DEPARTMENT OF MATHEMATICS
TECHNICAL REPORT

A Theoretic Control Approach in Signal-controlled Metabolic Pathways

Ramesh Garimella, Uma Garimella, and Weijiu Liu

January 2007

No. 2007 − 3

UNIVERSITY OF CENTRAL ARKANSAS
Conway, AR 72035

A Theoretic Control Approach in Signal-controlled Metabolic Pathways

Ramesh Garimella[1], Uma Garimella[2], and Weijiu Liu[1*]

[1]Department of Mathematics

[2]Department of Biology

University of Central Arkansas

201 Donaghey Avenue, Conway, AR 72035, USA

Abstract

Cells use signal transduction mechanism to regulate certain metabolic pathways. In this papers, the regulatory mechanism is analyzed mathematically. For this analysis, a mathematical model for the pathways is first established using a system of differential equations. Then its local linear stability, controllability, and observability of the system are investigated. We show that the linearized system is controllable, observable, and the real parts of all eigenvalues of the linearized system are non-positive using Routh's stability criterion. Finally observer-based and proportional-integral output feedback controllers as a function of the end-product are designed to regulate the end-product to its desired level. Applications to the regulation of blood glucose levels are discussed.

Keywords: Cell signaling, metabolic pathway, output feedback control, regulation.

AMS Subject Classification: 92C45, 92C40, 93D20, 34D05

*Corresponding author. Email: weijiul@uca.edu, Phone: 1-501-450-5660, Fax: 1-501-450-5662

1 Introduction

Biochemical reactions occurring in cells can be grouped into metabolic pathways containing sequences of chemical reactions in which each reaction is catalyzed by specific enzyme, and the product of one reaction is the substrate for the next one. The compounds formed at each step are the metabolic intermediates (or metabolites) that lead ultimately to the formation of an end product. Figure 1 shows a generic metabolic pathway.

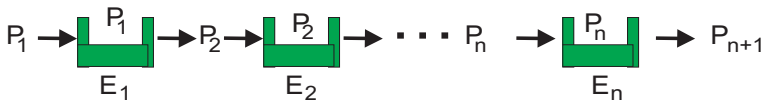

Figure 1: A generic metabolic pathway.

Cells are always in a homeostatic condition and therefore the amount of product present or produced is always within certain range of concentrations. Homeostasis is maintained by metabolic regulation primarily by feedback inhibition. In feedback inhibition, the enzyme catalyzing the first committed step in a metabolic pathway is temporarily inactivated when the end product binds to allosteric site of that enzyme. However there are other ways of regulating the metabolic pathways. One such pathway is activation or inactivation of enzymes by phosphorylation by kinases and dephosphorylation by phosphatases through cell signaling and signal transduction mechanisms.

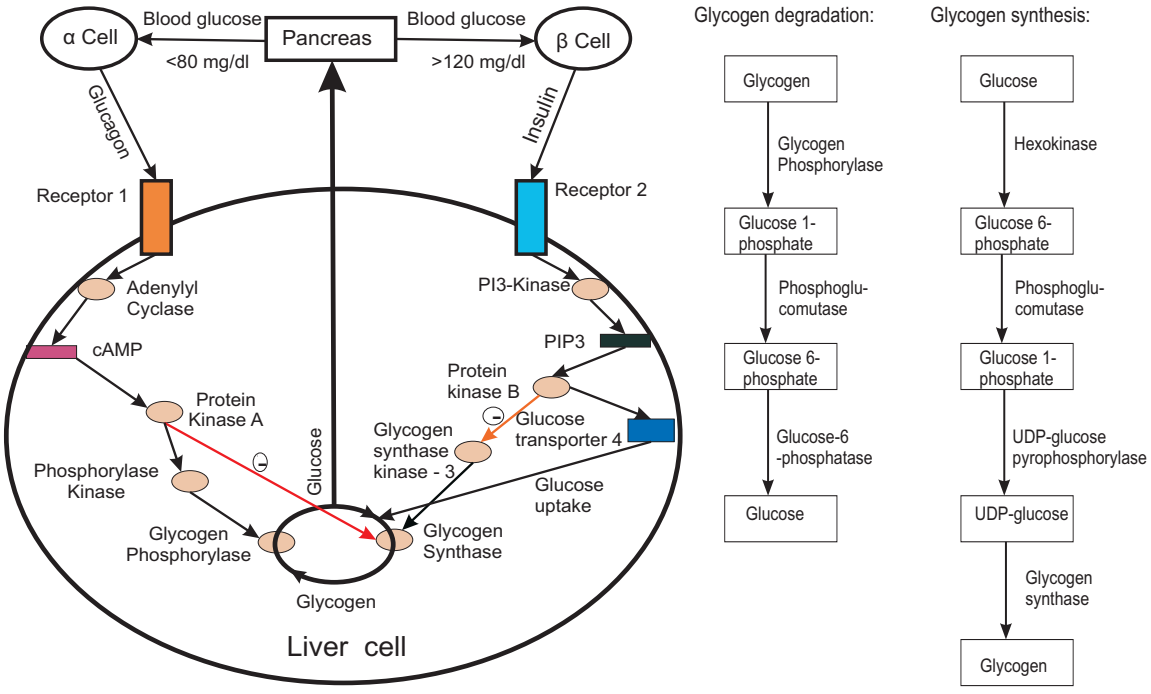

Figure 2: Regulation of blood glucose levels.

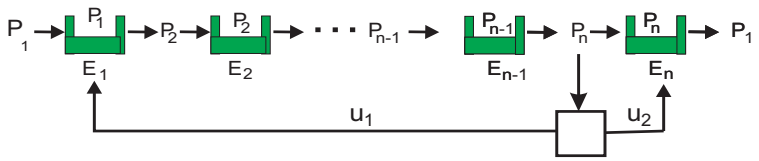

Figure 3: A generic signal-controlled metabolic pathway.

Example of such system of cell signaling can be seen in the regulation of blood glucose levels (Figure 2). Our bodies spend considerable effort maintaining blood glucose levels within a narrow range. The levels of glucose in the circulation are monitored by the pancreas. In response to low blood glucose levels, the α cells of the pancreas produce the hormone glucagon. The glucagon binds to its specific receptors, which are on the outer surface of the plasma membrane of target cells. Binding of the hormone initiates a series of reactions that leads to the activation of the enzyme glycogen phosphorylase, which catalyze the breakdown of glycogen into glucose 1-phosphate, and then glucose 6-phosphate, and finally glucose. In addition, the binding of the hormone leads to the inhibition of the enzyme glycogen synthase, which catalyses the opposing reaction in which glucose is converted to glycogen.

In response to high blood glucose levels, the β cells of the pancreas secret insulin. The insulin functions as an extracellular messenger molecule triggering a cascade of reactions to transport glucose into the cells and subsequent conversion into glycogen. In presence of insulin, a signal is generated through IRS-PI3K-PKB pathway that generates the transfer of glucose transporter 4 (GLUT4) onto the membrane. This IRS-PI3K-PKB pathway also leads to the decrease in the glycogen synthase kinase-3 (GSK-3) activity, resulting in an increase in glycogen synthase activity [2, 7].

Motivated by this example, we consider an abstract metabolic pathway as shown in Figure 3. In this figure, P_1 stands for substrate such as glycogen, P_n stands for the end-product such as glucose, and P_i $(i = 2, \cdots, n-1)$ are other metabolites like glucose 1-phosphate. E_i $(i = 1, \cdots, n)$ are enzymes like the glycogen phosphorylase and glycogen synthase. u_1 and u_2 are extracellular control signals such as glucagon and insulin. Like the glycogen degradation pathway, we assume that the activity of the enzymes E_1 and E_n is controlled by the extracellular signals u_1 and u_2 so that the end-production P_n reaches its desired level. The aim of this paper is to use mathematical control theory [8, 12, 14] to design an output feedback controller $u_1 = u_1(p_1, p_n)$ and $u_2 = u_2(p_1, p_n)$ as a function of p_1 and p_n to regulate P_n to a desired level P_n^d, where, as usual, the lower case p_1 and p_n denote the concentrations of P_1 and P_n, respectively. Since u_1 and u_2 denote the rate at which the hormones glucagon and insulin are produced in the situation of blood glucose, the designed controllers could help us understand how the hormones are produced so that the blood glucose can reach a desired level.

Theoretical control approaches have successfully aided in the research on cell signaling and signal transduction [1, 4, 5, 6, 9, 11, 15, 17, 18, 19]. Tyson, Chen, and Novak [16] pointed out that recent advances by theoretical biologists have demonstrated that molecular regulatory networks can be accurately modeled in mathematical terms. These models shed light on the design principles of biological control systems and make predictions that have been verified experimentally. Such success has been seen in the control of gene expression. The transcriptional factor NF-κB (nuclear factor κB) regulates many genes that play important

roles in intra- and extracellular signaling [9]. Hoffmann, Levchenko, Scott, and Baltimore [6] presented a computational model that describes the temporal negative feedback control of NF-κB activation by the coordinated degradation and synthesis of IκB proteins. Using ordinary differential equations, Lipniacki, Paszek, Brasier, Luxon, and Kimmel [10] modeled the two-feedback-loop regulatory module of NF-κB signaling pathway. Their model allows detailed analysis of kinetics of the involved proteins and their complexes and gives the predictions of the possible responses of whole kinetics to the change in the level of a given activator or inhibitor. Zak, Pearson, Vadigepalli, Gonye, Schwaber, and Doyle [20] developed a continuous-time approach to identify gene expression models based on ordinary differential equations to overcome limit applicability of discrete-time expression models to common biological data sets.

In this paper, employing the law of mass action, we first model the signal-controlled metabolic pathways by a system of differential equations in Section 2. Since we could not construct a Lyapunov function to address the global stability of the system, we instead consider its local linear stability, controllability, and observability in Section 3. In fact, we show that the linearized system is controllable and observable and the real parts of all eigenvalues of the linearized system are non-positive using Routh's stability criterion. Finally in Section 4, we first design the following proportional output feedback controller

$$u_1 = -K_1 \min(0, p_n - P_n^d), \quad u_2 = K_2 \min(0, p_n - P_n^d) + K_3 \max(0, p_n - P_n^d), \tag{1.1}$$

where the control gains K_1, K_2 and K_3 are positive constant. This controller is motivated by the function of pancreas. In response to low blood glucose levels ($p_n < P_n^d$), the α cells of the pancreas produce the hormone glucagon, which increases the activity of the enzyme glycogen phosphorylase and decreases the activity of the enzyme glycogen synthase. In response to high blood glucose levels ($p_n > P_n^d$), the β cells of the pancreas secret insulin which results in an increase in glycogen synthase activity, but does not impact glycogen phosphorylase. In the above controller, $-K_1 \min(0, p_n - P_n^d)$ denotes the increase of the activity of the enzyme glycogen phosphorylase by the glucagon and no impact from the insulin, $K_2 \min(0, p_n - P_n^d)$ denotes the decrease of the activity of the enzyme glycogen synthase by the glucagon, and $K_3 \max(0, p_n - P_n^d)$ denotes the increase of the activity of the enzyme glycogen synthase by the insulin. Since the system controlled by the proportional controller (1.1) contains zero eigenvalues, we also design the following dynamical observer-based controller

$$u_1 = -\sum_{j=1}^{2n+1} g_{1,j} z_j, \tag{1.2}$$

$$u_2 = -\sum_{j=1}^{2n+1} g_{2,j} z_j, \tag{1.3}$$

$$\frac{d\mathbf{z}}{dt} = (\mathbf{A} - \mathbf{BG} - \mathbf{HC})\mathbf{z} + \mathbf{H} \begin{pmatrix} p_1 - P_1^d \\ p_n - P_n^d \end{pmatrix}, \tag{1.4}$$

where $\mathbf{A}$ is the matrix of a linearized system, $\mathbf{B}$ is a control matrix, $\mathbf{C}$ is an observer matrix, and the feedback gain $\mathbf{G}$ and the observer gain $\mathbf{H}$ are defined by

$$\mathbf{G} = \begin{pmatrix} g_{1,1} & g_{1,2} & \cdots & g_{1,2n+1} \\ g_{2,1} & g_{2,2} & \cdots & g_{2,2n+1} \end{pmatrix}, \quad \mathbf{H} = \begin{pmatrix} h_{1,1} & h_{1,2} & \cdots & h_{1,2n+1} \\ h_{2,1} & h_{2,2} & \cdots & h_{2,2n+1} \end{pmatrix}^T$$

such that both $\mathbf{A}-\mathbf{BG}$ and $\mathbf{A}-\mathbf{HC}$ are Hurwitz. With this observer-based controller, the controlled system is locally exponentially stable. We note that in the observer-based controller, the error $p_1-P_1^d$ is mathematically required to be available. This requirement may not be met in real biological situations such as the glycogen degradation, where the glycogen is stored in liver cells and the pancreas can not detect it. This mathematical requirement may imply that the blood glucose regulatory system may contain zero eigenvalues and then may not be asymptotically stable.

2 Mathematical Models

The series of enzymatic reactions in the signal-controlled metabolic pathway in Figure 3 can be described by the following reaction diagram

$$\begin{aligned}
u_1 \longrightarrow P_1 + E_1 \underset{k_{1,2}}{\overset{k_{1,1}}{\rightleftharpoons}} C_1 &\xrightarrow{k_{1,3}} P_2 + E_1 \\
P_2 + E_2 \underset{k_{2,2}}{\overset{k_{2,1}}{\rightleftharpoons}} C_2 &\xrightarrow{k_{2,3}} P_3 + E_2 \\
&\vdots \\
P_{n-1} + E_{n-1} \underset{k_{n-1,2}}{\overset{k_{n-1,1}}{\rightleftharpoons}} C_{n-1} &\xrightarrow{k_{n-1,3}} P_n + E_{n-1}, \\
u_2 \longrightarrow P_n + E_n \underset{k_{n,2}}{\overset{k_{n,1}}{\rightleftharpoons}} C_n &\xrightarrow{k_{n,3}} P_1 + E_n,
\end{aligned} \tag{2.1}$$

where k_{ij} denote the reaction constants, and u_1, u_2 the coming control signals to activate or inactivate the enzymes E_1 and E_n.

In real biological situations, concentrations of molecules in a cell may vary in different locations, and so may not be homogeneous. However, for simplicity, we here focus on a particular tissue and hence we can assume that the concentrations are uniform. Therefore, by the law of mass action [13, 17], the dynamics of the signal-controlled metabolic pathway

(2.1) can be modeled by the following system of nonlinear ordinary differential equations

$$\begin{aligned}
\frac{dp_1}{dt} &= -k_{1,1}e_1p_1 + k_{1,2}c_1 + k_{n,3}c_n, && (2.2)\\
\frac{de_1}{dt} &= -k_{1,1}e_1p_1 + (k_{1,2}+k_{1,3})c_1 + u_1, && (2.3)\\
\frac{de_1^i}{dt} &= -u_1, && (2.4)\\
\frac{de_j}{dt} &= -k_{j,1}e_jp_j + (k_{j,2}+k_{j,3})c_j, \quad j = 2,\cdots,n-1, && (2.5)\\
\frac{dc_j}{dt} &= k_{j,1}e_jp_j - (k_{j,2}+k_{j,3})c_j, \quad j = 1,\cdots,n, && (2.6)\\
\frac{dp_j}{dt} &= -k_{j,1}p_je_j + k_{j-1,3}c_{j-1} + k_{j,2}c_j, \quad j = 2,\cdots,n-1, && (2.7)\\
\frac{dp_n}{dt} &= -k_{n,1}p_ne_n + k_{n-1,3}c_{n-1} + k_{n,2}c_n, && (2.8)\\
\frac{de_n}{dt} &= -k_{n,1}p_ne_n + (k_{n,2}+k_{n,3})c_n + u_2, && (2.9)\\
\frac{de_n^i}{dt} &= -u_2, && (2.10)\\
p_1(0) &= P_1^0,\ p_n(0) = P_n^0,\ e_1(0) = E_1^0,\ e_1^i(0) = E_1^{i,0},\ e_n(0) = E_n^0,\ e_n^i(0) = E_n^{i,0}, &&\\
p_j(0) &= c_j(0) = 0,\ e_j(0) = E_j^0,\ c_1(0) = c_n(0) = 0 \quad j = 2,\cdots,n-1 && (2.11)
\end{aligned}$$

where, as usual, the lower case letters denote the concentrations of corresponding biological species and P_1^0, P_n^0, E_j^0 the initial concentrations of p_1, p_n, e_j, respectively. Here we have introduced the the inactive form e_j^i $(j = 1, n)$ of the enzymes E_1 and E_n (the superscript i stands for inactive). The reasonably available outputs are

$$\mathbf{y} = \begin{pmatrix} p_1 \\ p_n \end{pmatrix}.$$

From the above system, we can readily derive that

$$\begin{aligned}
\frac{d}{dt}(e_j + e_j^i + c_j) &= 0, \quad j = 1, n,\\
\frac{d}{dt}(e_j + c_j) &= 0, \quad j = 2,\cdots,n-1,\\
\frac{d}{dt}\left(\sum_{j=1}^n p_j + \sum_{j=1}^n c_j\right) &= 0,
\end{aligned}$$

and then

$$\begin{aligned}
e_j + e_j^i + c_j &= E_j^0 + E_j^{i,0}, \quad j = 1, n, && (2.12)\\
c_j + e_j &= E_j^0, \quad j = 2,\cdots,n-1, && (2.13)\\
\sum_{j=1}^n p_j + \sum_{j=1}^n c_j &= P_1^0. && (2.14)
\end{aligned}$$

These equations reflect conservation of enzymes and substrates, and hence, the system (2.2)-(2.10) can be reduced to

$$\begin{aligned}
\frac{dp_1}{dt} &= -k_{1,1}e_1p_1 + k_{1,2}c_1 + k_{n,3}c_n, && (2.15)\\
\frac{de_1}{dt} &= -k_{1,1}e_1p_1 + (k_{1,2}+k_{1,3})c_1 + u_1, && (2.16)\\
\frac{de_1^i}{dt} &= -u_1, && (2.17)\\
\frac{de_j}{dt} &= -k_{j,1}e_jp_j + (k_{j,2}+k_{j,3})c_j, \quad j = 2,\cdots,n-1, && (2.18)\\
\frac{dp_j}{dt} &= -k_{j,1}p_je_j + k_{j-1,3}c_{j-1} + k_{j,2}c_j, \quad j = 2,\cdots,n-1, && (2.19)\\
\frac{dp_n}{dt} &= -k_{n,1}p_ne_n + k_{n-1,3}c_{n-1} + k_{n,2}c_n, && (2.20)\\
\frac{de_n}{dt} &= -k_{n,1}p_ne_n + (k_{n,2}+k_{n,3})c_n + u_2, && (2.21)\\
p_1(0) &= P_1^0,\ p_n(0) = P_n^0,\ e_1(0) = E_1^0,\ e_1^i(0) = E_1^{i,0},\ e_n(0) = E_n^0,\\
p_j(0) &= 0,\ e_j(0) = E_j^0, \quad j = 2,\cdots,n-1 && (2.22)
\end{aligned}$$

with the output

$$\mathbf{y} = \begin{pmatrix} p_1 \\ p_n \end{pmatrix}. \tag{2.23}$$

3 Linear Stability and Controllability

Before we design a control law, we first study the linear stability and controllability of the nonlinear system (2.15)-(2.23). The global stability and controllability of the system are left open since it seems difficulty to construct a Lyapunov function for the system.

Throughout this paper, we consider only nonnegative solutions in accord with the biological situations.

The linearized system of the nonlinear system (2.15)-(2.21) at any equilibrium point

$$e_1^i = E_1^i, \quad p_j = P_j, \quad e_j = E_j, \quad j = 1,\cdots,n$$

is given by

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{x} + \mathbf{B}u, \quad \mathbf{y} = \mathbf{C}\mathbf{x}, \tag{3.1}$$

where

$$\begin{aligned}
\mathbf{x} &= (p_1 - P_1, e_1 - E_1, e_1^i - E_1^i, p_2 - P_2, e_2 - E_2, \cdots,\\
&\quad p_{n-1} - P_{n-1}, e_{n-1} - E_{n-1}, p_n - P_n, e_n - E_n)^T,\\
\mathbf{B} &= \begin{pmatrix} 0 & 1 & -1 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 & 1 \end{pmatrix}^T,\\
\mathbf{C} &= \begin{pmatrix} 1 & 0 & 0 & 0 & \cdots & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \cdots & 0 & 1 & 0 \end{pmatrix},
\end{aligned}$$

and $\mathbf{A}$ is the linearized Jacobian matrix given by

$$\mathbf{A} = \begin{pmatrix} \mathbf{A}_1 & \mathbf{F} & \mathbf{F} & \cdots & \mathbf{F} & \mathbf{F} & \mathbf{Q} \\ \mathbf{D}_1 & \mathbf{A}_2 & 0 & \cdots & 0 & 0 & 0 \\ 0 & \mathbf{D}_2 & \mathbf{A}_3 & \cdots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & \mathbf{A}_{n-2} & 0 & 0 \\ 0 & 0 & 0 & \cdots & \mathbf{D}_{n-2} & \mathbf{A}_{n-1} & 0 \\ \mathbf{R} & \mathbf{U} & \mathbf{U} & \cdots & \mathbf{U} & \mathbf{D}_{n-1} & \mathbf{A}_n \end{pmatrix}, \tag{3.2}$$

$$\mathbf{A}_1 = \begin{pmatrix} -k_{1,1}E_1 - k_{n,3} & -k_{1,1}P_1 - k_{1,2} + k_{n,3} & -k_{1,2} + k_{n,3} \\ -k_{1,1}E_1 & -k_{1,1}P_1 - k_{1,2} - k_{1,3} & -k_{1,2} - k_{1,3} \\ 0 & 0 & 0 \end{pmatrix}, \tag{3.3}$$

$$\mathbf{A}_i = \begin{pmatrix} -k_{i,1}E_i & -k_{i,1}P_i - k_{i,2} \\ -k_{i,1}E_i & -k_{i,1}P_i - k_{i,2} - k_{i,3} \end{pmatrix}, \quad i = 2, \cdots, n-1, \tag{3.4}$$

$$\mathbf{A}_n = \begin{pmatrix} -k_{n,1}E_n - k_{n,1} & -k_{n,1}P_n \\ -k_{n,1}E_n - k_{n,2} - k_{n,3} & -k_{n,1}P_n \end{pmatrix}, \tag{3.5}$$

$$\mathbf{D}_1 = \begin{pmatrix} 0 & -k_{1,3} & -k_{1,3} \\ 0 & 0 & 0 \end{pmatrix}, \tag{3.6}$$

$$\mathbf{D}_i = \begin{pmatrix} 0 & -k_{i,3} \\ 0 & 0 \end{pmatrix}, \quad i = 2, \cdots, n-2, \tag{3.7}$$

$$\mathbf{D}_{n-1} = \begin{pmatrix} -k_{n,2} & -k_{n-1,3} + k_{n,2} \\ -k_{n,2} - k_{n,3} & k_{n,2} + k_{n,3} \end{pmatrix}, \tag{3.8}$$

$$\mathbf{F} = \begin{pmatrix} -k_{n,3} & k_{n,3} \\ 0 & 0 \\ 0 & 0 \end{pmatrix}, \tag{3.9}$$

$$\mathbf{Q} = \begin{pmatrix} -k_{n,3} & 0 \\ 0 & 0 \\ 0 & 0 \end{pmatrix}, \tag{3.10}$$

$$\mathbf{R} = \begin{pmatrix} -k_{n,2} & k_{n,2} & k_{n,2} \\ -k_{n,2} - k_{n,3} & k_{n,2} + k_{n,3} & k_{n,2} + k_{n,3} \end{pmatrix}, \tag{3.11}$$

$$\mathbf{U} = \begin{pmatrix} -k_{n,2} & k_{n,2} \\ -k_{n,2} - k_{n,3} & k_{n,2} + k_{n,3} \end{pmatrix}. \tag{3.12}$$

Glycogen synthase and glycogen phosphorylase are the two regulatory enzymes of glycogen synthesis and glycogen degradation, respectively. Both catalyze non-equilibrium reversible reactions and are subject to control by allosteric and covalent modulation. We will consider only these two enzymes in the following analysis. Thus, in what follows, we will assume that $n = 2$. In the general case, we guess some of the following results are still true,

but need to justify. In the case of $n = 2$, the Jacobian matrix is equal to

$$\mathbf{A} = \begin{pmatrix} -k_{1,1}E_1 - k_{2,3} & -k_{1,1}P_1 - k_{1,2} + k_{2,3} & -k_{1,2} + k_{2,3} & -k_{2,3} & 0 \\ -k_{1,1}E_1 & -k_{1,1}P_1 - k_{1,2} - k_{1,3} & -k_{1,2} - k_{1,3} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ -k_{2,2} & -k_{1,3} + k_{2,2} & -k_{1,3} + k_{2,2} & -k_{2,1}E_2 - k_{2,2} & -k_{2,1}P_2 \\ -k_{2,2} - k_{2,3} & k_{2,2} + k_{2,3} & k_{2,2} + k_{2,3} & -k_{2,1}E_2 - k_{2,2} - k_{2,3} & -k_{2,1}P_2 \end{pmatrix}.$$

Theorem 3.1. *Assume that $n = 2$.*

(i) If $E_1 = E_2 = 0$, then the characteristic polynomial of the Jacobian matrix $\mathbf{A}$ is equal to

$$\det(\lambda\mathbf{I} - \mathbf{A}) = (\lambda + k_{1,1}P_1 + k_{1,2} + k_{1,3})(\lambda + k_{2,1}P_2 + k_{2,2} + k_{2,3})\lambda^3. \tag{3.13}$$

(ii) If either E_1 or E_2 is not equal to zero, then the characteristic polynomial of the Jacobian matrix $\mathbf{A}$ is equal to

$$\det(\lambda\mathbf{I} - \mathbf{A}) = \lambda^2\left(a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4\right), \tag{3.14}$$

and the real parts of all roots of the polynomial are non-positive, where

$$\begin{aligned} a_1 &= 1, \\ a_2 &= k_{2,1}E_2 + k_{2,1}P_2 + k_{2,2} + k_{1,1}P_1 + k_{1,3} + k_{1,2} + k_{1,1}E_1 + k_{2,3}, \\ a_3 &= k_{1,2}k_{2,1}E_2 + k_{2,2}k_{1,2} + k_{1,2}k_{2,3} + k_{1,3}k_{2,1}P_2 + k_{1,2}k_{2,1}P_2 + k_{1,1}E_1k_{2,1}P_2 \\ &\quad + k_{1,3}k_{2,2} + k_{1,1}E_1k_{2,3} + k_{1,1}P_1k_{2,1}E_2 + k_{1,3}k_{2,3} + k_{2,3}k_{2,1}E_2 + k_{1,1}E_1k_{1,3} \\ &\quad + k_{1,1}P_1k_{2,3} + k_{1,1}P_1k_{2,1}P_2 + k_{1,1}E_1k_{2,1}E_2 + k_{1,3}k_{2,1}E_2 + k_{2,2}k_{1,1}P_1 + k_{1,1}E_1k_{2,2}, \\ a_4 &= k_{1,1}E_1k_{1,3}k_{2,2} + k_{2,1}E_2k_{1,1}E_1k_{2,3} + k_{1,1}E_1k_{1,3}k_{2,1}P_2 + k_{2,3}k_{1,2}k_{2,1}E_2 \\ &\quad + k_{1,3}k_{2,3}k_{2,1}E_2 + k_{1,1}E_1k_{1,3}k_{2,1}E_2 + k_{2,3}k_{1,1}E_1k_{1,3} + k_{2,3}k_{1,1}P_1k_{2,1}E_2. \end{aligned}$$

Proof. All the above polynomials are computed by the Maple software. It suffices to prove that the real parts of all roots of the cubic polynomial are non-positive. We use the Routh's stability criterion to prove it. The Routh's array for the polynomial is as follows:

$$\begin{array}{lll} \lambda^3: & a_1 & a_3 \\ \lambda^2: & a_2 & a_4 \\ \lambda^1: & b_1 & 0 \\ \lambda^0: & a_4 & \end{array}$$

where

$$b_1 = a_2a_3 - a_4.$$

We can easily check that every term in a_4 is contained in a_2a_3. So the first column of Routh's array is all positive and then all the real parts of the roots of the cubic polynomial are negative. □

Theorem 3.2. *Assume that $n = 2$.*

(i) if $P_2 \neq \frac{k_{2,3}+k_{2,2}+k_{2,1}E_2}{k_{2,1}}$, then the linear system (3.1) is controllable.

(ii) if $P_1 \neq \frac{k_{2,3}-k_{1,2}}{k_{1,1}}$, then the linear system (3.1) is observable.

Proof. It is well known [12] that it suffices to show that the Kalman controllability matrices

$$\begin{aligned} \mathcal{C}_1 &= [\mathbf{B}|\ \mathbf{AB}|\ \mathbf{A}^2\mathbf{B}|\ \mathbf{A}^3\mathbf{B}|\ \mathbf{A}^4\mathbf{B}], \\ \mathcal{C}_2 &= [\mathbf{C}^T|\ \mathbf{A}^T\mathbf{C}^T|\ (\mathbf{A}^T)^2\mathbf{C}^T|\ (\mathbf{A}^T)^3\mathbf{C}^T|\ (\mathbf{A}^T)^4\mathbf{C}^T] \end{aligned}$$

have rank 5. For this, we used the Maple software to compute the determinant of the matrix $\mathbf{M}$ consisting of the first five columns of $\mathcal{C}_1$ and obtained

$$\det(\mathbf{M}) = 2\,{k_{1,1}}^2{P_1}^2k_{1,3}(k_{2,3}+k_{2,2}-k_{2,1}(P_2-E_2)) \neq 0.$$

In the same way, the determinant of the matrix $\mathbf{M}$ consisting of the first five columns of $\mathcal{C}_2$ is equal to

$$\det(\mathbf{M}) = k_{1,1}k_{2,1}{P_1}^2P_2(k_{1,3}+k_{2,3})(k_{2,3}-k_{1,2}-k_{1,1}P_1) \neq 0.$$

So they have rank 5, respectively. □

We recall that P_1, P_2, and E_2 in the above theorem denote the equilibrium of the system (2.15)-(2.21), which has infinite equilibria. The equilibrium P_2 of the end-product is the target of regulation. Hence the controllability condition $P_2 \neq \frac{k_{2,3}+k_{2,2}+k_{2,1}E_2}{k_{2,1}}$ implies that if the desired level of the end-product is not equal to $\frac{k_{2,3}+k_{2,2}+k_{2,1}E_2}{k_{2,1}}$, then a controller exist to regulate the end-product to it. The observability condition $P_1 \neq \frac{k_{2,3}-k_{1,2}}{k_{1,1}}$ implies that if the substrate is not equal to $\frac{k_{2,3}-k_{1,2}}{k_{1,1}}$ at equilibrium, then the system is observable.

If we use only the end-product p_n as the output $y = p_n$, then $\mathbf{C} = (0, 0, 0, 1, 0)$. Using the Maple software, we compute that the rank of $\mathcal{C} = [\mathbf{C}^T|\ \mathbf{A}^T\mathbf{C}^T|\ (\mathbf{A}^T)^2\mathbf{C}^T|\ (\mathbf{A}^T)^3\mathbf{C}^T|\ (\mathbf{A}^T)^4\mathbf{C}^T]$ is equal to 4. So the linear system (3.1) is not observable.

4 Output Feedback Controllers

For a desired level P_n^d of the end-product, we now design a number of controllers to regulate it to the desired level. We start with the well-known proportional controllers.

4.1 Proportional Controllers

At an equilibrium, we wish that the end-product reaches the desired level P_n^d, that is, $\bar{p}_n = P_n^d$, where the bar $^-$ denotes the steady state. It is clear that the system (2.15)-(2.21) has infinite equilibria, but the equilibrium that makes sense biologically is

$$\bar{p}_1 = P_1^0 + P_n^d - P_n^d,\ p_j = 0\ (j = 2, \cdot, n-1),\ \bar{p}_n = P_n^d, \tag{4.1}$$

$$\bar{e}_1 = 0,\ e_j = E_j^0\ (j = 2, \cdot, n-1),\ e_n = 0, \tag{4.2}$$

$$\bar{e}_1^i = E_0^1,\ e_2^i = E_n^0. \tag{4.3}$$

We first propose the following proportional feedback controller

$$u_1 = -K_1(p_n - P_n^d), \quad u_2 = K_2(p_n - P_n^d), \tag{4.4}$$

where the feedback gains K_1, K_2 are nonnegative constants.

Theorem 4.1. *Assume that $n = 2$. Then the characteristic polynomial of the Jacobian matrix of the nonlinear system (2.15)-(2.20) with the proportional controller (4.4) at the equilibrium point*

$$\bar{p}_j = P_j, \quad \bar{e}_j = 0, \quad j = 1, 2$$

is given by

$$\det(\lambda \mathbf{I} - \mathbf{A}) \;=\; \lambda \left(a_1 \lambda^4 + a_2 \lambda^3 + a_3 \lambda^2 + a_4 \lambda + a_5 \right), \tag{4.5}$$

where

$$\begin{aligned}
a_1 &= 1, \\
a_2 &= k_{2,2} + k_{1,2} + k_{1,3} + k_{2,1}P_2 + k_{1,1}P_1 + k_{2,3}, \\
a_3 &= k_{1,1}P_1 k_{2,1}P_2 + k_{2,1}P_2 K_{\mathit{2}} + k_{1,3}k_{2,2} + k_{2,2}k_{1,2} + k_{1,2}k_{2,1}P_2 \\
&\quad + k_{1,2}k_{2,3} + k_{2,2}k_{1,1}P_1 + k_{1,3}k_{2,1}P_2 + k_{1,3}k_{2,3} + k_{1,1}P_1 k_{2,3}, \\
a_4 &= k_{1,1}P_1 k_{1,3}K_{\mathit{1}} + k_{1,3}k_{2,1}P_2 K_{\mathit{2}} + k_{1,1}P_1 k_{2,1}P_2 K_{\mathit{2}} + k_{2,3}k_{2,1}P_2 K_{\mathit{2}} + k_{1,2}k_{2,1}P_2 K_{\mathit{2}}, \\
a_5 &= K_{\mathit{2}}\, k_{1,3}k_{2,3}k_{2,1}P_2 + k_{1,3}K_{\mathit{1}}\, k_{2,1}P_2 k_{1,1}P_1 + K_{\mathit{2}}\, k_{1,2}k_{2,3}k_{2,1}P_2 \\
&\quad + k_{2,3}k_{1,1}P_1 k_{1,3}K_{\mathit{1}} + k_{2,2}k_{1,1}P_1 k_{1,3}K_{\mathit{1}} + k_{1,1}P_1 k_{2,3}k_{2,1}P_2 K_{\mathit{2}}.
\end{aligned}$$

Moreover, if $K_1, K_2 \geq 0$ and K_1 is sufficiently smaller than K_2, then the real parts of all roots of the quartic polynomial in the above expression are negative.

Proof. The polynomial (4.5) is obtained by using the Maple software. We now use the Routh's stability criterion to prove that the real parts of all roots of the quartic polynomial are negative.

Routh's array for the quratic polynomial is given by

$$\begin{array}{lllll}
\lambda^4: & a_1, & a_3, & a_5 \\
\lambda^3: & a_2, & a_4 & 0 \\
\lambda^2: & b_1, & a_5 & 0 \\
\lambda^1: & c_1, & 0 \\
\lambda^0: & a_5,
\end{array}$$

where

$$\begin{aligned}
a_2 b_1 &= a_2 a_3 - a_1 a_4 \\
&= {k_{2,1}}^2 {P_2}^2 K_{\mathit{2}} - k_{1,1}P_1 k_{1,3}K_{\mathit{1}} + 2\, k_{1,1}P_1 k_{1,3}k_{2,2} + {k_{1,1}}^2 {P_1}^2 k_{2,1}P_2 \\
&\quad + 2\, k_{1,1}P_1 k_{2,2}k_{1,2} + 2\, k_{1,1}P_1 k_{1,3}k_{2,3} + 2\, k_{1,1}P_1 k_{1,2}k_{2,3} + 2\, k_{2,1}P_2 k_{1,3}k_{2,2} \\
&\quad + 2\, k_{2,1}P_2 k_{2,2}k_{1,2} + {k_{2,1}}^2 {P_2}^2 k_{1,1}P_1 + 2\, k_{2,3}k_{1,2}k_{2,1}P_2 + 2\, k_{2,3}k_{1,3}k_{2,1}P_2 \\
&\quad + 2\, k_{2,3}k_{2,2}k_{1,1}P_1 + 2\, k_{1,3}k_{1,2}k_{2,1}P_2 + k_{1,3}{k_{2,3}}^2 + k_{1,2}{k_{2,3}}^2 + {k_{1,3}}^2 k_{2,2} + {k_{1,3}}^2 k_{2,3} \\
&\quad + k_{1,3}{k_{2,2}}^2 + {k_{2,2}}^2 k_{1,2} + k_{2,2}{k_{1,2}}^2 + {k_{1,2}}^2 k_{2,3} + 2\, k_{1,3}k_{1,2}k_{2,3} + 2\, k_{1,3}k_{2,2}k_{1,2} + 2\, k_{2,3}k_{2,2}k_{1,2} \\
&\quad + 2\, k_{2,3}k_{1,3}k_{2,2} + {k_{1,2}}^2 k_{2,1}P_2 + {k_{2,2}}^2 k_{1,1}P_1 + {k_{1,3}}^2 k_{2,1}P_2 + {k_{2,1}}^2 {P_2}^2 k_{1,3} \\
&\quad + {k_{2,1}}^2 {P_2}^2 k_{1,2} + k_{1,1}P_1 {k_{2,3}}^2 + {k_{1,1}}^2 {P_1}^2 k_{2,2} + {k_{1,1}}^2 {P_1}^2 k_{2,3} + 2\, k_{1,1}P_1 k_{1,3}k_{2,1}P_2 \\
&\quad + 2\, k_{1,1}P_1 k_{1,2}k_{2,1}P_2 + 2\, k_{2,1}P_2 k_{2,2}k_{1,1}P_1 + 2\, k_{2,3}k_{1,1}P_1 k_{2,1}P_2 + k_{2,2}k_{2,1}P_2 K_{\mathit{2}},
\end{aligned}$$

$$
\begin{aligned}
c_1b_1a_2 &= a_2a_3a_4 - a_1a_4^2 - a_2^2a_5 \\
&= 2\,{k_{2,1}}^3{P_2}^3k_{1,3}k_{1,2}K_2 - {k_{2,1}}^2{P_2}^2k_{1,2}k_{1,1}P_1k_{1,3}K_1 - {k_{1,1}}^2{P_1}^2{k_{2,3}}^2k_{1,3}K_1 \\
&\quad +{k_{1,1}}^3{P_1}^3k_{2,2}k_{2,1}P_2K_2 - 2\,k_{2,1}P_2k_{2,2}{k_{1,1}}^2{P_1}^2k_{1,3}K_1 + 2\,{k_{2,1}}^2{P_2}^2k_{2,2}{k_{1,1}}^2{P_1}^2K_2 \\
&\quad -2\,k_{2,3}{k_{1,1}}^2{P_1}^2k_{2,1}P_2k_{1,3}K_1 + k_{2,2}k_{2,1}P_2K_2\,k_{1,1}P_1k_{1,3}K_1 + k_{2,2}{k_{2,1}}^2{P_2}^2{K_2}^2k_{1,3} \\
&\quad +k_{2,2}{k_{2,1}}^2{P_2}^2{K_2}^2k_{1,1}P_1 + k_{2,2}{k_{2,1}}^2{P_2}^2{K_2}^2k_{2,3} + k_{2,2}{k_{2,1}}^2{P_2}^2{K_2}^2k_{1,2} \\
&\quad -{k_{1,3}}^2k_{2,1}P_2K_2\,k_{1,1}P_1K_1 - {k_{1,1}}^2{P_1}^2k_{2,1}P_2K_2\,k_{1,3}K_1 - k_{1,2}k_{2,1}P_2K_2\,k_{1,1}P_1k_{1,3}K_1 \\
&\quad +{k_{2,1}}^2{P_2}^2K_2\,k_{1,1}P_1k_{1,3}K_1 + {k_{2,1}}^3{P_2}^3{K_2}^2k_{1,1}P_1 - k_{2,3}k_{2,1}P_2K_2\,k_{1,1}P_1k_{1,3}K_1 \\
&\quad +3\,k_{1,1}P_1{k_{1,3}}^2k_{2,2}k_{2,1}P_2K_2 + 3\,{k_{1,1}}^2{P_1}^2k_{1,3}k_{2,2}k_{2,1}P_2K_2 + 2\,k_{1,1}P_1k_{1,3}k_{2,2}k_{2,3}k_{2,1}P_2K_2 \\
&\quad +6\,k_{1,1}P_1k_{1,3}k_{2,2}k_{1,2}k_{2,1}P_2K_2 + 3\,{k_{1,1}}^2{P_1}^2{k_{2,1}}^2{P_2}^2k_{1,3}K_2 + {k_{1,1}}^3{P_1}^3{k_{2,1}}^2{P_2}^2K_2 \\
&\quad +{k_{1,1}}^2{P_1}^2{k_{2,1}}^2{P_2}^2k_{2,3}K_2 + 3\,{k_{1,1}}^2{P_1}^2{k_{2,1}}^2{P_2}^2k_{1,2}K_2 + {k_{2,1}}^3{P_2}^3{K_2}^2k_{1,3} \\
&\quad +{k_{2,1}}^3{P_2}^3{K_2}^2k_{2,3} + {k_{2,1}}^3{P_2}^3{K_2}^2k_{1,2} + {k_{1,2}}^3{k_{2,1}}^2{P_2}^2K_2 + {k_{1,3}}^3{k_{2,1}}^2{P_2}^2K_2 \\
&\quad +{k_{2,1}}^3{P_2}^3{k_{1,3}}^2K_2 + {k_{2,1}}^3{P_2}^3{k_{1,2}}^2K_2 - {k_{1,1}}^2{P_1}^2{k_{1,3}}^2{K_1}^2 \\
&\quad +3\,{k_{1,1}}^2{P_1}^2k_{2,2}k_{1,2}k_{2,1}P_2K_2 + 2\,k_{1,1}P_1k_{2,2}k_{1,2}k_{2,3}k_{2,1}P_2K_2 + 3\,k_{1,1}P_1k_{2,2}{k_{1,2}}^2k_{2,1}P_2K_2 \\
&\quad -2\,k_{2,1}P_2{k_{1,3}}^2k_{2,2}k_{1,1}P_1K_1 + 2\,{k_{2,1}}^2{P_2}^2{k_{1,3}}^2k_{2,2}K_2 + 4\,{k_{2,1}}^2{P_2}^2k_{1,3}k_{2,2}k_{1,1}P_1K_2 \\
&\quad +4\,{k_{2,1}}^2{P_2}^2k_{1,3}k_{2,2}k_{1,2}K_2 - 2\,k_{2,1}P_2k_{2,2}k_{1,2}k_{1,1}P_1k_{1,3}K_1 + 4\,{k_{2,1}}^2{P_2}^2k_{2,2}k_{1,2}k_{1,1}P_1K_2 \\
&\quad +2\,{k_{2,1}}^2{P_2}^2k_{2,2}{k_{1,2}}^2K_2 - {k_{2,1}}^2{P_2}^2{k_{1,1}}^2{P_1}^2k_{1,3}K_1 + 2\,{k_{2,1}}^3{P_2}^3k_{1,1}P_1k_{1,3}K_2 \\
&\quad +{k_{2,1}}^3{P_2}^3{k_{1,1}}^2{P_1}^2K_2 + 2\,{k_{2,1}}^3{P_2}^3k_{1,1}P_1k_{1,2}K_2 - 2\,k_{2,3}k_{1,2}k_{2,1}P_2k_{1,1}P_1k_{1,3}K_1 \\
&\quad +2\,k_{2,3}k_{1,2}{k_{2,1}}^2{P_2}^2k_{1,3}K_2 + 2\,k_{2,3}k_{1,2}{k_{2,1}}^2{P_2}^2k_{1,1}P_1K_2 + k_{2,3}{k_{1,2}}^2{k_{2,1}}^2{P_2}^2K_2 \\
&\quad -2\,k_{2,3}{k_{1,3}}^2k_{2,1}P_2k_{1,1}P_1K_1 + k_{2,3}{k_{1,3}}^2{k_{2,1}}^2{P_2}^2K_2 + 2\,k_{2,3}k_{1,3}{k_{2,1}}^2{P_2}^2k_{1,1}P_1K_2 \\
&\quad -2\,k_{2,3}k_{2,2}{k_{1,1}}^2{P_1}^2k_{1,3}K_1 + k_{2,3}k_{2,2}{k_{1,1}}^2{P_1}^2k_{2,1}P_2K_2 \\
&\quad +3\,{k_{1,3}}^2k_{1,2}{k_{2,1}}^2{P_2}^2K_2 + 6\,k_{1,3}k_{1,2}{k_{2,1}}^2{P_2}^2k_{1,1}P_1K_2 \\
&\quad +3\,k_{1,3}{k_{1,2}}^2{k_{2,1}}^2{P_2}^2K_2 - {k_{1,3}}^2{k_{2,3}}^2k_{1,1}P_1K_1 - k_{1,2}{k_{2,3}}^2k_{1,1}P_1k_{1,3}K_1 \\
&\quad +{k_{1,3}}^3k_{2,2}k_{2,1}P_2K_2 + {k_{1,3}}^2k_{2,2}k_{2,3}k_{2,1}P_2K_2 + 3\,{k_{1,3}}^2k_{2,2}k_{1,2}k_{2,1}P_2K_2 \\
&\quad -{k_{1,3}}^2k_{2,2}{}^2k_{1,1}P_1K_1 + {k_{1,3}}^2k_{2,2}{}^2k_{2,1}P_2K_2 + 2\,k_{1,3}k_{2,2}{}^2k_{1,1}P_1k_{2,1}P_2K_2 \\
&\quad +2\,k_{1,3}k_{2,2}{}^2k_{1,2}k_{2,1}P_2K_2 - k_{2,2}{}^2k_{1,2}k_{1,1}P_1k_{1,3}K_1 + 2\,k_{2,2}{}^2k_{1,2}k_{1,1}P_1k_{2,1}P_2K_2 \\
&\quad +k_{2,2}{}^2k_{1,2}{}^2k_{2,1}P_2K_2 + 3\,k_{2,2}k_{1,2}{}^2k_{1,3}k_{2,1}P_2K_2 + k_{2,2}k_{1,2}{}^2k_{2,3}k_{2,1}P_2K_2 \\
&\quad +k_{2,2}k_{1,2}{}^3k_{2,1}P_2K_2 + 2\,k_{1,3}k_{2,2}k_{1,2}k_{2,3}k_{2,1}P_2K_2 - 2\,k_{2,3}k_{2,2}k_{1,2}k_{1,1}P_1k_{1,3}K_1 \\
&\quad -2\,k_{2,3}{k_{1,3}}^2k_{2,2}k_{1,1}P_1K_1 + 3\,k_{1,2}{}^2k_{2,1}{}^2P_2{}^2k_{1,1}P_1K_2 \\
&\quad -k_{2,2}{}^2k_{1,1}{}^2P_1{}^2k_{1,3}K_1 + k_{2,2}{}^2k_{1,1}{}^2P_1{}^2k_{2,1}P_2K_2 \\
&\quad +3\,{k_{1,3}}^2{k_{2,1}}^2P_2{}^2k_{1,1}P_1K_2 - {k_{2,1}}^2P_2{}^2{k_{1,3}}^2k_{1,1}P_1K_1 \\
&\quad -3\,k_{2,3}{k_{2,1}}^2P_2{}^2k_{1,3}K_1\,k_{1,1}P_1 - 3\,{k_{2,3}}^2k_{2,1}P_2k_{1,1}P_1k_{1,3}K_1 \\
&\quad -6\,k_{2,3}k_{2,1}P_2k_{2,2}k_{1,1}P_1k_{1,3}K_1 - 3\,k_{2,2}{k_{2,1}}^2P_2{}^2k_{1,3}K_1\,k_{1,1}P_1 \\
&\quad -3\,{k_{2,2}}^2k_{2,1}P_2k_{1,1}P_1k_{1,3}K_1 - {k_{2,1}}^3P_2{}^3k_{1,3}K_1\,k_{1,1}P_1 - 3\,{k_{2,3}}^2k_{2,2}k_{1,1}P_1k_{1,3}K_1 \\
&\quad -3\,k_{2,3}{k_{2,2}}^2k_{1,1}P_1k_{1,3}K_1 - {k_{2,2}}^3k_{1,1}P_1k_{1,3}K_1 - {k_{2,3}}^3k_{1,1}P_1k_{1,3}K_1.
\end{aligned}
$$

In the expression of a_2b_1, the only negative term is $-k_{1,1}P_1k_{1,3}K_1$. In the expression of $c_1b_1a_2$, we checked it carefully and found out that all negative terms contain K_1. Hence if K_1 is sufficiently smaller than K_2, then the first column of Routh's array is all positive and then all the real parts of the roots of the quartic polynomial are negative. □

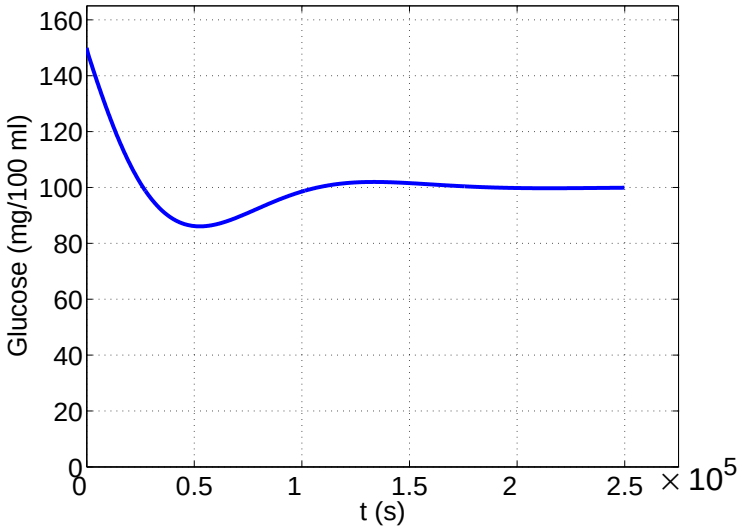

Figure 4: The proportional controller (4.4) with $K_1 = 0.00001$ and $K_2 = 0.00005$ is working in regulating the glucose levels.

To estimate how smaller K_1 is than K_2, we just need to estimate the expression of $c_1 b_1 a_2$.

Although $\mathbf{A}$ has a zero eigenvalue, its multiplicity is equal to 1 and smaller than the multiplicity 3 of zero eigenvalue of $\mathbf{A}$ without control as shown in Theorem 3.1. So the proportional controller does promote stability.

We now numerically test whether the proportional controller works in regulating the end-product level using the example of the glycogen degradation and synthesis pathway. We take the following reaction constants

$$k = \begin{pmatrix} .000520 & .000454 & .0000871 \\ .0000271 & .0000880 & .0000246 \end{pmatrix}.$$

We assume that the initial concentrations of the active or inactive glycogen phosphorylase are 1.33/4, 1.33 (μg/100 mg), respectively (the proportionality between active and inactive is 20:80), and the initial concentrations of active or inactive glycogen synthase are 1.33, 1.33/4 (μg/100 mg), respectively (the proportionality between active and inactive is 80:20). We also suppose the initial concentrations of the glycogen and glucose are 500 and 150 (mg/100 ml), respectively. The desired glucose level is 100 (mg/100 ml), an average normal level in our bodies. We then use the MATLAB to numerically solve the system (2.15)-(2.21) with the controller (4.4). Figure 4 shows that with $K_1 = 0.00001$ and $K_2 = 0.00005$ the controller works well in regulating the glucose levels. Notice that $K_1 = 0.00001$ is smaller than $K_2 = 0.00005$ as claimed in Theorem 4.1.

The proportional controller can be further modified in accord with the function of the pancreas. In response to low blood glucose levels ($p_n < P_n^d$), the α cells of the pancreas produce the hormone glucagon, which increases the activity of the enzyme glycogen phosphorylase and decreases the activity of the enzyme glycogen synthase. In response to high blood glucose levels ($p_n > P_n^d$), the β cells of the pancreas secret insulin which results in an increase in glycogen synthase activity, but does not impact glycogen phosphorylase. This

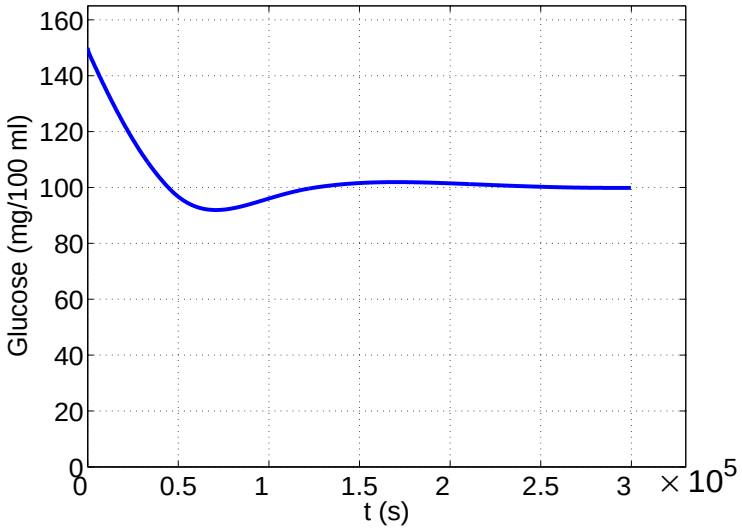

Figure 5: The proportional controller (4.6) with $K_1 = 0.00001, K_2 = 0.00005$, and $K_3 = 0.00003$ is working in regulating the glucose levels.

function of the pancreas can be mathematically translated into

$$u_1 = -K_1 \min(0, p_n - P_n^d), \quad u_2 = K_2 \min(0, p_n - P_n^d) + K_3 \max(0, p_n - P_n^d), \tag{4.6}$$

where $-K_1 \min(0, p_n - P_n^d)$ denotes the increase of the activity of the enzyme glycogen phosphorylase by the glucagon and no impact from the insulin, $K_2 \min(0, p_n - P_n^d)$ denotes the decrease of the activity of the enzyme glycogen synthase by the glucagon, and $K_3 \max(0, p_n - P_n^d)$ denotes the increase of the activity of the enzyme glycogen synthase by the insulin. Figure 5 shows that this modified controller is also working.

4.2 Proportional-Integral Controllers

Since the proportional controller (4.4) does not stabilize the system exponentially, we propose an integral controller to see if we can improve it. Hence we introduce the following integrator

$$\frac{d\xi}{dt} = p_n - P_n^d. \tag{4.7}$$

Then the design of an integral controller is reduced to design a feedback controller to stabilize the augmented nonlinear system (2.15)-(2.21) and (4.7) at the equilibrium (4.1)-(4.3).

We consider a linear feedback control law of the form

$$u_1 = -K_1(p_n - P_n^d) - K_2\xi, \quad u_2 = K_3(p_n - P_n^d) + K_4\xi, \tag{4.8}$$

where K_i's are non-negative constants. For $n = 2$, the characteristic polynomial of the augmented nonlinear system (2.15)-(2.20) and (4.7) with the proportional-integral controller

at the equilibrium (4.1)-(4.3) is given by

$$\begin{aligned}\det(\lambda\mathbf{I}-\mathbf{A}) &= \lambda\big(\lambda^5 + k_{2,1}P_2\lambda^4 + k_{1,1}P_1\lambda^4 + k_{2,3}\lambda^4 + k_{2,2}\lambda^4\\
&+k_{1,3}\lambda^4 + k_{1,2}\lambda^4 + K_3\, k_{2,1}P_2\lambda^3 + k_{1,2}k_{2,3}\lambda^3 + k_{1,3}k_{2,3}\lambda^3\\
&+k_{2,2}k_{1,2}\lambda^3 + k_{2,2}k_{1,1}P_1\lambda^3 + k_{1,2}k_{2,1}P_2\lambda^3 + k_{1,3}k_{2,2}\lambda^3\\
&+k_{1,3}k_{2,1}P_2\lambda^3 + k_{1,1}P_1k_{2,3}\lambda^3 + k_{1,1}P_1k_{2,1}P_2\lambda^3 + K_4\, k_{2,1}P_2\lambda^2\\
&+k_{1,1}P_1K_3\, k_{2,1}P_2\lambda^2 + k_{1,2}K_3\, k_{2,1}P_2\lambda^2 + k_{1,1}P_1k_{1,3}K_1\,\lambda^2\\
&+k_{2,3}K_3\, k_{2,1}P_2\lambda^2 + k_{1,3}K_3\, k_{2,1}P_2\lambda^2\\
&+k_{1,1}P_1k_{1,3}k_{2,3}K_1\,\lambda + k_{1,1}P_1K_4\, k_{2,1}P_2\lambda\\
&+k_{1,1}P_1k_{1,3}K_1\, k_{2,1}P_2\lambda + K_4\, k_{2,3}k_{2,1}P_2\lambda\\
&+k_{1,2}K_4\, k_{2,1}P_2\lambda + k_{1,3}K_4\, k_{2,1}P_2\lambda\\
&+k_{1,2}k_{2,3}K_3\, k_{2,1}P_2\lambda + k_{2,2}k_{1,1}P_1k_{1,3}K_1\,\lambda + k_{1,3}k_{2,3}K_3\, k_{2,1}P_2\lambda\\
&+k_{1,1}P_1k_{1,3}K_2\,\lambda + k_{1,1}P_1k_{2,3}K_3\, k_{2,1}P_2\lambda + k_{2,2}k_{1,1}P_1k_{1,3}K_2\\
&+k_{1,1}P_1k_{1,3}K_2\, k_{2,1}P_2 + k_{1,3}K_4\, k_{2,1}P_2k_{2,3} + k_{1,1}P_1K_4\, k_{2,1}P_2k_{2,3}\\
&+k_{1,2}K_4\, k_{2,1}P_2k_{2,3} + k_{1,1}P_1k_{1,3}k_{2,3}K_2\big).\end{aligned}$$

Thus the proportional-integral controller does not exponentially stabilize the system either, but, like the proportional controller, it also works in regulating the glucose levels when we did numerical simulations.

4.3 Observer-based Dynamic Controllers

The reason why the proportional-integral controller does not exponentially stabilize the systems may be because the observation on only the error $p_n - P_n^d$ is not enough. Therefore, we assume that the error $p_1 - P_1^d$ is also available. This assumption is reasonable since the metabolic pathway is substrate-conservative. To make sure that these errors are well processed and synthesized, we propose an observer-based dynamic controller.

Since the pair $(\mathbf{A}, \mathbf{B})$ is stabilizable and the pair $(\mathbf{A}, \mathbf{C})$ is detectable, there exist a feedback gain

$$\mathbf{G} = \begin{pmatrix} g_{1,1} & g_{1,2} & \cdots & g_{1,2n+1} \\ g_{2,1} & g_{2,2} & \cdots & g_{2,2n+1} \end{pmatrix}$$

and an observer gain

$$\mathbf{H} = \begin{pmatrix} h_{1,1} & h_{1,2} & \cdots & h_{1,2n+1} \\ h_{2,1} & h_{2,2} & \cdots & h_{2,2n+1} \end{pmatrix}^T$$

such that both $\mathbf{A}-\mathbf{BG}$ and $\mathbf{A}-\mathbf{HC}$ are Hurwitz, that is, the real parts of their eigenvalues are negative. Then we can design an observer-based dynamic feedback controller for the linear system (3.1) as follows

$$\frac{d\mathbf{x}}{dt} = \mathbf{Ax} - \mathbf{BGz}, \tag{4.9}$$

$$\frac{d\mathbf{z}}{dt} = (\mathbf{A} - \mathbf{BG} - \mathbf{HC})\mathbf{z} + \mathbf{HCx}. \tag{4.10}$$

Since

$$\det\left(\lambda\mathbf{I} - \begin{bmatrix} \mathbf{A} & -\mathbf{BG} \\ \mathbf{HC} & \mathbf{A}-\mathbf{BG}-\mathbf{HC} \end{bmatrix}\right) = \det(\lambda\mathbf{I} - (\mathbf{A}-\mathbf{BG}))\det(\lambda\mathbf{I} - (\mathbf{A}-\mathbf{HC})),$$

we have the following theorem.

Theorem 4.2. *The feedback control system (4.9) and (4.10) is exponentially stable.*

Applying this linear controller to the original nonlinear system, we obtain the regulatory feedback system

$$\begin{aligned}
\frac{dp_1}{dt} &= -k_{1,1}e_1p_1 + k_{1,2}c_1 + k_{n,3}c_n + p_n, && (4.11)\\
\frac{de_1}{dt} &= -k_{1,1}e_1p_1 + (k_{1,2}+k_{1,3})c_1 - \sum_{j=1}^{2n+1} g_{1,j}z_j, && (4.12)\\
\frac{de_1^i}{dt} &= \sum_{j=1}^{2n+1} g_{1,j}z_j, && (4.13)\\
\frac{de_j}{dt} &= -k_{j,1}e_jp_j + (k_{j,2}+k_{j,3})c_j, \quad j=2,\cdots,n-1, && (4.14)\\
\frac{dp_j}{dt} &= -k_{j,1}p_je_j + k_{j-1,3}c_{j-1} + k_{j,2}c_j, \quad j=2,\cdots,n-1, && (4.15)\\
\frac{dp_n}{dt} &= -k_{n,1}p_ne_n + k_{n-1,3}c_{n-1} + k_{n,2}c_n - p_n, && (4.16)\\
\frac{de_n}{dt} &= -k_{n,1}p_ne_n + (k_{n,2}+k_{n,3})c_n - \sum_{j=1}^{2n+1} g_{2,j}z_j, && (4.17)\\
\frac{d\mathbf{z}}{dt} &= (\mathbf{A}-\mathbf{BG}-\mathbf{HC})\mathbf{z} + \mathbf{H}\begin{pmatrix} p_1 - P_1^d \\ p_n - P_n^d \end{pmatrix}, && (4.18)\\
p_1(0) &= P_1^0,\ p_n(0) = P_n^0,\ e_1(0) = E_1^0,\ \mathbf{z}(0) = 0,\ e_1^i(0) = E_1^{i,0},\ e_n(0) = E_n^0,\\
p_j(0) &= 0,\ e_j(0) = E_j^0, \quad j=2,\cdots,n-1, && (4.19)
\end{aligned}$$

where c_j satisfies (2.12) –(2.14).

As a result of Theorem 4.2, we have

Corollary 4.1. *The feedback control system (4.11)–(4.19) is locally exponentially stable near any of its equilibrium with $\bar{p}_1 = P_1^d$ and $\bar{p}_n = P_n^d$.*

To numerically test the effectiveness of the observer-based controller, we use the same data from subsection 4.1. By trying different feedback gains and observer gains, we find the following gains

$$\mathbf{G} = \begin{pmatrix} 0.0 & 0.5 & 0.0 & 0.0 & 0.05 \\ 1.9 & 1.5 & 1.6 & 0.0 & 0.08 \end{pmatrix}, \quad \mathbf{H} = \begin{pmatrix} 0.004 & 0.002 & 0.006 & 0.0 & 0.007 \\ 0.005 & 0.0025 & 0.0 & 0.003 & 0.0002 \end{pmatrix},$$

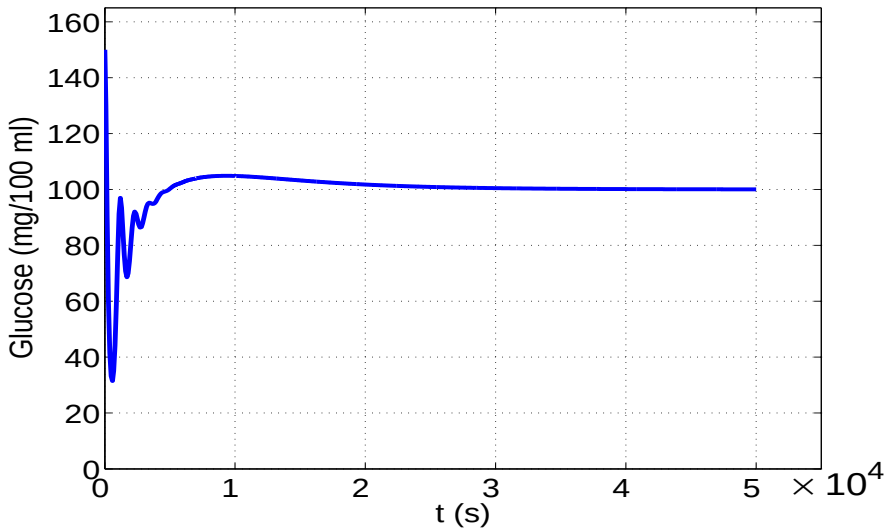

Figure 6: The glucose is regulated to the desired level by the observer-based control law (4.18).

which make $\mathbf{A} - \mathbf{BG}$ and $\mathbf{A} - \mathbf{HC}$ Hurwitz. In fact, the eigenvalues of $\mathbf{A} - \mathbf{BG}$ are

$$\begin{gathered} -0.85546552487663, \\ -0.00686816245514 + 0.241834915476 08i, \\ -0.00686816245514 - 0.241834915476 08i, \\ -0.00005762913352, \\ -0.00010422107958, \end{gathered}$$

and the eigenvalues of $\mathbf{A} - \mathbf{HC}$ are

$$\begin{gathered} -0.28856712327522, \\ -0.00630648446476, \\ -0.00067034886358 + 0.00311076161066i, \\ -0.00067034886358 - 0.00311076161066i, \\ -0.00014939453286. \end{gathered}$$

Figure 6 shows that the glucose is regulated to the desired level 100 (mg/100 ml) by the observer-based control law (4.18). Also notice that the glucose is oscillating before it reach its equilibrium because some of eigenvalues of $\mathbf{A} - \mathbf{BG}$ and $\mathbf{A} - \mathbf{HC}$ are complex.

In the real situation, the blood glucose level is always oscillating within a certain range. This is because, in response to the low blood glucose levels, the α cells of the pancreas produce glucagon discontinuously with respect to the glucose levels. Binding to a receptor on the outside of a cell membrane and activating sequences of enzymes, the glucagon then sends a discontinuous signal u_1 to the glycogen phosphorylase E_1. This signal should be of the on-off nature, which results in the oscillation. In our model, we idealized the problem by assuming that the signal is continuous. This is why the glucose reaches the fixed level without oscillation in our theoretical results.

5 Conclusions

We have developed a mathematical model for a signal-controlled metabolic pathway using a system of differential equations. We analyzed its local linear stability, controllability, and observability. We showed that the linearized system is controllable and observable and the real parts of all eigenvalues of the linearized system are non-positive using Routh's stability criterion. We designed observer-based and proportional-integral output feedback controllers as a function of the substrate and end-product to regulates the end-product to its desired level.

The global stability of the signal-controlled metabolic pathway model is open since we could not construct a Lyapunov function for the model. From the numerical results in the paper, we guess that there may be no Lyapunov functions for it because the behavior of the solution of the system is oscillating and can be very complex before it reaches its steady state.

For simplicity, we did not consider the molecular diffusion of the end-product. But in real biological situations, the end-product like glucose diffuses through the membranes out of the cell. Therefore a more accurate model should take such diffusion into account and then the mathematical models will become a hybrid system of ordinary and partial differential equations. We will consider this more complicated problem in a future work.

Acknowledgments

This work was supported by the University Research Council Fund of the University of Central Arkansas. The authors thank M. Moran, N. Runge, and S. Runge for their valuable comments on biological issues and D. Arrigo for his useful suggestions on mathematics.

References

[1] Angeli, D., Ferrell, J.E., and Sontag, E. D., Detection of multistability, bifurcations, and hysteresis in a large class of biological positive-feedback systems. *Proceedings of the National Academy of Sciences*. **101** (2004), 1822-1827

[2] Bevan, P., Insulin signaling. *J. Cell Sci*. 114 (2001), 1429-1430.

[3] Dua, P., Doyle, F.J., and Pistikopoulos, E.N., Model-based blood glucose control for type 1 diabetes via parametric programming. *IEEE Transactions on Biomedical Engineering*. **53**, no: 8 (2006), 1478– 1491.

[4] Fujarewicz, K., Kimmel, M., and Swierniak, A., On Fitting Of Mathematical Models Of Cell Signaling Pathways Using Adjoint Systems. *Mathematical Biosciences and Engineering*. **2**, no. 3, (2005), 527-534.

[5] Heinrich R., and Schuster, S., The Regulation of Cellular Systems. Chapman & Hall, International Thomson Publishing, New York, 1996.

[6] Hoffmann, A., Levchenko, A., Scott, M. L., and Baltimore, D., The IκB-NF-κB signaling module: temporal control and selective gene activation. *Science*. **298**, no. 8 (2002), 1241–1245.

[7] Karp, G., Cell and molecular Biology, 4th edition. John Wiley & Sons, Inc. 2005.

[8] Khalil, H.K., Nonlinear Systems. Prentice Hall, New Jersey, 2001.

[9] Lee, E.G., Boone, D.L., Chai, S., Libby, S.L., Chien, M., Lodolce, J.P., and Ma, A., Failure to regulate TNF-induced NF-κB and cell death responses in A20-deficient mice. *Science*. **289**, no.29 (2000), 2350–2354.

[10] Lipniacki, T., Paszek, P., Brasier, A.R., Luxon R., and Kimmel, M., Mathematical model of NF-κB regulatory module. *Journal of Theoretical Biology*. **228**, no. 2 (2004), 195–215.

[11] Lou, Y., Nie, Q., and Wan, F. Y. M., Effects of sog on DPP-receptor binding. SIAM J. Appl. Math. 65, no. 5, (2005), 1748–1771.

[12] Morris, K. A., Introduction to Feedback Control. Academic Press, San Diego, 2001.

[13] Murray, J.D., Mathematical Biology I: An Introduction. Springer, New York, 2002.

[14] Ogata, K., Mordern Control Engineering, Fouth Edtion. Prentice Hall, Upper Saddle River, New Jersey, 2002.

[15] Sontag, E.D., Some new directions in control theory inspired by systems biology. *IEE Proceedings - Systems Biology*. **1** (2004), no. 1, p. 9-18.

[16] Tyson, J.J., Chen, K. C., and Novak, B., Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell. *Current Opinion in Cell Biology*. **15**, no. 2 , (2003), 221–231.

[17] Vaidhyanathan, V.S., Regulation and Control Mechanisms in Biological Systems. P T R Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1993.

[18] Wearing, H.J., and Sherratt, J. A., Nonlinear analysis of juxtacrine patterns. *SIAM J. Appl. Math.* **62**, no. 1 (2001), 283–309.

[19] Yi, T. M., Huang, Y., Simon, M. I., and Doyle, J., Robust perfect adaptation in bacterial chemotaxis through integral feedback control. *PNAS*, **97**, no. 9, (2000), 4654–4659.

[20] Zak, D. K., Pearson, R. K., Vadigepalli, R., Gonye, G. E., Schwaber, J.S., Doyle III, F. J., Continuous-Time Identification of Gene Expression Models. *Journal of Integrative Biology*. **7**, no. 4, (2003), 373–386.