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Optimal Control of Cellular Uptake in Tissue Engineering

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Abstract— **The optimal control of a distributed parameter system with reaction, diffusion, and convection is investigated. The problem is motivated by tissue engineering where the control of the uptake of growth factors (signaling molecules) is required to spatially and temporally regulate cellular processes for the growth or regeneration of a tissue. Four approaches for solving the optimal control problem are compared: (i) basis function expansion, (ii) method of moments, (iii) internal model control, and (iv) model predictive control. This comparison suggests that these approaches should be combined to solve the optimal control problem for multiple spatial dimensions.**

I. INTRODUCTION

The primary goal of tissue engineering is the production of biological tissues for clinical use. One of the main manufacturing strategies utilizes the attachment or encapsulation of cells within a tissue matrix that is typically made of collagen or synthetic polymers [12]. Beyond receiving nutrients and releasing waste products, the development of a healthy functioning tissue requires that the cells uptake hormones, drugs, or signaling molecules in a controlled way [11]. For example, in the development of tissues from stem cells, the stem cells must uptake growth factors which are proteins to regulate cellular processes such as stimulating cellular proliferation and cell differentiation. The spatial and temporal control of the cellular uptake can be achieved through localized release (e.g., [20]).

Many materials and devices have been created for releasing molecules in a controlled way [19]. Biodegradable polymeric nano- or microparticles have been developed that can be placed within a tissue matrix to provide localized timed release [10]. These particles include spheres, core-shell particles, and capsules that encapsulate small molecules, protein, or DNA including growth factors or other signalling molecules or, in the case of microcapsules, can contain cells that excrete hormones or other macromolecules [12]. Techniques have been established to make particles with highly uniform physical properties, that produce a wide variety of highly reproducible release profiles by manipulating physical dimensions or by combining different types of particles [22]. These particles can be accurately positioned and attached to a tissue matrix using such technologies as solid free-form fabrication [3] and layer-by-layer stereolithography [15], so as not to move until the particles have released their payloads to the cells.

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The tissue engineering application motivates the formulation of an optimal control problem for the release of molecules from biodegradable polymeric nano- or microparticles to achieve a desired temporal and spatial uptake rate for cells within a tissue matrix. A potential application is to control the development of a tissue from stem cells within a matrix, so that the timed release of different growth factors in various locations form the multiple types of cells needed for the functioning components of a tissue. The shape and dimensions of these components would be a function of both the spatial and temporal release of growth factors (e.g., [20]).

The mathematical formulation as a distributed parameter optimal control problem is followed by a comparison of four methods for solving the problem. The results suggest how to best solve higher dimensional problems by a combination of methods.

II. PROBLEM SETUP

To keep the nomenclature consistent, the term "growth factor" will be used to refer to the molecule being released, although the theory and algorithms also directly apply to other molecules. Spatial and temporal control of the cellular uptake rate in a biological tissue under the influence of diffusion and convection can be formulated as a distributed parameter optimal control problem:

$$\min_{u_i \in \mathcal{U}_i} \sum_i \int_0^{t_f} \int_V \left(J_{des,i}(x,y,z,t) - R_i(x,y,z,t)\right)^2 dV\,dt, \tag{1}$$

where $J_{des,i}$ is the desired cellular uptake rate for species i, R_i is its cellular uptake rate, and its concentration C_i is the solution to the reaction-diffusion-convection equation (RDCE) [21]

$$\frac{\partial C_i}{\partial t} + v \cdot \nabla C_i = \nabla \cdot (D_i \nabla C_i) - R_i, \tag{2}$$

(x, y, z) are the spatial coordinates defined over domain V, t_f is the final time of interest, v is a known velocity field as a function of the spatial coordinates, and D_i is the diffusion coefficient for species i. Depending on the specific tissue engineering application, the optimal control variables u_i can be either distributed throughout the spatial domain such as in the case that controlled release particles are intermingled with the biological tissue, or can be a subset $\mathcal{U}_i$ of the boundary conditions on the surface of the domain V. This model (2) considers applications in which the minimum physical dimensions in the domain V are larger than the maximum dimensions of the molecules, cells, and polymer particles that

release growth factors. The cellular uptake kinetics and the $J_{des,i}$ are determined in small-scale biological experiments so as to produce a desired response, such as differentiation to form a desired type of cell [2], [12], [21]. The model (2) is appropriate in the early stages of tissue development, before substantial cell migration and proliferation occurs. The situation in which signaling molecules are produced by cells which are then taken up by other cells (cell-cell communication) requires only minor modification of (2).

The standard approach to solving the above optimal control problem is control vector parameterization [17], where the control variable $u_i(x, y, z, t)$ is discretized with respect to the spatial and time variables, inserted into (1)-(2), and solved numerically as an algebraic optimization problem. The difficulty in applying this approach using the standard discretization of the control input (i.e., $u(0), u(\Delta t), u(2\Delta t), \dots$) is the large number of degrees of freedom. For example, in the case where a single control variable is spatially distributed throughout the domain, 100 discretization points in each spatial dimension and in time results in $100^4 = 10^8$ degrees of freedom in the algebraic optimization. This large dimensionality problem is well recognized in the optimal control literature (e.g., [9], [18]). While many approaches have been proposed, no single algorithm dominates either the literature or applications and it is generally accepted that the best approach depends on the details on the optimal control problem being solved.

To gain insight into how to best solve the three-dimensional (3D) optimal control problem (1)-(2), this manuscript solves the 1-dimensional (1D) version of the optimal control problem for a single species with manipulatable boundary condition and linear cellular uptake kinetics:

$$\min_{u(t)\geq 0} \int_0^{t_f} (J_{des}(t) - kC(1,t))^2 dt \tag{3}$$

subject to the partial differential equation (PDE)

$$\frac{\partial C}{\partial t} + v\frac{\partial C}{\partial x} = D\frac{\partial^2 C}{\partial x^2} - kC, \ \forall x \in (0,1), \ \forall t > 0, \tag{4}$$

with

$$C(x,0) = 0, \tag{5}$$

$$C(0,t) = u(t), \tag{6}$$

$$D\frac{\partial C}{\partial x}\Big|_{x=1} = 0. \tag{7}$$

The reference trajectory $J_{des}(t) \geq 0, \forall t > 0$ is a desired cellular uptake rate at one boundary (at $x = 1$) and the control trajectory is the concentration $u(t)$ at the other boundary ($x = 0$) (see Fig. 1). This problem arises when the objective is to ensure that a desired time-varying uptake of a growth factor occurs at a specified distance (of 1 dimensionless unit) from a position where the growth factor is released through micro- or nanoparticles or is carried with fluid entering the tissue at $x = 0$ (this fluid brings nutrients such as glucose to the cells). The cells within the domain would uptake at least as much

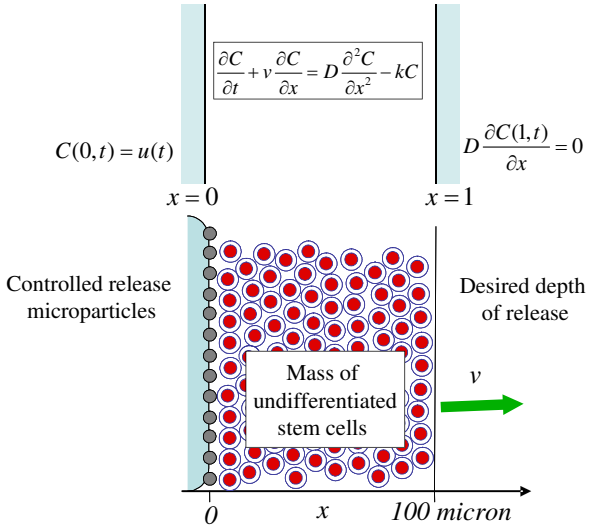


Fig. 1. Boundary control at $x = 0$ with a Neumann boundary condition at $x = 1$.

growth factor as cells at $x = 1$, ensuring that all of the cells within the domain respond to the growth factor.

The optimal control problem (3)-(7) was solved by four different methods: (i) basis function expansion, (ii) method of moments, (iii) internal model control, and (iv) model predictive control.

III. BASIS FUNCTION EXPANSION

This method generalizes an approach studied in the mid-1980s to solve optimal control problems for systems described by ordinary differential equations [18] to partial differential equations, in a similar manner as has been done for sheet and film processes (e.g., see [6], and citations therein) as well as nonlinear PDEs such as Burgers equation [9]. To apply this method, start with the analytical solution to the PDE (4)-(7) $C(1,t) =$

$$e^{\frac{v}{2D}} D \sum_{n=1}^{\infty} B_n \mu_n \sin\sqrt{\mu_n} \int_0^t u(\tau) e^{-(\frac{v^2}{4D} + k + \mu_n D)(t-\tau)} d\tau \tag{8}$$

where

$$B_n = 4\frac{\frac{v}{v+2D}\left(\frac{\sin(\sqrt{\mu_n})}{\sqrt{\mu_n}} - \cos(\sqrt{\mu_n})\right) + \cos(\sqrt{\mu_n}) - 1}{\sin(2\sqrt{\mu_n}) - 2\sqrt{\mu_n}} \tag{9}$$

and μ_n is the nth root of $\tan(\sqrt{\mu_n}) = -2\sqrt{\mu_n}D/v$. Parameterize $u(t)$ by a basis function expansion:

$$u(t) = \sum_{i=1}^{n} a_i \phi_i(t) = a^T \phi(t), \tag{10}$$

where $\{\phi_i(t)\}$ is any set of basis functions, and

$$a = \begin{bmatrix} a_1 \\ a_2 \\ \vdots \\ a_n \end{bmatrix}, \ \phi(t) = \begin{bmatrix} \phi_1(t) \\ \phi_2(t) \\ \vdots \\ \phi_n(t) \end{bmatrix}. \tag{11}$$

Let $f_i(t)$ be the solution to the PDE (4)-(7) for input $\phi_i(t)$: $f_i(t) =$

$$e^{\frac{v}{2D}} D \sum_{n=1}^{\infty} B_n \mu_n \sin\sqrt{\mu_n} \int_0^t \phi_i(\tau) e^{-(\frac{v^2}{4D}+k+\mu_n D)(t-\tau)} d\tau \tag{12}$$

and

$$f(t) = \begin{bmatrix} f_1(t) \\ f_2(t) \\ \vdots \\ f_n(t) \end{bmatrix}, \tag{13}$$

then the optimal control problem with $u(t)$ given by (10) can be written as

$$\min_{u(t)\geq 0} \int_0^{t_f} (J_{des}(t) - ka^T f(t))^2 dt \tag{14}$$

since the function (8) is a linear operator on $u(t)$. An approximate analytical solution to the optimal control problem can be obtained by dropping the non-negativity constraint:

$$\frac{d}{da} \int_0^{t_f} \left(J_{des}^2(t) - 2kJ_{des}(t)a^T f(t) + (ka^T f(t))^2 \right) dt$$

$$= \int_0^{t_f} \left(-2kJ_{des}(t) f(t) + 2k^2 f(t) f^T(t) a \right) dt = 0, \tag{15}$$

$$a = \frac{1}{k} \left(\int_0^{t_f} f(t) f^T(t) dt \right)^{-1} \int_0^{t_f} J_{des}(t) f(t) dt, \tag{16}$$

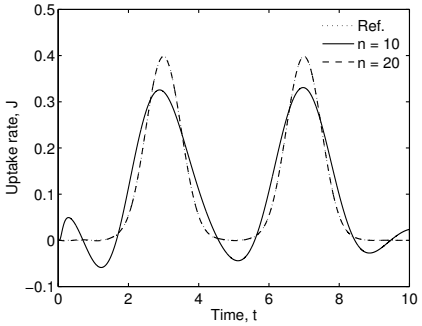
$$u(t) = \phi^T(t) a = \frac{\phi^T(t)}{k} \left(\int_0^{t_f} f(t) f^T(t) dt \right)^{-1} \int_0^{t_f} J_{des}(t) f(t) dt. \tag{17}$$

There are many choices of basis functions [5], [6] for which the temporal accuracy to the solution of the unconstrained optimal control problem is specified directly by the number of basis functions, whereas the number of terms in the summation in (12) specifies the spatial accuracy. Fig. 2a shows excellent tracking performance of this approach for a Gaussian reference trajectory, using 20 terms in a truncated Fourier cosine series [7] as the basis functions $\phi_i(t)$ (see Fig. 2a). Drawbacks of this method are that (i) it can result in ringing at discontinuities along the time axis due to the Gibbs phenomenon [8], [23], and (ii) it does not take the non-negativity constraint on the control variable in (3) into account, which can result in constraint violations. Fig. 2b shows both deficiencies occurring for a step reference trajectory.

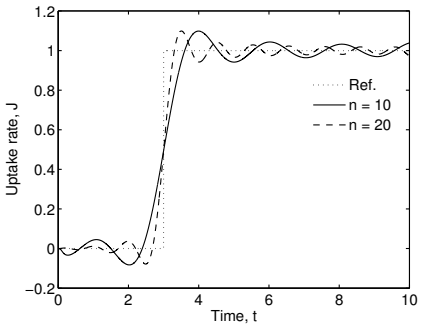
IV. METHOD OF MOMENTS

In the method of moments, analytical expressions are derived for moments of output variables in a PDE in terms of the moments of input variables [1]. More specifically, it can be shown for a linear system that a compact control input $u(t)$ and the output variable $y(t)$ are related by

$$\mu_y = \mu_g + \mu_u, \tag{18}$$



(a)



(b)

Fig. 2. Outputs for the basis function expansion approach when the reference trajectories are Gaussian [4] and step functions (for $D = v = 1$ and $k = 7.6$, which are the parameters used for the entire paper). The number of basis functions is n and the number of eigenfunctions for the spatial variable was 10. The negative uptake rate is the result of a negative control input, which is not physically realizable.

$$\sigma_y^2 = \sigma_g^2 + \sigma_u^2, \tag{19}$$

where μ is the mean time (which is related to the first-order moment), σ^2 is the variance of the signal about its mean time (which is related to the second-order moment), and the subscripts y refers to output, u refers to input, and g refers to the linear system relating u and y. Analytical expressions for μ_g and σ_g^2 are derived by taking integrals of the PDE [1].

We apply this method to optimal control by decomposing the reference trajectory into a linear combination of non-negative basis functions, each of which is parameterized by mean time and variance. The form of the basis function is selected such that the shape of the optimal control trajectory is known and parameterized by mean time and variance which are computed from (18) and (19). The overall optimal control trajectory is computed by summing the optimal control trajectories corresponding to each of the basis functions. Fig. 3 shows nearly perfect tracking for a Gaussian reference trajectory using Gaussian basis functions, for which the optimal control trajectories are Gaussian-like functions. This approach is very computationally efficient for computing a non-negative optimal control trajectory, but does not directly address state or other types of control constraints.

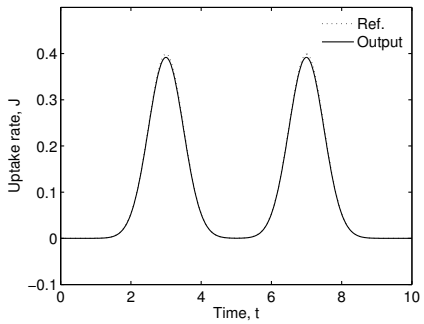


Fig. 3. Uptake rate using the method of moments approach (the magnitude of the control input was adjusted by dividing the reference input by the DC gain of the plant; which gives the same total amount of the growth factor uptake as desired).

V. INTERNAL MODEL CONTROL

Internal model control (IMC) is based on inverting a transfer function model. The transfer function obtained by taking the Laplace transform of (4)-(7) is irrational (see Table I), as the model is described by a PDE (4). Since the IMC design equations [16] only apply to finite-dimensional or highly restrictive classes of infinite-dimensional models, the spatial variable was discretized (Method of lines, MOL) to obtain an approximate rational transfer function (see Table I) by using the finite difference method, which is an accurate representation of the exact transfer function over the frequency range of the interest (see Bode plots in Fig. 4). The rational transfer function was minimum phase, so the resulting IMC control transfer function is the inverse of the rational transfer function augmented by a filter designed to make the overall system proper [16]. Applications of IMC for Gaussian and step reference trajectories are shown in Fig. 5, with λ tuned so that the control variable is non-negative. While this approach can give insight into the form of the optimal control trajectory, it is sub-optimal and does not handle general control constraints, and extensions of IMC to handle constraints [24] are not optimal with respect to the optimization objective (3).

VI. MODEL PREDICTIVE CONTROL

Model predictive control (MPC) is a well-known method for solving optimal control problems with constraints [13]. In contrast to the usual application of MPC to closed-loop control problems, here MPC is used to solve an open-loop optimal control problem. Most MPC formulations assume a staircase control trajectory. To compute the smooth control trajectory desired in this application, the process model was augmented by an integrator and the actual control variable was computed from the integral of the MPC control variable.

A. MPC Formulation and Results

Discretization of the PDE (3)-(7) results in a state-space model

$$x(k+1) = Ax(k) + Bu(k) \tag{20}$$

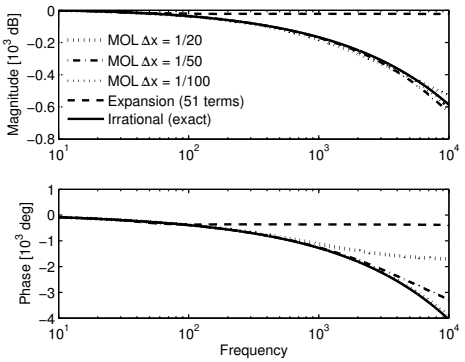


Fig. 4. Bode plots of various transfer functions: The first three transfer functions are obtained by MOL, where Δx is the grid size. The "Expansion" transfer function was obtained from the first 51 terms of the eigenfunction expansion and the exact transfer function is obtained by taking the Laplace transform of the PDE. The "Expansion" transfer function is less accurate than the finite discretization for the same number of terms due to a slow convergence rate for the summation in (8). The transfer functions are listed in Table I.

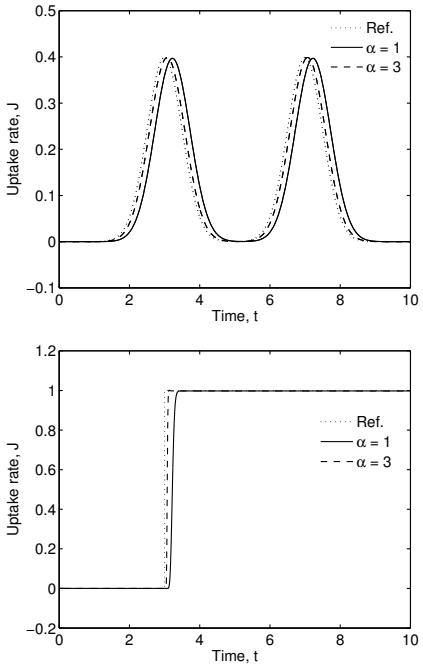


Fig. 5. Outputs obtained using the IMC approach. The control trajectory is calculated by using a transfer function with $\Delta x = 1/20$ and augmenting with a filter $f = 1/(\lambda s + 1)^{20}$, where the filter parameter is $\lambda =$ (the slowest plant pole)$/1000\alpha$.

$$y(k) = Cx(k), \tag{21}$$

where x is the state vector, u is the control variable, and y is the model output. The state space equations of the system augmented with an integrator are

$$x_a(k+1) = A_a x_a(k) + B_a u_a(k), \tag{22}$$

$$y(k) = C_a x_a(k), \tag{23}$$

TABLE I

TRANSFER FUNCTIONS BETWEEN THE CONTROL VARIABLE AND THE UPTAKE RATE FOR THE (1) EIGENFUNCTION EXPANSION OF THE PDE, (2) FULL PDE, AND (3) SPATIAL DISCRETIZATION OF THE PDE.

Method	Transfer function
Eigenfunction expansion	$G(s) = ke^{\frac{v}{2D}} \sum_{n=1}^{\infty} \frac{\mu_n D}{s + \frac{v^2}{4D} + k + \mu_n D} B_n \sin(\sqrt{\mu_n})$
PDE	$G(s) = k\frac{(\xi_1 - \xi_2)e^{\xi_1 + \xi_2}}{\xi_1 e^{\xi_1} - \xi_2 e^{\xi_2}}$, where $\xi_1 = \frac{v + \sqrt{v^2 + 4(k+s)D}}{2D}$, $\xi_2 = \frac{v - \sqrt{v^2 + 4(k+s)D}}{2D}$
Method of lines	$G(s) = C(sI - A)^{-1}B$ where $A = \begin{bmatrix} -\frac{2D}{\Delta x^2} - k & \frac{D}{\Delta x^2} - \frac{v}{2\Delta x} & 0 & 0 & 0 \\ \frac{D}{\Delta x^2} + \frac{v}{2\Delta x} & -\frac{2D}{\Delta x^2} - k & \frac{D}{\Delta x^2} - \frac{v}{2\Delta x} & 0 & 0 \\ 0 & \frac{D}{\Delta x^2} + \frac{v}{2\Delta x} & -\frac{2D}{\Delta x^2} - k & \frac{D}{\Delta x^2} - \frac{v}{2\Delta x} & 0 \\ 0 & \ddots & \ddots & \ddots & \ddots \\ 0 & \cdots & \cdots & \frac{2D}{\Delta x^2} & -\frac{2D}{\Delta x^2} - k \end{bmatrix}$, $B = \begin{bmatrix} \frac{D}{\Delta x^2} + \frac{v}{2\Delta x} \\ 0 \\ \vdots \\ \\ 0 \end{bmatrix}$, $C = \begin{bmatrix} 0 & \cdots & \cdots & 0 & k \end{bmatrix}$

where x_a is the state vector with an integrator, u_a is the control variable to the augmented system (its derivative is u), and y is the model output which is the same as previous y. The state matrices A_a, B_a and C_a are obtained by discritizing the transfer function of the integrator augmented system in continuous model.

For the case in which there are no constraints on the control variable, the control variable at time instant k is obtained by solving the optimization:

$$\min_{\substack{\Delta u_a(k|k) \\ \vdots \\ \Delta u_a(k+m-1|k)}} \quad \sum_{i=1}^{p} |y(k+i|k) - r(k+i)|^2 \qquad (24)$$

subject to

$$\Delta u_a(k+i|k) = 0, \quad i = m, \ldots, p-1, \qquad (25)$$

where p is the prediction horizon, m is the control horizon, $r(k)$ is the reference variable at time instant k, $\Delta u_a(k)$ is the control increment

$$\Delta u_a(k) \equiv u_a(k) - u_a(k-1), \qquad (26)$$

and "$(k+i|k)$" is the value predicted for time instant $k+i$ based on the information available at time instant k. At time instant k, $u_a(k) = u_a(k-1) + \Delta u_a(k|k)^*$ is implemented, where $\Delta u_a(k|k)^*$ is the first element of the optimal sequence, and the above optimization is calculated at the next time instant based on the updated variables.

The constrained MPC problem solves (24) with the additional linear inequalities which constrain the control variable $u(k)$ to be non-negative:

$$\Delta t \begin{bmatrix} 1 & 0 & \cdots & \cdots & 0 \\ 2 & 1 & 0 & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ p-1 & \ddots & \ddots & 1 & 0 \\ p & \cdots & \cdots & 2 & 1 \end{bmatrix} \begin{bmatrix} \Delta u_a(k) \\ \vdots \\ \Delta u_a(k+p-1) \end{bmatrix} \geq -\begin{bmatrix} 1 \\ 1 \\ \vdots \\ \vdots \\ 1 \end{bmatrix} u(k) - \Delta t \begin{bmatrix} 1 \\ 2 \\ \vdots \\ \vdots \\ p \end{bmatrix} u_a(k-1), \qquad (27)$$

where Δt is the sampling time.

MPC gave good reference tracking with short control and prediction horizons as long as the sampling time was small enough (see Fig. 6). Such short horizons have a much lower computational cost than long horizons. The computational cost of MPC is an important consideration when extending this approach to a larger number of spatial dimensions (1)-(2).

B. Comparison with Control Vector Parameterization

MPC has much lower memory requirements and computational expense than the standard control vector parameterization (CVP) approach [17] which is obtained by choosing m and p to span the entire length of the reference trajectory and dropping the use of the receding horizon. Although MPC requires an optimization to be solved at each sampling instance, the optimization only has m degrees of freedom and a much smaller cost for the objective calculation (24) which

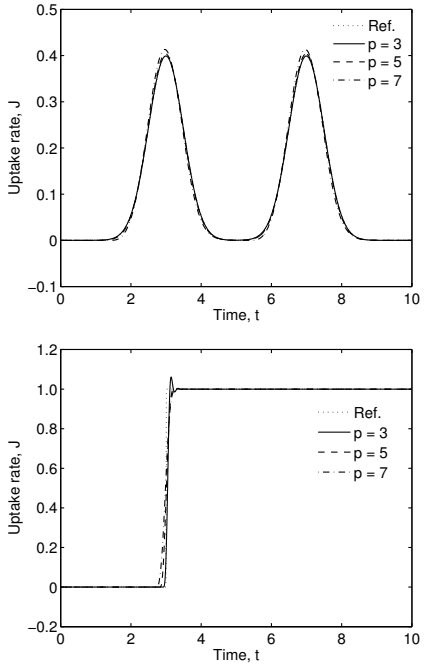


Fig. 6. MPC Outputs for a control horizon of $m = 2$ and a sampling time $\Delta t = 0.1$, transfer function with $\Delta x = 1/20$.

scales linearly with p. The 1D optimal control problem is simple enough that CVP could be implemented, in which case a regularization term of

$$10^{-10} \sum_k |\Delta u_a(k|1)|^2 \tag{28}$$

was added to the objective function (24) to remove numerical ill-conditioning that arose due to the large number of degrees of freedom. The time-domain plots were virtually indistinguishable from those obtained from the best MPC tuning (Fig. 6). Applying MPC to the optimal control problem resulted in nearly globally optimal results, with many orders-of-magnitude reduction in memory requirements and total calculation time. This makes MPC more suitable than CVP for the solution of the optimal control problem (1) with larger number of spatial dimensions.

VII. A COMPOSITE APPROACH FOR THE 3D CASE

Recall that the 3D control problem (1)-(2) has too many degrees of freedom to be solved directly, such as by CVP. The results in Sections III-VI suggest that the 3D optimal control problem can be solved by a combination of multiple design methods. The near optimality of MPC observed in Section III suggests that MPC is a much better approach than CVP for solving the 3D control problem (1)-(2), due to the much fewer degrees of freedom (dof). In addition, the near optimality of the basis function expansion approach in Section III suggests that parameterization of the control input in terms of basis functions within such a 3D MPC algorithm would lead to minimal loss in performance while further reducing the dof. The near optimality of IMC and the method of moments observed in Sections IV and V motivate the development of 3D extensions to provide initial guesses for the 3D MPC optimization, to greatly speed its convergence. The method of moments would be generalized to utilize cross-moments (e.g., [14]). IMC would be best generalized so that it can be directly applied to PDE models, to avoid the spatial discretization used in Section V to be produce the nominal transfer function model. Once a numerically efficient solution to the 3D linear control problem is obtained, it can be bootstrapped to address nonlinear uptake kinetics.

REFERENCES

[1] R. Aris. On the dispersion of a solute in a fluid flowing through a tube. *Proc. R. Soc. London, Ser. A*, 235:67–77, 1956.

[2] C. E. Beaty and W. M. Saltzman. Controlled growth-factor delivery induces differential neurite outgrowth in 3-dimensional cell-cultures. *J. of Controlled Release*, 24:15–23, 1993.

[3] L. G. Cima and M. J. Cima. Tissue regeneration matrices by solid free form fabrication techniques, 1996. U.S. Patent.

[4] A. de Moivre. *The Doctrine of Chances*. H. Woodfall, London, 2nd edition, 1738.

[5] S. R. Duncan, W. P. Heath, A. Halouskova, and M. Karny. Application of basis functions to the cross-directional control of web processes. In *Proc. UKACC Int. Conf. on Control '96*, pages 1278–1283, 1996.

[6] A. P. Featherstone, J. G. VanAntwerp, and R. D. Braatz. *Identification and Control of Sheet and Film Processes*. Springer Verlag, London, 2000.

[7] J. Fourier. *Thorie Analytique de la Chaleur*. Académie des Sciences, Paris, France, 1822.

[8] J. W. Gibbs. Fourier series. *Nature*, 59:200, 1898.

[9] I. Kucuk and I. Sadek. An efficient computational method for the optimal control problem for the Burgers equation. *Mathematical & Computer Modelling*, 44:973–982, 2006.

[10] R. Langer. Drug delivery and targeting. *Nature*, 392(6679):5–10 Suppl. S, 1998.

[11] R. Langer. Perspectives: Drug delivery - drugs on target. *Science*, 293(5527):58–59, 2001.

[12] R. Langer and J. P. Vacanti. Tissue engineering. *Science*, 260(5110):920–926, 1993.

[13] J. H. Lee, M. Morari, and C. E. Garcia. State-space interpretation of model predictive control. *Automatica*, 30:707–717, 1994.

[14] D. L. Ma, D. K. Tafti, and R. D. Braatz. High resolution simulation of multidimensional crystal growth. *Ind. Eng. Chem. Res.*, 41:6217–6223, 2002.

[15] G. Mapili, Y. Lu, S. C. Chen, and K. Roy. Laser-layered microfabrication of spatially patterned functionalized tissue-engineering scaffolds. *J. of Biomedical Materials Research Part B-Applied Biomaterials*, 75B:414–424, 2005.

[16] M. Morari and E. Zafiriou. *Robust Process Control*. Upper Saddle River, NJ, 1989.

[17] W. H. Ray. *Advanced Process Control*. McGraw-Hill, New York, 1980.

[18] M. Razzaghi, A. Tahai, and A. Arabshahi. Solution of linear 2-point boundary-value problems via Fourier-series and application to optimal-control of linear systems. *J. Franklin Inst.*, 326:523–533, 1989.

[19] W. M. Saltzman. *Drug Delivery - Engineering Principles for Drug Therapy*. Oxford University Press, Oxford, UK, 2001.

[20] N. M. Shah and D. J. Anderson. Integration of multiple instructive cues by neural crest stem cells reveals cell-intrinsic biases in relative growth factor responsiveness. *PNAS*, 94:11369–11374, 1997.

[21] G. A. Truskey, F. Yuan, and D. F. Katz. *Transport Phenomena in Biological Systems*. Prentice Hall, Upper Saddle River, NJ, 2004.

[22] N. K. Varde and D. W. Pack. Microspheres for controlled release drug delivery. *Expert Opinion on Biological Therapy*, 4:35–51, 2004.

[23] H. Wilbraham. On a certain periodic function. *Cambridge & Dublin Math. J.*, 3:198–201, 1848.

[24] A. Zheng, M. V. Kothare, and M. Morari. Anti-windup design for internal model control. *Int. J. of Control*, 60:1015–1024, 1994.