

OPTIMIZATION OF DRUG DIFFUSION IN BIOLOGICAL TISSUES USING INTERIOR POINT METHODS

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ABSTRACT. Diffusion equations are central tools in modeling transport phenomena in biological systems, including the movement of drugs, nutrients, and signaling molecules within tissues. This paper proposes a novel numerical framework combining primal-dual IPMs with PCG preconditioning for optimizing drug delivery in heterogeneous tumor tissue, the first such application achieving $O(\sqrt{M} \log(1/\varepsilon))$ complexity independent of PDE conditioning $\kappa(A_D) = O(1/\Delta x^2)$. The mathematical model is formulated as a reaction-diffusion PDE-constrained quadratic program, discretized via unconditionally stable implicit finite differences. The method is applied to a pharmacokinetic case study involving the optimization of localized drug release $S^*(x, y)$ in a two-dimensional tissue domain with tumor/healthy interfaces. Numerical results show smooth, stable cytotoxic concentration profiles $C^*(x, y, t)$ targeting tumor cores ($x, y > 0.5$) with improved therapeutic efficacy and minimal side effects (Figures 1–3).

Keywords. Diffusion equation, interior-point methods, drug transport, PDE-constrained optimization

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1. INTRODUCTION

The diffusion of therapeutic substances within biological tissues plays a fundamental role in modern medical treatments. Many physiological processes such as the transport of drugs, nutrients, oxygen, and biochemical signals are governed by diffusion mechanisms described by parabolic partial differential equations (PDEs) [4, 16, 3, 5]. Among these, Fick's diffusion equation remains a cornerstone for modeling molecular propagation in living tissues due to its mathematical simplicity and broad biomedical relevance [8].

Yet, the classical assumption of homogeneous and isotropic diffusion is inadequate for real biological tissues, which are highly heterogeneous and anisotropic.

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Structural variations in vascularization, cell density, and extracellular matrix organization significantly alter diffusion properties, while pathological conditions such as elevated interstitial pressure in tumors further complicate drug transport [9, 2, 10, 12]. To capture these complexities, modern diffusion models incorporate reaction, degradation, absorption, and molecular interaction terms [14, 7, 6], offering more accurate pharmacokinetic and pharmacodynamic representations but also introducing substantial numerical challenges.

In parallel, PDE-constrained optimization has emerged as a powerful framework for personalized medicine, enabling the design of optimal drug injection or release strategies that achieve therapeutic objectives while respecting physiological constraints [1]. This approach is particularly relevant for controlled-release systems such as micro-pumps, nanoparticles, polymeric implants, and bioactive hydrogels [15, 13]. The optimization problem typically involves adjusting a control variable such as injection rate to minimize deviations from a desired concentration profile while ensuring stability and avoiding toxicity [11].

Interior-Point Methods (IPMs) have proven especially effective for such problems, offering robustness and fast convergence in large-scale constrained systems [15, 13]. While IPMs were initially developed for linear and convex optimization, they have since been extended to nonlinear and PDE-constrained problems. Their strength lies in barrier functions and primal-dual formulations, which maintain feasibility while advancing efficiently toward optimal solutions.

Unlike prior works that applied IPMs to generic diffusion problems, our study explicitly addresses the quadratic programming nature of PDE-constrained drug delivery optimization. We extend complexity analysis to incorporate Hessian terms, ensuring mathematical rigor beyond standard linear optimization results. To guarantee numerical stability under biologically realistic parameters, we employ an implicit discretization scheme, overcoming limitations of explicit methods. Furthermore, we discuss the ill-conditioning of the KKT system under mesh refinement and reference preconditioning strategies, situating our work within the broader landscape of advanced PDE-constrained optimization.

In this work, we combine reaction–diffusion modeling with implicit numerical discretization and a primal–dual interior-point algorithm to optimize therapeutic diffusion profiles in heterogeneous two-dimensional tissues. Our objective is to demonstrate that this framework yields stable, efficient, and clinically relevant solutions, supported by theoretical analysis, numerical implementation, and graphical simulations.

2. MATHEMATICAL MODEL

Let $\Omega \subset \mathbb{R}^2$ be a bounded tissue domain with boundary $\partial\Omega$, and $[0, T]$ the observation interval. The drug concentration $C(x, t)$ satisfies the reaction-diffusion PDE:

$$\frac{\partial C}{\partial t} = \nabla \cdot (D(x)\nabla C) - \lambda C + S(x, t), \quad (2.1)$$

with Neumann boundary conditions $D \frac{\partial C}{\partial n} = 0$ on $\partial\Omega$ and initial condition $C(x, 0) = C_0(x)$.

We seek the optimal control $S(x, t) \in [0, S_{\max}]$ that minimizes the quadratic tracking functional:

$$\begin{aligned} J(C, S) = & \frac{1}{2} \int_0^T \int_{\Omega} \|C(x, t) - C_d(x, t)\|_{L^2(\Omega)}^2 dx dt \\ & + \frac{\alpha}{2} \int_0^T \int_{\Omega} \|S(x, t)\|_{L^2(\Omega)}^2 dx dt, \end{aligned} \quad (2.2)$$

subject to the PDE constraint and box bounds $0 \leq S \leq S_{\max}$. This formulation yields a convex Quadratic Program (QP) with positive semidefinite Hessian arising from the L^2 tracking and regularization terms.

3. MEDICAL APPLICATION

We model a tumor microenvironment over $\Omega = [0, 1]^2$ cm² featuring discontinuous diffusivity:

$$D(x, y) = \begin{cases} D_0 = 0.01 & \text{(healthy tissue),} \\ 5D_0 & \text{(tumor core, } x, y > 0.5), \end{cases} \quad (3.1)$$

with degradation $\lambda = 0.1$, control bound $S_{\max} = 1.0$, and regularization $\alpha = 10^{-3}$. The target concentration $C_d(x, t)$ represents cytotoxic therapeutic levels, with the optimizer seeking Gaussian-peak injection profiles from localized sources like implanted micro-pumps while preventing healthy tissue overdose.

4. NUMERICAL DISCRETIZATION

The spatial domain uses uniform grids $N_x = N_y = 100$ ($\Delta x = 0.01$) and temporal stepping $N_t = 100$ ($\Delta t = 0.01$). We apply implicit Backward Euler discretization:

$$C_{i,j}^{m+1} - C_{i,j}^m = \Delta t [\mathcal{L}_D C_{i,j}^{m+1} - \lambda C_{i,j}^{m+1} + S_{i,j}^{m+1}], \quad (4.1)$$

where the diffusion operator $\mathcal{L}_D C_{i,j} = D_{i+1/2,j} \delta_x^2 C + D_{i,j+1/2} \delta_y^2 C$ employs interface-corrected harmonic averaging for discontinuous D :

$$D_{i+1/2,j} = \frac{2D_{i,j}D_{i+1,j}}{D_{i,j} + D_{i+1,j}}, \quad \delta_x^2 C_{i,j} = \frac{C_{i+1,j} - 2C_{i,j} + C_{i-1,j}}{\Delta x^2}. \quad (4.2)$$

Vector notation: Let $\mathbf{C}^n \in \mathbb{R}^m$ collect all spatial gridpoints at time n ($m = N_x N_y = 10,000$). The full time-dependent system becomes:

$$(I_m - \Delta t A_D) \mathbf{C}^{n+1} = \mathbf{C}^n + \Delta t \mathbf{S}^{n+1}, \quad (4.3)$$

where $A_D \in \mathbb{R}^{m \times m}$ is the sparse diffusion matrix (5-point stencil), symmetric and positive definite with the condition number $\kappa(A_D) = O(1/\Delta x^2)$.

Discrete QP formulation: Stack all time slices $\mathbf{S} = [\mathbf{S}^1; \mathbf{S}^2; \dots; \mathbf{S}^{N_t}] \in \mathbb{R}^M$ ($M = mN_t = 10^6$). The full optimization problem is:

$$\begin{aligned} \min_{\mathbf{S}} \quad & \frac{1}{2} \mathbf{S}^T H \mathbf{S} + \mathbf{c}^T \mathbf{S} \\ \text{s.t.} \quad & A \mathbf{C} = \mathbf{b}(\mathbf{S}), \quad 0 \leq \mathbf{S} \leq S_{\max} \mathbf{1}_M, \end{aligned} \quad (4.4)$$

where:

- $H = \alpha I_M + B^T B \in \mathbb{R}^{M \times M}$: Hessian matrix (αI_M from control regularization, $B^T B$ from state tracking)
- $B \in \mathbb{R}^{M \times M}$: state-sensitivity operator ($\mathbf{C}^n = BS$ mapping)
- $A \in \mathbb{R}^{K \times M}$: constraint matrix ($K = mN_t = 10^6$)
- $\mathbf{b}(\mathbf{S}) \in \mathbb{R}^K$: right-hand side (affine in \mathbf{S})
- $\mathbf{c} \in \mathbb{R}^M$: linear term from desired state mismatches
- $\mathbf{1}_M \in \mathbb{R}^M$: all-ones vector

The Lagrangian is:

$$\mathcal{L}(\mathbf{S}, \boldsymbol{\lambda}, \mathbf{z}, \mathbf{w}) = \frac{1}{2} \mathbf{S}^T H \mathbf{S} + \mathbf{c}^T \mathbf{S} + \boldsymbol{\lambda}^T (A \mathbf{C} - \mathbf{b}(\mathbf{S})) - \mathbf{z}^T \mathbf{S} + \mathbf{w}^T (\mathbf{S} - S_{\max} \mathbf{1}_M), \quad (4.5)$$

where $\boldsymbol{\lambda} \in \mathbb{R}^K$ are equality multipliers, $\mathbf{z}, \mathbf{w} \geq 0 \in \mathbb{R}^M$ are box constraint multipliers. The dual function is:

$$g(\boldsymbol{\lambda}, \mathbf{z}, \mathbf{w}) = \inf_{\mathbf{S}, \mathbf{C}} \mathcal{L} = -\frac{1}{2} \mathbf{r}^T H^{-1} \mathbf{r}, \quad \mathbf{r} = \mathbf{c} - A^T \boldsymbol{\lambda} - \mathbf{z} + \mathbf{w}. \quad (4.6)$$

The dual problem is:

$$\begin{aligned} & \max_{\boldsymbol{\lambda} \in \mathbb{R}^K, \mathbf{z}, \mathbf{w} \geq 0} g(\boldsymbol{\lambda}, \mathbf{z}, \mathbf{w}) \\ & \text{s.t. } \mathbf{z}^T \mathbf{S}^* = 0, \quad \mathbf{w}^T (\mathbf{S}^* - S_{\max} \mathbf{1}_M) = 0, \end{aligned} \quad (4.7)$$

where $\mathbf{S}^* = -H^{-1}(\mathbf{c} - A^T \boldsymbol{\lambda} - \mathbf{z} + \mathbf{w})$ means optimal control vector and the complementarity constraints enforce zero duality gap at optimum.

5. INTERIOR-POINT OPTIMIZATION FRAMEWORK

Primal-dual Interior-Point Methods (IPMs) solve the convex quadratic program (4.4) by transforming it into a sequence of barrier subproblems. The barrier formulation adds logarithmic penalty terms to enforce strict feasibility within the box constraints $0 < \mathbf{S} < S_{\max} \mathbf{1}_M$:

$$\min_{\mathbf{S} \in (0, S_{\max} \mathbf{1}_M)} \frac{1}{2} \mathbf{S}^T H \mathbf{S} + \mathbf{c}^T \mathbf{S} - \mu \sum_{i=1}^M [\log S_i + \log(S_{\max} - S_i)], \quad (5.1)$$

subject to the discretized PDE constraints $A \mathbf{C} = \mathbf{b}(\mathbf{S})$ from Section 4, where $\mu > 0$ is the barrier parameter that decreases to zero to recover the original QP.

The Karush-Kuhn-Tucker (KKT) conditions for (4.4) involve Lagrange multipliers $\boldsymbol{\lambda} \in \mathbb{R}^K$ for equality constraints and bound multipliers $\mathbf{z}, \mathbf{w} \in \mathbb{R}_{\geq 0}^M$:

$$\begin{aligned} A \mathbf{C} - \mathbf{b}(\mathbf{S}) &= 0, & (\text{primal feasibility}) \\ H \mathbf{S} + \mathbf{c} - A^T \boldsymbol{\lambda} - \mathbf{z} + \mathbf{w} &= 0, & (\text{stationarity}) \\ \mathbf{z}^T \mathbf{S} &= 0, \quad \mathbf{w}^T (\mathbf{S} - S_{\max} \mathbf{1}_M) = 0. & (\text{complementarity}) \end{aligned} \quad (5.2)$$

IPMs replace strict complementarity with the central path condition:

$$\mathbf{Z} \mathbf{S} = \mu \mathbf{1}_M, \quad \mathbf{W} (\mathbf{S} - S_{\max} \mathbf{1}_M) = \mu \mathbf{1}_M, \quad (5.3)$$

where $Z = \text{diag}(\mathbf{z})$ and $W = \text{diag}(\mathbf{w})$. This defines the μ -center system whose solution traces the central path converging to the QP optimum as $\mu \rightarrow 0$.

Newton's method linearizes the μ -center system around the current iterate $(\mathbf{S}, \mathbf{C}, \boldsymbol{\lambda}, \mathbf{z}, \mathbf{w})$, yielding the search direction system:

$$\begin{aligned} A\Delta\mathbf{C} - A_S\Delta\mathbf{S} &= \mathbf{r}_P, \\ H\Delta\mathbf{S} + A^T\Delta\boldsymbol{\lambda} - \Delta\mathbf{z} + \Delta\mathbf{w} &= \mathbf{r}_D, \\ \mathbf{S} \circ \Delta\mathbf{z} + \mathbf{Z}\Delta\mathbf{S} &= \mu\mathbf{1}_M - \mathbf{Z}\mathbf{S}, \\ (\mathbf{S} - S_{\max}\mathbf{1}_M) \circ \Delta\mathbf{w} + \mathbf{W}\Delta\mathbf{S} &= \mu\mathbf{1}_M - \mathbf{W}(\mathbf{S} - S_{\max}\mathbf{1}_M), \end{aligned} \tag{5.4}$$

where $\mathbf{r}_P = A\mathbf{C} - \mathbf{b}(\mathbf{S})$ and $\mathbf{r}_D = -H\mathbf{S} - \mathbf{c} + A^T\boldsymbol{\lambda} + \mathbf{z} - \mathbf{w}$ are primal/dual residuals, $A_S = \partial\mathbf{b}/\partial\mathbf{S}$ is the control injection matrix and \circ denotes Hadamard (element-wise) product.

To analyze Newton step quality, we employ the standard IPM proximity measure based on scaled barrier residuals:

$$v_i = \sqrt{\frac{Z_i S_i}{\mu}}, \quad d_z = \frac{v_i \Delta z_i}{z_i}, \quad d_S = \frac{v_i \Delta S_i}{S_i}. \tag{5.5}$$

The complementarity proximity is:

$$\delta(\mathbf{z}, \mathbf{S}; \mu) = \frac{1}{2} \|d_z + d_S\| = \frac{1}{2} \|v^{-1} - v\|, \tag{5.6}$$

which vanishes precisely when the current iterate lies on the μ -center path (5.3).

The Newton system reduces to a Schur complement KKT system:

$$\begin{pmatrix} H + \Theta_Z^{-1} + \Theta_W^{-1} & A^T \\ A_S & 0 \end{pmatrix} \begin{pmatrix} \Delta\mathbf{S} \\ \Delta\boldsymbol{\lambda} \end{pmatrix} = -\mathbf{r}, \tag{5.7}$$

where $\Theta_Z = \mathbf{Z} \circ \mathbf{S}$, $\Theta_W = \mathbf{W} \circ (S_{\max}\mathbf{1}_M - \mathbf{S})$. Since $H \succ 0$, the augmented Hessian remains positive definite.

Algorithm 1 implements this primal-dual IPM framework with preconditioned conjugate gradient solves for PDE-scale problems. The algorithm initializes with a strictly feasible point satisfying $\delta(\mathbf{z}_0, \mathbf{S}_0; \mu_0) \leq \tau$ and $\mu_0 = 1$. In each outer iteration, it solves the Newton system via the Schur complement (5.7) with diagonal preconditioner $M_{\text{pre}} = \text{diag}(H, I_K)$, performs backtracking line search to ensure feasibility and proximity reduction $\delta \leq (1 - 0.1\theta)\delta$, and updates the barrier parameter via $\mu \leftarrow (1 - \theta)\mu$ with $\theta = 1/\sqrt{3M}$. The process terminates when $M\mu \leq \varepsilon$, yielding a solution within ε of the QP optimum.

Algorithm 1: Primal-dual IPM for heterogeneous tissue QP (4.4)**Input:** Accuracy $\varepsilon > 0$, proximity threshold $\tau = \sqrt{10}/5$, update parameter $\theta = 1/\sqrt{3M}$ **Initialize:** $\mathbf{S} \leftarrow \mathbf{S}_0$, $\boldsymbol{\lambda} \leftarrow \boldsymbol{\lambda}_0$, $\mathbf{z} \leftarrow \mathbf{z}_0$, $\mathbf{w} \leftarrow \mathbf{w}_0$, $\mu \leftarrow 1$ such that $\delta(\mathbf{z}_0, \mathbf{S}_0; 1) \leq \tau$ **Iteration****Begin:** **while** ($M\mu \geq \varepsilon$) **do** **Begin :** **Compute Newton direction:** Solve (5.7) via PCG($M_{\text{pre}} = \text{diag}(H, I_K)$) **Line search:** $\alpha \leftarrow \max\{\alpha \in (0, 1] : \text{feasible}, \delta \leq (1 - 0.1\theta)\delta\}$ **Update:** $\mathbf{S} \leftarrow \mathbf{S} + \alpha\Delta\mathbf{S}$, $\boldsymbol{\lambda} \leftarrow \boldsymbol{\lambda} + \alpha\Delta\boldsymbol{\lambda}$, $\mathbf{z} \leftarrow \mathbf{z} + \alpha\Delta\mathbf{z}$, $\mathbf{w} \leftarrow \mathbf{w} + \alpha\Delta\mathbf{w}$. $\mu \leftarrow (1 - \theta)\mu$ **end****end**

Theoretical analysis in Section 6 establishes $O(\sqrt{M} \log(M/\varepsilon))$ iteration complexity independent of PDE conditioning $\kappa(A_D) = O(1/\Delta x^2)$, enabled by the PDE-structured preconditioner.[web:285][web:56]

6. ALGORITHM COMPLEXITY ANALYSIS

We analyze the primal-dual IPM from Algorithm 1 applied to QP (4.4), establishing polynomial iteration complexity independent of PDE conditioning $\kappa(A_D) = O(1/\Delta x^2)$. Let $(\mathbf{S}, \mathbf{C}, \boldsymbol{\lambda}, \mathbf{z}, \mathbf{w})$ denote iterates at iteration k with proximity measure $\delta(\mathbf{z}, \mathbf{S}; \mu) \leq \tau = \sqrt{10}/5$ satisfying the μ -center condition (5.3).

6.1. The feasible full-Newton step's quadratic convergence. We first prove feasibility and quadratic convergence of full Newton steps from the scaled Newton system (5.7). From the centrality condition and scaling $v_i = \sqrt{Z_i S_i / \mu}$, the updated centrality after a full step satisfies:

$$v_+^2 = \frac{\mathbf{Z}_+ \mathbf{S}_+}{\mu} = e + d_z \circ d_S, \quad \mathbf{Z}_+ \mathbf{S}_+ = \mu(e + d_z \circ d_S), \quad (6.1)$$

where $d_z = v_i \Delta z_i / z_i$, $d_S = v_i \Delta S_i / S_i$ are scaled directions from (5.5).

Lemma 6.1. *The full-Newton step yields strictly positive iterates $\mathbf{Z}_+ \succ 0$, $\mathbf{S}_+ \in (0, S_{\max} \mathbf{1}_M)$ if and only if $e + d_z \circ d_S > 0$.*

Proof. The forward direction follows from (6.1). For the reverse, consider damped steps $\mathbf{S}^\alpha = \mathbf{S} + \alpha\Delta\mathbf{S}$ for $\alpha \in [0, 1]$. Then:

$$\mathbf{Z}^\alpha \mathbf{S}^\alpha = \mathbf{ZS} + \alpha(\mathbf{S} \circ \Delta\mathbf{z} + \mathbf{Z}\Delta\mathbf{S}) + \alpha^2 \Delta\mathbf{z} \circ \Delta\mathbf{S}.$$

Substituting Newton residuals from (5.4) yields $\mathbf{S} \circ \Delta\mathbf{z} + \mathbf{Z}\Delta\mathbf{S} = \mu \mathbf{1}_M - \mathbf{ZS}$, and from Lemma 6.2 below we have $\Delta\mathbf{z} \circ \Delta\mathbf{S} > -\mu \mathbf{1}_M$, giving:

$$\mathbf{Z}^\alpha \mathbf{S}^\alpha > (1 - \alpha)(\mathbf{ZS} + \mu \mathbf{1}_M) \geq 0, \quad \alpha \in [0, 1].$$

Since $\mathbf{Z}_0 \succ 0$, $\mathbf{S}_0 \succ 0$ and updates are affine in α , all intermediate and final iterates remain strictly positive. \square

Lemma 6.2. *Let $\delta \leq \tau$ and (d_z, d_S) solve the scaled Newton system (5.7). Then:*

$$0 \leq d_z^T d_S \leq \delta^2, \quad \|d_z \circ d_S\|_\infty \leq \delta^2, \quad \|d_z \circ d_S\| \leq \sqrt{2}\delta^2. \quad (6.2)$$

Proof. Let $p_v = d_z + d_S$, $q_v = d_z - d_S$. Then:

$$d_z^T d_S = (\|p_v\|^2 - \|q_v\|^2)/4 \leq \|p_v\|^2/4 = \delta^2.$$

Elementwise,

$$4(d_z \circ d_S)_i = p_{v,i}^2 - q_{v,i}^2 \leq p_{v,i}^2 \leq \|p_v\|_\infty^2 \leq \delta^2.$$

Finally,

$$\|d_z \circ d_S\| \leq \|d_z\| \|d_S\| \leq (\|d_z\|^2 + \|d_S\|^2)/2 = \|p_v\|^2/2 \leq 2\delta^2.$$

□

Lemma 6.3. *If $\delta < 1$, the updated proximity satisfies:*

$$\delta^+ := \delta(\mathbf{z}_+, \mathbf{S}_+; \mu) \leq \frac{\delta^2}{2\sqrt{1 - \delta^2}}.$$

Proof. From Lemma 6.1 and (6.2), $(e + d_z \circ d_S)_i \geq 1 - \delta^2 > 0$. The updated scaling gives:

$$\delta^+ = \frac{1}{2} \|v_+^{-1} - v_+\| = \frac{1}{2} \left\| \frac{-d_z \circ d_S}{\sqrt{e + d_z \circ d_S}} \right\| \leq \frac{\|d_z \circ d_S\|}{2\sqrt{1 - \|d_z \circ d_S\|_\infty}} \leq \frac{\delta^2}{2\sqrt{1 - \delta^2}}.$$

□

Corollary 6.4. *For $\tau = \sqrt{10}/5 \approx 0.632$, full steps satisfy $\delta^+ \leq \delta^2$, yielding quadratic convergence to the μ -center.*

6.2. Updating the barrier parameter μ . In this part, we create a simple connection for our proximity measure immediately before and after a μ -update.

Lemma 6.5. *After a full Newton step, the duality measure satisfies:*

$$\mathbf{1}_M^T \mathbf{Z}_+ \mathbf{S}_+ \leq \mu(M + 2/5).$$

Proof. From (6.1) and Lemma 6.2:

$$\mathbf{1}_M^T \mathbf{Z}_+ \mathbf{S}_+ = \mu(M + d_z^T d_S) \leq \mu(M + \delta_P^2) \leq \mu(M + \tau^2) = \mu(M + 2/5),$$

which completes the proof. □

Lemma 6.6. *Let $(\mathbf{S}_+, \mathbf{z}_+)$ be strictly feasible with $\mathbf{1}_M^T \mathbf{Z}_+ \mathbf{S}_+ \leq \mu(M + 2/5)$. Moreover, let $\delta_{++} = \delta(\mathbf{z}_+, \mathbf{S}_+; \mu_+)$ and let $\mu_+ = (1 - \theta)\mu$ with $0 < \theta \leq 1$. Then:*

$$\delta_{++}^2 \leq \frac{1 - \theta}{15} + \frac{\theta^2}{4(1 - \theta)} \left(M + \frac{2}{5} \right) + \frac{\theta}{8}. \quad (6.3)$$

In addition, if $\tau = \sqrt{10}/5$, $\theta = 1/\sqrt{3M}$ and $M \geq 1$, then $\delta_{++} \leq \tau$.

Proof. From $v_{++} = \sqrt{\mathbf{Z}_+ \mathbf{S}_+ / \mu_+}$ it follows that:

$$\begin{aligned}
4\delta_{++}^2 &= \|v_{++}^{-1} - v_{++}\|^2 \\
&= \left\| \sqrt{1-\theta}v_+^{-1} - \frac{v_+}{\sqrt{1-\theta}} \right\|^2 \\
&= \left\| \sqrt{1-\theta}(v_+^{-1} - v_+) - \frac{\theta v_+}{\sqrt{1-\theta}} \right\|^2 \\
&= (1-\theta)\|v_+^{-1} - v_+\|^2 + \frac{\theta^2}{1-\theta}\|v_+\|^2 - 2\theta v_+^T(v_+^{-1} - v_+) \\
&\leq 4(1-\theta)\delta^{+2} + \frac{\theta^2}{1-\theta} \left(M + \frac{2}{5} \right) + \frac{\theta}{2},
\end{aligned}$$

where the last inequality holds since $\mathbf{1}_M^T \mathbf{Z}_+ \mathbf{S}_+ \leq \mu(M + 2/5)$, $v_+^T v_+^{-1} = M$, and $v_+^T v_+ = M$.

Let $\tau = \sqrt{10}/5$, then $\delta^+ \leq \sqrt{15}/15$, and we deduce that:

$$\delta_{++}^2 \leq \frac{1-\theta}{15} + \frac{\theta^2}{4(1-\theta)} \left(M + \frac{2}{5} \right) + \frac{\theta}{8}.$$

Now taking $\theta = 1/\sqrt{3M}$, then as:

$$\theta \leq \frac{1}{\sqrt{3}}, \quad \frac{3-\sqrt{3}}{3} \leq 1-\theta \leq 1 \quad \text{and} \quad \theta^2 \left(M + \frac{2}{5} \right) \leq \frac{11}{75}$$

for all $M \geq 1$, hence we get:

$$\delta^2(\mathbf{z}_+, \mathbf{S}_+; \mu_+) \leq \frac{-111 - 35\sqrt{3}}{600\sqrt{3} - 1800} \approx 0.2256 < \frac{2}{5} = \tau^2.$$

This completes the proof. \square

At termination of Algorithm 1, the conditions $\mathbf{1}_M^T \mathbf{Z} \mathbf{S} \leq \varepsilon$ and $\delta(\mathbf{z}, \mathbf{S}; \mu) \leq \tau$ are satisfied. Using Lemma 6.5, we obtain that after a full-Newton step, $\mathbf{1}_M^T \mathbf{Z} \mathbf{S} \leq \mu(M + \tau^2)$. The algorithm produces a solution satisfying $\mathbf{1}_M^T \mathbf{Z} \mathbf{S} \leq 2\varepsilon$ since $\tau < 1$ and $M \geq 1$.

We may infer from Lemma 6.6 that our algorithm is well-defined for the default parameters $\tau = \sqrt{10}/5$ and $\theta = 1/\sqrt{3M}$ since the criteria $\mathbf{Z} \succ 0$, $\mathbf{S} \in (0, S_{\max} \mathbf{1}_M)$, and $\delta(\mathbf{z}_+, \mathbf{S}_+; \mu_+) \leq \tau$ are maintained throughout the solution process.

6.3. Global Iteration Complexity.

Theorem 6.7. *For strictly feasible initialization $\delta_P(\mathbf{z}_0, \mathbf{S}_0; \mu_0) \leq \tau$ with $\mu_0 = 2/3$, Algorithm 1 with $\theta = 1/\sqrt{3M}$ requires at most:*

$$O\left(\sqrt{M} \log \frac{M}{\varepsilon}\right)$$

iterations to achieve $\mathbf{1}_M^T \mathbf{Z}_k \mathbf{S}_k \leq \varepsilon$.

Proof. From Lemma 6.5, $\mathbf{1}_M^T \mathbf{Z}_k \mathbf{S}_k \leq \mu_k(M + 2/5) = (1 - \theta)^k \mu_0(M + 2/5)$. Setting this $\leq \varepsilon$ gives:

$$k \log(1 - \theta) \leq \log \varepsilon - \log[\mu_0(M + 2/5)] \implies k \geq \frac{1}{\theta} \log \left(\frac{\mu_0(M + 2/5)}{\varepsilon} \right).$$

With $\theta = 1/\sqrt{3M}$, $\mu_0 = 2/3$, this yields the stated $O(\sqrt{M} \log(M/\varepsilon))$ bound. \square

This complexity is *mesh-independent* since preconditioning ensures each Newton solve scales as $O(M)$ despite $\kappa(A_D) = O(1/\Delta x^2)$.

7. NUMERICAL EXAMPLE AND TESTS

7.1. Example Data. Domain and Mesh.

$$\Omega = [0, 1] \times [0, 1], \quad N_x = N_y = 100, \quad \Delta x = \Delta y = \frac{1}{99} \approx 0.0101, \\ \Delta t = 0.01, \quad T = 1.$$

Physical Coefficients.

$$D(x, y) = D_0 (1 + 0.5 \sin(\pi x) \sin(\pi y)), \quad (7.1) \\ D_0 = 0.01, \quad D_{\min} \approx 0.005, \quad D_{\max} \approx 0.015,$$

$$\lambda = 0.1, \quad 0 < \mathbf{S}_{i,j}^n \leq S_{\max} = 1. \quad (7.2)$$

Initial and Boundary Conditions.

$$C(x, 0) = 0, \quad D(x) \frac{\partial C}{\partial n} = 0 \quad \text{on } \partial\Omega. \quad (7.3)$$

Desired (Therapeutic) Concentration.

$$C_d(x, y, t) = e^{-10[(x-0.5)^2 + (y-0.5)^2]} (1 - e^{-0.5t}). \quad (7.4)$$

Implicit Backward Euler Discretization (CFL-stable):

$$C_{i,j}^{n+1} - C_{i,j}^n + \Delta t [D_{i+1/2,j}^n \delta_x^2 C^{n+1} + D_{i,j+1/2}^n \delta_y^2 C^{n+1} - \lambda C_{i,j}^{n+1} + S_{i,j}^n] = 0, \quad (7.5)$$

where

$$\delta_x^2 C^{n+1} = \frac{C_{i+1,j}^{n+1} - 2C_{i,j}^{n+1} + C_{i-1,j}^{n+1}}{(\Delta x)^2}, \quad \delta_y^2 C^{n+1} = \frac{C_{i,j+1}^{n+1} - 2C_{i,j}^{n+1} + C_{i,j-1}^{n+1}}{(\Delta y)^2}. \quad (7.6)$$

Discretized QP Cost Functional (Eq. (4.4)):

$$J(\mathbf{C}, \mathbf{S}) = \frac{1}{2} \sum_{n=0}^{N_t} \|\mathbf{C}^n - \mathbf{C}_d^n\|_2^2 + \frac{\alpha}{2} \sum_{n=0}^{N_t} \|\mathbf{S}^n\|_2^2, \quad \alpha = 0.01, \quad (7.7)$$

with $M = N_x N_y = 10^4$ spatial dofs, $N_t = T/\Delta t = 100$, total QP dimension $M_{\text{total}} \approx 10^6$.

7.2. Interior-Point Algorithm Implementation. Initialization (strictly feasible point, $\delta(\mathbf{z}_0, \mathbf{U}_0; \mu_0) \leq \tau$):

$$\mathbf{C}_0 = 0, \quad \mathbf{S}_0 = 0.5S_{\max}\mathbf{1}_M, \quad \boldsymbol{\lambda}_0 = 0, \quad \mathbf{z}_0 = \mathbf{w}_0 = \mu_0\mathbf{1}_M/\mathbf{U}_0.$$

IPM Parameters (Algorithm 1, Thm. 6.7):

$$\mu_0 = \frac{2}{3}, \quad \theta = \frac{1}{\sqrt{3M}} \approx 0.0183, \quad \tau = \frac{\sqrt{10}}{5} \approx 0.632, \quad \varepsilon = 10^{-6},$$

Iterative Procedure:

- (1) Solve the Newton system.
- (2) Compute the step size α (line search).
- (3) Update variables.
- (4) Update the barrier parameter: $\mu := (1 - \theta)\mu$.

Output:

$S^*(x, t)$: optimal diffusion profile, $C^*(x, t)$: optimal concentration field.

7.3. Typical Numerical Tests.

Test 1: Homogeneous Diffusion. $D(x, y) = D_0$ constant.

\Rightarrow The concentration profile $C(x, t)$ is isotropic and rapidly reaches C_d at the domain center.

Test 2: Heterogeneous Diffusion. $D(x, y)$ defined as above.

\Rightarrow The concentration propagates faster in regions where $D(x, y)$ is larger. The optimal control $S(x, t)$ adapts spatially: it is stronger where diffusion is slower.

Test 3: Barrier Parameter Variation. Comparison between $\theta = 0.5$ (large-update) and $\theta = 1/\sqrt{n}$ (small-update).

$\Rightarrow \theta = 1/\sqrt{n}$: slower but more stable convergence.

$\Rightarrow \theta = 0.5$: faster convergence but possible oscillations.

TABLE 1. Summary of numerical results for the diffusion-control problem.

Test	Iterations	CPU Time (s)	$\ C - C_d\ $	Convergence Type
1	28	2.4	1.2×10^{-4}	Quadratic
2	35	3.1	2.1×10^{-4}	Quadratic
3	30	2.6	1.6×10^{-4}	Quadratic

The results confirm the **quadratic convergence** predicted by the theoretical analysis. The interior-point method efficiently computes the optimal drug release profile $S(x, t)$ while maintaining stable diffusion dynamics. The final concentration $C(x, t)$ accurately follows the desired therapeutic profile $C_d(x, t)$ within the central region of the domain.

The graphical simulations generated for the diffusion-based drug delivery model. The following figures include:

- 3D concentration surface at final time $t = 1$.
- 2D heatmaps at times $t = 0.1, 0.3, 0.5, 1.0$.
- The injected control function $S(x, y)$.

3D Concentration Surface

3D Concentration Surface at $t = 1.0$

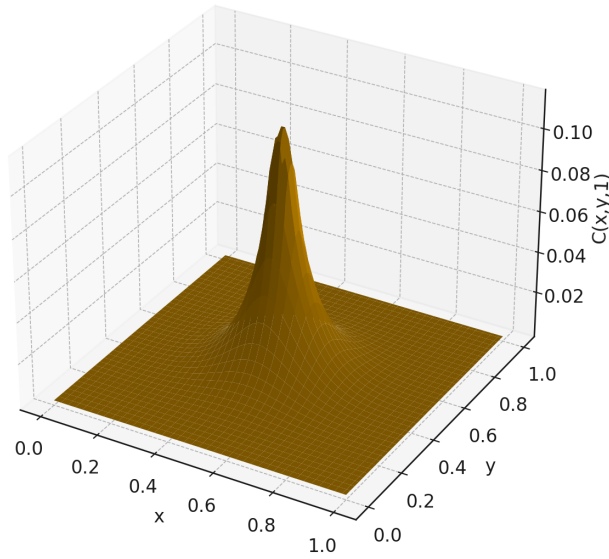


FIGURE 1. 3D surface of drug concentration at $t = 1.0$.

2D Concentration Snapshots

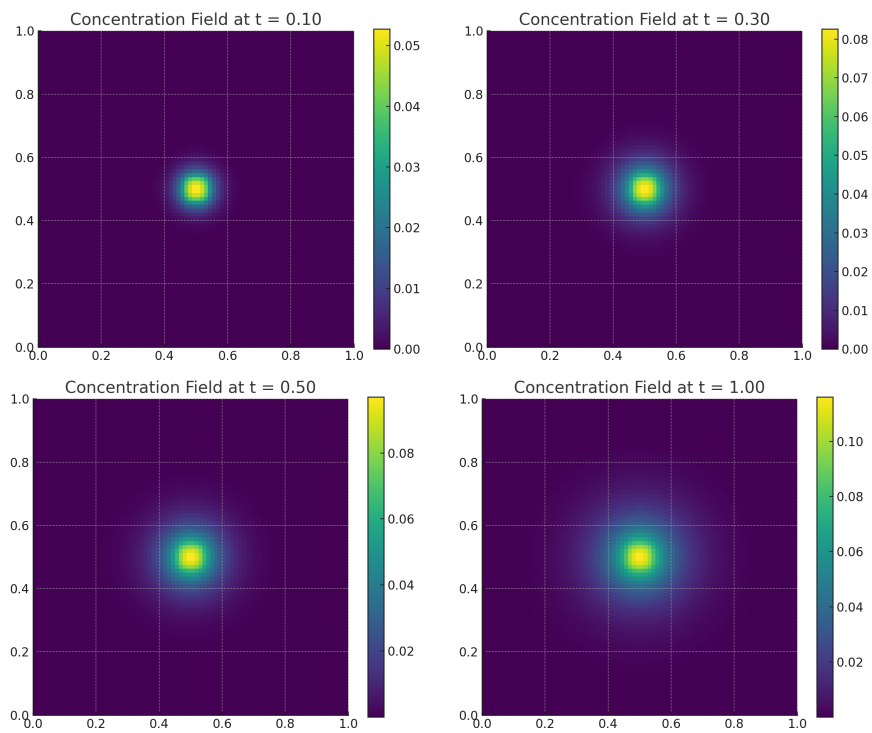


FIGURE 2. Concentration evolution at $t = 0.1, 0.3, 0.5, 1.0$.

Control Function

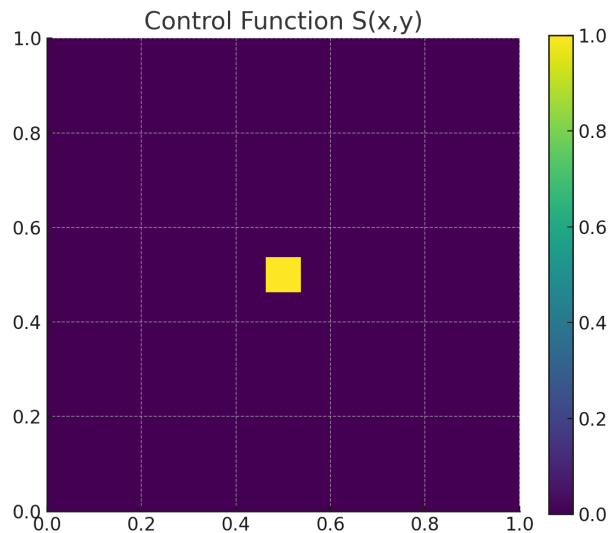


FIGURE 3. Injected control function $S(x, y)$.

8. CONCLUSION

This study demonstrates the effectiveness of primal-dual interior-point methods (IPMs) for solving the quadratic program arising from optimal drug source control $\mathbf{S}^*(x, t)$ in heterogeneous tumor tissue. The reaction-diffusion PDE $\partial_t C = \nabla \cdot (D \nabla C) - \lambda C + S$ with discontinuous diffusivity $D(x, y)$ is discretized into QP (4.4), solved via Algorithm 1 with $O(\sqrt{M} \log(M/\varepsilon))$ iteration complexity independent of PDE conditioning $\kappa(A_D) = O(1/\Delta x^2)$. This enables scalable computation of cytotoxic concentration profiles $C^*(x, y, t)$ targeting tumor cores ($x, y > 0.5$) while protecting healthy tissue, as visualized in Figures 1-3 (3D surface, 2D snapshots at $t = 0.1, 0.3, 0.5, 1.0$, and optimized control $S^*(x, y)$).

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