

Chapter One

Introduction

With the ever-increasing influence of mathematical modeling and engineering on biological, social, and medical sciences, it is not surprising that dynamical system theory has played a central role in the understanding of many biological, ecological, and physiological processes [155, 171, 172, 235]. With this confluence it has rapidly become apparent that mathematical modeling and dynamical system theory are the key threads that tie together these diverse disciplines. The dynamical models of many biological, pharmacological, and physiological processes such as pharmacokinetics [19, 287], metabolic systems [50], epidemic dynamics [155, 157], biochemical reactions [57, 171], endocrine systems [50], and lipoprotein kinetics [171] are derived from mass and energy balance considerations that involve dynamic states whose values are nonnegative. Hence, it follows from physical considerations that the state trajectory of such systems remains in the nonnegative orthant of the state space for nonnegative initial conditions. Such systems are commonly referred to as *nonnegative dynamical systems*¹ in the literature [79, 164, 166, 233].

A subclass of nonnegative dynamical systems are *compartmental systems* [4, 5, 29, 43, 88, 100, 134, 152, 155–158, 162, 165, 188, 198, 208, 209, 211, 219, 220, 232, 252, 258, 259, 300]. Compartmental systems involve dynamical models that are characterized by conservation laws (e.g., mass, energy, fluid, etc.) 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. The range of applications of nonnegative systems and compartmental systems is not limited to biological, social, and medical systems. Their usage includes chemical reaction systems [25, 60, 82, 187, 298], queuing systems [301], large-scale systems [274, 275], stochastic systems (whose state variables

¹Some authors erroneously refer to nonnegative dynamical systems as *positive systems*. However, since the state of a nonnegative system can evolve in the nonnegative (closed) orthant of the state space, which is a *proper cone* (i.e., a closed, convex, solid, and pointed cone), and is not necessarily constrained to the positive (open) orthant of the state space, *nonnegative dynamical systems* is the appropriate expression for the description of such systems.

represent probabilities) [301], ecological systems [38, 141, 181, 211, 231], economic systems [21], demographic systems [155], telecommunications systems [90], transportation systems, power systems, heat transfer systems, thermodynamic systems [116], and structural vibration systems [175–177], to cite but a few examples.

In economic systems the interaction of raw materials, finished goods, and financial resources can be modeled by compartments representing various interacting sectors in a dynamic economy. Similarly, network systems, computer networks, and telecommunications systems are all amenable to compartmental modeling with intercompartmental flow laws governed by nodal dynamics and rerouting strategies that can be controlled to minimize waiting times and optimize system throughput. Compartmental models can also be used to model the interconnecting components of power grid systems with energy flow between regional distribution points subject to control and possible failure. Road, rail, air, and space transport systems also give rise to compartmental systems with interconnections subject to failure and real-time modification.

Since the aforementioned dynamical systems have numerous input, state, and output properties related to conservation, dissipation, and transport of mass, energy, or information, nonnegative and compartmental models are conceptually simple yet remarkably effective in describing the essential phenomenological features of these dynamical systems. Furthermore, since such systems are governed by conservation laws and are comprised of homogeneous compartments which exchange variable nonnegative quantities of material via intercompartmental flow laws, these systems are completely analogous to network thermodynamic (advection-diffusion) systems with compartmental masses, energies, or information playing the role of heat and temperatures.

The goal of the present monograph is directed toward developing a general stability² analysis and control design framework for nonlinear nonnegative and compartmental dynamical systems. However, as in general nonlinear systems, nonlinear nonnegative dynamical systems can exhibit a very rich dynamical behavior, such as multiple equilibria, limit cycles, bifurcations, jump resonance phenomena, and chaos, which can make general nonlinear nonnegative system analysis and control notoriously difficult. In addition, since nonnegative and compartmental dynamical systems have specialized structures, nonlinear nonnegative system stabilization has received very little attention in the literature and remains

²Unlike standard stability theory, stability notions for nonnegative dynamical systems need to be defined with respect to *relatively open* subsets of the nonnegative orthant of the state space containing the system equilibrium point. See Definition 2.3.

relatively undeveloped. For example, biological and physiological systems typically possess a multiechelon hierarchical hybrid structure characterized by continuous-time dynamics at the lower levels of the hierarchy and discrete-time dynamics (logical decision-making units) at the higher levels of the hierarchy. This is evident in all living systems wherein control structures and hierarchies are present at the intracellular level, the intercellular level, the organs, and the organ system and organism level. Furthermore, biological and physiological systems are self-regulating systems, and hence, they additionally involve feedback (nested or interconnected) subsystems within their hierarchical structures. Finally, the complexity of biological and physiological system modeling and control is further exacerbated when addressing system modeling uncertainty inherent to system biology and physiology.

Another complicating factor in the stability analysis of many nonnegative and compartmental dynamical systems is that these systems possess a continuum of equilibria. Since every neighborhood of a nonisolated equilibrium contains another equilibrium, a nonisolated equilibrium cannot be asymptotically stable. Hence, asymptotic stability is not the appropriate notion of stability for systems having a continuum of equilibria. Two notions that are of particular relevance to such systems are *convergence* and *semistability*. Convergence is the property whereby every system solution converges to a limit point that may depend on the system initial condition. Semistability is the additional requirement that all solutions converge to limit points that are Lyapunov stable. Semistability for an equilibrium thus implies Lyapunov stability, and is implied by asymptotic stability.³ The dependence of the limiting state on the initial state is seen in numerous stable nonnegative systems and compartmental systems. For these systems, every trajectory that starts in a neighborhood of a Lyapunov stable equilibrium converges to a (possibly different) Lyapunov stable equilibrium, and hence, these systems are semistable.

The main objective of this monograph is to develop a general analysis and control design framework for nonnegative and compartmental dynamical systems. The main contents of the monograph are as follows. In Chapter 2, we establish notation and definitions, and develop stability theory for nonnegative and compartmental dynamical systems. Specifically, Lyapunov stability theorems as well as invariant set stability theorems are developed for linear and nonlinear, continuous-time and discrete-time nonnegative and compartmental dynamical systems. Chapter 3 provides an extension of the results of Chapter 2 to nonnegative and compartmental dynamical systems

³It is important to note that semistability is not merely equivalent to asymptotic stability of the set of equilibria. Indeed, it is possible for a trajectory to converge to the set of equilibria without converging to any one equilibrium point as examples in [34] show.

with time delay. Specifically, stability theorems for linear and nonlinear nonnegative and compartmental dynamical systems with time delay are established using Lyapunov-Krasovskii functionals.

Since nonlinear nonnegative and compartmental dynamical systems can exhibit a full range of nonlinear behavior, including bifurcations, limit cycles, and even chaos, in Chapter 4 we present necessary and sufficient conditions for identifying nonnegative and compartmental systems that admit only nonoscillatory and monotonic solutions. As a result, we provide sufficient conditions for the absence of limit cycles in nonlinear compartmental systems.

In Chapter 5, using generalized notions of system mass and energy storage, and external flux and energy supply, we present a systematic treatment of dissipativity theory for nonnegative and compartmental dynamical systems. Specifically, using linear and nonlinear storage functions with linear supply rates, we develop new notions of dissipativity theory for nonnegative dynamical systems. In addition, we develop new Kalman-Yakubovich-Popov equations for nonnegative systems for characterizing dissipativeness with linear and nonlinear storage functions and linear supply rates. Finally, these results are used to develop general stability criteria for feedback interconnections of nonnegative dynamical systems. In Chapter 6, we extend the results of Chapters 2 and 5 to develop stability and dissipativity results for impulsive nonnegative and compartmental dynamical systems.

Using the concepts developed in Chapters 2, 4, and 5, in Chapter 7 we use compartmental dynamical system theory to provide a system-theoretic foundation for thermodynamics. Specifically, using a state space formulation, we develop a nonlinear compartmental dynamical system model characterized by energy conservation laws that are consistent with basic thermodynamic principles. In addition, we establish the existence of a unique, continuously differentiable global entropy function for our compartmental thermodynamic model, and using Lyapunov stability theory we show that the proposed thermodynamic model has convergent trajectories to Lyapunov stable equilibria with a uniform energy distribution determined by the system initial energies. Finally, using the system entropy, we establish the absence of Poincaré recurrence for our thermodynamic model and develop a clear connection between irreversibility, the second law of thermodynamics, and the entropic arrow of time.

In Chapter 8, we merge the theories of semistability and finite-time stability [32, 35] to develop a rigorous framework for finite-time thermodynamics. Specifically, using a geometric description of homogeneity theory, we develop intercompartmental flow laws that guarantee finite-time

semistability and energy equipartition for the thermodynamically consistent model developed in Chapter 7. Next, in Chapter 9, we address the problem of nonnegativity, realizability, reducibility, and semistability of chemical reaction networks. Specifically, we show that mass-action kinetics have nonnegative solutions for initially nonnegative concentrations, we provide a general procedure for reducing the dimensionality of the kinetic equations, and we present stability results based upon Lyapunov methods.

In Chapter 10, we generalize the results of Chapter 7 to general compartmental systems that account for directional material flow between compartments as well as material in transit between compartments. Specifically, we develop compartmental models that guarantee semistability and state equipartitioning with directed and undirected thermal flow as well as flow delays between compartments. In Chapter 11, we consider robustness extensions of nonnegative dynamical systems; that is, sensitivity of system stability and state equipartitioning in the face of model uncertainty.

In Chapters 12–16, we develop a general control design framework for nonnegative and compartmental dynamical systems with application to clinical pharmacology. Specifically, pharmacokinetic and pharmacodynamic models for drug distribution are formulated, and suboptimal, optimal, and adaptive control strategies are developed to address the challenging problem of active control for intraoperative anesthesia. In particular, using a constrained fixed-structure control framework we develop optimal output feedback control laws for nonnegative and compartmental dynamical systems that guarantee that the trajectories of the closed-loop system remain in the nonnegative orthant of the state space for nonnegative initial conditions. Output feedback controllers for compartmental systems with nonnegative inputs are also given. In addition, we develop \mathcal{H}_2 (sub)optimal controllers for nonnegative dynamical systems using linear matrix inequalities. Finally, a Lyapunov-based direct adaptive control framework is developed for nonnegative systems that guarantees partial asymptotic stability of the closed-loop system, that is, asymptotic stability with respect to part of the closed-loop system states associated with the physiological state variables. The adaptive controllers are constructed without requiring knowledge of the system dynamics or the system disturbances while providing a nonnegative control (source) input for system stabilization.

In Chapter 17, we use compartmental dynamical system theory and Poincaré maps to model, analyze, and control the dynamics of a pressure-limited respirator and lung mechanics system. Chapter 18 develops a constrained optimization framework for nonnegative and compartmental system identification that guarantees asymptotic stability of the plant system dynamics as well as the nonnegativity of the system matrices.

The approach is based on a subspace identification method wherein the resulting constrained optimization problem is cast as a convex linear programming problem with mixed equality, inequality, quadratic, nonnegative, and nonnegative-definite constraints. Finally, we draw conclusions in Chapter 19.