant hyperthermia, nerve injury and postoperative delirium. High-risk factors such as advanced age, diabetes, cardiovascular disease, hypertension and smoking further complicate administration [3]. To mitigate risks, anesthesia delivery must adhere to pharmacotherapeutic principles, integrating pharmacokinetic (PK) and pharmacodynamic (PD) data [4]. PK describes drug absorption and distribution, while PD analyzes drug effects [5].

Existing PK/PD models employ diverse mathematical approaches [6, 9], with implementations varying across methodologies [2, 10, 11]. Schnider et al. [12] fitted PK/PD parameters, while [6] compared propofol models by Schnider and Marsh et al. [13], advocating Schniders model for effect-site targetingthough cautioning against paradoxical lean body mass (LBM) calculations in morbid obesity. Robust maintenance-phase control strategies [14] and induction-phase optimal control [15] have also been explored (see [8, 16] for related work).

In this work, we aim to bridge the gap between theory and application by first developing a comprehensive mathematical formulation of the control problem and then applying numerical methods to solve it. Our objective is to demonstrate how advanced control techniques can enhance

the safety and efficiency of drug delivery, using anesthesia as a case study. This study is organized as follows: Section 2 revisits the PK/PD model of Bailey and Haddad [19], the Schnider model [12], and key concepts such as the bispectral index (BIS) and equilibrium analysis [14]. Section 3 formulates the time-optimal control problem for anesthesia induction, presenting solutions via both the shooting method (correcting inconsistencies in [15]) and Euler discretization approach. Section 4 validates the methods numerically using Schnider-derived parameters, comparing their performance in computing optimal infusion rates . Finally, Section 5 concludes with insights and future research directions.

Chapter 1

Numerical Methods for Solving Linear Optimal Control Problems

This chapter revisits the fundamental concepts of optimal control theory. It is structured as follows: First, we provide a concise overview of control theory and optimal control. Next, we introduce the concept of controllability for both linear and nonlinear systems. We then present two types of numerical methods for solving an optimal control problem: direct and indirect methods. Direct methods consist of discretizing the original optimal control problem and transforming it into a constrained linear or nonlinear optimization problem. Indirect methods, such as the shooting method, rely on applying Pontryagins maximum principle to derive a boundary value problem. The shooting method also requires the use of Newtons method. While indirect methods offer high numerical accuracy, they are very sensitive to the choice of initial conditions.

1.1 Problem Statement

Consider the following optimal control problem with fixed final time t_f, state and control constraints and a linear cost functional:

$$(S): \begin{cases} \min_u \; c'x(t_f) + \displaystyle\int_0^{t_f} w'x(t) + d'u(t)dt \\ \dot{x}(t) = Ax(t) + Bu(t) + r(t), \quad x(0) = x_0, \\ Hx(t_f) = g, \\ \alpha \leq u(t) \leq \beta, \quad t \in [0, t_f], \end{cases} \tag{1.1}$$

where $x(t) = (x_1(t), x_2(t), \ldots, x_n(t))'$ is the vector of states at the instant t, and $u(t) = (u_1(t), u_2(t), \ldots, u_m(t))'$ is the vector of controls at the instant t, which are measurable and locally bounded functions on $[0, t_f]$, with values in the subset $\Omega = [\alpha, \beta] \subset \mathbb{R}^m$, where $\alpha, \beta, d \in \mathbb{R}^m$, $c, w \in \mathbb{R}^n$, $H \in \mathcal{M}_{p,n}(\mathbb{R})$, $A \in \mathcal{M}_n(\mathbb{R})$, $B \in \mathcal{M}_{m,n}(\mathbb{R})$, $g \in \mathbb{R}^p$ and t_f is fixed.

1.1.1 Bounded Control

In many control problems, the control inputs $u_j(t)$ (for $j = 1, \ldots, m$) can be bounded above and below by constants. Here, we consider such problems under the constraints $a_j \leq u_j \leq b_j$.

Note that u_j can be transformed into a normalized control variable v_j by setting:

$$u_j = \frac{1}{2}(a_j + b_j) - \frac{1}{2}(a_j - b_j)v_j,$$

where v_j remains integrable and satisfies $-1 \leq v_j \leq 1$. Thus, when the control set $\mathcal{U}$ is bounded, it is often convenient to normalize the controls to the interval $[-1, 1]$.

1.1.2 Bang-Bang Control

Assume that $\mathcal{U}$ is a polyhedron (e.g., the hypercube $[-1, 1]^m \subset \mathbb{R}^m$). A control $u \in \mathcal{U}$ is called a *Bang-Bang control* if, for every time t and each index $j = 1, \ldots, m$, the control satisfies $|u_j(t)| = 1$.

In other words, a Bang-Bang control is a piecewise-constant control that switches between its extreme values (e.g., $+1$ and -1) at certain switching times.

1.2 Controllability

To solve a problem of this type, the first question to ask is:

Question 1: Does there exist a control $u(t) \in U$ such that the associated trajectory $x(t)$ connects an initial point $x_0 \in M_0$ to a terminal target $x_f \in M_f$ in finite time?

The concept that allows us to answer this question is the study of **controllability** of the system, also referred to as the *reachability problem*.

Question 2: If the system is controllable, we may then wish to determine a control $u \in U$ such that the associated trajectory drives the system from the initial state $x_0 \in M_0$ to the terminal state $x_f \in M_f$, while also **minimizing a cost functional** $J(u)$.

1.2.1 Accessible set

The controlled system

$$\dot{x}(t) = A(t)x(t) + B(t)u(t) + r(t), \tag{1.2}$$

is said to be controllable in time t_f if $Acc(x_0, t_f) = \mathbb{R}^n$, i.e., for all $x_0, x_f \in \mathbb{R}^n$, there exists a control $u(t),\ t \in [0, t_f]$ such that the associated trajectory connects x_0 to x_f in time t_f.

Consider the controlled system (1.1):

$$\forall t \in [0, t_f], \quad \dot{x}(t) = A(t)x(t) + B(t)u(t) + r(t), \quad x(0) = x_0. \tag{1.3}$$

Definition 1.1 *The set of reachable points from x_0 at time $t_f > 0$ is defined by:*

$$Acc(x_0, t_f) = \{x_u(t_f) \mid u \in L^\infty([0, t_f], \Omega)\}, \tag{1.4}$$

where $x_u(\cdot)$ is the solution of system (1.2) associated with control $u(t),\ t \in [0, t_f]$.

In other words, Acc(x_0, t_f) is the set of endpoints of the solutions of (1.2) at time t_f, when the control $u(t),\ t \in [0, t_f]$ varies for consistency, we define:

$$\text{Acc}(x_0, 0) = \{x_0\}. \tag{1.5}$$

The system (1.2) is controllable if for any initial state x_0 and any final state x_f, there exists a control $u(t)$ that can drive x_0 to x_f in finite time.

1.2.2 Controllability of autonomous linear systems

Kalman's Criterion:

The system is controllable if and only if the controllability matrix:

$$C = [B, AB, A^2B, \ldots, A^{n-1}B],$$

has rank equal to n (i.e., the columns are linearly independent).

Exemple 1.2 *Consider an non controllable system*

$$A = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 2 & 0 \\ 0 & 0 & -1 \end{pmatrix}, \quad B = \begin{pmatrix} 1 \\ 1 \\ 0 \end{pmatrix}.$$

Computation of matrix $\mathcal{C}$

$$AB = \begin{pmatrix} 1 \\ 2 \\ 0 \end{pmatrix}, \quad A^2B = \begin{pmatrix} 1 \\ 4 \\ 0 \end{pmatrix}$$

then

$$\mathcal{C} = \begin{pmatrix} 1 & 1 & 1 \\ 1 & 2 & 4 \\ 0 & 0 & 0 \end{pmatrix}.$$

The rank of $\mathcal{C}$ is $2 < 3$: the system is not controllable.

Exemple 1.3 *Consider an non controllable system:*

$$A = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ -1 & -2 & -3 \end{pmatrix}, \quad B = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$$

Computation of matrix $\mathcal{C}$

$$AB = \begin{pmatrix} 0 \\ 1 \\ -3 \end{pmatrix}, \quad A^2B = \begin{pmatrix} 1 \\ -3 \\ 7 \end{pmatrix}$$

then

$$\mathcal{C} = \begin{pmatrix} 0 & 0 & 1 \\ 0 & 1 & -3 \\ 1 & -3 & 7 \end{pmatrix}.$$

Its determinant is $-1 \neq 0$, so rank$(\mathcal{C}) = 3$: the system is controllable.

1.2.3 Controllability of non-autonomous linear systems

1.2.3.1 Controllability of Non-Autonomous Linear Systems

A non-autonomous linear system in $\mathbb{R}^n$ given by

$$\dot{x}(t) = A(t)x(t) + B(t)u(t) + r(t), \tag{1.6}$$

is controllable in time T if and only if the matrix

$$C = \int_0^T (\Phi(t,s))B(t)B'(t)(\Phi'(t,s))dt, \tag{1.7}$$

is invertible.

Remark 1 *The matrix C is called the controllability matrix. It does not depend on the initial condition x_0, but it does depend on the final time T. In other words, if a non-autonomous linear system is controllable in time T from x_0, then it is controllable in time T from any point.*

For a non-autonomous system, the controllability matrix $C(t)$ is given by:

$$C(t) = \int_{t_0}^{t} \Phi(t,s)B(s)B'(s)\Phi'(t,s)\,ds,$$

where $\Phi(t,s)$ is the state transition matrix, satisfying:

$$\frac{\partial \Phi(t,s)}{\partial t} = A(t)\Phi(t,s), \quad \Phi(s,s) = I.$$

Exemple 1.4 *Consider the following non-autonomous dynamical system:*

$$\dot{x}(t) = A(t)x(t) + B(t)u(t), \;\; t \in [0, t_f],$$

where

$$A(t) = \begin{pmatrix} 0 & 1 \\ 0 & 0 \end{pmatrix}, \quad B(t) = \begin{pmatrix} 0 \\ t \end{pmatrix}.$$

For this system, $A(t)$ is piecewise constant, so the state transition matrix is:

$$\Phi(t,s) = e^{A(t-s)} = \begin{pmatrix} 1 & t-s \\ 0 & 1 \end{pmatrix}.$$

Substituting $\Phi(t,s)$ and $B(s)$, we obtain:

$$C(t) = \int_{t_0}^{t} \begin{pmatrix} 1 & t-s \\ 0 & 1 \end{pmatrix} \begin{pmatrix} 0 \\ s \end{pmatrix} \begin{pmatrix} 0 & s \end{pmatrix} \begin{pmatrix} 1 & 0 \\ t-s & 1 \end{pmatrix} ds.$$

After calculation, we find that $C(t)$ is full rank (rank 2) for all $t > 0$, which proves that the system is controllable.

This non-autonomous system is controllable because its controllability matrix $C(t)$ is full rank for all $t_f > t_0$. This means it is possible to transition from any initial state $x(t_0)$ to any final state $x(t_f)$ using an appropriate control input $u(t)$.

Exemple 1.5 *Show that the system*

$$\begin{cases} \dot{x}(t) = -x_1(t) + u(t)\sin t, \\ \dot{x}_2(t) = x_2(t) + u(t)\cos t, \end{cases} \tag{1.8}$$

is not controllable. Consider the system:

$$\begin{cases} \dot{x}_1(t) = -x_1(t) + u(t)\sin(t), \\ \dot{x}_2(t) = x_2(t) + u(t)\cos(t), \end{cases}$$

Let $x(t) = \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix}$. *The system can be written as:*

$$\dot{x}(t) = A(t)x(t) + B(t)u(t),$$

where:

$$A(t) = \begin{pmatrix} -1 & 0 \\ 0 & 1 \end{pmatrix}, \quad B(t) = \begin{pmatrix} \sin(t) \\ \cos(t) \end{pmatrix}.$$

The controllability Gramian is:

$$C(t_f) = \int_0^{t_f} \Phi(t,s)B(s)B'(s)\Phi'(t,s)\,ds,$$

where $\Phi(t,s)$ *is the state transition matrix. For this system:*

$$\Phi(t,s) = e^{A(t-s)} = \begin{pmatrix} e^{-(t-s)} & 0 \\ 0 & e^{t-s} \end{pmatrix}.$$

$$\Phi(t,s)B(s) = \begin{pmatrix} e^{-(t-s)}\sin s \\ e^{t-s}\cos s \end{pmatrix},$$

$$\begin{aligned} \Phi(t,s)B(s)B'(s)\Phi'(t,s) &= \begin{pmatrix} e^{-(t-s)}\sin s \\ e^{t-s}\cos s \end{pmatrix} \begin{pmatrix} \sin(t) \\ \cos(t) \end{pmatrix} \begin{pmatrix} e^{-(t-s)} & 0 \\ 0 & e^{t-s} \end{pmatrix} \\ &= \begin{pmatrix} e^{-2(t-s)}\sin^2 s & \sin s\cos s \\ \sin s\cos s & e^{2(t-s)}\cos^2 s \end{pmatrix} \end{aligned} \tag{1.9}$$

The integrand is always rank 1 because:

$$\textit{rank}\left(\Phi(t,s)B(s)B'(s)\Phi'(t,s)\right) = 1 \quad \forall s \in [0, t_f].$$

Therefore, $C(t)$ *is an integral of rank 1 matrices and cannot have rank higher than 1.*

Since the controllability Gramian $C(t)$ *cannot achieve full rank (rank 2) for any* $t > t_0$*, the system is*

not controllable.

Interpretation:

If C has rank n, it means that all states of the system can be influenced using the control $u(t)$. Otherwise, some states are inaccessible, and the system is not completely controllable.

1.3 Numerical methods to solve linear optimal control

Two principal numerical approaches exist for solving optimal control problems: direct methods and indirect methods. Direct methods operate by discretizing the original optimal control problem and reformulating it as a constrained linear optimization problem, offering advantages in implementation simplicity and constraint handling. The shooting method represents the most common indirect approach, employing Pontryagin's Maximum Principle to transform the problem into a two-point boundary value problem that requires solving adjoint equations derived from optimality conditions coupled with Newton-type iterative refinement. While indirect methods achieve superior numerical precision, they demonstrate notable sensitivity to initial condition specification, particularly regarding co-state variable initialization.

1.3.1 Indiret method to solve linear optimal control problem

1.3.1.1 Pontryagin's Maximum Principle:

In this section, we present a general version of Pontryagin's Maximum Principle. This theorem is difficult to prove. However, when there are no constraints on the control, the proof is simple, leading to what is known as the weak maximum principle. We will first focus on this simpler version before moving on to the general case.

Define the Hamiltonian Let us show that a singular trajectory can be parameterized as the projection of a solution to a constrained Hamiltonian system. Consider again the general control system:

$$\dot{x}(t) = Ax(t) + Bu(t) + r(t),$$

The Hamiltonian H is defined by

$$H(t, x(t), u(t), p(t)) = p^0 \left(c'x(t) + d'u(t)\right) + p'(Ax(t) + Bu(t) + r(t)). \tag{1.10}$$

where $p(t) = (p_1(t), p_2(t), \dots p_n(t)), \quad t \in [0, t_f]$ called the adjoint vector, such that

$$\begin{cases} \dot{x}(t) = \dfrac{\partial H}{\partial p}, \\ \dot{p}(t) = -\dfrac{\partial H}{\partial x}. \end{cases} \tag{1.11}$$

Moreover, the minimality condition

$$H(t, x^*(t), u^*(t), p^*(t)) = \max_{0 \le u(t) \le U_{\max}} H(t, x(t), u(t), p(t)), \tag{1.12}$$

holds almost everywhere on $t \in [0, t_f]$.

Since the final time t_f is fixed, according to the transversality condition of PMP, we obtain:

$$H(t_f, x(t_f), u(t_f), p(t_f)) = c. \tag{1.13}$$

Solving the minimality condition (1.12) on the interior of the set of admissible controls gives the necessary condition

$$u^*(t) = \begin{cases} 0 & \text{if } l\ p(t) > 0, \\ U_{\max} & \text{if } l\ p(t) < 0, \end{cases} \tag{1.14}$$

where p is obtained from the adjoint system (1.11), that is,

$$\dot{p}(t) = -A'p(t), \tag{1.15}$$

Transversality conditions where the final point $x(T)$ is free. The optimality condition is given by:

$$p(T) = p^0 \frac{\partial g}{\partial x}(T, x(T)), \tag{1.16}$$

with the necessary condition $p^0 \neq 0$ (typically, we take $p^0 = -1$). Moreover, if g does not explicitly depend on time, it is customary to write:

$$p(T) = -\nabla g(x(T)).$$

Remark 2 *For autonomous systems, the Hamiltonian $H(t, x(t), p(t), u(t)), \ t \in [0, T]$ remains constant along trajectories. Specifically, when f and L are time-independent, the Hamiltonian H becomes time-invariant ($H = const$).*

Remark 3 *The sign convention for p_0 determines the optimality condition: $p_0 \le 0$ yields the maximum principle, while $p_0 \ge 0$ gives the minimum principle. Consequently, condition (1.17) would represent a maximization condition.*

1.3.2 Shooting Method

The shooting method is an iterative numerical approach for solving boundary value problems (BVPs) in differential equations and optimal control theory. By converting the BVP into an initial value problem through estimation of unknown boundary conditions, the method iteratively refines these estimates until the boundary conditions are satisfied.

Using equations (1.11), (1.10), (1.13) and (1.14), we formulate the following optimal control problem:

$$\begin{cases} \dot{x}(t) = Ax(t) + B \times \max(0, \text{sign}(lp(t))U_{\max}, \\ \dot{p}(t) = -A'p(t) + c', \\ Hx(t) = g, \end{cases} \tag{1.17}$$

Let $z(t) = (x(t), p(t))$. This yields a two-point boundary value problem:

where $A^* \in M_{2n\times 2n}(\mathbb{R})$ is the matrix given by

$$A^* = \begin{pmatrix} A & 0_{4\times 4} \\ 0_{4\times 4} & -A' \end{pmatrix}. \tag{1.18}$$

We consider the following Cauchy problem:

$$\begin{cases} \dot{z}(t) = A^* z(t) + B^*, \\ z(0) = z_0. \end{cases} \tag{1.19}$$

If we define the shooting function $S : \mathbb{R}^{2n} \longrightarrow \mathbb{R}^{2n}$ by

$$R(z(t_f) - zf, z(0) - z_0) = 0,$$

where $z(t, z_0)$ is the solution of the Cauchy problem (1.19), then the two points' boundary value problem (1.17) is equivalent to

$$S(z_0) = 0. \tag{1.20}$$

To solve (1.20), we use Newton's method[23].

1.3.2.1 Direct methods

Direct methods consist of transforming the optimal control problem into a finite-dimensional linear, quadratic, or nonlinear optimization problem. One example is the full discretization method.

Full Discretization This method involves choosing the controls in a finite-dimensional space and using a numerical integration method for the differential equations. Consider a subdivision $0 = t_0 < t_1 < \cdots < t_N = T$ of the interval $[0, T]$. We reduce the control space by considering (for example) piecewise constant controls on this subdivision. Moreover, we discretize the differential equationhere, for simplicity, we use the explicit Euler method. We then obtain, with $h_i = t_{i+1} - t_i$,

$$x_{i+1} = x_i + h_i f(t_i, x_i, u_i).$$

This discretization leads to the following nonlinear programming problem:

$$\begin{aligned} &\min F(Z) \\ &x_{i+1} = x_i + h_i f(t_i, x_i, u_i), \quad i = 0, \ldots, N-1, \\ &u_i \in \Omega, \quad i = 0, \ldots, N-1, \end{aligned}$$

where Ω is a subset of $\mathbb{R}^m$, and $Z = (x_1, x_2, \ldots, x_N, u_0, u_1, \ldots, u_{N-1})$, with x_0 given.

1.4 Numerical comparaison

1.4.1 Advantages of Direct Methods over Indirect Methods

— Easier implementation: They don't require preliminary theoretical analysis like indirect methods. Specifically, they eliminate the need to study adjoint variables or pre-determine switching structures.

— Greater robustness: More tolerant to variations in problem parameters.

— Lower sensitivity to initial conditions: Unlike indirect methods which are highly sensitive.

— Efficient constraint handling: Particularly effective for state constraints.

— Feedback control capability: Can compute optimal controls in feedback form.

1.4.2 Limitations of Direct Methods

— Lower precision: For example, in aerospace optimal control problems (as studied in the next chapter), direct methods often prove insufficiently accurate despite increasing discretization steps.

— Local minima issues: The direct discretization often creates multiple local minima, and the solution found may be far from the true global optimum.

— Memory intensive: Can become inefficient for high-dimensional problems after discretization.

1.4.3 Advantages of Indirect Methods

— Exceptional numerical precision

— Parallel computing capability: The multiple shooting method is inherently parallelizable and can be implemented on computer clusters.

1.4.4 Disadvantages of Indirect Methods

— Open-loop solutions: Compute optimal controls in open-loop form.

— Necessary condition limitation: Based on the maximum principle which provides only necessary conditions, requiring *a posteriori* verification of solution optimality.

— Structural rigidity: Requires advance knowledge of switching structures (e.g., through geometric analysis of the problem).

— State constraints are difficult to incorporate and may complicate the optimal trajectory structure.

Chapter 2

Induction phase of Anesthsia

This study revisits [15] induction-phase problem, applying the shooting method [17] via Pontryagins minimum principle [18] while addressing algorithmic inconsistencies in termination criteria and equilibrium computation. We further propose an analytical alternative to time-optimal control, circumventing the shooting methods sensitivity to initial adjoint conditions. Our approach eliminates convergence dependencies and extends to other PK/PD models. Numerical simulations for a 53-year-old male (77 kg, 177 cm) confirm agreement between methods in determining minimal anesthesia time and optimal infusion rates.

2.1 Pharmacokinetic/Pharmacodynamic (PK/PD) model :

The PK/PD model comprises four physiologically distinct compartments: Intravascular blood ($x_1(t)$), Muscle ($x_2(t)$), Fat ($x_3(t)$) and Effect site (brain) ($x_4(t)$). The effect site compartment is included to model the delayed equilibration between plasma drug concentrations and central nervous system effects [19].

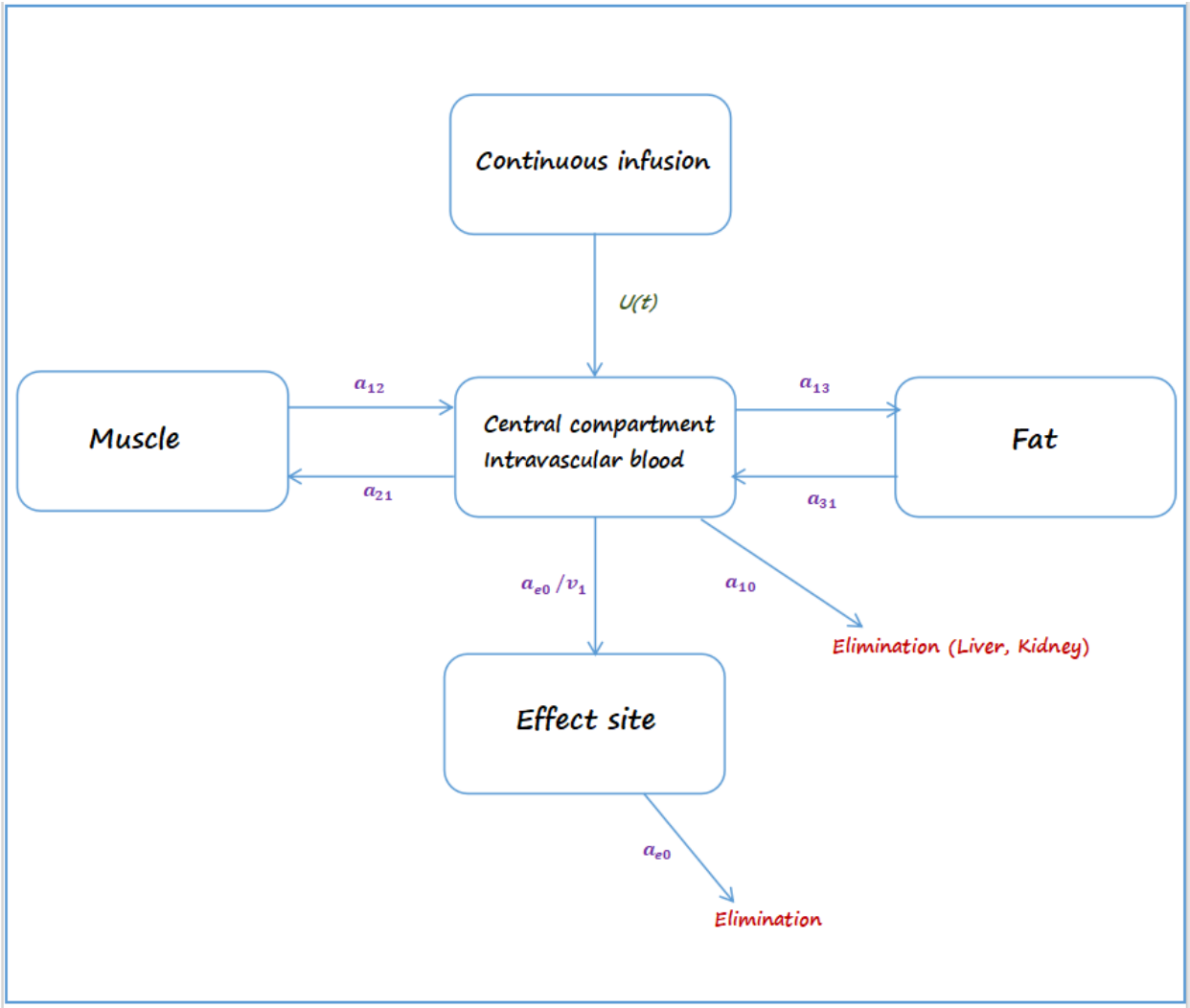


Figure 2.1: Schematic diagram of the PK/PD model with the effect site compartment of Bailey and Haddad [19].

The state variables $x_1(t)$, $x_2(t)$, $x_3(t)$, and $x_4(t)$ represent the propofol mass in the blood (central compartment), muscle, fat and effect site compartments, respectively, at time t. The control input $u(t)$ denotes the continuous anesthetic infusion rate. Key pharmacokinetic parameters include: a_{10} (central compartment clearance rate), a_{e0} (effect site elimination rate), and the intercompartmental transfer rates a_{12} (blood→muscle), a_{31} (blood→fat), a_{21} (muscle→blood), a_{13} (fat→blood), with a_{e0}/v_1 governing drug transfer to the effect site, where v_1 is the volume of the central compartment.

The system dynamics is governed by the following differential equations:

$$\begin{cases} \dot{x}_1(t) = -(a_{10} + a_{12} + a_{13})x_1(t) + a_{21}x_2(t) + a_{31}x_3(t) + u(t), \\ \dot{x}_2(t) = a_{12}x_1(t) - a_{21}x_2(t), \\ \dot{x}_3(t) = a_{13}x_1(t) - a_{31}x_3(t), \\ \dot{x}_4(t) = \dfrac{a_{e0}}{v_1}x_1(t) - a_{e0}x_4(t). \quad t \in [0, t_f] \end{cases} \tag{2.1}$$

The state variables for system (2.1) are subject to the following initial conditions:

$$x(0)' = (x_1(0), x_2(0), x_3(0), x_4(0)) = (0, 0, 0, 0).$$

2.1.1 Schnider's Model

Following Schnider et al. [12], the lean body mass (LBM) is calculated using the James formula. Although this method demonstrates satisfactory accuracy for normal and moderately obese patients, its performance diminishes in cases of severe obesity [20]. The gender-specific equations are defined as:

$$\text{LBM} = \begin{cases} 1.1 \times \text{weight} - 128 \times \left(\dfrac{\text{weight}}{\text{height}}\right)^2 & \text{for males,} \\ 1.07 \times \text{weight} - 148 \times \left(\dfrac{\text{weight}}{\text{height}}\right)^2 & \text{for females.} \end{cases} \tag{2.2}$$

where:

— **Weight** is in kilograms (kg)

— **Height** is in centimeters (cm)

The parameters of the PK/PD model (2.1) are then estimated according to Table 2.1

Parameter	**Estimation**
$a_{10}\,(\text{min}^{-1})$	$0.443 + 0.0107(\text{weight} - 77) - 0.0159(\text{LBM} - 59) + 0.0062(\text{height} - 177)$
$a_{12}\,(\text{min}^{-1})$	$0.302 - 0.0056(\text{age} - 53)$
$a_{13}\,(\text{min}^{-1})$	0.0196
$a_{21}\,(\text{min}^{-1})$	$(1.29 - 0.024(\text{age} - 53))/(1.89 - 0.391(\text{age} - 53))$
$a_{31}\,(\text{min}^{-1})$	0.0035
$a_{e0}\,(\text{min}^{-1})$	0.456
$v_1\,(l)$	4.27

Table 2.1: Parameter values for model (2.1) according to Schniders model

2.1.2 The Equilibrium Point

Following [14], the equilibrium point is obtained by setting the right-hand side of the system (2.1) equations to zero:

$$\begin{cases} -(a_{10}+a_{12}+a_{13})x_1(t)+a_{21}x_2(t)+a_{31}x_3+u(t)=0, \\ a_{12}x_1(t)-a_{21}x_2(t)=0, \\ a_{13}x_1(t)-a_{31}x_3(t)=0, \\ \dfrac{a_{e0}}{v_1}x_1(t)-a_{e0}x_4(t)=0, \end{cases} \tag{2.3}$$

subject to the constraint:

$$x_4 = EC_{50}. \tag{2.4}$$

The equilibrium point $x'_e = (x_{e1}, x_{e2}, x_{e3}, x_{e4})$ is then given by:

$$x_{e1} = v_1 EC_{50}, \quad x_{e2} = \frac{a_{12}v_1 EC_{50}}{a_{21}}, \quad x_{e3} = \frac{a_{13}v_1 EC_{50}}{a_{31}}, \quad x_{e4} = EC_{50}, \tag{2.5}$$

with the corresponding equilibrium infusion rate:

$$u_e = a_{10}v_1 EC_{50}. \tag{2.6}$$

The fast state variables are defined as:

$$\mathrm{x}_{eF}(t) = (x_3(t), x_4(t)). \tag{2.7}$$

The control of the fast dynamics is crucial because the BIS is a direct function of the concentration at the effect site.

Here, the continuous infusion rate $u(t)$ must be selected to drive the system (2.1) from its initial wake state to the desired anesthetized state in minimal time. This constitutes a time-optimal control problem [15], formally stated as:

$$\begin{cases} \min\limits_{u} J = x_1(t_f) \\ \dot{x}(t) = Ax(t) + Bu(t) + r(t), \quad x(0)' = (0,0,0,0) \\ Hx(t_f) = g \\ 0 \le u(t) \le U_{\max}, \quad \forall t \in [0, t_f], \end{cases} \tag{2.8}$$

where

$$H = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}, g = \begin{pmatrix} 9.6 \\ 3.4 \end{pmatrix}, \quad t_f = 1.90.$$

Let $x(t) = (x_1(t), x_2(t), x_3(t), x_4(t)) \in \mathbb{R}^4$. We can write the dynamical system (2.1) in a matrix form as follows:

$$\dot{x}(t) = Ax(t) + Bu(t) + r(t), \tag{2.9}$$

where

$$A = \begin{pmatrix} -(a_{10} + a_{12} + a_{13}) & a_{21} & a_{31} & 0 \\ a_{12} & -a_{21} & 0 & 0 \\ a_{13} & 0 & -a_{31} & 0 \\ \frac{a_{e0}}{v_1} & 0 & 0 & -a_{e0} \end{pmatrix} \quad \text{and} \quad B = \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Chapter 3

Numerical resolution of linear optimal control problem of Induction phase of Anesthsia

In this section, we construct the mathematical model of the linear optimal control corresponding to the induction phase of anesthesia for a 29-year-old female patient weighing 70 kg with a height of 170 cm.

. We solve the problem using two methods: the analytical method combined with the shooting method, and a discretization technique using the Euler formula. Then, we compare the results obtained by performing several numerical simulations with MATLAB.

The problem is formulated as follows:

$$\begin{cases} \min\limits_{u} J = x_1(t_f) \\ \dot{x}(t) = Ax(t) + Bu(t), \quad x(0)' = (0,0,0,0) \\ Hx(t_f) = g \\ 0 \leq u(t) \leq U_{\max}, \quad \forall t \in [0, t_f], \end{cases} \tag{3.1}$$

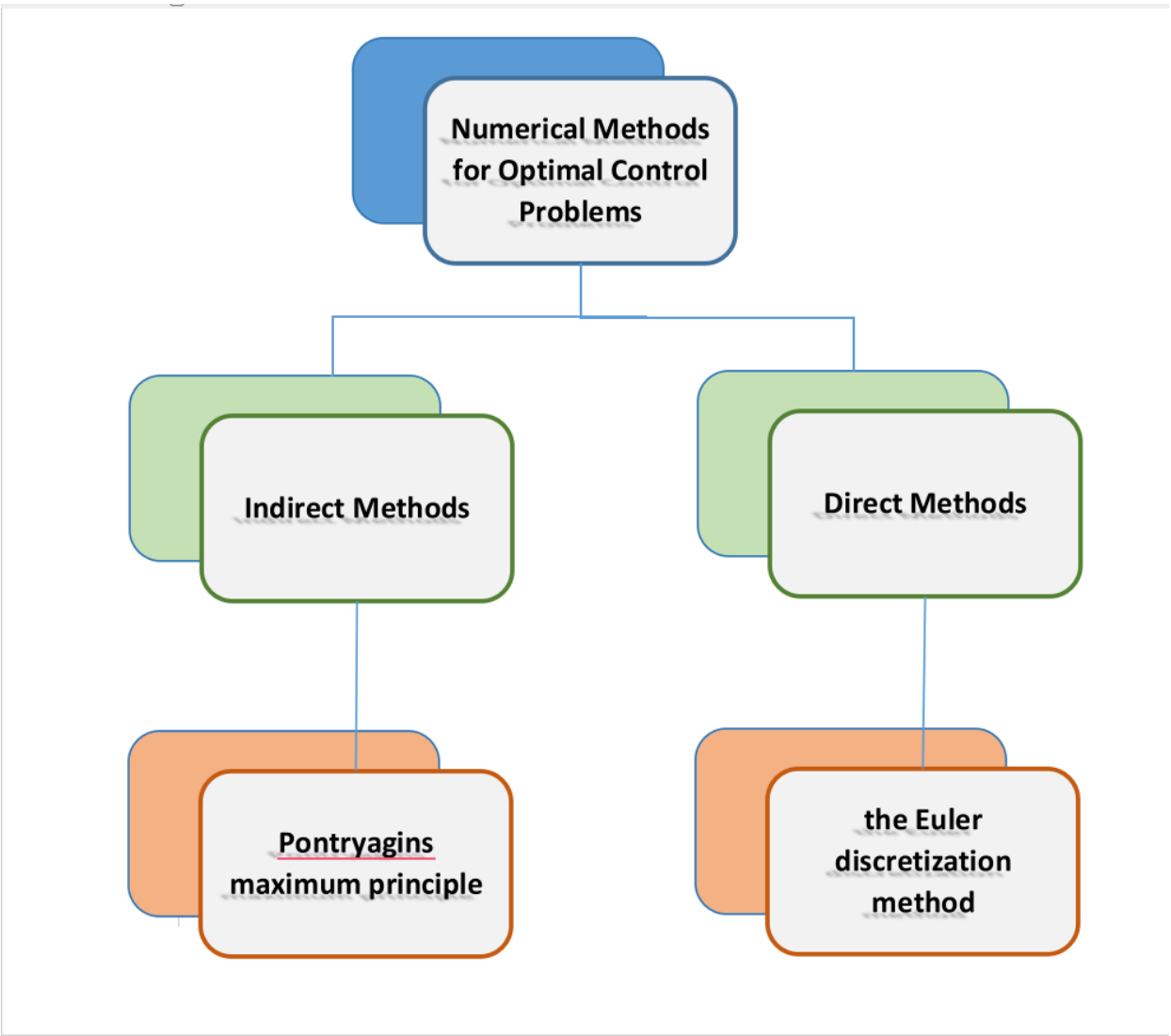


Figure 3.1: Diagram of the Classification of Numerical Methods in Optimal Control

3.1 Numerical resolution by using indirect method

Resolution by the Analytical Method. In order to solve the problem (3.1), we first apply the Pontryagins maximum principle. The Hamiltonian of the problem (3.1) is given by:

$$\begin{aligned} H(x(t),p(t),u(t)) = \quad & p_1(t)(-(a_{10}+a_{12}+a_{13})x_1(t)+a_{21}x_2(t)+a_{31}x_3+u(t)) \\ & +p_2(t)(a_{12}x_1(t)-a_{21}x_2(t)) \\ & +p_3(t)(a_{13}x_1(t)-a_{31}x_3(t)) \\ & +p_4(t)(\frac{a_{e0}}{v_1}x_1(t)-a_{e0}x_4(t)) \end{aligned}$$

The adjoint vectors are the solutions of the system corresponding to the following Euler-Lagrange equations:

$$\begin{cases} \dot{p_1}(t) = (a_{10}+a_{12}+a_{13})p_1(t)-a_{12}p_2(t)-a_{13}p_3(t)-a_{14}p_4(t), \\ \dot{p_2}(t) = -a_{21}p_1(t)+a_{21}p_2(t), \\ \dot{p_3}(t) = -a_{31}p_1(t)+a_{31}p_3(t), \\ \dot{p_4}(t) = a_{e0}p_4(t). \end{cases} \tag{3.2}$$

From the system (3.2), we deduce that

$$\begin{cases} p_1(T) = -\dfrac{\partial g(x(T))}{\partial x_1(T)} = -1, \\ p_2(T) = -\dfrac{\partial g(x(T))}{\partial x_2(T)} = 0, \\ p_3(T) = -\dfrac{\partial g(x(T))}{\partial x_3(T)} = 0, \\ p_4(T) = -\dfrac{\partial g(x(T))}{\partial x_4(T)} = 0. \end{cases} \tag{3.3}$$

The maximum of the Hamiltonian is given by:

$$\begin{aligned} H(x^*(t),p^*(t),u^*(t)) \quad & = \max_{0\le u(t)\le U_{\max}} H(x(t),p(t),u(t)) \\ & = p_1(t)(-(a_{10}+a_{12}+a_{13})x_1(t)+a_{21}x_2(t)+a_{31}x_3) \\ & +p_2(t)(a_{12}x_1(t)-a_{21}x_2(t))+p_3(t)(a_{13}x_1(t)-a_{31}x_3(t)) \\ & +p_4(t)(\frac{a_{e0}}{v_1}x_1(t)-a_{e0}x_4(t))+\max[p_1(t)u(t)] \end{aligned} \tag{3.4}$$

The Pontryagin maximum principle leads us to the following boundary value problem:

$$\begin{cases} \dot{x}_1(t) = -(a_{10} + a_{12} + a_{13})x_1(t) + a_{21}x_2(t) + a_{31}x_3(t) + \max[p_1(t)u(t)] \\ \dot{x}_2(t) = a_{12}x_1(t) - a_{21}x_2(t) \\ \dot{x}_3(t) = a_{13}x_1(t) - a_{31}x_3(t) \\ \dot{x}_4(t) = \dfrac{a_{e0}}{v_1}x_1(t) - a_{e0}x_4(t) \\ \dot{p_1}(t) = (a_{10} + a_{12} + a_{13})p_1(t) - a_{12}p_2(t) - a_{13}p_3(t) - a_{14}p_4(t), \\ \dot{p_2}(t) = -a_{21}p_1(t) + a_{21}p_2(t), \\ \dot{p_3}(t) = -a_{31}p_1(t) + a_{31}p_3(t), \\ \dot{p_4}(t) = a_{e0}p_4(t), \end{cases} \tag{3.5}$$

where

$$x(t) = (x_j(t), j = 1 \dots 4) = (x_1(t), x_2(t), x_3(t), x_4(t), \tag{3.6}$$

and

$$p(t) = (p_j(t), j = 1 \dots 4) = (p_1(t), p_2(t), p_3(t), p_4(t)). \tag{3.7}$$

We construct the following shooting function:

$$\begin{array}{lll} G: & \mathbb{R}^8 & \to \mathbb{R}^8 \\ & p(0), p(T)) & \mapsto G(p(0), p(T)), \end{array} \tag{3.8}$$

with

$$G(p(0), p(T)) = \begin{pmatrix} p_1(0) - \lambda_1 \\ p_2(0) - \lambda_2 \\ p_3(0) - \lambda_3 \\ p_4(0) - 0 \\ p_1(T) + 1 \\ p_2(T) - 0 \\ p_3(T) - 0 \\ p_4(T) - 0 \end{pmatrix}$$

Hence, the problem (3.5) is equivalent to the following problem:

$$\begin{cases} \dot{z}_1(t) = -(a_{10} + a_{12} + a_{13})z_1(t) + a_{21}z_2(t) + a_{31}z_3(t) + \max[p_1(t)u(t)] \\ \dot{z}_2(t) = a_{12}z_1(t) - a_{21}z_2(t) \\ \dot{z}_3(t) = a_{13}z_1(t) - a_{31}z_3(t) \\ \dot{z}_4(t) = \dfrac{a_{e0}}{v_1}z_1(t) - a_{e0}z_4(t) \\ \dot{z}_5(t) = (a_{10} + a_{12} + a_{13})z_5(t) - a_{12}z_6(t) - a_{13}z_7(t) - a_{14}z_8(t), \\ \dot{z}_6(t) = -a_{21}z_5(t) + a_{21}z_6(t), \\ \dot{z}_7(t) = -a_{31}z_5(t) + a_{31}z_7(t), \\ \dot{z}_8(t) = a_{e0}z_8(t), \end{cases} \tag{3.9}$$

We determine the numerical solution of the nonlinear system $G(p(0), p(T)) = 0$ using Newton method. By implementing this method with Matlab.

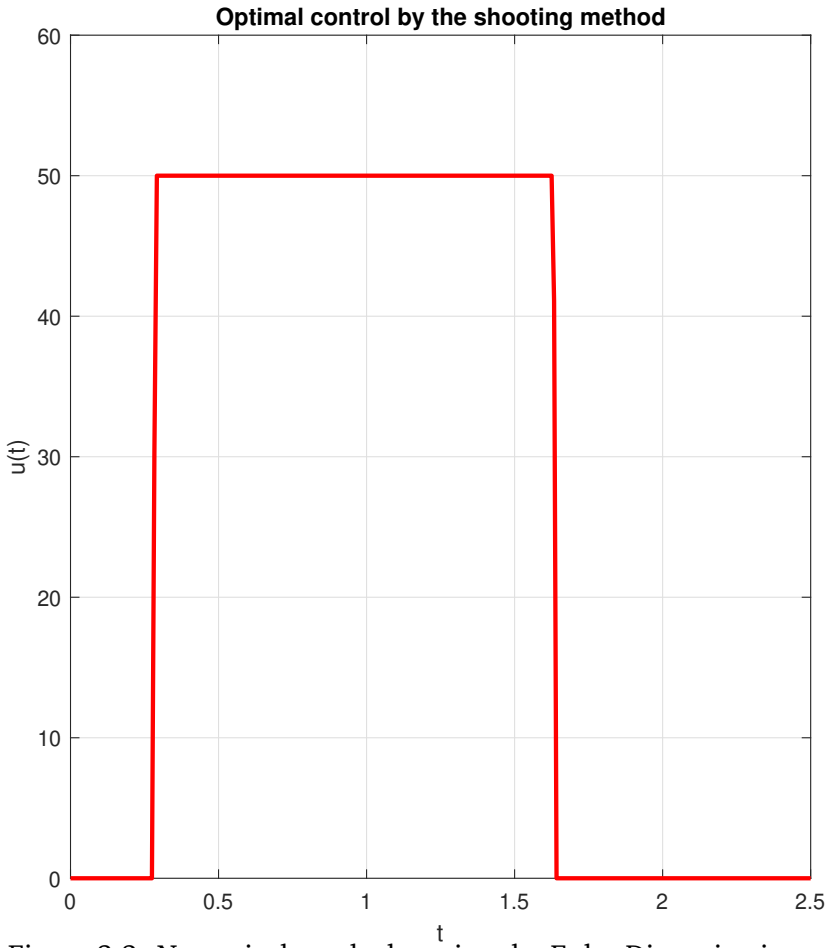


Figure 3.2: Numerical results by using the Euler Discretization method

3.2 Numerical resolution by the Euler discretization method

For a given number of discretization subintervals N, the step size is $h = \frac{T}{N}$ and the time instants are:

$$0 = t_0 < t_1 < \cdots < t_{N-1} < t_N = T.$$

Applying the Euler scheme to solve the Cauchy problem gives the following discretized system:

$$x_{j,i+1} = x_{j,i} + h(A_j x_i + B_j u_i), \quad j = 1, \ldots, n\ , \quad i = 1, \ldots, N\ .$$

where $x_i \in \mathbb{R}^n$. This can be written as:

$$\begin{cases} x_{1,i+1} - x_{1,i} - h(A_1 x_i + B_1 u_{p,i}) & = h r_{1,i} \\ x_{2,i+1} - x_{2,i} - h(A_2 x_i + B_2 u_i) & = h r_{2,i} \\ \vdots & \\ x_{j,i+1} - x_{j,i} - h(A_j x_i + B_j u_i) & = h r_{j,i} \\ \vdots & \\ x_{n,i+1} - x_{n,i} - h(A_n x_i + B_n u_i) & = h r_{n,i} \end{cases}$$

where

$$A = \begin{pmatrix} A_1 \\ A_2 \\ \vdots \\ A_n \end{pmatrix}, \quad B = \begin{pmatrix} B_1 \\ B_2 \\ \vdots \\ B_n \end{pmatrix}, \quad r = \begin{pmatrix} r_1 \\ r_2 \\ \vdots \\ r_n \end{pmatrix}.$$

Expressing A_j as:

$$A_j = (\alpha_{j,1}, \alpha_{j,2}, \ldots, \alpha_{j,k}, \ldots, \alpha_{j,n}),$$

we can write:

$$A_j = \alpha_{j,j} e_j + M_j.$$

Thus,

$$x_{j,i+1} - x_{j,i} - h(\alpha_{j,j} e_j x_i + M_j x_i + B_j u_i) = h r_{j,i},$$

and since $e_j x_i = x_{j,i}$, we obtain:

$$x_{j,i+1} + (-1 - \alpha_{j,j} h) x_{j,i} - h(M_j x_i + B_j u_i) = h r_{j,i}.$$

Define the vector:

$$x' = (x_{1,0}, x_{1,1}, \ldots, x_{1,N}, x_{2,0}, x_{2,1}, \ldots, x_{2,N}, \ldots, x_{n,0}, x_{n,1}, \ldots, x_{n,N}),$$

$$u' = (u_{1,0}, u_{1,1}, \dots, u_{1,N-1}, u_{2,0}, u_{2,1}, \dots, u_{2,N-1}, \dots, u_{m,0}, u_{m,1}, \dots, u_{m,N-1}),$$

$$X = \begin{pmatrix} x \\ u \end{pmatrix}.$$

For $i = 0, \dots, N-1$, we obtain the system:

$$\begin{cases} x_{1,i+1} + (-1 - \alpha_{1,1}h)x_{1,i} - h(M_1 x_i + b_1 u_i) = h r_{1,i}, \\ x_{2,i+1} + (-1 - \alpha_{2,2}h)x_{2,i} - h(M_2 x_i + B_2 u_i) = h r_{2,i}, \\ \vdots \\ x_{n,i+1} + (-1 - \alpha_{n,n}h)x_{n,i} - h(M_n x_i + B_n u_i) = h r_{n,i}. \end{cases}$$

This leads to the matrix system for $j = 1, \dots, n$ and $k = 1, \dots, n$:

— If $j = k$:

$$P_{j,j} = \begin{pmatrix} -1 - \alpha_{j,j}h & 1 & 0 & \dots & 0 \\ 0 & -1 - \alpha_{j,j}h & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & -1 - \alpha_{j,j}h & 1 \\ 0 & 0 & \dots & 0 & -1 - \alpha_{j,j}h \end{pmatrix}.$$

— If $j \neq k$:

$$P_{j,k} = h\alpha_{j,k} \begin{pmatrix} -1 & 0 & \dots & 0 & 0 \\ 0 & -1 & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & -1 & 0 \\ 0 & 0 & \dots & 0 & -1 \end{pmatrix}.$$

— And for the control terms:

$q = 1 \dots m$

$$P_{j,n+q} = hb_{j,q} \begin{pmatrix} -1 & 0 & \dots & 0 & 0 \\ 0 & -1 & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & -1 & 0 \\ 0 & 0 & \dots & 0 & -1 \end{pmatrix}.$$

and

$$V_j = h \begin{pmatrix} r_j(t_1) \\ r_j(t_2) \\ \vdots \\ r_j(t_N) \end{pmatrix},$$

$$V = \{V_j, j = 1 \dots n\}.$$

Thus, the system can be written as:

$$PX = V.$$

$$\min \left(\mathrm{c}'\mathrm{x}(t_f) + \int_0^{t_f} \left(\mathrm{w}'\mathrm{x}(t) + \mathrm{d}'\mathrm{u}(t) \right) dt \right),$$

Applying the Euler scheme to solve the Cauchy problem gives the following discretized system:

$$\int_0^{t_f} \left(\mathrm{w}'\mathrm{x}(t) + \mathrm{d}'\mathrm{u}(t) \right) dt \approx h \sum_{k=0}^{N-1} \left(\mathrm{w}'\mathrm{x}_k + \mathrm{d}'\mathrm{u}_k \right),$$

optimization problem becomes:

$$\min \left(\mathrm{C}'\mathrm{X} + h \sum_{k=0}^{N-1} \left(\mathrm{w}'\mathrm{x}_k + \mathrm{d}'\mathrm{u}_k \right) \right) \simeq \min \left(\mathrm{C}'\mathrm{X} + W'X \right). \tag{1}$$

First, let's start with:

$$\mathrm{c}'\mathrm{x}(t_f) = \widetilde{c}'x + 0_{\mathbb{R}_\geqslant} u = (\widetilde{c}', 0_{\mathbb{R}_{m*n}})X = C'X$$

where:

$$c' = \left[c_1, c_2, \dots, c_n, 0, \dots, 0 \right].$$

Secondly

$$\begin{aligned} \int_0^{t_f} \left(\mathrm{w}'\mathrm{x}(t) + \mathrm{d}'\mathrm{u}(t) \right) dt &\simeq h \sum_{k=0}^{N-1} \left(\mathrm{w}'\mathrm{x}_k + \mathrm{d}'\mathrm{u}_k \right) \\ &= \widetilde{w}'x + \widetilde{d}'u \\ &= (\widetilde{w}', \widetilde{d}')X \\ &= W'X. \end{aligned} \tag{3.10}$$

where

$$W = \begin{pmatrix} \widetilde{w} \\ \widetilde{d} \end{pmatrix}, \quad et \quad \widetilde{w}' = h(\underbrace{w_1, w_1, \dots, w_1}_{N \text{ copies}}, w_2, w_2, \dots, w_2, \dots w_n, w_n, \dots, w_n),$$

$$\widetilde{d}' = h(\underbrace{d_1, d_1, \dots, d_1}_{N-1 \text{ copies}}, d_2, d_2, \dots, d_2, \dots d_n, d_n, \dots, d_m).$$

Third, we can write

$$Hx(t_f) = g \Rightarrow \widetilde{H}X = g, \tag{2}$$

where:

$$g = \Big(g_1, g_2, \ldots, g_p\Big)'.$$

$$\widetilde{H} = \begin{pmatrix} \overbrace{0\ldots0}^{N \text{ copies}} & h_{1,1} & 0\ldots0 & h_{1,2} & \ldots & \ldots & 0\ldots0 & h_{1,n} & \overbrace{0\ldots\ldots\ldots\ldots0}^{\text{m*N-1}} \\ 0\ldots0 & h_{2,1} & 0\ldots0 & h_{2,2} & \ldots & \ldots & 0\ldots0 & h_{2,n} & 0\ldots\ldots\ldots\ldots0 \\ \vdots & & & & & & & & \\ 0\ldots0 & h_{p,1} & 0\ldots0 & h_{p,2} & \ldots & \ldots & 0\ldots0 & h_{p,n} & 0\ldots\ldots\ldots\ldots0 \end{pmatrix}.$$

Fourth

$$\begin{pmatrix} x_1(0) \\ x_2(0) \\ \vdots \\ x_n(0) \end{pmatrix} = \begin{pmatrix} x_{10} \\ x_{20} \\ \vdots \\ x_{n0} \end{pmatrix},$$

we find:

$$RX = \widetilde{x}, \tag{3}$$

where:

$$R = \begin{pmatrix} 1 & 0\ldots0 & \ldots\ldots\ldots & 0\ldots0 & \overbrace{0\ldots0 \quad 0\ldots0}^{\text{m*N-1}} \\ 0\ldots0 & 1 & 0\ldots\ldots & 0 & 0\ldots0 \quad 0\ldots0 \\ \vdots & & & & \\ 0\ldots0 & \ldots\ldots\ldots & \ldots\ldots0 & 1 & 0\ldots0 \quad 0\ldots0 \end{pmatrix}, \widetilde{x} = \begin{pmatrix} x_{10} \\ x_{20} \\ \vdots \\ x_{n0} \end{pmatrix}.$$

Finally:

$$\alpha \leq u(t) \leq \beta,$$

this can be expressed in terms of state variables as:

$$L \leq X \leq U, \tag{4}$$

where the lower and upper bound vectors are constructed through component-wise repetition:

$$L' = \left(0, \ldots, 0, \overbrace{\alpha_1, \ldots, \alpha_1}^{N \text{ copies}}, \alpha_2, \ldots, \alpha_2, \ldots, \alpha_m, \ldots, \alpha_m\right),$$

$$U' = \left(+\infty, \ldots, +\infty, \overbrace{\beta_1, \ldots, \beta_1}^{N \text{ copies}}, \beta_2, \ldots, \beta_2, \ldots, \beta_m, \ldots, \beta_m\right).$$

N	CPU
200	0.0012
500	0.0554
800	0.1807
1200	0.1726
2000	1.8344

Table 3.1: Numerical Simulation Using the Euler Discretization Technique

By combining Equations (1), (2), (3), and (4), we obtain:

$$(S): \begin{cases} \min\left(\mathrm{C'X} + W'X\right) \\ PX = V, \quad RX = \widetilde{x}, \\ \widetilde{H}X = g, \\ L \leq X \leq U, \end{cases} \tag{3.11}$$

This problem can be reformulated in a more compact linear programming form as follows:

$$(S): \begin{cases} \min FX \\ MX = f \\ L \leq X \leq U, \end{cases} \tag{3.12}$$

where:

$$F = (C' + W'), \quad M = \begin{pmatrix} P \\ R \\ \widetilde{H} \end{pmatrix}, \quad f = \begin{pmatrix} V \\ \widetilde{x} \\ g \end{pmatrix}.$$

We also solved the linear program using MATLAB's interior point method. From Table (3.1), it can be noticed that the Euler discretization method is very fast. However, it can achieve the desired accuracy.

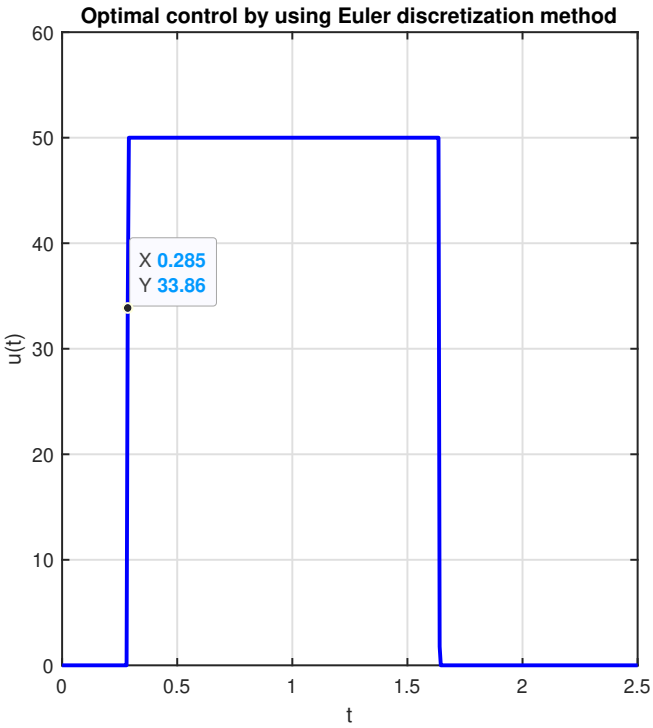


Figure 3.3: Numerical results by using the Euler Discretization method.

3.3 Numerical Comparaison

The direct method based on Euler discretization offers significant advantages over the indirect approach combining the Pontryagin Maximum Principle (PMP) and the shooting method.

Ease of Use:

— The Euler method is simpler to implement since it does not require solving a boundary value problem iteratively, unlike the shooting method.

— The shooting method, however, critically depends on the initial guess for convergence, adding an extra layer of complexity.

Comparable Results with Fewer Constraints:

— The results obtained via Euler discretization are similar to those of the shooting method but without the numerical challenges tied to sensitivity in initial conditions.

— The shooting method may fail to converge if the initial guess is poorly chosen, making it less robust in certain scenarios.

— In conclusion, while the shooting method can provide high theoretical precision, the Euler method is often preferable due to its simplicity, reliability, and practical efficiency.

Conclusion

This study presented numerical methods for solving linear optimal control problems, with applications in biomedical systems. We began by analyzing the controllability of the system and formulating the problem mathematically. Both indirect and direct methods were implemented to solve the control problem efficiently.

Euler's discretization method proved to be a simple yet effective approach for approximating the systems dynamics. In the second part, we applied the developed models to the anesthesia induction process using a PK/PD framework.

The simulations highlighted the importance of control strategies in maintaining safe drug levels during anesthesia. Overall, the work demonstrated the power of numerical control techniques in healthcare. Future improvements may involve adapting these models to nonlinear systems or real-time monitoring tools.

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