MATHEMATICAL MODELING OF THE CIRCULATORY SYSTEM

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Summary

This chapter focuses on modeling the general features of circulatory system, emphasizing the interaction of various elements including hemodynamic properties, local and global control mechanisms, various circulatory subsystems, and other factors that unify the overall cardiovascular function into a complex interacting system. This chapter is a companion to the chapter on Hemodynamics and like that chapter, focuses on the human circulatory system though many features carry over to other systems. In this chapter we provide various examples of models at the system level and provide insight into how models of such systems can be validated with special emphasis given to the information provided by sensitivity analysis for carrying out efficient parameter estimation. An important sub-theme of this chapter is the presentation of heath problems related to the circulatory system which can be studied via modeling, clinical manifestations of these problems that represent important challenges to health care, and challenges to adapting models to study such problems in individual subjects.

1. Introduction

The subject of this chapter is the *Circulatory System* which is written to be a companion chapter to *Hemodynamics in human: Physiology and Mathematical Models.* The hemodynamics chapter focuses on physical determinants of blood flow including pressures, resistances, compliances, the pumping heart, and characteristics of blood, while the current chapter emphasizes systemic characteristics of overall circulatory system structure and function. This chapter includes discussion of control mechanisms that stabilize the system in response to challenges or perturbations of the system. This division of subject matter for the two chapters is clearly somewhat arbitrary due to the interrelationships between the various component elements of hemodynamics and the structure and function of the overall circulatory system that is built from these elements. In particular, heart function overlaps both topics and we will often use the phrase *cardiovascular system* interchangeably with *circulatory system.*

2. Circulatory System Organization and Physiology

In this section we review important elements of the circulatory and cardiovascular system (CVS). Important resources for further reading include J. R. Levick (2003), L. B. Rowell (1993), and A.C. Guyton and J.E. Hall (2006).

2.1. Principal Elements of the CVS System Structure and Function

The circulatory system together with the heart as a pump has as its primary purpose the distribution of nutrients and substrates needed for metabolism and the removal of unwanted by-products. The ultimate target for the transport system is the cell where exchange is carried out at the microvascular-intercellular fluid boundary. Transport to the cell is over a physical distance and hence the system of vessels must not only distribute blood effectively but efficiently so that the work of transport is not too expensive in terms of energy or time. This requires many specialized compromises

between cost and benefit and innovation in the design of the system. One example is the compromise in the number of red blood cells which raises not only oxygen carrying capacity but also viscosity and hence the work in transporting the red cells. Furthermore, if not for the efficiency of hemoglobin in loading oxygen, the number of red cells needed would create enormous problems in distribution.

2.2. Vascular Structure, Relation to Hemodynamics and Blood Flow, Interstitial Fluid and Lymph

The total circulatory system consists of two subcircuits as follows:

- The systemic circuit transports blood from the left ventricle through the systemic arteries to the tissues and returns blood via the systemic venous system to the right atrium of the heart.
- The pulmonary system represents a similar pathway from the right ventricle to the lungs, returning to the left atrium.
- The arterial components of each circuit are high pressure components since they receive blood pumped from a ventricle while the venous components are at low pressure since blood has already passed along pathways with an inherent resistance to flow.
- Starting at the main artery joining the ventricle, the vasculature branches many times, terminating in the capillaries whose walls are sufficiently thin to allow efficient exchange of nutrients and waste products with intercellular fluid in tissue and with alveoli in the lungs. The exchange is by passive diffusion alone, based on the balance of various pressure differences such as osmotic pressure.
- On the venous side of the systemic capillary network the blood is collected by small veins which in turn merge into larger veins finally returning systemic blood by the superior and inferior vena cava to the right atrium. Venous valves are needed to keep blood moving toward the heart given the low pressure. In fact the "muscle pump" is an important contributor in creating the venous return flow. In the pulmonary circuit blood is similarly collected and returned to the left atrium via four pulmonary veins.

The anatomy and organization of the vascular tree is quite complex. The system can be modeled via a lumped compartmental modeling approach or a distributed modeling approach depending on whether extension in space is a central element in the phenomenon under study. See for example the work of N. Westerhof and N. Stergiopulos (1998) for a discussion of modeling issues related to the vasculature. The vasculature can be divided into the microvasculature and macrovasculature. The former consists of capillaries and small arterioles and venules less than approximately 50 microns while the latter consist of larger vessels. This distinction is important because the characteristics of blood flow are different at these two levels. Fluid that filters out of the capillaries enters the interstitial or intercellular space. This fluid is available to be reabsorbed when Starling pressures allow diffusion back into the capillaries. This can happen, for example, if hematocrit (the proportion of red blood cells to total blood volume), albumin, or other blood constituents are increased which changes the osmotic pressure gradient. Excess fluid can also be returned to the blood via the lymphatic

system which allows for interstitial fluid to circulate back via lymph vessels to the venous blood stream. These features supplement the function of the circulatory system.

3. Control Mechanisms

Control system behavior can be classified as global or local. Global control refers to those controls that respond to the state of the system as a whole as measured by key quantities such as arterial blood pressure, blood volume, and blood CO_2 and O_2 levels. Local control responds with local mechanisms to influence local conditions.

Global control utilizes sensory systems to evaluate the state of the system. Information on the state of the system is sent to control centers in the brain, which transform this information into response signals that are transmitted via the peripheral nervous system to the sites where the control responses are implemented. Global control influences many aspects of the circulatory system. The control acts to redistribute blood flow to various tissues via variation in systemic resistance and mobilization of unstressed volume. It also acts to increase or decrease the pumping action of the heart. The response of the control is designed to maintain overall stable system function.

Sensory System

Effective global control of circulatory and cardiovascular function depends on adequate monitoring of the state of the system. This is primarily accomplished by monitoring key blood pressures as well as blood gases. Systemic arterial blood pressure is monitored by baroreceptors located in the carotid arteries and aorta. These cells stretch in response to an increase in blood pressure, causing an increase in their firing rate which is transmitted to the control centers in the brain. Reduction in pressure allows the baroreceptors to contract with the opposite effect.

Cardiopulmonary receptors are located at the opening of the right atrium, allowing for monitoring central venous pressure and indirectly blood volume. Receptors are also scattered in the right atrial-ventricular regions, allowing for monitoring ventricular filling, as well as scattered in the pulmonary arterial vasculature allowing for monitoring pulmonary pressures. Chemoreceptors in the carotid bodies and aortic arch monitor levels of blood CO_2 and O_2 which is indicative of respiratory system status (see article *Respiratory System*) and also indirectly indicates blood perfusion of these sensory cells. Reduced perfusion implies reduced blood gas stimulation of chemosensors which translates into information on blood pressure and flow status particularly in special circumstances and critical situations.

All information from sensory sites is transmitted to control centers in the brain where this information is integrated and transformed into system response. These control loops act as negative feedback controls, generating responses that return the system to its normal operating point when a perturbation occurs (such as a drop in blood pressure when one stands up). The distribution of sensory sites is depicted in Figure 1.

The Autonomic Nervous System

The control system for maintaining stable and appropriate circulatory system function operates almost completely via the autonomic nervous system (ANS). This neuronal system includes nerve pathways and neuronal centers such as the spinal cord, brain stem, medulla, and hypothalamus. The autonomic nervous system consists of two major subdivisions (or pathways) called the sympathetic system and the parasympathetic system. The sympathetic system influences cardiovascular function by adjusting heart rate H, heart muscle contractility S, systemic vascular resistance R, venous compliance C_v, and unstressed volume V_u (see *Hemodynamics in human: Physiology and Mathematical Models*). The parasympathetic system contributes first and foremost to regulation of heart function. Parasympathetic nerve stimulation has an opposite effect to the sympathetic stimulation of the heart. This antagonistic (or complementary) interaction of sympathetic and parasympathetic actions can also be observed in other contexts as well. The vasomotor center in the brain is the primary ANS center for transforming cardiovascular sensory information into response signals transmitted by the sympathetic and parasympathetic systems.
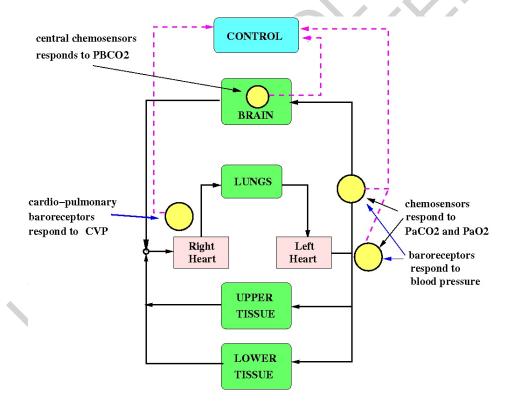
Sympathetic Action and Its Effects on Circulation

Figure 1. Control sensors responding to partial pressures of carbon dioxide (Pa CO$_2$), oxygen (Pa O$_2$), and brain carbon dioxide PB CO$_2$ and arterial blood pressure and central venous pressure CVP.

Sympathetic nerves innervate most tissues. Cardiovascular control via sympathetic pathways depends on sympathetic nerve contact with heart muscle and the vasculature. Sympathetic stimulation acting on blood vessel vasculature results primarily in vasoconstriction and increased resistance to flow. This effect occurs at the level of small arteries and terminal resistance arterioles in the arterial system with constriction at the

smallest arterioles locally generated by metabolic effects. The venous system is similarly organized in regards to distribution of nerves and constrictive action with constriction resulting in reduction in venous capacitance. Sympathetic stimulation of heart muscle increases heart rate and heart contractility. Reduction in sympathetic firing has the opposite effects to those listed above.

Since sympathetic innervation is widespread, global control responses can generate a generalized vascular constriction to respond to system challenges, but can also target vascular constriction to particular regions in specific situations. .

Parasympathetic Action and Its Effects on Circulation

As mentioned above, the parasympathetic system has a primary role in controlling heart rate. Parasympathetic nerve firing slows down heart rate while parasympathetic signal withdrawal allows the heart rate to accelerate. Parasympathetic signals reach the heart via the vagus nerve with innervation of other tissues primarily restricted to certain organs - the parasympathetic connections are significantly less distributed than sympathetic connections.

It is important to note that parasympathetic inhibition is the dominant factor in determining heart rate at rest, given that the intrinsic pacemaker rhythm of the heart is about 100 beats per minute, which is higher than the typical normal rate of 60 - 70 beats per minute. Furthermore, changes in parasympathetic activity influence heart action much more quickly than changes in sympathetic activity. In general, the reduction in inhibitive effects of parasympathetic withdrawal is combined with increased sympathetic stimulation to increase heart rate. The reverse pattern decreases heart rate.

3.1. Control of Blood Pressure

Control of blood pressure can be divided into two categories: short-term control and long-term control. Figure 1 indicates the elements in the short-term control (baroreflex control) loop of the CVS while Figure 2 indicates the action involved in the short-term response to a drop in blood volume which causes a drop in blood pressure. A drop in arterial blood pressure P_{as}, regardless of cause, would precipitate a similar cascade of responses which include the following:

- The drop in pressure reduces the stretch in the baroreceptors which reduces the neural afferent signal to the central controller in the brain.
- This causes an increase in sympathetic neural activity and a decrease in parasympathetic neural activity. Both these actions increase heart rate.
- Sympathetic activity also raises contractility of heart muscle which supports cardiac output and also increases vasoconstriction and hence systemic resistance.
- Sympathetic action also reduces venous capacitance, which reduces unstressed volume and adds blood to the stressed volume and hence dynamic component of blood flow.
- All these actions cause an increase in blood pressure.

Several important points should be emphasized. Short-term control responds within seconds to changes in pressure and in a very few minutes returns arterial blood pressure to normal. The baroreflex, which is responsible for this control, reacts both to absolute changes in mean arterial pressure (MAP) as well as the rate of change in pressure and also transmits information about pulse pressure. The baroreflex can reset its operating point so that deviations around this new operating will trigger the control responses. This is one of the complicating problems in hypertension. Exercise typically raises blood pressure and cardiac output so it is clear that system response to exercise involves additional control pathways besides the baroreflex to set the appropriate system operating state. An interesting question is why high blood pressure due to exercise is apparently beneficial while static hypertension is not. Clearly, duration may be a factor in the difference but there may be other factors that play a role as well.

Clearly, various combinations of changes in H, R, S, and V_u can achieve the same result. Individuals show a wide diversity of individualized patterns of responses, with specialized groups such as athletes reflecting group-related patterns. A key question is whether the response pattern is always the same or varies for an individual and if there are variations what determines the choice of response strategy. The baroreflex may or may not play a role in setting the long term level of P_{as} but the kidneys definitely have a key role in long term control as discussed below.
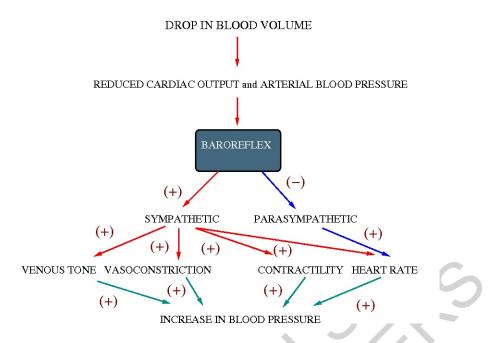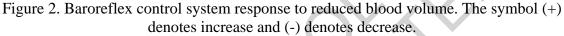
3.2. Control of Blood Volume

Reduction in blood volume, such as could occur during hemorrhage or during dialysis treatment, reduces central venous pressure (CVP) and hence atrial filling which lowers cardiac output, resulting in a drop in arterial pressure. Figure 2 illustrates the baroreflex response. The cardiopulmonary sensors respond to such changes in blood volume and trigger sympathetic effects that may target mobilization of unstressed volume. Clearly the arterial baroreflex also becomes involved as P_{as} is influenced as well by the reduced cardiac output. During small changes in blood volume the cardiopulmonary baroreflex may play the dominant role in setting system response. How, in fact, information from the cardiopulmonary and arterial baroreceptors is integrated and how responses are organized based on two sensory streams is still a topic for investigation. It is possible, based on the organization of the transfer of information from the two sensory sites and the responses generated by the stimulation from these sites, that the effectiveness of the response of the system could be either reduced or magnified, depending on circumstances of the interaction.

3.3. The Kidneys and Cardiovascular Control

The role of the kidneys is extensively discussed in *Hemodynamics in human: Physiology and Mathematical Models*. We mention here that the kidneys play an important role in controlling blood volume both over longer time scales (minutes to hours) via direct manipulation of fluid retention or elimination as well over shorter time scales (minutes) via hormonal control pathways. Given that the kidneys play a role in modulating sympathetic tone and blood volume they may also have a role in the emergence of hypertension.

Figure 2. Baroreflex control system response to reduced blood volume. The symbol (+) denotes increase and (-) denotes decrease.

3.4. Local Control and Autoregulation

Local control of blood flow responds to two primary stimuli: a change in local blood pressure and a change in metabolic activity. Local responses act to maintain proper flow for metabolic needs.

Autoregulation refers to the ability to counteract and smooth out surges in pressure that would unnecessarily alter flow. It also acts to ensure stable capillary pressure and glomular filtration rate. Metabolic hyperemia, which is a form of metabolic demand control, results from vasodilation when metabolic activity increases (CO_2 rises and O_2 falls) ensuring sufficient blood perfusion locally to meet metabolic demand.

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Biographical Sketches

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He is currently Research Associate at the Institute for Mathematics and Scientific Computing at the University of Graz, Austria. He has coauthored the book Cardiovascular and Respiratory Systems: Modeling analysis and control, Siam Philadelphia, 2007. Current interests include modeling physiological systems and inverse problems.

Mostafa Bachar received his PhD from University of Pau et Pays de l'Adour in December, 1999 with areas of research applied mathematics, recently he is working as Assistant Professor in Department of Mathematics, in King Saud University, Saudi Arabia, and his current research are mathematical modeling in mathematical biology and mathematical analysis.

Franz Kappel received his PhD from University of Graz in 1963, was Associate Professor at the University of Würzburg (Germany) from 1971 – 1975 and was Full Professor at the University of Graz from 1975 – 2008.