

Advances Of Optimal Control In Biomedical Engineering

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Abstract— Controlled optimization problems constitute a fundamental mathematical framework with wide-ranging applications in biomedical engineering and related fields. This paper surveys recent biomedical applications that employ optimal control formulations governed by ordinary and partial differential equations, including treatment procedures, neuroscience, medical imaging, epidemiological modelling, and emerging nanomedical technologies. The literature highlights both single-time and multi-time optimization approaches. We aim to bridge theoretical developments in controlled optimization with practical biomedical applications.

Keywords— Biomedical Applications; Multi-Time; Optimal Control Problem; Single-Time.

I. INTRODUCTION

A basic mathematical tool arising in different real-life applications including biomedical engineering, mechanical engineering, industrial process control, control space structures of flight control designing and machine learning is the controlled optimization problem [1], [8]. Over time, the controlled optimization problem has been extensively studied, leading to the development of two principal approaches: single-time and multi-time optimization problem [2], [3]. To extremize a functional refers to finding its minimum or maximum subject to given constraints, typically governed by ordinary differential equations (ODEs) or partial differential equations (PDEs) describing the underlying biological or physical system.

We review biomedical applications that integrate controlled optimization problems to model, analyze, and improve complex biological and medical processes. The literature on integrating optimization models into biomedical applications is quite extensive. In this context, we will discuss the following topics: the design of nanorobots (potentially for drug targeting), treatment procedures, neuroscience, medical imaging (acquisition and analysis), and epidemiological modelling.

Nevertheless, for a deep understanding of the studies presented in Section II, let us consider some mathematical settings [13], [16]. In many applications, the (multiobjective) optimal control problem is formulated as follows

$$\min \int_a^b f(t, x, u) dt \text{ (equivalent to } \max \int_a^b -f(t, x, u) dt)$$

subject to

$$\dot{x} = X(t, x, u), t \in \mathbb{R}_+,$$

$$G(t, x, u) \leq 0,$$

$$x(a) = p, x(b) = r.$$

Here, t is the parameter of evolution (time), $x(t)=(x_1(t), x_2(t), \dots, x_n(t))$ represents the state function and $u(t)=(u_1(t), u_2(t), \dots, u_m(t))$ is the cost function. Also, $f(t, x, u)=(f_1(t, x, u), f_2(t, x, u), \dots, f_z(t, x, u))$, $X(t, x, u)=(X_1(t, x, u), X_2(t, x, u), \dots, X_n(t, x, u))$, $G(t, x, u)=(G_1(t, x, u), G_2(t, x, u), \dots, G_q(t, x, u))$ are continuously differentiable functions. If $t=(t_1, t_2, \dots, t_k)$, the previous problem becomes a multi-time problem.

The Pontryagin Maximum Principle is widely regarded as the standard approach for solving continuous optimal control problems. To solve an optimization problem using Pontryagin's Maximum Principle, several preliminary steps are required, including the formal formulation of the optimization problem and the introduction of appropriate notation for the PMP framework. We will enumerate some objects of the mathematical language, especially when the problem involves a multi-time approach: Kronecker symbol δ_b^a , Einstein summation (summation after repetitive indices), $\wedge$ = exterior product [13].

II. OPTIMAL CONTROL APPROACHES IN BIOMEDICAL ENGINEERING

The work of Udriște and Tevy [16] is the first to introduce a mathematical multi-time control model for a multi-robot system with potential biomedical applications, including minimally invasive medical diagnosis, monitoring, toxin detection, and drug delivery. They applied the (weak and strong) multi-time maximum principle and the Hamilton–Jacobi–Bellman PDE to address the optimal control volume problem describing a set of planar micro-robots moving in the same direction. In addition, the mathematical ingredients of this approach were the m -flow evolution, state, control, and co-state functions, as well as an elapsed-volume functional. The authors assumed the initial points fixed and different partial speeds during robot motion and the objective was to drive the system to the origin while minimizing the elapsed time volume. Most importantly, the outcomes of this study emphasise the tremendous potential of a multi-time approach for modelling the dynamics of micro and nanoscale robotic systems.

In [6], Grigorenko et al. proposed a mathematical model for the treatment of psoriasis over a finite time horizon. The model is defined by a system of three nonlinear differential equations describing the interactions among T lymphocytes, keratinocytes, and dendritic cells. Two bounded, time-dependent control functions are included to represent pharmacological suppression of the interactions between T lymphocytes and keratinocytes and between T lymphocytes and dendritic cells. The control objective is to minimize a weighted sum of the total keratinocyte concentration and the overall cost of treatment, formulated as an integral involving the squared control functions. Pontryagin's Maximum Principle is employed to characterize the optimal control structure. The numerical results lead the authors to conclude that treatment with different medications is more effective than treatment with a single drug.

In [4], the authors address uncertainty and stochasticity in dynamic healthcare systems (i.e., clinical treatment management for septic patients) by proposing an evidence-based optimal control (EBOC) approach that integrates traditional optimal control with Machine Learning. Several machine learning algorithms (Clustering, Supervised Regression, Decision Tree, Neural Network) were evaluated. According to the reported results, the Neural Network performed best and was subsequently combined with the traditional control method. Computational results demonstrate that EBOC outperforms traditional optimal control in managing disease progression and reducing costs under uncertain or noisy conditions. Furthermore, genetic algorithms were employed to identify optimal parameter settings, thereby addressing the nondeterministic polynomial-time hardness of parameter selection and enhancing the effectiveness of the control strategy. Most importantly, this approach enables application of the EBOC method to stochastic systems

while providing an effective optimal control strategy; its application to systems with random errors demonstrated substantially improved effectiveness in controlling disease progression and managing overall costs.

The research [15] addresses the minimization of tumor cell populations while maintaining effector-immune cells above a healthy threshold using minimal chemotherapy. A mathematical model based on ordinary differential equations was formulated, and the multi-objective optimal control problem (MOOCP) was solved using both Pure and Hybrid approaches. Notably, the authors formulated the necessary criteria. Swarm Intelligence and Evolutionary Algorithms were employed to analyze the solutions, visualized via the Pareto Optimal Front and assessed with the Hypervolume Indicator. Results indicate that the Hybrid MOOCP method, particularly using Multi-Objective Differential Evolution (MODE), outperforms the Pure MOOCP approach by yielding solutions closer to the optimal trade-off between objectives.

In [11], the authors aimed to formulate an optimal control-based method for brain source localization, equivalent to relate the electric potential measured at electrodes to either the potential or the electric current on the cortex. More specifically, Malovichko et al. [11] formulated the inverse electroencephalography (EEG) problem as a constrained optimal control problem governed by Poisson's equation. Using appropriate techniques (e.g., by introducing Lagrange multipliers), they transformed the problem into an unconstrained one. The resulting optimality conditions yield a variational Euler-Lagrange system, which is discretised using finite-element methods (FEM), yielding a sparse Karush-Kuhn-Tucker linear system. The approach naturally accommodates Magnetic Resonance Imaging (MRI)-based meshes of high geometric complexity. Compared to the mixed quasi-reversibility method, this approach explicitly incorporates pointwise noisy electrode data, thereby avoiding interpolation to the scalp surface. The method also circumvents the explicit construction of the lead-field matrix, which is advantageous for large-scale problems. Numerical experiments on both spherical and realistic MRI-based meshes demonstrated accurate reconstruction of cortical activity. In addition, the proposed approach eliminates the need to simulate dipolar right-hand-side sources, a well-known limitation of standard FEM-based MNE (Minimum Norm Estimation)/LORETA methods. At the same time, it retains the flexibility of FEM-based estimators, including the ability to handle anatomically realistic head models with complex geometries, spatially varying conductivities, and non-smooth or perforated interfaces.

Using network control theory, Gu et al. [7] analysed the optimal transitions between the default mode and sensorimotor systems under finite-time and energy constraints. The study evaluated how white matter connectivity influences the energetic efficiency and regional specificity of these transitions, comparing different control strategies commonly used in dynamical systems. Also, they compared healthy individuals and patients with mild traumatic brain injury, revealing alterations in network control profiles associated with structural damage, providing insights into how brain network architecture constrains state transitions and how injury modifies these constraints. More precisely, to address this issue, the authors incorporate mathematical objects or tools, such as the Hamiltonian, Legendrian duality and Pontryagin's minimum principle. These findings provide fundamental insights into the mechanisms underlying brain state transitions in healthy cognition and their alteration following brain injury.

In [9], the researchers proposed a novel framework for quantifying brain control costs using a linear stochastic model that addresses the limitations of previous deterministic approaches. The framework evaluates the minimal Kullback–Leibler divergence between uncontrolled and controlled processes, thereby decomposing control costs into contributions from mean and covariance dynamics. Applied to human whole-brain imaging data, the method identifies key regions involved in state transitions: lower visual

areas in controlling mean activity and the posterior cingulate cortex in controlling covariance, providing insights into the neural mechanisms underlying cognitive state transitions. A key contribution of this framework is its inclusion of stochasticity in the measurement of control cost, an aspect that previous neuroscience studies have not adequately addressed. A notable feature of the proposed control cost is its decomposition into contributions from mean and covariance dynamics, enabling a clear separation of these two aspects in the analysis of brain state transitions.

Khouldi et al. [10] investigated a mathematical model for stress phenomena throughout the medical student population. They integrated variables (time-dependent functions) representing stress dynamics, resilience, workload impact, and secondary symptoms, along with two control functions related to resilience and workload. The framework employs optimal control strategies to reduce stress levels and enhance long-term resilience (i.e., to minimise the objective functional encompassing the negative impacts of prolonged stress). More specifically, the main result presents a system of nonlinear ODEs that captures the interactions among the aforementioned variables. It models the dynamics of stress development, the release of workload and symptoms in response to stress, and the recovery mechanisms that counteract stress over time. According to the authors, this work contributes to evidence-based decision-making in academic and psychological support systems by providing insights into stress management within demanding educational environments. They reported results that illustrate the complexity of stress dynamics and how interventions such as relaxation techniques, physical exercise, and medication can be optimally timed and adjusted. Beyond its theoretical relevance, the model has practical implications for stress management. By enabling the quantification and prediction of intervention outcomes, the framework can inform educators, policymakers, and health professionals in designing and evaluating strategies to enhance resilience, manage workload intensity, and mitigate stress-related symptoms.

Medical image analysis is another area of biomedical engineering in which optimal theoretical tools have driven numerous advances. In this way, PDE-constrained optimization problems have different applications in neuroimaging, cardiovascular imaging, and oncologic imaging, including registration and segmentation of images. Image registration is a classical problem in medical image analysis, aiming to establish pointwise correspondences between two or more images. Closely related data assimilation problems employ PDE-constrained formulations to couple biophysical models with patient-specific data derived from medical imaging. The resulting optimality systems typically consist of large-scale, nonlinear, multicomponent PDEs, posing significant challenges for efficient numerical solution. Mang et al. [12] analysed three topics: data assimilation in brain tumour imaging, diffeomorphic image registration, and feature extraction in cardiac imaging. Also, Ashouri and Eslahchi [2] developed an automated technique to identify a set of suitable PDE terms for computer vision tasks and presented a new PDE-constrained optimization model. Notably, they highlight that the optimization problem can be reformulated as a least-squares problem by assuming time independence, without introducing an adjoint system of equations. The PDE constraints are assumed to be linear combinations of differential operators, with the corresponding coefficients learned from a set of training samples. Numerical results indicate that the proposed model improves peak signal-to-noise ratio while reducing computational cost and exhibits robustness with respect to noise type and variance, as well as to the size and characteristics of the noisy images and datasets. Notably, the method achieves effective noise removal already in the first iteration.

Rund et al. [14] focus on the optimal control problem employed in simultaneous multislice imaging. More specifically, their aim is to determine the minimum-duration RF

(Radiofrequency) pulses and slice-selective gradient shapes for MRI using time-optimal control subject to physical constraints. The problem is formulated as a bilevel optimization, minimizing pulse duration in the upper level while satisfying refocusing and physical constraints in the lower level, with heuristics introduced to mitigate nonconvexity and approach a near-global optimum. Numerical examples demonstrate substantial temporal reductions, 87.1% for double diffusion and 74% for turbo spin echo pulses, compared to conventional approaches, and the optimized pulses are experimentally validated on a 3T scanner using phantom measurements. Time-optimal refocusing pulses can benefit a wide range of simultaneous multislice applications, including diffusion and spin-echo-based sequences, by reducing echo spacing and improving signal quality and motion robustness.

The paper [5] presents an optimal control model problem at minimizing the number of coronavirus-infected individuals while reducing intervention costs. Time-dependent control variables include supportive care, mask usage, public awareness campaigns, and treatment. The model incorporates time-dependent controls, such as supportive care, surgical masks, treatment, and public awareness campaigns, and captures the dynamics of six population groups. These groups refer to the susceptible population, the exposed population, the symptomatic and infectious population, the asymptomatic but infectious population, the hospitalized population and the recovered population. In addition, the authors consider that the patients can recover naturally or with treatment. Numerical simulations show that the proposed strategies effectively reduce infections, asymptomatic cases, hospitalizations, and disease reservoirs, while increasing susceptible and recovered populations.

A summary of the discussed studies is provided in Table I.

TABLE I SUMMARY OF DIFFERENT OPTIMAL ONTROL APPROACHES IN BIOMEDICAL APPLICATIONS

Authors	Keywords/ MSC	Main findings
Integral-type functional		
Nanorobots		
Udriște and Tevy, 2020 [16]	multi-time motion planning; multi-time multi-robot systems; multi-time optimal control; multi-time Hamilton-Jacobi-Bellman PDE MSC:49K20; 90C46; 68T40; 93C85 Multiple integral functional	It is the first study to investigate the theory of minirobots (micro- and nanoscale) moving at different partial speeds (across multiple time scales), but all must move in the same partial direction. To analyze multi-temporal evolution, the authors have seen the dependence on multiple time variables as an immersion, a diffeomorphism, or a submersion, with the partial order in $\mathbb{R}_+^m$ inducing a corresponding partial order on the image of the mapping.
Treatment procedures		
Grigorenko et al., 2019 [6]	Psoriasis; nonlinear controlled system; optimal control; Pontryagin maximum principle; indicator function	This paper investigates psoriasis treatment using a mathematical model in which differential equations describe the interactions among T lymphocytes, keratinocytes, and dendritic cells.

	MSC: 49J15. Simple integral functional	Compared to related works, the model employs more detailed differential equations to capture the dynamics of cell concentrations.
Chen et al., 2019 [4]	dynamic system; sepsis healthcare; optimal control; EBOC method; Machine learning MSC: 49J15; 68T20. Simple integral functional	The study shows that the proposed evidence-based optimal control (EBOC) method, which integrates traditional optimal control with machine learning, significantly outperforms classical approaches in stochastic systems by effectively managing uncertainty, suppressing disease spread, and reducing overall costs.
Samy et al., 2023 [15]	multi-objective optimal control problem; Pontryagin maximum principle; swarm intelligence; evolutionary algorithm MSC: 90C29; 68W50. Simple integral functional	Besides other approaches to minimise the tumor cell population, it focuses on tumor cells, effector cells, Circulating Lymphocytes, or drugs for any specific type. The study demonstrates that the Hybrid MOOCP method, especially using Multi-Objective Differential Evolution, outperforms the Pure approach in minimizing tumor cells while preserving effector-immune cells, providing solutions closer to the optimal trade-off between objectives.
Neurosciences		
Malovichko et al., 2024 [11]	optimal control; inverse problems; electroencephalography MSC: 49J15; 49K20. Multiple integral functional	An optimal control formulation of the inverse EEG problem is shown to enable accurate source reconstruction on realistic MRI-based geometries without constructing the lead-field matrix or modelling dipole sources.
Gu et al., 2017 [7]	network neuroscience; control theory; traumatic brain injury; cognitive control; diffusion imaging MSC: 49J15. Simple integral functional	White matter connectivity determines the energetic efficiency of brain-state transitions, and structural damage from mild traumatic brain injury significantly alters the underlying network control mechanisms.
Kamiya et al., 2023 [9]	brain state transition; control theory; optimal control MSC: 49J15. Simple integral functional	It is one of the first studies to incorporate stochasticity not only in brain dynamics but also in control cost. The study identifies key brain regions involved in the optimal control of cognitive task-related state transitions using human whole-brain imaging data.

Khouldi et al., 2025 [10]	stress, mathematical modelling; medical analysis; medical education; optimal control theory MSC: 92C20. Simple integral functional	The model demonstrates that optimal control strategies can effectively regulate stress dynamics in medical students by coordinating workload, resilience, and symptom management, enabling both system stabilization and quantitative evaluation of intervention outcomes.
Medical imaging		
Ashouri and Eslahchi, 2022 [2]	PDE learning; image denoising; partial differential equation; regularization MSC: 49M41. Multiple integral functional	The study proposes an automated PDE-constrained optimization framework that learns task-specific combinations of differential operators from training data for image processing and computer vision applications.
Rund et al., 2017 [14]	pulse design; refocusing; simultaneous multislice excitation; time optimal control MSC: 49M25. Simple discrete objective functional	The study demonstrates that time-optimal control enables the design of minimum-duration RF pulses for simultaneous multislice MRI, achieving substantial reductions in pulse duration while improving signal quality and robustness under physical constraints.
Epidemiologic modelling		
Fatima et al., 2023 [5]	epidemic model; MERS-CoV; next generation matrix technique; stability analysis; sensitivity analysis; optimal control; numerical simulations MSC: 37J25; 49M25. Simple integral functional	The study develops a deterministic transmission model with time-dependent optimal control functions for supportive care, mask use, public awareness campaigns, and treatment. By identifying the key factors driving transmission of Middle East Respiratory Syndrome coronavirus, this study provides guidance for designing effective control strategies to mitigate the disease's impact on public health.

*n.a - not available

III. CONCLUSIONS

This paper presents the design of effective optimal control models in numerous biomedical engineering applications, including medical imaging, epidemiologic modelling, neuroscience, and treatment procedures. We provide a comprehensive review of existing approaches in the field, illustrating the recent advances in these related areas. While predictive mathematical models of complex biological systems hold great promise for computational medicine, their practical deployment in optimal control frameworks is limited unless uncertainties are rigorously quantified, ensuring reliable control strategies and robust predictions of clinically relevant outcomes.

Acknowledgement

Not applicable.

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