Observer-Based Feedback Control of a Mathematical Model of Intimal Hyperplasia*

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Abstract

A theoretical model of a potential treatment for intimal hyperplasia due to hemodialysis is proposed. This model consists of two parts. The first part is modeling the development of intimal hyperplasia as a diffusion process of muscle cells from the media to the lumen, for which the governing equation is a partial differential equation. The second part is designing an observer-based feedback controller to stabilize the equilibrium point of the system, corresponding to no intimal hyperplasia. Simulation results show that the intimal hyperplasia can be reduced by 90% in nearly 30 days of treatment.

1 Introduction

Patients with kidney disease need hemodialysis to replace the function of healthy kidneys, which is to clean the metabolic waste products from the blood. It has been shown that prolonged hemodialysis treatment can lead to local onset of intimal hyperplasia in curved veins downstream of fistulas inserted to facilitate hemodialysis. If unchecked, this intimal hyperplasia may lead to stenosis, or blockage, in the afflicted vessel [8]. Several factors have been demonstrated to contribute to intimal hyperplasia, but mainly it is because hemodialysis changes the chemical and physical (hemodynamic conditions) environment within the blood vessel. These changes activate different kinds of growth factors, such as TGF-β and PDGF, that will in turn cause the proliferation of smooth muscle cells and fibroblasts within the media vascular layer. Consequently, the density of muscle cells in the media becomes high, and some of the cells will migrate through the intima, and the accumulation of smooth muscle cells will finally build up as intimal hyperplasia within the lumen, which is the inner region of the vessel occupied by the blood [12]. Intimal hyperplasia changes the shape of the cross section of the lumen, thereby altering the hemodynamic conditions within the blood vessel. Therefore, the process

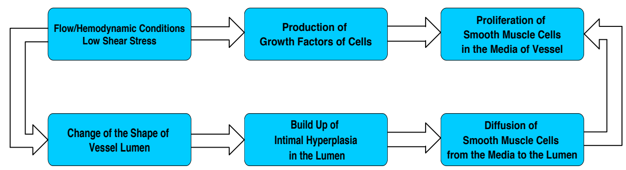

Figure 1: Schematic of physiological feedback loop that leads to intimal hyperplasia.

of formation of intimal hyperplasia can be regarded as a feedback loop in which changing hemodynamics leads to intimal hyperplasia, which results in further changes to the hemodynamics that influence subsequent intimal hyperplasia as illustrated in Figure 1. Note that it is the change in shape of the lumen that acts as the feedback in this mechanism. This motivates us to model the development of intimal hyperplasia as a feedback-control system.

The major mechanisms involved in the development of intimal hyperplasia are the proliferation and migration of smooth muscle cells from the media layer of the vessel into the lumen. This migration of cells can be modeled as a diffusion process governed by the classical diffusion equation, which is a parabolic partial differential equation (PDE). The proliferation of smooth muscle cells is taken into account through the boundary conditions of the PDE; therefore, modeling the mechanism of intimal hyperplasia as described above is formulated as a control problem for a parabolic PDE. There are several methods available for control PDEs. Typically, finite difference methods, such as the method of lines, can be used to discretize the infinite-dimensional PDE system to obtain a finite-dimensional ODE approximation [15]. This approach allows for the application of control strategies developed for ODEs to be applied to PDEs. Another method is motivated by making use of the special structure of the eigenspectrum of the spatial differential operator of parabolic PDEs [1]. One of the features of the eigenspectrum is that it can be partitioned into a set of finite-dimensional slow modes and an infinite-dimensional set of stable fast ones. Therefore, the controller synthesis can be based

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on the finite-dimensional slow subsystem, and accuracy can be guaranteed if certain conditions are satisfied. However, both of the methods mentioned above approximate the infinite-dimensional problem by a finite-dimensional problem. The approximation will result in the loss of some crucial behavior within the original PDE system. In the present work, we consider an infinite-dimensional controller synthesis problem of the PDE to rigorously preserve all the behavior of the original system.

2 Model of Intimal Hyperplasia

The mathematical model for the development of intimal hyperplasia [12] is based on the following classical diffusion equation

$$\frac{\partial s}{\partial t}(x,t) = \nabla(D_s \nabla s), \quad \forall\ x \in \Omega, \tag{2.1}$$

where Ω is the control domain, which in this case is the lumen of the vessel. The cross-section of the domain is assumed to be a circle of radius R_0, where R_0 is the average radius of the lumen. That is, the cross-section of the lumen is axisymmetric with respect to the centerline. The density of smooth muscle cells at the radial location $x \in \Omega$ at some moment $t > 0$ is given by $s(x,t)$. The diffusion coefficient of smooth muscle cells in the lumen is D_s, which is assumed to be constant in this paper.

The boundary of the control domain Ω is denoted by Γ, which is the boundary between the lumen and the media. Note that the thickness of the intima is negligible compared to the radius of the lumen R_0. Therefore, the boundary condition for equation (2.1) is

$$\nabla s \frac{x}{|x|}(x,t)\bigg|_{x\in\Gamma} = u(x,t)\bigg|_{x\in\Gamma}. \tag{2.2}$$

Here we model the proliferation of the smooth muscle cells as the boundary control input, which is denoted by $u(x,t)$. It takes account of all the factors that will cause the proliferation of the smooth muscle cells, such as TGF-β and PDGF.

For simplicity, we only consider the one-dimensional spatial (radial) coordinate. Then, equation (2.1) is expressed as a differential equation in $L_2(0,R_0)$ of the general form

$$\frac{\partial s}{\partial t} = \mathcal{A}s + \mathcal{B}u, \tag{2.3}$$

and the output of the system is defined by

$$y = \mathcal{C}s = [y_1, y_2]^T = [\langle s, 1\rangle, \langle s, \delta(x-R_0)\rangle]^T, \tag{2.4}$$

where $s \in D(\mathcal{A}) = \{f \in L_2(0,R_0) |\ f$ is absolutely continuous, $f'(0) = 0,\ f'(R_0) = 0\}$, $\mathcal{A}s := D_s \frac{\partial^2 s}{\partial x^2}$, $\mathcal{B}u := \delta(x-R_0)u(t)$, y_1 is the thickness of intimal hyperplasia in the domain Ω, y_2 is an indicator of the proliferation of muscle cells in the media. The initial condition is

$$s(x, t=0) = s_0(x), \tag{2.5}$$

and the boundary conditions are

$$\frac{\partial s}{\partial x}(x=0,t) = 0, \tag{2.6}$$

$$\frac{\partial s}{\partial x}(x=R_0,t) = 0. \tag{2.7}$$

The boundary condition (2.6) corresponds to the symmetric condition at the center of the cross-section of the vessel.

3 Controller Synthesis

In order to treat intimal hyperplasia, it is desired to reduce the total amount of smooth muscle cells inside the lumen. The ideal case is that there is no intimal hyperplasia in the lumen, which corresponds to $s(x,t) = 0$. So the objective is to stabilize the PDE system at the equilibrium point $s(x,t) = 0$. We apply semi-group theory, which provides a rigorous technique to deal with PDEs in the time domain. It is used to derive inequality conditions of operators for a stabilizing controller. The operator inequalities are then transferred to a feasibility problem for polynomials.

Definition 3.1. *Let X be a Banach space, and suppose that to every $t \in [0,+\infty)$ is associated an operator $Q(t) \in \mathscr{B}(X)$, in such a way that*

i) $Q(0) = I$,

ii) $Q(s+t) = Q(s)Q(t), \quad \forall s \geq 0, \quad t \geq 0$,

iii) $\lim_{t\to 0} \|Q(t)x - x\| = 0, \quad \forall x \in X$.

If (i) and (ii) hold, $\{Q(t)\}$ is called a semi-group. Such semi-groups have the following exponential representation if (iii) is satisfied

$$\|Q(t)\| \leq Ce^{\gamma t}, \quad (0 \leq t < +\infty),$$

for some constants C and γ. Moreover, if $\gamma < 0$, then $\{Q(t)\}$ is called an exponentially stable semi-group.

Definition 3.2. *Consider the operators $\mathcal{A}_\epsilon$ associated with $\{Q(t)\}$, which is*

$$\mathcal{A}_\epsilon x = \frac{1}{\epsilon}[Q(\epsilon)x - x], \quad (x \in X,\ \epsilon > 0).$$

If $\lim_{\epsilon\to 0}\mathcal{A}_\epsilon x$ *exists, define the operator* $\mathcal{A}$ *such that*

$$\mathcal{A}x = \lim_{\epsilon\to 0}\mathcal{A}_\epsilon x,$$

then $\mathcal{A}$ *is called the infinitesimal generator of the semi-group* $\{Q(t)\}$.

THEOREM 3.1. *Consider the linear system described by equations (2.3) and (2.4), and assume that it is exponentially stabilizable and exponentially detectable. If there exist* $\mathcal{F} \in \mathscr{L}(L_2(0,R_0),\mathbb{R})$ *and* $\mathcal{L} \in \mathscr{L}(\mathbb{R}, L_2(0,R_0))$ *such that* $\mathcal{A}+\mathcal{BF}$ *and* $\mathcal{A}+\mathcal{LC}$ *generate exponentially stable semi-groups, then the controller* $u = \mathcal{F}\hat{s}$, *where* $\hat{s}$ *is the state of the Luenberger observer with output injection* $\mathcal{L}$, *stabilizes the closed-loop system at* $s(x,t) = 0$. *The stabilizing compensator is given by*

$$\frac{\partial \hat{s}}{\partial t} = \mathcal{A}\hat{s} + \mathcal{B}u - \mathcal{L}(y - \mathcal{C}\hat{s}), \tag{3.8}$$

$$u(t) = \mathcal{F}\hat{s}. \tag{3.9}$$

LEMMA 3.1. *The operator* $\mathcal{A}+\mathcal{LC}$ *is an infinitesimal generator of an exponentially stable* $\mathcal{C}_0$ *semi-group if there exists a positive-definite operator* $\mathcal{P}_1 \in \mathscr{L}(L_2(0,R_0))$, *such that*

$$\langle(\mathcal{A}+\mathcal{LC})s, \mathcal{P}_1 s\rangle + \langle \mathcal{P}_1 s, (\mathcal{A}+\mathcal{LC})s\rangle < 0, \tag{3.10}$$

for all $s \in D(\mathcal{A})$. *Similarly, the operator* $\mathcal{A}+\mathcal{BF}$ *is an infinitesimal generator of an exponentially stable* $\mathcal{C}_0$ *semi-group if there exists a positive-definite operator* $\mathcal{P}_2 \in \mathscr{L}(L_2(0,R_0))$, *such that*

$$\langle(\mathcal{A}+\mathcal{BF})s, \mathcal{P}_2 s\rangle + \langle \mathcal{P}_2 s, (\mathcal{A}+\mathcal{BF})s\rangle < 0, \tag{3.11}$$

for all $s \in D(\mathcal{A})$.

Proof of Theorem 3.1 and Lemma 3.1 can be found in [3].

THEOREM 3.2. *The operator* $\mathcal{A}+\mathcal{LC}$ *is an infinitesimal generator of an exponentially stable* $\mathcal{C}_0$ *semi-group if there exist polynomials* $M_1(x)$ *and* $N_1(x)$ *defined on* $x \in [0,R_0]$, *such that*

$$M_1(x) > 0, \qquad \mathbf{Z}_1 < 0, \tag{3.12}$$

for all $x \in [0,R_0]$, *where*

$$\mathbf{Z}_1 = \begin{bmatrix} \frac{D_s M_1''(x)}{2} & 0 & \frac{N_1(x)}{2} \\ 0 & \frac{D_s M_1'(0)}{2R_0} & 0 \\ \frac{N_1(x)}{2} & 0 & -\frac{D_s M_1'(R_0)}{2R_0} \end{bmatrix},$$

and the operator $\mathcal{L}$ *and the positive-definite operator* $\mathcal{P}_1$ *are defined by*

$$\mathcal{L}y = [0, M_1^{-1}(x)N_1(x)]\cdot[y_1,y_2]^T, \tag{3.13}$$

and

$$\mathcal{P}_1 s = M_1(x)s, \tag{3.14}$$

respectively

Proof. Because $M_1(x) > 0$, the positive definiteness of $\mathcal{P}_1$ is assured. Based on Lemma 3.1, in order to prove $\mathcal{A}+\mathcal{LC}$ is an infinitesimal generator of exponentially stable $\mathcal{C}_0$ semi-group, it is sufficient to prove that

$$\langle(\mathcal{A}+\mathcal{LC})s, \mathcal{P}_1 s\rangle + \langle \mathcal{P}_1 s, (\mathcal{A}+\mathcal{LC})s\rangle < 0.$$

The left hand side of the above inequality is indefinite in the presence of the integration of the terms such as $s''(x)s(x)$ and $s'(x)s(x)$. So in order to transfer the left hand side of the inequality to a definite form, the following mathematical equalities are used

$$\int_0^{R_0} (s''(x)M_1(x)s(x) + s'(x)(M_1(x)s(x))')dx = \langle h_1, 1\rangle = 0, \tag{3.15}$$

$$\int_0^{R_0} \Big(2M_1'(x)s'(x)s(x) + M_1''(x)s^2(x) - \frac{1}{R_0}M_1'(R_0)s^2(R_0) + \frac{1}{R_0}M_1'(0)s^2(0)\Big)dx = \langle h_2, 1\rangle = 0, \tag{3.16}$$

which are derived from integration by parts. Note that the boundary conditions have already been applied in equations (3.15) and (3.16), and we have that

$$h_1(s'',s',s,x) = s''(x)M_1(x)s(x) + s'(x)(M_1(x)s(x))',$$

and

$$h_2(s'',s',s,x) = 2M_1'(x)s'(x)s(x) + M_1''(x)s^2(x) - \frac{1}{R_0}M_1'(R_0)s^2(R_0) + \frac{1}{R_0}M_1'(0)s^2(0).$$

Now consider the main part of the proof. Suppose λ_1 and λ_2 are constants to be determined, then

$$\begin{aligned} &\langle(\mathcal{A}+\mathcal{LC})s, \mathcal{P}_1 s\rangle \\ &= \langle(\mathcal{A}+\mathcal{LC})s, \mathcal{P}_1 s\rangle + \lambda_1\langle h_1,1\rangle + \lambda_2\langle h_2,1\rangle \\ &= \langle \mathcal{A}s, \mathcal{P}_1 s\rangle + \langle \mathcal{P}_1\mathcal{LC}s, s\rangle + \lambda_1\langle h_1,1\rangle + \lambda_2\langle h_2,1\rangle \\ &= \int_0^{R_0} D_s s''(x)M_1(x)s(x)dx + \langle N_1(x)s(R_0), s(x)\rangle \\ &\quad + \lambda_1\langle h_1,1\rangle + \lambda_2\langle h_2,1\rangle \\ &= \int_0^{R_0} ((D_s+\lambda_1)s''(x)M_1(x)s(x) \\ &\quad + \lambda_1 s'(x)(M_1(x)s(x))')dx + \langle N_1(x)s(R_0), s(x)\rangle \\ &\quad + \lambda_2\langle h_2,1\rangle. \end{aligned}$$

To eliminate the indefinite term $(D_s + \lambda_1)s''(x)M_1(x)s(x)$, let $\lambda_1 = -D_s$, for which the above result becomes

$$\begin{aligned}
&= -D_s \int_0^{R_0} s'(x)(M_1(x)s(x))'dx \\
&\quad + \langle N_1(x)s(R_0), s(x)\rangle + \lambda_2\langle h_2, 1\rangle \\
&= -D_s \int_0^{R_0} (s'(x)M_1(x)s'(x) + s'(x)M_1'(x)s(x))dx \\
&\quad + \langle N_1(x)s(R_0), s(x)\rangle + \lambda_2\langle h_2, 1\rangle \\
&= -D_s \int_0^{R_0} M_1(x)[s'(x)]^2dx + \langle N_1(x)s(R_0), s(x)\rangle \\
&\quad + \int_0^{R_0} \Big((-D_s + 2\lambda_2)M_1'(x)s'(x)s(x) \\
&\quad + \lambda_2 M_1''(x)s^2(x) \\
&\quad - \frac{\lambda_2}{R_0}(M_1'(R_0)s^2(R_0) - M_1'(0)s^2(0))\Big)dx.
\end{aligned}$$

To eliminate the indefinite term $(-D_s + 2\lambda_2)M_1'(x)s'(x)s(x)$, let $\lambda_2 = \frac{D_s}{2}$, which leads to

$$\begin{aligned}
&= -D_s \int_0^{R_0} M_1(x)[s'(x)]^2dx \\
&\quad + \frac{D_s}{2}\int_0^{R_0} M_1''(x)s^2(x)dx \\
&\quad - \frac{D_s}{2R_0}\int_0^{R_0} M_1'(R_0)s^2(R_0)dx \\
&\quad + \frac{D_s}{2R_0}\int_0^{R_0} M_1'(0)s^2(0)dx \\
&\quad + \int_0^{R_0} N_1(x)s(R_0)s(x)dx \\
&= -D_s \int_0^{R_0} M_1(x)[s'(x)]^2dx \\
&\quad + \int_0^{R_0} \begin{bmatrix} s(x) \\ s(0) \\ s(R_0)\end{bmatrix}^T \mathbf{Z}_1 \begin{bmatrix} s(x) \\ s(0) \\ s(R_0)\end{bmatrix} dx.
\end{aligned}$$

Thus, once condition (3.12) is satisfied, $\langle(\mathcal{A} + \mathcal{LC})s, \mathcal{P}_1 s\rangle < 0$ holds for all $s \in D(\mathcal{A})$. Recall that all the functions mentioned above are real, hence

$$\langle(\mathcal{A} + \mathcal{LC})s, \mathcal{P}_1 s\rangle = \langle\mathcal{P}_1 s, (\mathcal{A} + \mathcal{LC})s\rangle.$$

Then the condition (3.10) is satisfied, and $\mathcal{A} + \mathcal{LC}$ is an infinitesimal generator of an exponentially stable $\mathcal{C}_0$ semi-group based on Lemma 3.1.

THEOREM 3.3. *The operator $\mathcal{A}+\mathcal{BF}$ is an infinitesimal generator of an exponentially stable $\mathcal{C}_0$ semi-group if there exist polynomials $M_2(x)$, $N_2(x)$ and $N_3(x)$ defined on $x \in [0, R_0]$, such that*

$$M_2(x) > 0 \quad, \mathbf{Z}_2 < 0, \tag{3.17}$$

for all $x \in [0, R_0]$, where

$$\mathbf{Z}_2 = \begin{bmatrix} \frac{D_s M_2''(x)}{2} & 0 & \frac{N_2(x)}{2} \\ 0 & \frac{D_s M_2'(0)}{2R_0} & -\frac{N_3(0)}{2R_0} \\ \frac{N_2(x)}{2} & -\frac{N_3(0)}{2R_0} & -\frac{D_s M_2'(R_0)}{2R_0} + \frac{N_3(R_0)}{R_0}\end{bmatrix},$$

and the operator $\mathcal{B}$ and the positive-definite operator $\mathcal{P}_2$ are defined by

$$\mathcal{F}s = \int_0^{R_0}\Big(K_1(x)s(x) + \frac{\partial}{\partial x}(K_2(x)s(x))\Big)dx, \tag{3.18}$$

and

$$\mathcal{P}_2 s = M_2^{-1}(x)s, \tag{3.19}$$

where the feedback gains K_1 and K_2 are defined by

$$K_1(x) = M_2^{-1}(x)N_2(x), \qquad K_2(x) = M_2^{-1}(x)N_3(x). \tag{3.20}$$

Proof. First, let $p(x) := (\mathcal{P}_2 s)(x) = M_2^{-1}(x)s(x)$. Because $M_2(x) > 0$, the positive definiteness of $\mathcal{P}_2$ is assured. Based on Lemma 3.1, in order to prove $\mathcal{A}+\mathcal{BF}$ is an infinitesimal generator of an exponentially stable $\mathcal{C}_0$ semi-group, it is sufficient to prove that

$$\langle(\mathcal{A} + \mathcal{BF})s, \mathcal{P}_2 s\rangle + \langle\mathcal{P}_2 s, (\mathcal{A} + \mathcal{BF})s\rangle < 0. \tag{3.21}$$

Similar to before, we need to eliminate terms such as $s''(x)s(x)$ and $s'(x)s(x)$, and the following mathematical equalities are used

$$\begin{aligned}
&\int_0^{R_0}\Big(p'(x)(M_2(x)p(x))' + M_2(x)p''(x)p(x) \\
&\quad -\frac{p'(R_0)M_2(R_0)p(R_0)}{R_0} + \frac{p'(0)M_2(0)p(0)}{R_0}\Big)dx \\
&\qquad = \langle h_3, 1\rangle = 0,
\end{aligned} \tag{3.22}$$

$$\begin{aligned}
&\int_0^{R_0}\Big(2M_2'(x)p(x)p'(x) + M_2''(x)p^2(x) \\
&\quad -\frac{M_2'(R_0)p^2(R_0)}{R_0} + \frac{M_2'(0)p^2(0)}{R_0}\Big)dx \\
&\qquad = \langle h_4, 1\rangle = 0,
\end{aligned} \tag{3.23}$$

which are consequences of integration by parts. Here

$$\begin{aligned}
h_3(s'', s', s, x) &= p'(x)(M_2(x)p(x))' + M_2(x)p''(x)p(x) \\
&\quad -\frac{p'(R_0)M_2(R_0)p(R_0)}{R_0} + \frac{p'(0)M_2(0)p(0)}{R_0},
\end{aligned}$$

$$h_4(s'',s',s,x) = 2M_2'(x)p(x)p'(x) + M_2''(x)p^2(x) - \frac{M_2'(R_0)p^2(R_0)}{R_0} + \frac{M_2'(0)p^2(0)}{R_0}.$$

From the boundary conditions (2.6) and (2.7), we have

$$s'(0) = p'(0)M_2(0) + M_2'(0)p(0) = 0,$$

$$s'(R_0) = p'(R_0)M_2(R_0) + M_2'(R_0)p(R_0) = 0.$$

Therefore,

$$p'(0)M_2(0) = -M_2'(0)p(0),$$

$$p'(R_0)M_2(R_0) = -M_2'(R_0)p(R_0).$$

Substituting the equations above into equation (3.22) gives

$$\int_0^{R_0}\Big(p'(x)(M_2(x)p(x))' + M_2(x)p''(x)p(x) + \frac{M_2'(R_0)p^2(R_0)}{R_0} - \frac{M_2'(0)p^2(0)}{R_0}\Big)dx = \langle h_3, 1\rangle = 0. \tag{3.24}$$

The following is the main part of the proof. Suppose λ_3 and λ_4 are constants to be determined, then

$$\begin{aligned}
&\frac{1}{D_s}\langle \mathcal{A}s, \mathcal{P}_2 s\rangle\\
&= \frac{1}{D_s}\langle \mathcal{A}s, \mathcal{P}_2 s\rangle + \lambda_3\langle h_3, 1\rangle + \lambda_4\langle h_4, 1\rangle\\
&= \int_0^{R_0} s''(x)M_2^{-1}(x)s(x)dx + \lambda_3\langle h_3,1\rangle + \lambda_4\langle h_4,1\rangle)\\
&= \int_0^{R_0} (M_2(x)p(x))''p(x)dx + \lambda_3\langle h_3,1\rangle + \lambda_4\langle h_4,1\rangle\\
&= \int_0^{R_0} [M_2''(x)p(x)\\
&\quad +2M_2'(x)p'(x) + M_2(x)p''(x)]\,p(x)dx\\
&\quad + \lambda_3\langle h_3,1\rangle + \lambda_4\langle h_4,1\rangle\\
&= \int_0^{R_0} M_2''(x)p^2(x)dx + \int_0^{R_0} 2M_2'(x)p'(x)p(x)dx\\
&\quad + \lambda_4\langle h_4,1\rangle + \int_0^{R_0}\Big((1+\lambda_3)M_2(x)p''(x)p(x)\\
&\quad + \lambda_3 p'(x)(M_2(x)p(x))' + \frac{\lambda_3}{R_0}M_2'(R_0)p^2(R_0)\\
&\quad - \frac{\lambda_3}{R_0}M_2'(0)p^2(0)\Big)dx,
\end{aligned}$$

which becomes

$$\begin{aligned}
&= \int_0^{R_0} M_2''(x)p^2(x)dx + \int_0^{R_0}\lambda_3 M_2(x)[p'(x)]^2dx\\
&\quad + \int_0^{R_0}(1+\lambda_3)M_2(x)p''(x)p(x)dx\\
&\quad + \int_0^{R_0}(2+\lambda_3+2\lambda_4)M_2'(x)p'(x)p(x)dx\\
&\quad + \int_0^{R_0}\lambda_4 M_2''(x)p^2(x)dx\\
&\quad + \int_0^{R_0}\frac{1}{R_0}(\lambda_3-\lambda_4)M_2'(R_0)p^2(R_0)dx\\
&\quad - \int_0^{R_0}\frac{1}{R_0}M_2'(0)p^2(0)dx.
\end{aligned}$$

To eliminate the indefinite terms $(1 + \lambda_3)M_2(x)p''(x)p(x)$ and $(2+\lambda_3+2\lambda_4)M_2'(x)p'(x)p(x)$, the coefficients are set to be zero according to

$$\begin{cases} 1+\lambda_3 = 0\\ 2+\lambda_3+2\lambda_4 = 0\end{cases} \Longrightarrow \begin{cases}\lambda_3 = -1\\ \lambda_4 = -\frac{1}{2}\end{cases}.$$

Therefore,

$$\begin{aligned}
&\frac{1}{D_s}\langle \mathcal{A}s, \mathcal{P}_2 s\rangle\\
&= \frac{1}{2}\int_0^{R_0} M''(x)p^2(x)dx - \int_0^{R_0} M_2(x)[p'(x)]^2dx\\
&\quad - \frac{1}{2R_0}\int_0^{R_0}\big(M_2'(R_0)p^2(R_0)dx - M_2'(0)p^2(0)\big)\,dx.
\end{aligned}$$

Given the above results, the first term on the left hand side of equation (3.21) now can be written as

$$\begin{aligned}
&\langle \mathcal{A}s, \mathcal{P}_2 s\rangle + \langle \mathcal{BF}s, \mathcal{P}_2 s\rangle\\
&= \frac{D_s}{2}\int_0^{R_0} M''(x)p^2(x)dx\\
&\quad - D_s\int_0^{R_0} M_2(x)[p'(x)]^2dx\\
&\quad + \int_0^{R_0}\Big(-\frac{D_s}{2R_0}M_2'(R_0) + \frac{N_3(R_0)}{R_0}\Big)p^2(R_0)dx\\
&\quad + \frac{D_s}{2R_0}\int_0^{R_0} M_2'(0)p^2(0)dx\\
&\quad + \int_0^{R_0} N_2(x)p(x)p(R_0)dx\\
&\quad - \frac{1}{R_0}\int_0^{R_0} N_3(0)p(0)p(R_0)dx\\
&= -D_s\int_0^{R_0} M_2(x)[p'(x)]^2dx\\
&\quad + \int_0^{R_0}\begin{bmatrix}p(x)\\ p(0)\\ p(R_0)\end{bmatrix}^T \mathbf{Z}_2\begin{bmatrix}p(x)\\ p(0)\\ p(R_0)\end{bmatrix}dx.
\end{aligned}$$

Once condition (3.17) is satisfied, $\langle(\mathcal{A}+\mathcal{BF})s, \mathcal{P}_2 s\rangle < 0$ holds for all $s \in D(\mathcal{A})$, and because all the functions mentioned above are real, hence

$$\langle(\mathcal{A}+\mathcal{BF})s, \mathcal{P}_2 s\rangle = \langle\mathcal{P}_2 s, (\mathcal{A}+\mathcal{BF})s\rangle.$$

Then the condition (3.21) is satisfied, and $\mathcal{A}+\mathcal{BF}$ is an infinitesimal generator of an exponentially stable $\mathcal{C}_0$ semi-group based on Lemma 3.1.

4 Results

Solution of the feedback-control problem requires determination of the polynomials $M_1(x)$, $N_1(x)$, $M_2(x)$, $N_2(x)$, and $N_3(x)$. This is accomplished by constructing the problem as a feasibility problem with constraints [13], which can be solved using SOSTOOLS. More details about SOSTOOLS can be found in [13]. In order to treat intimal hyperplasia, it is desired to reduce the total amount of smooth muscle cells inside the lumen. This will be accomplished through controlling the 'negative diffusion' of smooth muscle cells out of the lumen and back into the media layer of the vessel wall. This is the reverse of the physiologically occurring processes that lead to intimal hyperplasia. Physiologically, such control would be accomplished through manipulation of the mechanisms that connect the hemodynamics in the vessel, such as wall shear stress, to the proliferation of smooth muscle cells via the growth factors. The ideal case is that there is no intimal hyperplasia in the lumen, which corresponds to $s(x,t) = 0$. Therefore, the objective is to stabilize the PDE system about the equilibrium point $s(x,t) = 0$.

Results are illustrated for the case with an initial lumen radius of $R_0 = 1.35\ mm$ and the diffusion coefficient given by $D_s = 8\times10^{-10}\ cm^2/s$ corresponding to [12]. The resulting control input is shown in Figure 2. As expected, this corresponds to negative diffusion of smooth muscle cells out of the lumen in order to reduce intimal hyperplasia. This boundary-based control input leads to the solution for the distribution of smooth muscle cell density $s(x,t)$ throughout the lumen Ω given in Figure 3. It can be seen that $s(x,t)$ converges to zero uniformly as t increases. In order to observe the corresponding overall reduction in intimal hyperplasia, see Table 1, which shows how long is required to reach certain reduction milestones. For example, reduction of intimal hyperplasia by 90% requires nearly 30 days of treatment. To accomplish this, however, the density of smooth muscle cells near $x = R_0$ at the beginning stages of the simulation is negative, which corresponds to the negative diffusion of smooth muscle cells near the boundary from the lumen to the media. This is consistent with the behavior observed in the control input shown in Figure 2. Figure 4 shows the behavior

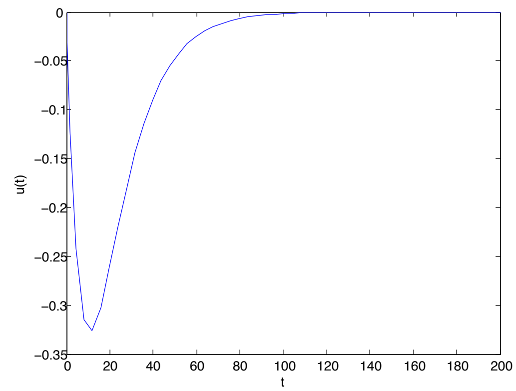

Figure 2: Control input $u(x,t)$ at vessel wall.

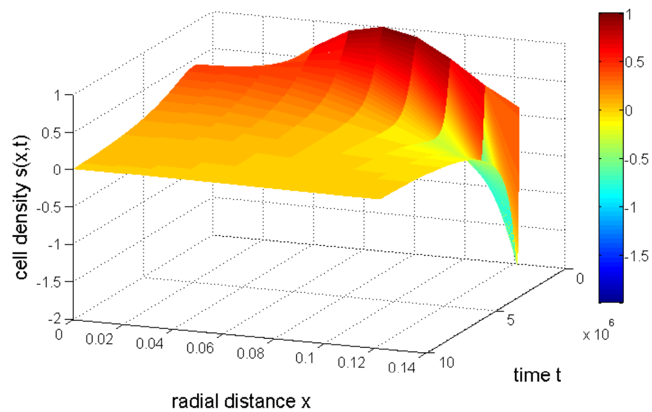

Figure 3: Distribution of cell density $s(x,t)$ resulting from feedback control.

of one of the outputs of the system, $y_1(t) = \langle s(x,t), 1\rangle$, which is the thickness of the intimal hyperplasia in the lumen measured from the initial vessel radius R_0. Observe that after only approximately two minutes, $y_1(t)$ has already converged to near zero. Compared with 92 days for a 99% reduction in the density of smooth muscle cells, we can conclude that it is much harder to remove all of the smooth muscle cells in the lumen than just reducing the thickness of the intimal hyperplasia. Potential improvements to the existing model include constraining the state variable and control input to physiologically acceptable values.

5 Conclusion

The development of intimal hyperplasia has been modeled as a diffusion process of smooth muscle cells from the media to the lumen. The classical diffusion equation, which is a parabolic PDE, with Neumann boundary conditions is used as the governing equation. To cure intimal hyperplasia, a Luenberger observer-based

Table 1: Reduction in L_2-norm of intimal hyperplasia due to control.

% Reduction	$\|\|s(x,t)\|\|_2$	**Time (sec)**
0	1.9365	0
20	1.5491	2.73×10^4
50	0.9684	1.54×10^5
70	0.5811	5.39×10^5
90	0.1935	2.56×10^6
99	0.0193	7.95×10^6

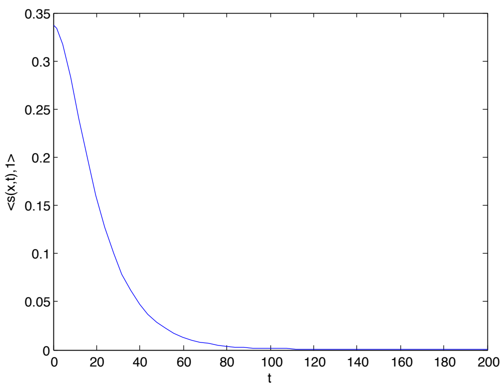

Figure 4: Thickness of intimal hyperplasia in lumen ($\langle s(x,t), 1\rangle = 0$ corresponds to no intimal hyperplasia).

controller has been used to stabilize the PDE system at the equilibrium point $s(x,t) = 0$, which corresponds to the case of zero intimal hyperplasia. The controller synthesis has been done with SOSTOOLS, and both the controller and the model have been kept infinite dimensional to avoid the loss of crucial physics due to discretization in a finite-dimensional approximation.

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