To the Graduate Council:

I am submitting herewith a dissertation written by Jayanthy Ramakrishnan entitled "Analysis and Control of Nonnegative Systems". I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Mechanical Engineering.

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Analysis and Control of Nonnegative Systems

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Jayanthy Ramakrishnan
December 2006

Acknowledgements

Upon completion of the most important work of my life, writing the acknowledgements is the most pleasant part. I would like to take this opportunity to express my appreciation to the people who have influenced, stimulated, expedited, and warmly supported my work in various ways.

My first debt of gratitude goes to my advisor Professor VijaySekhar Chellaboina. He patiently provided the vision, advice, and encouragement necessary for me to proceed through the doctoral program and complete my dissertation. He has not only been my academic advisor, but also been a great mentor in my graduate life, guiding me through many difficult situations, while I was away from home. Working with him on various research topics has been one of the most invaluable experiences of my career. Knowing and working with him has really been a rewarding experience. I would also like to thank his family for always making me feel welcome in their home. I sincerely feel that this graduate experience has made me a better person on a professional as well as personal level.

I am thankful to Professor William R. Hamel, Professor Dongjun Lee, and Professor Seddik M. Djouadi for taking the time to serve on my committee and for their useful comments and suggestions to improve this dissertation. I also thank Professor Gary V. Smith for being on my proposal committee.

I am thankful to my co-authors Dr. Wassim H. Haddad, Dr. James M. Bailey, Dr. Tomohisa Hayakawa, and Mr. Qing Hui for their assistance and suggestions in our collaborations. I would also like to express my gratitude to all my teachers at the University of Missouri, Columbia and at the University of Tennessee, Knoxville.

I am greatly indebted to one of my research group members Ajeet Kamath for his patience, suggestions, and timely help during all my years in graduate school. I would like to extend my special thanks to my best friend Makarand Joshi for his support, love, help, and understanding in dealing with all the challenges I faced. I would also like to thank Alexander M. Melin and Hancao Li, members of my research group for their support and suggestions.

Lastly, but by no means least, my heartfelt appreciation and gratitude goes to my parents for their "time-invariant" love, support, patience, and encouragement. They have waited five years for me to complete the doctoral program and it is beyond words to describe the love and respect I feel for them. I would like to extend special thanks to my brother, Anand Ramakrishnan, who encouraged me to join the Ph.D.

program and always motivated me to aim higher and never give up. He has always set an excellent example for me to follow and his advice has helped me become a better person. I would like to thank my sister-in-law Sudha Mani for her enthusiasm, support, and timely advice in various matters. Nothing in a simple paragraph can express the love and respect I have for the four of you.

Dedication

This dissertation is dedicated to my parents Mr. A. A. Ramakrishnan and Mrs. Rajalakshmy Ramakrishnan for all their love, support, and blessings and to whom I owe more than they will ever know.

Abstract

Nonnegative systems are dynamical systems with nonnegative states for random nonnegative initial conditions. A subclass of nonnegative systems are compartmental systems characterized by conservation laws.Nonnegative and compartmental systems have widespread applications in biological systems, medical systems, thermodynamic systems, network systems, economic systems, etc.

In this dissertation we have investigated the applications of nonnegative systems in biological and network systems. The specific focus in biological systems has been in the area of pharmacokinetics and we have addressed the consensus problem in network systems. We have specifically focused on the time-delay present in compartmental systems and have investigated the behavior of these systems in the presence of time-delay.

This dissertation describes necessary and sufficient conditions that guarantee monotonic decline of the drug concentration after drug administration to the patient has been discontinued. Results are presented for the cases when there is no delay in the transfer of the drugs between the body compartments and when there are multiple delays present in the system.

We developed an adaptive controller for uncertain linear nonnegative systems. The adaptive controller framework developed guarantees set-point regulation of the system in addition to guaranteeing nonnegativity of the control signal. We demonstrated the framework on a drug delivery model for general anesthesia.

Nonnegative and compartmental models are also widespread in agreement problems in networks with directed graphs and switching topologies. We use compartmental dynamical system models to characterize dynamic algorithms for linear and nonlinear networks of dynamic agents in the presence of inter-agent communication delays that possess a continuum of *semistable* equilibria, that is, protocol algorithms that guarantee convergence to Lyapunov stable equilibria. In addition, we show that the steady-state distribution of the dynamic network is uniform, leading to system state equipartitioning or consensus.

Finally, we incorporated the inertial effects into the dynamics of the multiagent system and have extended existing results in the literature to develop time-domain sufficient conditions in order to achieve consensus of the agents in the presence of time-delay.

Contents

List of Tables

List of Figures

Notation

$\mathbb{R}$, $\mathbb{R}^{m\times n}$	real numbers, $m \times n$ real matrices
x_i	ith entry of the vector $x \in \mathbb{R}^n$
e_i	vector with unity in the ith position and zeros elsewhere
e	$[1,\ 1,\ \ldots, 1]^{\mathrm{T}}$
$A \geq\geq 0$, $(A >> 0)$	$A_{(i,j)} \geq 0$, ($A_{(i,j)} > 0$ for all i and j)
$\mathbb{R}^n_+$, $\bar{\mathbb{R}}^n_+$	$\{x \in \mathbb{R}^n : x >> 0\}$, $\{x \in \mathbb{R}^n : x \geq\geq 0\}$
spec(A)	spectrum of matrix $A \in \mathbb{R}^{n\times n}$
$\rho(A)$	spectral radius of A, that is $\max\{\mid \lambda \mid : \lambda \in \mathrm{spec}(A)\}$
rank(A)	rank of $A \in \mathbb{R}^{n\times n}$
A^{T}	transpose of A
$A^{\#}$	group generalized inverse of A
$\mathcal{R}(A)$, $\mathcal{N}(A)$	range space of A, null space of A
$\Vert \cdot \Vert$	vector or matrix norm
ind(A)	index of $A \in \mathbb{R}^{n\times n}$

Chapter 1

Introduction

1.1. Motivation

Complexity is one of the main characteristics of a physical process, especially physiological processes, and there should be a method to address this. As a result of this it is not often possible to measure directly (*in vivo*) the quantities of interest. Indirect methods have to be used, implying the need for some model to be able to infer the value of the quantity of real interest. Also, often we have to deal with measurement constraints in the process. Thus, complexity of the process coupled with limitations on the measurement process calls for a model of the system that can aid to our understanding [1]. In an effort to model systems accurately, it has been observed that dynamical systems theory has played a very important role, especially in understanding biological and physiological processes [2].

One of the most interesting questions to ask about a dynamical system is: what is the behavior of the trajectories of the system as time increases? It is natural to expect that almost all the trajectories either converge to an equilibrium or asymptotically approach a periodic trajectory. Unfortunately, there are many systems that not only lack this convenient property, but cannot even be approximated by systems that have it. Thus, it is very hard to discover the end-behavior of any systems other than the simplest systems.

As a consequence, much research has gone into determining the end-behavior of special systems or a class of systems that arise in biology, chemistry, economics and similar fields [3–8]. Algebraic techniques play a very prominent role in the analysis of these systems. The specific systems that we are considering in this dissertation have been used to model a variety of biological, chemical, network and economic systems [9–12]. They are known as *Nonnegative Systems*.

The trajectories of nonnegative systems always stay in the positive orthant of the state space. An important observation is that generally the quantities of interest for example in biological systems are blood values in body tissue, respiratory rate/volume, concentration of gases, blood pressure etc have values that are zero or positive classifying biological systems into a specific class of systems called *nonnegative systems*. Nonnegative systems are dynamical models derived from mass and energy balance considerations that involve dynamic states whose values are nonnegative [13–15]. The dynamical models of many biological and physiological processes such as pharmacokinetics, metabolic systems, epidemic dynamics, biochemical reactions, endocrine systems. Nonnegative systems are essential in capturing the phenomenological behavior of a wide range of dynamical systems involving dynamic states whose values are nonnegative [13–16]. It follows from physical considerations that the state trajectories of such systems remain in the nonnegative orthant of the state space for nonnegative initial conditions. Consider the linear dynamical system of the form

$$\dot{x}(t) = Ax(t) + Bu(t), \quad x(0) = x_0, \quad t \geq 0$$

where $x(t)$ is the state of the system, $u(t)$ is the input to the system and A and B are the system matrices. For nonnegative initial conditions x_0, if the input $u(t)$ to the system in nonnegative then the state of the system $x(t)$ is nonnegative.

Consider a simple continuous-time second order system with a nonnegative input and random nonnegative initial conditions. Figures 1.1 and 1.2 show the trajectories of the system for random initial conditions.

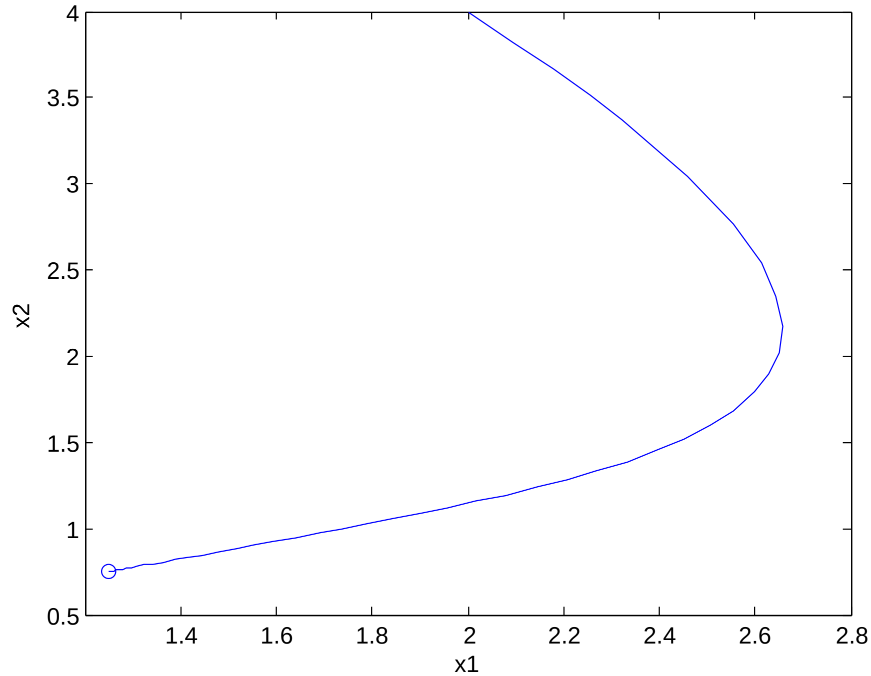


Figure 1.1: Positive Initial Conditions

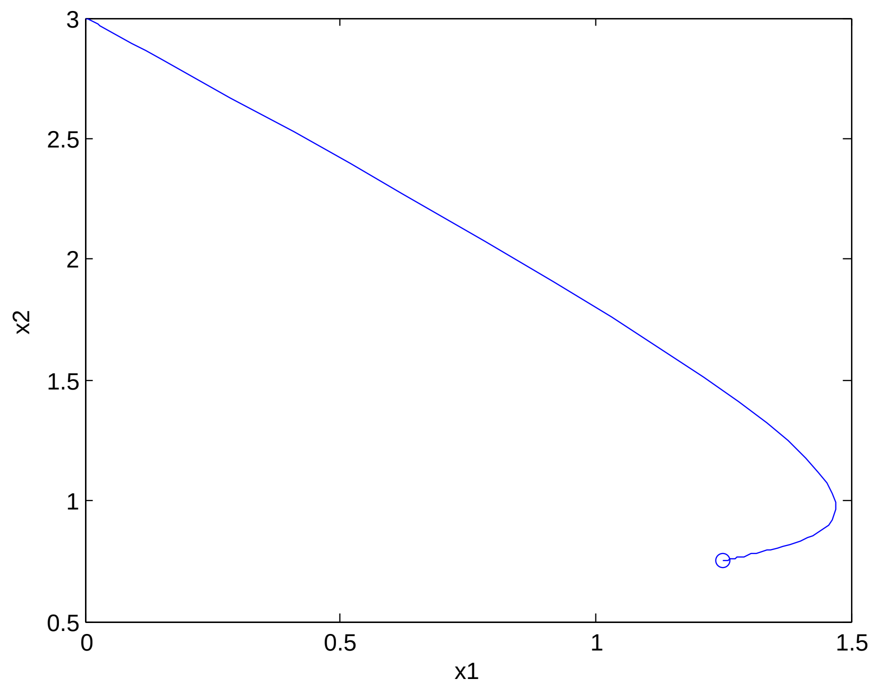


Figure 1.2: Zero Initial Conditions

Some other examples of nonnegative systems are chemical reaction systems [3, 4], large-scale systems [5, 6], ecological systems [8], pharmacokinetics [17, 18] and metabolic systems [19].

A subclass of nonnegative dynamical systems are *compartmental systems* [8,20–28] whose dynamical models are characterized by conservation laws (e.g., mass,energy and information) capturing the exchange of material between coupled macroscopic subsystems known as compartments. Each compartment is assumed to be kinetically homogeneous; that is any material entering the compartment is instantaneously mixed with the material of the compartment. A compartmental system may be used to model either the kinetics of one substance, in which case the compartments occupy different spaces and the inter-compartment transfers represent flow of material from one location to another, or the kinetics of two or more substances (such as a drug and its metabolites) in which case different compartments may occupy the same space and some of the inter-compartment transfers represent transformation from one substance to another.

Figure 1.3 shows a linear compartmental system where $x_i(t)$, $i = 1, \ldots, n$, denotes the mass of the ith subsystem of the compartmental system, $a_{ii} \geq 0$ denotes the loss coefficient of the ith subsystem, $w_i(t) \geq 0$, $i = 1, \ldots, n$, denotes the flux (inflow) supplied to the ith subsystem, and $\phi_{ij}(t)$, $i \neq j$, $i, j = 1, \ldots, n$, denotes the net flow from the jth subsystem to the ith subsystem given by $\phi_{ij}(t) = a_{ij}x_j(t) - a_{ji}x_i(t)$, $t \geq 0$, where the transfer coefficient $a_{ij} \geq 0$, $i \neq j$, $i, j = 1, \ldots, n$. The compartmental system with no inflows, that is $w_i(t) = 0$, $i = 1, \ldots, n$, is said to be *inflow-closed* [26]. If there are no losses(outflows) from the system it is said to be *outflow-closed* [26]. A compartmental system is said to be *closed* if it is inflow-closed and outflow-closed.

The range of applications of nonnegative systems and compartmental systems includes biological and medical systems, network systems, chemical reaction systems [29,30], queuing systems [31], large-scale systems [5], stochastic systems (whose state variables represent probabilities) [31], ecological systems [32], economic systems [7],

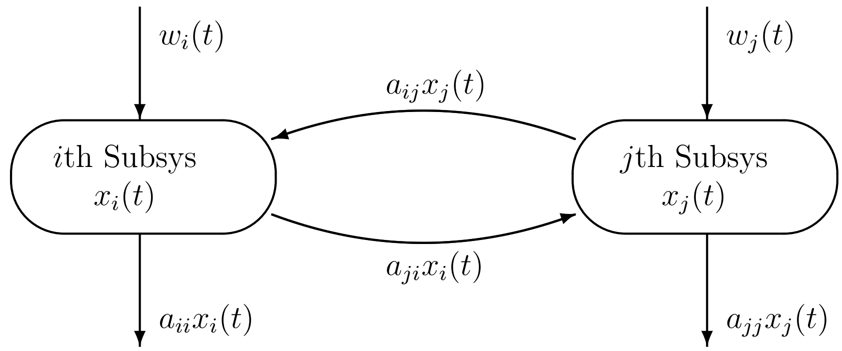


Figure 1.3: Linear Interconnected Compartmental System

demographic systems [26], telecommunication systems [33], transportation systems, power systems, thermodynamic systems [34], and structural vibration systems.

In the next section, we are going to discuss the presence of time-delay in compartmental systems and present the effect of time-delay on the behavior of these systems.

1.2. Compartmental Systems with Delays

Nonnegative and compartmental dynamical system models are derived from mass, energy and information balance considerations and involve the exchange of nonnegative quantities between subsystems or compartments. It is often assumed that the transfer of material between the compartments is instantaneous. The model of the system does not take into account the material that is currently transferred from one compartment to another. Thus, there is no account for the material in transit. Thus, the transfers between compartments is not instantaneous and realistic models for capturing the dynamics of such systems should account for material, energy or information in transit between the compartments [26, 35, 36].

Hence, to accurately describe the evolution of compartmental systems, it is necessary to include in any mathematical model of the system dynamics, some information of the past system states. This leads to (infinite-dimensional) delay systems [37–39].

In the specific field of pharmacokinetics [40, 41], the state variables of compartmental dynamical systems represent masses or concentrations of drug disposition from the body. If a bolus of drug is injected into the circulation of a physiological process and we seek its concentration level in the extracellular and intercellular space of some organ, there exists a time lag before it is detected in that organ. Hence, assuming instantaneous drug transfer between the compartments will lead to inaccurate models of the system. Introduction of time-delay in the system could destabilize the equilibria of the system. It could introduce oscillations into the system which may otherwise be nonoscillatory. Hence, when dealing with drug administration in biological models it is important to take into account the delay present in the system.

In applications involving multiagent/multivehicle systems, the agents of the system are remotely located. The time taken for the information to transmit from one agent to another gives rise to a delay in the system. One of the other factors which could cause a delay in the system is the unreliability of the communication medium. Some systems have switching networks in which existing links between the agents are disconnected and links with new agents are formed. This delay in the system causes the transmission time of the information in between the agents to increase. It could also result in unstable behavior of the system. Thus, it is very important to take into account the time-delay present when modeling the system.

1.3. Applications of Compartmental Modeling

Next, we will consider some areas where compartmental modeling has played a major role in the better understanding and modeling of these systems that we have focussed on in this dissertation.

1.3.1. Pharmacology

Compartmental systems have been found useful for the analysis of experiments in various branches of biology. The majority of the work on compartmental systems upto the early 1940s was of a qualitative nature. During the 1940s, there was a trend of towards treating the data in a more quantitative manner, so that differential equations and, consequently, compartments can be used to describe the behavior of tracers. The term "compartment" was first introduced by Sheppard in 1948. One of the significant early papers was that of [42] discussing the mathematical basis for interpreting tracer experiments. Teorell was one of the earliest to conduct a systematic study of the kinetics of drugs [43, 44]. Some other work carried out in the area of bio-modeling is in the regulation of blood glucose level [45], model gas exchange in lungs [46]. Extensive work has been done in the field of pharmacokinetics in the early 1970s. The use of compartmental models in ecosystem modeling began in the late 1950s.

The area of clinical pharmacology is a discipline in which mathematical modeling has had a prominent role. Some of the most important advances in modern medicine have been in the area of pharmacology. In this dissertation we will talk about compartmental modeling in drug-delivery systems. Pharmacology is the study of the interactions of the drug with the body and study their effects. Pharmacokinetics is the study of the concentration of the drugs in various tissues as a function of time. Pharmacodynamics is the study of the relationship between drug concentration and effect. By developing techniques to relate the drug concentration (pharmacokinetics) and the drug effect (pharmacodynamics) we can generate a model for a drug-delivery system.

The most common pharmacokinetic models are linear and *mammillary*. These models consist of a central compartment which receives the intravenous drug. The central compartment exchanges material reversibly with one or more peripheral compartments or metabolizes and eliminates the drug from the body. Drug elimination from the peripheral compartment is ignored since this compartment is identified with tissues such as muscle or fat which do not metabolize the drug. Most drugs are metabolized in the liver or kidney, organs that, along with the heart and brain, equilibrate rapidly with the intravascular blood and are identified with a central compartment that receives the intravenous dose. The transfer between the central and peripheral compartments is governed by linear kinetics. Figure 1.4 shows a three compartment mammillary model The state-space model can be described as

$$\dot{x}(t) = Ax(t) + Bu(t), \quad x(0) = x_0, \quad t \geq 0,$$

where,

$$A = \begin{bmatrix} -(a_{11} + a_{21} + a_{31}) & a_{12} & a_{13} \\ a_{21} & -a_{12} & 0 \\ a_{31} & 0 & -a_{13} \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}$$

with $x = [x_1,\ x_2,\ x_3]^{\mathrm{T}}$ is the state vector representing the masses of the drug in the three compartments, a_{ij} is the transfer coefficients from the jth compartment to the ith compartment, a_{11} is the rate at which the drug is eliminated from the central compartment.

Doctors have often observed that once the drug is injected into the body, their concentrations do not decay monotonically but in fact, in some cases oscillations of the drug concentrations in the compartments has been exhibited leading to errors between the model predictions and experimental data. In the presence of time-delay in the system, even non-oscillatory systems could exhibit oscillations. This could result in the destabilization of the equilibrium of the system. Hence, it is important to identify compartmental dynamical systems which guarantee nonoscillatory and

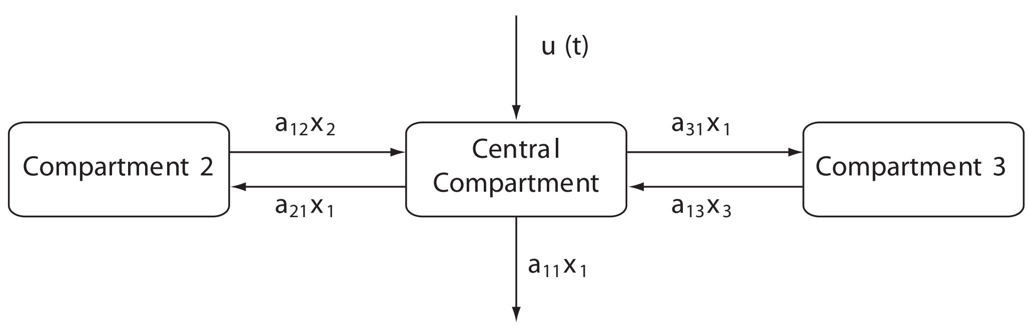


Figure 1.4: Three Compartment Mammillary Model

monotonic solutions.

1.3.2. Clinical Anesthesia

Anesthesiologists use general anesthetics to prevent the awareness of pain and attenuate the body's "stress" response to injury. Until the mid-20th century, only inhaled anesthetics were available to create the state of general anesthesia. Their onset of action was slow and was accompanied by other side-effects. In the 1940s, intravenous agents were introduced and nowadays anesthesiologists have access to agents that can act within a minute of their administration and can block specific mechanisms such as cognition, awareness, memory, stress response and muscle movement. These anesthetic agents are characterized by their fast metabolism and elimination.

The unconsciousness produced by general anesthesia is accompanied by a depression of the respiratory(e.g., hyperventilation), cardiovascular(e.g., increased heart rate and blood pressure) and endocrine responses to surgery. Since the degree of surgical stimulation changes during surgery, anesthesiologists must constantly adjust the extent of anesthetic depression to avoid both under- and over dosing. Otherwise, excessive activation of the sympathetic nervous system or pharmacological depression could in turn lead to injury of critical organs, especially in patients with limited respiratory and cardiovascular reserves. Hence, constant monitoring of the delivery of these drugs is necessary to provide patients with an adequate drug regimen during surgery.

Anesthesiologists have succeeded in making anesthesia a safe procedure. It is therefore natural to wonder whether automation in clinical anesthesia is a valuable research endeavor. But it is important to realize that the complex highly uncertain and hostile environment of surgery places stringent performance requirements for regulation of the physiological variables. For example, during cardiac surgery, blood pressure control is vital and is subject to numerous highly uncertain exogenous disturbances. Vasoactive and cardioactive drugs are administered resulting in large disturbance oscillations of the drug. Low anesthetic levels may cause the patient to react to painful stimuli, thereby changing the patient response characteristics. Thus, extensive research is going on for the development of reliable system models for high performance drug delivery systems [47–50].

Open-loop control by clinical personnel can be very tedious, imprecise, time consuming, and sometimes of poor quality. It is convenient to compare the closed-loop control of anesthesia to that of an automated flight control [51]. The role of the anesthesiologist is that of a pilot: after take-off (induction), the pilot usually maintains an adequate flight trajectory (hypnosis, analgesia, immobility). Nowadays such tasks are performed by flight controllers able to plan ahead, optimize fuel consumption and minimize the duration of the flight. In this sense closed loop anesthesia is somehow similar since by changing the concentration of the intravenous drug, the anesthesiologist can drive the patient into a deeper or lighter analgesic state according to the requirements of the surgical procedure.

Using proper feedback quantities and drug models the possibility to automate the drug delivery and to allow the anesthesiologist to concentrate on higher level tasks seems attractive. It is important to realize that closed loop anesthesia would not replace the anesthesiologist but on the contrary the workload of the anesthesiologist will be reduced allowing him to attend to emergencies when the override of the controller will still be required. Even though the comparisons are not exactly justified it just demonstrates the importance of closed-loop control in anesthesia.

Closed-loop control can achieve desirable system performance in the face of such highly uncertain and hostile environment of surgery and intensive care unit. Robust controllers may unnecessarily sacrifice system performance whereas adaptive controllers are useful since they can tolerate far greater system uncertainty levels to improve system performance [52–55]. Fixed-gain robust controllers maintain specified constants within the feedback control law to sustain robust performance but adaptive controllers directly or indirectly adjust feedback gains to maintain closed-loop stability and improve performance in the face of system uncertainties. Specifically, indirect adaptive controllers utilize parameter update laws to identify unknown system parameters and adjust feedback gains to account for system variations, while direct adaptive controllers directly adjust the controller gains in response to system variations.

Consider the general anesthesia model as shown in the Figure 1.5. The anesthetic agent is injected directly into the blood volume from where it is exchanged with the various organs and tissue groups and finally eliminated from the blood volume. Note that $x_1(t)$, $x_2(t)$ and $x_3(t)$ are the masses of the anesthetic agent in the three compartments, $u(t)$, $t \geq 0$, is the infusion rate of the drug, $a_{ij} \geq 0$, $i \neq j$, $i, j = 1, 2, 3$, are the rate constants for the transfer of drug between the compartments, $a_{11} \geq 0$ is the rate constant for the elimination of the drug from the central compartment and τ represents the transfer times between the compartments. This system can be represented in state-space form as:

$$\dot{x}(t) = Ax(t) + A_{\mathrm{d}}x(t-\tau) + Bu(t)$$

where,

$$A = \begin{bmatrix} -(a_{11}+a_{21}+a_{31}) & 0 & 0 \\ 0 & -a_{12} & 0 \\ 0 & 0 & -a_{13} \end{bmatrix}, A_{\mathrm{d}} = \begin{bmatrix} 0 & a_{12} & a_{13} \\ a_{21} & 0 & 0 \\ a_{31} & 0 & 0 \end{bmatrix}, B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}.$$

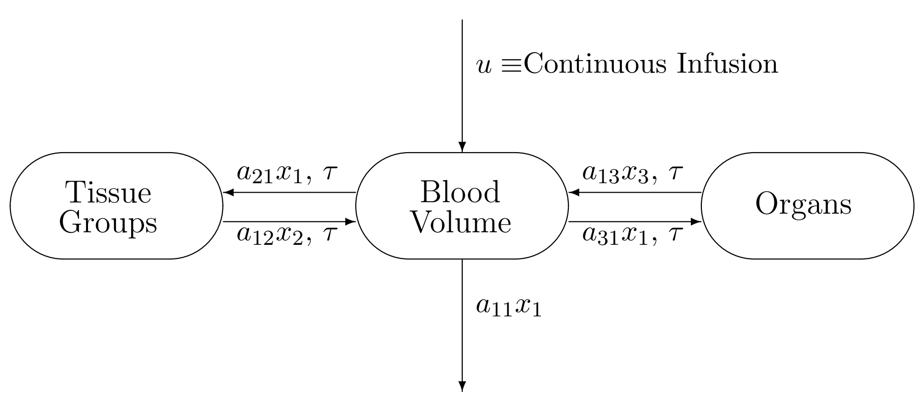


Figure 1.5: General Anesthesia Model

Critical care patients, undergoing surgery or recovering in intensive care units, require drug administration to regulate key physiological state variables within desired levels. The rate of infusion of each administered drug is critical and any changes in the infused drug level along with uncertain exogenous disturbances will effect the patient response characteristics. Even though the drug transfer and loss coefficients are nonnegative, they can be uncertain due to patient gender, weight, pre-existing disease, age and concomitant medication. Thus, the system matrices A, A_{d} and B are uncertain and unknown. Hence, the need for a adaptive control drug administration is severe.

Even though active control of drug delivery systems for physiological applications additionally require control inputs to be nonnegative, in many applications such as biological systems, population dynamics, and ecological systems, the positivity constraint on the control input is not natural. For example, in biological systems involving interacting species, a nonnegative input constraint effectively implies that species can only be injected into the system and no species can be eliminated (killed) from the system. Hence, it is important to develop an adaptive controller without any restriction on the sign of the control signal but at the same time the controller guarantees that the system states remain in the nonnegative orthant and converge to a desired equilibrium state.

1.3.3. Network Systems

Over the last few years the problems of coordinating the motion of multiple autonomous agents has attracted significant attention [11, 33, 56, 57]. Research in this area is motivated by recent advances in communication and computation, as well as inspiring links to problems in biology, statistical physics, and computer graphics [57–59]. Efforts have been directed in trying to understand how a group of autonomous moving creatures such as flocks of birds, schools of fish, crowds of people, mobile autonomous agents, can cluster in formations without centralized coordination [58–66]. Control of dynamic agents coupled to each other through an information flow network has emerged as a topic of major interest in recent years. Such a setting can be used to model many real-life situations, such as air traffic control, satellite clusters, swarms of robots, UAV formations.

Over the last few years there has been extensive research reported in the area of distributed coordination of networks of dynamic agents [67]. This is due to the broad applications of multiagent systems in areas like unmanned air vehicles (UAVs), formation control [59, 61, 62, 68], flocking [63, 64, 69], distributed sensor networks [65], congestion control in communication networks [58].

Consensus problems have a long history in the field of computer science particularly in automata theory and distributed computation [57]. In network of agents (or dynamic systems), "consensus" means to reach an agreement regarding a certain quantity of interest that depends on the state of all agents. A "consensus algorithm" (or protocol) is an interaction rule that specifies the information exchange between an agent and all of its neighbors on the network [56].

Formal study of consensus problems in groups of experts originated in *management science and statistics* in 1960s [70]. The theoretical framework for posing and solving consensus problems for networked dynamic systems was introduced [60, 68]. Graph Laplacians and their spectral properties are important graph-related matrices that play a crucial role in convergence analysis of consensus and alignment algorithms [71–74].

Consider the network system as shown in Figure 1.6. The agents i and j exchange information with each other. This information exchange is governed by transfer coefficients a_{ij} and a_{ji}. The information transferred between the agents could be attitude, position, temperature or velocity of the agents. Since there is a transfer of information between the agents, the network system is a compartmental system. In many applications, involving multiagent/multivehicle systems, groups of agents need to agree upon certain quantities of interest. The main area of research in network systems is the development of consensus protocols for a network of dynamic agents. Distributed

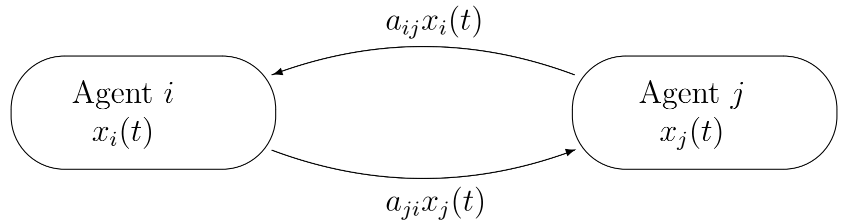


Figure 1.6: Network System

decision-making for coordination of networks of dynamic agents involving information flow can be naturally captured by compartmental systems.

One of the challenges of this multiagent agreement problem is to analyze the effects of information flow topology among the agents. This determines how the local action of each agent propagates throughout the group of agents. Scientists from diverse disciplines including animal behavior, physics and biophysics, social sciences and computer science have been fascinated by consensus in multiagent systems via local interactions [63, 64, 69, 75–84].

The primary aim of any consensus problem is to achieve agreement among the agents. For example, if we have n agents then we want $x_i(t) \to x_k(t)$ or $x_i(t) - x_k(t) \to 0$, $\forall i,\, k \in \{1, 2, \ldots, n\}$. Here, $x_i(t)$ is the variable of interest for the agent i. Depending on the applications this variable $x_i(t)$ could be position [66], velocity [85], or orbiting speed [86].

The main idea behind the consensus problem is to develop consensus protocols for network of agents with directed information flow, switching network topologies and in the presence of time-delays. We have developed linear and nonlinear consensus protocols for network systems with directed and undirected information flow in the presence of time-delays.

Even though the main focus of this dissertation is on nonnegative systems, the network systems may not always satisfy the nonnegativity condition. But they are still compartmental systems and hence compartmental modeling can be used for the analysis of these systems. All the results that we have for nonnegative systems can be easily extended to network systems by imposing the nonnegativity constraint on the system.

1.4. Brief Outline of the Dissertation

Nonnegative and compartmental dynamical system models are widespread in biological, physiological, ecological sciences, and network systems and play a key role in understanding these processes.

In this dissertation Chapters 2 and 3 focus on the application of compartmental models in biological systems and results for monotonicity and set-point regulation of the drug concentration are presented. Chapter 4 presents the linear and nonlinear consensus protocols that we developed for network systems, which guarantees semistability and equipartitioning of the system states. In Chapter 5, we present the conclusions of our research. We also discuss possible future extensions in solving the consensus problem.

In the specific field of pharmacokinetics involving the study of drug concentrations (in various tissue groups) as a function of time and dose, nonnegative and compartmental models are vital in understanding system wide effects of pharmacological agents. Since drug concentrations are often assumed to monotonically decline after discontinuation of drug administration, standard pharmacokinetic modeling may ignore the possibility of system oscillation. However, nonnegative and compartmental system models may exhibit non-monotonic solutions resulting in differences between model predictions and experimental data.

Hence, it is necessary to determine conditions for identifying nonnegative and compartmental systems that only admit nonoscillatory and monotonic solutions. We have developed necessary and sufficient conditions that guarantee nonoscillatory and monotonicity of nonnegative and compartmental systems with specific focus on pharmacokinetic models. We have also developed analogous necessary and sufficient conditions that guarantee monotonic solutions for discrete-time nonnegative and compartmental systems.

As explained in the previous section since time-delay arises in all systems in order to develop a more realistic model we have to consider the delay present in pharmacokinetic models. This time-delay in the dynamical pharmacokinetic model may destabilize equilibria and thus introduce oscillations in the system solutions that may otherwise be nonoscillatory in the absence of time delay. In Chapter 3 we present necessary and sufficient conditions for identifying nonnegative and compartmental dynamical systems that only admit nonoscillatory and monotonic solutions.

Thus, the necessary and sufficient conditions presented in Chapters 2 and 3 guarantee monotonic solutions that can be used to develop refined pharmacokinetic models.

The highly complex uncertain and hostile environment of surgery places imposes stringent performance requirements for closed-loop set-point regulation of physiological variables. The uncertainty in the patient response characteristics requires an adaptive controller which can tolerate system uncertainty and improve the system performance. We developed a direct adaptive controller which directly adjusts the controller gains in response to the system variations during drug administration. These results are presented in Chapter 4. We develop a direct adaptive control framework for uncertain linear nonnegative and compartmental dynamical systems with unknown time delay. The specific focus is on compartmental pharmacokinetic models and their applications to drug delivery systems. In particular, we develop a Lyapunov-Krasovskii-based direct adaptive control framework for guaranteeing set-point regulation of the closed-loop system in the nonnegative orthant in the presence of unknown system time delay. The framework additionally guarantees nonnegativity of the control signal. Finally, we demonstrate the framework on a drug delivery model for general anesthesia involving system time delays.

From Chapter 5 we focus on network systems and use compartmental models to analyze these systems and develop consensus protocols for the system. A network system consists of computing elements, processors or spatially distributed agents located at the nodes of a directed network graph. We have addressed the problem of reaching a consensus among a group of agents in a network in the presence of time-delays. It is important to develop consensus protocols for networks of dynamic agents with directed information flow, switching network topologies, and possible system time-delays. We use compartmental dynamical system models to characterize dynamic algorithms for linear and nonlinear networks of dynamic agents in the presence of inter-agent communication delays that possess a continuum of *semistable* equilibria, that is, protocol algorithms that guarantee convergence to Lyapunov stable equilibria. In addition, we show that the steady-state distribution of the dynamic network is uniform, leading to system state equipartitioning or consensus. These results extend the results in the literature on consensus protocols for linear balanced networks to linear and nonlinear unbalanced networks with time-delays.

In Chapter 6, we provide concluding remarks and discuss future extensions of this research. One of the main extensions we discuss is the development of consensus protocols for network systems with second-order dynamics for the agents. We discuss the effects of time-delay on the behavior of the systems and we propose a consensus protocol of the system.

Throughout the dissertation numerous illustrative examples and specific applications to the to the problems of drug-delivery systems and network systems is provided to demonstrate the efficiency of our proposed methods.

Chapter 2

On Nonoscillation and Monotonicity of Solutions of Nonnegative and Compartmental Dynamical Systems

2.1. Introduction

In recent years, dynamical systems have played an increasing role in the understanding of biological and physiological processes [2]. Many biological and physiological processes such as pharmacokinetics [17, 18], metabolic systems [19], epidemic dynamics [2], biochemical reactions [2, 87], endocrine systems [19], and lipoprotein kinetics [2] are nonnegative systems and mathematical modeling of these systems help us in understanding the behavior of these systems. Compartmental systems have wide applicability in biology and medicine, but their use in the specific field of pharmacokinetics [40, 41] is particularly noteworthy.

The goal of pharmacokinetic analysis often is to characterize the kinetics of drug disposition in terms of the parameters of a compartmental model. This is accomplished by postulating a model, collecting experimental data (typically drug concentrations in blood as a function of time), and then using statistical analysis to estimate parameter values which best describe the data. Differences between experimental data and that predicted by the model are attributed to measurement noise.

Because the ultimate disposition of exogenous drugs is metabolism and elimination from the body, it is frequently assumed that drug concentrations will monotonically decline after discontinuation of drug administration.

However, compartmental systems may admit non-monotonic solutions (e.g., underdamped oscillations); that is, they can predict drug concentrations which do not decay monotonically with time after discontinuation of drug administration. Hence, it would be useful to identify compartmental systems which guarantee monotonicity of solutions in order to avoid attributing error (differences between model predictions and experimental data) to random noise, when the problem is in fact model-misspecification. Similar considerations are also relevant to the other applications of nonnegative and compartmental dynamical systems. In this chapter, we present necessary and sufficient conditions for identifying nonnegative and compartmental dynamical systems that only admit nonoscillatory and monotonic solutions. Furthermore, we provide sufficient conditions that guarantee the absence of limit cycles in nonlinear compartmental systems. Then, we proceed to extend our results to show monotonicity in the case of discrete-time nonnegative systems.

2.2. Mathematical Preliminaries

In this section, we introduce some key results concerning linear nonnegative dynamical systems [7,13,16,27] that are necessary for developing our main results. The following definition introduces the notion of a nonnegative function.

Definition 2.1. Let $T > 0$. A real function $u : [0, T] \to \mathbb{R}^m$ is a *nonnegative* (resp., *positive*) *function* if $u(t) \geq\geq 0$ (resp., $u(t) >> 0$) on the interval $[0, T]$.

The next definition introduces the notion of essentially nonnegative matrices.

Definition 2.2 [16,27]. Let $A \in \mathbb{R}^{n\times n}$. A is *essentially nonnegative* if $A_{(i,j)} \geq 0$, $i, j = 1, \ldots, n$, $i \neq j$.

We begin by considering a linear nonnegative dynamical system of the form

$$\dot{x}(t) = Ax(t), \qquad x(0) = x_0, \qquad t \geq 0, \tag{2.1}$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, and $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative. The solution to (2.1) is standard and is given by $x(t) = e^{At}x(0)$, $t \geq 0$.

Lemma 2.1 [16,27]. Let $A \in \mathbb{R}^{n\times n}$. Then A is essentially nonnegative if and only if e^{At} is nonnegative for all $t \geq 0$. Furthermore, if A is essentially nonnegative and $x_0 \geq\geq 0$, then $x(t) \geq\geq 0$, $t \geq 0$, where $x(t)$, $t \geq 0$, denotes the solution to (2.1).

Next, we consider a subclass of nonnegative systems; namely, compartmental systems. As discussed in the Introduction, linear compartmental dynamical systems are of major importance in biological and physiological systems. For example, almost the entire field of distribution of tracer labeled materials in steady state systems can be captured by linear compartmental dynamical systems [26].

Definition 2.3. Let $A \in \mathbb{R}^{n\times n}$. A is a *compartmental matrix* if A is essentially nonnegative and $\sum_{i=1}^{n} A_{(i,j)} \leq 0$, $j = 1, 2, \ldots, n$.

If A is a compartmental matrix, then the nonnegative system (2.1) is called an *inflow-closed compartmental system* [16,26,28]. Recall that an inflow-closed compartmental system possesses a dissipation property and hence is Lyapunov stable since the total mass in the system given by the sum of all components of the state $x(t)$, $t \geq 0$, is nonincreasing along the forward trajectories of (2.1). In particular, with $V(x) = \mathbf{e}^{\mathrm{T}}x$, where $\mathbf{e} \triangleq [1, 1, \cdots, 1]^{\mathrm{T}}$, it follows that $\dot{V}(x) = \mathbf{e}^{\mathrm{T}}Ax = \sum_{j=1}^{n}\left[\sum_{i=1}^{n} A_{(i,j)}\right] x_j \leq 0$, $x \in \overline{\mathbb{R}}_+^n$. Furthermore, since $\mathrm{ind}(A) \leq 1$ [16,27], where $\mathrm{ind}(A)$ denotes the index of A [13], it follows that A is semistable; that is, $\lim_{t\to\infty} e^{At}$ exists. Hence, all solutions of inflow-closed linear compartmental systems are convergent. Of course, if $\det A \neq 0$, where $\det A$ denotes the determinant of A, then A is asymptotically stable. For details of the above facts see [16,27].

2.3. Nonoscillation of Linear Nonnegative Dynamical Systems

In this section, we present sufficient conditions that guarantee nonoscillatory behavior of nonnegative systems. Consider a linear nonnegative dynamical system of the form

$$\dot{x}(t) = Ax(t), \qquad x(0) = x_0, \qquad t \geq 0, \tag{2.2}$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, and $A \in \mathbb{R}^{n \times n}$ is essentially nonnegative. The solution to (2.2) is standard and is given by $x(t) = e^{At}x(0)$, $t \geq 0$. We, first introduce the following definition.

Definition 2.4. The linear nonnegative dynamical system (2.2) is *nonoscillatory* if there exists a finite time $T > 0$ and a matrix $Q \in \mathbb{R}^{n \times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, 2, \ldots, n$, and for every $x_0 \in \overline{\mathbb{R}}_+^n$, $Qx(t_2) \leq\leq Qx(t_1)$, $T \leq t_1 \leq t_2$, where $x(t)$, $t \geq 0$, denotes the solution to (2.2).

Next, we present a result that shows that every two-dimensional compartmental dynamical system is nonoscillatory. First, however, the following lemma is needed.

Lemma 2.2. Consider the linear nonnegative dynamical system (2.2) where $n = 2$ and $A \in \mathbb{R}^{2 \times 2}$ is a compartmental matrix. Then the following statements hold:

i) For every $x_0 \in \overline{\mathbb{R}}_+^2$ such that $Ax_0 \leq\leq 0$, $\dot{x}(t) = Ax(t) \leq\leq 0$, $t \geq 0$.

ii) For every $x_0 \in \overline{\mathbb{R}}_+^2$, $\mathbf{e}^{\mathrm{T}}\dot{x}(t) \leq 0$, $t \geq 0$.

iii) For $i = 1, 2$, if $\dot{x}_i(0) < 0$, then $\dot{x}_i(t) \leq 0$, $t \geq 0$.

Proof. *i*) Since A is essentially nonnegative it follows from Lemma 2.1 that $e^{At} \geq\geq 0$, $t \geq 0$. The result now follows immediately by noting $\dot{x}(t) = Ae^{At}x_0 = e^{At}Ax_0$.

ii) Since A is essentially nonnegative it follows from Lemma 2.1 that $x(t) \geq\geq 0$, $t \geq 0$. Now, since A is additionally a compartmental matrix, it follows that $\mathbf{e}^{\mathrm{T}}\dot{x}(t) = \mathbf{e}^{\mathrm{T}}Ax(t) = \sum_{j=1}^{2}\left[\sum_{i=1}^{2} A_{(i,j)}\right]x_j(t) \leq\leq 0$, $t \geq 0$.

iii) Assume $\dot{x}_1(0) < 0$. If $\dot{x}_2(0) \leq 0$, then it follows from *i*) that $\dot{x}(t) \leq\leq 0$, $t \geq 0$. Alternatively, let $\dot{x}_2(0) > 0$ and suppose, *ad absurdum*, there exists a finite time $T > 0$ such that $\dot{x}_1(T) > 0$. Now, since $\dot{x}(t)$, $t \geq 0$, is continuous it follows that there exists $\tau > 0$ such that $\dot{x}_1(\tau) = 0$. In this case, it follows from *ii*) that $0 \geq \mathbf{e}^{\mathrm{T}}\dot{x}(\tau) = \dot{x}_1(\tau) + \dot{x}_2(\tau) = \dot{x}_2(\tau)$. Hence, it follows from *i*) that $\dot{x}(t) \leq\leq 0$, $t \geq \tau$, which is a contradiction. The proof of the case in which $x_2(0) < 0$ is completely analogous and hence is omitted. □

Theorem 2.1. Consider the linear nonnegative dynamical system (2.2) where $n = 2$ and $A \in \mathbb{R}^{2\times 2}$ is a compartmental matrix. Then the linear compartmental dynamical system (2.2) is nonoscillatory.

Proof. It follows from *ii*) of Lemma 2.2 that for every $x_0 \in \overline{\mathbb{R}}_+^2$, $\mathbf{e}^{\mathrm{T}}\dot{x}(0) \leq\leq 0$ which implies that either (a) $\dot{x}_1(0) \leq 0$, $\dot{x}_2(0) \leq 0$, (b) $\dot{x}_1(0) > 0$, $\dot{x}_2(0) < 0$, or (c) $\dot{x}_1(0) < 0$, $\dot{x}_2(0) > 0$ holds. If (a) holds, then it follows from *i*) of Lemma 2.2 that $\dot{x}(t) \leq\leq 0$, $t \geq 0$. Alternatively, if (b) holds, then it follows from *iii*) of Lemma 2.2 that $\dot{x}_2(t) \leq 0$, $t \geq 0$. In this case, if $\dot{x}_1(t) \geq 0$, $t \geq 0$, then $\dot{x}_i(t)$, $t \geq 0$, $i = 1, 2$, is monotonic. However, if there exists a finite time $T > 0$ such that $\dot{x}_1(T) \leq 0$, then it follows from *i*) of Lemma 2.2 that $\dot{x}(t) \leq\leq 0$, $t \geq T$. Similarly it can be shown that if (c) holds, then there exists $T > 0$ such that $\dot{x}_i(t)$, $t \geq T$, $i = 1, 2$, is monotonic. Hence, for every $x_0 \in \overline{\mathbb{R}}_+^2$, there exists $T > 0$ such that $\dot{x}_i(t)$, $t \geq T$, $i = 1, 2$, is monotonic or, equivalently, there exists $Q = \mathrm{diag}[q_1, q_2]$, $q_i = \pm 1$, $i = 1, 2$, such that $Q\dot{x}(t) \leq\leq 0$, $t \geq T$. Now, it follows from (2.2) that for every $T \leq t_1 \leq t_2$,

$$Qx(t_2) = Qx(t_1) + \int_{t_1}^{t_2} Q\dot{x}(t)\mathrm{d}t \leq\leq Qx(t_1),$$

which proves that (2.2) is nonoscillatory. □

Theorem 2.1 shows that two-dimensional compartmental systems have monotonic solutions after a *finite time* T. However, this result is not true in the case of higher dimensions. In the next section, we give necessary and sufficient conditions for *mono-*

tonicity of solutions over all time of nonlinear n-dimensional nonnegative dynamical systems.

2.4. Monotonicity of Nonlinear Nonnegative Dynamical Systems

In this section we consider monotonicity of solutions over all time of nonlinear nonnegative dynamical systems. Specifically, we consider nonlinear dynamical systems $\mathcal{G}$ of the form

$$\dot{x}(t) = f(x(t)) + G(x(t))u(t), \qquad x(0) = x_0, \qquad t \geq 0, \tag{2.3}$$

where $x \in \mathbb{R}^n$, $u \in \mathbb{R}^m$, $f : \mathbb{R}^n \to \mathbb{R}^n$, and $G : \mathbb{R}^n \to \mathbb{R}^{n\times m}$. We assume that $f(\cdot)$ and $G(\cdot)$ are continuously differentiable mappings and $f(x_\mathrm{e}) = 0$, $x_\mathrm{e} \in \mathbb{R}^n$. The following definition generalizes the notion of essential nonnegativity to vector fields.

Definition 2.5 [4, 16]. Let $f = [f_1, \cdots, f_n]^\mathrm{T} : \mathbb{R}^n \to \mathbb{R}^n$. Then f is *essentially nonnegative* if $f_i(x) \geq 0$, for all $i = 1, \ldots, n$, and $x \in \overline{\mathbb{R}}_+^n$ such that $x_i = 0$, where x_i denotes the ith element of x.

Note that if $f(x) = Ax$, where $A \in \mathbb{R}^{n\times n}$, then f is essentially nonnegative if and only if A is essentially nonnegative.

Definition 2.6. The nonlinear dynamical system given by (2.3) is *nonnegative* if for every $x(0) \in \overline{\mathbb{R}}_+^n$ and $u(t) \geq\geq 0$, $t \geq 0$, the solution $x(t)$, $t \geq 0$, to (2.3) is nonnegative.

The following proposition is required for the main theorem of this section.

Proposition 2.1 [16]. Consider the nonlinear dynamical system $\mathcal{G}$ given by (2.3). If $f : \mathbb{R}^n \to \mathbb{R}^n$ is essentially nonnegative and $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^n$, then $\mathcal{G}$ is nonnegative.

Definition 2.7. Consider the nonlinear nonnegative dynamical system (2.3) where $x_0 \in \mathcal{X}_0 \subseteq \overline{\mathbb{R}}_+^n$, $f : \mathbb{R}^n \to \mathbb{R}^n$ is essentially nonnegative, $G(x) \geq\geq 0$, $u(t)$, $t \geq 0$, is nonnegative, and $\mathcal{X}_0$ denotes a set of initial conditions contained in $\overline{\mathbb{R}}_+^n$. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(t) \triangleq [x_{k_1}(t), \ldots, x_{k_{\hat{n}}}(t)]^{\mathrm{T}}$. The nonlinear nonnegative dynamical system (2.3) is *partially monotonic with respect to* $\hat{x}$ if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \operatorname{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and for every $x_0 \in \mathcal{X}_0$, $Qx(t_2) \leq\leq Qx(t_1)$, $0 \leq t_1 \leq t_2$, where $x(t)$, $t \geq 0$, denotes the solution to (2.3). The nonlinear nonnegative dynamical system (2.3) is *monotonic* if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \operatorname{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, and for every $x_0 \in \mathcal{X}_0$, $Qx(t_2) \leq\leq Qx(t_1)$, $0 \leq t_1 \leq t_2$.

Remark 2.1. The notion of partial monotonicity with respect to part of the system states is very important in pharmacokinetic modeling since it allows for some compartmental masses/concentrations to exhibit oscillations while guaranteeing nonoscillation in the other compartments which can include the central compartment.

Next, we present necessary and sufficient conditions for monotonicity of a nonlinear nonnegative dynamical system.

Theorem 2.2. Consider the nonlinear nonnegative dynamical system $\mathcal{G}$ given by (2.3) where $x_0 \in \overline{\mathbb{R}}_+^n$, $f : \mathbb{R}^n \to \mathbb{R}^n$ is essentially nonnegative, $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^n$, and $u(t)$, $t \geq 0$, is nonnegative. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(t) \triangleq [x_{k_1}(t), \ldots, x_{k_{\hat{n}}}(t)]^{\mathrm{T}}$. Then the following statements hold:

i) If there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \operatorname{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, $Qf(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$, and $QG(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$, then $\mathcal{G}$ is partially monotonic with respect to $\hat{x}$.

ii) If $u(t) \equiv 0$, then $\mathcal{G}$ is partially monotonic with respect to $\hat{x}$ if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \operatorname{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and $Qf(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$.

Proof. *i*) It follows from (2.3) that

$$Q\dot{x}(t) = Qf(x(t)) + QG(x(t))u(t), \qquad x(0) = x_0, \qquad t \geq 0,$$

which further implies that

$$Qx(t_2) = Qx(t_1) + \int_{t_1}^{t_2} [Qf(x(t)) + QG(x(t))u(t)]\mathrm{d}t.$$

Next, since $f : \mathbb{R}^n \to \mathbb{R}^n$ is essentially nonnegative, $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^n$, and $u(t)$, $t \geq 0$, is nonnegative it follows from Proposition 2.1 that $x(t) \geq\geq 0$, $t \geq 0$. Hence, since $-Qf(x)$ and $-QG(x)$ are nonnegative for all $x \in \overline{\mathbb{R}}_+^n$ it follows that $Qf(x(t)) \leq\leq 0$ and $QG(x(t))u(t) \leq\leq 0$, $t \geq 0$, which implies that for every $x_0 \in \overline{\mathbb{R}}_+^n$, $Qx(t_2) \leq\leq Qx(t_1)$, $0 \leq t_1 \leq t_2$.

ii) Sufficiency follows from *i*) with $u(t) \equiv 0$. To show necessity assume that $\mathcal{G}$ with $u(t) \equiv 0$ is partially monotonic with respect to $\hat{x}$. In this case, it follows from (2.3) that

$$Q\dot{x}(t) = Qf(x(t)), \quad x(0) = x_0, \quad t \geq 0,$$

which further implies that for every $\tau > 0$,

$$Qx(\tau) = Qx_0 + \int_0^\tau Qf(x(t))\mathrm{d}t.$$

Now, suppose, *ad absurdum*, there exist $J \in \{1, 2, \ldots, n\}$ and $x_0 \in \overline{\mathbb{R}}_+^n$ such that $[Qf(x_0)]_J > 0$. Since the mapping $Qf(\cdot)$ and the solution $x(t)$, $t \geq 0$, to (2.3) are continuous it follows that there exists $\tau > 0$ such that $[Qf(x(t))]_J > 0$, $0 \leq t \leq \tau$, which implies that $[Qx(\tau)]_J > [Qx_0]_J$, which is a contradiction. Hence, $Qf(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$. □

Corollary 2.1. Consider the nonlinear nonnegative dynamical system $\mathcal{G}$ given by (2.3) where $x_0 \in \overline{\mathbb{R}}_+^n$, $f : \mathbb{R}^n \to \mathbb{R}^n$ is essentially nonnegative, $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^n$, and $u(t)$, $t \geq 0$, is nonnegative. Then the following statements hold:

i) If there exists a matrix $Q \in \mathbb{R}^{n \times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, $Qf(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$, and $QG(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$, then $\mathcal{G}$ is monotonic.

ii) If $u(t) \equiv 0$, then $\mathcal{G}$ is monotonic if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, and $Qf(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$.

Proof. The proof is a direct consequence of Theorem 2.2 with $\hat{n} = n$ and $\{k_1, \ldots, k_{\hat{n}}\} = \{1, \ldots, n\}$. $\square$

Corollary 2.1 provides some interesting ramifications with regards to the absence of limit cycles of inflow-closed nonlinear compartmental systems. To see this, consider the inflow-closed ($u(t) \equiv 0$) compartmental system (2.3) where $f(x) = [f_1(x), \cdots, f_n(x)]^{\mathrm{T}}$ is such that

$$f_i(x) = -a_{ii}(x) + \sum_{j=1, i\neq j}^{n} [a_{ij}(x) - a_{ji}(x)] \tag{2.4}$$

and where the instantaneous rates of compartmental material losses $a_{ii}(\cdot)$, $i = 1, \ldots, n$, and intercompartmental material flows $a_{ij}(\cdot)$, $i \neq j$, $i, j = 1, \ldots, n$, are such that $a_{ii}(x) \geq 0$ and $a_{ij}(x) \geq 0$, $x \in \overline{\mathbb{R}}_+^n$, $i, j = 1, \ldots, n$. Since all mass flows as well as compartment sizes are nonnegative, it follows that for all $i = 1, \ldots, n$, $f_i(x) \geq 0$ for all $x \in \overline{\mathbb{R}}_+^n$ whenever $x_i = 0$ and whatever the values of x_j, $j \neq i$. Hence, f is essentially nonnegative. As in the linear case, inflow-closed nonlinear compartmental systems are Lyapunov stable since the total mass in the system given by the sum of all components of the state $x(t)$, $t \geq 0$, is nonincreasing along the forward trajectories of (2.3). To see this, let $V(x) = \mathbf{e}^{\mathrm{T}} x$ and assume $a_{ij}(0) = 0$, $i, j = 1, \ldots, n$, then it follows that

$$\begin{aligned} \dot{V}(x) &= \sum_{i=1}^{n} \dot{x}_i = -\sum_{i=1}^{n} a_{ii}(x) + \sum_{i=1}^{n} \sum_{j=1, i\neq j}^{n} [a_{ij}(x) - a_{ji}(x)] \\ &= -\sum_{i=1}^{n} a_{ii}(x) \leq 0, \quad x \in \overline{\mathbb{R}}_+^n, \end{aligned} \tag{2.5}$$

which shows that the zero solution $x(t) \equiv 0$ of the inflow-closed nonlinear compartmental system (2.3) is Lyapunov stable and hence for every $x_0 \in \overline{\mathbb{R}}_+^n$, the solution to (2.3) is bounded. However, unlike the case of linear compartmental systems [16, 27], the zero solution $x(t) \equiv 0$ to (2.3) with $u(t) \equiv 0$ is *not* necessarily convergent. In fact, (2.3) with $f(x)$ given by (2.4) can exhibit limit cycles, bifurcations, and even chaos [28].

In light of the above, it is of interest to determine sufficient conditions under which masses/concentrations for nonlinear compartmental systems are Lyapunov stable *and* convergent, guaranteeing the absence of limit cycling behavior. The following result is a direct consequence of Corollary 2.1 and provides sufficient conditions for the absence of limit cycles in nonlinear compartmental systems.

Theorem 2.3. Consider the nonlinear nonnegative dynamical system $\mathcal{G}$ given by (2.3) with $u(t) \equiv 0$ and $f(x) = [f_1(x), \cdots, f_n(x)]^{\mathrm{T}}$ such that (2.4) holds. If there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \cdots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, and $Qf(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$, then for every $x_0 \in \overline{\mathbb{R}}_+^n$, $\lim_{t\to\infty} x(t)$ exists.

Proof. Let $V(x) = \mathbf{e}^{\mathrm{T}}x$, $x \in \overline{\mathbb{R}}_+^n$. Now, it follows from (2.5) that $\dot{V}(x(t)) \leq 0$, $t \geq 0$, where $x(t)$, $t \geq 0$, denotes the solution of $\mathcal{G}$, which implies that $V(x(t)) \leq V(x_0) = \mathbf{e}^{\mathrm{T}}x_0$, $t \geq 0$, and hence for every $x_0 \in \overline{\mathbb{R}}_+^n$, the solution $x(t)$, $t \geq 0$, of $\mathcal{G}$ is bounded. Hence, for every $i \in \{1, \cdots, n\}$, $x_i(t)$, $t \geq 0$, is bounded. Furthermore, it follows from Corollary 2.1 that $x_i(t)$, $t \geq 0$, is monotonic. Now, since $x_i(\cdot)$, $i \in \{1, \cdots, n\}$, is continuous and every bounded nonincreasing or nondecreasing scalar sequence converges to a finite real number, it follows that $\lim_{t\to\infty} x_i(t)$, $i = 1, \ldots, n$, exists. Hence, $\lim_{t\to\infty} x(t)$ exists. $\square$

2.5. Monotonicity of Linear Nonnegative Dynamical Systems

In this section, we specialize the results of Section 2.4 to linear nonnegative dynamical systems of the form

$$\dot{x}(t) = Ax(t) + Bu(t), \qquad x(0) = x_0, \qquad t \geq 0, \tag{2.6}$$

where $x \in \mathbb{R}^n$, $u \in \mathbb{R}^m$, $A \in \mathbb{R}^{n\times n}$, and $B \in \mathbb{R}^{n\times m}$. Recall that the linear dynamical system given by (2.6) is nonnegative if and only if $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative and $B \in \mathbb{R}^{n\times m}$ is nonnegative [16].

Theorem 2.4. Consider the linear nonnegative dynamical system given by (2.6) where $x_0 \in \overline{\mathbb{R}}_+^n$, $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $B \in \mathbb{R}^{n\times m}$ is nonnegative, and $u(t)$, $t \geq 0$, is nonnegative. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(t) \triangleq [x_{k_1}(t), \ldots, x_{k_{\hat{n}}}(t)]^{\mathrm{T}}$. Then the following statements holds:

i) If there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and $QA \leq\leq 0$ and $QB \leq\leq 0$, then (2.6) is partially monotonic with respect to $\hat{x}$.

ii) If $u(t) \equiv 0$, then (2.6) is partially monotonic with respect to $\hat{x}$ if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and $QA \leq\leq 0$.

Proof. The proof is a direct consequence of Theorem 2.2 with $f(x) = Ax$ and $G(x) = B$. □

Corollary 2.2. Consider the linear nonnegative dynamical system given by (2.6) where $x_0 \in \overline{\mathbb{R}}_+^n$, $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $B \in \mathbb{R}^{n\times m}$ is nonnegative, and $u(t)$, $t \geq 0$, is nonnegative. Then the following statements hold:

i) If there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, and $-QA$ and $-QB$ are nonnegative, then (2.6) is monotonic.

ii) If $u(t) \equiv 0$, then (2.6) is monotonic if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, 2, \ldots, n$, and $QA \leq\leq 0$.

Proof. The proof is a direct consequence of Theorem 2.4 with $\hat{n} = n$ and $\{k_1, \ldots, k_{\hat{n}}\} = \{1, \ldots, n\}$. □

Finally, we present a sufficient condition for *weighted monotonicity* for a linear nonnegative dynamical system.

Proposition 2.2. Consider the linear dynamical system given by (2.2) where A is essentially nonnegative and $x_0 \in \mathcal{X}_0 \triangleq \{SAx_0 \leq\leq 0 : x_0 \in \mathbb{R}^n\}$, where $S \in \mathbb{R}^{n\times n}$

is an invertible matrix. If SAS^{-1} is essentially nonnegative, then for every $x_0 \in \mathcal{X}_0$, $S\dot{x}(t) = SAx(t) \leq\leq 0$, $t \geq 0$, and $Sx(t_2) \leq\leq Sx(t_1)$, $0 \leq t_1 \leq t_2$.

Proof. Let $y(t) \triangleq -SAx(t)$ and note that $y(0) = -SAx_0 \in \overline{\mathbb{R}}_+^n$. It follows from (2.2) that

$$\dot{y}(t) = -SA\dot{x}(t) = -SA^2x(t) = SAS^{-1}y(t), \qquad t \geq 0.$$

Next, since SAS^{-1} is essentially nonnegative, it follows from Lemma 2.1 that $y(t) \in \overline{\mathbb{R}}_+^n$, $t \geq 0$. Now the result follows immediately by noting that $y(t) = -SAx(t)$, $t \geq 0$. $\square$

2.6. Mammillary Systems

The most common pharmacokinetic models are linear and *mammillary*, that is, they are comprised of a central compartment from which there is outflow from the system and which exchanges material reversibly with one or more peripheral compartments. An inflow-closed mammillary system is given by (2.2) with A given by

$$A = \begin{bmatrix} -(k_{11}+k_{21}+k_{31}) & k_{12} & k_{13} \\ k_{21} & -k_{12} & 0 \\ k_{31} & 0 & -k_{13} \end{bmatrix}, \tag{2.7}$$

where the transfer coefficients k_{ij}, $i \neq j$, $i, j = 1, 2, 3$, and the loss coefficient k_{11} are nonnegative. It follows from Theorem 2.4 and Corollary 2.2 that mammillary models are neither monotonic nor partially monotonic with respect to any compartment. In numerous pharmacological applications, the initial state (at $t = 0$) is characterized by a non-zero concentration in the central compartment with all other compartments having zero initial concentrations. This, for example, can happen when a drug that is not synthesized by the body is administered as an impulsive intravenous injection. It is well documented via simulations that in this case the central compartment concentration monotonically decays. In the next theorem we state and prove this result for three-dimensional mammillary models. For the following theorem $x_1(t)$, $x_2(t)$, and $x_3(t)$, $t \geq 0$, denote the concentrations of the first (central), second, and third compartments, respectively.

Theorem 2.5. Consider the mammillary system given by (1) where A is given by (2.7). If $x_0 = [1\ 0\ 0]^{\mathrm{T}}$, then the following statements hold:

i) If $\dot{x}_2(t) \geq 0$ and $\dot{x}_3(t) \geq 0$, $t \geq 0$, then $\dot{x}_1(t) \leq 0$, $t \geq 0$.

ii) If $k_{12} \geq k_{13}$ and there exists $T > 0$ such that $\dot{x}_1(t) \leq 0$, $t \leq T$, and $\dot{x}_2(T) < 0$ or $\dot{x}_3(T) < 0$, then there exists $\hat{T} < T$ such that $\dot{x}_2(t) \geq 0$, $\dot{x}_3(t) \geq 0$, $t \leq \hat{T}$, and $\dot{x}_2(\hat{T}) = 0$.

iii) If $k_{12} \leq k_{13}$ and there exists $T > 0$ such that $\dot{x}_1(t) \leq 0$, $t \leq T$, and $\dot{x}_3(T) < 0$ or $\dot{x}_2(T) < 0$, then there exists $\hat{T} < T$ such that $\dot{x}_2(t) \geq 0$, $\dot{x}_3(t) \geq 0$, $t \leq \hat{T}$, and $\dot{x}_3(\hat{T}) = 0$.

iv) $\dot{x}_1(t) \leq 0$, $t \geq 0$, or, equivalently, the mammillary system is partially monotonic with respect to x_1.

Proof. *i*) Assume that $\dot{x}_2(t) \geq 0$ and $\dot{x}_3(t) \geq 0$, $t \geq 0$. It follows from (2.7) that $\dot{x}_1(t) + \dot{x}_2(t) + \dot{x}_3(t) = -k_{11}x_1(t)$, $t \geq 0$, which implies that $\dot{x}_1(t) = -k_{11}x_1(t) - \dot{x}_2(t) - \dot{x}_3(t) \leq 0$, $t \geq 0$.

ii) Since $\ddot{x}(t) = A\dot{x}(t)$, $t \geq 0$, it follows from Lagrange's formula that $\dot{x}_j(t) = e^{-k_{1j}t}\dot{x}_j(0) + \int_0^t e^{-k_{1j}(t-\tau)}k_{j1}\dot{x}_1(\tau)\mathrm{d}\tau$, $j = 2, 3$. Next, since $x_0 = [1\ 0\ 0]^{\mathrm{T}}$, it follows that $\dot{x}_j(0) = k_{j1}$, $j = 2, 3$. Hence, it follows that

$$\dot{x}_j(t) = e^{-k_{ij}(t)}k_{j1}\left[1 + \int_0^t e^{k_{1j}\tau}\dot{x}_1(\tau)\mathrm{d}\tau\right], \qquad j = 2, 3. \tag{2.8}$$

Now, if there exists $T > 0$ such that $\dot{x}_1(t) \leq 0$, $t \leq T$, and $\dot{x}_2(T) < 0$, then it follows from the continuity of $\dot{x}_2(\cdot)$ that there exists $\hat{T} < T$ such that $\dot{x}_2(\hat{T}) = 0$. Hence, it follows from (2.8) that $1 + \int_0^{\hat{T}} e^{k_{12}\tau}\dot{x}_1(\tau)\mathrm{d}\tau = 0$. Furthermore, since $\dot{x}_1(t) \leq 0$, $t \leq T$, and $k_{12} \geq k_{13}$ it follows that $1 + \int_0^t e^{k_{13}\tau}\dot{x}_1(\tau)\mathrm{d}\tau \geq 0$, $t \leq \hat{T}$, and (2.8) implies that $\dot{x}_3(t) \geq 0$, $t \leq \hat{T}$. In the case where there exists $T > 0$ such that $\dot{x}_1(t) \leq 0$, $t \leq T$ and $\dot{x}_3(T) < 0$ the proof is similar and hence is omitted.

iii) The proof is identical to that of *ii*) and hence is omitted.

iv) Assume $k_{12} \geq k_{13}$. If $\dot{x}_2(t) \geq 0$ and $\dot{x}_3(t) \geq 0$, $t \geq 0$, then it follows from *i*) that $\dot{x}_1(t) \leq 0$, $t \geq 0$. Alternatively, if there exists $T > 0$ such that $\dot{x}_1(t) \leq 0$, $t \leq T$, and $\dot{x}_2(T) < 0$ or $\dot{x}_3(T) < 0$, then it follows from *ii*) that there exists $\hat{T} < T$ such that $\dot{x}_2(t) \geq 0$, $\dot{x}_3(t) \geq 0$, $t \leq \hat{T}$, and $\dot{x}_2(\hat{T}) = 0$. Next, suppose, *ad absurdum*, there exists $T_1 > 0$ such that $\dot{x}_1(T_1) > 0$. It follows from the continuity of $\dot{x}_1(\cdot)$ that there exists $T_2 \in [\hat{T}, T_1)$ such that $\dot{x}_1(t) \leq 0$, $t \leq T_2$, $\dot{x}_1(T_2) = 0$, and $\ddot{x}_1(T_2) > 0$. Note that $\ddot{x}_1(T_2) = k_{12}\dot{x}_2(T_2) + k_{13}\dot{x}_3(T_2)$. Furthermore, note that $\dot{x}_2(T_2) + \dot{x}_3(T_2) = -k_{11}x_1(T_2) \leq 0$. Now, since $\dot{x}_2(\hat{T}) = 0$, $\dot{x}_1(t) \leq 0$, $t \in [\hat{T}, T_2]$, it follows from (2.8) that $\dot{x}_2(T_2) \leq 0$. Hence, $\ddot{x}_1(T_2) = k_{12}\dot{x}_2(T_2) + k_{13}\dot{x}_3(T_2) \leq k_{13}(\dot{x}_2(T_2) + \dot{x}_3(T_2)) \leq 0$, which is a contradiction. Hence, $\dot{x}_1(t) \leq 0$, $t \geq 0$. The proof for the case where $k_{13} \geq k_{12}$ is similar and hence is omitted. $\square$

While identifying monotonicity of the central compartment when it is the only compartment to have a non-zero initial condition is interesting, it should be noted that the results in this chapter provide necessary and sufficient conditions for monotonicity and partial monotonicity for all initial conditions. Thus, the main application of this research is for models in which the initial conditions are less constrained, with non-zero initial states in multiple compartments. Noteworthy among potential applications is the exogenous administration of a pharmacological agent that is also endogenously synthesized. For example, consider the endogenous modulator of coagulation, antithrombin III (AT-3). The action of the exogenous anticoagulant, heparin is dependent on activation of AT-3. AT-3 deficiency (congenital and acquired) is not uncommon and sometimes necessitates exogenous administration of AT-3. Hence, there has been interest in the pharmacokinetics of AT-3. In a study of transgenic AT-3, Lu *et al.* [88] assumed partial monotonicity of the central compartment with a two-compartment mammillary model. Since there is endogenous synthesis of AT-3, it is not immediately clear that the assumption of central compartment monotonicity after a single bolus dose was valid. However, Lemma 2.2 indicates that this assumption was, indeed, valid since $\dot{x}_1(0) < 0$. Note, however, that this lemma is applicable only to two compartment models. There are numerous examples of other endogenously synthesized pharmacological agents, such as hormones, whose kinetics are described by more complex models after exogenous supplementation. Theorem 2.4 and Proposition 2.2 (weighted monotonicity) should aid in identifying monotonic behavior for these more complex models.

Another area of potential applicability of our results is the kinetics of plasma volume expanders, especially hypertonic volume expanders. The kinetics of intravenous fluids, such as hypertonic saline, used for plasma volume expansion can be described by compartment models, and, obviously, the initial conditions will be comprised of material (in this case, fluid volume) in all compartments [89]. The dilution of various compartments could be complex depending on the exact initial conditions.

An interesting, although more speculative, application is to the effect of cardiopulmonary bypass (CPB) on pharmacokinetics. The institution of CPB can be expected to result in a nearly step-wise decrease in the central compartment concentration of any drugs previously administered, due to the mixing of the patients circulating blood volume with the priming volume of the extra-corporeal circulation circuit. In contrast to bolus administration into the central compartment, in which the initial state is non-zero for this compartment only, the initial state at the institution of CPB may be characterized by a central compartment concentration that is less than the peripheral compartments due to hemodilution of the central compartment. As an example, consider a three compartment mammillary CPB model. Applying Theorem 2.4 rules out partial monotonicity with respect to any compartment.

Figure 2.1 shows a simulation of a three compartment mammillary model with model parameters $k_{11} = 0.001$, $k_{21} = 0.2$, $k_{12} = 0.2$, $k_{31} = 0.01$, and $k_{13} = 0.02$ and initial conditions $x_1(0) = 0.5$, $x_2(0) = 1$, and $x_3(0) = 1$. While these parameters and initial conditions are arbitrary, they serve to illustrate the implications of Theorem 2.4. There is a monotonic decrease in the concentration of compartment 3. However, the concentration of compartment 1 increases, then decreases before settling into a

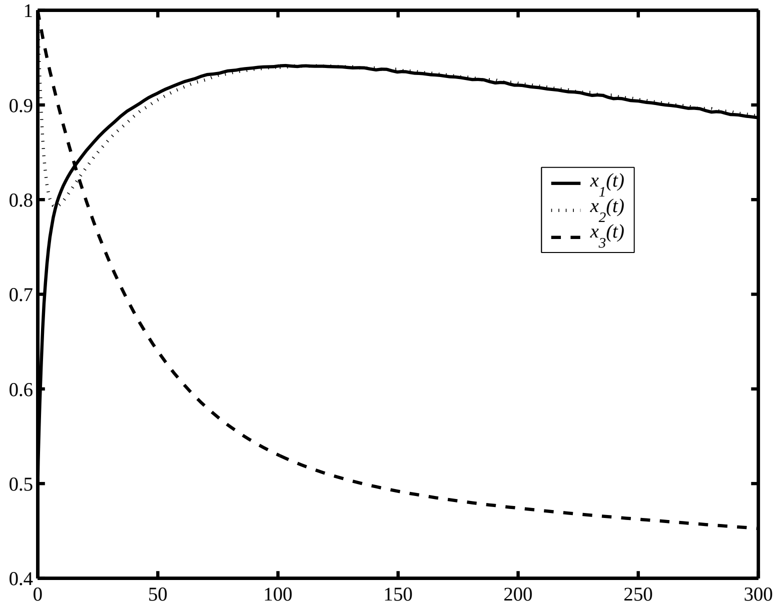


Figure 2.1: Nonmonotonicity of a Mammillary Model

monotonic decay. Alternatively, the concentration of compartment 2 decreases, then increases before settling into a monotonic decay. If compartment 2 is also identified as the site of biological effect, for example a peripheral compartment comprised of primarily of muscle and hence the site of action of muscle relaxants, then institution of CPB could be expected to result in a sudden decrease in the concentration of the muscle relaxant at its site of action which, if treated with additional muscle relaxant, could result in a subsequent relative overdose.

2.7. Monotonicity of Solutions of Discrete-Time Nonnegative and Compartmental Dynamical Systems

In this section we present analogous results for monotonicity of linear nonnegative dynamical systems. We introduce several definitions and some key results concerning discrete-time, linear nonnegative dynamical systems.

Definition 2.8. A real function $u : \mathcal{N} \to \mathbb{R}^m$ is a *nonnegative* (resp., *positive*) *function* if $u(k) \geq\geq 0$ (resp., $u(k) >> 0$), $k \in \mathcal{N}$.

Consider the discrete-time, linear nonnegative dynamical system of the form

$$x(k+1) = Ax(k) + Bu(k), \qquad x(0) = x_0, \qquad k \in \mathcal{N}, \tag{2.9}$$

where $x \in \mathbb{R}^n$, $u \in \mathbb{R}^m$, $A \in \mathbb{R}^{n\times n}$, and $B \in \mathbb{R}^{n\times m}$.

Definition 2.9. The linear dynamical system given by (2.9) is *nonnegative* if for every $x(0) \in \overline{\mathbb{R}}_+^n$ and $u(k) \geq\geq 0$, $k \in \mathcal{N}$, the solution $x(k)$, $k \in \mathcal{N}$, to (2.9) is nonnegative.

Proposition 2.3 [90]. The linear dynamical system given by (2.9) is nonnegative if and only if $A \in \mathbb{R}^{n\times n}$ is nonnegative and $B \in \mathbb{R}^{n\times m}$ is nonnegative.

Definition 2.10. Let $A \in \mathbb{R}^{n\times n}$. A is a *compartmental matrix* if A is nonnegative and $\sum_{k=1}^{n} A_{(k,j)} \leq 1$, $j = 1, 2, \ldots, n$.

If A is a compartmental matrix and $u(k) \equiv 0$, then the nonnegative system (2.9) is called an *inflow-closed compartmental system* [26,28,90]. Recall that an inflow-closed compartmental system possesses a dissipation property and hence is Lyapunov stable since the total mass in the system given by the sum of all components of the state $x(k)$, $k \in \mathcal{N}$, is non-increasing along the forward trajectories of (2.9). In particular, with $V(x) = e^{\mathrm{T}}x$, where $e = [1, 1, \cdots, 1]^{\mathrm{T}}$, it follows that $\Delta V(x(k)) = e^{\mathrm{T}}(A - I)x(k) = \sum_{j=1}^{n} \left[\sum_{i=1}^{n} A_{(i,j)} - 1\right] x_j \leq 0$, $x \in \overline{\mathbb{R}}_+^n$. Hence, all solutions of inflow-closed linear compartmental systems are bounded. Of course, if $\det A \neq 0$, where $\det A$ denotes the determinant of A, then A is asymptotically stable. For details of the above facts see [90].

2.8. Monotonicity of Linear Nonnegative Dynamical Systems

The definition of monotonicity for the discrete-time linear nonnegative dynamical system given by (2.9) is stated as follows.

Definition 2.11. Consider the discrete-time, linear nonnegative dynamical system (2.9) where $x_0 \in \mathcal{X}_0 \subseteq \overline{\mathbb{R}}_+^n$, A is nonnegative, B is nonnegative, $u(k)$, $k \in \mathcal{N}$, is nonnegative, and $\mathcal{X}_0$ denotes a set of feasible initial conditions contained in $\overline{\mathbb{R}}_+^n$. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(k) \triangleq [x_{k_1}(k), \ldots, x_{k_{\hat{n}}}(k)]^{\mathrm{T}}$. The discrete-time, linear nonnegative dynamical system (2.9) is *partially monotonic with respect to* $\hat{x}$ if there exists a matrix $Q \in \mathbb{R}^{n \times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and for every $x_0 \in \mathcal{X}_0$, $Qx(k_2) \leq\leq Qx(k_1)$, $0 \leq k_1 \leq k_2$, where $x(k)$, $k \in \mathcal{N}$, denotes the solution to (2.9). The discrete-time, linear nonnegative dynamical system (2.9) is *monotonic* if there exists a matrix $Q \in \mathbb{R}^{n \times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, and for every $x_0 \in \mathcal{X}_0$, $Qx(k_2) \leq\leq Qx(k_1)$, $0 \leq k_1 \leq k_2$.

Next, we present a sufficient condition for monotonicity of a discrete-time, linear nonnegative dynamical system.

Theorem 2.6. Consider the discrete-time, linear nonnegative dynamical system given by (2.9) where $x_0 \in \overline{\mathbb{R}}_+^n$, $A \in \mathbb{R}^{n \times n}$ is nonnegative, $B \in \mathbb{R}^{n \times m}$ is nonnegative, and $u(k)$, $k \in \mathcal{N}$, is nonnegative. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(k) \triangleq [x_{k_1}(k), \ldots, x_{k_{\hat{n}}}(k)]^{\mathrm{T}}$. Assume there exists a matrix $Q \in \mathbb{R}^{n \times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and $QA \leq\leq Q$ and $QB \leq\leq 0$. Then the discrete-time, linear nonnegative dynamical system (2.9) is partially monotonic with respect to $\hat{x}$.

Proof. It follows from (2.9) that

$$Qx(k+1) = QAx(k) + QBu(k), \qquad x(0) = x_0, \qquad k \in \mathcal{N},$$

which implies that

$$Qx(k_2) = Qx(k_1) + \sum_{k=k_1}^{k_2-1} [Q(A-I)x(k) + QBu(k)].$$

Next, since A and B are nonnegative and $u(k)$, $k \in \mathcal{N}$, is nonnegative it follows from Proposition 2.3 that $x(k) \geq\geq 0$, $k \in \mathcal{N}$. Hence, since $-Q(A - I)$ and $-QB$ are nonnegative it follows that $Q(A-I)x(k) \leq\leq 0$ and $QBu(k) \leq\leq 0$, $k \in \mathcal{N}$, which implies that for every $x_0 \in \overline{\mathbb{R}}_+^n$, $Qx(k_2) \leq\leq Qx(k_1)$, $0 \leq k_1 \leq k_2$. $\square$

Corollary 2.3. Consider the discrete-time, linear nonnegative dynamical system given by (2.9) where $x_0 \in \overline{\mathbb{R}}_+^n$, $A \in \mathbb{R}^{n\times n}$ is nonnegative, $B \in \mathbb{R}^{n\times m}$ is nonnegative, and $u(k)$, $k \in \mathcal{N}$, is nonnegative. Assume there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \operatorname{diag}[q_1,\ldots,q_n]$, $q_i = \pm 1$, $i = 1,\ldots,n$, and $QA \leq\leq Q$ and $QB \leq\leq 0$ are nonnegative. Then the discrete-time, linear nonnegative dynamical system given by (2.9) is monotonic.

Proof. The proof is a direct consequence of Theorem 2.6 with $\hat{n} = n$ and $\{k_1,\ldots,k_{\hat{n}}\} = \{1,\ldots,n\}$. $\square$

Next, we present partial converses to Theorem 2.6 and Corollary 2.3 in the case where $u(k) \equiv 0$.

Theorem 2.7. Consider the discrete-time, linear nonnegative dynamical system given by (2.9) where $x_0 \in \overline{\mathbb{R}}_+^n$, $A \in \mathbb{R}^{n\times n}$ is nonnegative, and $u(k) \equiv 0$. Let $\hat{n} \leq n$, $\{k_1, k_2,\ldots,k_{\hat{n}}\} \subseteq \{1,2,\ldots,n\}$, and $\hat{x}(k) \triangleq [x_{k_1}(k),\ldots,x_{k_{\hat{n}}}(k)]^{\mathrm{T}}$. The discrete-time, linear nonnegative dynamical system (2.9) is partially monotonic with respect to $\hat{x}$ if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \operatorname{diag}[q_1,\ldots,q_n]$, $q_i = 0$, $i \notin \{k_1,\ldots,k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1,\ldots,k_{\hat{n}}\}$, and $QA \leq\leq Q$.

Proof. Sufficiency follows from Theorem 2.6 with $u(k) \equiv 0$. To show necessity assume the discrete-time, linear dynamical system given by (2.9) with $u(k) \equiv 0$ is partially monotonic with respect to $\hat{x}$. In this case it follows from (2.9) that

$$Qx(k+1) = QAx(k), \qquad x(0) = x_0, \qquad k \in \mathcal{N},$$

which further implies that

$$Qx(k_2) = Qx(k_1) + \sum_{k=k_1}^{k_2-1}[Q(A-I)A^k x_0].$$

Now, suppose, *ad absurdum*, there exists $I, J \in \{1, 2, \ldots, n\}$ such that $M_{(I,J)} > 0$, where $M \triangleq QA - Q$. Next, let $x_0 \in \overline{\mathbb{R}}_+^n$ be such that $x_{0J} > 0$ and $x_{0i} = 0$, $i \neq J$, and define $v(k) \triangleq A^k x_0$ so that $v(0) = x_0$, $v_J(k) \geq\geq 0$, $k \in \mathcal{N}$, and $v_J(0) > 0$. Thus, it follows that

$$\begin{aligned}
[Qx(1)]_J &= [Qx_0]_J + \sum_{k=k_1}^{k_2-1} [Mv(k)]_J \\
&= [Qx_0]_J + \sum_{k=k_1}^{k_2-1} M_{(I,J)} v_J(k) \\
&> [Qx_0]_J,
\end{aligned}$$

which is a contradiction. Hence, $QA \leq\leq Q$. □

Corollary 2.4. Consider the discrete-time, linear nonnegative dynamical system given by (2.9) where $x_0 \in \overline{\mathbb{R}}_+^n$, $A \in \mathbb{R}^{n\times n}$ is nonnegative and $u(k) \equiv 0$. The linear nonnegative dynamical system (2.9) is monotonic if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, 2, \ldots, n$, and $QA \leq\leq Q$.

Proof. The proof is a direct consequence of Theorem 2.7 with $\hat{n} = n$ and $\{k_1, \ldots, k_{\hat{n}}\} = \{1, \ldots, n\}$. □

Finally, we present a sufficient condition for *weighted monotonicity* for a discrete-time, linear nonnegative dynamical system.

Proposition 2.4. Consider the discrete-time, linear dynamical system given by (2.9) where A is nonnegative, $u(k) \equiv 0$, $x_0 \in \mathcal{X}_0 \triangleq \{x_0 \in \mathbb{R}^n : S(A - I)x_0 \leq\leq 0\}$, where $S \in \mathbb{R}^{n\times n}$ is an invertible matrix. If SAS^{-1} is nonnegative, then for every $x_0 \in \mathcal{X}_0$, $Sx(k_2) \leq\leq Sx(k_1)$, $0 \leq k_1 \leq k_2$.

Proof. Let $y(k) \triangleq -S(A - I)x(k)$ and note that $y(0) = -S(A - I)x_0 \in \overline{\mathbb{R}}_+^n$. Hence, it follows from (2.9) that

$$\begin{aligned}
y(k+1) &= -S(A - I)x(k+1) \\
&= -S(A - I)Ax(k)
\end{aligned}$$

$$= -SAS^{-1}S(A-I)x(k)$$
$$= SAS^{-1}y(k).$$

Next, since SAS^{-1} is nonnegative, it follows that $y(k) \in \overline{\mathbb{R}}_+^n$, $k \in \mathcal{N}$. Now the result follows immediately by noting that $y(k) = -S(A-I)x(k) >> 0, k \in \mathcal{N}$, and hence $S(A-I)x(k) \leq\leq 0$, $k \in \mathcal{N}$, or, equivalently, $Sx(k+1) \leq\leq Sx(k)$, $k \in \mathcal{N}$, which implies that $Sx(k_2) \leq\leq Sx(k_1)$, $0 \leq k_1 \leq k_2$. □

2.9. Monotonicity of Nonlinear Nonnegative Dynamical Systems

In this section we extend the results of Section 2.8 to nonlinear nonnegative dynamical systems. Specifically, we consider discrete-time, nonlinear dynamical systems $\mathcal{G}$ of the form

$$x(k+1) = f(x(k)) + G(x(k))u(k), \qquad x(0) = x_0, \qquad k \in \mathcal{N}, \tag{2.10}$$

where $x(k) \in \mathcal{D}$, $\mathcal{D}$ is an open subset of $\mathbb{R}^n$ with $0 \in \mathcal{D}$, $u(k) \in \mathbb{R}^m$, $f : \mathcal{D} \to \mathbb{R}^n$, and $G : \mathcal{D} \to \mathbb{R}^{n\times m}$. We assume that $f(\cdot)$ and $G(\cdot)$ are continuous in $\mathcal{D}$ and $f(x_\mathrm{e}) = x_\mathrm{e}$, $x_\mathrm{e} \in \mathcal{D}$. For the nonlinear dynamical system $\mathcal{G}$ given by (2.10) the definitions of monotonicity and partial monotonicity hold with (2.9) replaced by (2.10). The following definition generalizes the notion of nonnegativity to vector fields.

Definition 2.12 [90]. Let $f = [f_1, \cdots, f_n]^\mathrm{T} : \mathcal{D} \to \mathbb{R}^n$, where $\mathcal{D}$ is an open subset of $\mathbb{R}^n$ that contains $\mathbb{R}^n$. Then f is *nonnegative* if $f_i(x) \geq 0$, for all $i = 1, \ldots, n$, and $x \in \overline{\mathbb{R}}_+^n$.

Note that if $f(x) = Ax$, where $A \in \mathbb{R}^{n\times n}$, then f is nonnegative if and only if A is nonnegative. The following proposition is required for the main theorem of this section.

Proposition 2.5 [90]. Consider the discrete-time, nonlinear dynamical system $\mathcal{G}$ given by (2.10). If $f : \mathcal{D} \to \mathbb{R}^n$ is nonnegative and $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^n$, then $\mathcal{G}$ is nonnegative.

Next, we present a sufficient condition for monotonicity of a nonlinear nonnegative dynamical system.

Theorem 2.8. Consider the discrete-time, nonlinear nonnegative dynamical system $\mathcal{G}$ given by (2.10) where $x_0 \in \overline{\mathbb{R}}_+^n$, $f : \mathcal{D} \to \mathbb{R}^n$ is nonnegative, $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^n$, and $u(k)$, $k \in \mathcal{N}$, is nonnegative. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(k) \triangleq [x_{k_1}(k), \ldots, x_{k_{\hat{n}}}(k)]^{\mathrm{T}}$. Assume there exists a matrix $Q \in \mathbb{R}^{n \times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, $Qf(x) \leq\leq Qx$, $x \in \overline{\mathbb{R}}_+^n$, and $QG(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$. Then the discrete-time, nonlinear nonnegative dynamical system $\mathcal{G}$ is partially monotonic with respect to $\hat{x}$.

Proof. The proof is similar to the proof of Theorem 2.6 with Proposition 2.5 invoked in place of Proposition 2.3 and hence is omitted. □

Corollary 2.5. Consider the discrete-time, nonlinear nonnegative dynamical system $\mathcal{G}$ given by (2.10) where $x_0 \in \overline{\mathbb{R}}_+^n$, $f : \mathcal{D} \to \mathbb{R}^n$ is nonnegative, $G(x) \geq\geq 0$, $x \in \overline{\mathbb{R}}_+^n$, and $u(k)$, $k \in \mathcal{N}$, is nonnegative. Assume there exists a matrix $Q \in \mathbb{R}^{n \times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, $Qf(x) \leq\leq Qx$, $x \in \overline{\mathbb{R}}_+^n$, and $QG(x) \leq\leq 0$, $x \in \overline{\mathbb{R}}_+^n$. Then the discrete-time, nonlinear nonnegative dynamical system $\mathcal{G}$ is monotonic.

Proof. The proof is a direct consequence of Theorem 2.8 with $\hat{n} = n$ and $\{k_1, \ldots, k_{\hat{n}}\} = \{1, \ldots, n\}$. □

Next, we present necessary and sufficient conditions for partial monotonicity and monotonicity for (2.10) in the case where $u(k) \equiv 0$.

Theorem 2.9. Consider the discrete-time, nonlinear nonnegative dynamical system $\mathcal{G}$ given by (2.10) where $x_0 \in \overline{\mathbb{R}}_+^n$, $f : \mathcal{D} \to \mathbb{R}^n$ is nonnegative, and $u(k) \equiv 0$. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(k) \triangleq [x_{k_1}(k), \ldots, x_{k_{\hat{n}}}(k)]^{\mathrm{T}}$. The discrete-time, nonlinear nonnegative dynamical system $\mathcal{G}$ is partially monotonic with respect to $\hat{x}$ if and only if there exists a matrix $Q \in \mathbb{R}^{n \times n}$ such that

$Q = \operatorname{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and $Qf(x) \leq\leq Qx$, $x \in \overline{\mathbb{R}}_+^n$.

Proof. Sufficiency follows from Theorem 2.8 with $u(k) \equiv 0$. To show necessity assume the nonlinear dynamical system given by (2.10) with $u(k) \equiv 0$ is partially monotonic with respect to $\hat{x}$. In this case, it follows from (2.10) that

$$Qx(k+1) = Qf(x(k)), \quad x(0) = x_0, \quad k \in \mathcal{N},$$

which implies that for every $k \in \mathcal{N}$,

$$Qx(k_2) = Qx(k_1) + \sum_{k=k_1}^{k_2-1} [Qf(x(k))].$$

Now, suppose, *ad absurdum*, there exist $J \in \{1, 2, \ldots, n\}$ and $x_0 \in \overline{\mathbb{R}}_+^n$ such that $[Qf(x_0))]_J > [Qx_0]_J$. Hence,

$$\begin{aligned} [Qx(1)]_J &= [Qx_0]_J + [Qf(x_0) - Qx_0]_J \\ &> [Qx_0]_J, \end{aligned}$$

which is a contradiction. Hence, $Qf(x) \leq\leq Qx$, $x \in \overline{\mathbb{R}}_+^n$. □

Corollary 2.6. Consider the discrete-time, nonlinear nonnegative dynamical system $\mathcal{G}$ given by (2.10) where $x_0 \in \overline{\mathbb{R}}_+^n$, $f : \mathcal{D} \to \mathbb{R}^n$ is nonnegative, and $u(k) \equiv 0$. The discrete-time, nonlinear nonnegative dynamical system $\mathcal{G}$ is monotonic if and only if there exists a matrix $Q \in \mathbb{R}^{n \times n}$ such that $Q = \operatorname{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, and $Qf(x) \leq\leq Qx$, $x \in \overline{\mathbb{R}}_+^n$.

Proof. The proof is a direct consequence of Theorem 2.9 with $\hat{n} = n$ and $\{k_1, \ldots, k_{\hat{n}}\} = \{1, \ldots, n\}$. □

Corollary 2.6 provides some interesting ramifications with regards to the absence of limit cycles of inflow-closed nonlinear compartmental systems. To see this, consider the inflow-closed ($u(k) \equiv 0$) compartmental system (2.10) where $f(x) = [f_1(x), \cdots, f_n(x)]$ is such that

$$f_i(x) = x_i - a_{ii}(x) + \sum_{j=1, i\neq j}^{n} [a_{ij}(x) - a_{ji}(x)] \tag{2.11}$$

and where the instantaneous rates of compartmental material losses $a_{ii}(\cdot)$, $i = 1, \ldots, n$, and intercompartmental material flows $a_{ij}(\cdot)$, $i \neq j$, $i, j = 1, \ldots, n$, are such that $a_{ij}(x) \geq 0$, $x \in \overline{\mathbb{R}}_+^n$, $i, j = 1, \ldots, n$. Since all mass flows as well as compartment sizes are nonnegative, it follows that for all $i = 1, \ldots, n$, $f_i(x) \geq 0$ for all $x \in \overline{\mathbb{R}}_+^n$. Hence, f is nonnegative. As in the linear case, inflow-closed nonlinear compartmental systems are Lyapunov stable since the total mass in the system given by the sum of all components of the state $x(k)$, $k \in \mathcal{N}$, is nonincreasing along the forward trajectories of (2.10). In particular, taking $V(x) = e^{\mathrm{T}}x$ and assuming $a_{ij}(0) = 0$, $i, j = 1, \ldots, n$, it follows that

$$\begin{aligned}\Delta V(x) &= \sum_{i=1}^{n} \Delta x_i = -\sum_{i=1}^{n} a_{ii}(x) + \sum_{i=1}^{n} \sum_{j=1, i\neq j}^{n} [a_{ij}(x) - a_{ji}(x)] \\ &= -\sum_{i=1}^{n} a_{ii}(x) \leq 0, \quad x \in \overline{\mathbb{R}}_+^n, \end{aligned} \tag{2.12}$$

which shows that the zero solution $x(k) \equiv 0$ of the inflow-closed nonlinear compartmental system (2.10) is Lyapunov stable and for every $x_0 \in \overline{\mathbb{R}}_+^n$, the solution to (2.10) is bounded.

In light of the above, it is of interest to determine sufficient conditions under which masses/concentrations for nonlinear compartmental systems are Lyapunov stable *and* convergent, guaranteeing the absence of limit cycling behavior. The following result is a direct consequence of Corollary 2.6 and provides sufficient conditions for the absence of limit cycles in nonlinear compartmental systems.

Theorem 2.10. Consider the nonlinear nonnegative dynamical system $\mathcal{G}$ given by (2.10) with $u(k) \equiv 0$ and $f(x) = [f_1(x), \cdots, f_n(x)]$ such that (2.11) holds. If there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \cdots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, and $Qf(x) \leq\leq Qx$, $x \in \overline{\mathbb{R}}_+^n$, then for every $x_0 \in \overline{\mathbb{R}}_+^n$, $\lim_{k\to\infty} x(k)$ exists.

Proof. Let $V(x) = e^{\mathrm{T}}x$, $x \in \overline{\mathbb{R}}_+^n$. Now, it follows from (2.12) that $\Delta V(x(k)) \leq 0$, $k \in \mathcal{N}$, where $x(k)$, $k \in \mathcal{N}$, denotes the solution of $\mathcal{G}$, which implies that $V(x(k)) \leq V(x_0) = e^{\mathrm{T}}x_0$, $k \in \mathcal{N}$, and hence for every $x_0 \in \overline{\mathbb{R}}_+^n$, the solution $x(k)$, $k \in \mathcal{N}$, of $\mathcal{G}$ is bounded. Hence, for every $i \in \{1, \cdots, n\}$, $x_i(k)$, $k \in \mathcal{N}$, is bounded. Furthermore, it follows from Corollary 2.6 that $x_i(k)$, $k \in \mathcal{N}$, is monotonic. Now, since $x_i(\cdot)$, $i \in \{1, \cdots, n\}$, is bounded and monotonic, it follows that $\lim_{k\to\infty} x_i(k)$, $i = 1, \ldots, n$, exists. Hence, $\lim_{k\to\infty} x(k)$ exists. □

2.10. A Taxonomy of Three-Dimensional Monotonic Compartmental Systems

In this section, we use the results of Section 2.8 to provide a taxonomy of linear three-dimensional, inflow-closed compartmental dynamical systems that exhibit monotonic solutions. A similar classification can be obtained for nonlinear and higher-order compartmental systems but we do not do so here for simplicity of exposition. To characterize the class of all three-dimensional monotonic compartmental systems, let $\mathcal{Q} \triangleq \{Q \in \mathbb{R}^{3\times 3}\colon Q = \mathrm{diag}[q_1, q_2, q_3],\ q_i = \pm 1,\ i = 1, 2, 3\}$. Furthermore, let $A \in \mathbb{R}^{3\times 3}$ be a compartmental matrix and let $x_1(k), x_2(k), x_3(k)$, $k \in \mathcal{N}$, denote compartmental masses for compartments 1, 2, and 3, respectively. Note that there are exactly eight matrices in the set $\mathcal{Q}$. Now, it follows from Corollary 2.4 that if $QA \leq\leq Q$, $Q \in \mathcal{Q}$, then the corresponding compartmental dynamical system is monotonic. Hence, for every $Q \in \mathcal{Q}$ we seek all compartmental matrices $A \in \mathbb{R}^{3\times 3}$ such that $q_i A_{(i,i)} \leq q_i$, $i = 1, 2, 3$ and $q_i A_{(i,j)} \leq 0$, $i \neq j$, $i, j = 1, 2, 3$.

First, we consider the case where $Q = \mathrm{diag}[1,\ 1,\ 1]$. In this case, $q_i A_{(i,i)} \leq q_i$, $i = 1, 2, 3$ and $q_i A_{(i,j)} \leq 0$, $i \neq j$, $i, j = 1, 2, 3$, if and only if $A_{(1,2)} = A_{(1,3)} = A_{(2,1)} = A_{(3,1)} = A_{(3,2)} = A_{(2,3)} = 0$. This corresponds to a trivial (decoupled) case since there are no intercompartmental flows between the three compartments. Next, let $Q = \mathrm{diag}[1,\ -1,\ -1]$ and note that $q_i A_{(i,i)} \leq q_i$, $i = 1, 2, 3$ and $q_i A_{(i,j)} \leq 0$, $i \neq j$, $i, j = 1, 2, 3$, if and only if $A_{(2,2)} = A_{(3,3)} = 1$ and $A_{(1,2)} = A_{(1,3)} = A_{(2,3)} = A_{(3,2)} = 0$.

Finally, let $Q = \text{diag}[-1,\ 1,\ 1]$. In this case, $q_i A_{(i,i)} \leq q_i$, $i = 1, 2, 3$ and $q_i A_{(i,j)} \leq 0$, $i \neq j$, $i, j = 1, 2, 3$, if and only if $A_{(1,1)} = 1$ and $A_{(2,1)} = A_{(3,1)} = A_{(3,2)} = A_{(2,3)} = 0$. Figures 2.2(a), (b) and (c) show the corresponding compartmental structures.

It is important to note that in the case where $Q = \text{diag}[-1,\ -1,\ -1]$, there does not exist a compartmental matrix satisfying $QA \leq\leq Q$ except for the identity matrix. This case would correspond to a compartmental dynamical system where all three states are monotonically increasing. Hence, the compartmental system would be unstable contradicting the fact that all compartmental systems are Lyapunov stable. Finally, the remaining four cases corresponding to $Q = \text{diag}[-1,\ 1, -1]$, $Q = \text{diag}[-1,\ -1,\ 1]$, $Q = \text{diag}[1,\ -1,\ 1]$, and $Q = \text{diag}[1,\ 1,\ -1]$ are dual to the cases where $Q = \text{diag}[1,\ -1,\ -1]$ and $Q = \text{diag}[-1,\ 1,\ 1]$ and hence are not presented.

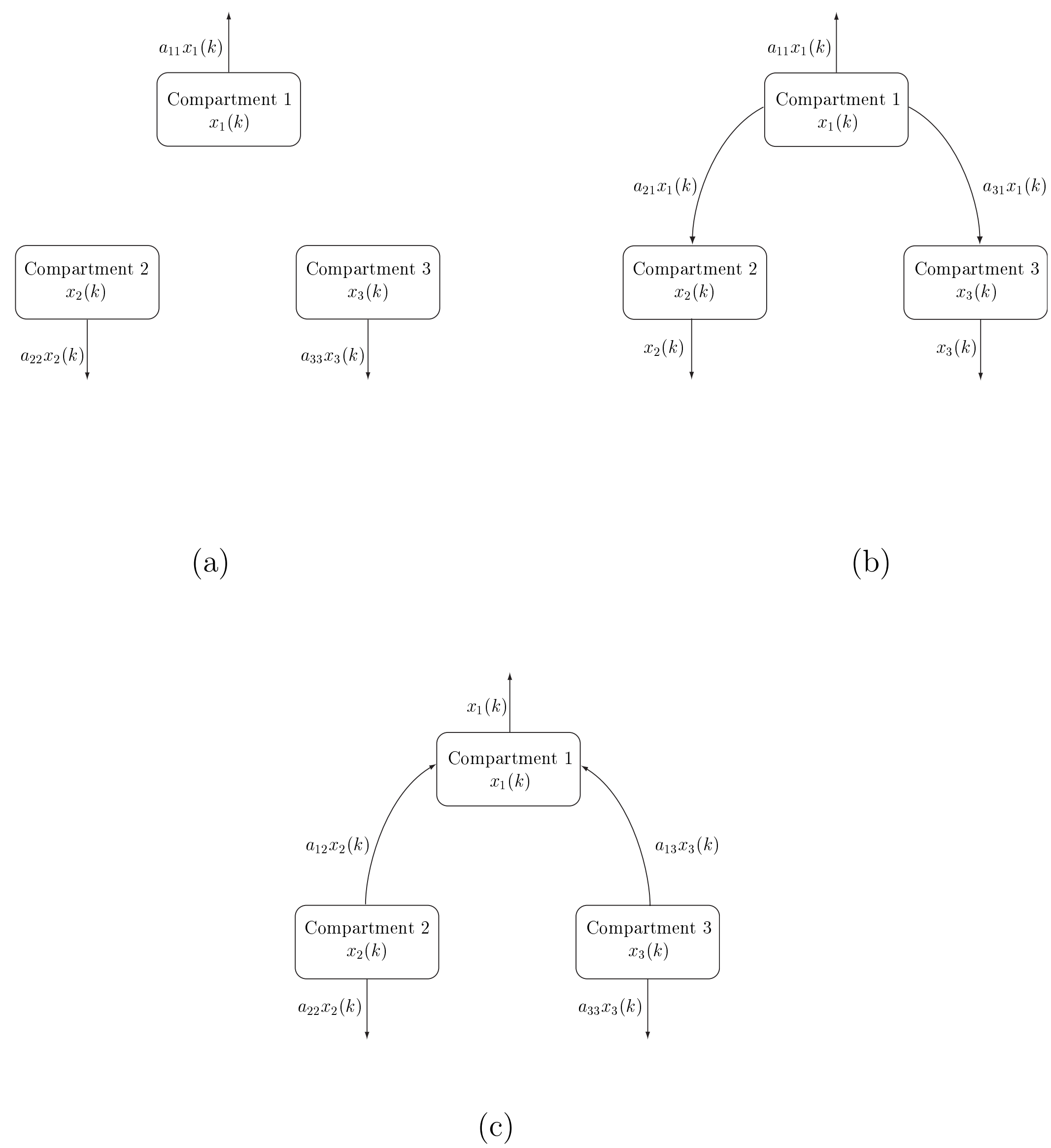


Figure 2.2: Three-Dimensional Monotonic Compartmental Systems

Chapter 3

On Monotonicity of Solutions of Nonnegative and Compartmental Dynamical Systems with Time Delays

3.1. Introduction

In the specific field of pharmacokinetics [40, 41], the state variables of compartmental dynamical systems represent masses or concentrations of drug disposition from the body. If a bolus of drug is injected into the circulation of a physiological process and we seek its concentration level in the extracellular and intercellular space of some organ, there exists a time lag before it is detected in that organ. However, the introduction of time delay into the dynamical pharmacokinetic model may destabilize equilibria and thus introduce oscillations in the system solutions that may otherwise be nonoscillatory in the absence of time delay [26, 91]. Since drug concentrations should monotonically decline after discontinuation of drug administration, it is of interest to determine necessary and sufficient conditions under which these systems possess monotonic solutions. In Chapter 2, necessary and sufficient conditions were developed for identifying nonnegative and compartmental dynamical systems that only admit nonoscillatory and monotonic solutions in the absence of time lags. In this chapter we present analogous results for nonnegative and compartmental systems with time delays for both continuous and discrete-time nonnegative systems.

3.2. Notation and Mathematical Preliminaries

In this chapter we consider linear time-delay dynamical systems $\mathcal{G}$ of the form

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}x(t-\tau_i) + Bu(t), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0 \quad (3.1)$$

where $x(t) \in \mathbb{R}^n$, $u(t) \in \mathbb{R}^m$, $t \geq 0$, $A \in \mathbb{R}^{n\times n}$ is an essentially nonnegative matrix, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n_{\mathrm{d}}$, and $B \in \mathbb{R}^{n\times m}$ are nonnegative matrices, $\bar{\tau} = \max_{i\in\{1,\ldots,n_{\mathrm{d}}\}}\tau_i$, $\eta(\cdot) \in \mathcal{C} = \mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$ is a continuous vector valued function specifying the initial state of the system.

The following definition is needed for the main results.

Definition 3.1. The linear time-delay dynamical system $\mathcal{G}$ given by (3.1) is *nonnegative* if for every $\eta(\cdot) \in \mathcal{C}_+$, where $\mathcal{C}_+ \triangleq \{\psi(\cdot) \in \mathcal{C} : \ \psi(\theta) \geq\geq 0, \ \theta \in [-\bar{\tau},0]\}$, and $u(t) \geq\geq 0$, $t \geq 0$, the solution $x(t)$, $t \geq 0$, to (3.1) is nonnegative.

Proposition 3.1 [92, 93]. The linear time-delay dynamical system $\mathcal{G}$ given by (3.1) is nonnegative if and only if $\eta(\cdot) \in \mathcal{C}_+$, $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n_{\mathrm{d}}$ is nonnegative, and $B \geq\geq 0$. In the case where $u(t) \equiv 0$, $\mathcal{G}$ is nonnegative if and only if $\phi(\cdot) \in \mathcal{C}_+$, $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, and $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n_{\mathrm{d}}$ is nonnegative.

3.3. Monotonicity of Nonnegative Dynamical Systems with Time Delay

Consider the linear time-delay dynamical systems $\mathcal{G}$ of the form

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}x(t-\tau_i) + Bu(t), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0 \quad (3.2)$$

where $x(t) \in \mathbb{R}^n$, $u(t) \in \mathbb{R}^m$, $t \geq 0$, $A \in \mathbb{R}^{n\times n}$ is an essentially nonnegative matrix, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n_{\mathrm{d}}$, and $B \in \mathbb{R}^{n\times m}$ are nonnegative matrices, $\bar{\tau} =$

$\max_{i\in\{1,\ldots,n_{\rm d}\}}\tau_i$, $\eta(\cdot)\in\mathcal{C}=\mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$ is a continuous vector valued function specifying the initial state of the system and $\mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$ denotes a Banach space of continuous functions mapping the interval $[-\bar{\tau},0]$ into $\mathbb{R}^n$ with the topology of uniform convergence. Note that the state of (3.2) at time t is the *piece of trajectories* x between $t-\bar{\tau}$ and t, or, equivalently, the *element* x_t in the space of continuous functions defined on the interval $[-\bar{\tau},0]$ and taking values in $\mathbb{R}^n$; that is, $x_t\in\mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$, where $x_t(\theta)\triangleq x(t+\theta)$, $\theta\in[-\bar{\tau},0]$. Furthermore, since for a given time t the piece of the trajectories x_t is defined on $[-\bar{\tau},0]$, the uniform norm $|||x_t|||=\sup_{\theta\in[-\bar{\tau},0]}\|x(t+\theta)\|$, where $\|\cdot\|$ denotes the Euclidean vector norm, is used for the definitions of Lyapunov and asymptotic stability of (3.2) with $u(t)\equiv 0$. For further details see [37, 94]. The following definition is needed for the main results.

Next, we present a definition for the monotonicity of solutions over all time for a time-delay nonnegative dynamical system of the form given by (3.2).

Definition 3.2. Consider the linear nonnegative time-delay dynamical system (3.2) where $\phi(\cdot)\in\mathcal{C}_+$, A is essentially nonnegative, $A_{{\rm d}i}$ is nonnegative, $i=1,\ldots,n_{\rm d}$, B is nonnegative, and $u(t)$, $t\geq 0$, is nonnegative. Let $\hat{n}\leq n$, $\{k_1,k_2,\ldots,k_{\hat{n}}\}\subseteq\{1,2,\ldots,n\}$, and $\hat{x}(t)\triangleq[x_{k_1}(t),\ldots,x_{k_{\hat{n}}}(t)]^{\rm T}$. The linear nonnegative time delay dynamical system (3.2) is *partially monotonic with respect to* $\hat{x}$ if there exists a matrix $Q\in\mathbb{R}^{n\times n}$ such that $Q=\operatorname{diag}[q_1,\ldots,q_n]$, $q_i=0$, $i\notin\{k_1,\ldots,k_{\hat{n}}\}$, $q_i=\pm 1$, $i\in\{k_1,\ldots,k_{\hat{n}}\}$, and for every $\phi(\cdot)\in\mathcal{C}_+$, $Qx(t_2)\leq\leq Qx(t_1)$, $0\leq t_1\leq t_2$, where $x(t)$, $t\geq 0$, denotes the solution to (3.2). The linear nonnegative time delay dynamical system (3.2) is *monotonic* if there exists a matrix $Q\in\mathbb{R}^{n\times n}$ such that $Q=\operatorname{diag}[q_1,\ldots,q_n]$, $q_i=\pm 1$, $i=1,\ldots,n$, and for every $\phi(\cdot)\in\mathcal{C}_+$, $Qx(t_2)\leq\leq Qx(t_1)$, $0\leq t_1\leq t_2$.

Next, we present our main results. Specifically, we present necessary and sufficient conditions that guarantee partial monotonicity and monotonicity for nonnegative dynamical systems with multiple time delays.

Theorem 3.1. Consider the linear nonnegative dynamical system with multiple delays given by (3.2), where $\eta(\cdot)\in\mathcal{C}_+$, $A\in\mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{{\rm d}i}\in$

$\mathbb{R}^{n\times n}$ is nonnegative, $i = 1,\ldots,n_{\rm d}$, $B \in \mathbb{R}^{l\times m}$ is nonnegative, and $u(t)$, $t \geq 0$, is nonnegative. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(t) \triangleq [x_{k_1}(t), \ldots, x_{k_{\hat{n}}}(t)]^{\rm T}$. Assume there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \operatorname{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and $QA \leq\leq 0$, $QA_{{\rm d}i} \leq\leq 0$, $i = 1,\ldots,n_{\rm d}$, and $QB \leq\leq 0$. Then the linear nonnegative dynamical system (3.2) is partially monotonic with respect to $\hat{x}$.

Proof. The proof is a direct consequence of Theorem 2.2 with B replaced by $[\sum_{i=1}^{n_{\rm d}} A_{{\rm d}i}\ B]$, $i = 1,\ldots,n_{\rm d}$, and $u(t)$, $t \geq 0$, replaced by $[x^{\rm T}(t-\tau_i)\ u^{\rm T}(t)]^{\rm T}$, $t \geq 0$. □

The following result gives necessary and sufficient conditions for monotonicity in the case where $u(t) \equiv 0$.

Theorem 3.2. Consider the linear time-delay nonnegative dynamical system given by (3.2), where $\phi(\cdot) \in \mathcal{C}_+$, $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{{\rm d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n$, is nonnegative, $B \in \mathbb{R}^{l\times m}$ is nonnegative and $u(t) \equiv 0$. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(t) \triangleq [x_{k_1}(t), \ldots, x_{k_{\hat{n}}}(t)]^{\rm T}$. Then the linear time delay dynamical system is partially monotonic with respect to $\hat{x}$ if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \operatorname{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, $QA \leq\leq 0$ and $QA_{{\rm d}i} \leq\leq 0$.

Proof. Sufficiency follows from Theorem 3.1 with $u(t) \equiv 0$. To show necessity assume the linear time-delay dynamical system given by (3.2) is partially monotonic with respect to $\hat{x}$. In this case, it follows from (3.2) that

$$Q\dot{x}(t) = QAx(t) + \sum_{i=1}^{n_{\rm d}} QA_{{\rm d}i}x(t-\tau_i), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0,$$

which implies that for some $t_1 \geq 0$ and $t_2 > t_1$,

$$Qx(t_2) = Qx(t_1) + \int_{t_1}^{t_2} [QAx(t) + \sum_{i=1}^{n_{\rm d}} QA_{{\rm d}i}x(t-\tau_i)]{\rm d}t.$$

Now suppose, *ad absurdum*, there exists $I, J \in \{1, 2, \ldots, n\}$ such that $M_{(I,J)} > 0$, where $M \triangleq QA$. Next, let $\eta(\cdot) \in \mathcal{C}_+$ be such that $\eta(t) = 0$, $-\bar{\tau} < t < \eta - \tau_{\min}$, and let $\phi(0) = e_J$, where $\tau_{\min} > \eta > 0$ and $e_J \in \mathbb{R}^n$ is a vector of zeros with one in the Jth entry. Next, it follows from continuity if solutions that there exists $0 < \varepsilon \leq \eta$ such that $x_J(t) > 0$, $0 \leq t \leq \varepsilon$. Thus, for every $t \in [0, \varepsilon]$, it follows that

$$\begin{aligned}
[Qx(t)]_I &= [Qx(0)]_I + \int_0^t [QAx(s) + \sum_{i=1}^{n_{\mathrm{d}}} QA_{\mathrm{d}i}x(s-\tau_i)]_I \mathrm{d}s \\
&= [Qx(0)]_I + \int_0^t [QAx(s)]_I \mathrm{d}s + \int_{-\tau_i}^{t-\tau_i} [\sum_{i=1}^{n_{\mathrm{d}}} QA_{\mathrm{d}i}x(s)]_I \mathrm{d}s \\
&= [Qx(0)]_I + \int_0^t [QAx(s)]_I \mathrm{d}s \\
&> [Qx(0)]_I, \qquad (3.3)
\end{aligned}$$

which is a contradiction. Hence, $QA \leq\leq 0$. Now, suppose, *ad absurdum*, there exists $I, J \in \{1, 2, \ldots, n\}$ such that $M_{(I,J)} > 0$, where $M \triangleq QA_{\mathrm{d}i}$. It follows from Lagrange's formula that the solution to (3.2) is given by

$$x(t) = e^{At}x(0) + \int_0^t e^{A(t-\theta)} \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}x(\theta - \tau_i)\mathrm{d}\theta$$

which can be rewritten as

$$\begin{aligned}
Qx(t) &= Qe^{At}x(0) + \int_0^t Qe^{A(t-\theta)} \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}x(\theta - \tau_i)\mathrm{d}\theta \\
&= Qe^{At}x(0) + \int_0^t Qe^{A(t-\theta)} [A_{\mathrm{d}i}x(\theta - \tau_i) + \sum_{j=1, j\neq i}^{n_{\mathrm{d}}} A_{\mathrm{d}j}x(\theta - \tau_j)]\mathrm{d}\theta \qquad (3.4)
\end{aligned}$$

Next, let $\{v_n\}_{n=1}^{\infty} \subset \mathcal{C}_+$ denote a sequence of functions such that $\lim_{n\to\infty} v_n(\theta) = e_J\delta(\theta - \eta + \tau_i)$, where $0 < \eta < \min(\tau_i - \tau_j)$ and $\delta(\cdot)$ denotes the Dirac delta function. Furthermore, let $\phi(\cdot) \in \mathcal{C}_+$ be such that $\phi(t) = \lim_{n\to\infty} v_n(t)$, $-\bar{\tau} < t < 0$, where $\bar{\tau} = \max_{i=1,\ldots,n_{\mathrm{d}}} \tau_i$. In this case, it follows from (3.4) that for all $t > \eta$

$$Qx_n(t) = Qe^{At}x(0) + \int_0^t Qe^{A(t-\theta)}[A_{\mathrm{d}i}e_J\delta(\theta - \eta) + \sum_{j=1, j\neq i}^{n_{\mathrm{d}}} A_{\mathrm{d}j}e_J\delta(\theta - \eta + \tau_i - \tau_j)]\mathrm{d}\theta \qquad (3.5)$$

where $x_n(\cdot)$ denotes the solution to (3.2) with $\phi(\cdot) = v_n(t)$. Now, note that

$$\hat{x}(t) \triangleq \lim_{n\to\infty} [Qx_n(t)]_I = QA_{\mathrm{d}i}e_J.$$

Hence, $\hat{x}_I(t) = [Qx(t)]_I > [Qx(0)]_I = \hat{x}_I(0) = 0$. $\square$

Corollary 3.1. Consider the linear time-delay dynamical system given by (3.2) where $\phi(\cdot) \in \mathcal{C}_+$, $A \in \mathbb{R}^{n\times n}$ in essentially nonnegative, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_{\mathrm{d}}$, is nonnegative, $B \in \mathbb{R}^{n\times n}$ is nonnegative, and $u(t) \equiv 0$. The linear time delay dynamical system is monotonic if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, 2, \ldots, n$, $QA \leq\leq 0$, and $QA_{\mathrm{d}i} \leq\leq 0$, $i = 1, \ldots, n_{\mathrm{d}},$.

Proof. The proof is a direct consequence of Theorem 3.2 with $\hat{n} = n$ and $\{k_1, \ldots, k_{\hat{n}}\} = \{1, \ldots, n\}$. □

3.4. Monotonicity of Discrete-Time Nonnegative Dynamical Systems with Time Delay

Next, we consider the linear discrete-time nonnegative time-delay dynamical system $\mathcal{G}$ of the form

$$x(k+1) = Ax(k) + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i} x(k-\kappa_i) + Bu(k), \quad x(\theta) = \eta(\theta), \quad -\kappa \leq \theta \leq 0, \quad k \in \mathcal{N} \tag{3.6}$$

where $x(k) \in \mathbb{R}^n$, $u(k) \in \mathbb{R}^m$, $k \in \mathcal{N}$, $A \in \mathbb{R}^{n\times n}$, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_{\mathrm{d}}$, $\kappa \in \mathcal{N}$, $B \in \mathbb{R}^{l\times m}$, are nonnegative matrices, $\eta(\cdot) \in \mathcal{C} = \mathcal{C}(\{-\kappa, \cdots, 0\}, \mathbb{R}^n)$ is a vector sequence specifying the initial state of the system, and $\mathcal{C}$ denotes the space of all sequences mapping $\{-\kappa, \cdots, 0\}$ into $\mathbb{R}^n$ with norm $|||\phi||| = \max_{k\in\{-\kappa,\cdots,0\}} \|\phi(k)\|$. The following definition proves nonnegativity of (3.6).

Definition 3.3. The discrete-time, linear time-delay dynamical system $\mathcal{G}$ given by (3.6) is *nonnegative* if for every $\eta(\cdot) \in \mathcal{C}_+$, where $\mathcal{C}_+ \triangleq \{\psi(\cdot) \in \mathcal{C} : \ \psi(\theta) \geq\geq 0,\ \theta \in \{-\kappa, \cdots, 0\}\}$ and $u(k) \geq\geq 0$, $k \in \mathcal{N}$, the solution $x(k)$, $k \in \mathcal{N}$, to (3.6) is nonnegative.

Proposition 3.2 [92]. The discrete-time, linear time-delay dynamical system $\mathcal{G}$ given by (3.6) is nonnegative if and only if $\eta(\cdot) \in \mathcal{C}_+$, and $A \in \mathbb{R}^{n\times n}$ and $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$,

$i = 1, \ldots, n_{\mathrm{d}}$ are nonnegative and $B \geq\geq 0$. In the case where $u(k) \equiv 0$, $\mathcal{G}$ is nonnegative if and only if $\eta(\cdot) \in \mathcal{C}_+$, $A \in \mathbb{R}^{n\times n}$ and $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_{\mathrm{d}}$ are nonnegative.

Definition 3.4. Consider the discrete-time, linear nonnegative time-delay dynamical system (3.6) where $\eta(\cdot) \in \mathcal{C}_+$, A and $A_{\mathrm{d}i}$, $i = 1, \ldots, n_{\mathrm{d}}$, are nonnegative, $B \geq\geq 0$, $u(k)$, $k \in \mathcal{N}$, is nonnegative. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(k) \triangleq [x_{k_1}(k), \ldots, x_{k_{\hat{n}}}(k)]^{\mathrm{T}}$. The discrete-time, linear nonnegative time-delay dynamical system (3.6) is *partially monotonic with respect to* $\hat{x}$ if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and for every $x_0 \in \mathcal{X}_0$, $Qx(k_2) \leq\leq Qx(k_1)$, $0 \leq k_1 \leq k_2$, where $x(k)$, $k \in \mathcal{N}$, denotes the solution to (3.6). The discrete-time, linear nonnegative time-delay dynamical system (3.6) is *monotonic* if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, \ldots, n$, and for every $x_0 \in \mathcal{X}_0$, $Qx(k_2) \leq\leq Qx(k_1)$, $0 \leq k_1 \leq k_2$.

The following theorem presents a sufficient condition for the monotonicity of a discrete-time linear nonnegative dynamical system with time-delays of the form (3.6).

Theorem 3.3. Consider the discrete-time linear time-delay nonnegative dynamical system given by (3.6) where $\eta(\cdot) \in \mathcal{C}_+$, $A \in \mathbb{R}^{n\times n}$, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_{\mathrm{d}}$, and $B \in \mathbb{R}^{l\times m}$ are nonnegative, and $u(k)$, $k \in \mathcal{N}$, is nonnegative. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(k) \triangleq [x_{k_1}(k), \ldots, x_{k_{\hat{n}}}(k)]^{\mathrm{T}}$. Assume there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, and $QA \leq\leq Q$, $QA_{\mathrm{d}i} \leq\leq 0$, $i = 1, \ldots, n_{\mathrm{d}}$, and $QB \leq\leq 0$. Then the discrete-time linear time-delay nonnegative dynamical system (3.6) is partially monotonic with respect to $\hat{x}$.

Proof. The proof is a direct consequence of Theorem 2.7 with B replaced by $[\sum_{i=1}^{\mathrm{d}} A_{\mathrm{d}i}\ B]$, $i = 1, \ldots, n_{\mathrm{d}}$, and $u(k)$, $k \in \mathcal{N}$, replaced by $[x^{\mathrm{T}}(k - \kappa_i)\ u^{\mathrm{T}}(k)]^{\mathrm{T}}$, $k \in \mathcal{N}$. $\square$

The following result gives necessary and sufficient conditions for monotonicity in the case where $u(k) \equiv 0$.

Theorem 3.4. Consider the discrete-time linear time-delay nonnegative dynamical system given by (3.6) where $\eta(\cdot) \in \mathcal{C}_+$, $A \in \mathbb{R}^{n\times n}$, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$ and $B \in \mathbb{R}^{l\times m}$ are nonnegative, and $u(k) \equiv 0$. Let $\hat{n} \leq n$, $\{k_1, k_2, \ldots, k_{\hat{n}}\} \subseteq \{1, 2, \ldots, n\}$, and $\hat{x}(k) \triangleq [x_{k_1}(k), \ldots, x_{k_{\hat{n}}}(k)]^{\mathrm{T}}$. Then the discrete-time linear time-delay nonnegative dynamical system is partially monotonic with respect to $\hat{x}$ if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$ such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = 0$, $i \notin \{k_1, \ldots, k_{\hat{n}}\}$, $q_i = \pm 1$, $i \in \{k_1, \ldots, k_{\hat{n}}\}$, $QA \leq\leq Q$ and $QA_{\mathrm{d}i} \leq\leq 0$, $i = 1, \ldots, n_{\mathrm{d}}$.

Proof. Sufficiency follows from Theorem 3.3 with $u(k) \equiv 0$. The discrete-time linear time-delay nonnegative dynamical system given by (3.6) is equivalent to

$$\begin{bmatrix} x_1(k+1) \\ x_2(k+1) \\ x_3(k+1) \\ x_4(k+1) \\ \vdots \\ x_{(\kappa+1)}(k+1) \end{bmatrix} = \underbrace{\begin{bmatrix} A & A_{\mathrm{d}1} & A_{\mathrm{d}2} & \cdots & A_{\mathrm{d}m-1} & A_{\mathrm{d}m} \\ I & 0 & 0 & \cdots & 0 & 0 \\ 0 & I & 0 & \cdots & 0 & 0 \\ 0 & 0 & I & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & I & 0 \end{bmatrix}}_{\hat{A}} \begin{bmatrix} x_1(k) \\ x_2(k) \\ x_3(k) \\ x_4(k) \\ \vdots \\ x_{(\kappa+1)}(k) \end{bmatrix} \qquad (3.7)$$

From Theorem 2.7 we know that the necessary and sufficient conditions for the system (3.6) to be monotonic are $QA \leq\leq Q$ and $QA_{\mathrm{d}i} \leq\leq 0$, where $i = 1, \ldots, n_{\mathrm{d}}$. Thus, the necessary and sufficient condition for the first compartment of the system given by (3.7) to be monotonic is $\hat{Q}\hat{A} \leq\leq \hat{Q}$ where $\hat{Q}$ is defined as $\hat{Q} = \mathrm{blockdiag}[Q,\ 0,\ \cdots, 0]$. This implies that $QA \leq\leq Q$ and $QA_{\mathrm{d}i} \leq\leq 0$, $i = 1, \ldots, n_{\mathrm{d}}$, and hence the result follows. $\square$

Corollary 3.2. Consider the discrete-time linear time-delay nonnegative dynamical system given by (3.6) where $\eta(\cdot) \in \mathcal{C}_+$, $A \in \mathbb{R}^{n\times n}$, $A_{\mathrm{d}} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_{\mathrm{d}}$, and $B \in \mathbb{R}^{l\times m}$ are nonnegative, and $u(k) \equiv 0$. The discrete-time linear time-delay nonnegative dynamical system is monotonic if and only if there exists a matrix $Q \in \mathbb{R}^{n\times n}$

such that $Q = \mathrm{diag}[q_1, \ldots, q_n]$, $q_i = \pm 1$, $i = 1, 2, \ldots, n$, $QA \leq\leq Q$ and $QA_{\mathrm{d}i} \leq\leq 0$, $i = 1, \ldots, n_{\mathrm{d}}$.

Proof. The proof is a direct consequence of Theorem 3.4 with $\hat{n} = n$ and $\{k_1, \ldots, k_{\hat{n}}\} = 1, \ldots, n$. $\square$

3.5. A Taxonomy of Three-Dimensional Monotonic Compartmental Systems

In this section, we use the results of Section 3.3 to provide a taxonomy of linear three-dimensional, *inflow-closed* (i.e., $u(t) \equiv 0$) compartmental dynamical systems that exhibit monotonic solutions. To characterize the class of all three-dimensional monotonic compartmental systems with time delay, let $\mathcal{Q} \triangleq \{Q \in \mathbb{R}^{3\times 3} : Q = \mathrm{diag}[q_1, q_2, q_3],\ q_i = \pm 1,\ i = 1, 2, 3\}$. It has been shown in [92] that a compartmental dynamical system with a single time delay satisfies the property that $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{\mathrm{d}} \in \mathbb{R}^{n\times n}$ is nonnegative, and $A + A_{\mathrm{d}}$ is a compartmental matrix. Let $x_1(t)$, $x_2(t)$ and $x_3(t)$, $t \geq 0$, denote compartmental masses for compartments 1, 2, and 3 respectively. Note that there are exactly eight matrices in the set $\mathcal{Q}$. Now it follows from Corollary 3.1 that if $QA \leq\leq 0$ and $QA_{\mathrm{d}} \leq\leq 0$, $Q \in \mathcal{Q}$, then the corresponding compartmental dynamical system is monotonic. Hence, for every $Q \in \mathcal{Q}$ we seek all matrices $A \in \mathbb{R}^{3\times 3}$ and $A_{\mathrm{d}} \in \mathbb{R}^{3\times 3}$ such that $q_i A_{(i,j)} \leq 0$ and $q_i A_{\mathrm{d}(i,j)} \leq 0$, $i, j = 1, 2, 3$.

First, we consider the case where $Q = \mathrm{diag}[1,\ 1,\ 1]$. In this case, $q_i A_{(i,j)} \leq 0$ and $q_i A_{\mathrm{d}(i,j)} \leq 0$, $i, j = 1, 2, 3$, if and only if $A_{(1,2)} = A_{(1,3)} = A_{(2,1)} = A_{(3,1)} = A_{(3,2)} = A_{(2,3)} = 0$. Similarly, $q_i A_{\mathrm{d}(i,j)} \leq 0$ if and only if $A_{\mathrm{d}} = 0$. This corresponds to the trivial (decoupled) case since there are no intercompartmental flows between the three compartments. Next, let $Q = \mathrm{diag}[1,\ -1,\ 1]$ and note that $q_i A_{\mathrm{d}(i,j)} \leq 0$, $i, j = 1, 2, 3$ if and only if $A_{(1,2)} = A_{(1,3)} = 0$. In addition, since $A + A_{\mathrm{d}}$ is a compartmental matrix, it follows that $A_{(2,2)} = A_{(3,2)} = A_{(2,3)} = A_{(3,3)} = 0$. Finally, let $Q = \mathrm{diag}[-1,\ 1,\ 1]$. In this case $q_i A_{\mathrm{d}(i,j)} \leq 0$, $i, j = 1, 2, 3$ if and only if $A_{(2,1)} = A_{(2,3)} = A_{(3,1)} = A_{(3,2)} = 0$.

Since, $A + A_{\rm d}$ is compartmental, $A_{(2,2)} = 0$. Figures 3.1 (a), (b) and (c) show the corresponding compartmental structures.

It is important to note that in the case where $Q = \mathrm{diag}[-1,\ -1,\ -1]$, there does not exist a compartmental matrix $A + A_{\rm d}$ satisfying $QA \leq\leq 0$ and $QA_{\rm d} \leq\leq 0$ except for the zero matrix. This case would correspond to a compartmental dynamical system where all three states are monotonically increasing. Hence, the compartmental system would be unstable contradicting the fact that all compartmental systems are Lyapunov stable [16, 92]. Finally, the remaining four cases corresponding to $Q = \mathrm{diag}[-1,\ 1, -1]$, $Q = \mathrm{diag}[-1,\ -1,\ 1]$, $Q = \mathrm{diag}[1,\ -1,\ 1]$, and $Q = \mathrm{diag}[1,\ 1,\ -1]$ are dual to the cases where $Q = \mathrm{diag}[1,\ -1,\ -1]$ and $Q = \mathrm{diag}[-1,\ 1,\ 1]$ and hence are not presented.

3.6. Illustrative Numerical Example

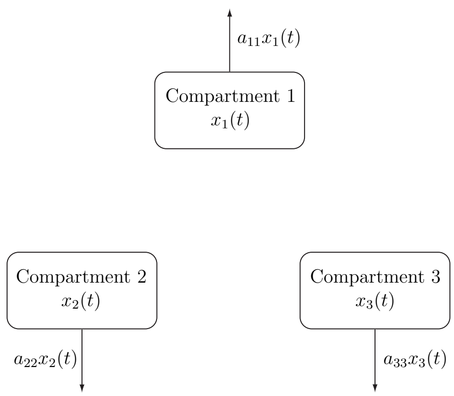
In this section we consider a numerical example involving a compartmental system with three compartments. Here, for simplicity of exposition, we assume that all transfer times between compartments are equal and given by τ. Now, a mass balance for the compartmental system, with state variables and transfer coefficients $a_{ij} \geq 0$, $i = 1, 2, 3$, yields (3.2) with $u(t) \equiv 0$, and A and $A_{\rm d}$ given by

$$A_{(i,j)} = \begin{cases} -\sum_{k=1}^{3} a_{ki}, & i = j, \\ 0, & i \neq j, \end{cases} \qquad A_{{\rm d}(i,j)} = \begin{cases} 0, & i = j, \\ a_{ij}, & i \neq j, \end{cases} \tag{3.8}$$

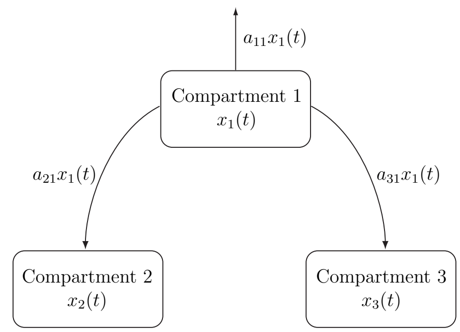
where $i, j = 1, 2, 3$. Note that A is essentially nonnegative, $A_{\rm d}$ is nonnegative, and $A + A_{\rm d}$ is a compartmental matrix.

Here, we are interested in the monotonicity of the first compartment and hence choose $Q = \mathrm{diag}[1,\ 0,\ 0]$. Now, it follows from Theorem 3.2 that if $QA \leq\leq 0$ and $QA_{\rm d} \leq\leq 0$, then the first compartment is monotonic. Note that $QA \leq\leq 0$ and $QA_{\rm d} \leq\leq 0$ if and only if

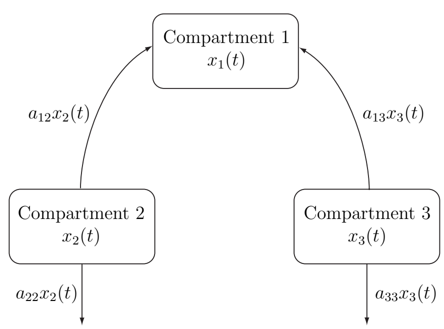
$$A_{(1,2)} = A_{(1,3)} = A_{{\rm d}(1,1)} = A_{{\rm d}(1,2)} = A_{{\rm d}(1,3)} = 0. \tag{3.9}$$



(a)



(b)



(c)

Figure 3.1: Three-Dimensional Monotonic Compartmental Systems with Time-Delay

For our simulation we let

$$A = \begin{bmatrix} -5 & 0 & 0 \\ 0 & -5 & 0 \\ 0 & 0 & -5 \end{bmatrix}, \quad A_{\mathrm{d}} = \begin{bmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 2 & 0 & 0 \end{bmatrix}.$$

With $\tau = 2$ and the initial condition $\phi(t) = [1,\ 0,\ 0]^{\mathrm{T}}$, $-\tau \leq t \leq 0$, Figure 3.2 shows that the mass of the first compartment is monotonic. Next, let

$$A = \begin{bmatrix} -5 & 0 & 0 \\ 0 & -5 & 0 \\ 0 & 0 & -5 \end{bmatrix}, \quad A_{\mathrm{d}} = \begin{bmatrix} 0 & 2 & 2 \\ 1 & 0 & 0 \\ 2 & 0 & 0 \end{bmatrix}.$$

Figure 3.3 shows the mass of the first compartment with respect to time for $\tau = 2$ and the initial condition $\phi(t) = [1,\ 0,\ 0]^{\mathrm{T}}$, $-\tau \leq t \leq 0$. However, since (3.9) is a necessary and sufficient condition for monotonicity for the first compartment, the mass in the first compartment does not exhibit a monotonic behavior. Next, we consider a compartmental system involving three compartments with the transfer times between the compartments given by τ_1 and τ_2.

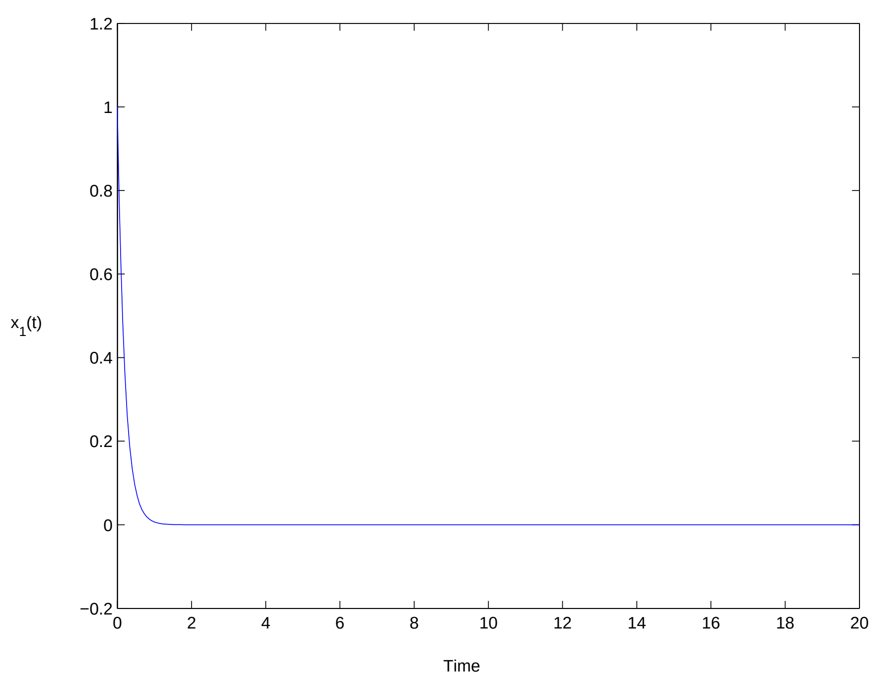


Figure 3.2: Monotonicity of the First Compartment with $\tau = 2$

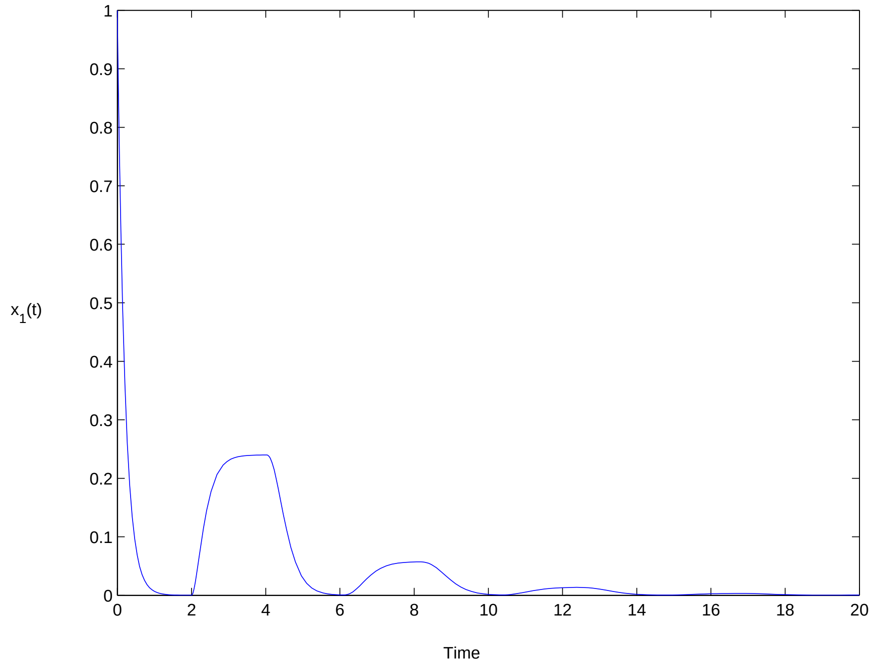


Figure 3.3: Nonmonotonicity of the First Compartment with $\tau = 2$

Now, a mass balance for the compartmental system, with state variables and transfer coefficients $a_{ij} \geq 0$, $i = 1, 2, 3$, yields (3.2) with $u(t) \equiv 0$, $n_{\rm d} = 2$ and A and $A_{{\rm d}i}$ given by

$$A_{(i,j)} = \begin{cases} -\sum_{k=1}^{3} a_{ki}, & i = j, \\ 0, & i \neq j, \end{cases} \qquad A_{{\rm d}i(i,j)} = \begin{cases} 0, & i = j, \\ a_{ij}, & i \neq j, \end{cases} \tag{3.10}$$

where $i, j = 1, 2, 3$. Note that A is essentially nonnegative, $A_{{\rm d}i}$ is nonnegative, and $A + \sum_{i=1}^{2} A_{{\rm d}i}$ is a compartmental matrix. Here, we are interested in the monotonicity of the first compartment and hence choose $Q = \mathrm{diag}[1,\ 0,\ 0]$. Now, it follows from Theorem 3.2 that if $QA \leq\leq 0$ and $QA_{{\rm d}i} \leq\leq 0$, where $i = 1, 2$, then the first compartment is monotonic. Note that $QA \leq\leq 0$ and $QA_{{\rm d}i} \leq\leq 0$ if and only if

$$A_{(1,2)} = A_{(1,3)} = A_{{\rm d}1(1,1)} = A_{{\rm d}1(1,2)} = A_{{\rm d}1(1,3)} = A_{{\rm d}2(1,1)} = A_{{\rm d}2(1,2)} = A_{{\rm d}2(1,3)} = 0. \tag{3.11}$$

For our simulation we let

$$A = \begin{bmatrix} -5 & 0 & 0 \\ 0 & -5 & 0 \\ 0 & 0 & -5 \end{bmatrix}, \quad A_{{\rm d}1} = \begin{bmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 2 & 0 & 0 \end{bmatrix}, \quad A_{{\rm d}2} = \begin{bmatrix} 0 & 0 & 0 \\ 1 & 0 & 0 \\ 3 & 0 & 0 \end{bmatrix}.$$

With $\tau_1 = 2$ and $\tau_2 = 3$ and the initial condition $\phi(t) = [1,\ 0,\ 0]^{\rm T}$, $-\tau \leq t \leq 0$,

Figure 3.4 shows that the mass of the first compartment is monotonic. Next, let

$$A = \begin{bmatrix} -5 & 0 & 0 \\ 0 & -5 & 0 \\ 0 & 0 & -5 \end{bmatrix}, \quad A_{\mathrm{d}1} = \begin{bmatrix} 0 & 1 & 2 \\ 1 & 0 & 0 \\ 2 & 0 & 0 \end{bmatrix}, \quad A_{\mathrm{d}2} = \begin{bmatrix} 0 & 1 & 0 \\ 1 & 0 & 0 \\ 3 & 0 & 0 \end{bmatrix}.$$

Figure 3.5 shows the mass of the first compartment with respect to time for $\tau_1 = 2$ and $\tau_2 = 3$ for the initial condition $\phi(t) = [1,\ 0,\ 0]^{\mathrm{T}}$, $-\tau \leq t \leq 0$. However, since (3.11) is a necessary and sufficient condition for monotonicity for the first compartment, the mass in the first compartment does not exhibit a monotonic behavior.

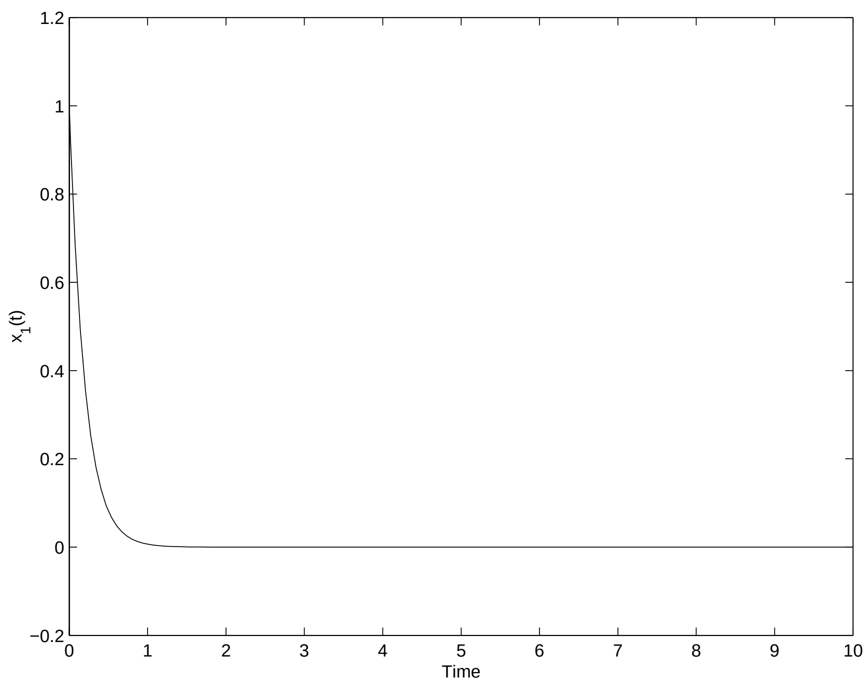


Figure 3.4: Monotonicity of the First Compartment with $\tau_1 = 2$ and $\tau_2 = 3$

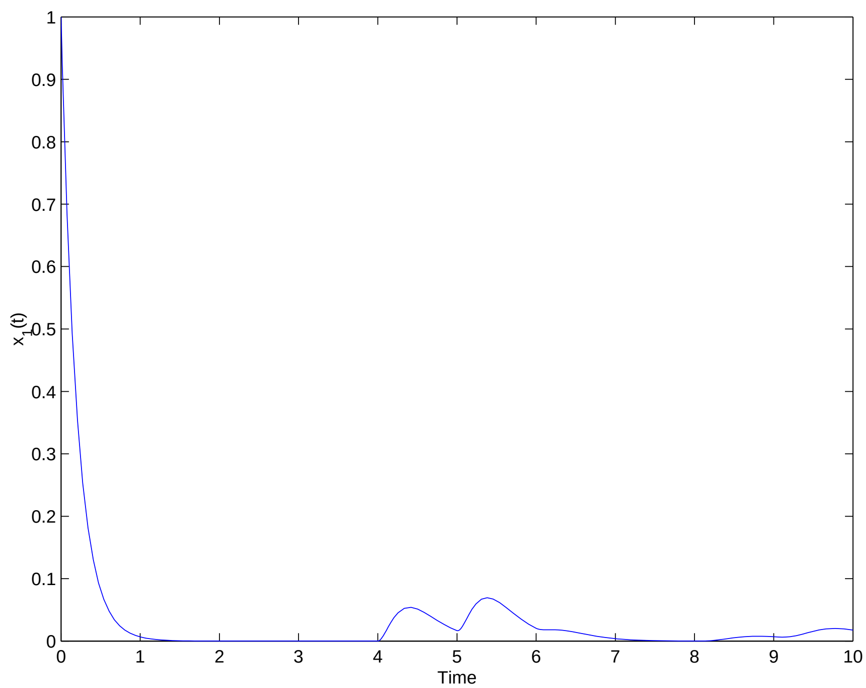


Figure 3.5: Monotonicity of the First Compartment with $\tau_1 = 2$ and $\tau_2 = 3$

Chapter 4

Direct Adaptive Control of Nonnegative and Compartmental Dynamical Systems with Time Delay

4.1. Introduction

Even though advanced robust and adaptive control methodologies have been (and are being) extensively developed for highly complex engineering systems, modern active control technology has received far less consideration in medical systems. The main reason for this state of affairs is the steep barriers to communication between mathematics/control engineering and medicine. However, this is slowly changing and there is no doubt that control-system technology has a great deal to offer medicine. For example, critical care patients, whether undergoing surgery or recovering in intensive care units, require drug administration to regulate key physiological (state) variables (e.g., blood pressure, cardiac output, heart rate, glucose, etc.) within desired levels. The rate of infusion of each administered drug is *critical*, requiring constant monitoring and frequent adjustments. Open-loop control (manual control) by clinical personnel can be very tedious, imprecise, time consuming, and often of poor quality. Hence, the need for active control (closed-loop control) in medical systems is severe; with the potential in improving the quality of medical care as well as curtailing the increasing cost of health care.

The complex highly uncertain and hostile environment of surgery places stringent performance requirements for closed-loop set-point regulation of physiological variables. For example, during cardiac surgery, blood pressure control is vital and is subject to numerous highly uncertain exogenous disturbances. Vasoactive and cardioactive drugs are administered resulting in large disturbance oscillations to the system (patient). The arterial line may be flushed and blood may be drawn, corrupting sensor blood pressure measurements. Low anesthetic levels may cause the patient to react to painful stimuli, thereby changing system response characteristics. The flow rate of vasodilator drug infusion may fluctuate causing transient changes in the infusion delay time. Hemorrhage, patient position changes, cooling and warming of the patient, and changes in anesthesia levels will also effect system response characteristics.

In light of the complex and highly uncertain nature of system response characteristics under surgery requiring controls, it is not surprising that reliable system models for many high performance drug delivery systems are unavailable. In the face of such high levels of system uncertainty, robust controllers may unnecessarily sacrifice system performance whereas adaptive controllers can tolerate far greater system uncertainty levels to improve system performance [95–98]. In contrast to fixed-gain robust controllers, which maintain specified constants within the feedback control law to *sustain* robust performance, adaptive controllers directly or indirectly adjust feedback gains to maintain closed-loop stability and *improve* performance in the face of system uncertainties. Specifically, indirect adaptive controllers utilize parameter update laws to identify unknown system parameters and adjust feedback gains to account for system variation, while direct adaptive controllers directly adjust the controller gains in response to system variations (drug administration).

In a recent paper [99], the authors present a direct adaptive control framework for set-point regulation of linear nonnegative and compartmental systems with applications to clinical pharmacology. In this chapter, we extend the results of [99] to the case of nonnegative and compartmental dynamical systems with unknown system time delay. Specifically, we develop a Lyapunov-Krasovskii-based direct adaptive control framework for guaranteeing set-point regulation for linear uncertain nonnegative and compartmental dynamical systems with unknown time delay. The specific focus of the chapter is on pharmacokinetic models and their applications to drug delivery systems. In particular, we develop direct adaptive controllers with nonnegative control inputs as well as adaptive controllers with the absence of such a restriction. Finally, we demonstrate the framework on a drug delivery model for general anesthesia that involves system time delays.

4.2. Mathematical Preliminaries

The following results are necessary for the development of the main results.

Lemma 4.1 [100]. Let $A \in \mathbb{R}^{n\times n}$ be an essentially nonnegative matrix. Then A is Hurwitz if and only if there exists a vector $q \in \mathbb{R}^n$ such that $q >> 0$ satisfies $A^{\mathrm{T}}q \leq\leq 0$.

Corollary 4.1. Let $A \in \mathbb{R}^{n\times n}$ be an essentially nonnegative matrix such that $A = A^{\mathrm{T}}$. If there exists $q \in \mathbb{R}^n_+$ such that $A^{\mathrm{T}}q \leq\leq 0$ then $A \leq 0$.

Lemma 4.2. Let $X \in \mathbb{R}^{n\times n}$ and $Z \in \mathbb{R}^{m\times m}$ be such that $X = X^{\mathrm{T}}$ and $Z = Z^{\mathrm{T}}$, and let $Y \in \mathbb{R}^{n\times m}$ be such that $Y = YZ^{\#}Z$. Then

$$M \triangleq \begin{bmatrix} X & Y \\ Y^{\mathrm{T}} & Z \end{bmatrix} \leq 0 \tag{4.1}$$

if and only if $Z \leq 0$ and $X - YZ^{\#}Y^{\mathrm{T}} \leq 0$.

Proof. Let $T = \begin{bmatrix} I & -YZ^{\#} \\ 0 & I \end{bmatrix}$ and note that $\det T \neq 0$. Now, noting that $TMT^{\mathrm{T}} \leq 0$ if and only if $M \leq 0$ and

$$TMT^{\mathrm{T}} = \begin{bmatrix} I & -YZ^{\#} \\ 0 & I \end{bmatrix} \begin{bmatrix} X & Y \\ Y^{\mathrm{T}} & Z \end{bmatrix} \begin{bmatrix} I & 0 \\ -Z^{\#}Y^{\mathrm{T}} & I \end{bmatrix}$$

$$= \begin{bmatrix} X - YZ^{\#}Y^{\mathrm{T}} & 0 \\ 0 & Z \end{bmatrix}$$
$$\leq 0,$$

the result follows immediately. $\square$

Lemma 4.3. Let $A \in \mathbb{R}^{n\times n}$ be an essentially nonnegative matrix and let $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, p$, be nonnegative matrices such that $\hat{A}\mathbf{e} \leq\leq 0$ and $\hat{A}^{\mathrm{T}}\mathbf{e} \leq\leq 0$ where $\hat{A} \triangleq A + \sum_{i=1}^{p} A_{\mathrm{d}i}$. Then there exist diagonal matrices $Q_i \geq 0$, $i = 1, \ldots, p$, such that

$$A^{\mathrm{T}} + A + \sum_{i=1}^{p}(Q_i + A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i}) \leq 0. \tag{4.2}$$

Proof. For each $i \in \{1, \ldots, p\}$, let Q_i be the diagonal matrix defined by

$$Q_{i(l,l)} = \sum_{m=1}^{n} A_{\mathrm{d}i(l,m)}.$$

Now note that $(A + \sum_{i=1}^{p} Q_i)\mathbf{e} = (A + \sum_{i=1}^{p} A_{\mathrm{d}i})\mathbf{e} \leq\leq 0$, $(A_{\mathrm{d}i} - Q_i)\mathbf{e} = 0$, and $Q_i Q_i^{\#} A_{\mathrm{d}i} = A_{\mathrm{d}i}$. Hence, $M\mathbf{e} \leq\leq 0$ where

$$M \triangleq \begin{bmatrix} A^{\mathrm{T}} + A + \sum_{i=1}^{p} Q_i & A_{\mathrm{d}1}^{\mathrm{T}} & A_{\mathrm{d}2}^{\mathrm{T}} & \cdots & A_{\mathrm{d}p}^{\mathrm{T}} \\ A_{\mathrm{d}1} & -Q_1 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ A_{\mathrm{d}p} & 0 & 0 & \cdots & -Q_p \end{bmatrix}. \tag{4.3}$$

Now, it follows from Corollary 4.1 that $M \leq 0$ and since $Q_i Q_i^{\#} A_{\mathrm{d}i} = A_{\mathrm{d}i}$, $i = 1, \ldots, p$, it follows from Lemma 4.2 that $M \leq 0$ if and only if (4.2) holds. $\square$

Theorem 4.1. Let $A \in \mathbb{R}^{n\times n}$ be an essentially nonnegative matrix and let $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, p$, be nonnegative matrices such that $\hat{A} \triangleq A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is Hurwitz. Then there exist diagonal matrices P, $Q_i \in \mathbb{R}^{n\times n}$, $P > 0$ and $Q_i \geq 0$, $i = 1, \ldots, p$, such that

$$A^{\mathrm{T}}P + PA + \sum_{i=1}^{p}(Q_i + A_{\mathrm{d}i}^{\mathrm{T}} P Q_i^{\#} P A_{\mathrm{d}i}) < 0. \tag{4.4}$$

Proof. Since $\hat{A} \triangleq A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is essentially nonnegative and Hurwitz, by Lemma 4.1 there exists $l \in \mathbb{R}_{+}^{n}$, $l = [l_1, \ldots, l_n]^{\mathrm{T}}$, such that $\hat{A}^{\mathrm{T}}l << 0$, which implies that

$\hat{A}^{\mathrm{T}} L\mathbf{e} << 0$, where $L = \mathrm{diag}[l_1, \ldots, l_n]$. This further implies that $L\hat{A}$ is compartmental and Hurwitz.

Since $L\hat{A}$ is compartmental and Hurwitz it follows that $\hat{A}^{\mathrm{T}} L$ is essentially nonnegative and Hurwitz and by Lemma 4.1 there exists $m \in \mathbb{R}_+^n$, $m = [m_1, \ldots, m_n]^{\mathrm{T}}$ such that $L\hat{A}m << 0$, which further implies that $L\hat{A}M\mathbf{e} << 0$, where $M = \mathrm{diag}[m_1, \ldots, m_n]$. Furthermore, since $\hat{A}^{\mathrm{T}} L\mathrm{e} << 0$ it follows that $M\hat{A}^{\mathrm{T}} L\mathrm{e} << 0$ and hence $L\hat{A}M$ is compartmental and Hurwitz.

Next, we define $\tilde{A} \triangleq LAM$ and $\tilde{A}_{\mathrm{d}i} \triangleq LA_{\mathrm{d}i}M$, $i = 1, \ldots, p$. By construction $\tilde{A}$ is an essentially nonnegative matrix and $\tilde{A}_{\mathrm{d}i}$, $i = 1, \ldots, p$, are nonnegative matrices. Hence, $\tilde{A} + \sum_{i=1}^{p} \tilde{A}_{\mathrm{d}i}$ is essentially nonnegative and Hurwitz by noting that $\tilde{A} + \sum_{i=1}^{p} \tilde{A}_{\mathrm{d}i} = L\hat{A}M$. Now since $(\tilde{A} + \sum_{i=1}^{p} \tilde{A}_{\mathrm{d}i})\mathbf{e} \leq\leq 0$ and $(\tilde{A} + \sum_{i=1}^{p} \tilde{A}_{\mathrm{d}i})^{\mathrm{T}}\mathbf{e} \leq\leq 0$, by Lemma 4.3 there exist diagonal matrices $\tilde{Q}_i$, $i = 1, \ldots, p$, such that

$$\tilde{A}^{\mathrm{T}} + \tilde{A} + \sum_{i=1}^{p} (\tilde{Q}_i + \tilde{A}_{\mathrm{d}i}^{\mathrm{T}} \tilde{Q}_i^{\#} \tilde{A}_{\mathrm{d}i}) \leq 0 \tag{4.5}$$

which further implies that

$$MA^{\mathrm{T}} L + LAM + \sum_{i=1}^{p} (\tilde{Q}_i + MA_{\mathrm{d}i}^{\mathrm{T}} L\tilde{Q}_i^{\#} LA_{\mathrm{d}i}M) \leq 0, \tag{4.6}$$

and hence

$$A^{\mathrm{T}} LM^{-1} + M^{-1}LA + \sum_{i=1}^{p} (M^{-1}\tilde{Q}_i M^{-1} + A_{\mathrm{d}i}^{\mathrm{T}} L\tilde{Q}_i^{\#} LA_{\mathrm{d}i} \leq 0.$$

Now, (4.4) follows with $Q_i = M^{-1}\tilde{Q}_i M^{-1}$, $i = 1, \ldots, p$, and $P = LM^{-1}$ as a soft inequality. The strict inequality follows by noting that the proof remains valid by replacing A with $A + \varepsilon I_n$ for sufficiently small $\varepsilon > 0$. □

In this chapter, we consider a controlled linear time-delay dynamical system $\mathcal{G}$ of the form

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{p} A_{\mathrm{d}i} x(t - \tau_i) + Bu(t),\ x(\theta) = \eta(\theta),\ -\bar{\tau} \leq \theta \leq 0,\ t \geq 0, \tag{4.7}$$

where $x(t) \in \mathbb{R}^n$, $u(t) \in \mathbb{R}^m$, $t \geq 0$, $A \in \mathbb{R}^{n \times n}$ is an unknown essentially nonnegative matrix, $A_{\mathrm{d}i} \in \mathbb{R}^{n \times n}$, $i = 1, \ldots, p$, and $B \in \mathbb{R}^{n \times m}$ are unknown nonnegative matrices,

$\bar{\tau} = \max_{i\in\{1,\ldots,p\}}\tau_i$, $\eta(\cdot) \in \mathcal{C} = \mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$ is a continuous vector valued function specifying the initial state of the system, and $\mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$ denotes a Banach space of continuous functions mapping the interval $[-\bar{\tau},0]$ into $\mathbb{R}^n$ with the topology of uniform convergence. Note that the state of (4.7) at time t is the *piece of trajectories* x between $t-\bar{\tau}$ and t, or, equivalently, the *element* x_t in the space of continuous functions defined on the interval $[-\bar{\tau},0]$ and taking values in $\mathbb{R}^n$; that is, $x_t \in \mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$, where $x_t(\theta) \triangleq x(t+\theta)$, $\theta \in [-\bar{\tau},0]$. Furthermore, since for a given time t the piece of the trajectories x_t is defined on $[-\bar{\tau},0]$, the uniform norm $|||x_t||| = \sup_{\theta\in[-\bar{\tau},0]} \|x(t+\theta)\|$, where $\|\cdot\|$ denotes the Euclidean vector norm, is used for the definitions of Lyapunov and asymptotic stability of (4.7) with $u(t) \equiv 0$. For further details see [37,94]. Finally, note that since $\eta(\cdot)$ is continuous it follows from Theorem 2.1 of [37, p. 14] that there exists a unique solution $x(\eta)$ defined on $[-\bar{\tau},\infty)$ that coincides with η on $[-\bar{\tau},0]$ and satisfies (4.7) for all $t \geq 0$.

Theorem 4.2 [92, 93]. Consider the linear nonnegative dynamical system $\mathcal{G}$ given by (4.7) where $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,p$, is nonnegative, and $u(t) \equiv 0$. Then, $\mathcal{G}$ is asymptotically stable for all $\bar{\tau} \in [0,\infty)$ if and only if there exist $p, r \in \mathbb{R}^n$ such that $p >> 0$ and $r >> 0$ satisfy

$$0 = (A + \sum_{i=1}^{p} A_{\mathrm{d}i})^{\mathrm{T}} p + r. \tag{4.8}$$

Remark 4.1. It follows from Lemma 4.1 and Theorems 4.1 and 4.2 that $\mathcal{G}$ is asymptotically stable for all $\bar{\tau} \in [0,\infty)$ if and only if there exist diagonal matrices $P, Q_i \in \mathbb{R}^{n\times n}$, $P > 0$ and $Q_i \geq 0$, $i = 1,\ldots,p$, such that

$$A^{\mathrm{T}}P + PA + \sum_{i=1}^{p}(Q_i + A_{\mathrm{d}i}^{\mathrm{T}} P Q_i{}^{\#} P A_{\mathrm{d}i}) < 0.$$

The proof follows from standard arguments using the Lyapunov-Krasovskii functional

$$V(\psi(\cdot)) = \psi^{\mathrm{T}}(0)P\psi(0) + \sum_{i=1}^{p}\int_{-\tau_i}^{0} \psi^{\mathrm{T}}(\theta) A_{\mathrm{d}i}^{\mathrm{T}} P Q_i{}^{\#} P A_{\mathrm{d}i}^{\mathrm{T}} \psi(\theta)\mathrm{d}\theta.$$

The following proposition is needed for the main results of the chapter.

Proposition 4.1 [92, 93]. The linear dynamical system $\mathcal{G}$ given by (4.7) is *nonnegative* if and only if $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$ is nonnegative, and $B \in \mathbb{R}^{n\times m}$ is nonnegative.

It follows from Proposition 4.1 that the control input signal $Bu(t)$, $t \geq 0$, needs to be nonnegative to guarantee the nonnegativity of the state of (4.7). This is due to the fact that when the initial state of (4.7) belongs to the boundary of the nonnegative orthant, a negative input can destroy the nonnegativity of the state of (4.7). Alternatively, however, if the initial state is in the interior of the nonnegative orthant, then it follows from continuity of solutions with respect to the system initial conditions that, over a small interval of time, nonnegativity of the state of (4.7) is guaranteed *irrespective* of the sign of each element of the control input $Bu(t)$ over this time interval. However, unlike open-loop control wherein lack of coordination between the input and the state necessitates nonnegativity of the control input, a *feedback* control signal predicated on the system state variables allows for the anticipation of loss of nonnegativity of the state. Hence, state feedback control signals can take negative values while assuring nonnegativity of the system states. For further discussion of the above fact see [99, 101].

Next, we present a time-varying extension to Proposition 4.1 needed for the main theorems of this chapter. Specifically, we consider the linear time-varying delay dynamical system

$$\dot{x}(t) = A(t)x(t) + \sum_{i=1}^{p} A_{\mathrm{d}i}(t)x(t-\tau_i) + Bu(t),\ \ x(\theta) = \eta(\theta),\ \ \theta \in [-\bar{\tau}, 0],\ \ t \geq 0, \quad (4.9)$$

where $A : [0,\infty) \to \mathbb{R}^{n\times n}$ and $A_{\mathrm{d}i} : [0,\infty) \to \mathbb{R}^{n\times n}$, $i = 1,\ldots,p$ are continuous. For the following result the definition of nonnegativity holds with (4.7) replaced by (4.9).

Proposition 4.2. Consider the time-varying delay dynamical system (4.9) where $A : [0,\infty) \to \mathbb{R}^{n\times n}$ and $A_{\mathrm{d}i} : [0,\infty) \to \mathbb{R}^{n\times n}$, $i = 1,\ldots,p$, are continuous. If for every

$t \in [0,\infty)$, $A : [0,\infty) \to \mathbb{R}^{n\times n}$ is essentially nonnegative, $A_{\mathrm{d}i} : [0,\infty) \to \mathbb{R}^{n\times n}$, $i = 1,\ldots,p$, is nonnegative, $B \in \mathbb{R}^{n\times m}$ is nonnegative, and $u(t)$ is nonnegative, then the solution $x(t)$, $t \geq 0$, to (4.9) is nonnegative.

Proof. The result is a direct consequence of the nonlinear analogue to Proposition 4.1 by equivalently representing the time-varying delay dynamical system (4.9) as an autonomous nonlinear time-delay system by appending another state to represent time. □

Since stabilization of nonnegative systems naturally deals with equilibrium points in the interior of the nonnegative orthant $\overline{\mathbb{R}}_+^n$, the following proposition provides necessary conditions for the existence of an interior equilibrium state $x(\theta) = x_{\mathrm{e}} \in \mathbb{R}_+^n$, $\theta \in [-\bar{\tau}, 0]$, of (4.7) in terms of the stability properties of the system matrices A and $A_{\mathrm{d}i}$. For this result, recall that a matrix $M \in \mathbb{R}^{n\times n}$ is *semistable* if and only if $\lim_{t\to\infty} e^{Mt}$ exists.

Proposition 4.3. Consider the nonnegative time-delay dynamical system (4.7) and assume there exist $x_{\mathrm{e}} \in \mathbb{R}_+^n$ and $u_{\mathrm{e}} \in \overline{\mathbb{R}}_+^m$ such that

$$0 = (A + \sum_{i=1}^{p} A_{\mathrm{d}i})x_{\mathrm{e}} + Bu_{\mathrm{e}}. \tag{4.10}$$

Then, $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is semistable.

Proof. The proof is a direct consequence of *ii*) of Theorem 3.2 in [100] with A replaced by $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$, $p = x_{\mathrm{e}}$, and $r = Bu_{\mathrm{e}}$. □

It follows from Proposition 4.3 that the existence of an equilibrium state $x(\theta) = x_{\mathrm{e}} \in \mathbb{R}_+^n$, $\theta \in [-\bar{\tau}, 0]$, for (4.7) implies that the matrix $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is semistable. Hence, if (4.10) holds for $x_{\mathrm{e}} \in \mathbb{R}_+^n$ and $u_{\mathrm{e}} \in \overline{\mathbb{R}}_+^m$, then $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is Hurwitz or $0 \in \mathrm{spec}(A + \sum_{i=1}^{p} A_{\mathrm{d}i})$, where $\mathrm{spec}(A + \sum_{i=1}^{p} A_{\mathrm{d}i})$ denotes the spectrum of $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$, is a simple eigenvalue of $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ and all other eigenvalues of $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ have negative real parts since $-(A + \sum_{i=1}^{p} A_{\mathrm{d}i})$ is an M-matrix [7].

Definition 4.1 [92, 93]. The linear time-delay dynamical system (4.7) is called a *compartmental dynamical system* if A and $A_{\mathrm{d}} \triangleq \sum_{i=1}^{p} A_{\mathrm{d}i}$, are such that A is essentially nonnegative, $A_{\mathrm{d}i}$, $i = 1, \ldots, p$, is nonnegative, and $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is a compartmental matrix.

Note that if A and A_{d} are such that

$$A_{(i,j)} = \begin{cases} -\sum_{k=1}^{n} a_{ki}, & i = j, \\ 0, & i \neq j, \end{cases} \quad A_{\mathrm{d}(i,j)} = \begin{cases} 0, & i = j, \\ a_{ij}, & i \neq j, \end{cases} \tag{4.11}$$

where $a_{ii} \geq 0$, $i \in \{1, \cdots, n\}$, denote the loss coefficients of the ith compartment and $a_{ij} \geq 0$, $i \neq j$, $i, j \in \{1, \cdots, n\}$, denote the transfer coefficients from the jth compartment to the ith compartment then the linear dynamical system (4.7) is a compartmental system.

4.3. Adaptive Control for Linear Nonnegative Uncertain Dynamical Systems with Time Delay

In this section we consider the problem of characterizing adaptive feedback control laws for nonnegative and compartmental uncertain dynamical systems with time delay to achieve *set-point* regulation in the nonnegative orthant. Specifically, consider the following controlled linear uncertain time-delay dynamical system $\mathcal{G}$ given by

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{p} A_{\mathrm{d}i} x(t - \tau_i) + Bu(t), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \tag{4.12}$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, is the state of the system, $u(t) \in \mathbb{R}^m$, $t \geq 0$, is the control input, $A \in \mathbb{R}^{n \times n}$ is an *unknown* essentially nonnegative matrix, $A_{\mathrm{d}i} \in \mathbb{R}^{n \times n}$ and $B \in \mathbb{R}^{n \times m}$ are *unknown* nonnegative matrices, $\eta(\cdot) \in \{\psi(\cdot) \in \mathcal{C}_+([-\bar{\tau}, 0], \mathbb{R}^n) : \psi(\theta) \geq\geq 0, \theta \in [-\bar{\tau}, 0]\}$, and $\bar{\tau} \geq 0$, $\bar{\tau} = \max_{i \in \{1, \ldots, p\}} \tau_i$ is an *unknown* system delay amount. The control input $u(\cdot)$ in (4.12) is restricted to the class of admissible controls consisting of measurable functions such that $u(t) \in \mathbb{R}^m$, $t \geq 0$.

It follows from Proposition 4.1 that the state trajectories of nonnegative and compartmental dynamical systems remain in the nonnegative orthant of the state space for nonnegative initial conditions and nonnegative inputs. However, even though active control of drug delivery systems for physiological applications requires control (source) inputs to be nonnegative, in many applications of nonnegative systems such as biological systems, population dynamics, and ecological systems, the positivity constraint on the control input is not natural. Hence, in this section we do not place any restriction on the sign of the control signal and design an adaptive controller that guarantees that the system states remain in the nonnegative orthant and converge to a desired equilibrium state. Specifically, for a given desired set point $x_{\rm e} \in \overline{\mathbb{R}}_+^n$, our aim is to design a control input $u(t)$, $t \geq 0$, such that $\lim_{t\to\infty} \|x(t) - x_{\rm e}\| = 0$. However, since in many applications of nonnegative systems and in particular, compartmental systems, it is often necessary to regulate a subset of the nonnegative state variables which usually include a central compartment, here we require that $\lim_{t\to\infty} x_i(t) = x_{{\rm d}i} \geq 0$ for $i = 1, \cdots, m \leq n$, where $x_{{\rm d}i}$ is a desired set point for the ith state $x_i(t)$. Furthermore, we assume that control inputs are injected directly into m separate compartments such that the input matrix is given by

$$B = \begin{bmatrix} B_u \\ 0_{(n-m)\times m} \end{bmatrix}, \tag{4.13}$$

where $B_u \triangleq \mathrm{diag}[b_1, \cdots, b_m]$ and $b_i \in \mathbb{R}_+$, $i = 1, \cdots, m$. For compartmental systems this assumption is not restrictive since control inputs correspond to control inflows to each individual compartment. Here, we assume that for $i \in \{1, \cdots, m\}$, b_i is *unknown*. For the statement of our main result define $x_{\rm e} \triangleq [x_{\rm d}^{\rm T}, x_{\rm u}^{\rm T}]^{\rm T}$, where $x_{\rm d} \triangleq [x_{{\rm d}1}, \cdots, x_{{\rm d}m}]^{\rm T}$ and $x_{\rm u} \triangleq [x_{{\rm u}1}, \cdots, x_{{\rm u}(n-m)}]^{\rm T}$.

Theorem 4.3. Consider the linear uncertain time-delay dynamical system $\mathcal{G}$ given by (4.12) where A is essentially nonnegative, $A_{{\rm d}i}$, $i = 1, \ldots, p$, is nonnegative, and B is nonnegative and given by (4.13). Assume there exist nonnegative vectors $x_{\rm u} \in \overline{\mathbb{R}}_+^{n-m}$ and $u_{\rm e} \in \overline{\mathbb{R}}_+^m$ such that

$$0 = (A + \sum_{i=1}^{p} A_{{\rm d}i}) x_{\rm e} + B u_{\rm e}. \tag{4.14}$$

Furthermore, assume there exists a diagonal matrix $K_{\mathrm{g}} = \mathrm{diag}[k_{\mathrm{g}1}, \cdots, k_{\mathrm{g}m}]$, such that $A_{\mathrm{s}} + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is Hurwitz where $A_{\mathrm{s}} \triangleq A + B\tilde{K}_{\mathrm{g}}$ and $\tilde{K}_{\mathrm{g}} \triangleq [K_{\mathrm{g}}\ 0_{m\times(n-m)}]$. Finally, let q_i and $\hat{q}_i$, $i = 1, \cdots, m$, be positive constants. Then the adaptive feedback control law

$$u(t) = K(t)(\hat{x}(t) - x_{\mathrm{d}}) + \phi(t), \tag{4.15}$$

where $K(t) = \mathrm{diag}[k_1(t), \cdots, k_m(t)]$, $\hat{x}(t) = [x_1(t), \cdots, x_m(t)]^{\mathrm{T}}$, and $\phi(t) \in \mathbb{R}^m$, $t \geq 0$, or, equivalently,

$$u_i(t) = k_i(t)(x_i(t) - x_{\mathrm{d}i}) + \phi_i(t), \quad i = 1, \cdots, m, \tag{4.16}$$

where $k_i(t) \in \mathbb{R}$, $t \geq 0$, and $\phi_i(t) \in \mathbb{R}$, $t \geq 0$, $i = 1, \cdots, m$, with update laws

$$\dot{k}_i(t) = -q_i(x_i(t) - x_{\mathrm{d}i})^2, \quad k_i(0) \leq 0, \quad i = 1, \cdots, m, \tag{4.17}$$

$$\dot{\phi}_i(t) = \begin{cases} 0, & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) \geq x_{\mathrm{d}i},\ \phi_i(0) \geq 0, \\ -\hat{q}_i(x_i(t) - x_{\mathrm{d}i}), & \text{otherwise},\ i = 1, \cdots, m, \end{cases} \tag{4.18}$$

guarantees that the solution $(x(t), K(t), \phi(t)) \equiv (x_{\mathrm{e}}, K_{\mathrm{g}}, u_{\mathrm{e}})$ of the closed-loop system given by (4.12), (4.15), (4.17), (4.18) is Lyapunov stable and $x_i(t) \to x_{\mathrm{d}i}$, $i = 1, \cdots, m$, as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$. Furthermore, $x(t) \geq\geq 0$, $t \geq 0$, for all $\eta(\cdot) \in \mathcal{C}_+$.

Proof. Note that with $u(t)$, $t \geq 0$, given by (4.15) it follows from (4.12) that

$$\begin{aligned} \dot{x}(t) &= Ax(t) + \sum_{i=1}^{p} A_{\mathrm{d}i}x(t - \tau_i) + BK(t)(\hat{x}(t) - x_{\mathrm{d}}) + B\phi(t), \\ & \qquad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \end{aligned} \tag{4.19}$$

or, equivalently, using (4.14) we obtain

$$\begin{aligned} \dot{x}(t) &= A_{\mathrm{s}}(x(t) - x_{\mathrm{e}}) + \sum_{i=1}^{p} A_{\mathrm{d}i}(x(t - \tau_i) - x_{\mathrm{e}}) \\ &\quad + B(K(t) - K_{\mathrm{g}})(\hat{x}(t) - x_{\mathrm{d}}) + B(\phi(t) - u_{\mathrm{e}}), \\ & \qquad\qquad x(\theta) = \eta(\theta),\ -\bar{\tau} \leq \theta \leq 0,\ t \geq 0. \end{aligned} \tag{4.20}$$

Since $A_{\mathrm{s}} + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is essentially nonnegative and Hurwitz it follows from Theorem 4.1 that there exists diagonal matrices $P > 0$ and $\tilde{Q}_i \geq 0$, $i = 1, \ldots, p$, and a positive-definite matrix $R \in \mathbb{R}^{n\times n}$ such that

$$A_{\mathrm{s}}{}^{\mathrm{T}}P + PA_{\mathrm{s}} + \sum_{i=1}^{p}(\tilde{Q}_i + A_{\mathrm{d}i}^{\mathrm{T}}P\tilde{Q}_i^{\#}PA_{\mathrm{d}i}) + R = 0 \tag{4.21}$$

To show Lyapunov stability of the closed-loop system (4.17), (4.18), and (4.20) consider the Lyapunov-Krasovskii functional candidate $V : \mathcal{C}_+ \times \mathbb{R}^{m\times m} \times \mathbb{R}^m \to \mathbb{R}$ given by

$$\begin{aligned} V(\psi, K, \phi) \;=\; & (\psi(0) - x_{\mathrm{e}})^{\mathrm{T}}P(\psi(0) - x_{\mathrm{e}}) \\ & + \sum_{i=1}^{p}\int_{-\tau_i}^{0}(\psi(\theta) - x_{\mathrm{e}})^{\mathrm{T}}A_{\mathrm{d}i}^{\mathrm{T}}P\tilde{Q}_i^{\#}PA_{\mathrm{d}i}(\psi(\theta) - x_{\mathrm{e}})\mathrm{d}\theta \\ & + \mathrm{tr}(K - K_{\mathrm{g}})^{\mathrm{T}}Q^{-1}(K - K_{\mathrm{g}}) + (\phi - u_{\mathrm{e}})^{\mathrm{T}}\hat{Q}^{-1}(\phi - u_{\mathrm{e}}), \end{aligned} \tag{4.22}$$

or, equivalently,

$$\begin{aligned} V(\psi, K, \phi) \;=\; & \sum_{i=1}^{n}p_i(\psi_i(0) - x_{\mathrm{e}i})^2 + \sum_{i=1}^{p}\int_{-\tau_i}^{0}(\psi(\theta) - x_{\mathrm{e}})^{\mathrm{T}}A_{\mathrm{d}i}^{\mathrm{T}}P\tilde{Q}_i^{\#}PA_{\mathrm{d}i}(\psi(\theta) - x_{\mathrm{e}})\mathrm{d}\theta \\ & + \sum_{i=1}^{m}\frac{p_ib_i}{q_i}(k_i - k_{g_i})^2 + \sum_{i=1}^{m}\frac{p_ib_i}{\hat{q}_i}(\phi_i - u_{\mathrm{e}i})^2, \end{aligned}$$

where $Q = \mathrm{diag}\left[\frac{q_1}{p_1b_1}, \cdots, \frac{q_m}{p_mb_m}\right]$ and $\hat{Q} = \mathrm{diag}\left[\frac{\hat{q}_1}{p_1b_1}, \cdots, \frac{\hat{q}_m}{p_mb_m}\right]$. Note that $V(\psi_{\mathrm{e}}, K_{\mathrm{g}}, u_{\mathrm{e}}) = 0$, where $\psi_{\mathrm{e}}(\theta) = x_{\mathrm{e}}, \theta \in [-\bar{\tau}, 0]$. Furthermore, note that there exist $\mathcal{K}$-class functions $\alpha_1(\cdot), \alpha_2(\cdot), \alpha_3(\cdot)$ such that

$$V(\psi, K, \phi) \geq \alpha_1(\|\psi(0) - x_{\mathrm{e}}\|) + \alpha_2(\|K - K_{\mathrm{g}}\|_{\mathrm{F}}) + \alpha_3(\|\phi - u_{\mathrm{e}}\|),$$

where $\|\cdot\|$ denotes the Euclidean vector norm and $\|\cdot\|_{\mathrm{F}}$ denotes the Frobenius matrix norm. Now, letting $x(t)$, $t \geq 0$, denote the solution to (4.20) and using (4.17) and (4.18), it follows that the Lyapunov-Krasovskii directional derivative along the closed-loop system trajectories is given by

$$\begin{aligned} \dot{V}(x_t, K(t), \phi(t)) \;=\; & 2(x(t) - x_{\mathrm{e}})^{\mathrm{T}}P\dot{x}(t) + \sum_{i=1}^{p}(x(t) - x_{\mathrm{e}})^{\mathrm{T}}A_{\mathrm{d}i}^{\mathrm{T}}P\tilde{Q}_i^{\#}PA_{\mathrm{d}i}(x(t) - x_{\mathrm{e}}) \\ & - \sum_{i=1}^{p}(x(t - \tau_i) - x_{\mathrm{e}})^{\mathrm{T}}A_{\mathrm{d}i}^{\mathrm{T}}P\tilde{Q}_i^{\#}PA_{\mathrm{d}i}(x(t - \tau_i) - x_{\mathrm{e}}) \\ & + 2\sum_{i=1}^{m}\frac{p_ib_i}{q_i}(k_i(t) - k_{\mathrm{g}_i})\dot{k}_i(t) + 2\sum_{i=1}^{m}\frac{p_ib_i}{\hat{q}_i}(\phi_i(t) - u_{\mathrm{e}i})\dot{\phi}_i(t), \end{aligned} \tag{4.23}$$

and it follows from (4.20) that

$$\begin{aligned}
\dot{V}(x_t, K(t), \phi(t)) &= (x(t)-x_{\rm e})^{\rm T}(A_{\rm s}{}^{\rm T}P + PA_{\rm s})(x(t)-x_{\rm e}) \\
&+ 2(x(t)-x_{\rm e})^{\rm T}P\sum_{i=1}^{p} A_{{\rm d}i}(x(t-\tau_i)-x_{\rm e}) \\
&+2(x(t)-x_{\rm e})^{\rm T}PB(K(t)-K_{\rm g})(\hat{x}(t)-x_{\rm d}) + 2(x(t)-x_{\rm e})^{\rm T}PB(\phi(t)-u_{\rm e}) \\
&+ \sum_{i=1}^{p}(x(t)-x_{\rm e})^{\rm T}A_{{\rm d}i}^{\rm T}P\tilde{Q}_i^{\#}PA_{{\rm d}i}(x(t)-x_{\rm e}) \\
&- \sum_{i=1}^{p}(x(t-\tau_i)-x_{\rm e})^{\rm T}A_{{\rm d}i}^{\rm T}P\tilde{Q}_i^{\#}PA_{{\rm d}i}(x(t-\tau_i)-x_{\rm e}) \\
&+ 2\sum_{i=1}^{m}\frac{p_ib_i}{q_i}(k_i(t)-k_{{\rm g}i})\dot{k}_i(t) + 2\sum_{i=1}^{m}\frac{p_ib_i}{\hat{q}_i}(\phi_i(t)-u_{{\rm e}i})\dot{\phi}_i(t). \qquad (4.24)
\end{aligned}$$

Now, using (4.21), (4.24) yields

$$\begin{aligned}
\dot{V}(x_t, K(t), \phi(t)) &= -(x(t)-x_{\rm e})^{\rm T}R(x(t)-x_{\rm e}) \\
&-\sum_{i=1}^{p}[\tilde{Q}_i(x(t)-x_{\rm e}) - PA_{{\rm d}i}(x(t-\tau_i)-x_{\rm e})]^{\rm T}\tilde{Q}_i^{\#}[\tilde{Q}_i(x(t)-x_{\rm e}) - PA_{{\rm d}i}(x(t-\tau_i)-x_{\rm e})] \\
&+ 2\sum_{i=1}^{m}p_ib_i(k_i(t)-k_{{\rm g}i})(x_i(t)-x_{\rm d})^2 \\
&+ 2\sum_{i=1}^{m}p_ib_i(x_i(t)-x_{\rm e})(\phi_i(t)-u_{{\rm e}i}) \\
&+ 2\sum_{i=1}^{m}\frac{p_ib_i}{q_i}(k_i(t)-k_{{\rm g}i})\dot{k}_i(t) \\
&+ 2\sum_{i=1}^{m}\frac{p_ib_i}{\hat{q}_i}(\phi_i(t)-u_{{\rm e}i})\dot{\phi}_i(t) \\
&\leq -(x(t)-x_{\rm e})^{T}R(x(t)-x_{\rm e}) \\
&+ 2\sum_{i=1}^{m}p_ib_i(\phi_i(t)-u_{{\rm e}i})[(x_i(t)-x_{{\rm d}i}) + \frac{1}{\hat{q}_i}\dot{\phi}_i(t)], \quad t \geq 0. \qquad (4.25)
\end{aligned}$$

Now for the two cases given in (4.18), the last term on the right-hand side of (4.25) gives:

i) If $\phi_i(t) = 0$ and $x_i(t) \geq x_{{\rm d}i}$, then $\dot{\phi}_i(t) = 0$ and hence

$$p_ib_i(\phi_i(t)-u_{{\rm e}i})[(x_i(t)-x_{{\rm d}i}) + \frac{1}{\hat{q}_i}\dot{\phi}_i(t)] = -p_ib_iu_{{\rm e}i}(x_i(t)-x_{{\rm d}i}) \leq 0.$$

ii) Otherwise, $\dot{\phi}_i(t) = -\hat{q}_i(x_i(t) - x_{\mathrm{d}i})$ and hence

$$p_i b_i(\phi_i(t) - u_{\mathrm{e}i})[(x_i(t) - x_{\mathrm{d}i}) + \frac{1}{\hat{q}_i}\dot{\phi}_i(t)] = 0.$$

Hence, it follows that in either case

$$\dot{V}(x_t, K(t), \phi(t)) \leq -(x(t) - x_{\mathrm{e}})^{\mathrm{T}} R(x(t) - x_{\mathrm{e}}) \leq 0, \quad t \geq 0, \tag{4.26}$$

which proves that the solution $(x(t), K(t), \phi(t)) \equiv (x_{\mathrm{e}}, K_{\mathrm{g}}, u_{\mathrm{e}})$ to (4.17), (4.18), and (4.20) is Lyapunov stable. Furthermore, since the positive orbit $\gamma^+(\eta(\theta), K_0, \phi_0)$ of the closed-loop system (4.17), (4.18), and (4.20) is bounded and $\gamma^+(\eta(\theta), K_0, \phi_0)$ belongs to a compact subset of $\mathcal{C}_+ \times \mathbb{R}^{m\times m} \times \mathbb{R}^m$ [102], and since $R > 0$ it follows from the Krasovskii-LaSalle invariant set theorem for infinite dimensional systems [37, p. 143] that $x(t) \to x_{\mathrm{e}}$ as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$.

Finally, to show that $x(t) \geq\geq 0$, $t \geq 0$, for all $\eta(\cdot) \in \mathcal{C}_+$, note that the closed-loop system (4.12), (4.15), (4.17), and (4.18) is given by

$$\begin{aligned}
\dot{x}(t) &= Ax(t) + \sum_{i=1}^{p} A_{\mathrm{d}i} x(t - \tau_i) + BK(t)(\hat{x}(t) - x_{\mathrm{d}}) + B\phi(t) \\
&= (A + B[K(t),\, 0_{m\times(n-m)}])x(t) + \sum_{i=1}^{p} A_{\mathrm{d}i} x(t - \tau_i) - BK(t)x_{\mathrm{d}} + B\phi(t) \\
&= \tilde{A}(t)x(t) + \sum_{i=1}^{p} A_{\mathrm{d}i} x(t - \tau_i) + v(t) + w(t),
\end{aligned} \tag{4.27}$$

where

$$\tilde{A}(t) \triangleq \begin{bmatrix}
a_{11} + b_1 k_1(t) & a_{12} & \cdots & a_{1m} & a_{1\,m+1} & \cdots & a_{1n} \\
a_{21} & a_{22} + b_2 k_2(t) & & \vdots & \vdots & \ddots & a_{2n} \\
\vdots & & \ddots & & & & \vdots \\
a_{m1} & \cdots & & a_{mm} + b_m k_m(t) & a_{m\,m+1} & \cdots & a_{mn} \\
a_{m+1\,1} & \cdots & & a_{m+1\,m} & a_{m+1\,m+1} & \cdots & a_{m+1\,n} \\
\vdots & \ddots & & \vdots & \vdots & \ddots & \vdots \\
a_{n1} & \cdots & & a_{nm} & a_{n\,m+1} & \cdots & a_{nn}
\end{bmatrix}$$

$$v(t) \triangleq - \begin{bmatrix} b_1 k_1(t) x_{\mathrm{d}1} \\ \vdots \\ b_m k_m(t) x_{\mathrm{d}m} \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \qquad w(t) \triangleq \begin{bmatrix} b_1 \phi_1(t) \\ \vdots \\ b_m \phi_m(t) \\ 0 \\ \vdots \\ 0 \end{bmatrix}.$$

Now, since by (4.17) and (4.18), $k_i(t) \leq 0$, $t \geq 0$, $i = 1, \cdots, m$, and $\phi_i(t) \geq 0$, $t \geq 0$, $i = 1, \cdots, m$, it follows that $v(t) \geq\geq 0$, $t \geq 0$, and $w(t) \geq\geq 0$, $t \geq 0$. Hence, since for every $t \in [0, \infty)$, $\tilde{A}(t)$ is essentially nonnegative, it follows from Proposition 4.2 that $x(t) \geq\geq 0$, $t \geq 0$, for all $\eta(\cdot) \in \mathcal{C}_+$. □

Remark 4.2. Note that the conditions in Theorem 4.3 imply that $x(t) \to x_{\mathrm{e}}$ as $t \to \infty$ and hence it follows from (4.17) and (4.18) that $(x(t), K(t), \phi(t)) \to \mathcal{M} \triangleq \{(x_t, K, \phi) \in \mathcal{C}_+ \times \mathbb{R}^{m \times m} \times \mathbb{R}^m : x_t = x_{\mathbf{e}},\ \dot{K} = 0,\ \dot{\phi} = 0\}$ as $t \to \infty$.

It is important to note that the adaptive control law (4.15), (4.17), and (4.18) does not require the explicit knowledge of the system matrices A, $A_{\mathrm{d}i}$, $i = 1, \ldots, p$, and B, the gain matrix K_{g}, and the nonnegative constant vector u_{e}; even though Theorem 4.3 requires the existence of K_{g} and nonnegative vectors x_{u} and u_{e} such that $A_{\mathrm{s}} + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is asymptotically stable and that the conditions (4.14) holds. Furthermore, in the case where $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is semistable and minimum phase with respect to the output $y = \hat{x}$, or $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is asymptotically stable, then there always exists a diagonal matrix $K_{\mathrm{g}} \in \mathbb{R}^{m \times m}$ such that $A_{\mathrm{s}} + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is asymptotically stable. In addition, note that for $i = 1, \cdots, m$, the control input signal $u_i(t)$, $t \geq 0$, can be negative depending on the values of $x_i(t)$, $k_i(t)$, and $\phi_i(t)$, $t \geq 0$. However, as is required in nonnegative and compartmental dynamical systems the closed-loop plant states remain nonnegative.

In the case where our objective is zero set-point regulation, that is, $\psi_{\mathbf{e}}(\theta) = x_{\mathrm{e}} = 0$, $\theta \in [-\bar{\tau}, 0]$, the adaptive controller given in Theorem 4.3 can be considerably simplified. Specifically, since in this case $x(t) \geq\geq x_{\mathrm{e}} = 0$, $t \geq 0$, and condition (4.14) is trivially satisfied with $u_{\mathrm{e}} = 0$, we can set $\phi(t) \equiv 0$ so that update law (4.18) is superfluous. Furthermore, since (4.14) is trivially satisfied, A can possess eigenvalues in the open right-half plane. Alternatively, exploiting a *linear* Lyapunov-Krasovskii functional construction for the plant dynamics, an even simpler adaptive controller can be derived. This result is given in the following theorem.

Theorem 4.4. Consider the linear uncertain time-delay system $\mathcal{G}$ given by (4.12) where B is nonnegative and given by (4.13). Assume there exists a diagonal matrix $K_{\rm g} = \operatorname{diag}[k_{{\rm g}1}, \cdots, k_{{\rm g}m}]$ such that $A_{\rm s} + \sum_{i=1}^{p} A_{{\rm d}i}$ is asymptotically stable, where $A_{\rm s} = A + B\tilde{K}_{\rm g}$ and $\tilde{K}_{\rm g} = [K_{\rm g}, 0_{m\times(n-m)}]$. Furthermore, let q_i, $i = 1, \cdots, m$, be positive constants. Then the adaptive feedback control law

$$u(t) = K(t)\hat{x}(t), \tag{4.28}$$

where $K(t) = \operatorname{diag}[k_1(t), \cdots, k_m(t)]$ and $\hat{x}(t) = [x_1(t), \cdots, x_m(t)]^{\rm T}$, or, equivalently,

$$u_i(t) = k_i(t)x_i(t), \quad i = 1, \cdots, m, \tag{4.29}$$

where $k_i(t) \in \mathbb{R}$, $i = 1, \cdots, m$, with update law

$$\dot{K}(t) = -\operatorname{diag}[q_1 x_1(t), \cdots, q_m x_m(t)], \quad K(0) \leq\leq 0, \tag{4.30}$$

guarantees that the solution $(x(t), K(t)) \equiv (0, K_{\rm g})$ of the closed-loop system given by (4.12), (4.28), (4.30) is Lyapunov stable and $x(t) \to 0$ as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$.

Proof. Note that with $u(t)$, $t \geq 0$, given by (4.28) it follows from (4.12) that

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{p} A_{{\rm d}i}x(t-\tau_i) + BK(t)\hat{x}(t), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0. \tag{4.31}$$

Now, since for every $t \in [0, \infty)$, $\tilde{A}(t) \triangleq A + B[K(t), 0_{m\times n-m}]$ is essentially nonnegative and $A_{{\rm d}i}$ is nonnegative it follows from Proposition 4.2 that $x(t) \geq\geq 0$, $t \geq 0$, for all $x_0 \in \overline{\mathbb{R}}_+^n$. Next, using $A_{\rm s} = A + B\tilde{K}_{\rm g}$, note that (4.31) can be equivalently written as

$$\dot{x}(t) = A_{\rm s}x(t) + \sum_{i=1}^{p} A_{{\rm d}i}x(t-\tau_i) + B(K(t) - K_{\rm g})\hat{x}(t), \ x(\theta) = \eta(\theta) \ -\bar{\tau} \leq \theta \leq 0, \ t \geq 0. \tag{4.32}$$

Furthermore, since $A_{\rm s}$ is essentially nonnegative, $A_{{\rm d}i}$ is nonnegative, and $A_{\rm s}+\sum_{i=1}^{p} A_{{\rm d}i}$ is asymptotically stable it follows from Theorem 4.2 that there exist vectors $p >> 0$ and $r >> 0$ satisfying

$$0 = (A_{\rm s} + \sum_{i=1}^{p} A_{{\rm d}i})^{\rm T} p + r. \tag{4.33}$$

To show Lyapunov stability of the closed-loop system (4.30) and (4.32) consider the Lyapunov-Krasovskii functional candidate $V : \mathcal{C}_+ \times \mathbb{R}^{m\times m} \to \mathbb{R}$ given by

$$V(\psi, K) = p^{\rm T}\psi(0) + \sum_{i=1}^{p} \int_{-\tau_i}^{0} p^{\rm T} A_{{\rm d}i}\psi(\theta){\rm d}\theta + \frac{1}{2}{\rm tr}(K - K_{\rm g})^{\rm T} Q^{-1}(K - K_{\rm g}), \tag{4.34}$$

where $Q = {\rm diag}[\frac{q_1}{p_1 b_1}, \cdots, \frac{q_m}{p_m b_m}]$. Furthermore, note that $V(\psi_{\bf e}, K_{\rm g}) = 0$, where $\psi_{\bf e}(\theta) = 0$, $\theta \in [-\bar{\tau}, 0]$, and there exist $\mathcal{K}$-class functions $\alpha_1(\cdot), \alpha_2(\cdot)$ such that

$$V(\psi, K, \phi) \geq \alpha_1(\|\psi(0)\|) + \alpha_2(\|K - K_{\rm g}\|_{\rm F}).$$

Now, letting $x(t)$, $t \geq 0$, denote the solution to (4.32) and using (4.30), it follows that the Lyapunov-Krasovskii directional derivative along the closed-loop system trajectories is given by

$$\begin{aligned}
\dot{V}(x_t, K(t)) &= p^{\rm T} A_{\rm s} x(t) + p^{\rm T} \sum_{i=1}^{p} A_{{\rm d}i} x(t - \tau_i) + p^{\rm T} B(K(t) - K_{\rm g})\hat{x}(t) + p^{\rm T} \sum_{i=1}^{p} A_{{\rm d}i} x(t) \\
&\quad - p^{\rm T} \sum_{i=1}^{p} A_{{\rm d}i} x(t - \tau_i) + {\rm tr}(K(t) - K_{\rm g})^{\rm T} Q^{-1} \dot{K}(t) \\
&= -r^{\rm T} x(t) \\
&\leq 0, \quad t \geq 0,
\end{aligned}$$

which proves that the solution $(x(t), K(t)) \equiv (0, K_{\rm g})$ to (4.30) and (4.32) is Lyapunov stable. Furthermore, since $r >> 0$ it follows from Corollary 3.1 of [37, p. 143] that $x(t) \to 0$ as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$. □

4.4. Adaptive Control for Linear Nonnegative Dynamical Systems with Nonnegative Control and Time Delay

In drug delivery systems for physiological processes, control (source) inputs are usually constrained to be nonnegative as are the system states. Hence, in this section we develop adaptive control laws for nonnegative retarded systems with nonnegative control inputs. However, since condition (4.10) is required to be satisfied for $x_{\rm e} \in \overline{\mathbb{R}}_+^n$ and $u_{\rm e} \in \overline{\mathbb{R}}_+^m$, it follows from Brockett's necessary condition for asymptotic stabilizability [101] that there does not exist a continuous stabilizing *nonnegative* feedback if $0 \in \operatorname{spec}(A + \sum_{i=1}^p A_{{\rm d}i})$ and $x_{\rm e} \in \mathbb{R}_+^n$ (see [99] for further details). Hence, in this section we assume that $A + \sum_{i=1}^p A_{{\rm d}i}$ is an asymptotically stable compartmental matrix. Thus, we proceed with the aforementioned assumptions to design adaptive controllers for uncertain time-delay compartmental systems that guarantee that $\lim_{t\to\infty} x_i(t) = x_{{\rm d}i} \geq 0$ for $i = 1, \cdots, m \leq n$, where $x_{{\rm d}i}$ is a desired set point for the ith compartmental state while guaranteeing a nonnegative control input.

Theorem 4.5. Consider the linear uncertain time-delay system $\mathcal{G}$ given by (4.12), where A is essentially nonnegative, $A_{{\rm d}i}$, $i = 1, \ldots, p$, is nonnegative, $A + \sum_{i=1}^p A_{{\rm d}i}$ is asymptotically stable, and B is nonnegative and given by (4.13). For a given $x_{\rm d} \in \mathbb{R}^m$, assume there exist vectors $x_{\rm u} \in \mathbb{R}_+^{n-m}$ and $u_{\rm e} \in \overline{\mathbb{R}}_+^m$ such that (4.14) holds. Furthermore, let q_i and $\hat{q}_i$, $i = 1, \cdots, m$, be positive constants. Then, the adaptive feedback control law

$$u_i(t) = \max\{0, \hat{u}_i(t)\}, \quad i = 1, \cdots, m, \tag{4.35}$$

where

$$\hat{u}_i(t) = k_i(t)(x_i(t) - x_{{\rm d}i}) + \phi_i(t), \quad i = 1, \cdots, m, \tag{4.36}$$

$k_i(t) \in \mathbb{R}$, $t \geq 0$, and $\phi_i(t) \in \mathbb{R}$, $t \geq 0$, $i = 1, \cdots, m$, with update laws

$$\dot{k}_i(t) = \begin{cases} 0, & \text{if } \hat{u}_i(t) < 0, \\ -q_i(x_i(t) - x_{{\rm d}i})^2, & \text{otherwise,} \end{cases} \quad k_i(0) \leq 0, \quad i = 1, \cdots, m, \tag{4.37}$$

$$\dot{\phi}_i(t) = \begin{cases} 0, & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) > x_{{\rm d}i}, \text{ or if } \hat{u}_i(t) \leq 0, \\ -\hat{q}_i(x_i(t) - x_{{\rm d}i}), & \text{otherwise,} \end{cases}$$
$$\phi_i(0) \geq 0, \ i = 1, \cdots, m, \tag{4.38}$$

guarantees that the solution $(x(t), K(t), \phi(t)) \equiv (x_{\rm e}, 0, u_{\rm e})$ of the closed-loop system given by (4.12), (4.35), (4.37), (4.38) is Lyapunov stable and $x_i(t) \to x_{{\rm d}i}$, $i = 1, \cdots, m$, as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$. Furthermore, $u(t) \geq\geq 0$, $t \geq 0$, and $x(t) \geq\geq 0$, $t \geq 0$, for all $\eta(\cdot) \in \mathcal{C}_+$.

Proof. First, define $K_{\mathrm{u}} \triangleq \mathrm{diag}[k_{\mathrm{u}1}(t), \cdots, k_{\mathrm{u}m}]$ and $\phi_{\mathrm{u}}(t) \triangleq [\phi_{\mathrm{u}1}(t), \cdots, \phi_{\mathrm{u}m}]^{\mathrm{T}}$, where

$$k_{\mathrm{u}i}(t) = \begin{cases} 0, & \text{if } \hat{u}_i(t) < 0, \\ k_i(t), & \text{otherwise}, \end{cases} \qquad i = 1, \cdots, m, \tag{4.39}$$

$$\phi_{\mathrm{u}i}(t) = \begin{cases} 0, & \text{if } \hat{u}_i(t) < 0, \\ \phi_i(t), & \text{otherwise}, \end{cases} \qquad i = 1, \cdots, m. \tag{4.40}$$

Now, note that with $u(t)$, $t \geq 0$, given by (4.35) it follows from (4.12) that

$$\begin{aligned} \dot{x}(t) \;&=\; Ax(t) + \sum_{i=1}^{p} A_{\mathrm{d}i}x(t-\tau_i) + BK_{\mathrm{u}}(t)(\hat{x}(t) - x_{\mathrm{d}}) + B\phi_{\mathrm{u}}(t), \\ &x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \end{aligned} \tag{4.41}$$

or, equivalently, using (4.14),

$$\begin{aligned} \dot{x}(t) \;&=\; A(x(t) - x_{\mathrm{e}}) + \sum_{i=1}^{p} A_{\mathrm{d}i}(x(t-\tau_i) - x_{\mathrm{e}}) + BK_{\mathrm{u}}(t)(\hat{x}(t) - x_{\mathrm{d}}) + B(\phi_{\mathrm{u}}(t) - u_{\mathrm{e}}), \\ &x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0. \end{aligned} \tag{4.42}$$

Since $A + \sum_{i=1}^{p} A_{\mathrm{d}i}$ is essentially nonnegative and Hurwitz it follows from Theorem 4.1 that there exists diagonal matrices $P > 0$ and $\tilde{Q}_i \geq 0$, $i = 1, \ldots, p$, and a positive-definite matrix $R \in \mathbb{R}^{n \times n}$ such that

$$A^{\mathrm{T}}P + PA + \sum_{i=1}^{p}(\tilde{Q}_i + A_{\mathrm{d}i}^{\mathrm{T}}P\tilde{Q}_i^{\#}PA_{\mathrm{d}i}) + R = 0 \tag{4.43}$$

To show Lyapunov stability of the closed-loop system (4.37), (4.38), and (4.42) consider the Lyapunov-Krasovskii functional candidate $V : \mathcal{C}_+ \times \mathbb{R}^{m \times m} \times \mathbb{R}^m \to \mathbb{R}$ given by

$$\begin{aligned} V(\psi, K, \phi) \;&=\; (\psi(0) - x_{\mathrm{e}})^{\mathrm{T}}P(\psi(0) - x_{\mathrm{e}}) \\ &\quad + \sum_{i=1}^{p}\int_{-\tau_i}^{0}(\psi(\theta) - x_{\mathrm{e}})^{\mathrm{T}}A_{\mathrm{d}i}^{\mathrm{T}}P\tilde{Q}_i^{\#}PA_{\mathrm{d}i}(\psi(\theta) - x_{\mathrm{e}})\mathrm{d}\theta \\ &\quad + \mathrm{tr}K^{\mathrm{T}}Q^{-1}K + (\phi - u_{\mathrm{e}})^{\mathrm{T}}\hat{Q}^{-1}(\phi - u_{\mathrm{e}}), \end{aligned} \tag{4.44}$$

or, equivalently,

$$\begin{aligned}V(\psi, K, \phi) \;=\; & \sum_{i=1}^{n} p_i(\psi_i(0) - x_{\mathrm{e}i})^2 + \sum_{i=1}^{p} \int_{-\tau_i}^{0} (\psi(\theta) - x_{\mathrm{e}})^{\mathrm{T}} A_{\mathrm{d}i}^{\mathrm{T}} P \tilde{Q}_i^{\#} P A_{\mathrm{d}i}(\psi(\theta) - x_{\mathrm{e}}) \mathrm{d}\theta \\ & + \sum_{i=1}^{m} \frac{p_i b_i}{q_i} k_i^2 + \sum_{i=1}^{m} \frac{p_i b_i}{q_i} (\phi_i - u_{\mathrm{e}i})^2,\end{aligned}$$

where $Q = \mathrm{diag}[\frac{q_1}{p_1 b_1}, \cdots, \frac{q_m}{p_m b_m}]$ and $\hat{Q} = \mathrm{diag}[\frac{\hat{q}_1}{p_1 b_1}, \cdots, \frac{\hat{q}_m}{p_m b_m}]$. Note that $V(\psi_{\mathrm{e}}, 0, u_{\mathrm{e}}) = 0$, where $\psi_{\mathrm{e}}(\theta) = x_{\mathrm{e}}$, $\theta \in [-\bar{\tau}, 0]$. Furthermore, there exist $\mathcal{K}$-class functions $\alpha_1(\cdot)$, $\alpha_2(\cdot)$, $\alpha_3(\cdot)$ such that

$$V(\psi, K, \phi) \geq \alpha_1(\|\psi(0) - x_{\mathrm{e}}\|) + \alpha_2(\|K\|_{\mathrm{F}}) + \alpha_3(\|\phi - u_{\mathrm{e}}\|).$$

Now, letting $x(t)$, $t \geq 0$, denote the solution to (4.42) and using (4.37) and (4.38), it follows that the Lyapunov-Krasovskii directional derivative along the closed-loop system trajectories is given by

$$\begin{aligned}\dot{V}(x_t, K(t), \phi(t)) \;=\; & -(x(t) - x_{\mathrm{e}})^{\mathrm{T}} R (x(t) - x_{\mathrm{e}}) \\ & - \sum_{i=1}^{p} [\tilde{Q}_i(x(t) - x_{\mathrm{e}}) - P A_{\mathrm{d}i}(x(t - \tau_i) - x_{\mathrm{e}})]^{\mathrm{T}} \tilde{Q}_i^{\#} [\tilde{Q}_i(x(t) - x_{\mathrm{e}}) - P A_{\mathrm{d}i}(x(t - \tau_i) - x_{\mathrm{e}})] \\ & + 2\sum_{i=1}^{m} p_i b_i k_{\mathrm{u}i}(t)(x_i(t) - x_{\mathrm{d}})^2 + 2\sum_{i=1}^{m} p_i b_i (x_i(t) - x_{\mathrm{e}})(\phi_{\mathrm{u}i}(t) - u_{\mathrm{e}i}) \\ & + 2\sum_{i=1}^{m} \frac{p_i b_i}{q_i}(k_i(t) - k_{\mathrm{g}i})\dot{k}_i(t) + 2\sum_{i=1}^{m} \frac{p_i b_i}{\hat{q}_i}(\phi_i(t) - u_{\mathrm{e}i})\dot{\phi}_i(t) \\ \leq\; & -(x(t) - x_{\mathrm{e}})^{\mathrm{T}} R (x(t) - x_{\mathrm{e}}) + 2\sum_{i=1}^{m} p_i b_i \Big[k_{\mathrm{u}i}(t)(x_i(t) - x_{\mathrm{d}i})^2 + \frac{1}{q_i} k_i(t)\dot{k}_i(t)\Big] \\ & + 2\sum_{i=1}^{m} p_i b_i \Big[(x_i(t) - x_{\mathrm{d}i})(\phi_{\mathrm{u}i}(t) - u_{\mathrm{e}i}) + \frac{1}{\hat{q}_i}(\phi_i(t) - u_{\mathrm{e}i})\dot{\phi}_i(t)\Big]. \end{aligned} \tag{4.45}$$

Now, for the two cases given in (4.37) and (4.38), the last two terms on the right-hand side of (4.45) give:

i) If $\hat{u}_i(t) < 0$, then $k_{\mathrm{u}i}(t) = 0$, $\phi_{\mathrm{u}i}(t) = 0$, $\dot{k}_i(t) = 0$, and $\dot{\phi}_i(t) = 0$. Furthermore, since $\phi_i(t) \geq 0$ and $k_i(t) \leq 0$ for all $t \geq 0$ and $i = 1, \cdots, m$, it follows from

(4.36) that $\hat{u}_i(t) < 0$ only if $x_i(t) > x_{\mathrm{d}i}$ and hence

$$k_{\mathrm{u}i}(t)(x_i(t) - x_{\mathrm{d}i})^2 + \tfrac{1}{q_i}k_i(t)\dot{k}_i(t) = 0,$$
$$(x_i(t) - x_{\mathrm{d}i})(\phi_{\mathrm{u}i}(t) - u_{\mathrm{e}i}) + \tfrac{1}{q_i}(\phi_i(t) - u_{\mathrm{e}i})\dot{\phi}_i(t) = -(x_i(t) - x_{\mathrm{d}i})u_{\mathrm{e}i} \le 0.$$

ii) Otherwise, $k_{\mathrm{u}i}(t) = k_i(t)$ and $\phi_{\mathrm{u}i}(t) = \phi_i(t)$ and hence

$$k_{\mathrm{u}i}(x_i(t) - x_{\mathrm{d}i})^2 + \frac{1}{q_i}k_i(t)\dot{k}_i(t) = 0,$$
$$\begin{aligned}(x_i(t) - x_{\mathrm{d}i})(\phi_{\mathrm{u}i}(t) - u_{\mathrm{e}i}) &+ \frac{1}{\hat{q}_i}(\phi_i(t) - u_{\mathrm{e}i})\dot{\phi}_i(t) \\ &= \begin{cases} -(x_i(t) - x_{\mathrm{d}i})u_{\mathrm{e}i} \le 0, & \text{if } \phi_i(t) = 0 \text{ and } x_i(t) \ge x_{\mathrm{d}i}, \\ 0, & \text{otherwise.} \end{cases}\end{aligned}$$

Hence, it follows that in either case

$$\dot{V}(x_t, K(t), \phi(t)) \le -(x(t) - x_{\mathrm{e}})^{\mathrm{T}}R(x(t) - x_{\mathrm{e}}) \le 0, \quad t \ge 0, \tag{4.46}$$

which proves that the solution $(x(t), K(t), \phi(t)) \equiv (x_{\mathrm{e}}, 0, u_{\mathrm{e}})$ to (4.37), (4.38), and (4.42) is Lyapunov stable. Furthermore, since the positive orbit $\gamma^+(\eta(\theta), K_0, \phi_0)$ of the closed-loop system (4.37), (4.38), and (4.42) is bounded and $\gamma^+(\eta(\theta), K_0, \phi_0)$ belongs to a compact subset of $\mathcal{C}_+ \times \mathbb{R}^{m\times m} \times \mathbb{R}^m$ [102], and since $R > 0$ it follows from the Krasovskii-LaSalle invariant set theorem for infinite dimensional systems [37, p. 143] that $x(t) \to x_{\mathrm{e}}$ as $t \to \infty$ for all $\eta(\cdot) \in \mathcal{C}_+$.

Finally, $u(t) \ge\ge 0$, $t \ge 0$, is a restatement of (4.35). Now, since $B \ge\ge 0$ and $u(t) \ge\ge 0$, $t \ge 0$, it follows from Proposition 4.1 that $x(t) \ge\ge 0$, $t \ge 0$, for all $\eta(\cdot) \in \mathcal{C}_+$. □

As in the case of Theorem 4.3, it is important to note that the adaptive control law (4.35), (4.37), and (4.38) does not require the explicit knowledge of the nonnegative constant vector u_{e}; even though Theorem 4.5 requires the existence of nonnegative vectors x_{u} and u_{e} such that the condition (4.14) holds.

4.5. Adaptive Control for General Anesthesia

In this section, we illustrate the adaptive control framework developed in this chapter on a model for the disposition of the intravenous anesthetic propofol [99, 103, 104] for induction and maintenance of general anesthesia. This model is discussed in [99] and is based on the three-compartment mammillary model shown in Figure 4.1 with the first compartment acting as the central compartment and the remaining two compartments exchanging with the central compartment. The three-compartment mammillary system with all transfer times between compartments given by $\tau > 0$ provides a pharmacokinetic model for a patient describing the distribution of propofol into the central compartment (identified with the intravascular blood volume as well as highly perfused organs) and other various tissue groups of the body. A mass balance for the whole compartmental system yields

$$\begin{aligned} \dot{x}_1(t) &= -(a_{11} + a_{21} + a_{31})x_1(t) + a_{12}x_2(t-\tau) + a_{13}x_3(t-\tau) + u(t), \\ & \qquad x_1(\theta) = \eta_1(\theta), \quad -\tau \le \theta \le 0, \quad t \ge 0, \quad (4.47) \\ \dot{x}_2(t) &= -a_{12}x_2(t) + a_{21}x_1(t-\tau), \quad x_2(\theta) = \eta_2(\theta), \quad -\tau \le \theta \le 0, \quad (4.48) \\ \dot{x}_3(t) &= -a_{13}x_3(t) + a_{31}x_1(t-\tau), \quad x_3(\theta) = \eta_3(\theta), \quad -\tau \le \theta \le 0, \quad (4.49) \end{aligned}$$

where $x_1(t)$, $x_2(t)$, $x_3(t)$, $t \ge 0$, are the masses in grams of propofol in the central compartment and compartments 2 and 3, respectively, $u(t)$, $t \ge 0$, is the infusion rate in grams/min of the anesthetic (propofol) into the central compartment, $a_{ij} > 0$, $i \ne j$, $i, j = 1, 2, 3$, are the rate constants in min^{-1} for drug transfer between

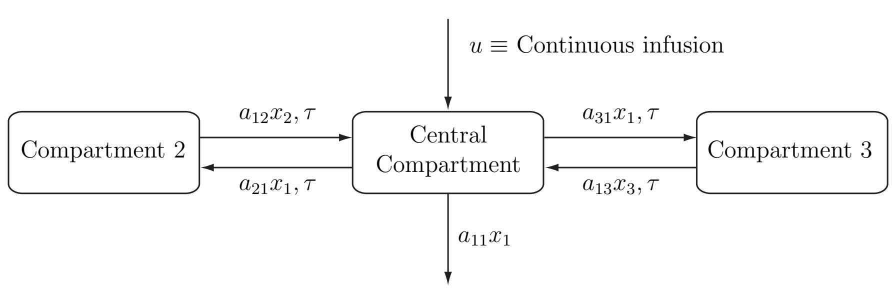


Figure 4.1: Three-Compartment Mammillary Model for Disposition of Propofol

compartments, and $a_{11} > 0$ is the rate constant in $\min^{-1}$ for elimination from the central compartment. Even though these transfer and loss coefficients are positive, they can be uncertain due to patient gender, weight, pre-existing disease, age, and concomitant medication. Hence, adaptive control for propofol set-point regulation can significantly improve the outcome for drug administration over manual control.

It has been reported in [105] that a 2.5–6 μg/mℓ blood concentration level of propofol is required during the maintenance stage in general anesthesia depending on patient fitness and extent of surgical stimulation. Hence, continuous infusion control is required for maintaining this desired level of anesthesia. Here we assume that the transfer and loss coefficients a_{11}, a_{12}, a_{21}, a_{13}, and a_{31} are unknown and our objective is to regulate the propofol concentration level of the central compartment to the desired level of 3.4 μg/mℓ in the face of system uncertainty. Furthermore, since propofol mass in the blood plasma cannot be measured directly, we measure the concentration of propofol in the central compartment; that is, x_1/V_c, where V_c is the volume in liters of the central compartment. As noted in [104], V_c can be approximately calculated by $V_c = (0.159\,\ell/\mathrm{kg})(M\,\mathrm{kg})$, where M is the weight (mass) in kilograms of the patient.

Next, note that (4.47)–(4.49) can be written in the state space form (4.12) with $x = [x_1,\ x_2,\ x_3]^{\mathrm{T}}$,

$$A = \begin{bmatrix} -(a_{11}+a_{21}+a_{31}) & 0 & 0 \\ 0 & -a_{12} & 0 \\ 0 & 0 & -a_{13} \end{bmatrix}, \quad A_{\mathrm{d}} = \begin{bmatrix} 0 & a_{12} & a_{13} \\ a_{21} & 0 & 0 \\ a_{31} & 0 & 0 \end{bmatrix}, \quad B = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}. \tag{4.50}$$

Now, it can be shown that for $x_{\mathrm{d}1}/V_c = 3.4$ μg/mℓ, all the conditions of Theorem 4.5 are satisfied. Even though propofol concentration levels in the blood plasma are a good indication of the depth of anesthesia, they cannot be measured in *real time* during surgery. Furthermore, we are more interested in drug *effect* (depth of hypnosis) rather than drug *concentration*. Hence, we consider a more realistic model involving pharmacokinetics (drug concentration as a function of time) and pharmacodynamics (drug effect as a function of concentration) for control of anesthesia. Specifically, we use an electroencephalogram (EEG) signal as a measure of drug effect of anesthetic compounds on the brain [106]. Since electroencephalography provides real-time monitoring of the central nervous system activity, it can be used to quantify levels of consciousness and hence is amenable for feedback (closed-loop) control in general anesthesia. Furthermore, we use the Bispectral Index (BIS), a new EEG indicator, as a measure of anesthetic effect [107]. This index quantifies the nonlinear relationships between the component frequencies in the electroencephalogram, as well as analyzing their phase and amplitude. The BIS signal is a nonlinear monotonically decreasing function of the level of consciousness and is given by

$$\mathrm{BIS}(c_{\mathrm{eff}}) = \mathrm{BIS}_0 \left(1 - \frac{c_{\mathrm{eff}}^{\gamma}}{c_{\mathrm{eff}}^{\gamma} + \mathrm{EC}_{50}^{\gamma}}\right), \tag{4.51}$$

where BIS_0 denotes the base line (awake state) value and, by convention, is typically assigned a value of 100, c_{eff} is the propofol concentration in grams/liter in the effect site compartment (brain), EC_{50} is the concentration at half maximal effect and represents the patient's sensitivity to the drug, and γ determines the degree of nonlinearity in (4.51). Here, the effect site compartment is introduced as a correlate between the central compartment concentration and the central nervous system concentration [108]. The effect site compartment concentration is related to the concentration in the central compartment by the first-order delay model

$$\dot{c}_{\mathrm{eff}}(t) = a_{\mathrm{eff}}(x_1(t)/V_{\mathrm{c}} - c_{\mathrm{eff}}(t)), \quad c_{\mathrm{eff}}(0) = x_1(0), \quad t \geq 0, \tag{4.52}$$

where a_{eff} in min^{-1} is an unknown positive time constant. In reality, the effect site compartment equilibrates with the central compartment in a matter of a few minutes. The parameters a_{eff}, EC_{50} , and γ are determined by data fitting and vary from patient to patient. BIS index values of 0 and 100 correspond, respectively, to an isoelectric EEG signal and an EEG signal of a fully conscious patient; while the range between 40 and 60 indicates a moderate hypnotic state [109].

In the following numerical simulation we set $\mathrm{EC}_{50} = 3.4$ μg/mℓ, $\gamma = 3$, and $\mathrm{BIS}_0 = 100$, so that the BIS signal is shown in Figure 4.2. The target (desired) BIS

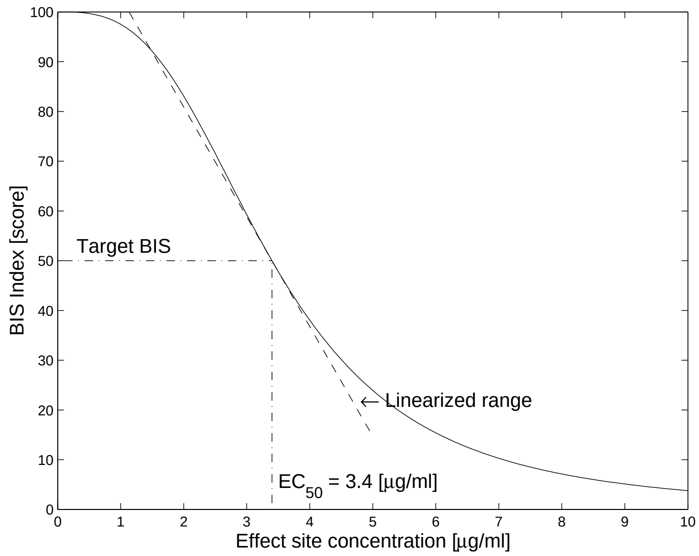


Figure 4.2: BIS Index Versus Effect Site Concentration

value, $\mathrm{BIS}_{\mathrm{target}}$, is set at 50. In this case, the linearized BIS function about the target BIS value is given by

$$\mathrm{BIS}(c_{\mathrm{eff}}) \simeq \mathrm{BIS}(\mathrm{EC}_{50}) - \mathrm{BIS}_0 \cdot \mathrm{EC}_{50}^{\gamma} \cdot \left. \frac{\gamma c_{\mathrm{eff}}^{\gamma-1}}{(c_{\mathrm{eff}}^{\gamma} + \mathrm{EC}_{50}^{\gamma})^2} \right|_{c_{\mathrm{eff}}=\mathrm{EC}_{50}} \cdot c_{\mathrm{eff}} = 125 - 22.06 c_{\mathrm{eff}}. \tag{4.53}$$

Furthermore, for simplicity of exposition, we assume that the effect site compartment equilibrates instantaneously with the central compartment; that is, we assume that $a_{\mathrm{eff}} \to \infty$ and hence $c_{\mathrm{eff}}(t) = x_1(t)/V_{\mathrm{c}}$, $t \geq 0$. Now, using the adaptive feedback controller

$$u_1(t) = \max\{0, \hat{u}_1(t)\}, \tag{4.54}$$

where

$$\hat{u}_1(t) = -k_1(t)(\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}}) + \phi_1(t), \tag{4.55}$$

$k_1(t) \in \mathbb{R}$, $t \geq 0$, and $\phi_1(t) \in \mathbb{R}$, $t \geq 0$, with update laws

$$\dot{k}_1(t) = \begin{cases} 0, & \text{if } \hat{u}_1(t) < 0, \\ -q_{\mathrm{BIS}_1}(\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}})^2, & \text{otherwise,} \end{cases} \quad k_1(0) \leq 0, \tag{4.56}$$

$$\dot{\phi}_1(t) = \begin{cases} 0, & \begin{array}{l} \text{if } \phi_1(t) = 0 \text{ and } \mathrm{BIS}(t) > \mathrm{BIS}_{\mathrm{target}}, \\ \text{or if } \hat{u}_1(t) \leq 0, \end{array} \\ \hat{q}_{\mathrm{BIS}_1}(\mathrm{BIS}(t) - \mathrm{BIS}_{\mathrm{target}}), & \text{otherwise,} \end{cases} \quad \phi_1(0) \geq 0, \tag{4.57}$$

Table 4.1: Pharmacokinetic parameters

Set	a_{11} (min^{-1})	a_{21} (min^{-1})	a_{12} (min^{-1})	a_{31} (min^{-1})	a_{13} (min^{-1})
A	0.152	0.207	0.092	0.040	0.0048
B	0.119	0.114	0.055	0.041	0.0033

where q_{BIS_1} and $\hat{q}_{\text{BIS}_1}$ are arbitrary positive constants, it follows from Theorem 4.5 that the control input (anesthetic infusion rate) $u(t) \geq 0$ for all $t \geq 0$ and $\text{BIS}(t) \to \text{BIS}_{\text{target}}$ as $t \to \infty$ for any (uncertain) positive values of the transfer and loss coefficients in the range of c_{eff} where the linearized BIS equation (4.53) is valid. It is important to note that during actual surgery or intensive care unit sedation the BIS signal is obtained directly from the EEG and not (4.51). Furthermore, since our adaptive controller only requires the error signal $\text{BIS}(t) - \text{BIS}_{\text{target}}$ over the linearized range of (4.51), we do not require knowledge of the slope of the linearized equation (4.53), nor do we require knowledge of the parameters γ and EC_{50}. To illustrate the robustness properties of the proposed adaptive control law, we use the average set of pharmacokinetic parameters given in [110] for 29 patients requiring general anesthesia for noncardiac surgery. For our design we assume $M = 70$ kg and we switch from Set A to Set B given in Table 4.1 [110] at $t = 25$ min. Furthermore, we assume that at $t = 25$ min the pharmacodynamic parameters EC_{50} and γ are switched from 3.4 μg/mℓ and 3 to 4.0 μg/mℓ and 4, respectively. Here we consider noncardiac surgery since cardiac surgery often utilizes hypothermia which itself changes the BIS signal. With $q_{\text{BIS}_1} = 1 \times 10^{-6}$ g/min^2, $\hat{q}_{\text{BIS}_1} = 1 \times 10^{-3}$ g/min^2, and initial conditions $x(0) = [0, 0, 0]^{\text{T}}$ g, $k_1(0) = 0$ min^{-1}, and $\phi_1(0) = 0.01$ g/min^{-1}, Figure 4.3 shows the masses of propofol in all three compartments versus time. Figure 4.4 shows the BIS index versus time. Figure 4.5 shows the propofol concentration in the central compartment and the control signal (propofol infusion rate) versus time. Finally, Figure 4.6 shows the adaptive gain history versus time.

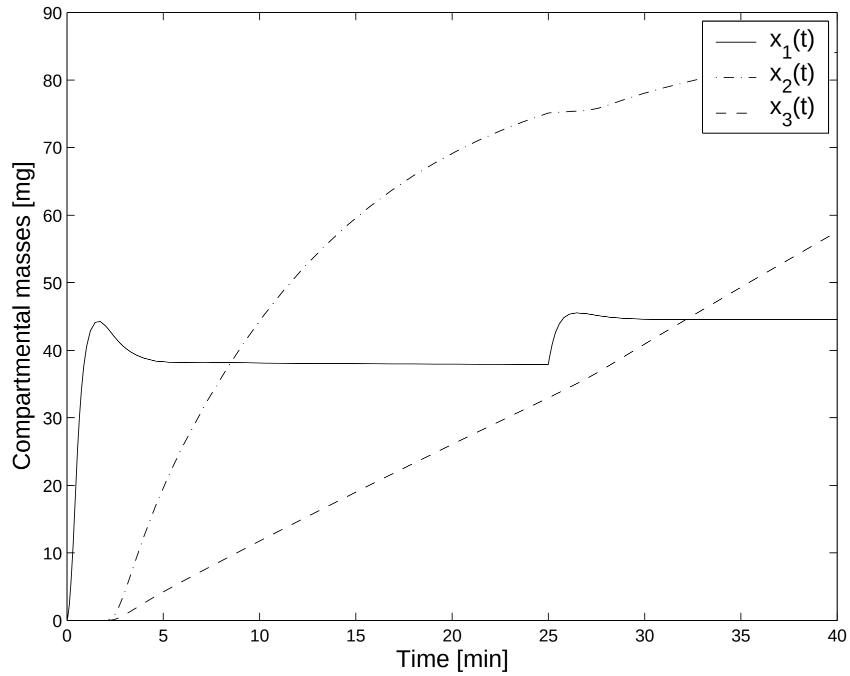


Figure 4.3: Compartmental Masses vs. Time

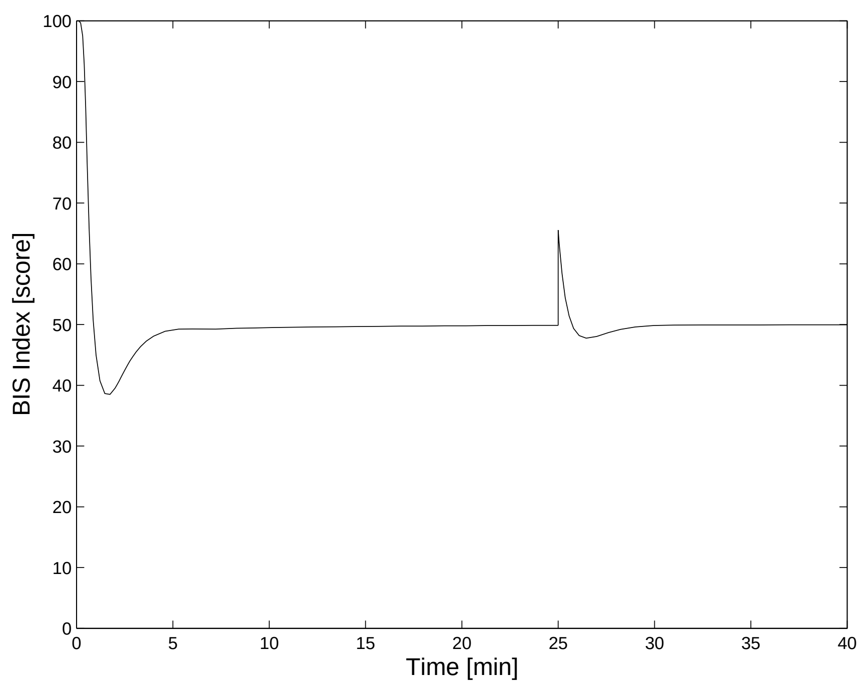


Figure 4.4: BIS Index vs. Time

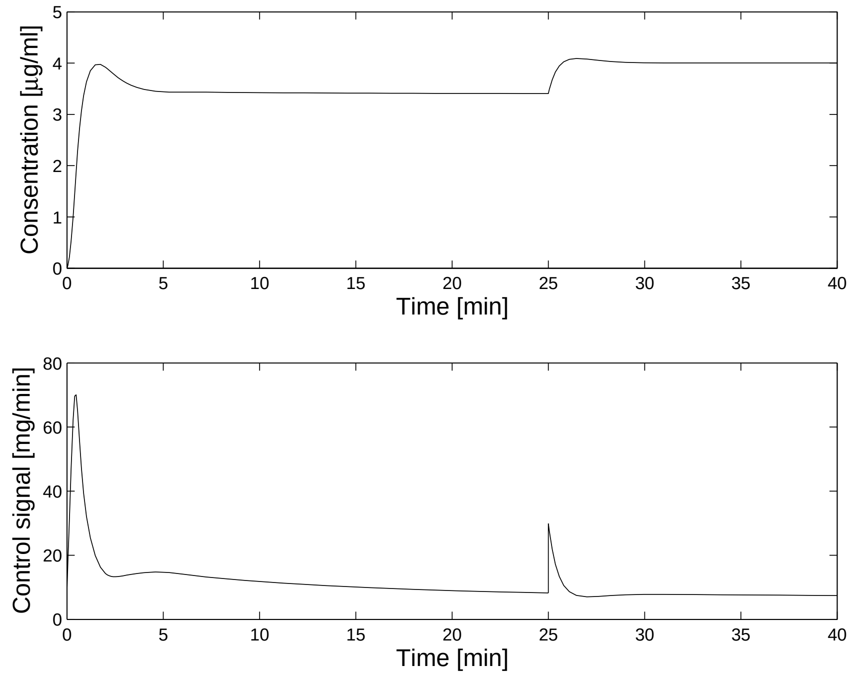


Figure 4.5: Drug Concentration in the Central Compartment and Control Signal (Infusion Rate) vs. Time

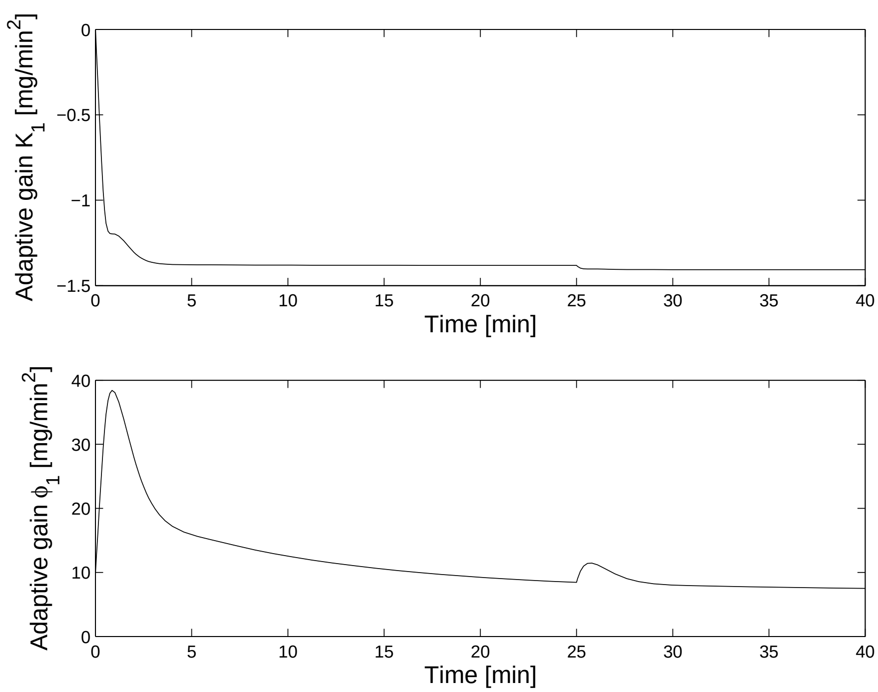


Figure 4.6: Adaptive Gain History vs. Time

Chapter 5

On System State Equipartitioning and Semistability in Network Dynamical Systems with Arbitrary Time-Delays

5.1. Introduction

Nonnegative and compartmental models are also widespread in agreement problems in networks with directed graphs and switching topologies [60, 111]. Specifically, distributed decision-making for coordination of networks of dynamic agents involving information flow can be naturally captured by compartmental models. These dynamical network systems cover a very broad spectrum of applications including cooperative control of unmanned air vehicles, distributed sensor networks, swarms of air and space vehicle formations [59, 68], and congestion control in communication networks [58]. In many applications involving multiagent systems, groups of agents are required to agree on certain quantities of interest. In particular, it is important to develop consensus protocols for networks of dynamic agents with directed information flow, switching network topologies, and possible system time-delays. In this chapter, we use compartmental dynamical system models to characterize dynamic algorithms for linear and nonlinear networks of dynamic agents in the presence of inter-agent communication delays that possess a continuum of *semistable* equilibria, that is, protocol algorithms that guarantee convergence to Lyapunov stable equilibria. In addition, we show that the steady-state distribution of the dynamic network is uniform, leading to system state equipartitioning or consensus. These results extend the results in the literature on consensus protocols for linear balanced networks to linear and nonlinear unbalanced networks with time-delays.

5.2. Mathematical Preliminaries

In the first part of this chapter, we consider linear, time-delay dynamical systems $\mathcal{G}$ of the form

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{n_{\rm d}} A_{{\rm d}i}x(t-\tau_i), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \le \theta \le 0, \quad t \ge 0, \tag{5.1}$$

where $x(t) \in \mathbb{R}^n$, $t \ge 0$, $A \in \mathbb{R}^{n\times n}$, $A_{{\rm d}i} \in \mathbb{R}^{n\times n}$, $i = 1,\ldots,n_{\rm d}$, $\bar{\tau} = \max_{i\in\{1,\ldots,n_{\rm d}\}}\tau_i$, $\eta(\cdot) \in \mathcal{C}_+ \triangleq \{\psi(\cdot) \in \mathcal{C}([-\bar{\tau},0],\mathbb{R}^n) : \psi(\theta) \ge\ge 0, \theta \in [-\bar{\tau},0]\}$ is a continuous vector-valued function specifying the initial state of the system, and $\mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$ denotes a Banach space of continuous functions mapping the interval $[-\bar{\tau},0]$ into $\mathbb{R}^n$ with the topology of uniform convergence. Note that the state of (5.1) at time t is the *piece of trajectories* x between $t-\tau$ and t, or, equivalently, the *element* x_t in the space of continuous functions defined on the interval $[-\bar{\tau},0]$ and taking values in $\mathbb{R}^n$, that is, $x_t \in \mathcal{C}([-\bar{\tau},0],\mathbb{R}^n)$, where $x_t(\theta) \triangleq x(t+\theta)$, $\theta \in [-\bar{\tau},0]$. Furthermore, since for a given time t the piece of the trajectories x_t is defined on $[-\bar{\tau},0]$, the uniform norm $|||x_t||| = \sup_{\theta\in[-\bar{\tau},0]} \|x(t+\theta)\|$, where $\|\cdot\|$ denotes the Euclidean vector norm, is used for the definitions of Lyapunov and asymptotic stability of (5.1). For further details, see [37, 94]. In addition, note that since $\eta(\cdot)$ is continuous it follows from Theorem 2.1 of [37, p. 14] that there exists a unique solution $x(\eta)$ defined on $[-\bar{\tau},\infty)$ that coincides with η on $[-\bar{\tau},0]$ and satisfies (5.1) for all $t \ge 0$. Finally, recall that if the positive orbit $\gamma^+(\eta(\theta))$ of (5.1) is bounded, then $\gamma^+(\eta(\theta))$ is *precompact* [102], that is, $\gamma^+(\eta(\theta))$ can be enclosed in the union of a finite number of ε-balls around elements of $\gamma^+(\eta(\theta))$.

The following theorem gives necessary and sufficient conditions for asymptotic stability of a linear time-delay nonnegative dynamical system $\mathcal{G}$ given by (5.1). For this result, the definition 3.1 and proposition 3.1 with $u(t) \equiv 0$ are needed.

Theorem 5.1 [93, 112]. Consider the linear time-delay dynamical system $\mathcal{G}$ given by (5.1) where $A \in \mathbb{R}^{n\times n}$ is essentially nonnegative and $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_{\mathrm{d}}$, is nonnegative. If there exist $p, r \in \mathbb{R}^n$ such that $p >> 0$ and $r \geq\geq 0$ (resp., $r >> 0$) satisfying

$$0 = \left(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}\right)^{\mathrm{T}} p + r, \tag{5.2}$$

then $\mathcal{G}$ is Lyapunov (resp., asymptotically) stable for all $\bar{\tau} \in [0, \infty)$. Conversely, if $\mathcal{G}$ is asymptotically stable for all $\bar{\tau} \in [0, \infty)$, then there exist $p, r \in \mathbb{R}^n$ such that $p >> 0$ and $r >> 0$ satisfying (5.2).

Definition 5.1 [93, 112]. The linear time-delay dynamical system (5.1) is called a *compartmental dynamical system* if $A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$ is a compartmental matrix.

Note that the linear time-delay dynamical system (5.1) is compartmental if A and $A_{\mathrm{d}} \triangleq \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}$ are given by

$$A_{(i,j)} = \begin{cases} -\sum_{k=1}^{n} a_{ki}, & i = j, \\ 0, & i \neq j, \end{cases} \qquad A_{\mathrm{d}(i,j)} = \begin{cases} 0, & i = j, \\ a_{ij}, & i \neq j, \end{cases} \tag{5.3}$$

where $a_{ii} \geq 0$, $i \in \{1, \ldots, n\}$, denotes the loss coefficients of the ith compartment and $a_{ij} \geq 0$, $i \neq j$, $i, j \in \{1, \ldots, n\}$, denotes the transfer coefficients from the jth compartment to the ith compartment. The following results are necessary for developing some of the main results of this chapter.

Proposition 5.1 [113]. Let $A \in \mathbb{R}^{n\times n}$ be essentially nonnegative and assume there exists $p \in \mathbb{R}^n_+$ such that $A^{\mathrm{T}} p \leq\leq 0$. Then A is semistable, that is, $\operatorname{Re} \lambda < 0$, or $\lambda = 0$ and λ is semisimple, where $\lambda \in \operatorname{spec}(\mathrm{A})$.

5.3. Semistability and Equipartition of Linear Compartmental Systems with Time-Delay

In this section, we present sufficient conditions for semistability and system state equipartition for linear compartmental dynamical systems with time delay. Note that for addressing the stability of the zero solution of a time delay nonnegative system, the usual stability definitions given in [37] need to be slightly modified. In particular, stability notions for nonnegative dynamical systems need to be defined with respect to relatively open subsets of $\overline{\mathbb{R}}_+^n$ containing the equilibrium solution $x_t \equiv 0$. For a similar definition see [113]. In this case, standard Lyapunov-Krasovskii stability theorems for linear and nonlinear time delay systems [37] can be used directly with the required sufficient conditions verified on $\overline{\mathbb{R}}_+^n$. The following lemma is needed for the main theorem of this section.

Lemma 5.1. Let $A \in \mathbb{R}^{n\times n}$ and $A_{\mathrm{d}i} \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_\mathrm{d}$, be given by (5.3). Then there exist nonnegative definite matrices $Q_i \in \mathbb{R}^{n\times n}$, $i = 1, \ldots, n_\mathrm{d}$, such that

$$A + A^\mathrm{T} + \sum_{i=1}^{n_\mathrm{d}} (Q_i + A_{\mathrm{d}i}^\mathrm{T} Q_i^{\#} A_{\mathrm{d}i}) \leq 0. \tag{5.4}$$

Proof. For each $i \in \{1, \ldots, n_\mathrm{d}\}$, let Q_i be the diagonal matrix defined by

$$Q_{i(l,l)} \triangleq \sum_{m=1, l\neq m}^{n} A_{\mathrm{d}i(l,m)}, \tag{5.5}$$

and note that $A + \sum_{i=1}^{n_\mathrm{d}} Q_i = 0$, $(A_{\mathrm{d}i} - Q_i)\mathbf{e} = 0$, and $Q_i Q_i^{\#} A_{\mathrm{d}i} = A_{\mathrm{d}i}$, $i = 1, \ldots, n_\mathrm{d}$. Hence, $M\mathbf{e} = 0$, where

$$M \triangleq \begin{bmatrix} A + A^\mathrm{T} + \sum_{i=1}^{n_\mathrm{d}} Q_i & A_{\mathrm{d}1}^\mathrm{T} & A_{\mathrm{d}2}^\mathrm{T} & \cdots & A_{\mathrm{d}n_\mathrm{d}}^\mathrm{T} \\ A_{\mathrm{d}1} & -Q_1 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ A_{\mathrm{d}n_\mathrm{d}} & 0 & 0 & \cdots & -Q_{n_\mathrm{d}} \end{bmatrix}. \tag{5.6}$$

Now, it follows from Corollary 4.1 that $M \leq 0$ and since $Q_i Q_i^{\#} A_{\mathrm{d}i} = A_{\mathrm{d}i}$, $i = 1, \ldots, n_\mathrm{d}$, it follows from Lemma 4.2 that $M \leq 0$ if and only if (5.4) holds. $\square$

For the next result, recall that the equilibrium solution $x_t \equiv x_\mathrm{e}$ to (5.1) is *semistable* if and only if x_e is Lyapunov stable and $\lim_{t\to\infty} x(t)$ exists.

Theorem 5.2. Consider the linear time-delay dynamical system given by (5.1) where A and $A_{\mathrm{d}i}$, $i = 1, \ldots, n_{\mathrm{d}}$, are given by (5.3). Assume that $(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})^{\mathrm{T}}\mathbf{e} = (A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})\mathbf{e} = 0$ and $\mathrm{rank}(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}) = n - 1$. Then for every $\alpha \geq 0$, $\alpha\mathbf{e}$ is a semistable equilibrium point of (5.1). Furthermore, $x(t) \to \alpha^*\mathbf{e}$ as $t \to \infty$, where

$$\alpha^* = \frac{\mathbf{e}^{\mathrm{T}}\eta(0) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} \mathbf{e}^{\mathrm{T}} A_{\mathrm{d}} \eta(\theta) \mathrm{d}\theta}{n + \sum_{i=1}^{n_{\mathrm{d}}} \tau_i \mathbf{e}^{\mathrm{T}} A_{\mathrm{d}i} \mathbf{e}}. \tag{5.7}$$

Proof. It follows from Lemma 5.1 that there exist nonnegative matrices Q_i, $i = 1, \ldots, n_{\mathrm{d}}$, such that (5.4) holds. Now, consider the Lyapunov-Krasovskii functional $V : \mathcal{C}_+ \to \mathbb{R}$ given by

$$V(\psi(\cdot)) = \psi^{\mathrm{T}}(0)\psi(0) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} \psi^{\mathrm{T}}(\theta) A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i} \psi(\theta) \mathrm{d}\theta, \tag{5.8}$$

and note that the directional derivative of $V(x_t)$ along the trajectories of (5.1) is given by

$$\begin{aligned}
\dot{V}(x_t) &= 2x^{\mathrm{T}}(t)\dot{x}(t) + \sum_{i=1}^{n_{\mathrm{d}}} x^{\mathrm{T}}(t) A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i} x(t) - \sum_{i=1}^{n_{\mathrm{d}}} x^{\mathrm{T}}(t-\tau_i) A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i} x(t-\tau_i) \\
&= 2x^{\mathrm{T}}(t) A x(t) + 2x^{\mathrm{T}}(t) \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i} x(t-\tau_i) + \sum_{i=1}^{n_{\mathrm{d}}} x^{\mathrm{T}}(t) A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i} x(t) \\
&\quad - \sum_{i=1}^{n_{\mathrm{d}}} x^{\mathrm{T}}(t-\tau_i) A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i} x(t-\tau_i) \\
&\leq -\sum_{i=1}^{n_{\mathrm{d}}} [x^{\mathrm{T}}(t) Q_i x(t) - 2x^{\mathrm{T}}(t) A_{\mathrm{d}i} x(t-\tau_i) + x^{\mathrm{T}}(t-\tau_i) A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i} x(t-\tau_i)] \\
&= -\sum_{i=1}^{n_{\mathrm{d}}} [-Q_i x(t) + A_{\mathrm{d}i} x(t-\tau_i)]^{\mathrm{T}} Q_i^{\#} [-Q_i x(t) + A_{\mathrm{d}i} x(t-\tau_i)] \\
&\leq 0, \qquad t \geq 0.
\end{aligned} \tag{5.9}$$

Next, let $\mathcal{R} \triangleq \{\psi(\cdot) \in \mathcal{C}_+ : -Q_i\psi(0) + A_{\mathrm{d}i}\psi(-\tau_i) = 0, i = 1, \ldots, n_{\mathrm{d}}\}$ and note that since the positive orbit $\gamma^+(\eta(\theta))$ of (5.1) is bounded, $\gamma^+(\eta(\theta))$ belongs to a compact subset of $\mathcal{C}_+$, and hence, it follows from Theorem 3.2 of [37] that $x_t \to \mathcal{M}$, where $\mathcal{M}$ denotes the largest invariant set contained in $\mathcal{R}$. Now, since $A + \sum_{i=1}^{n_{\mathrm{d}}} Q_i = 0$, it follows that $\mathcal{R} \subset \hat{\mathcal{R}} \triangleq \{\psi(\cdot) \in \mathcal{C}_+ : A\psi(0) + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}\psi(-\tau_i) = 0\}$. Hence, since

$\mathrm{rank}(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}) = n - 1$ and $(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})\mathbf{e} = 0$, it follows that the largest invariant set $\hat{\mathcal{M}}$ contained in $\hat{\mathcal{R}}$ is given by $\hat{\mathcal{M}} = \{\psi \in \mathcal{C}_+ : \psi(\theta) = \alpha\mathbf{e}, \theta \in [-\bar{\tau}, 0], \alpha \geq 0\}$. Furthermore, since $\hat{\mathcal{M}} \subset \mathcal{R} \subset \hat{\mathcal{R}}$, it follows that $\mathcal{M} = \hat{\mathcal{M}}$.

Next, define the functional $E : \mathcal{C}_+ \to \mathbb{R}$ by

$$E(\psi(\cdot)) = \mathbf{e}^{\mathrm{T}}\psi(0) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} \mathbf{e}^{\mathrm{T}} A_{\mathrm{d}i}\psi(\theta)\mathrm{d}\theta, \tag{5.10}$$

and note that $\dot{E}(x_t) \equiv 0$ along the trajectories of (5.1). Thus, for all $t \geq 0$,

$$E(x_t) = E(\eta(\cdot)) = \mathbf{e}^{\mathrm{T}}\eta(0) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} \mathbf{e}^{\mathrm{T}} A_{\mathrm{d}i}\eta(\theta)\mathrm{d}\theta, \tag{5.11}$$

which implies that $x_t \to \mathcal{M} \cap \mathcal{E}$, where $\mathcal{E} \triangleq \{\psi(\cdot) \in \mathcal{C}_+ : E(\psi(\cdot)) = E(\eta(\cdot))\}$. Hence, since $\mathcal{M} \cap \mathcal{E} = \{\alpha^*\mathbf{e}\}$, it follows that $x(t) \to \alpha^*\mathbf{e}$, where α^* is given by (5.7).

Finally, Lyapunov stability of $\alpha\mathbf{e}$, $\alpha \geq 0$, follows by considering the Lyapunov-Krasovskii functional

$$V(\psi(\cdot)) = (\psi(0) - \alpha\mathbf{e})^{\mathrm{T}}(\psi(0) - \alpha\mathbf{e}) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} (\psi(\theta) - \alpha\mathbf{e})^{\mathrm{T}} A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i}(\psi(\theta) - \alpha\mathbf{e})\mathrm{d}\theta$$

and noting that $V(\psi) \geq \|\psi(0) - \alpha\mathbf{e}\|_2^2$. □

Note that if $n_{\mathrm{d}} = n^2 - n$, $A_{\mathrm{d}} = A_{\mathrm{d}}^{\mathrm{T}}$, and $(A + A_{\mathrm{d}})\mathbf{e} = 0$, then (5.1) can be rewritten as

$$\dot{x}_i(t) = -\sum_{j=1, j\neq i}^{n} a_{ij}[x_i(t) - x_j(t - \tau_{ij})], \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \tag{5.12}$$

where $i = 1, \ldots, n$, and $\tau_{ij} \in [0, \bar{\tau}]$, $i \neq j$, $i, j = 1, \ldots, n$, which implies that the rate of material transfer from ith compartment to jth compartment is proportional to the difference $x_j(t - \tau_{ij}) - x_i(t)$. Hence, the rate of material transfer is positive (resp., negative) if $x_j(t - \tau_{ij}) > x_i(t)$ (resp., $x_j(t - \tau_{ij}) < x_i(t)$). Equation (5.12) is an information flow balance equation that governs the information exchange among coupled subsystems and is completely analogous to the equations of thermal transfer with subsystem information playing the role of temperatures. Furthermore, note that since $a_{ij} \geq 0$, $i \neq j$, $i, j = 1, \ldots, n$, information energy flows from more energetic subsystems to less energetic subsystems, which is consistent with the second law of thermodynamics requiring that heat (energy) must flow in the direction of lower temperatures.

5.4. Semistability and Equipartition of Nonlinear Compartmental Systems with Time Delay

In this section, we extend the results of Section 5.3 to nonlinear compartmental systems with time delay. Specifically, we consider nonlinear time-delay dynamical systems $\mathcal{G}$ of the form

$$\dot{x}(t) = f(x(t)) + f_{\mathrm{d}}(x(t-\tau_1), \ldots, x(t-\tau_{n_{\mathrm{d}}})), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \tag{5.13}$$

where $x(t) \in \mathbb{R}^n$, $t \geq 0$, $f : \mathbb{R}^n \to \mathbb{R}^n$ is locally Lipschitz continuous and $f(0) = 0$, $f_{\mathrm{d}} : \mathbb{R}^n \times \cdots \times \mathbb{R}^n \to \mathbb{R}^n$ is locally Lipschitz continuous and $f_{\mathrm{d}}(0, \ldots, 0) = 0$, $\bar{\tau} = \max_{i \in \{1,\ldots,n_{\mathrm{d}}\}} \tau_i$, $\tau_i \geq 0$, $i = 1, \ldots, n_{\mathrm{d}}$, and $\eta(\cdot) \in \mathcal{C} = \mathcal{C}([-\bar{\tau}, 0], \mathbb{R}^n)$ is a continuous vector-valued function specifying the initial state of the system. Note that since $\eta(\cdot)$ is continuous it follows from Theorem 2.3 of [37, p. 44] that there exists a unique solution $x(\eta)$ defined on $[-\bar{\tau}, \infty)$ that coincides with η on $[-\bar{\tau}, 0]$ and satisfies (5.13) for all $t \geq 0$. In addition, recall that if the positive orbit $\gamma^+(\eta(\theta))$ of (5.13) is bounded, then $\gamma^+(\eta(\theta))$ is precompact [102]. The following definitions generalize the notions of essential nonnegativity and nonnegativity to vector fields.

Definition 5.2 [113]. Let $f = [f_1, \ldots, f_n]^{\mathrm{T}} : \mathcal{D} \to \mathbb{R}^n$, where $\mathcal{D}$ is an open subset of $\mathbb{R}^n$ that contains $\overline{\mathbb{R}}_+^n$. Then f is *essentially nonnegative* if $f_i(x) \geq 0$ for all $i = 1, \ldots, n$ and $x \in \overline{\mathbb{R}}_+^n$ such that $x_i = 0$, where x_i denotes the ith element of x. f is *compartmental* if f is essentially nonnegative and $\mathbf{e}^{\mathrm{T}} f(x) \leq 0$, $x \in \overline{\mathbb{R}}_+^n$.

Definition 5.3 [114]. Let $f = [f_1, \ldots, f_n]^{\mathrm{T}} : \mathcal{D} \to \mathbb{R}^n$, where $\mathcal{D}$ is an open subset of $\mathbb{R}^n$ that contains $\overline{\mathbb{R}}_+^n$. Then f is *nonnegative* if $f_i(x) \geq 0$ for all $i = 1, \ldots, n$ and $x \in \overline{\mathbb{R}}_+^n$.

Note that if $f(x) = Ax$, where $A \in \mathbb{R}^{n\times n}$, then $f(\cdot)$ is essentially nonnegative if and only if A is essentially nonnegative, and $f(\cdot)$ is nonnegative if and only if A is nonnegative.

Definition 5.4 [112]. The nonlinear time-delay dynamical system $\mathcal{G}$ given by (5.13) is *nonnegative* if for every $\eta(\cdot) \in \mathcal{C}_+$, where $\mathcal{C}_+ \triangleq \{\psi(\cdot) \in \mathcal{C} : \psi(\theta) \geq\geq 0,\ \theta \in [-\bar{\tau}, 0]\}$, the solution $x(t)$, $t \geq 0$, to (5.13) is nonnegative.

Proposition 5.2 [112]. Consider the nonlinear time-delay dynamical system $\mathcal{G}$ given by (5.13). If $f(\cdot)$ is essentially nonnegative and $f_{\mathrm{d}}(\cdot)$ is nonnegative, then $\mathcal{G}$ is nonnegative.

For the remainder of this chapter, we assume that $f(\cdot)$ is essentially nonnegative and $f_{\mathrm{d}}(\cdot)$ is nonnegative so that for every $\eta(\cdot) \in \mathcal{C}_+$, the nonlinear time-delay dynamical system $\mathcal{G}$ given by (5.13) is nonnegative. Next, we consider a subclass of nonlinear nonnegative systems, namely, nonlinear compartmental systems.

Definition 5.5. The nonlinear time-delay dynamical system (5.13) is called a *compartmental dynamical system* if $F(\cdot)$ is compartmental, where $F(x) \triangleq f(x) + f_{\mathrm{d}}(x, x, \ldots, x)$.

Note that the nonlinear time-delay dynamical system is compartmental if $f(\cdot)$ and $f_{\mathrm{d}}(\cdot)$ are given by

$$\begin{aligned} f_i(x(t)) &= -\sum_{j=1, j\neq i}^{n} a_{ji}(x(t)), \quad f_{\mathrm{d}i}(x(t-\tau_1), \ldots, x(t-\tau_{n_{\mathrm{d}}})) \\ &= \sum_{j=1, j\neq i}^{n} a_{ij}(x(t-\tau_{ij})), \end{aligned} \tag{5.14}$$

where $a_{ii}(x(\cdot)) \geq 0$, $x(\cdot) \in \mathcal{C}_+$, $a_{ii}(0) = 0$, $i \in \{1, \ldots, n\}$, denotes the instantaneous rate of flow of material loss of the ith compartment, $a_{ij}(x(\cdot)) \geq 0$, $x(\cdot) \in \mathcal{C}_+$, $i \neq j$, $i, j \in \{1, \ldots, n\}$, denotes the instantaneous rate of material flow from the jth compartment to the ith compartment, τ_{ij}, $i \neq j$, $i, j \in \{1, \ldots, n\}$, denotes the transfer time of material flow from the jth compartment to the ith compartment, and $a_{ii}(\cdot)$ and $a_{ij}(\cdot)$ are such that if $x_i = 0$, then $a_{ii}(x) = 0$ and $a_{ji}(x) = 0$ for all $i, j = 1, \ldots, n$, and $x \in \overline{\mathbb{R}}_+^n$. Note that the above constraints imply that $f(\cdot)$ is essentially nonnegative and $f_{\mathrm{d}}(\cdot)$ is nonnegative. The next result generalizes Theorem 5.2 to nonlinear time-delay compartmental systems of the form

$$\dot{x}(t) = f(x(t)) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}(x(t-\tau_i)), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \tag{5.15}$$

where $f : \overline{\mathbb{R}}_+^n \to \overline{\mathbb{R}}_+^n$ is given by $f(x) = [f_1(x_1), \ldots, f_n(x_n)]^{\mathrm{T}}$, $f(0) = 0$, $f_{\mathrm{d}i} : \overline{\mathbb{R}}_+^n \to \overline{\mathbb{R}}_+^n$, $i = 1, \ldots, n_{\mathrm{d}}$, and $f_{\mathrm{d}}(0) = 0$. Furthermore, we assume that $f_i(\cdot)$, $i = 1, \ldots, n$, is a strictly decreasing function.

Theorem 5.3. Consider the nonlinear time-delay dynamical system given by (5.15) where $f_i(\cdot)$, $i = 1, \ldots, n$, is strictly decreasing and $f_i(0) = 0$. Assume that $\mathbf{e}^{\mathrm{T}}[f(x) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}(x)] = 0$, $x \in \overline{\mathbb{R}}_+^n$, and $f(x) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}(x) = 0$ if and only if $x = \alpha\mathbf{e}$ for some $\alpha \geq 0$. Furthermore, assume there exist nonnegative diagonal matrices $P_i \in \overline{\mathbb{R}}_+^{n \times n}$, $i = 1, \ldots, n_{\mathrm{d}}$, such that $P \triangleq \sum_{i=1}^{n_{\mathrm{d}}} P_i > 0$,

$$P_i^{\#} P_i f_{\mathrm{d}i}(x) \;=\; f_{\mathrm{d}i}(x), \quad x \in \overline{\mathbb{R}}_+^n, \quad i = 1, \ldots, n_{\mathrm{d}}, \tag{5.16}$$

$$\sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}^{\mathrm{T}}(x) P_i f_{\mathrm{d}i}(x) \;\leq\; f^{\mathrm{T}}(x) P f(x), \quad x \in \overline{\mathbb{R}}_+^n. \tag{5.17}$$

Then, for every $\alpha \geq 0$, $\alpha\mathbf{e}$ is a semistable equilibrium point of (5.15). Furthermore, $x(t) \to \alpha^* \mathrm{e}$ as $t \to \infty$, where α^* satisfies

$$n\alpha^* + \sum_{i=1}^{n_{\mathrm{d}}} \tau_i \mathbf{e}^{\mathrm{T}} f_{\mathrm{d}i}(\alpha^* \mathbf{e}) = \mathbf{e}^{\mathrm{T}} \eta(0) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} \mathbf{e}^{\mathrm{T}} f_{\mathrm{d}i}(\eta(\theta)) \mathrm{d}\theta. \tag{5.18}$$

Proof. Consider the Lyapunov-Krasovskii functional $V : \mathcal{C}_+ \to \mathbb{R}$ given by

$$V(\psi(\cdot)) = -2 \sum_{i=1}^{n} \int_0^{\psi_i(0)} P_{(i,i)} f_i(\zeta) \mathrm{d}\zeta + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} f_{\mathrm{d}i}^{\mathrm{T}}(\psi(\theta)) P_i f_{\mathrm{d}i}(\psi(\theta)) \mathrm{d}\theta. \tag{5.19}$$

Since, $f_i(\cdot)$, $i = 1, \ldots, n$, is a strictly decreasing function it follows that $V(\psi) \geq 2\sum_{i=1}^{n} P_{(i,i)}[-$

$f_i(\delta_i\psi_i(0))]\psi_i(0) > 0$ for all $\psi(0) \neq 0$, where $0 < \delta_i < 1$, and hence, there exists a class $\mathcal{K}$ function $\alpha(\cdot)$ such that $V(\psi) \geq \alpha(\|\psi(0)\|)$. Now, note that the directional derivative of $V(x_t)$ along the trajectories of (5.15) is given by

$$\begin{aligned}
\dot{V}(x_t) &= -2f^{\mathrm{T}}(x(t))P\dot{x}(t) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}^{\mathrm{T}}(x(t))P_i f_{\mathrm{d}i}(x(t)) \\
&\quad - \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}^{\mathrm{T}}(x(t-\tau_i))P_i f_{\mathrm{d}i}(x(t-\tau_i)) \\
&= -2f^{\mathrm{T}}(x(t))Pf(x(t)) - 2\sum_{i=1}^{n_{\mathrm{d}}} f^{\mathrm{T}}(x(t))Pf_{\mathrm{d}i}(x(t-\tau_i)) \\
&\quad + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}^{\mathrm{T}}(x(t))P_i f_{\mathrm{d}i}(x(t)) - \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}^{\mathrm{T}}(x(t-\tau_i))P_i f_{\mathrm{d}i}(x(t-\tau_i)) \\
&\leq -f^{\mathrm{T}}(x(t))Pf(x(t)) - 2\sum_{i=1}^{n_{\mathrm{d}}} f^{\mathrm{T}}(x(t))PP_i^{\#}P_i f_{\mathrm{d}i}(x(t-\tau_i)) \\
&\quad - \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}^{\mathrm{T}}(x(t-\tau_i))P_i P_i^{\#} P_i f_{\mathrm{d}i}(x(t-\tau_i)) \\
&= -\sum_{i=1}^{n_{\mathrm{d}}} [Pf(x(t)) + P_i f_{\mathrm{d}i}(x(t-\tau_i))]^{\mathrm{T}} P_i^{\#} [Pf(x(t)) + P_i f_{\mathrm{d}i}(x(t-\tau_i))] \\
&\leq 0, \quad t \geq 0,
\end{aligned} \tag{5.20}$$

where the first inequality in (5.20) follows from (5.16) and (5.17), and the last equality in (5.20) follows from the fact that $f^{\mathrm{T}}(x)Pf(x) = \sum_{i=1}^{n_{\mathrm{d}}} f^{\mathrm{T}}(x)PP_i^{\#}Pf(x)$, $x \in \overline{\mathbb{R}}_+^n$.

Next, let $\mathcal{R} \triangleq \{\psi(\cdot) \in \mathcal{C}_+ : Pf(\psi(0)) + P_i f_{\mathrm{d}i}(\psi(-\tau_i)) = 0, i = 1, \ldots, n_{\mathrm{d}}\}$ and note that since the positive orbit $\gamma^+(\eta(\theta))$ of (5.15) is bounded, $\gamma^+(\eta(\theta))$ belongs to a compact subset of $\mathcal{C}_+$, and hence, it follows from Theorem 3.2 of [37] that $x_t \to \mathcal{M}$, where $\mathcal{M}$ denotes the largest invariant set (with respect to (5.15)) contained in $\mathcal{R}$. Now, since $\mathbf{e}^{\mathrm{T}}(f(x) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}}(x)) = 0, x \in \overline{\mathbb{R}}_+^n$, it follows that

$$\begin{aligned}
\mathcal{R} \subset \hat{\mathcal{R}} &\triangleq \{\psi(\cdot) \in \mathcal{C}_+ : f(\psi(0)) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}(\psi(-\tau_i)) = 0\} \\
&= \{\psi(\cdot) \in \mathcal{C}_+ : \psi(\theta) = \alpha\mathbf{e},\ \theta \in [-\bar{\tau}, 0],\ \alpha \geq 0\},
\end{aligned}$$

which implies that $x_t \to \hat{\mathcal{R}}$ as $t \to \infty$.

Next, define the functional $E : \mathcal{C}_+ \to \mathbb{R}$ by

$$E(\psi(\cdot)) = \mathbf{e}^{\mathrm{T}}\psi(0) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} \mathbf{e}^{\mathrm{T}} f_{\mathrm{d}i}(\psi(\theta))\mathrm{d}\theta, \tag{5.21}$$

and note that $\dot{E}(x_t) \equiv 0$ along the trajectories of (5.15). Thus, for all $t \geq 0$,

$$E(x_t) = E(\eta(\cdot)) = \mathbf{e}^{\mathrm{T}}\eta(0) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} \mathbf{e}^{\mathrm{T}} f_{\mathrm{d}i}(\eta(\theta))\mathrm{d}\theta, \tag{5.22}$$

which implies that $x_t \to \hat{\mathcal{R}} \cap \mathcal{E}$, where $\mathcal{E} \triangleq \{\psi(\cdot) \in \mathcal{C}_+ : E(\psi(\cdot)) = E(\eta(\cdot))\}$. Hence, $\hat{\mathcal{R}} \cap \mathcal{E} = \{\alpha^* \mathrm{e}\}$, it follows that $x(t) \to \alpha^*\mathbf{e}$, where α^* satisfies (5.18).

Finally, Lyapunov stability of $\alpha\mathbf{e}$, $\alpha \geq 0$, follows by considering the Lyapunov-Krasovskii functional

$$\begin{aligned} V(\psi(\cdot)) \;=\; & -2\sum_{i=1}^{n} \int_{\alpha}^{\psi_i(0)} P_{(i,i)}(f_i(\zeta) - f_i(\alpha))\mathrm{d}\zeta \\ & + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} [f_{\mathrm{d}i}(\psi(\theta)) - f_{\mathrm{d}i}(\alpha\mathbf{e})]^{\mathrm{T}} P_i [f_{\mathrm{d}i}(\psi(\theta)) - f_{\mathrm{d}i}(\alpha\mathbf{e})]\mathrm{d}\theta, \end{aligned}$$

and noting that $V(\psi) \geq 2\sum_{i=1}^{n} P_{(i,i)}[f_i(\alpha) - f_i(\alpha + \delta_i(\psi_i(0) - \alpha))](\psi_i(0) - \alpha) > 0$, for all $\psi_i(0) \neq \alpha$, where $0 < \delta_i < 1$. $\square$

Theorem 5.3 establishes semistability and state equipartition for the special case of nonlinear compartmental systems of the form (5.14) where $f(\cdot)$ and $f_{\mathrm{d}i}(\cdot)$, $i = 1, \ldots, n$, satisfy (5.16) and (5.17). For general n-dimensional nonlinear compartmental systems with time-delay and vector fields given by (5.15) it is not possible to guarantee semistability and state equipartition. However, semistability without state equipartition may be shown. For example, consider the nonlinear time-delay compartmental dynamical system given by

$$\dot{x}_1(t) \;=\; -a_{21}(x_1(t)) + a_{12}(x_2(t-\tau_{12})), x_1(\theta) = \eta_1(\theta), -\bar{\tau} \leq \theta \leq 0, t \geq 0, \tag{5.23}$$

$$\dot{x}_2(t) \;=\; -a_{12}(x_2(t)) + a_{21}(x_1(t-\tau_{21})), x_2(\theta) = \eta_2(\theta), -\bar{\tau} \leq \theta \leq 0, t \geq 0, \tag{5.24}$$

where $x_1(t), x_2(t) \in \mathbb{R}$, $t \geq 0$, $a_{12} : \overline{\mathbb{R}}_+ \to \overline{\mathbb{R}}_+$ and $a_{21} : \overline{\mathbb{R}}_+ \to \overline{\mathbb{R}}_+$ satisfy $a_{12}(0) = a_{21}(0) = 0$ and $a_{12}(\cdot)$ and $a_{21}(\cdot)$ are strictly increasing, $\tau_{12}, \tau_{21} > 0$, $\bar{\tau} = \max\{\tau_{12}, \tau_{21}\}$, and $\eta_1(\cdot), \eta_2(\cdot) \in \mathcal{C}_+ = \mathcal{C}([-\bar{\tau}, 0], \overline{\mathbb{R}}_+)$. Note that (5.23) and (5.24) can have multiple equilibria with all the equilibria lying on the curve $a_{21}(u) = a_{12}(v)$, $u, v \geq 0$. It follows from the conditions on $a_{12}(\cdot)$ and $a_{21}(\cdot)$ that all system equilibria lie on the curve $y = a_{12}^{-1}(a_{21}(x))$ in the (x, y) plane, where $a_{12}^{-1}(\cdot)$ denotes the inverse function of $a_{12}(\cdot)$.

Consider the functional $E : \mathcal{C}_+ \times \mathcal{C}_+ \to \mathbb{R}$ given by

$$E(\psi_1, \psi_2) = \psi_1(0) + \psi_2(0) + \int_{-\tau_{12}}^{0} a_{12}(\psi_2(\theta))\mathrm{d}\theta + \int_{-\tau_{21}}^{0} a_{21}(\psi_1(\theta))\mathrm{d}\theta. \tag{5.25}$$

Now, it can be easily shown that the directional derivative of $E(\psi_1, \psi_2)$ along the trajectories of (5.23) and (5.24) is identically zero for all $t \geq 0$, which implies that, for all $t \geq 0$,

$$\begin{aligned} E(x_{1t}, x_{2t}) \;&=\; E(\eta_1, \eta_2) = \eta_1(0) + \eta_2(0) + \int_{-\tau_{12}}^{0} a_{12}(\eta_2(\theta))\mathrm{d}\theta \\ &\quad + \int_{-\tau_{21}}^{0} a_{21}(\eta_1(\theta))\mathrm{d}\theta. \end{aligned} \tag{5.26}$$

Next, consider the functional $V : \mathcal{C}_+ \times \mathcal{C}_+ \to \mathbb{R}$ given by

$$\begin{aligned} V(\psi_1, \psi_2) \;&=\; 2\int_{0}^{\psi_1(0)} a_{21}(\theta)\mathrm{d}\theta + 2\int_{0}^{\psi_2(0)} a_{12}(\theta)\mathrm{d}\theta \\ &\quad + \int_{-\tau_{12}}^{0} a_{12}^2(\psi_2(\theta))\mathrm{d}\theta + \int_{-\tau_{21}}^{0} a_{21}^2(\psi_1(\theta))\mathrm{d}\theta, \end{aligned} \tag{5.27}$$

and note that the directional derivative of $V(\psi_1, \psi_2)$ along the trajectories of (5.23) and (5.24) is given by

$$\begin{aligned} \dot{V}(x_{1t}, x_{2t}) \;&=\; -[a_{21}(x_1(t)) - a_{12}(x_2(t - \tau_{12}))]^2 \\ &\quad -\; [a_{12}(x_2(t)) - a_{21}(x_1(t - \tau_{21}))]^2. \end{aligned} \tag{5.28}$$

Now, using similar arguments as in the proof of Theorem 5.3 it follows that

$$(x_1(t), x_2(t)) \to (\alpha^*, a_{12}^{-1}(a_{21}(\alpha^*)))$$

as $t \to \infty$, where α^* is the solution to the equation

$$\begin{aligned} \alpha^* + a_{12}^{-1}(a_{21}(\alpha^*)) \;+\; (\tau_{12} + \tau_{21})a_{21}(\alpha^*) &= \eta_1(0) + \eta_2(0) \\ &\quad + \int_{-\tau_{12}}^{0} a_{12}(\eta_2(\theta))\mathrm{d}\theta + \int_{-\tau_{21}}^{0} a_{21}(\eta_1(\theta))\mathrm{d}\theta, \end{aligned} \tag{5.29}$$

and $(\alpha^*, a_{12}^{-1}(a_{21}(\alpha^*)))$ is a Lyapunov stable equilibrium state. The above analysis shows that all two-dimensional nonlinear compartmental dynamical systems of the form (5.23) and (5.24) are semistable with system states reaching equilibria lying on the curve $y = a_{12}^{-1}(a_{21}(x))$ in the (x, y) plane.

To demonstrate the utility of Theorem 5.3 we consider a nonlinear two-compartment time-delay dynamical system given by

$$\begin{aligned}\dot{x}_1(t) &= -\sum_{i=1}^{n_{\mathrm{d}}} a_i(x_1(t)) + a_i(x_2(t-\tau_i)), x_1(\theta) = \eta_1(\theta), -\bar{\tau} \le \theta \le 0, t \ge 0, &(5.30)\\ \dot{x}_2(t) &= \sum_{i=1}^{n_{\mathrm{d}}} a_i(x_1(t-\tau_i)) - a_i(x_2(t)), x_2(\theta) = \eta_2(\theta), -\bar{\tau} \le \theta \le 0, &(5.31)\end{aligned}$$

where $a_i : \overline{\mathbb{R}}_+ \to \overline{\mathbb{R}}_+$, $i = 1, \ldots, n_{\mathrm{d}}$, are such that for every $i = 1, \ldots, n_{\mathrm{d}}$,

$$[a_i(x_1) - a_i(x_2)](x_1 - x_2) > 0, \quad x_1 \neq x_2, \tag{5.32}$$

and $a_i(0) = 0$, $i = 1, \ldots, n_{\mathrm{d}}$. If x_1 and x_2 represent system energies, then (5.30) and (5.31) capture energy flow balance between the two compartments, and (5.32) is consistent with the second law of thermodynamics, that is, energy flows from the more energetic compartment to the less energetic compartment [34]. Furthermore, since $a_i(0) = 0$, (5.32) implies that $a_i(\cdot)$, $i = 1, 2$, is strictly increasing. Now, note that (5.30) and (5.31) can be written in the form of (5.15) with

$$f(x) = \begin{bmatrix} -\sum_{i=1}^{n_{\mathrm{d}}} a_i(x_1) \\ -\sum_{i=1}^{n_{\mathrm{d}}} a_i(x_2) \end{bmatrix}, \quad f_{\mathrm{d}i}(x) = \begin{bmatrix} a_i(x_2) \\ a_i(x_1) \end{bmatrix}, \quad i = 1, 2, \tag{5.33}$$

which implies that $f_j(x_j)$, $j = 1, 2$, are strictly decreasing. Next, with $P_i = I_n$, $i = 1, \ldots, n_{\mathrm{d}}$, (5.16) and (5.17) are trivially satisfied, and hence, it follows from Theorem 5.3 that $x_1(t) - x_2(t) \to 0$ as $t \to \infty$.

Next, we consider nonlinear compartmental time-delay dynamical systems of the form

$$\dot{x}_i(t) = -\sum_{j=1, j\neq i}^{n} a_{ji}(x_i(t)) + \sum_{j=1, j\neq i}^{n} a_{ij}(x_j(t-\tau_i)), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \le \theta \le 0, \quad t \ge 0, \tag{5.34}$$

where $i = 1, \ldots, n$, $a_{ij} : \overline{\mathbb{R}}_+ \to \overline{\mathbb{R}}_+$, $i \neq j$, $i, j \in \{1, \ldots, n\}$, are such that $a_{ij}(0) = 0$ and $a_{ij}(\cdot)$, $i \neq j$, $i, j = 1, \ldots, n$, is strictly increasing. Note that since each transfer coefficient $a_{ij}(\cdot)$ is only a function of x_j and not x, the nonlinear compartmental system (5.34) is a *nonlinear donor controlled compartmental system* [28]. In this case, (5.34) can be written in the form given by (5.15) with $n_{\mathrm{d}} = n$,

$$f_i(x_i) = -\sum_{j=1, j\neq i}^{n} a_{ji}(x_i), \quad f_{\mathrm{d}i}(x) = \mathbf{e}_i \sum_{j=1}^{n} a_{ij}(x_j), \quad i = 1, \ldots, n. \tag{5.35}$$

Next, with $P_i = \mathbf{e}_i \mathbf{e}_i^{\mathrm{T}}$, $i = 1, \ldots, n$, so that $P = I_n$, it follows that (5.16) is trivially satisfied and (5.17) holds if and only if

$$\sum_{i=1}^{n} \left[\sum_{j=1, i\neq j}^{n} a_{ij}(x_j) \right]^2 \leq \sum_{i=1}^{n} \left[\sum_{j=1, i\neq j}^{n} a_{ji}(x_i) \right]^2, \ x \in \overline{\mathbb{R}}_+^n. \tag{5.36}$$

In the case where $n = 2$, (5.36) is trivially satisfied, and hence, it follows from Theorem 5.3 that $x_1(t) - x_2(t) \to 0$ as $t \to \infty$. In general, (5.36) does not hold for arbitrary strictly increasing functions $a_{ij}(\cdot)$. However, if $a_{ij}(\cdot) = \sigma(\cdot)$, $i \neq j$, $i, j = 1, \ldots, n$, where $\sigma : \overline{\mathbb{R}}_+ \to \overline{\mathbb{R}}_+$ is such that $\sigma(0) = 0$ and strictly increasing, (5.36) holds if and only if

$$\sum_{i=1}^{n} \left[\sum_{j=1, i\neq j}^{n} \sigma(x_j) \right]^2 \leq \sum_{i=1}^{n} \left[\sum_{j=1, i\neq j}^{n} \sigma(x_i) \right]^2, \quad x \in \mathbb{R}_+^n. \tag{5.37}$$

In this case, since

$$\begin{aligned} 0 \ &\geq \ (n-1) \sum_{i=1}^{n} \sigma^2(x_i) + (n-2) \sum_{i=1}^{n} \sum_{j=1, j\neq i}^{n} \sigma(x_i)\sigma(x_j) - (n-1)^2 \sum_{i=1}^{n} \sigma^2(x_i) \\ &= \ (n-2) \sum_{i=1}^{n} \sum_{j=1, j\neq i}^{n} (\sigma(x_i) - \sigma(x_j))^2, \end{aligned}$$

(5.37) holds, and hence, it follows from Theorem 5.3 that $x_i(t) - x_j(t) \to 0$ as $t \to \infty$, where $i \neq j$, $i, j = 1, \ldots, n$.

Next, we specialize Theorem 5.3 to nonlinear time-delay compartmental systems of the form

$$\dot{x}(t) = A\hat{\sigma}(x(t)) + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i} \hat{\sigma}(x(t - \tau_i)), \ x(\theta) = \eta(\theta), \ -\bar{\tau} \leq \theta \leq 0, \ t \geq 0, \tag{5.38}$$

where $\hat{\sigma} : \overline{\mathbb{R}}_+^n \to \overline{\mathbb{R}}_+^n$ is given by $\hat{\sigma}(x) = [\sigma(x_1), \sigma(x_2), \ldots, \sigma(x_n)]^{\mathrm{T}}$, where $\sigma : \overline{\mathbb{R}}_+ \to \overline{\mathbb{R}}_+$ is such that $\sigma(u) = 0$ if and only if $u = 0$, and A and $A_{\mathrm{d}i}$, $i = 1, \ldots, n_{\mathrm{d}}$, are given by (5.3).

Theorem 5.4. Consider the nonlinear time-delay system given by (5.38) where $\sigma : \overline{\mathbb{R}}_+ \to \overline{\mathbb{R}}_+$ is such that $\sigma(0) = 0$ and $\sigma(\cdot)$ is strictly increasing. Assume that $(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})^{\mathrm{T}}\mathbf{e} = (A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i})\mathbf{e} = 0$ and $\mathrm{rank}(A + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}i}) = n - 1$. Then for every $\alpha \geq 0$, $\alpha\mathbf{e}$ is a semistable equilibrium point of (5.38). Furthermore, $x(t) \to \alpha^*\mathbf{e}$ as $t \to \infty$, where α^* satisfies

$$n\alpha^* + \sigma(\alpha^*) \sum_{i=1}^{n_{\mathrm{d}}} \tau_i \mathbf{e}^{\mathrm{T}} A_{\mathrm{d}i}\mathbf{e} = \mathbf{e}^{\mathrm{T}}\eta(0) + \sum_{i=1}^{n_{\mathrm{d}}} \int_{-\tau_i}^{0} \mathbf{e}^{\mathrm{T}} A_{\mathrm{d}i}\hat{\sigma}(\eta(\theta))\mathrm{d}\theta. \tag{5.39}$$

Proof. It follows from Lemma 5.1 that there exists Q_i, $i = 1, \ldots, n_{\mathrm{d}}$, such that (5.4) holds with Q_i given by (5.5). Now, since $A = -\sum_{i=1}^{n_{\mathrm{d}}} Q_i = -\sum_{i=1}^{n_{\mathrm{d}}} P_i^{\#} = -P^{-1}$, where $P = \sum_{i=1}^{n_{\mathrm{d}}} P_i$, it follows from (5.4) that, for all $x \in \overline{\mathbb{R}}_+^n$,

$$\begin{aligned} 0 \;&\geq\; 2\hat{\sigma}^{\mathrm{T}}(x)A\hat{\sigma}(x) + \hat{\sigma}^{\mathrm{T}}(x)\sum_{i=1}^{n_{\mathrm{d}}}(Q_i + A_{\mathrm{d}i}^{\mathrm{T}} Q_i^{\#} A_{\mathrm{d}i})\hat{\sigma}(x) \\ &=\; -f^{\mathrm{T}}(x)Pf(x) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}^{\mathrm{T}}(x)P_i f_{\mathrm{d}i}(x), \end{aligned}$$

where $f(x) = A\hat{\sigma}(x)$ and $f_{\mathrm{d}i}(x) = A_{\mathrm{d}i}\hat{\sigma}(x)$, $i = 1, \ldots, n_{\mathrm{d}}$, $x \in \overline{\mathbb{R}}_+^n$. Furthermore, since $P_i^{\#}P_i A_{\mathrm{d}i} = A_{\mathrm{d}i}$, $i = 1, \ldots, n_{\mathrm{d}}$, it follows that $P_i^{\#}P_i f_{\mathrm{d}i}(x) = f_{\mathrm{d}i}(x)$, $i = 1, \ldots, n_{\mathrm{d}}$, $x \in \overline{\mathbb{R}}_+^n$. Now, the result is an immediate consequence of Theorem 5.3 by noting that $\mathbf{e}^{\mathrm{T}}[f(x) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}(x)] = 0$ and $f(x) + \sum_{i=1}^{n_{\mathrm{d}}} f_{\mathrm{d}i}(x) = 0$ if and only if $x = \alpha\mathbf{e}$ for some $\alpha \geq 0$. □

5.5. The Consensus Problem in Dynamical Networks

In this section, we apply the results of Sections 3 and 4 to the consensus problem in dynamical networks [57,58,60,111,115]. The consensus problem appears frequently in coordination of multiagent systems and involves finding a dynamic algorithm that a enables a group of agents in a network to agree upon certain quantities of interest with directed information flow subject to possible link failures and time-delays. As in [60], we use directed graphs to represent a dynamical network and present solutions to the consensus problem for networks with *balanced* graph *topologies* (or information flow) [60] and unknown arbitrary time-delays. Specifically, let $\mathcal{G} = (\mathcal{V}, \mathcal{E}, \mathcal{A})$ be a weighted *directed graph* (or digraph) denoting the dynamical network (or dynamic graph) with the set of *nodes* (or vertices) $\mathcal{V} = \{v_1, \ldots, v_n\}$ denoting the agents, the set of *edges* $\mathcal{E} \subseteq \mathcal{V} \times \mathcal{V}$ denoting the direction of information flow, and a weighted *adjacency* matrix $\mathcal{A} \in \mathbb{R}^{n \times n}$ such that $\mathcal{A}_{(i,j)} = a_{ij} > 0$, $i, j = 1, \ldots, n$, if $(v_j, v_i) \in \mathcal{E}$, and $a_{ij} = 0$ otherwise. The *in-degree* and *out-degree* of node v_i are, respectively, defined as $\deg_{\mathrm{in}}(v_i) \triangleq \sum_{j=1}^{n} a_{ji}$ and $\deg_{\mathrm{out}}(v_i) \triangleq \sum_{j=1}^{n} a_{ij}$. We say that the node v_i of a digraph $\mathcal{G}$ is *balanced* if and only if $\deg_{\mathrm{in}}(v_i) = \deg_{\mathrm{out}}(v_i)$, and a graph $\mathcal{G}$ is called *balanced* if and only if all of its nodes are balanced, that is, $\sum_{j=1}^{n} a_{ij} = \sum_{j=1}^{n} a_{ji}$, $i = 1, \ldots, n$. Furthermore, we denote the *value* of the node v_i, $i = 1, \ldots, n$, at time t by $x_i(t) \in \mathbb{R}$. The consensus problem involves the design of a dynamic algorithm that guarantees system state equipartition, that is, $x_i(t) - x_j(t) \to 0$ as $t \to \infty$, $i \neq j$, $i, j = 1, \ldots, n$.

The consensus problem is a dynamic graph involving the trajectories of the dynamical network characterized by the dynamical system

$$\dot{x}(t) = u(t), \quad x(0) = x_0, \quad t \geq 0, \tag{5.40}$$

where $x(t) \triangleq [x_1(t), \ldots, x_n(t)]^{\mathrm{T}}$ is the state of the network and $u(t) \triangleq [u_1(t), \ldots, u_m(t)]^{\mathrm{T}}$ is the input to the network with components $u_i(t)$ only depending on the states of the nodes v_i and its neighbors. Specifically, the consensus problem deals with the design of an input $u(t)$ such that $x(t)$ converges to $\alpha\mathbf{e}$ as $t \to \infty$, where $\alpha \in \mathbb{R}$. Due to the presence of directional constraints on information flow and system time-delays, $u_i(t)$ is constrained to the feedback form $u_i(t) = f_i(x_i(t), x_{j_1}(t - \tau_{ij_1}), \ldots, x_{j_{mi}}(t - \tau_{ij_{mi}}))$, where $\tau_{ij_k} > 0$, $j_k \in \mathcal{N}_i \triangleq \{j \in \{1, \ldots, n\} : (v_j, v_i) \in \mathcal{E}\}$, are unknown constant time-delays between nodes v_i and v_{j_k}. For notational convenience we additionally define the parameters $\tau_{ij} \triangleq 0$ if $(v_j, v_i) \notin \mathcal{E}$.

As an example, consider the dynamical network given in Figure 5.1 where $\mathcal{V} = \{v_1, v_2, v_3\}$, $\mathcal{E} = \{(v_1, v_2), (v_2, v_3), (v_1, v_3), (v_3, v_1)\}$, with adjacency matrix $\mathcal{A}$ such that a_{13}, a_{21}, a_{31}, and $a_{32} > 0$, and with the remaining elements being zeros. In this case, the input to the network is given by

$$\begin{aligned}
u_1(t) &= f_1(x_1(t), x_3(t-\tau_{13})), \\
u_2(t) &= f_2(x_2(t), x_1(t-\tau_{21})), \\
u_3(t) &= f_3(x_3(t), x_2(t-\tau_{32}), x_1(t-\tau_{31})),
\end{aligned}$$

so that for $i = 1, 2, 3$, $\dot{x}_i(t)$ is only dependent on the states (values) of the nodes that are accessible by node v_i and with τ_{ij} denoting the communication delay from node v_j to node v_i.

Next, we apply Theorem 5.2 and 5.4 to present linear and nonlinear solutions for the consensus problem. Specifically, first we choose

$$f_i(x(t)) = -\sum_{j=1, i\neq j}^{n} a_{ji}x_i(t) + \sum_{j=1, i\neq j}^{n} a_{ij}x_j(t-\tau_{ij}), \quad i = 1, \ldots, n, \tag{5.41}$$

so that the *closed-loop* system is given by

$$\dot{x}_i(t) = -\sum_{j=1, i\neq j}^{n} a_{ji}x_i(t) + \sum_{j=1, i\neq j}^{n} a_{ij}x_j(t-\tau_{ij}), \quad x_i(\theta) = \eta_i(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \tag{5.42}$$

for all $i = 1, \ldots, n$, or, equivalently,

$$\dot{x}(t) = Ax(t) + \sum_{i=1}^{n_{\mathrm{d}}} A_{\mathrm{d}l}x(t-\tau_i), \qquad x(\theta) = \eta(\theta), \quad -\bar{\tau} \leq \theta \leq 0, \quad t \geq 0, \tag{5.43}$$

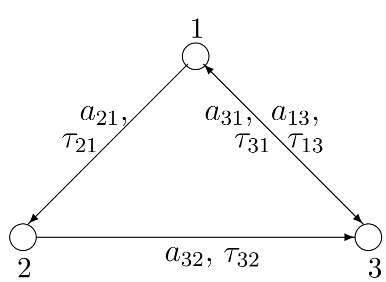


Figure 5.1: Dynamic Network

where $n_\mathrm{d} \triangleq n^2$, $A \in \mathbb{R}^{n\times n}$, and $A_{\mathrm{d}l} \in \mathbb{R}^{n\times n}$, $l = 1,\ldots,n_\mathrm{d}$, with

$$A = \operatorname{diag}\left[-\sum_{j=2}^{n} a_{j1},\ldots,-\sum_{j=1}^{n-1} a_{jn}\right], \tag{5.44}$$

$A_{\mathrm{d}((i-1)n+j)} = a_{ij}\mathbf{e}_i\mathbf{e}_j^\mathrm{T}$, and $\tau_{((i-1)n+j)} = \tau_{ij}$, $i,j = 1,\ldots,n$. Note that if (v_j, v_i) is not in $\mathcal{E}$, then $A_{\mathrm{d}((i-1)n+j)} = 0$, which implies that the algorithm is consistent with the directional constraints.

Furthermore, it can be easily shown that $(A + A_\mathrm{d})^\mathrm{T}\mathbf{e} = 0$, where $A_\mathrm{d} \triangleq \sum_{l=1}^{n_\mathrm{d}} A_{\mathrm{d}i}$, and $\operatorname{rank}(A + A_\mathrm{d}) = n - 1$ if and only if for every pair of nodes $v_i, v_j \in \mathcal{V}$ there exists a *path* from node v_i to node v_j [116]. Here, we assume that the adjacency matrix $\mathcal{A}$ is chosen such that $(A + A_\mathrm{d})\mathbf{e} = 0$ so that the linear time-delay closed-loop dynamical system (5.43) satisfies all the conditions of Theorem 5.2. Hence, it follows from Theorem 5.2 that the dynamical network given by (5.43) solves the consensus problem, that is, $\lim_{t\to\infty} x_i(t) = x_j(t) = \alpha^*$, $i,j = 1,\ldots,n$, $i \neq j$, where α^* is given by (5.7). Alternatively, it follows from Theorem 5.4 that the nonlinear dynamical network given by

$$\dot{x}(t) = A\hat{\sigma}(x(t)) + \sum_{i=1}^{n_\mathrm{d}} A_{\mathrm{d}i}\hat{\sigma}(x(t-\tau_i)), \quad x(\theta) = \eta(\theta), \quad -\bar{\tau} \le \theta \le 0, \quad t \ge 0, \tag{5.45}$$

also solves the nonlinear consensus problem where $\sigma(\cdot)$ and $\hat{\sigma}(\cdot)$ satisfy the conditions in Theorem 5.4. In this case, $\lim_{t\to\infty} x_i(t) = x_j(t) = \alpha^*$, $i,j = 1,\ldots,n$, $i \neq j$, where α^* is a solution to (5.39). Note that if $\sigma(\theta) = \theta$, (5.45) specializes to (5.43). Although both (5.43) and (5.45) solve the same network consensus problem, the nonlinear function $\sigma(\cdot)$ within $\hat{\sigma}(\cdot)$ may be used to enhance the performance of the dynamic algorithm or satisfy other constraints. For example, choosing $\sigma(\theta) = \tanh(\theta)$ we can constrain bandwidth information from one agent to another.

To illustrate the two algorithms given by (5.43) and (5.45) consider the dynamical network given by the graph shown in Figure 5.2 [60] where a_{ij} and τ_{ij} denote the weight and the time-delay for each edge shown. Here, we choose $a_{(i,j)} = 1$ if $(v_i, v_j) \in \mathcal{E}$ so that $(A + A_\mathrm{d})\mathbf{e} = 0$. In addition, it can be easily shown that $\operatorname{rank}(A + A_\mathrm{d}) = n - 1 =$

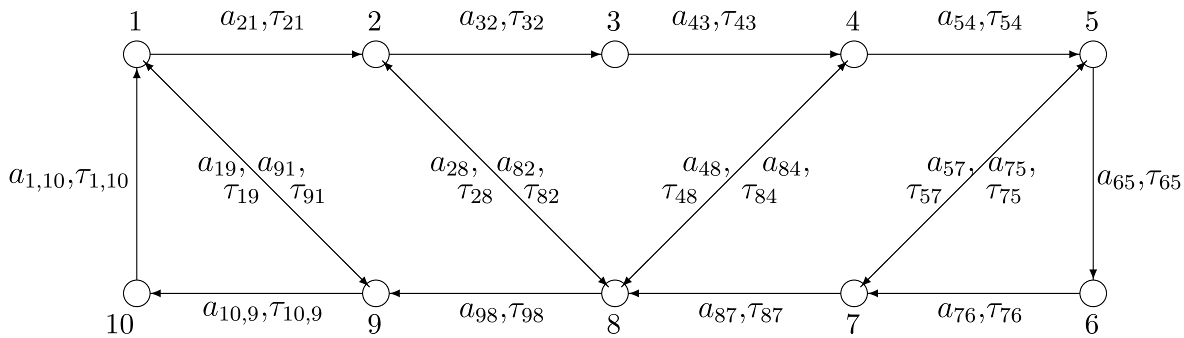


Figure 5.2: Balanced Dynamic Network

9. With $x_0 = [1\ 2\ 3\ 4\ 5\ 6\ 7\ 8\ 9\ 10]^{\mathrm{T}}$, Figures 5.3 and 5.4 demonstrate the agreement between all nodes for the algorithms given by (5.43) and (5.45), respectively, with $\sigma(\theta) = \tanh(\theta)$ in (5.45). Finally, Figures 5.5 and 5.6 show the control input versus time for both linear and nonlinear consensus algorithms. Note that the maximum amplitude of the linear consensus algorithm is about six times that of the nonlinear consensus algorithm and, as expected, the settling time of the nonlinear algorithm is longer than that of the linear algorithm.

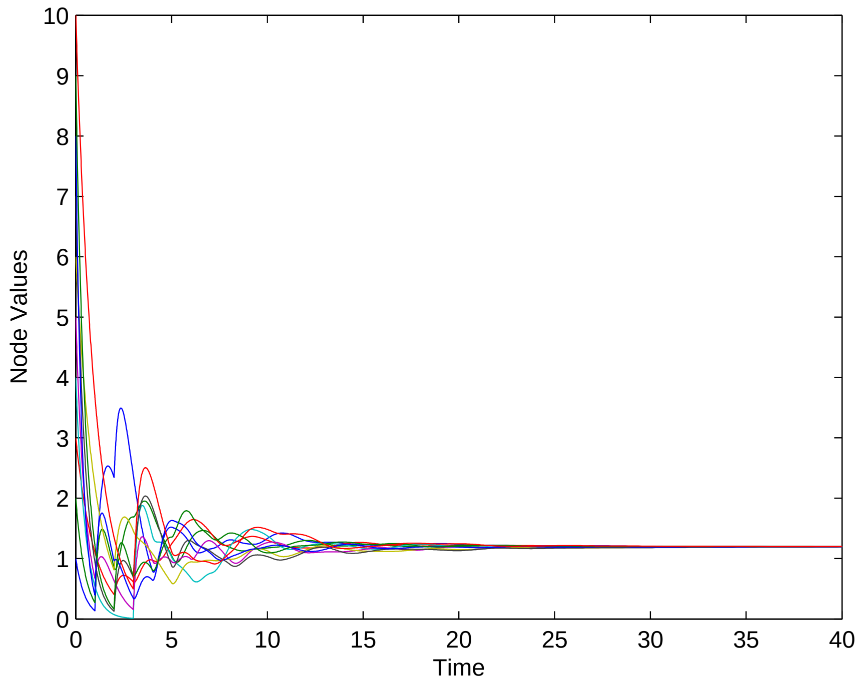


Figure 5.3: Linear Consensus Algorithm

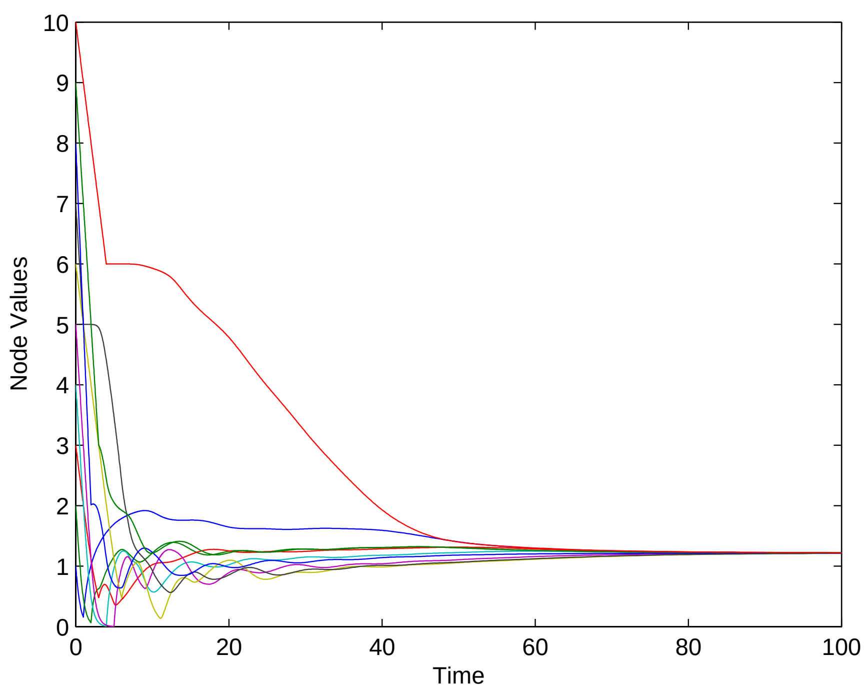


Figure 5.4: Nonlinear Consensus Algorithm

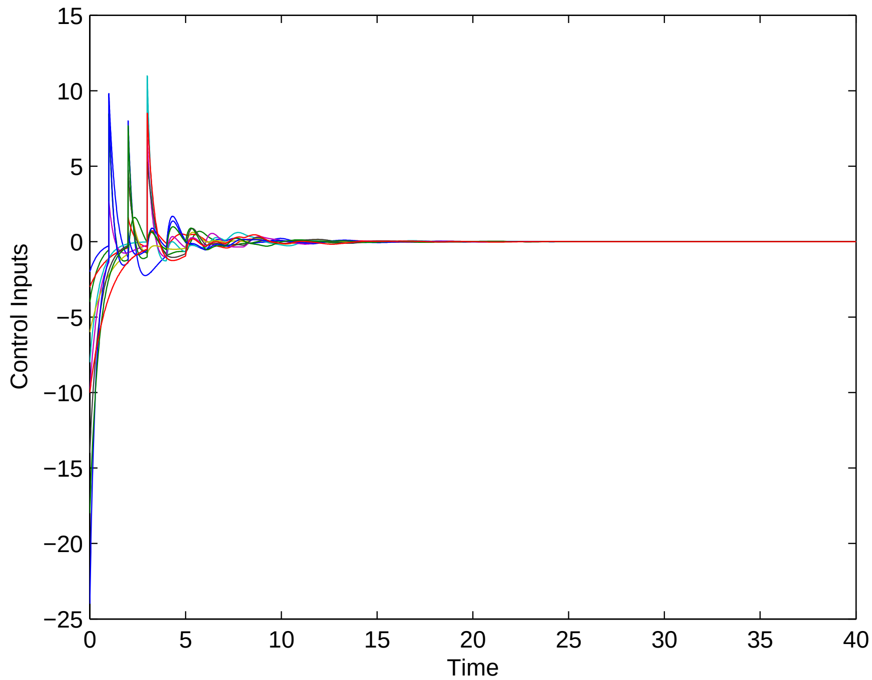


Figure 5.5: Control Inputs for Linear Consensus Algorithm

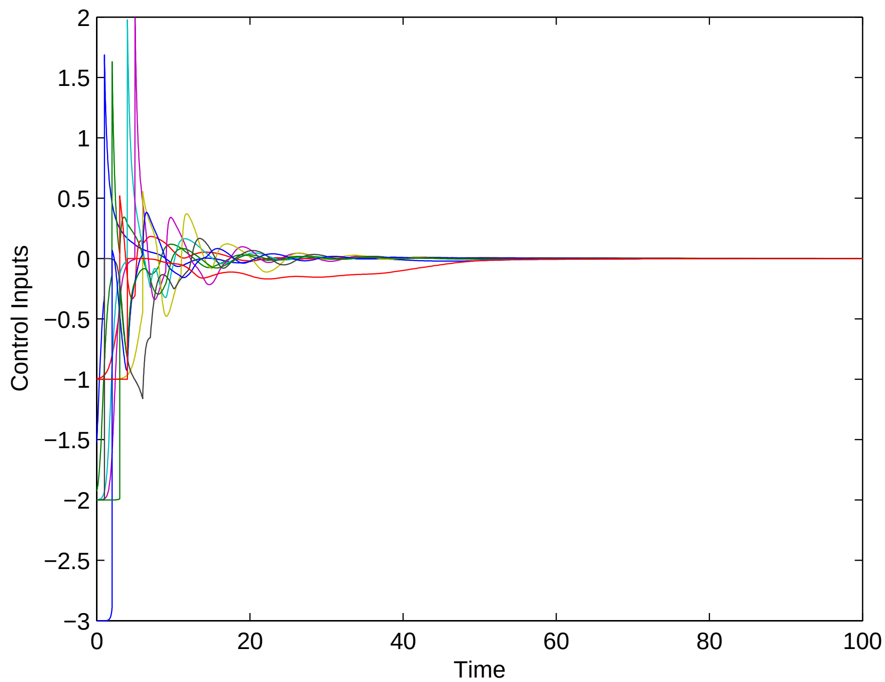


Figure 5.6: Control Inputs for Nonlinear Consensus Algorithm

Chapter 6

Conclusions

6.1. Concluding Remarks

The focus of this dissertation was to address several issues in the field of nonnegative systems with specific applications to biological systems and network systems.

In Chapter 2, necessary and sufficient conditions were given under which linear and nonlinear nonnegative and compartmental dynamical systems are guaranteed to possess monotonic solutions. Furthermore, sufficient conditions that guarantee the absence of limit cycles in nonlinear compartmental systems were also provided. Necessary and sufficient conditions were given under which linear and nonlinear discrete-time nonnegative and compartmental systems are guaranteed to possess monotonic solutions. The results presented in this chapter can be used to develop refined pharmacokinetic models that match experimental data thereby fostering the understanding of system wide effects of pharmacological agents.

Chapter 3 is an extension of Chapter 2 but here we have considered a more realistic situation in which there is a delay present in the transfers between the compartments. We have presented necessary and sufficient conditions for both continuous and discrete-time nonnegative dynamical systems with multiple time-delays.

We developed a direct adaptive control framework in Chapter 4 for linear uncertain nonnegative and compartmental dynamical systems with unknown time delay. In particular, a Lyapunov-Krasovskii based direct adaptive control framework for guaranteeing set-point regulation for nonnegative and compartmental time-delay systems with specific applications to mammillary pharmacokinetic models was developed. Finally, we demonstrated the framework on a drug delivery pharmacokinetic/pharmacodynamic model with time delay. The adaptive control law we developed does not require the explicit knowledge of the system matrices A, $A_{\rm d}$ and B, the gain matrix K_g, and the nonnegative constant vector $u_{\rm e}$. The control input signal $u(t)$ can be negative but the closed-loop plant input states remain nonnegative. We have also developed an adaptive controller which admits only nonnegative inputs to the system and also guarantees nonnegativity of the system.

In Chapter 5 we presented sufficient conditions for semistability and equipartition of energy in linear compartmental systems with time-delay. This result provides an extension of existing work on linear compartmental dynamical systems in the absence of time-delay. Next, we extend this result to two-dimensional nonlinear compartmental dynamical systems with time-delay. Our results extend the results in the literature on consensus protocols for linear balanced networks to linear and nonlinear unbalanced networks with time-delays. Finally, we presented an open problem involving semistabilty of higher dimensional nonlinear compartmental systems with time-delay.

Majority of the research in this area assumes that the evolution of each agent can be represented well enough by its kinematics, that is, by the single integrator dynamics [60,117–119]. But in many applications it is not directly possible to control the velocities and only the acceleration of the agents can be controlled through the inertia of the agents. Neglecting the inertial behaviors could cause unstable behaviors [120].

A future extension of our existing consensus protocols is to solve the consensus problem for multiagent systems by incorporating the inertial effects (that is, double integrator dynamics) in the presence of time-delays.

In the following sections we present some preliminary results that we have for solving the consensus problem for a network of dynamic agents with second-order dynamics. We first solve the consensus problem for the multiagent system with no delay. We then present the effects of delay on the system and also present a delay-independent condition that guarantees consensus of the agents.

6.2. Consensus of Multiagent Systems with Second-Order Dynamics

In this section, we consider the multiagent system with no delay present in the system. We show that the agents of system always arrive at a consensus. Consider a multiagent system $\mathcal{G}$ of the form:

$$\ddot{x}(t) = u(t), \tag{6.1}$$

where $x(t) \in \mathbb{R}^n$ and n is the number of agents in the system. Our objective is to design a consensus protocol $u(t)$ which will cause the agents to arrive at a consensus.

The simplest second-order system we can think of is a spring-mass-damper system. Hence, we propose a consensus protocol of the form

$$u(t) = -M^{-1}C\dot{x}(t) - M^{-1}Kx(t), \tag{6.2}$$

where $M, C, K \in \mathbb{R}^{n\times n}$ represent the mass, damping and stiffness parameters of the system respectively. Assume that M and C are diagonal matrices and $M > 0$, $C > 0$, $K \geq 0$. The structure of K is constrained by the information flow graph and hence $K \geq 0$. Also assume that $K\mathrm{e} = 0$ and rank $K = n - 1$.

We represent the system (6.1) in the state-space form for further analysis. Define $y(t) = [x(t)\ \dot{x}(t)]^{\mathrm{T}}$, then (6.1) is equivalent to

$$\dot{y}(t) = Ay(t), \quad y(0) = y_0, \quad t \geq 0, \tag{6.3}$$

where $A \triangleq \begin{bmatrix} 0 & I \\ -M^{-1}K & -M^{-1}C \end{bmatrix}$

The following lemma is needed for the main result of this chapter. This lemma provides a necessary and sufficient condition for the stability of (6.1).

Lemma 6.1 [121]. Consider the multiagent systems described by (6.1). Suppose $K \geq 0$. Then A is Lyapunov stable if and only if

$$\operatorname{rank}\begin{bmatrix} K \\ C \end{bmatrix} = n.$$

Remark 6.1. Note that the above lemma holds true even without the assumptions $C > 0$, $K \geq 0$ and $K\mathrm{e} = 0$.

The following theorem establishes semistability of $\mathcal{G}$, and shows that the agents of the system arrive at a consensus and the velocity of the agents decreases to zero.

Theorem 6.1. Consider the multiagent system given by (6.1), where $C > 0$, $K \geq 0$, $K\mathrm{e} = 0$ and rank $K = n - 1$. Then, $x(t) \to \alpha^*\mathrm{e}$ as $t \to \infty$, $\alpha^* \in \mathbb{R}$ and $\dot{x}(t) \to 0$ as $t \to \infty$.

Proof. It follows from Lemma 6.1 that since $C > 0$ and $\operatorname{rank}\begin{bmatrix} K \\ C \end{bmatrix} = n$, A is Lyapunov stable and hence the solutions to (6.3) or equivalently, (6.1) are bounded.

Next, consider the energy function

$$V(x(t), \dot{x}(t)) = \frac{1}{2}x^{\mathrm{T}}(t)Kx(t) + \frac{1}{2}\dot{x}^{\mathrm{T}}(t)M\dot{x}(t).$$

Then the time-derivative of $V(x(t), \dot{x}(t))$ is given by

$$\begin{aligned} \dot{V}(x(t), \dot{x}(t)) &= \dot{x}^{\mathrm{T}}(t)Kx(t) + \dot{x}^{\mathrm{T}}M\ddot{x}(t) \\ &= -\dot{x}^{\mathrm{T}}(t)C\dot{x}(t) \\ &\leq 0, \quad t \geq 0. \end{aligned} \tag{6.4}$$

Next, let $\mathcal{R} \triangleq \{(x, \dot{x}) \in \mathbb{R}^n \times \mathbb{R}^n : \dot{V}(x, \dot{x}) = 0\}$. It follows from (6.4), from the fact that $V(\alpha\mathrm{e}, 0) = 0$, and rank $K = n - 1$, that $\mathcal{M}$ is the largest invariant set contained in $\mathcal{R}$, where $\mathcal{M} = \{(x, \dot{x}) \in \mathbb{R}^n \times \mathbb{R}^n : x = \alpha\mathrm{e}, \dot{x} = 0\}$. Hence, it follows from the LaSalle invariant set theorem [37] that $(x(t), \dot{x}(t)) \to \mathcal{M}$ as $t \to \infty$. $\square$

Now that we have proved the consensus of a multiagent system, we apply Theorem 6.1 to a balanced multiagent system. Consider a balanced multiagent system where the dynamics of each agent i can be described as

$$\ddot{x}_i(t) = u_i(t) \tag{6.5}$$

where u_i is the consensus protocol for each agent i. Using (6.2) the consensus protocol can be described as

$$u_i(t) = -\frac{c_i}{m_i}\dot{x}_i(t) - \frac{1}{m_i}\sum_{j\in\mathcal{N}_i} k_{ij}(x_i(t) - x_j(t)) \tag{6.6}$$

where $i, j = 1, \ldots, n$ and $\mathcal{N}_i$ is the set of neighboring agents of the agent i. The values of k_{ij} are constrained by the information flow between the agents i and j.

The closed-loop group dynamics can be written as

$$M\ddot{x}(t) + C\dot{x}(t) + Kx(t) = 0$$

where

$$M = \mathrm{diag}[m_1,\ m_2, \ldots, m_n],$$

$$C = \mathrm{diag}[c_1,\ c_2, \ldots, c_n]$$

$$K_{(i,j)} = \begin{cases} -\sum_{i,j=1,i\neq j}^{n} k_{ij} & i = j \\ k_{ij} & i \neq j \end{cases}$$

Note that, $C > 0$, $K\mathrm{e} = 0$ and $K \geq 0$. Therefore, all conditions of Theorem 6.1 are satisfied and hence we have consensus of the agents.

6.3. Consensus of Multiagent Systems with Time-Delay

Next, we consider the time-delays present in the system in the information transfers between the agents in order to develop a more realistic model. In this section, we consider a time-delay multiagent system model and investigate the conditions for the agents to arrive at a consensus.

Consider the multigent time-delay system $\mathcal{G}$ of the form

$$\ddot{x}(t) = u(t) \tag{6.7}$$

We introduce a delay in the transfer of information from one agent to another. We propose a protocol of the form

$$u(t) = -M^{-1}C\dot{x}(t) - M^{-1}K_{\mathrm{d}}x(t) - M^{-1}K_{\mathrm{od}}x(t-\tau) \tag{6.8}$$

Note that the position matrix K now consists of two components, the no delay component denoted by K_{d} and the delayed component denoted by K_{od}. Also note that $K = K_{\mathrm{d}} + K_{\mathrm{od}}$ with $K\mathrm{e} = 0$. Then, (6.7) can be represented in the state space form as

$$\dot{x}(t) = Ax(t) + A_{\mathrm{d}}x(t-\tau),\ x(\theta) = \eta(\theta),\ -\tau \leq \theta \leq 0,\ t \geq 0,$$

where $A = \begin{bmatrix} 0 & I \\ -K_{\mathrm{d}} & -C \end{bmatrix}$ and $A_{\mathrm{d}} = \begin{bmatrix} 0 & 0 \\ -K_{\mathrm{od}} & 0 \end{bmatrix}$.

To demonstrate clearly, the effect of delay on the consensus problem, we present the example of a two-agent system. We show that even though for a particular value of τ, the agents arrive at a consensus, when we change τ, keeping all other parameters of the system constant, the agents may or may not arrive at a consensus.

The K and C matrices for a two-agent system have the form

$$K_{\mathrm{d}} = \begin{bmatrix} k & 0 \\ 0 & k \end{bmatrix},\ K_{\mathrm{od}} = \begin{bmatrix} 0 & -k \\ -k & 0 \end{bmatrix},\ C = \begin{bmatrix} c & -c \\ -c & c \end{bmatrix}.$$

For our simulation we chose $k = 0.1338$, $c = 0.2071$ with $\tau = 1$ for random initial conditions. Figure 6.1 below show the consensus of the agents and Figure 6.2 shows the convergence of the velocity of the agents to zero.

Keeping the values of k and c the same, we changed the delay values of the system to $\tau = 2$. Figure 6.3 shows that both the agents do not converge to the same point and Figure 6.4 shows that the velocity of the agents does not converge to zero. Thus, we cannot conclude that the system (6.7) is stable for all delays.

Having seen from the simulations we can conclude that the consensus of the agents are delay-dependent. Since, it is difficult to obtain delay-dependent conditions we impose additional conditions on our system, so that we can obtain a sufficient delay independent condition for the consensus of the agents of our system.

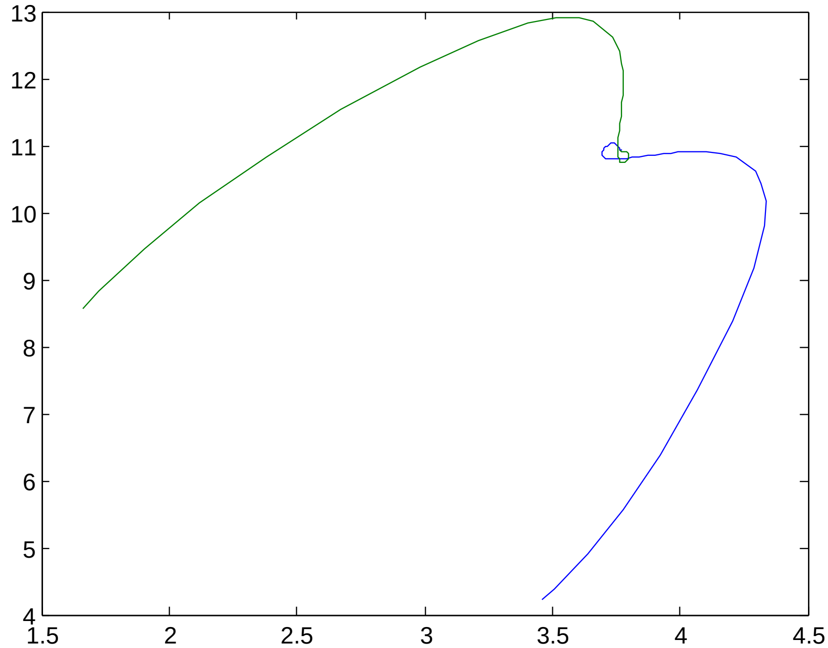


Figure 6.1: Positions of the Agents with $\tau = 1$

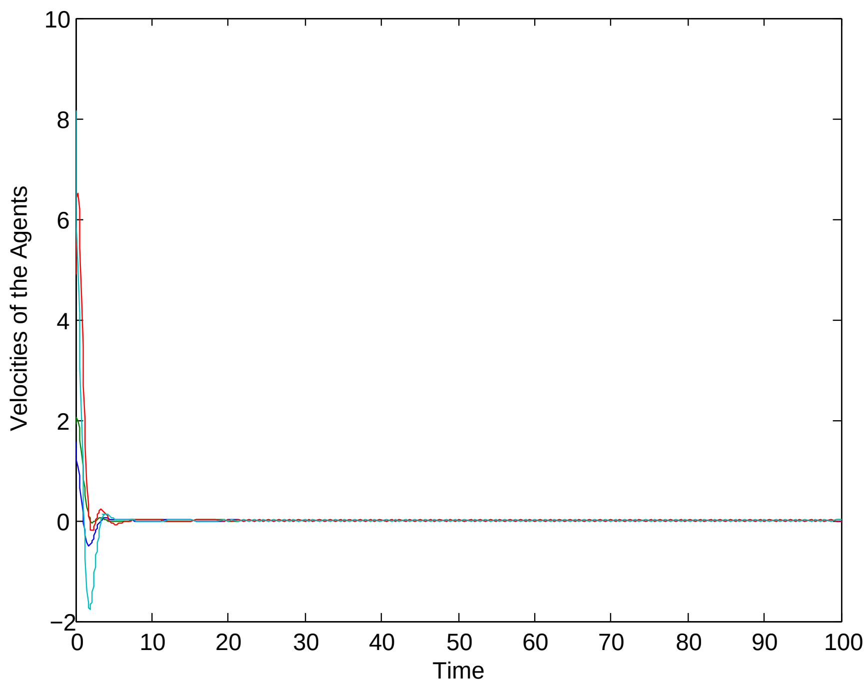


Figure 6.2: Velocities of the Agents with $\tau = 1$

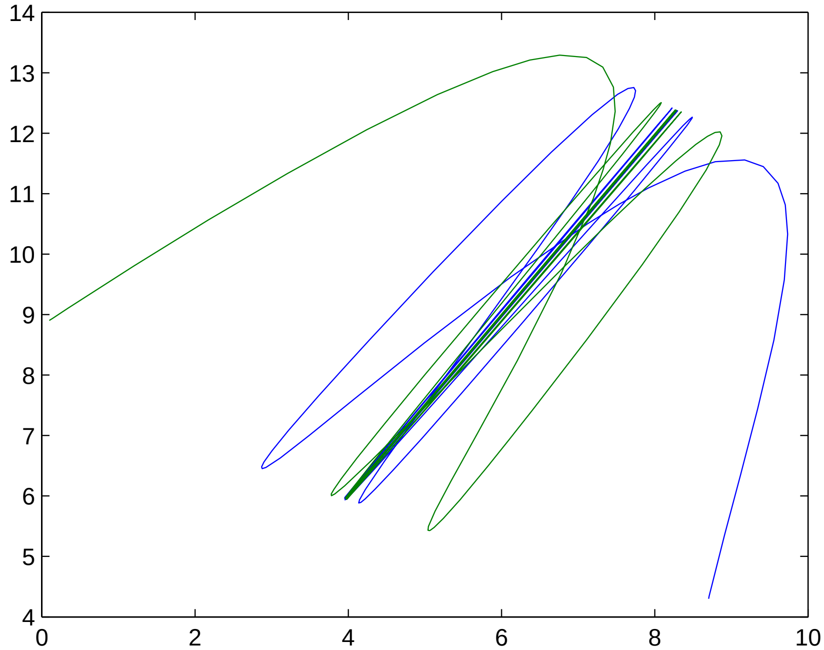


Figure 6.3: Positions of the Agents with $\tau = 2$

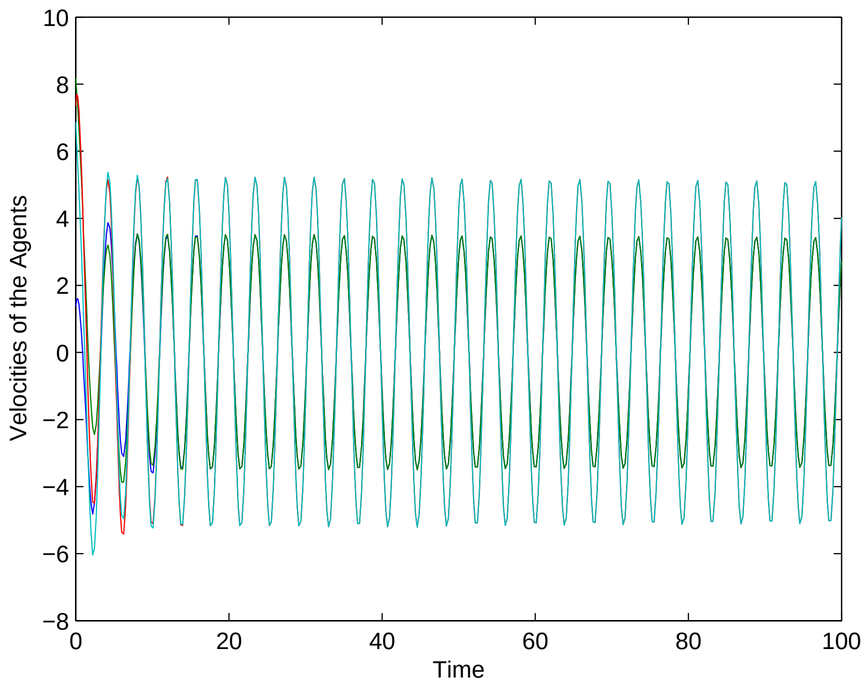


Figure 6.4: Velocities of the Agents with $\tau = 2$

Consider the multiagent system $\mathcal{G}_i$ with agent i having dynamics of the form:

$$\dot{x}_i(t) = A_i x_i(t) + B_i u_i(t) \tag{6.9}$$

$$y_i(t) = C_i x_i(t) \tag{6.10}$$

where $i = 1, \ldots, n$ and n is the number of agents in the system. Each agent i can be represented as shown in Figure 6.5 where $G_i \sim \left[\begin{array}{c|c} A_i & B_i \\ \hline C_i & 0 \end{array}\right]$ and the input to each agent i is given by $u_i(t) = \sum_{j\in\mathcal{N}_i} y_j(t-\tau_j)$ where τ_j is the time-delay for the information transfer from agent j to agent i.

We assume that for each agent i there exists $P_i \geq 0$ such that

$$\begin{bmatrix} A_i^{\mathrm{T}} P_i + P_i A_i + C_i^{\mathrm{T}} C_i & P_i B_i \\ B_i^{\mathrm{T}} P_i & -1 \end{bmatrix} \leq 0 \tag{6.11}$$

$$C_i A_i^{-1} B_i = -1. \tag{6.12}$$

where A_i is Hurwitz. Note that (6.11) implies $u_i^{\mathrm{T}} u_i - y_i^{\mathrm{T}} y_i \geq 0$, $t \geq 0$ where

$$u_i(t) = \sum_{j\in\mathcal{N}_i} w_{ij} y_j(t-\tau_j), \quad i, j = 1, \ldots, n \tag{6.13}$$

where $w_{(ij)} > 0$ is a weight assigned to each edge between the agent i and agent j and $\sum_{i=1, i\neq j}^{n} w_{ij} = 1$.

Then, the following theorem proves the consensus of the multiagent system.

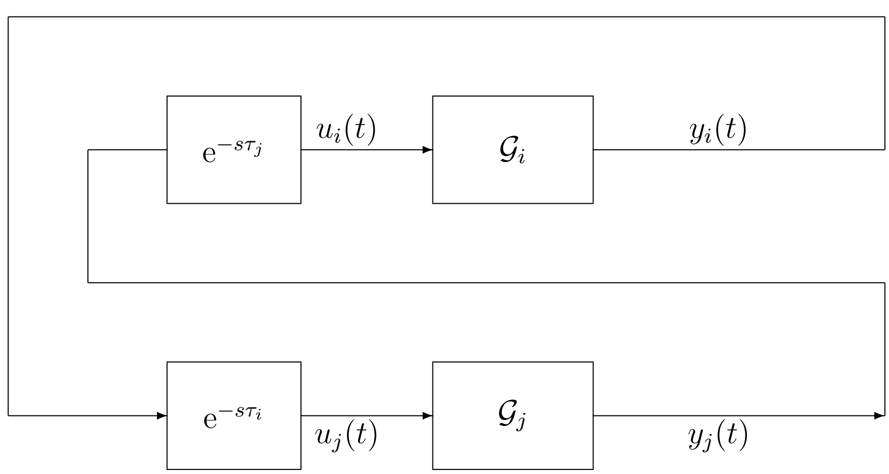


Figure 6.5: System Representation of Agent i

Theorem 6.2. Consider the multiagent system described by (6.9) and (6.10) satisfying conditions stated by (6.11) and (6.12). Then all the agents arrive at a consensus, that is, $y \to \alpha^* \mathrm{e}$, $\alpha^* \in \mathbb{R}$ and $y = [y_1, \ldots, y_n]^{\mathrm{T}}$.

Proof. The theorem can be proved by using the Lyapunov-Krasovskii function

$$V(x_i(t), y_i(t)) = \sum_{i=1}^{n} x_i^{\mathrm{T}}(t) P_i x_i(t) + \sum_{i=1}^{n} \int_{t-\tau_j}^{t} y_i^{\mathrm{T}}(t) y_i(t) \mathrm{d}t.$$

Consensus of the agents can be shown by using the LaSalle invariant set theorem. □

Consider the example of a two agent system of the form

$$\begin{aligned} \dot{x}_1(t) &= A_1 x_1(t) + B_1 u_1(t), \\ y_1(t) &= C_1 x_1(t), \end{aligned} \tag{6.14}$$

$$\begin{aligned} \dot{x}_2(t) &= A_2 x_2(t) + B_2 u_2(t), \\ y_2(t) &= C_2 x_2(t), \end{aligned} \tag{6.15}$$

where A_i, B_i and C_i are of the form

$$A_i = \begin{bmatrix} 0 & 1 \\ -\frac{k_i}{m_i} & -\frac{c_i}{m_i} \end{bmatrix}, \; B_i = \begin{bmatrix} 0 \\ -\frac{1}{m_i} \end{bmatrix}, \; C_i = \begin{bmatrix} k_i & 0 \end{bmatrix}, \; i = 1, 2. \tag{6.16}$$

It can be easily seen that the condition (6.12) is satisfied and the (6.11) can be satisfied by imposing the following condition on c_i, m_i and k_i, $\sqrt{2m_i k_i} < c_i$ ([122] See Corollary 12.3).

For our simulations we picked a random value of τ and picked values of k_i, c_i and m_i such that all conditions of Theorem 6.2 are satisfied. Figure 6.6 shows the consensus achieved by the two agents and Figure 6.7 shows that the velocities of the agents tend to zero.

Remark 6.2. The result presented by Theorem (6.1) shows the consensus of the agents at all times when the conditions on K and C are satisfied. But for the time-delay system given by (6.7), the consensus of the agents depends on the delay in

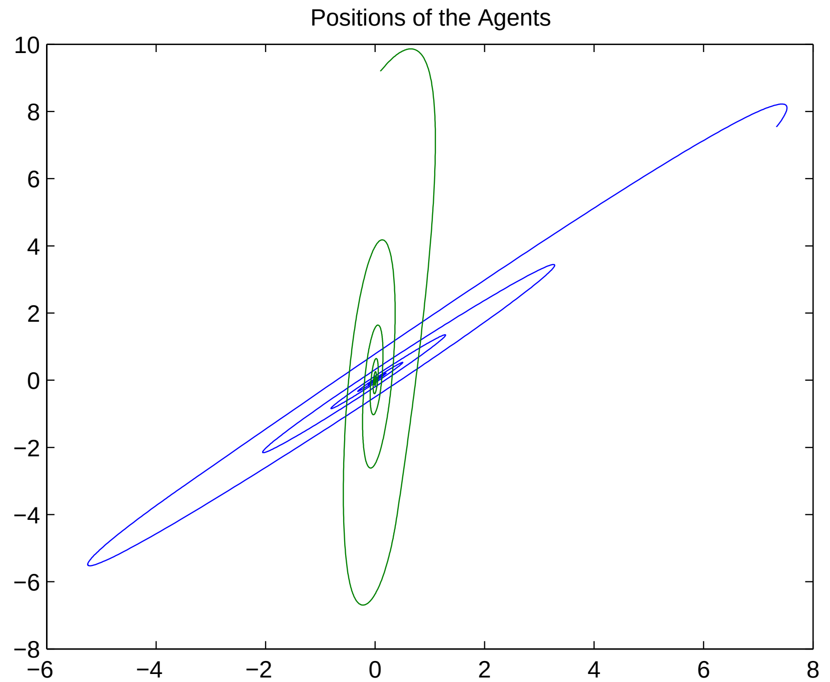


Figure 6.6: Positions of the Agents in a Two-Agent System

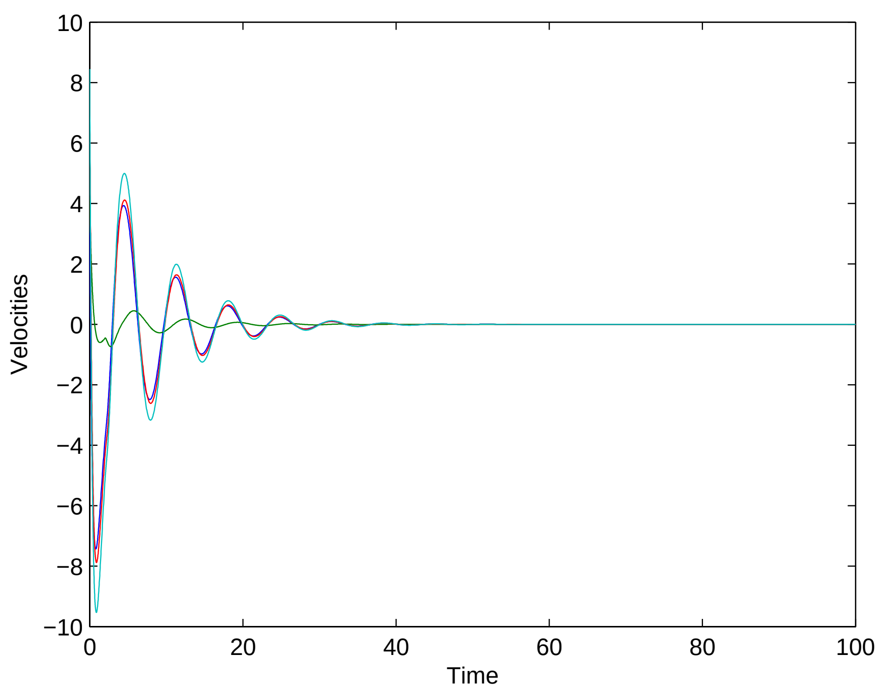


Figure 6.7: Velocities of the Agents in a Two-Agent System

the system. Hence, we need some additional conditions on the system to obtain an delay-independent result. This result is presented in Theorem 6.2.

The time-domain conditions (6.11) and (6.12) on $\mathcal{G}_i$ is equivalent to

$$\mid \mathcal{G}_i(j\omega) \mid \leq 1,\ \mathcal{G}_i(0) = -1,$$

where $\mathcal{G}_i(s),\ i = 1, \ldots, n$ is stable. These conditions are presented in [123]. The importance of a time-domain result is that the result can be extended to nonlinear systems. Note that the order of the multiagent system is not important.

The time-domain results we have can be applied to very general systems but the results are restrictive as they can be applied to only systems which satisfy (6.11) and (6.12). Thus, though the results are restrictive it is possible to develop consensus protocols for multiagent systems with nonlinear dynamics.

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