State-Constrained Optimal Spatial Field Control for Controlled Release in Tissue Engineering

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Abstract—Distributed parameter control problems involving manipulation within the spatial domain arise in a variety of applications including vibration control, active noise reduction, epidemiology, tissue engineering, and cancer treatment. A state-constrained spatial field control problem motivated by a biomedical application is solved in which the manipulation occurs over a spatial field and the state field is constrained both in spatial frequency and by a partial differential equation (PDE) that effects the manipulation. An optimization algorithm combines three-dimensional Fourier series, which are truncated to satisfy the spatial frequency constraints, with exploitation of structural characteristics of the PDEs. The computational efficiency and performance of the optimization algorithm are demonstrated in a numerical example, for which the spatial tracking error is almost entirely due to the limitation on the spatial frequency of the manipulated field. The numerical results suggest that optimal control approaches have promise for controlling the release of macromolecules in tissue engineering applications.

I. INTRODUCTION

In spatial field control, manipulation within a distributed parameter system (DPS) occurs as a spatial field. Spatial field control problems arise in a variety of applications including vibration control using internally placed piez actuators [1], active noise reduction in acoustic enclosures [2], active control of communicable disease carriers [3], the engineering of biological tissues and organs [4], and cancer treatment [5]. The ability to manipulate within the spatial domain provides much more controllability than the heavily studied boundary control problems (e.g., [6]), but the enhanced manipulation requires the determination of many more degrees of freedom. For example, for spatial field control problems with three spatial dimensions, the manipulated variable is \( u(x, y, z, t), \) \( \forall x, y, z, t, \) compared to boundary control in which manipulation is defined only on the external surface.

While many theoretical results have been derived for many classes of spatial field control problems [7], [8], [9], few contributions have proposed numerical algorithms that address all of the challenges that arise in real applications. While nonlinear programming methods for solving optimal control problems such as control vector parameterization [10], [11] and direct transcription [12], [13] are directly applicable to boundary control and most other optimal control problems, spatial field control for real applications problems must be carefully formulated to arrive at a computationally feasible solution. This is true whether the algorithms are implemented off-line or on-line with repeated solution at each time instance in a receding horizon manner (so-called model predictive control [14]).

For example, consider an attempt to solve a simple open-loop spatial field control problem using control vector parameterization with a standard finite-difference discretization of a single partial differential equation (PDE) over time and the three spatial dimensions with 100 grid points in each dimension. The resulting nonlinear program with \( 100^4 = 10^8 \) optimization variables is too computationally complex to be solved with existing computer hardware and software. The spatial control problems that arise in most real applications are even more complicated, involving multiple PDEs and typically requiring the satisfaction of spatial constraints on the state or manipulated fields.

This paper addresses a state-constrained spatial field control problem for a system described by tightly coupled PDEs. As is common in the optimal control of PDEs, basis function expansions are used to reduce the number of degrees of freedom to a manageable size [15], [16], [17]. Unlike the problem-independent basis functions such as Legendre polynomials, radial basis functions, and proper orthogonal decomposition that have been very popular in the last decade [18], [19], [20], [21], [22], the structural characteristics of the PDEs will be exploited to reduce computational complexity. The methodology is presented in the context of a spatial field control problem motivated by tissue engineering [4], [23], [24], [25], [26], [27], in which molecules are released within a biological tissue from fixed embedded polymer microparticles designed to provide controlled release [28], [29]. The transport of these molecules is described by reaction-diffusion-convection equations in three spatial dimensions, and the control problem is to provide a desired spatial and temporal uptake of these molecules throughout the biological tissue. The reader is directed to a past paper [4] for more details on the biological motivation for the optimal control problem, including additional references to relevant tissue engineering literature.

II. SPATIAL FIELD CONTROL PROBLEM

The system has a chemical species initially located in small biostable biocompatible polymer microparticles that are embedded, along with cells, in a tissue scaffold [26], [27]. Over time the chemical species is released from the microparticles and taken up by the surrounding cells, which cause the cells to change their behavior. The control objective is to provide for a desired spatial and temporal cellular uptake rate, which is related to the local chemical species
concentration by
\[ R_{\text{uptake}}(x, y, z, t) = f(C(x, y, z, t)), \] (1)
where \( f \) is an invertible algebraic function that can be identified from in vitro cell culture experiments [30], [31].
To simplify the mathematical formulation, (1) is inverted to derive an expression for a reference concentration field
\[ R(x, y, z, t) = f^{-1}(R_{\text{uptake,desired}}(x, y, z, t)), \] (2)
so that the mathematical control objective is to determine properties of the polymer microparticles that minimize the error between the reference and model species concentration fields.
The concentration field \( C(x, y, z, t) \) in the engineered tissue construct is modeled by the reaction-diffusion-convective equation
\[ \frac{\partial C}{\partial t} = D \nabla^2 C - v \cdot \nabla C - g(C) + u(x, y, z, t), \] (3)
which is a parabolic PDE with manipulated field \( u(x, y, z, t) \), effective diffusion coefficient \( D > 0 \), spatially uniform velocity vector field \( v \), spatial domain \( \Omega \) as the unit cube, and net chemical species consumption \( g(C) \) by cellular uptake and species degradation. The effects of chemical species reversibly binding with the extracellular matrix can be included with minor modifications of the model. The system is treated as a continuum, which is most accurate for length scales larger than the diameter of a cell (about 10 microns). To simplify the presentation, suppose the zero initial condition
\[ C(x, y, z, 0) = 0, \] (4)
and the Dirichlet boundary condition
\[ C(x, y, z, t) = 0, \text{ on } \partial \Omega. \] (5)
Each polymer microparticle is assumed to consist of a polymer core that initially contains a uniform concentration of chemical species to be released and a polymer shell that initially does not contain the chemical species (see Fig. 1). Technology is available for manufacturing these core-shell microparticles to have precisely specified physical properties [28]. The manipulated field \( u(x, y, z, t) \) associated with the release of a chemical species from core-shell microparticles embedded in the biological tissue is related to the core-shell microparticles by
\[ u(x, y, z, t) = 4\pi \rho R_p^2 f \bigg|_{r=R_p}, \] (6)
where \( R_p \) is the outer radius, \( 4\pi R_p^2 \) is the external surface area, \( \rho \) is the number density of the core-shell microparticles, and the flux at the surface of a single core-shell microparticle is
\[ J \bigg|_{r=R_p} = -\kappa \frac{\partial C_r}{\partial r} \bigg|_{r=R_p}, \] (7)
where \( C_r(r, x, y, z, t) \) is the concentration field and \( \kappa > 0 \) is the effective diffusion coefficient within the core-shell microparticle. To simplify manufacturing of the tissue construct, the core-shell microparticles are assumed to be identical except for having different initial loading \( C_{r0} \). Technology exists for embedding a specified spatial distribution of these microparticles within a tissue matrix [32], [33]. Changing the number density has exactly the same effect on the spatiotemporal release as changing the initial loading, so the number density \( \rho \) is assumed to be spatially uniform in \((x, y, z)\) without changing the achievable value for the control objective. The effective diffusion coefficient \( \kappa \) can be modified by changing the polymer chemistry, molecular weight distribution, porosity, or tortuosity [34].

The transport of species through a biostable biocompatible polymeric core-shell microparticle is described by
\[ \frac{\partial C_r}{\partial t} = \kappa \left( \frac{\partial^2 C_r}{\partial r^2} + \frac{2 \partial C_r}{r \partial r} \right), \] (8)
with initial condition
\[ C_r(r, x, y, z, t_p) = \begin{cases} C_{r0}(x, y, z), & 0 \leq r < r_p, \\ 0, & r_p \leq r < R_p, \end{cases} \] (9)
and boundary conditions
\[ \frac{\partial C_r}{\partial r} \bigg|_{r=0} = 0, \] (10)
\[ C_r(R_p, x, y, z, t) = k_p C(x, y, z, t), \] (11)
where \( r_p \) is the radius of the polymer core, \( k_p \) is the partition coefficient (which can be modified by changing the polymer chemistry), and \( t_p \) is the time for which the core-shell microparticles are activated by a spatially uniform environmental trigger. Many environmental triggers have been demonstrated in tissue engineering applications including pH, temperature, pressure, light, glucose, electric current, ultrasound, magnetic field, enzymes and other proteins, and ionic strength [35], [36], [37], [38], [39]. Many of these environmental triggers can be activated with spatial uniformity across the biological tissue.
To simplify the analysis, both tissue and microparticle models assume that the effective transport due to Brownian motion is spatially uniform and that the effective diffusion coefficient \( \kappa > 0 \) is the same in the polymer core and polymer shell. The inclusion of a polymer shell provides a much greater variety of release rates than microspheres, including the creation of a delay in the release profile [28]. The above system consists of two types of systems in feedback. Each microparticle, referred to as System 1 in Fig. 1, locally provides the manipulation, which is described by (8)-(11). These microparticles are embedded in the tissue.
construct described by (3)-(5), referred to as System 2, whose concentration field is to be controlled. The two types of systems are interconnected through (6)-(7). Recall that \( C_r \) is the concentration of the chemical species in the microparticles and \( C \) is the concentration of the same chemical species in the tissue construct.

The spatial field control problem is to determine the optimal properties of the polymer microparticles
\[
\{\rho, R_p, r_p, h_p, \kappa, t_p, C_{r0}(x, y, z)\} \tag{12}
\]
that specify a manipulated field \( u(x, y, z, t) \) of constrained spatial variation that minimizes the error between the reference and model species concentration fields
\[
E = \int_T \int_{\Omega} (R(x, y, z, t) - C(x, y, z, t))^2 dV dt, \tag{13}
\]
where \( T \) is the time range of interest, \( R(x, y, z, t) \) is \( C \) in time and \( C^2 \) in the spatial directions and satisfies the zero initial condition
\[
R(x, y, z, 0) = 0, \tag{14}
\]
and the Dirichlet boundary condition
\[
R(x, y, z, t) = 0, \text{ on } \partial \Omega. \tag{15}
\]

III. OPTIMAL SOLUTION

For a system with no convection, linear uptake kinetics \( g(C) = kC \), and zero partition coefficient, the optimization variables are
\[
\{\rho, R_p, r_p, \kappa, t_p, C_{r0}(x, y, z)\}. \tag{16}
\]
Separation of variables provides the analytical solution (17) in Table I for the microparticle equations (8)-(11). Insertion into the interconnection equations (6)-(7) results in the flux (18) and input to the model for the tissue construct as (19).

Defining
\[
\alpha(x, y, z) := 8\kappa\pi \rho R_p C_{r0}(x, y, z), \beta := r_p/R_p, \gamma := \kappa/R_p^2, \tag{28}
\]
reduces the number of optimization variables describing the manipulated field (20). The spatial frequency constraints on the manipulated field imply that the manipulated field be written as (21). Then the application of a Green’s function to derive the analytical solution for the PDE (3) for the tissue construct and the application of orthogonality results in the simplified optimization (27) over the control parameters
\[
\{\alpha_{\text{mnl}}, \beta, \gamma, t_p\}, \tag{29}
\]
where \( \alpha_{\text{mnl}} \) is the \((m,n,l)\) 3D Fourier series coefficient of \( \alpha(x, y, z) \). This optimization is largely decoupled and is solved by a combination of gridding and analytical methods:

1) grid \( \beta, \gamma, \) and \( t_p \) over ranges that are guaranteed to encompass the global solution,
2) for each combination of these parameter values, determine the optimal \( \alpha_{\text{mnl}} \) for each \( m, n, \) and \( l \) (this can be done analytically, as discussed below),
3) calculate and store the value of the optimization objective \( E \),
4) repeat Steps 2-3 for each grid point,
5) select the minimum \( E \) for all grid points, and
6) refine the grid until the optimal objective no longer reduces significantly.

An initial estimate for the trigger time \( t_p \) can be obtained as the time that maximizes \( \alpha_{\text{mnl}} \) and \( C_{\text{mnl}} \) for some \( m, n \) and \( l \). The optimization over \( \alpha_{\text{mnl}} \) in Step 2 is convex and so can be determined by basic calculus as
\[
\alpha_{\text{mnl}} = \frac{\int_{\min[0,t_p]}^{t_p} r_{\text{mnl}}(t) C_{\text{mnl}}(t - t_p)dt}{\int_{\min[0,t_p]}^{t_p} C_{\text{mnl}}(t - t_p)^2dt}. \tag{30}
\]
For initial ranges for \( \beta, \gamma, \) and \( t_p \) that encompass the global minimum, the convexity of the optimization over \( \alpha_{\text{mnl}} \) and the continuity of the solution of the PDEs as a function of the optimization parameters imply that the optimization algorithm will converge within any specific tolerance of the global optimum.

For the case with convection \( (v \neq 0) \), the determination of the \( \alpha_{\text{mnl}} \) are no longer decoupled. A suboptimal solution to (13) can be computed by inserting the optimal solution for a closely related surrogate control objective as an initial guess to a local optimizer. The details will appear in a Ph.D. thesis [43].

IV. NUMERICAL EXAMPLE

Consider the spatial field control problem (13) with the dimensionless constants \( D = 1, k = 0.1, \) and \( v = 0 \) and reference field
\[
R(x, y, z, t) = (e^{-x - e^{-3z}}(e^{-y} - e^{-4y})(e^{-2z} - e^{-4z})(e^{-t} - e^{-2t}). \tag{31}
\]
The manufacturing process that places microparticles within the 3D tissue scaffold is the most efficient when the spatial variation in the initial loading in the microparticles is constrained to low frequencies. First consider the objective of determining the optimal microparticle properties (16) when the maximum spatial frequency in any spatial direction is \( 10\pi \) \((M = N = L = 10)\).

Fig. 2. (Left) Reference field showing isosurfaces of 0.01, 0.008, 0.006, and 0.004 from inside to outside at \( t = 0.7 \). (Right) Optimal \( \alpha(x, y, z) \) for the microparticles showing isosurfaces of 16, 12, 8, and 4 from inside to outside for \( M = N = L = 10 \).

Fig. 2 shows the reference field (31) at a representative time. The optimal properties of the microparticles are
\[
\{r_p/R_p, \kappa/R_p^2, t_p\} = \{0.48, 0.08, -0.20\} \tag{32}
\]
The analytical solution to the microparticle equations (8)-(11) with $k_p = 0$:

$$C_r(x, y, z, t) = \frac{2C_r \bar{\alpha}(x, y, z)}{R_p \pi} \sum_{j=1}^{\infty} \exp \left( -\frac{\kappa^2 \pi^2}{R_p^2} \right) \left( \sin \frac{j \pi r}{R_p} \right) \left( \frac{R_p}{j \pi} \right)^2 \sin \frac{j \pi r}{R_p} - \frac{R_p r_p \cos j \pi r}{R_p}$$

was obtained by applying Maple to a more general expression in [40]. Insertion into (7) gives the flux at the microparticle surface:

$$J \bigg|_{r=R_p} = -\frac{2 \kappa \rho \bar{C}_r \bar{\alpha}(x, y, z)}{R_p^3} \sum_{j=1}^{\infty} \exp \left( -\frac{\kappa^2 \pi^2}{R_p^2} \right) j \pi (-1)^j \left( \frac{R_p}{j \pi} \right)^2 \sin \frac{j \pi r}{R_p} - \frac{R_p r_p \cos j \pi r}{R_p}$$

and insertion into (6) gives the manipulated field:

$$u(x, y, z, t) = 8 \kappa \pi \rho \bar{C}_r \bar{\alpha}(x, y, z) \sum_{j=1}^{\infty} \exp \left( -\gamma j^2 \pi^2 t \right) (-1)^j+1 \left( \frac{\sin j \pi \beta}{j \pi} - \beta \cos j \pi \beta \right).$$

Due to manufacturing constraints, the initial loading is restricted to lower spatial frequencies, $\alpha(x, y, z) = \sum_{M, N, L} \alpha_{mnl} \sin m \pi x \sin n \pi y \sin l \pi z$, where the 3D Fourier series coefficients $\alpha_{mnl}$ are to be determined. Insertion into (20) results in

$$u(x, y, z, t) = \sum_{M, N, L} u_{mnl}(t) \sin m \pi x \sin n \pi y \sin l \pi z$$

where $u_{mnl}(t) := \alpha_{mnl} \sum_{j=1}^{\infty} \exp \left( -\gamma j^2 \pi^2 t \right) (-1)^j+1 \left( \frac{\sin j \pi \beta}{j \pi} - \beta \cos j \pi \beta \right)$.

With the reference field written in terms of its 3D Fourier series expansion (also known as its spectral decomposition [42]):

$$R(x, y, z, t) = \sum_{M, N, L} r_{mnl}(t) \sin m \pi x \sin n \pi y \sin l \pi z$$

and taking into account a potentially nonzero trigger time $t_p$ which can be either positive or negative depending on the reference field and constraints on $t_p$, the optimization (13) can be written equivalently as

$$\min_{\alpha_{mnl}\beta\gamma t_p} \int_0^{t_f} \left( \sum_{1,1,1} (r_{mnl}(t) - \alpha_{mnl}(c_{mnl}(t-t_p))) \sin m \pi x \sin n \pi y \sin l \pi z \right)^2 dV dt$$

$$= \frac{1}{8} \min_{\alpha_{mnl}\beta\gamma t_p} \sum_{1,1,1} \int_0^{t_f} r_{mnl}^2(t) dt$$

by application of orthogonality, where $r_{mnl}(t) = 0, \forall t < 0$, and $t_f$ is the final time of interest.

TABLE I

Analytical Solutions of PDEs and Derivation of Simplified Optimization

The analytical solution to the microparticle equations (8)-(11) with $k_p = 0$:

$$C_r(x, y, z, t) = \frac{2C_r \bar{\alpha}(x, y, z)}{R_p \pi} \sum_{j=1}^{\infty} \exp \left( -\frac{\kappa^2 \pi^2}{R_p^2} \right) \left( \sin \frac{j \pi r}{R_p} \right) \left( \frac{R_p}{j \pi} \right)^2 \sin \frac{j \pi r}{R_p} - \frac{R_p r_p \cos j \pi r}{R_p}$$

was obtained by applying Maple to a more general expression in [40]. Insertion into (7) gives the flux at the microparticle surface:

$$J \bigg|_{r=R_p} = -\frac{2 \kappa \rho \bar{C}_r \bar{\alpha}(x, y, z)}{R_p^3} \sum_{j=1}^{\infty} \exp \left( -\frac{\kappa^2 \pi^2}{R_p^2} \right) j \pi (-1)^j \left( \frac{R_p}{j \pi} \right)^2 \sin \frac{j \pi r}{R_p} - \frac{R_p r_p \cos j \pi r}{R_p}$$

and insertion into (6) gives the manipulated field:

$$u(x, y, z, t) = 8 \kappa \pi \rho \bar{C}_r \bar{\alpha}(x, y, z) \sum_{j=1}^{\infty} \exp \left( -\gamma j^2 \pi^2 t \right) (-1)^j+1 \left( \frac{\sin j \pi \beta}{j \pi} - \beta \cos j \pi \beta \right).$$

Due to manufacturing constraints, the initial loading is restricted to lower spatial frequencies, $\alpha(x, y, z) = \sum_{M, N, L} \alpha_{mnl} \sin m \pi x \sin n \pi y \sin l \pi z$, where the 3D Fourier series coefficients $\alpha_{mnl}$ are to be determined. Insertion into (20) results in

$$u(x, y, z, t) = \sum_{M, N, L} u_{mnl}(t) \sin m \pi x \sin n \pi y \sin l \pi z$$

where $u_{mnl}(t) := \alpha_{mnl} \sum_{j=1}^{\infty} \exp \left( -\gamma j^2 \pi^2 t \right) (-1)^j+1 \left( \frac{\sin j \pi \beta}{j \pi} - \beta \cos j \pi \beta \right)$.

With the reference field written in terms of its 3D Fourier series expansion (also known as its spectral decomposition [42]):

$$R(x, y, z, t) = \sum_{M, N, L} r_{mnl}(t) \sin m \pi x \sin n \pi y \sin l \pi z$$

and taking into account a potentially nonzero trigger time $t_p$ which can be either positive or negative depending on the reference field and constraints on $t_p$, the optimization (13) can be written equivalently as

$$\min_{\alpha_{mnl}\beta\gamma t_p} \int_0^{t_f} \left( \sum_{1,1,1} (r_{mnl}(t) - \alpha_{mnl}(c_{mnl}(t-t_p))) \sin m \pi x \sin n \pi y \sin l \pi z \right)^2 dV dt$$

$$= \frac{1}{8} \min_{\alpha_{mnl}\beta\gamma t_p} \sum_{1,1,1} \int_0^{t_f} r_{mnl}^2(t) dt$$

by application of orthogonality, where $r_{mnl}(t) = 0, \forall t < 0$, and $t_f$ is the final time of interest.

with $\alpha(x, y, z)$, which is proportional to the optimal initial loading, shown in Fig. 2 (right). The number density $\rho$ and initial loading $C_r(x, y, z)$ of the core-shell microparticles appear as a product in $\alpha(x, y, z)$, so that the extra degree
of freedom can be used to simplify manufacturing. For example, for a fixed optimal $\alpha(x, y, z)$ the number density $\rho$ could be reduced so that fewer microparticles would need to be positioned in a 3D tissue scaffold, by increasing the initial loading. Similarly, the effective diffusion coefficient $\kappa$ and radius $R_p$ of the microparticles affect the chemical species release through the inverse time scale $\kappa/R_p^2$, so this extra degree of freedom can also be used to simplify manufacturing. By manufacturing to specify the pore size, the porous polymer microparticles can be made with $\kappa$ having any specified value from arbitrarily small to nearly the value of the effective diffusion coefficient $D$. This flexibility can be used to select the microparticle radius $R_p$ small enough that the initial loading $C_{r0}(x, y, z)$ and concentration in the model (3) behave like a continuum ($R_p \ll 1/\max\{N, M, L\}$). For example, $\kappa/R_p^2 = 0.08$ could be obtained by selecting $R_p = 0.01 \ll 1/10$, which is small enough to spatially resolve the initial loading, and selecting $\kappa = 0.08 (0.01)^2 = 8 \times 10^{-6}$, which can be implemented by using very small pore diameters in the polymeric microparticles.

Fig. 3. Approximated reference (magenta) and optimal concentration (cyan) fields for $M = N = L = 10$ showing the isosurface of 0.01 at $t = 0.7$.

The spatial complexity of the optimal initial loading in Fig. 2 indicates that it is unlikely that a person would be able to design the optimal initial loading by intuition, which motivates the application of numerical optimization. The concentration field obtained with optimal polymer microparticles is nearly indistinguishable by eye from the approximated reference field (truncated sum of (25)), indicating that the microparticles provide a very high degree of controllability within the constraint on the spatial resolution (see Fig. 3).

If the microparticles can be spaced more closely together, then $M$, $N$, and $L$ increase and the differences between the optimal and reference fields become smaller (compare Fig. 4 with Fig. 2). These differences vary with position. For example, the optimal concentration is mostly higher than the reference for the center of the spatial domain but mostly lower than the reference for the off-center position $x = y = z = 1/4$ (see Fig. 5).

Zeroing the trigger time increases the minimum control error (13) by a factor of 7, indicating that this is a useful optimization variable. Although the respective optimal concentration fields look similar at first glance (see Fig. 5), the zero trigger time is associated with an initial concentration increase at $t = 0$ that is less sharp, which is the primary contribution to the control error. A tissue engineer would have to assess whether the improvement in tracking the 3D concentration field is worth the extra experimental effort of implementing an environmental trigger.

V. Conclusions

This paper is the first to explicitly account for the dynamics within polymer microparticles while optimizing their spatial and temporal release of macromolecules within an engineered tissue construct. With its incorporation of state constraints in the form of partial differential equations for the microparticles and limitations on spatial frequencies, the mathematical formulation for the spatial field control problem is significantly more sophisticated than spatial field control problems described in the literature. Spectral decomposition was a useful approach for direct satisfaction of the spatial frequency constraints and reduction of the large number of degrees of freedom in the optimization...
problem. In the simulation results, the control error was mostly due to the limitation on the spatial resolution, which can be overcome by using smaller microparticles spaced more closely together.

Several directions are promising for future work. Microparticles of different design such as microcapsules or particles constructed with biodegradable polymers could be investigated. Nonlinear cellular uptake kinetics, chemical degradation kinetics, and chemical interactions with the extracellular matrix are also of practical importance. The ultimate objective of this research is to develop a suite of mathematical tools for controlling the spatial and temporal development of an engineered tissue construct that can be used to guide experimental designs and reduce trial-and-error experimentation.

VI. ACKNOWLEDGMENTS

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