A System Identification Approach to Characterizing Intermediate Term Hemodynamic Variability

by

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Submitted to the
Harvard-MIT Division of Health Sciences and Technology
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Medical Engineering
at the
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
February 1998

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Abstract

Hemodynamic variables such as heart rate (HR) and arterial blood pressure (ABP) fluctuate on a beat-to-beat basis. This inherent variability reflects the dynamic interaction between ongoing perturbations to the cardiovascular system and the response of feedback mechanisms that serve to regulate cardiovascular function. System identification analyses of short-term (minutes) hemodynamic fluctuations have provided important insights regarding short-term cardio-regulatory mechanisms but similar analyses have not previously been applied to long-term fluctuations. Below $10^{-2}$ Hz, power spectra of long-term (hours to days) heart rate fluctuations have been shown to be approximately inversely proportional to frequency ($1/f^\alpha$, where $\alpha$ is close to 1), but the origin of these fluctuations and similar fluctuations in other hemodynamic variables remains unknown.

In this investigation, system identification techniques were applied to quantitatively characterize a linear model of intermediate term hemodynamic variability with the objective of determining whether the $1/f^\alpha$ spectral character of hemodynamic fluctuations originates in one or more of the model coupling mechanisms or noise sources. Two to four hour continuous recordings of HR, ABP, cardiac output (CO) and lung volume were measured in conscious sheep under resting conditions, during fixed-rate atrial pacing and after separate administration of captopril, propranolol and phentolamine. Under resting conditions, HR, ABP, CO and stroke volume (SV) all exhibit $1/f^\alpha$-type fluctuations at low frequencies. None of the model transfer functions accounted for the production of the $1/f^\alpha$ fluctuations. The fluctuations originated in each of three model noise sources impinging on HR, ABP and SV. Addition of second- and third-order nonlinear terms to the model did not alter the $1/f^\alpha$ nature of the model noise sources. None of the experimental interventions eliminated the $1/f^\alpha$ pattern of fluctuations (except atrial pacing which trivially eliminated the $1/f^\alpha$ pattern in HR), although some altered the exponent, $\alpha$, in some signals.
Thus, the $1/f^\alpha$ fluctuations seen in hemodynamic signals are not due to linear or low-order nonlinear regulatory mechanisms coupling the signals. Rather, these fluctuations appear to arise from unmeasured perturbations to HR, ABP and SV. One may speculate that these perturbations are related to diffusive mechanisms associated with neural or local hormonal regulatory processes.

Thesis Supervisor: Richard J. Cohen, M.D., Ph.D.  
Title: Professor, Harvard-MIT Division of Health Sciences and Technology
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Chapter 1

Motivation

Cardiovascular parameters such as heart rate and blood pressure vary on a beat-to-beat basis. Figure 1-1 presents continuous measurements of heart rate and blood pressure during a six minute period. Both of the signals appear to fluctuate in a rather random way about a mean level. To estimate a mean level of heart rate and blood pressure, despite what one might consider the "noise" fluctuations about these mean levels, one could average the signals over time. In fact, this is one of the first things a physician does during a physical examination when he measures a patient's pulse. Although mean levels of heart rate and blood pressure are important clinical parameters for evaluating the function of the cardiovascular system or the overall health of a patient, it has become increasingly clear during the last two decades that analysis of the fluctuations in cardiovascular parameters such as heart rate and blood pressure provides additional insights into cardio-regulatory function. In fact, the fluctuations may often be more informative than the mean.

The beat-to-beat fluctuations of hemodynamic parameters about their mean values reflect the interaction between ongoing perturbations to the cardiovascular system and the response of feedback mechanisms that serve to regulate cardiovascular function. The utility of analyzing hemodynamic variability was first demonstrated by
analyses of short-term (minutes) measurements of heart rate variability (HRV). Although fluctuations in heart rate were recognized much earlier [74,78,93,156], it was not until 1981 that Akselrod et al. first demonstrated the relative roles of the two branches of the autonomic nervous system in mediating these fluctuations [2]. Since that time, there has been an explosion of interest in the study of heart rate variability. Investigators have applied a wide range of analytical techniques to this study. The simplest techniques are time domain approaches in which the fluctuations are typically evaluated based on characteristics of the statistical distribution of beat-to-beat intervals (i.e., standard deviations) or parameters derived from beat-to-beat intervals [30,96,110,163]. Other powerful techniques based on frequency domain analyses such as power spectral estimation have also been employed [1,2,11,92-94,146,149].

Longer term fluctuations in heart rate on the order of hours to days have also been investigated [3,31,34,97,151]. The mechanisms producing these longer term fluctuations remain unknown. However, long-term heart rate fluctuations demonstrate an interesting pattern. The power spectrum (Figure 1-2) of the fluctuations increases at low frequencies as $1/f^\alpha$ (where $\alpha$ is approximately one) [97,151]. The occurrence
of this power spectral shape is common to many natural phenomena and this type of variability is referred to as "1/f noise". The occurrence of 1/f noise is a classic problem in physics. 1/f noise has been measured, for example, in electronic devices, in the occurrence times of earthquakes, in the flow of rivers, and in the variations of pitch in music. Except perhaps in a few specific cases, the mechanisms underlying these fluctuations remain unclear. It is interesting to speculate that a common and fundamental mechanism might link these diverse systems, but it is difficult to envision such a link. Importantly, although the mechanisms underlying long-term HRV remain unknown, analyses of long-term heart rate variability seem to provide better predictive power in evaluating clinical outcomes (such as survival after myocardial infarction) when compared to short-term analyses [34].

The analysis of HRV is complicated by the fact that heart rate is an output of a complex regulatory system with many inputs. Given only measurements of heart rate, it is difficult to make statements regarding underlying regulatory systems. A change in an input such as respiration could be equally as likely to produce a change in heart rate fluctuations as would a change in the regulatory mechanisms. That
Figure 1-3 Simple model of cardiovascular regulation. The coupling mechanisms, \([\text{ILV} \rightarrow \text{HR}], [\text{CIRCULATORY MECHANICS}], [\text{HR BAROREFLEX}]\) and \([\text{ILV} \rightarrow \text{ABP}]\), may be directly characterized by system identification approaches from measurements of the electrocardiogram, arterial blood pressure, and lung volume. (from [127])

is, from measurements of the output of a regulatory system, it is not possible to distinguish changes in the input to the system from changes in the system itself. Multi-signal analyses which can characterize the couplings between hemodynamic parameters such as heart rate, blood pressure, and respiration have been implemented to overcome this limitation. From measurements of signals such as heart rate, blood pressure, and lung volume, one may estimate the transfer couplings in a model such as that in Figure 1-3. These analyses are referred to as "transfer function estimation" or "system identification" techniques, and they have been applied to more directly characterize short-term cardio-regulatory mechanisms [6, 9, 25, 44, 127, 151, 152, 154]. Although system identification procedures have been successfully employed for the analysis of short-term hemodynamics, they have yet to be applied to the analysis of
longer term data (hours).

Analysis of long-term hemodynamic variability offers a means to investigate the nature of the $1/f$ pattern of HRV. For example, it would be interesting to determine whether the $1/f$ fluctuations are attributable to a particular coupling mechanism characterized by system identification or whether the fluctuations arise as perturbations independent of the couplings. It would also be interesting to determine whether interventions such as pacing or blockade of the renin-angiotensin system alter the nature of the $1/f$ fluctuations. Analysis of longer term data may also provide insights into the function of intermediate- and long-term regulatory processes such as those mediated by hormonal mechanisms or by alterations in peripheral resistance. Such analyses may also provide better clinical diagnostic or prognostic measures than short-term system identification methods (as is the case for measures of HRV). This investigation was designed to answer some of these questions regarding the application of system identification approaches to longer term fluctuations with a particular focus on investigating the source and impact of $1/f$ fluctuations.

Chapter 2 will expand on this brief introduction and provide background regarding basic cardiovascular regulatory physiology, a brief review of previous work in analyses of hemodynamic variability, and a discussion of properties and theoretical models of $1/f$ processes. Chapters 3 and 4 present the surgical and experimental methods and results of the investigation, respectively. Chapter 5 provides a discussion of the implications of the important findings and Chapter 6 provides a brief summary and draws conclusions.
Chapter 2

Background

2.1 Cardiovascular Regulatory Physiology

The primary role of the cardiovascular system is to maintain sufficient blood flow to provide for the transport of nutrients and metabolic waste products to and from bodily tissues. The flow demands of individual tissues depend on tissue type and activity levels. Typically, blood flow is distributed to tissues approximately in proportion to their relative metabolic rates [28,103]. There are exceptions to this rule (most notably, the kidney in which proper organ function requires high flow), but it serves as a good first approximation. As metabolic needs of tissues change, blood flow is continually adjusted. For example, during heavy exercise, metabolic demand may increase as much as tenfold in large muscle groups and hemodynamic regulatory mechanisms must provide for this need.

A wide variety of systems contribute to the regulation of cardiovascular function. They may be broadly categorized as either local or central mechanisms. Local (or intrinsic) control of blood flow may be exerted in response to changes in demand within a tissue bed by local adjustment of vascular resistance. Central (or extrinsic) control may be exerted in response to sensed changes in, for example, arterial blood
pressure, central blood volumes, or arterial blood gas levels by adjustment of cardiac output, venous tone, or more global adjustment of peripheral resistance. Central mechanisms serve, in large part, to maintain a normal arterial blood pressure and an appropriate cardiac output, while local mechanisms serve to regulate tissue specific blood flow. This is, of course, a simplification and it is becoming increasingly clear that there are potent interactions between local and central mechanisms [144, 148]. Detailed reviews of cardiovascular control may be found in [28, 73, 103, 144, 148, 164].

We can explore hemodynamic regulatory mechanisms in a systematic fashion by considering the regulation of arterial blood pressure. Arterial blood pressure is maintained by control pathways which influence either total peripheral resistance or cardiac output [28, 73, 148].

2.1.1 Control of Peripheral Resistance

Total peripheral resistance is a function of the local resistance in tissue beds distributed throughout the body. The major controllable resistance vessels in the body are the arterioles, and their resistance is modulated by both central (nervous and hormonal) and local feedback mechanisms. The relative roles of central and local control varies dependent on tissue type. In tissues such as the heart and brain, local control mechanisms dominate while in skin and splanchnic regions, central nervous mechanisms play a larger role.

Local control of vascular resistance is exerted through a number of mechanisms including metabolic, myogenic, endothelial, thermoregulatory, or local hormonal (autacoid) mechanisms (see Table 2.1). A local mismatch in blood flow and demand may be signaled within a tissue by a local accumulation or depletion of either nutrients (e.g., oxygen) or metabolites (e.g., carbon dioxide, lactic acid). These metabolites and nutrients may serve as vasodilatory or vasoconstrictive agents with direct effects on vascular smooth muscle cells or they may induce the vascular endothelium to
<table>
<thead>
<tr>
<th>MECHANISM</th>
<th>STIMULI</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local Metabolites</td>
<td>Local Hypoxia</td>
<td>Vasodilation induced by adenosine, intracellular pH or mediated by endothelial factors</td>
</tr>
<tr>
<td></td>
<td>CO₂, Lactate,</td>
<td>Vasodilation through direct effect on smooth muscle cells or mediated by endothelial factors.</td>
</tr>
<tr>
<td></td>
<td>Local Acidosis</td>
<td></td>
</tr>
<tr>
<td>Myogenic Response</td>
<td>Transmural Pressure</td>
<td>Vasoconstriction — Increased transmural pressure leads to immediate distension followed by a reflexive contraction in most arterioles.</td>
</tr>
<tr>
<td>(Bayliss Effect)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermoregulation</td>
<td>Temperature</td>
<td>Primarily important in skin, associated with temperature dependence of α₂ receptor affinity. High T leads to vasodilation, Low T (within limits) leads to vasoconstriction.</td>
</tr>
<tr>
<td>Autacoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>Trauma, Allergy</td>
<td>Dilates arterioles, constricts veins. Released by mast cells and basophils.</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Inflammation</td>
<td>Vasodilation mediated through endothelial factors.</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>Inflammation,</td>
<td>Many types. Some vasoconstrict, others vasodilate. Released by macrophages, Hemostasis</td>
</tr>
<tr>
<td></td>
<td>Hemostasis</td>
<td>Vasoconstricts. Released by platelets.</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Hemostasis</td>
<td></td>
</tr>
<tr>
<td>Endothelium</td>
<td>Inflammation,</td>
<td>Release of a wide range of vasoconstrictive or vasodilatory substances dependent on stimulus. Some mentioned above. Response to shear stress is vasodilation mediated by nitric oxide.</td>
</tr>
<tr>
<td></td>
<td>Hemostasis, Shear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>stress and others</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.1: Summary of selected local mechanisms for control of blood vessels. Note that descriptions are for systemic vessels — pulmonary vessels or vessels of other specialized circulations may differ. Detailed descriptions are provided in [103].
synthesize and release vasoactive agents [28,103]. The endothelium, once thought to be a passive mechanical diffusion barrier, is now known to play a critical role in hemodynamic regulation [144]. It synthesizes and releases some of the most potent of known vasoactive substances including prostaglandins, endothelial-derived relaxing factor (EDRF, which has been identified as nitric oxide), and endothelin. The production of these substances by endothelium can be induced not only by changes in local concentrations of nutrients or metabolites but also by hormones, by interactions with white blood cells or platelets or by physical forces such as shear stress [28,144].

Tissues may also act to adjust their local resistance by myogenic control. When systemic arterioles are exposed to increases in transmural pressure, they immediately distend but then react by contracting. This phenomenon is known as the myogenic response or Bayliss Effect and serves as a means for local autoregulation of blood flow in the face of changes in perfusion pressure. (Note that since this is effectively a positive feedback response other mechanisms must serve to counteract or interrupt the cycle.)

There are many other agents and mechanisms of local control that have been and continue to be discovered. A large class of locally acting hormones called autacoids play an important role in local responses such as inflammation and hemostasis. Autacoids include, for example, histamine, bradykinin, prostaglandins, leukotrienes and platelet activation factor. Some other control mechanisms are tissue specific, such as the response of skin to temperature. This response is attributed to the increased density of $\alpha_2$ receptors in the skin and the sensitivity of these receptors to temperature. The relative importance of and interactions between these and other local autoregulatory mechanisms remain unclear. Local control mechanisms are responsible for the important circulatory adjustments known as autoregulation, metabolic hyperemia and reactive hyperemia [103].

Central control of peripheral resistance is achieved by autonomic vasomotor nerves
and by endocrine secretions. Feedback regarding the state of the hemodynamic system is provided by a range of sensors strategically located throughout the body. Information from these sensors is carried by afferent fibers to the brainstem where it is integrated with outflow from the hypothalamus, cerebellum, and cortex [28, 73, 103, 158]. Sensory inputs provide information regarding important parameters such as arterial blood pressure, central blood volumes, and arterial blood gases and will be discussed in greater detail in Section 2.1.3.

Autonomic vasomotor nerves impinge on smooth muscle in blood vessels. There are three classes of such nerves: sympathetic vasoconstrictor, sympathetic vasodilator and parasympathetic vasodilator nerves [103]. The sympathetic vasoconstrictor nerves are the most widely distributed of the three types of vasomotor neurons. They are tonically active and play the dominant role in central nervous control of peripheral resistance. Sympathetic vasoconstrictor fibers release norepinephrine which binds to $\alpha$-adrenoreceptors on vascular smooth muscle cells in the vessel walls. There are two types of $\alpha$ receptors: $\alpha_1$, which are most common and are widely distributed in vascular smooth muscle and $\alpha_2$, which are distributed primarily in skin arterioles and veins. Sympathetic vasodilator nerves are found in a limited number of tissues such as skin and sweat glands\(^1\). They are cholinergic fibers and are not tonically active. That is, they release acetylcholine when firing but do not maintain a baseline firing rate. It should also be noted that $\beta_2$-adrenergic receptors are found throughout skeletal muscle, the heart and the liver. When stimulated these receptors induce a vasodilation. However, they are typically not stimulated by sympathetic nerve fibers but rather by circulating catecholamines [103] as will be discussed below. The sympathetic vasodilator mechanism do not play a large role in control of peripheral resistance in humans. Finally, parasympathetic vasodilatory nerves, which also release acetylcholine, impinge only on selected tissues such as the salivary glands, exocrine

\(^1\)Sympathetic vasodilator nerves are widely distributed in skeletal muscle in other species but whether this is also true in humans remains controversial [103].
<table>
<thead>
<tr>
<th>Effector System</th>
<th>Receptor Type</th>
<th>Primary Locations</th>
<th>Effects</th>
<th>Tonic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic</td>
<td>(\alpha_1)-adrenergic</td>
<td>Vascular smooth muscle</td>
<td>vasoconstriction</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(\alpha_2)-adrenergic</td>
<td>Skin vascular smooth muscle</td>
<td>vasoconstriction</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>(\beta_1)-adrenergic</td>
<td>sinoatrial and atrioventricular nodes, myocardium</td>
<td>Increased heart rate and contractility</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Cholinergic</td>
<td>skin and possibly skeletal muscle</td>
<td>vasoconstriction</td>
<td>No</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>Cholinergic</td>
<td>gastrointestinal mucosa, salivary glands, exocrine pancreas</td>
<td>vasoconstriction</td>
<td>No</td>
</tr>
<tr>
<td>Circulating</td>
<td>(\beta_2)-adrenergic</td>
<td>Arterioles of skeletal muscle, liver and heart. Bronchiolar smooth muscle</td>
<td>vasoconstriction, bronchodilatation</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 2.2: Adrenergic and cholinergic systems in cardiovascular control.

pancreas, gastrointestinal mucosa, genital erectile tissue, and cerebral and coronary arteries [103]. They are activated only when the organ function demands greater blood flow. Thus, nervous control of peripheral resistance is almost exclusively mediated by the \(\alpha\)-sympathetic nervous system [28,103]. Table 2.2 provides a summary of the central adrenergic or cholinergic control pathways involved in cardiovascular regulation.

Endocrine or hormonal control of peripheral resistance is less important than nervous modulation in normal, short-term control. However, in pathological situations or in the long-term, endocrine control becomes more important. There are three major hormones which influence peripheral resistance: catecholamines, vasopressin, and angiotensin II.

The catecholamines (epinephrine and norepinephrine) are secreted from the adrenal medulla in response to exercise, hypotension, and hypoglycemia [28,103,148]. They affect peripheral resistance largely by inducing vasoconstriction by activation of \(\alpha\)-
adrenergic receptors in vascular smooth muscle. However, in skeletal muscle, myocardium, and liver, epinephrine induces a vasodilation due to the abundance of \(\beta\)-adrenergic receptors in these tissues and its high affinity for these receptors. Norepinephrine causes a vasoconstriction in muscle (as in other tissues) because it has a higher affinity for \(\alpha\) type receptors. Thus, since skeletal muscle is the most abundant bodily tissue, administration of norepinephrine alone causes an increase in total peripheral resistance while administration of epinephrine alone will slightly reduce total peripheral resistance.

Vasopressin is produced in the hypothalamus and released by the pituitary gland [28,103]. Its production is stimulated by a rise in plasma osmolarity (sensed by tissue fluid osmolarity sensors in the hypothalamus) or a fall in blood pressure or volume (sensed by cardiovascular pressure sensors). Its main action is to promote water retention in the kidney. However, at higher plasma concentrations it will cause a strong vasoconstriction in most tissues and a vasodilation in coronary and cerebral arteries and thereby acts to redistribute flow to the heart and brain.

Angiotensin II is part of the renin-angiotensin system. The formation of angiotensin II is mediated by the proteolytic enzyme, renin. Renin acts in plasma to cleave angiotensin I from angiotensinogen. Angiotensin I is then cleaved further by angiotensin converting enzyme (ACE) which is located on the surface of endothelial cells. The resulting molecule is angiotensin II. Angiotensin II has three important actions [28,36,50,103]. First, it stimulates the adrenals medulla to secrete aldosterone which promotes salt and water retention in the kidney. Second, at higher concentrations, it causes vasoconstriction. Vasoconstriction may be induced by a direct effect on vascular smooth muscle cells by stimulating release of norepinephrine or by increasing central sympathetic drive. Third, angiotensin II may increase cardiac contractility by increasing central sympathetic drive and by direct effects on cardiac muscle.
2.1.2 Control of Cardiac Output

The second major determinant of blood pressure is cardiac output. Cardiac output is, in turn, the product of heart rate and stroke volume which are largely controlled by central mechanisms.

Each normal heart beat is initiated in the heart's pacemaker — the sinoatrial (SA) node. The SA node has an intrinsic rate which is continually modulated by the autonomic nervous system. Both the parasympathetic and sympathetic branches of the autonomic nervous system impinge on the SA node and control heart rate in a complementary fashion [28,158]. Parasympathetic nerves release acetylcholine which causes a virtually immediate decrease in heart rate. Sympathetic nerves release norepinephrine which binds to $\beta_1$-adrenergic receptors and over the course of a few beats causes an increased heart rate$^2$. Heart rate is adjusted in response to feedback from peripheral receptors (as will be discussed in Section 2.1.3) but is, of course, also modulated by central linkages to other physiological systems. One important linkage, with respiratory centers, appears to contribute to the development of the respiratory sinus arrhythmia. Heart rate rises with inspiration and decreases with expiration, and the heart rate changes actually precede the respiratory changes (which implies a central linkage). It should also be noted that circulating levels of catecholamines may also increase heart rate (particularly as part of the “alerting response” [103]) but primary control is neural.

The second determinant of cardiac output is stroke volume. Stroke volume in a healthy individual is primarily a function of cardiac contractility and preload (Starling's Law)$^3$. Sympathetic nerves impinging on the ventricles provide the domi-$

$^2$The slow response of heart rate to sympathetic stimulation is attributable to the chain of biochemical events associated with $\beta$-adrenoreceptor activation [21,26,103].

$^3$In disease states such as heart failure or hypertension, afterload, the arterial pressure impeding ejection of blood, becomes an important determinant of stroke volume. In the normal heart, direct and indirect effects of changes in afterload on stroke volume compensate one another so that the normal total effect is minimal. For further discussion see [103]
nant means for control of cardiac contractility [28,158]. Similar to the sympathetic fibers innervating the SA node, these fibers release norepinephrine which binds to \( \beta_1 \)-adrenergic receptors in the ventricles, atria and electrical systems. Once again, circulating catecholamines affect contractility. Angiotensin II also plays a role but primary control is neural.

Preload is a term used to describe the filling pressures seen by the heart. Starlings law of the heart states that, within limits, increased stretch of myocardial tissue during diastole will lead to an increased stroke volume. That is, increasing end diastolic ventricular pressures leads to a stronger beat and the result is an increased stroke volume. The end diastolic pressure in the right ventricle is approximately equal to the central venous pressure. The term filling pressure refers to these central pressures and the corresponding pressures for the left ventricle. Central venous pressures are determined by a number of factors such as total blood volume and effects on venous return by gravity, the pump effect of skeletal muscles in the legs (the “muscle pump”), and respiration. Over the long-term, maintenance of appropriate blood volume plays a critical role in maintaining central venous pressures. However, over the shorter term, the primary means of central control is by alteration of smooth muscle tone in veins. Sympathetic fibers innervating venous smooth muscle release norepinephrine which binds to \( \alpha_1 \)-receptors and produces a constriction, thereby reducing venous capacity and increasing venous pressure and return.

2.1.3 Cardiovascular Receptors and Feedback Control

Central control of cardiac output and peripheral resistance is achieved by a complex closed-loop negative feedback system. The feedforward or control pathways have been presented in Sections 2.1.1 and 2.1.2. The feedback pathways provide the central control centers with information regarding the overall state of the cardiovascular system. Based on this feedback, the controls centers initiate their control adjustments. A
number of peripheral sensors provide the feedback information. A schematic diagram of the central nervous control system is provided in Figure 2-1. There are three major groups of receptors: the arterial baroreceptors, the cardiac and pulmonary receptors, and the chemoreceptors and muscle receptors.

The arterial baroreceptors are located in the aortic arch and in the carotid sinus. They are mechanoreceptors which respond to stretch of the arterial walls due to an increase in transmural pressure. In effect, they provide feedback regarding arterial blood pressure. A decrease in blood pressure leads to an unloading of the baroreceptors and the response is to dramatically increase heart rate and contractility and to constrict arterioles. If the pressure drop is large enough it may also lead, for example, to release of epinephrine from the adrenal medulla and constriction of veins in the splanchnic regions (to divert blood from the gut to the central veins). Cardiovascular control responses induced in response to changes in arterial pressure are called baroreflex responses and are perhaps the most important of all hemodynamic control processes (particularly over the short-term).

The cardiac and pulmonary receptors are often lumped into a single category, although they do not fulfill identical purposes [144]. This category includes a large variety of receptors located throughout the atria, ventricles, and pulmonary vessels. Some of the receptors are sensitive to stretch or distension, while others are chemosensitive and react to the presence of chemicals such as bradykinin or prostaglandins (which are known to be released in ischemic myocardium). The reflex responses to stimulation of these receptors also varies and may be quite specific. For example, stimulation of stretch receptors located at the venoatrial junction results in an increased heart rate through an increased sympathetic outflow to the SA node but no change in cardiac contractility. Other mechanoreceptors located throughout the atria and ventricle lead to a reflex bradycardia and peripheral vasodilation when stimulated. The complex roles of cardiac and pulmonary receptors in hemodynamic control continues to be ex-
Figure 2-1 Reflex and central control of the circulation (from [103]). CP, cardiopulmonary receptor group; CVP, central venous pressure; SV, stroke volume; HR, heart rate; TPR, total peripheral resistance; BP, arterial blood pressure; s, sympathetic fibers; X, vagal cardiac fibers. "Inhibitory" and "excitatory" refer to the net effect of receptor activation on cardiac output and blood pressure.
explored [144]. One widely recognized and important role of the cardiac or pulmonary receptors seems to be the reflex control of vascular tone when central blood volume changes [103].

Arterial chemoreceptors and muscle receptors both provide the cardiovascular system information to help in response to stresses. Arterial chemoreceptors are located primarily near the carotid sinus and in the aorta. They sense hypoxia, hypercapnia, and acidosis of arterial blood. They play an important role in the regulation of breathing and under normal circumstances play only a minimal role in hemodynamic control. However, when they sense hypoxia or hypercapnia the reflex response is an increase in peripheral resistance. There are two types of muscle receptors which both respond to exercise. The first type are metabolo-receptors which respond to an increase in chemicals released during exercise (such as lactic acid). The second type are mechanoreceptors which respond to active muscle tension. When stimulated these receptors may initiate a reflex increase in heart rate and contractility and a vasoconstriction.

2.1.4 Summary

In summary, short-term cardiovascular regulation is largely dependent on neural mechanisms mediated by the autonomic nervous system, while over longer time scales, a number of other systems play increasingly important roles. The parasympathetic branch of the autonomic nervous system provides a dominant control of heart rate in a resting individual but does not play a role in modulating cardiac contractility or peripheral resistance. Increasing parasympathetic outflow leads to a decrease in heart rate. The sympathetic branch of the autonomic nervous system mediates control of heart rate and contractility ($\beta_1$ fibers) as well as peripheral resistance ($\alpha_1$ fibers). Increasing sympathetic outflow leads to increased heart rate and contractility and an increase in peripheral resistance. A large number of local mechanisms may also exert
effects on short-term control of local peripheral resistance. Over longer time scales, a number of additional control mechanisms must be considered including hormonal mechanisms and interactions between local and central control systems.

Even from this brief overview of cardiovascular control, it is clear that the system is quite complex. However, simple signal processing and estimation approaches which focus on interpretation of the variability in cardiovascular parameters and the inter-relationships between multiple such parameters, have provided significant insight into underlying regulatory physiology and may potentially serve as diagnostic tools.

### 2.2 Hemodynamic Variability

Hemodynamic variables such as heart rate and blood pressure fluctuate on a beat-to-beat basis. Figure 2-2 presents representative six minute segments of heart rate and arterial blood pressure for a standing adult. One's first assessment of this data might be that each signal is well-characterized as a mean level with "noisy" fluctuations about the mean. The mean for the segment can be estimated by averaging the values
in the time series so, for example, mean heart rate might be approximately 105 bpm in the time series presented. The mean levels of hemodynamic data are certainly important parameters in determining the "state" of the cardio-regulatory system or in assessing the well-being of a patient. In fact, taking a pulse, by counting beats and averaging over a short time period, is one of the first evaluations a physician performs in a physical exam. However, in the last few decades it has become clear that the fluctuations that are characteristic of hemodynamic data are indeed not "noise" in the classic sense but rather contain significant additional information regarding underlying cardio-regulatory state.

Recognition of hemodynamic variability, and particularly heart rate variability is not new. In fact, in the early 18th century when Stephen Hales made the first quantitative measurements of arterial blood pressure, he noted a relationship between the respiratory cycle, the interbeat interval and blood pressure levels [74]. The fluctuation in heart rate associated with respiration became known as the respiratory sinus arrhythmia. One of the earliest attempts to investigate heart rate variability quantitatively was made by Sayers. He applied power spectral estimation to characterize fluctuations in heart rate (or more specifically RR intervals — the time intervals between successive R waves of the electrocardiogram) [156]. He found not only a significant fluctuation at the respiratory frequency but also significant variability at lower frequencies, which was later associated with vasomotor regulation. An explosion of interest in this field of study began in 1981 when Akselrod et al. first demonstrated that heart rate variability provided a measure of autonomic activity [2]. They found, through selective pharmacological parasympathetic and β-sympathetic blockade in conscious dogs, that while the parasympathetic nervous system was capable of modulating heart rate at all frequencies investigated (<0.5 Hz), the sympathetic system was capable of modulating heart rate only in the frequency range below approximately 0.1 Hz. In 1985, Pomeranz et al. [146], verified these studies in humans.
These studies were among the first to demonstrate that the variability in hemodynamic parameters such as heart rate could be used to quantify the activity of a specific hemodynamic regulatory system. A wide variety of subsequent studies has focused on investigating the regulatory mechanisms underlying hemodynamic variability [1,17,21,41,47,48,91,112,137,141,151]. Many of the techniques and findings have been well reviewed in [6,29,65,86,94,109,119,128,150,167,169].

Similarly, many other studies have focused on identifying clinical correlates of heart rate variability. In this type of study, hemodynamic variability is not used as a means of characterizing a regulatory system per se but rather as a clinical measurement which offers diagnostic or prognostic information regarding a specific disease or pathology. Although the presence of a strong respiratory sinus arrhythmia has long been accepted by clinicians as a sign of good health, it was not until the latter part of the 20th century that Hon and Lee first demonstrated a well-defined clinical application of heart rate variability in the area of fetal monitoring [78]. The clinical relevance of heart rate variability was re-emphasized in 1987 when Kleiger et al. reported that the degree of heart rate variability was a significant predictor of mortality after myocardial infarction⁴ [96]. Many other clinical studies have been performed examining heart rate variability in association not only with myocardial infarction [30–33,106,110,145] but also in association with fetal monitoring [87], sudden infant death syndrome [66,68], congestive heart failure [39,152], hypertension [111,114], diabetic autonomic neuropathy [51,55,56,126], cardiac transplant surgery [7,149], pediatric cardiac surgery [67], ventricular arrhythmias [136] and sudden cardiac death [16,81]. Selected examples of clinical studies are provided in Table 2.2 and reviewed in [38,112,163,167,169]. At present, the only generally accepted practical applications of heart rate variability in adult medicine are in evaluating mortality risk after acute myocardial infarction and in diagnosing diabetic autonomic

⁴A clinical correlation between heart rate variability and in-hospital mortality after myocardial infarction had been reported earlier by Wolf et al. in a smaller study [178].
<table>
<thead>
<tr>
<th>DISEASE STATE</th>
<th>INVESTIGATION PARAMETER</th>
<th>CLINICAL FINDING</th>
<th>POTENTIAL VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Spectral AR</td>
<td>↑ LF found in hypertensives compared with normals with blunting of circadian patterns Reduced parasympathetic in hypertensive patients</td>
<td>Hypertension is characterized by a depressed circadian rhythmicity of LF Support the use of non-pathological therapy of hypertension that ↑ vagal tone (e.g., exercise)</td>
</tr>
<tr>
<td></td>
<td>Spectral FFT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>Spectral Blackman-Tukey, 15-min acquisition</td>
<td>↓ spectral power at all frequencies, especially &gt;0.04 Hz in CHF patients Low HRV</td>
<td>In CHF, there is ↓ vagal but relatively preserved sympathetic modulation of HR Reduced vagal activity in CHF patients</td>
</tr>
<tr>
<td></td>
<td>Time domain RR interval histogram with 24-h Holter</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spectral FFT, 4-min supine acquisition</td>
<td>↓ HF power (&gt;0.1 Hz) in CHF ↑ LF/HF</td>
<td>Withdrawal of parasympathetic tone observed in CHF. CHF has imbalance of autonomic tone with ↓ parasympathetic and a predominance of sympathetic tone</td>
</tr>
<tr>
<td></td>
<td>Spectral FFT, Time domain, 24-48-h Holter</td>
<td>Alteration of HRV not tightly linked to severity of CHF; ↓ HRV was related to sympathetic excitation HRV ↑ during ACE inhibitor treatment</td>
<td>Significant augmentation of parasympathetic tone was associated with ACE inhibitor therapy Poincaré plots may assist analysis of sympathetic influences</td>
</tr>
<tr>
<td></td>
<td>Time domain, 24-h Holter</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spectral FFT, 4-min supine acquisition</td>
<td>12 weeks of ACE inhibitor treatment ↑ HF HRV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poincaré plots, Time domain, 24-h Holter</td>
<td>Complex plots are associated with ↑ norepinephrine levels and greater sympathetic activation</td>
<td></td>
</tr>
<tr>
<td>Heart Transplantation</td>
<td>Time domain, 24-h Holter</td>
<td>Reduced HRV in denervated donor hearts; recipient innervated hearts had more HRV</td>
<td>Patients with rejection documented biopsy show significantly more variability</td>
</tr>
<tr>
<td></td>
<td>Spectral FFT, 15-min supine acquisition</td>
<td>HRV from 0.02 to 1.0 Hz; 90% reduced</td>
<td></td>
</tr>
<tr>
<td>Chronic Mitral Regurgitation</td>
<td>Spectral FFT, Time domain, 24-h Holter</td>
<td>HR and measures of ULF by SDANN correlated with ventricular performance and predicted clinical events</td>
<td>May be a prognostic indicator of atrial fibrillation, mortality and progression to valve surgery</td>
</tr>
<tr>
<td>Mitral Valve Prolapse</td>
<td>Spectral AR, 10-min supine acquisition</td>
<td>MVP patients had ↓ HF</td>
<td>MVP patients had low vagal tone</td>
</tr>
<tr>
<td>Cardio-myopathy</td>
<td>Spectral FFT, Time domain, 24-h Holter</td>
<td>Global and specific vagal tone measurements of HRV were ↓ in symptomatic patients</td>
<td>HRV does not add to the predictive accuracy of known risk factors of HCM</td>
</tr>
<tr>
<td>Sudden Death or Cardiac Arrest</td>
<td>Spectral AR, Time domain, 24-h Holter</td>
<td>HRV as measured by LF power and SDNN were significantly related to 1-y mortality</td>
<td>HRV is clinically useful to risk stratify CA survivors for 1-y mortality</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>DISEASE STATE</th>
<th>INVESTIGATION PARAMETER</th>
<th>CLINICAL FINDING</th>
<th>POTENTIAL VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden Death or Cardiac Arrest</td>
<td>Spectral AR, Time domain, 24-h Holter</td>
<td>↓ HF powers in CA survivors; LF power did not discriminate CA survivors; Circadian pattern of HRV found in all patients</td>
<td>HRV may be used to estimate the risk of SD</td>
</tr>
<tr>
<td></td>
<td>Time domain, 24-h Holter</td>
<td>↓ short-term variation (0.05-0.50 Hz) independently increased by a factor of 2.6; ↓ long-term variation (0.02-0.05 Hz) increased the risk of SD by a factor of 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time and frequency domain, 24-h Holter</td>
<td>Both time and frequency domain indices separated normals from SD patients; ↓ HF power (0.35-0.5 Hz) was the best separator between heart disease patients with and without SD</td>
<td>HF power may be a useful predictor of SD</td>
</tr>
<tr>
<td></td>
<td>Time domain, 24-h Holter</td>
<td>SDNN index significantly lower in SD patients</td>
<td>Time domain indices may identify increased risk of SD</td>
</tr>
<tr>
<td>Ventricular Arrhythmias</td>
<td>Time domain, 24-h Holter</td>
<td>HRV indices do not change consistently before VF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spectral AR, 24-h Holter</td>
<td>All power spectra of HRV were significantly ↓ before the onset of sustained VT than before non-sustained VT</td>
<td>A temporal relation exists between the decrease of HRV and the onset of sustained VT</td>
</tr>
<tr>
<td></td>
<td>Spectral FFT, Time domain, 24-h Holter</td>
<td>MI patients; they differ strikingly in terms of baroreflex sensitivity</td>
<td>Baroreflex sensitivity, not HRV, distinguished post-MI patients with and without VF and VT</td>
</tr>
<tr>
<td>Supra-ventricular Arrhythmias</td>
<td>Spectral FFT, Time domain, 5-min supine acquisition, 24-h Holter</td>
<td>↑ HR, ↓ HRV, and ↓ parasympathetic components after radio frequency ablation</td>
<td>Parasympathetic ganglia and fibers may be more dense in the mid and anterior low septum</td>
</tr>
</tbody>
</table>

Table 2.3: Selected summaries of clinical studies of heart rate variability (modified from [167])
ACE=angiotensin converting enzyme; AR=autoregressive; CA=Cardiac Arrest; CHF=congestive heart failure; FFT=fast Fourier transform; HCM=hypertrophic cardiomyopathy; HF=high frequency; HRV=heart rate variability; LF=low frequency; MI=Myocardial Infarction; MVP=Mitral valve prolapse; SD=Sudden Death; SDANN=Standard deviation of averages of RR intervals; SDNN=Standard deviation of RR intervals; VF=ventricular fibrillation; VT=ventricular tachycardia. For additional details and reference information see [167]
neuropathy. Depressed heart rate variability serves both as an indicator of increased risk after infarction and as an early warning sign of diabetic neuropathy [167].

Most studies of hemodynamic variability (whether physiological or clinical in nature) focus on analysis of the spontaneous fluctuations of a single hemodynamic signal. Sections 2.2.1 and 2.2.2 will provide an outline of analysis techniques and emphasize the advantages of newer multi-signal analysis approaches.

2.2.1 Single-Signal Analyses

Although spontaneous fluctuations in blood pressure variability have also been studied (for review see [113, 116]), analyses of heart rate variability are much more common and have provided the most promising results. The popularity of heart rate variability relates to its direct and almost exclusive control by autonomic pathways and also to the ease with which the electrocardiogram can be measured. In this section, we will focus almost exclusively on analyses of heart rate variability. However, many of the techniques discussed have also been applied the analysis blood pressure variability in health [115, 139, 140] and disease [114]. Furthermore, as we shall see in Section 2.2.2, fluctuations in blood pressure are an important component of multi-signal analysis approaches.

It is important to note at this point that most investigations focus on variability arising over the course of 5–30 minute measurements. These analyses are referred to as “short-term” analyses and must be distinguished from “long-term” analyses of measurements taken over the course of multiple (2–48) hours. For the most part, long-term analyses have been investigated only as predictors of clinical outcomes (such as death or arrhythmia), while short-term analyses have also been used for investigating regulatory physiology.
Time Domain Analyses

There are two broad classes of techniques for investigating hemodynamic variability: time domain and frequency domain techniques. Time domain approaches are perhaps the most straightforward. Heart rate variability, for example, can be quantified in terms of changes in mean heart rate (or RR interval) in response to interventions such as the Valsalva maneuver or passive body tilt. It can also be quantified in terms of statistical measures such as the variance of rate or by ratios involving the variance and the mean. For example, one simple and widely used parameter is the standard deviation of normal RR intervals (SDNN). It is important to note that arrhythmic events (such as premature ventricular contractions) interfere with the analysis of heart rate variability. Any beat which does not originate in the sinoatrial node must be excluded from analysis. Therefore, the analysis of variability is often referred to as the analysis of Normal to Normal (or NN) intervals (hence the abbreviation SDNN). It is also important to note that, depending on the time period over which statistics, such as SDNN, are estimated, they may quantify short-term or both short- and long-term heart rate variability.

Another related class of time domain analysis techniques has been referred to collectively as "geometric approaches" [109,167]. These techniques typically call for producing plots of functions such as the sample density distribution of RR intervals or the sample distribution of differences between adjacent RR intervals. Changes in the distributions or geometric patterns are then quantified according to simple equations or curve fitting procedures. In general, these techniques are designed to separate high degrees of variability from low degrees of variability or fast beat-to-beat changes in heart rate from slow changes. High variability or fast beat-to-beat heart rate changes are interpreted as indicators of parasympathetic activity. A selection of common time domain measures is provided in Tables 2.4 and 2.5. A brief review of such techniques may be found in [109].
### Statistical Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>ms</td>
<td>Standard Deviation for all NN intervals.</td>
</tr>
<tr>
<td>SDANN</td>
<td>ms</td>
<td>Standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording</td>
</tr>
<tr>
<td>RMSSD</td>
<td>ms</td>
<td>The square root of the mean of the sum of the squares of differences between adjacent NN intervals</td>
</tr>
<tr>
<td>SDNN Index</td>
<td>ms</td>
<td>Mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording</td>
</tr>
<tr>
<td>SDSD</td>
<td>ms</td>
<td>Standard deviation of differences between adjacent NN Intervals</td>
</tr>
<tr>
<td>NN50 count</td>
<td></td>
<td>Number of pairs of adjacent NN intervals differing by more than 50 ms in the entire recording; three variants are possible counting all such NN interval pairs or only pairs in which the first or second interval is longer</td>
</tr>
<tr>
<td>pNN50</td>
<td>%</td>
<td>NN50 count divided by the total number of all NN intervals</td>
</tr>
</tbody>
</table>

Table 2.4: Selected statistical time domain measures of heart rate variability. (Modified from [167])

### Geometric Measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Units</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRV Triangular</td>
<td></td>
<td>Total number of all NN intervals divided by the height of the histogram of all NN intervals measured on a discrete scale with bins of 1/128 seconds.</td>
</tr>
<tr>
<td>TINN</td>
<td>ms</td>
<td>Baseline width of the minimum square difference triangular interpolation of the highest peak of the histogram of all NN intervals.</td>
</tr>
<tr>
<td>Differential Index</td>
<td>ms</td>
<td>Difference between the widths of the histogram of differences between adjacent NN intervals measured at selected heights (e.g., at the levels of 12,000 and 10,000 samples)</td>
</tr>
<tr>
<td>Logarithmic Index</td>
<td></td>
<td>Coefficient φ of the negative exponential curve $ke^{-\phi t}$ which is the best approximation of the histogram of absolute differences between adjacent NN intervals</td>
</tr>
</tbody>
</table>

Table 2.5: Selected geometric time domain measures of heart rate variability. (Modified from [167])
Frequency Domain Techniques

The second broad class of techniques for single-signal analyses of hemodynamic variability is based in the frequency domain. The most common frequency domain approach involves estimation of the power spectrum of short (minutes) segments of the heart rate time series. A representative power spectrum of short-term heart rate fluctuations is given in Figure 2-3a. In this spectrum, three peaks are discernible. The high-frequency peak is located at the respiratory frequency. The low frequency peaks are located between 0.05 and 0.15 Hz and often overlap. In 1981, Akselrod et al. [2] demonstrated the effects of autonomic blockade on the structure of the heart rate power spectrum. These effects are illustrated in Figure 2-3b. During parasympathetic blockade essentially all heart rate fluctuations above 0.1 Hz are abolished and fluctuations at frequencies less than 0.1 Hz appear reduced. Furthermore, during combined parasympathetic and β-sympathetic blockade, the SA node is chemically denervated and all heart rate variability is effectively abolished. This study demonstrated that the parasympathetic system can mediate heart rate fluctuations over a
wide range of frequencies but the sympathetic system can mediate fluctuations only below approximately 0.1 Hz. For short-term analyses, frequency domain approaches provide better resolution of parasympathetic and sympathetic components of heart rate variability than time domain approaches [29]. In most cases, in long-term analyses, time and frequency domain approaches perform equally well in predicting clinical outcomes [29,95].

2.2.2 Multi-Signal Analyses

Analysis of heart rate variability is a powerful tool for investigating the function of underlying regulatory mechanisms and, in particular the autonomic nervous system. However, such single-signal analyses are also subject to a number of limitations. Heart rate can be viewed as one output from an extremely complex regulatory system (see Figure 2-4). The regulatory system responds to a wide range of inputs and perturbations. In general, from the measurement of only a system output, it is impossible to independently characterize both the system and its input. That is, a change in a system output could be due to a change in system input or to a change in the regulatory system itself. For example, an increase in respiratory effort will lead to an increase in the respiratory peak of the heart rate power spectrum, as will an increase in the gain of the parasympathetically mediated coupling of respiration to heart rate.

A more informative approach to characterizing cardio-regulatory systems is to directly characterize the couplings between multiple signals. The most straightforward of such multi-signal analyses is calculation of cross-correlation functions between two signals such as respiration and heart rate [27] or blood pressure and heart rate [108]. As in single-signal analyses, however, frequency domain approaches provide a better means of resolving autonomic components of the coupling mechanisms. If considered as a linear system, the coupling between two signals such as respiration and heart
rate may be estimated in the frequency domain by non-parametric transfer function estimation [25, 26, 42, 154]. The transfer function, $H(f)$, between an input, $x$ and output, $y$, is given by

$$H(f) = \frac{S_{xy}(f)}{S_{xx}(f)}$$

(2.1)

where $S_{xx}(f)$ is the power spectrum of $x$, and $S_{xy}(f)$ is the cross spectrum of $x$ and $y$ [20, 138].

This technique has been successfully employed to study the respiratory sinus arrhythmia [25, 153–155]. In order to characterize all the modes of a coupling relation, one must excite the system with an input that is broad in its frequency content. Spontaneous respiration is normally rather narrow-band with most of its frequency content centered tightly around the mean respiratory rate. Therefore, randomized breathing protocols have been developed to broaden the frequency content of respiration [21, 25]. Group average transfer functions for subjects in a “vagal” state\(^5\) and a “sympathetic” state are given in Figure 2-5. Note that in the “vagal” state the magnitude of the transfer coupling is non-zero across a broad range of frequencies but that in the “sympathetic” state the pass band is more narrow with a cutoff frequency near 0.1 Hz. The transfer function magnitudes reflect the fact that the

\(^5\)Parasympathetic fibers are routed to the heart in the vagus nerve and therefore the term “vagal” is often used synonymously with parasympathetic.
sympathetic system is capable of modulating heart rate only below approximately 0.1 Hz, while the parasympathetic system may modulate heart rate across a wide range of frequencies [153, 154]. It is interesting to note that since normal respiratory rates are typically greater than six per minute, the respiratory sinus arrhythmia is largely mediated by the parasympathetic nervous system under normal conditions.

Another important hemodynamic parameter which is coupled to heart rate is arterial blood pressure. However, the coupling between heart rate and blood pressure is “closed-loop.” That is, blood pressure effects heart rate but heart rate, in turn, also effects blood pressure. In the case of respiration and heart rate, the physiological coupling is considered “open-loop”, since heart rate does not effect respiration. Non-parametric estimation of transfer functions does not enable one to distinguish feedforward couplings (e.g., the mechanical factors which determine how heart rate fluctuations affect arterial blood pressure) from feedback couplings (e.g., the neurally mediated baroreceptor reflex which determines how fluctuations in blood pressure af-
Figure 2-6 Simple model of cardiovascular regulation incorporating signals derived from measured electrocardiogram, arterial blood pressure and instantaneous lung volume.

To affect heart rate) in a closed-loop model. If one were to apply non-parametric transfer function estimation to such a system, the feedforward and feedback couplings would be intertwined into a single transfer relation (for further discussion see [127]). It is, however, possible to disentangle the feedforward and feedback couplings provided that each coupling is causal and that noise perturbations affecting each signal are uncorrelated [5, 10, 88, 127, 175]. Real physical systems are causal and the noise perturbations to heart rate and blood pressure may be assumed to be independent. Parametric system identification techniques provide a means of mathematically imposing causality so that the feedforward and feedback couplings of a closed loop system can be characterized.

Parametric system identification has been successfully employed to study closed-loop models of short-term hemodynamic regulation such as the one presented in Figure 2-6 [5, 6, 8, 9, 88, 126, 127, 143, 168]. This simple model includes four signals:
Instantaneous Lung Volume (ILV), Pulsatile Heart Rate (PHR), Heart Rate (HR) and Arterial Blood Pressure (ABP). ILV and ABP are directly measured. HR, which is a continuous representation of instantaneous heart rate, and PHR, which is defined as a train of impulses occurring at the times of contraction of the ventricle, are each derived directly from the surface electrocardiogram. Fluctuations in these signals are related by five coupling mechanisms shown in Figure 2-6: [SA NODE], [CIRCULATORY MECHANICS], [HR BAROREFLEX], [ILV ⇒ HR], and [ILV ⇒ ABP].

The sinoatrial node is responsible for converting autonomic outflow into discrete heart beats. The autonomic outflow codes the "desired" instantaneous heart rate and the sinoatrial node serves to effectively integrate this signal, initiate a beat when it reaches a threshold, and then reset to begin integrating again. This "integrate and fire" model of the sinoatrial node has been previously discussed [5, 22, 127]. Thus, [SA NODE] directly relates HR to PHR. Since the dynamics of [SA NODE] are known, [SA NODE] is not identified from experimental data. The other four coupling mechanisms are determined from analysis of the measured signals and provide a "snapshot" of cardiovascular regulation in an individual. [CIRCULATORY MECHANICS] represents the relationship between cardiac contraction and the generation of the ABP waveform. It is determined by the contractile properties of the heart, as well as the mechanical properties of the great vessels and peripheral circulation. [HR BAROREFLEX] represents the autonomically mediated baroreflex coupling between fluctuations in ABP and HR. [ILV ⇒ HR] represents the autonomically mediated coupling between respiration and HR which produces the respiratory sinus arrhythmia. [ILV ⇒ ABP] represents mechanical effects of respiration on ABP due to alterations in venous return and the filling of thoracic vessels and heart chambers associated with changes in intrathoracic pressure. In addition to the five coupling mechanisms, the model incorporates two perturbing noise sources, \( N_{HR} \) and \( N_{ABP} \). \( N_{HR} \) represents the fluctuations in HR not caused by fluctuations in ABP or ILV. Such fluctuations may result from HR pertur-
bations associated with cerebral activity. $N_{ABP}$ represents fluctuations in ABP not caused by fluctuations in PHR and ILV. Such blood pressure fluctuations might arise, for example, from fluctuations in peripheral resistance. A more detailed discussion of the model is given in [127].

The model in Figure 2-6 (except for \text{SA NODE} which is predefined) can be represented by a pair of linear time-invariant autoregressive moving-average difference equations of the form

\[
HR(t) = \sum_{i=1}^{m} a_i HR(t-i) + \sum_{i=1}^{n} b_i ABP(t-i) + \sum_{i=p'}^{p} c_i ILV(t-i) + W_{HR}(t)
\]

\[
ABP(t) = \sum_{i=1}^{q} d_i ABP(t-i) + \sum_{i=1}^{r} e_i PHR(t-i) + \sum_{i=s'}^{s} f_i ILV(t-i) + W_{ABP}(t)
\]

where $t$ is discrete time, $m$, $n$, $p$, $p'$, $q$, $r$, $s$ and $s'$ limit the number of terms in the model, and $W_{HR}$ and $W_{ABP}$ are noise terms referred to as residual errors. These equations include six sets of parameters, \{a_i\}, \{b_i\}, \{c_i\}, \{d_i\}, \{e_i\}, \{f_i\}, which are determined by analysis of continuous records of the measured ABP, ECG and ILV signals. Once the parameters are determined, the transfer relations describing the coupling mechanisms are fully defined and the power spectra of $N_{ABP}$ and $N_{HR}$ may be computed (for further discussion see [127]).

Typical system identification results for a single individual are given in Figure 2-7. The coupling mechanisms are represented as impulse responses with corresponding ninety-five percent confidence intervals. The impulse-response function is a means of fully describing the transfer relation of a linear time-invariant system. It represents the time evolution of the system output when given an arbitrarily narrow unit area impulse at time zero as the input. Each of the impulses responses is physiologically reasonable given the mechanisms it represents [127]. For example, the \text{HR BAROREFLEX} rapidly decreases towards negative values reflecting the decrease in heart rate expected in response to an increase in arterial blood pressure. The magnitude of the response is within a physiologically reasonable range for a sub-
Figure 2-7 Complete set of short-term system identification results for a single standing subject. Transfer couplings are represented as impulse responses with 95% confidence intervals. Noise sources are presented as power spectra (from [127]).
ject with normal baroreflex sensitivity. The dependence of the transfer couplings on autonomic regulation is well demonstrated by a comparison of data obtained during resting control with those obtained during joint blockade of the parasympathetic and $\beta$-sympathetic systems. These results are depicted in Figure 2-8. The impulses responses of the two coupling mechanisms that are autonomically mediated, $\text{HR BAROREFLEX}$ and $\text{ILV} \Rightarrow \text{HR}$ are essentially abolished by joint blockade. The $\text{CIRCULATORY MECHANICS}$ and $\text{ILV} \Rightarrow \text{ABP}$ couplings, which are primarily mechanically mediated, are largely unchanged. The coupling mechanisms have also been shown to be sensitive to more subtle alterations in autonomic activity such as those associated with change in posture [127].

One clinical application of the system identification approach has shown promising results. Mukkamala et al. [125, 126] applied system identification to evaluate autonomic neuropathy in a group of diabetic patients in comparison to normal control subjects. The diabetic patients were classified as either having minimal, moderate, or severe autonomic neuropathy based on standard autonomic tests. On the basis of these tests, the group with minimal autonomic neuropathy could not be distinguished from the normal control subjects. The group average system identification results for these subjects are presented in Figure 2-9. As one would expect, the mechanically mediated couplings, $\text{CIRCULATORY MECHANICS}$ and $\text{ILV} \Rightarrow \text{ABP}$ are not changed with autonomic neuropathy. However, the autonomically mediated $\text{ILV} \Rightarrow \text{HR}$ and $\text{HR BAROREFLEX}$ impulse responses show an incremental diminution with increasing neuropathy. In the severe neuropathy group, these responses are nearly abolished. The results also statistically significant differences between the control group and the minimal neuropathy group. These two groups were indistinguishable using standard tests, and these results suggest that system identification may provide a more sensitive

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6In fact, although $\text{CIRCULATORY MECHANICS}$ is determined by the mechanical properties of the heart and vasculature, these properties are subject to autonomic modulation. The group average $\text{CIRCULATORY MECHANICS}$ coupling shows small but statistically significant changes during joint autonomic blockade. [127].
Figure 2-8 Group average short-term system identification results for subjects before (solid lines) and after (dashed lines) administration of joint parasympathetic and β-sympathetic blockade (from [127]).
Figure 2-9 Group average system identification results for normal subjects and patients with varying degrees of diabetic autonomic neuropathy (from [125]). Solid, dashed, dashed-dotted and dotted lines respectively designate Control group and Minimal, Moderate and Severe neuropathy groups.
marker of autonomic neuropathy than standard tests [125, 126].

Multi-signal analyses based on system identification procedures offer a new, more powerful way of studying and monitoring cardiovascular function. Instead of simply interpreting cardiovascular signals, the signals are processed to characterize and quantify the mechanisms that generate them. These techniques, therefore, provide a more direct characterization of the regulatory systems under study and also allow more specific characterizations of individual couplings between hemodynamic variables than do single-signal analyses.

2.2.3 Special Considerations in Long-Term Analyses

Short-term fluctuations in cardiovascular parameters have been studied to a far greater extent than long-term (lower frequency) fluctuations. However, recent studies suggest that analyses of long-term fluctuations may provide improved clinical data compared to analyses of short-term fluctuations [31,96] and therefore interest in long-term analyses is growing.

The most common approaches to the study of long-term hemodynamic variability have been single-signal, time domain analyses of heart rate fluctuations. Typical time domain measures were discussed in Section 2.2.1 and summarized in Tables 2.4 and 2.5. The techniques have been most often applied to analysis of 24-hour Holter monitor measurements and have been used to evaluate a wide range of clinical conditions (Table 2.2). Clinical associations between a variety of measures of survival after myocardial infarction and changes in measures of heart rate variability have been the most promising outcomes of these time-domain studies [38,96]. Long-term analyses have been shown, in these cases, to provide better clinical prediction than short-term analyses. For example, Fei et al. compared the relative powers of short- and long-term time domain measures in predicting one-year total cardiac mortality after myocardial infarction. They found that although short-term analyses provided
Figure 2-10 A schematic representation of the 24-hour heart rate power spectrum. The shaded regions illustrate the standard power spectral bands used for predicting mortality and for physiological and pharmacological investigations. ULF=ultra-low frequency (0.00001–0.0033 Hz), VLF=very-low frequency (0.0033–0.04 Hz), LF=low frequency (0.04–0.15 Hz), HF=high frequency (0.15–0.4 Hz) The numbers in parentheses indicate typical values for the fraction of total power in each band. (from [29])

good predictive power, long-term analyses provided improved prediction [52].

Frequency domain analyses of long-term heart rate fluctuations have typically involved computation of the power spectrum of 24-hour recordings. Interestingly, the total power in ultra-low (0.00001-0.0033 Hz, ULF) and very-low (0.0033-.04 Hz, VLF) frequency bands are significant predictors of mortality after myocardial infarction. In fact, they are better predictors than the power in the low frequency (0.04-0.15 Hz, LF) and high frequency (0.15-0.4 Hz, HF) bands as determined from short-term analyses (see Figure 2-10) [29, 31]. Therefore, it seems that lower frequency heart rate variability may provide more relevant clinical or physiological information than short-term variability. That is, the improved predictive capability is not simply due to the addition of low frequency information but rather, low frequency information seems to be more informative than high frequency information. There have, as yet, been no direct associations between ULF and VLF heart rate fluctuations and underlying
physiological control systems. At higher frequencies, the autonomic nervous system has been clearly established as the main physiological control system mediating heart rate fluctuations, but it remains unclear which systems contribute to lower frequency fluctuations. Therefore, the questions remain as to why low frequency fluctuations are clinically important and what regulatory systems are involved in generating these fluctuations.

Frequency domain analyses have revealed an interesting pattern in the low frequency fluctuations. Kobayashi and Musha [97] first reported and numerous others have verified [82,139,151,166,179] that the power spectral density of heart rate over many decades of (low) frequency is approximately inversely proportional to frequency ($1/f^\alpha$, where $\alpha$ is close to 1). On a log-log scale, the spectrum appears as a line with slope close to -1 or equivalently $\alpha \approx 1$. This spectral shape is characteristic of a well known, widely occurring phenomenon known as “$1/f$ noise” (pronounced one-over-f noise). The occurrence of $1/f$ noise in many diverse systems is a classic problem in physics and the mechanisms which may lead to such fluctuations remain poorly understood in most systems. There are, however, numerous implications of this spectral pattern. For example, the heart rate waveform is scale invariant; that is, the waveform appears qualitatively the same regardless of the time scale. Furthermore, estimates of the variance of the HR waveform will depend on the observation duration since, as more low frequency power is included, the estimate will increase. This is clearly an important consideration in applying time-domain analysis based on estimates of the standard deviation of heart rate or RR intervals. $1/f$ noise and its characteristics will be further discussed in Section 2.3.

In a recent study, Bigger et al. have demonstrated that both the slope and intercept of the regression line fit to the log(power) versus log(frequency) curve are significantly altered in patients with myocardial infarction or with heart transplants relative to healthy subjects [34]. Furthermore, these regression parameters were signif-
ificant predictors of mortality and were even better predictors than were the ultra-low frequency band and very-low frequency band powers [34]. A number of other studies have focussed on evaluating the $1/f^\alpha$ spectral character of heart rate variability. Parati et al. have reported that $\alpha$ becomes more negative (steeper negative slope) with age due to a reduction of power at the higher frequencies [40]. This result may be interpreted to be due to the well-known reduction of autonomic modulation of heart rate variability with age [53, 115]. However, Yamamoto et al., in a study of ten healthy human subjects, reported that the slope of the (log-log) power spectrum of heart rate fluctuations was not altered by administration of $\beta$-adrenergic blockade [179]. This finding suggests that the sympathetic nervous system does not play a major role in modulating these $1/f$ fluctuations. It should be pointed out that some researchers may question the assumption that heart rate variability is well represented as a $1/f$-type signal. For example, Meesman et al. used a time domain technique based on counting statistics to evaluate the $1/f$ nature of heart rate fluctuations [121] over a 24 hour period. They report that heart rate variability in general is well approximated as $1/f$ but that intermittently during night hours, the fluctuations more closely resemble white noise.

Heart rate is not the only cardiovascular signal to exhibit $1/f$ noise. The power spectral density of arterial blood pressure has also been reported to demonstrate a $1/f^\alpha$ form [117, 139, 172, 173]. Wagner and Persson have suggested that the blood pressure power spectrum is best approximated by two distinct $1/f^\alpha$ regions with slightly differing values of $\alpha$ [172]. It has also been reported that renal blood flow in conscious dogs exhibits a $1/f^\alpha$ spectral shape with $\alpha = 0.94$ [173].

Many other physiological processes also exhibit $1/f$-type fluctuations (see Section 2.3.2) and the inherent complexity of these systems has led to a new concept in evaluating pathological conditions. These complex patterns of variability seem to be associated with normal regulatory processes in healthy individuals. Furthermore,
a reduction in the complexity of a physiological signal such as heart rate may be associated with pathology. For example, a reduction of high frequency heart rate variability has been associated with diabetic autonomic neuropathy and congestive heart failure. Furthermore, the transition of a physiological system from complex fluctuations to more simple rhythmic variability may indicate pathology as in the case, for example, of Cheyne-Stokes breathing\textsuperscript{7} [62,176]. Thus, it has been hypothesized that complexity is a sign of health and loss of complexity is associated with disease. These concepts are well reviewed in [18,176] and are discussed in the context of cardiovascular regulation in [59,60,63,64,159].

Some researchers have speculated that the $1/f$ spectral form reflects nonlinear dynamic features of the cardiovascular regulatory mechanisms [60]. However, there is no direct evidence for this hypothesis. Furthermore, over the short term, numerous studies have found that the couplings between small fluctuations about mean values of cardiovascular signals appear to be well approximated by linear systems [6,126,127,168]. While the $1/f^\alpha$ spectral form may indicate some fundamental principle of cardiovascular regulation, the mechanisms generating this remarkable feature must, as yet, be considered unknown.

2.3 $1/f^\alpha$ Power Spectra

Power spectral distributions of the $1/f^\alpha$ form are quite common in many natural phenomena. Signals or processes which produce this $1/f^\alpha$ spectral shape are often referred to as $1/f$ noises or $1/f$ processes. These terms are used generically to describe processes with values of $\alpha$ in the range $0 < \alpha < 2$ and are not reserved only for processes with $\alpha = 1$. It is interesting to note that when $\alpha = 0$ the process is a "white noise" with a flat power spectrum, and when $\alpha = 2$, the process is a "Brownian motion".

\textsuperscript{7}West [176] refers to this change as a "loss of spectral reserve," suggesting that the system has somehow lost its capacity to avoid oscillating at a set of discrete frequencies.
The ubiquity of $1/f$ noise is a classic problem in physics. Its widespread occurrence is suggestive of some fundamental principle or mechanism. However, such a mechanism has not been identified and in fact, given the diversity of systems which exhibit $1/f$ noise it is difficult to imagine how such a universal mechanism could apply.

One of the areas in which $1/f$ noise was first discovered was in electronic systems. Johnson first reported on $1/f$ noise in electronic devices in 1925 and, since that time, $1/f$ fluctuations have been seen in voltages and currents across diodes, transistors and vacuum tubes, in resistances of metallic thin-films, and in a range of other electronic devices [37]. Over the years, $1/f$ noise has gone by many names including “current noise”, “excess noise”, “flicker noise”, “semiconductor noise”, “contact noise”, and “pink noise” [37, 80]. Despite significant research effort, the physical origin of $1/f$ noise is not understood (except perhaps in a few specific cases). In some electronic devices, it is thought to be a surface effect (i.e., MOSFETs), but in others such as resistors, it is thought to be a bulk effect. In a homogeneous resistor, $1/f$ noise has been associated with random modulation of resistance due to fluctuations in either the mobility or number of charge carriers. Interestingly, $1/f$ fluctuations also appear in voltages and currents across aqueous ion solutions. The topic of $1/f$ noise in electronics is well reviewed in [37, 79] and in a special issue of IEEE Transactions on Electronic Devices [85].

$1/f$ noise also appears in natural phenomena such as the occurrence of earthquakes and thunderstorms [107], average seasonal temperature fluctuations [90], the flow of the river Nile [37, 90], and annual amounts of rainfall [90]. It is also seen in the fluctuations of the frequency of quartz crystal oscillators [90], computer network traffic [46], ecological and evolutionary models [75, 118], neural networks [124], music [57, 171], and flow of automobile traffic [43, 130, 131].

In physiological systems, $1/f$ fluctuations have been identified in the rate of insulin uptake by diabetics [89], brain wave fluctuations [72], voltages across nerve mem-
branes [135, 170] and synthetic membranes [135], human tapping intervals [58, 132],
daily neutrophil counts [61], protein dynamics [49], axonal action potential propa-
gation [133, 134], and optokinetic nystagmus [174]. Some of these systems will be further
discussed in Section 2.3.2. The topic is well reviewed in [18, 176].

2.3.1 Characteristics and Implications of $1/f^\alpha$ Power Spectra

Interest in $1/f^\alpha$ noise is largely due to its presence in such a diverse range of phe-
nomena. However, such processes demonstrate a number of inherently interesting
characteristics and consequences [18, 37, 157].

In simple terms, one may consider a $1/f$ process as one in which large events
occur infrequently while small events occur much more frequently. For example, the
distribution of energy released during earthquakes obeys the Gutenberg-Richter Law
which states that the frequency of occurrences of earthquakes scales as an inverse
power law of earthquake size [13]. Earthquakes which release a large amount of
energy are rare, while small tremors are quite common. From another perspective,
Keshner has pointed out that from a $1/f$ process one expects long-lived events. For
example, he notes that if weather patterns, such as the patterns of rainfall, may be
modeled as $1/f$ (as some empirical evidence suggests) then occasional occurrences
such as 40 days and 40 nights of rain are an expected consequence [89].

The most important characteristic of a true $1/f$ process is scale invariance. The
property of scale invariance implies that fluctuations occur in a similar manner at
all frequencies or on all time scales. If one were to view a time segment of a $1/f$
signal and then zoom in on a smaller time segment of the same signal, the two signals
would appear qualitatively similar. This property is illustrated in Figure 2-11. In
the frequency domain scale invariance is demonstrated by the distribution of power.
Consider the total power in a band of frequencies between $\omega_1$ and $\omega_2$ which is given
Figure 2-11 Demonstration of scale invariance in a $1/f^{\alpha}$ signal. Inset (b) is a magnified image of the boxed region in inset (a). Inset (c) is a magnified image of the boxed region in inset (b). The signals all appear qualitatively similar as magnification reveals smaller and smaller fluctuations. (from [176]).
by
\[ P_x(\omega_1, \omega_2) = \frac{1}{2\pi} \int_{\omega_1}^{\omega_2} S_x(\omega) \, d\omega. \] (2.2)

When \( S_x(\omega) \sim \frac{1}{\omega} \),
\[ P_x(\omega_1, \omega_2) = \left( \frac{c}{2\pi} \right) \ln \frac{\omega_1}{\omega_2}. \] (2.3)

For a constant frequency ratio, \( \omega_1/\omega_2 \), the integrated power is constant. That is, the total power in the frequency ranges 0.1–1 Hz, 1–10 Hz, 100–1000 Hz or any other decade of frequency are all equal.

A second important implication of a true \( 1/f \) noise (which has generated significant debate in the literature) is that a theoretical signal with a true \( 1/f \) power spectrum has an infinite variance (which implies an infinite power). Thus, many researchers assert that the only physically realizable \( 1/f \) process must non-stationary. The problem lies at the low frequency limit of the spectrum. If the process is truly \( 1/f \) down to zero frequency, then the total power diverges. Thus, some researchers have empirically sought low frequency limits below which the power spectrum flattens. However, in most systems, such a limit has not been identified. In fact, in practice, this is not a problem since any measurement of the waveform, no matter how long, will be finite in duration. Therefore, the lowest frequency measured will always be greater than zero and the total measured power will be finite. Buckingham demonstrates that a band pass filtered \( 1/f \) process may indeed be stationary although a low pass filtered \( 1/f \) process may not \[37]. Thus, by altering the theoretical model in a minutely detailed manner which is undetectable in practice, the process can be changed from non-stationary to stationary. He asserts that

The unavoidable conclusion is that there is no reason in principle why \( 1/f \) noise should show a flattening of the spectrum below some low-frequency limit; an infinity which appears only after looking for an infinite time is not a cause for concern.
In fact, although the physical realizability of such a process is not a need for concern, the variance remains an important practical concern. Estimates of the variance will depend on the observation time. This may be theoretically interpreted as meaning that the observation time was not long enough to allow the statistical measure to converge to a unique limiting form. However, from a practical standpoint, any applications or interpretations of the estimated variance of a $1/f$ process must be directly related to the observation time.

It should also be noted that the upper limit of the $1/f$ spectrum is also not a practical concern since in this range the low power values of the $1/f$ process are often masked by other noises or processes. Furthermore, the inherent physical limitations on the response time of the systems will limit the extent of high frequency $1/f$ noise [37].

A third important implication of $1/f$ noise is that of long-term memory. A white noise process has no memory in that the current value of the measured signal is not a function of the previous values of the signal. Each sample, by definition, is independent of the others. [89,90,157]. The influence of past history on the present value of a Brownian noise may be summarized in a single variable, the initial value. A $1/f^\alpha$ process with $\alpha$ near one is influenced equally by recent and distant past values. Keshner has shown that $1/f$ processes are best characterized as requiring one variable per decade of frequency to summarize effects of past events on current events [90]. Thus from an information standpoint, a $1/f$ process may be thought of as accumulating information into summaries so that very distant past events are summarized in large groups while more recent events are summarized in smaller groups.

2.3.2 $1/f^\alpha$ Noise in Other Physiological Systems

As mentioned above, variables exhibiting characteristics of $1/f$ noise have been identified in a wide range of physiological systems other than the cardiovascular system. In this section, a few of these cases will be discussed in further detail.
It may be argued that, due to the potential for wide ranging effects throughout the body, one of the most important places that 1/f fluctuations are seen in physiological systems is in the membrane potentials of neurons and in action potential propagation. The voltage across a nerve membrane exhibits 1/f fluctuations when the current across the membrane is clamped and similarly, current fluctuations are 1/f when the voltage is held constant [135, 170]. Thus, it seems that membrane "resistance" fluctuates as 1/f. It has been suggested that these fluctuations are associated with membrane potassium channel dynamics, but no definitive mechanisms have been identified [133]. Musha et al. have found that action potential interval fluctuations in a tonically active giant snail neuron are distributed as 1/f. They postulate that these fluctuations may be associated with membrane fluctuations causing alterations in the firing threshold but indicate that more data is necessary to support this conclusion [134]. Finally, in a later paper, Musha et al. reported on studies in which a squid giant axon was stimulated with a Gaussian, white impulse train. The action potential interval sequences measured from the axon acquired a 1/f distribution. This "filtering" effect of the neuron is attributed to the refractory period of the axon which eliminates pulses arriving after too short an interval and also modifies the propagations speeds [133].

In a retrospective study, Goldberger et al. [61] examined daily neutrophil (the most common form of white blood cell) counts collected from healthy patients over 64 consecutive days. They found that the counts fluctuated in a 1/f fashion. They did not propose a mechanism for these fluctuations, and it remains unclear whether these fluctuations may be attributed to the processes governing neutrophil production or release or to the processes governing their destruction and removal. Goldberger et al. emphasize, however, that these fluctuations represent the healthy system and that a loss of the broad-band 1/f fluctuations may be a good hematologic indicator of pathology. They provide as examples two pathological conditions, cyclic neutropenia and chronic granulocytic leukemia which have been associated with cyclical oscillations in
daily neutrophil counts.

1/f noise has also been associated with human cognition. If an individual attempts to tap at a constant interval, there is inevitably some error associated with each interval. The distribution of this error has been found to fluctuate as 1/f [58,132]. Musha et al. also found that when individuals listen to a metronome while tapping, the error is no longer 1/f but is white. Gilden et al. [58] extended these investigations to another perceptual domain by having subjects repeatedly reproduce a spatial interval. Once again the errors in spatial reproductions fluctuated as 1/j. Gilden et al. also recorded a series of reaction times in their subjects and found that the fluctuations in reaction times were not 1/f but rather were white. They conclude that the errors in reproducing spatial and temporal intervals are associated with cognitive processes related to judgment of magnitudes [58].

It is interesting to note that not only do many physiological variables fluctuate as 1/f but certain stimuli have been identified as most pleasing when they are characterized by 1/f fluctuations. Music is the classic example [57,129,171]. The power spectrum of both the loudness and the frequency fluctuations of most music are well approximated as 1/f. This applies to nearly all types of music but is particularly true of classical music. In fact, if music is artificially created based on white noise, Brownian noise (1/f²) and 1/f noise distributions, the 1/f version is typically found to be most pleasing [57,133]. The music derived from white noise is found to be “irritating” while that based on Brownian noise is “boring” [57,133]. Another stimuli which is most pleasing when it has a 1/f character is transcutaneous electrical nerve stimulation (TENS) which is used for the relief of chronic intractable pain. There is some evidence that such stimulation is most effective when the stimulating pulse frequencies and durations are derived from 1/f fluctuations [129].

Finally, the property of scale invariance exhibited by 1/f processes may be extended from time scales, as have been discussed thus far, to spatial scales. Structures
which demonstrate spatial scale invariance are referred to as self-similar structures or fractals. Much like $1/f$ noise, fractal-like structures are ubiquitous in nature. A wide range of physiological structures has been studied as fractals including, for example, arterial branching structures, the branching of airways in the lung, and the His-Purkinje conduction system of the heart. Some researchers have proposed that fractal spatial structures may give rise to $1/f$ fluctuations in the time sequences of physiological variables [59, 60, 64] but experimental evidence is lacking [23]. Investigations of fractal-like structures in physiology are well reviewed in [18, 176] and in a special issue of the *Annals of Biomedical Engineering* [120].

This brief review suggests that even within physiological systems, $1/f$ noise seems to arise in a range of quite diverse systems, and the mechanisms underlying these fluctuations remain poorly understood.

### 2.3.3 Examples of Simple Systems producing $1/f^\alpha$ signals

In this section, a few simple systems which produce $1/f$ noise are provided as examples. As a first example, the transfer of concentration associated with a one dimensional diffusion process is derived. The second and third examples are derived from simple electrical circuit models and demonstrate that simple linear systems may produce accurate approximations to $1/f$ noise. The fourth example, that of a simple sandpile which may produce $1/f$ fluctuations in sand avalanches, is an example of the theory of self-organized criticality. Finally, an example of a general statistical argument for the occurrence of $1/f$ noise is considered.

**Diffusion in One Dimension**

One simple system which generates $1/f^\alpha$ fluctuations when driven by random (white) noise is simple one dimensional diffusion. Consider the situation in which a solute is dripped or released in small quantities at one location (the origin) and is allowed to
Figure 2-12 Schematic representation of a simple one dimensional diffusion model. A white time distribution of concentration at the origin, free to diffuse in one dimension, leads to a 1/f distribution of concentration at points nearby. See text for details.

diffuse in one dimension away from that point. This model is depicted in Figure 2-12. If the solute is dripped at random intervals so that the spectrum of concentration at the origin is white then the fluctuations in the concentration of solute at a point a short distance away will acquire a 1/f pattern at low frequencies. Such a one dimensional diffusion is described by the “diffusion equation” [180]

$$\frac{\partial c(x,t)}{\partial t} = D \frac{\partial^2 c(x,t)}{\partial x^2} \quad \text{for} \quad t > 0$$  \hspace{1cm} (2.4)

where $c(x,t)$ is concentration as a function of time $t$ and linear dimension $x$, and $D$ is a diffusivity constant.

The initial condition of an impulse of concentration at the origin, $c(x,0) = \delta(x)$, gives the solution

$$c(x,t) = \frac{q}{2\sqrt{\pi Dt}} e^{-\frac{x^2}{4Dt}} \quad \text{for} \quad t > 0$$  \hspace{1cm} (2.5)

which is known as the fundamental solution of the diffusion equation [135,165,180].
The transfer function is then given by the Fourier transform with respect to time, $C(x, \omega)$. The strategy in deriving this transfer function is to first take the Fourier transform with respect to $x$ giving $C(\kappa, t)$ where $\kappa$ is spatial frequency, then transform the result with respect to time giving $C(\kappa, \omega)$ and finally take the inverse Fourier Transform with respect to space to arrive at $C(x, \omega)$.

The Fourier transform with respect to $x$, is given by

$$C(\kappa, t) = \int_{-\infty}^{\infty} \frac{1}{2\sqrt{\pi Dt}} e^{-\frac{x^2}{4Dt}} e^{-j\kappa x} \, dx$$

$$= \frac{1}{2\sqrt{\pi Dt}} \sqrt{4Dt\pi} e^{-16Dt\kappa^2}$$

$$= e^{-16Dt\kappa^2} \quad \text{for} \quad t > 0 \quad (2.6)$$

The Fourier transform with respect to time, $t$, is then

$$C(\kappa, \omega) = \int_{-\infty}^{\infty} e^{-16Dt\kappa^2} u(t)e^{-j\omega t} \, dt$$

$$= \frac{1}{j\omega + 16D\kappa^2} \quad (2.7)$$

where $u(t)$ is the unit step function.

Now, the last step is to invert the transform with respect to space

$$C(x, \omega) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{1}{j\omega + 16D\kappa^2} e^{j\kappa x} \, d\kappa$$

$$= \frac{1}{32D\pi} \int_{-\infty}^{\infty} \frac{1}{(\kappa - \sqrt{\frac{j\omega}{16D}})(\kappa + \sqrt{\frac{j\omega}{16D}})} e^{j\kappa x} \, d\kappa$$

and by substituting $\sqrt{j} = \frac{1+j}{\sqrt{2}}$ we arrive at

$$C(x, \omega) = \frac{1}{2\pi} \int_{-\infty}^{\infty} \frac{1}{16D(\kappa - (1+j)\sqrt{\frac{\omega}{32D}})(\kappa + (1+j)\sqrt{\frac{\omega}{32D}})} e^{j\kappa x} \, d\kappa \quad (2.9)$$

We now solve this via contour integration, recognizing that the two poles are at $\pm\sqrt{\frac{\omega}{32D}}(1+j)$. The two appropriate contours are schematically represented in
Figure 2-13. For $x > 0$ we use the solid semicircular contour and find

$$C(x, \omega) = 2\pi j \left[ \frac{1}{2\pi} \lim_{\kappa \to \sqrt{\frac{\omega}{32D}(1+j)}} \frac{\kappa - (1+j)\sqrt{\frac{\omega}{32D}}e^{j\kappa x}}{16D(\kappa - (1+j)\sqrt{\frac{\omega}{32D}})(\kappa + (1+j)\sqrt{\frac{\omega}{32D}})} \right]$$

$$= j \left( \frac{e^{j(1+j)x}\sqrt{\frac{\omega}{32D}}}{32D((1+j)\sqrt{\frac{\omega}{32D}})} \right)$$

(2.11)

Multiplying by $\frac{1-j}{1+j}$, converting all terms to polar coordinates and simplifying gives

$$C(x, \omega) = \left( \frac{\sqrt{2e^{\frac{j\pi}{4}}} e^{-\sqrt{\frac{\omega}{32D}}x} e^{j\sqrt{\frac{\omega}{32D}}x}}{64D \sqrt{\frac{\omega}{32D}}} \right)$$

(2.12)

Finally, the squared magnitude of the transfer function is

$$|C(x, \omega)|^2 = \frac{e^{-2\sqrt{\frac{\omega}{32D}}x}}{64D\omega} \quad \text{for} \quad x > 0$$

(2.13)

By symmetry or by a similar derivation using the second pole and dashed contour in Figure 2-13, it can be shown that

$$|C(x, \omega)|^2 = \frac{e^{2\sqrt{\frac{\omega}{32D}}x}}{64D\omega} \quad \text{for} \quad x < 0$$

(2.14)

Thus, for low frequencies (small $\omega$) or for small distances from the origin (small $x$), the transfer of concentration is approximately proportional to $\frac{1}{\omega}$. 67
**Figure 2-14** Lumped parameter representation of infinite RC transmission line.

a

![Diagram of an infinite RC transmission line](image)

b

![Diagram of an RC model producing \(1/f^\alpha\) power transfer](image)

RC models producing \(1/f^\alpha\) power transfer

A second system with a \(1/f^\alpha\) power transfer is an idealized continuous resistor-capacitor transmission line [90]. A lumped parameter representation of such a transmission line is illustrated in Figure 2-14a. Each RC element represents an impedance per unit length of the infinite line.

The impedance of the line may be calculated from the finite length circuit in Figure 2-14b with the knowledge that \(Z = Z_0\) (adding or removing a single RC element to the infinite length line has no effect on the impedance).

The impedance is given by

\[
Z = R + \frac{1}{j\omega C + \frac{1}{Z}}
\]  

(2.15)
Solving for $Z$ gives,

$$Z^2 - RZ - \frac{R}{j\omega C} = 0$$

$$Z = \frac{R}{2} \pm \sqrt{\frac{R^2}{4} + \frac{R}{j\omega C}}$$

(2.16)

For the continuous approximation, the unit length is allowed to approach zero which forces $R$ and $C$ to approach zero, but the ratio $\frac{R}{C}$ remains constant and the thus the total line impedance is

$$Z = \sqrt{\frac{R}{j\omega C}}$$

(2.17)

If a white noise current source is applied to the input of the line, the power spectral density of the voltage is given by

$$S(f) = T^2 \frac{R}{\omega C} = \left( \frac{I^2 R}{2\pi C} \right) \frac{1}{f}.$$  

(2.18)

Another linear system which can approximate $1/f^\alpha$ power transfer is a simple series of resistor-capacitor networks separated by unity gain buffer amplifiers [90] as illustrated in Figure 2-15. Each stage of the circuit adds a single pole and a single zero to the transfer function. When driven by a white noise source, the voltage $V_0$ can be made to have a power spectrum that approximates the $1/f$ shape to within an arbitrary error [90]. The approximation is improved by adding additional stages to the circuit. Keshner [90] calculated the number of stages required for a $\pm 5$ percent
Figure 2-16 Approximation of $1/f^\alpha$ transfer function with simple pole-zero pairs of a linear system. From [90]

fit for a range of values of $\alpha$. Figure 2-16 illustrates his results. To approximate a $1/f$ power spectrum ($\alpha = 1$ to within 5 percent requires only about one circuit segment (one pole and one zero) per decade. For values of $\alpha$ other than one, fewer and fewer circuit sections are required. As $\alpha$ approaches zero (white noise) and as $\alpha$ approaches 2 (Brownian motion) the number of poles and zeros decreases toward zero. Thus, for a $1/f$ power spectrum with $\alpha$ close to one, we can approximate the system with a finite number of linear elements. In fact, to approximate the four decades of biological fluctuations seen in the course of 24 hours, we can expect to need only four poles and four zeros for a five percent fit.

Self-Organized Criticality

One theory which has been proposed as a general mechanism for $1/f$ noise in a wide range of systems is self-organized criticality. This theory was first proposed by Bak et al. [14,15] and has been the subject of much interest over the past decade [12,69,83].

The basic tenet of the theory is that large dissipative dynamical systems with
a large number of both spatial and temporal degrees of freedom approach a critical state with no characteristic time or length scale. More simply stated, composite systems which contain millions of elements that interact over short ranges naturally evolve to a state in which a minor event can lead to a large or catastrophic event. The process of development of a catastrophic event generally involves a series of chain reactions where a minor event triggers multiple other events which in turn trigger more events. Although in the critical state, a minor event is much more likely to produce another minor event, the important point is that the same minor event under the right circumstances may effect any number of other elements. Thus, the mechanism that leads to minor events is the same as the mechanism leading to major events.

Bak et al. have developed simple models based on this theory that successfully describe $1/f$ fluctuations in the occurrence of earthquakes [13], evolutionary models [118] and economic fluctuations [12]. However, one of the simplest examples of the self-organized critical state is a pile of sand. Bak et al. have studied simplified computer models of sandpiles to demonstrate the features of self-organized criticality, and experimental studies of real sandpiles have been performed [12, 181] which confirm many of the simulations. If one builds a pile of sand on a table top by slowly dropping one particle of sand after another at random sites on the table, eventually the sand will form a pile with a characteristic slope. The angle of the slope is referred to as the "angle of repose." If the slope exceeds this value at some point on the pile, grains will slide downward causing an avalanche. The avalanche started by a single grain of sand may be any size. Most of the time a new grain of sand will fall so that no avalanche occurs, and small avalanches are much more likely than large avalanches. The sandpile self-organizes into this critical state where small events have the potential to propagate and magnify into large events. If the slope decreases from that of the critical state, the sand will accumulate again until the critical state is regained. If the slope exceeds the critical state, sand will slide off the pile and again
the critical state is restored. Such a system leads naturally to power law phenomena such as $1/f$ noise. In fact, if one measures the amount of sand falling off the pile as a function of time, the resulting signal is a $1/f$ noise\(^8\) [76].

The theory of self-organized criticality has come under some question and a number of authors have reported sandpile simulations producing $1/f^\alpha$ type fluctuations where $\alpha = 2$ and therefore, sandpiles may not be a good model for $1/f$ processes [45, 84]. Nevertheless, applications of the theory of self-organized criticality continue to be made and have had significant success in modeling $1/f$ processes associated with the occurrence of earthquakes. Self-organized criticality offers a new way of understanding complex dynamical systems and an intriguing potential for explaining $1/f$ noise in some systems.

A Statistical Model of $1/f^\alpha$ Noise

A few statistical models have also been proposed in attempts to explain the ubiquity of $1/f$ noise. Machlup [107] proposed a simple model based on an ensemble of random processes. If a single random process $x(t)$, has an autocorrelation function of the form $e^{-\omega \tau}$, then the power spectrum of such a process is given by

$$S_{xx}(\omega) \propto \frac{\tau}{(1 + \omega^2 \tau^2)} \quad (2.19)$$

Machlup envisioned an ensemble of such processes, each with its own relaxation time, $\tau$. If the statistical distribution of these relaxation times, $p(\tau)$, is scale invariant such that

$$p(\tau) \, d\tau = \frac{d\tau}{\tau} \quad (2.20)$$

\(^8\)This is true at least for small sand piles. There is some question as to whether larger sandpiles exhibit a similar characteristic [76]
then the power spectrum of the ensemble is
\[
\int_{\tau_1}^{\tau_2} S_\tau(\omega)p(\tau) \, d\tau \propto \int_{\tau_1}^{\tau_2} \frac{\tau}{1 + \omega^2 \tau^2} \frac{d\tau}{\tau} = \left. \tan^{-1} \frac{\omega \tau}{\omega} \right|_{\tau_1}^{\tau_2} = \frac{\tan^{-1} \omega \tau_2 - \tan^{-1} \omega \tau_1}{\omega} \tag{2.21}
\]

If the scale invariance extends over a range of many orders of magnitude then the power spectrum will be $1/f$ for a wide range of frequency. Thus, Machlup concluded that no special mechanism is required to produce $1/f$ noise. He asserts that the only requirement is a large ensemble of mechanisms with “no prejudice about scale” and that “nature is sufficiently chaotic to possess this lack of prejudice” [107].

Montroll and Shlesinger [122] have proposed a mechanism whereby nature may produce a distribution of relaxation times that is scale invariant. They demonstrate that the log-Normal distribution with a large variance is approximately scale invariant across a wide range and that larger variances widen the approximate $1/f$ range. Further, they assert that the log-Normal distribution is a limiting distribution for a product of random variables. This concept is similar to Central Limit Theorems which state that a sum of random variables approaches the Normal distribution as the number of summed variables increases. Consider a complex task whose successful outcome depends on the completion of a series of $n$ independent subtasks. Then the probability, $P$, that the task will be completed successfully is given by

\[
P = p_1 p_2 p_3 \cdots p_n \tag{2.22}
\]

where the $p_i$ are the probabilities that each subtask will be completed successfully. It follows that

\[
\ln P = \ln p_1 + \ln p_2 + \ln p_3 + \cdots + \ln p_n \tag{2.23}
\]

Under weak conditions, the Central Limit Theorem applies so that the distribution of $\ln P$ is the Normal distribution. Therefore, the distribution of $P$ should be log-
Normal. Montroll and Shlesinger suggest that if a distribution of relaxation times is determined by a multiplicative process as in Equation (2.22), then that distribution is log-Normal. Since the log-Normal distribution is scale invariant across a wide range, this distribution of relaxation times may lead naturally to $1/f$ noise as suggested by Machlup. Thus, they conclude that the widespread occurrence of $1/f$ noise may be attributed to this type of Central Limit Theorem which applies to complex processes dependent on a large number of subprocesses. They consider the statistics of flow in the river Nile which is a classic example of $1/f$ noise. They note that a drop of rain at the river’s source would need to pass through many stages to reach the mouth of the river. Atmospheric conditions must lead to the creation of the raindrop. Wind, rain, and ground conditions must then allow the drop to continue downstream at each stage of the river. A log-Normal distribution of the flow rate would lead to the $1/f$ noise in the observed level of the river at the mouth.

Other mathematical models have been proposed, but few offer insights into underlying physical mechanisms of $1/f$ noise [37, 123, 177]

### 2.4 Objectives

The general goal of this investigation was to extend the system identification approach to the study of cardiovascular regulation over a longer time scale and to incorporate measurement of cardiac output (CO) into the model in Figure 2-6. Using the augmented model, the specific objective was to determine whether the $1/f^\alpha$ spectral pattern seen in hemodynamic variables is due to one or more of the transfer function couplings or originated in the model noise sources. A secondary objective was to determine whether pharmacological interventions or fixed-rate atrial pacing altered the $1/f^\alpha$ pattern seen in spectra or transfer couplings.
Chapter 3

Methods

A conscious sheep model was studied under an experimental protocol approved by the MIT Committee on Animal Care (Protocol No. 90-110). Five castrated male sheep weighing approximately 30 kg were quarantined for a seven to fourteen day period during which cardiovascular and respiratory health was verified by physical examination and by evaluation of blood, sputum and fecal cultures, and hematocrit levels. Animals were excluded from the study for low hematocrit, respiratory or infectious disease, or cardiac arrhythmia. Low hematocrit and respiratory or infectious disease are predictors of poor surgical survival rates. Cardiac arrhythmias interfere with the accurate study of normal cardio-regulatory function, particularly when studied by means of hemodynamic variability. Each animal underwent a single surgery for implantation of cardiovascular instrumentation (Section 3.1). Subsequent to surgical recovery, a series of experiments were conducted on separate days in which two to four hour continuous measurements of cardiac output, lung volume (respiration), electrocardiogram, and blood pressure were made under a number of experimental conditions (Section 3.2). These data were studied via power spectral analyses and according to a simplified system identification model (Section 3.3).
Figure 3-1 Schematic representation of surgically placed instrumentation. A flow probe was placed around the ascending aorta. Catheters were placed in the descending aorta and the pulmonary artery. Bipolar epicardial electrodes were placed on the right atrium and on both ventricles.

3.1 Surgical Preparation

Surgical instrumentation was performed using aseptic technique. Anesthesia was induced with ketamine and maintained with isoflurane. After induction of anesthesia, endotracheal intubation and placement of a stomach tube (for prevention of bloating), a left lateral thoracotomy was performed in the fourth intercostal space. Polyvinyl catheters filled with a heparinized saline solution were placed in the descending aorta and in the pulmonary artery using the Herd-Barger technique. Bipolar epicardial electrodes were attached to the right atrial appendage, to the left ventricular surface, and to the right ventricular surface. These electrodes were used for atrial pacing and for the measurement of ventricular electrograms. An ultrasonic flow probe was placed around the ascending aorta for continuous measurement of cardiac output. The surgical placement of cardiovascular instrumentation is schematically illustrated in Figure 3-1.

All catheters and wires were tunneled subcutaneously to the animal’s back and exteriorized. After placement of a chest tube, the incision was closed in layers and the pneumothorax reduced. Negative pressure was applied to the chest tube at intervals
during the 12–48 hours following surgery, and the tube was subsequently removed. Each animal was fitted with a protective jacket that housed the wires and catheters. Post-operative care included a seven to fourteen day course of prophylactic antibiotics and a minimum of 36 hours of analgesia, extended as indicated by physical examination and observation. Intravascular catheters were flushed and refilled with heparinized saline every 24–48 hours. Experiments were initiated after a 7–14 day post-operative recovery period and were conducted at a rate of no greater than one per day thereafter.

### 3.2 Experiment Design

Experiments were performed while the animal was conscious and resting in a custom-made sling. The sling was adjustable in height and was positioned to allow the animal’s legs to reach the ground. Aortic blood pressure, aortic flow, instantaneous lung volume and a ventricular electrogram were continuously monitored throughout the experiments. Arterial blood pressure (ABP) was measured from the descending aortic catheter and the ventricular electrogram was recorded from a ventricular bipolar electrode.\(^1\) Cardiac output (CO) was measured from the flow probe on the ascending aorta.\(^2\) Instantaneous lung volume (ILV) was recorded non-invasively using two-belt inductance plethysmography.\(^3\) Experimental recordings were made in 2–4 hour sessions on separate days under each of the following conditions:

1. Baseline: No Intervention
2. Renin-Angiotensin System blockade: Captopril, 10 mg bolus and 5mg/hr
3. Fixed-rate atrial pacing
4. \(\beta\)-Sympathetic blockade: Propranolol, 0.2 mg/kg bolus and 0.2 mg/kg/hr
5. \(\alpha\)-Sympathetic blockade: Phentolamine, 10 mg/kg bolus and 75 mg/kg/hr

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\(^1\) EforM Inc., VR-16 System, Model V2203 Blood Pressure Module and V1205 ECG Module
\(^2\) Transonics Systems Inc., Model T-101, and S-series, 16–20 mm, perivascular probes
\(^3\) Respitrace System, Ambulatory Monitoring Systems, Model 10.9020, Transducer Model 10.7000
Effectiveness of pharmacological blockades in 2, 4, and 5 were verified at intervals during each experiment by administration of small bolus doses of angiotensin I, isoproterenol and phenylephrine, respectively. The doses of these agonists were selected to achieve a significant hemodynamic response prior to blockade. Complete blockade was presumed if the response to the agonist dose was abolished. Pharmacological agents were delivered through the pulmonary artery catheter. Atrial pacing was achieved through an atrial bipolar electrode at a current level of twice the capture threshold (typically < 5mA) and a rate 10-20 bpm above sinus rate.

The animal preparation has a limited period of utility due to occlusion of catheters or other instrumentation failures or due to physiological issues such as development of arrhythmias or post-operative morbidity. Therefore, experimental interventions were prioritized and performed in the order listed above.

3.3 Analytical Methods

3.3.1 Data Acquisition and Preprocessing

The ventricular electrogram, ABP, CO, and ILV were directly digitized using a portable computer (Compaq, Inc.) and customized laboratory software [104]. Signals were passed through a six-pole Butterworth filter for anti-aliasing and sampled at 360 Hz. The filtered signals were simultaneously recorded to FM tape for backup purposes. Data analyses were completed on Sun Microsystems computers and Pentium-based computers running the Linux operating system. The ABP, CO, and ILV signals were digitally filtered and decimated to sampling rates of 3.0, 0.5 and 0.1 Hz for subsequent analyses. ABP and CO calibrations were completed using the internal calibration signals available from each instrument. The accuracy of the blood pressure calibration was verified periodically by a sphygmomanometer. Flow probes were calibrated by the manufacturer, and accurate measurement of mean flow.
was verified in each probe prior to implantation. ILV measurements are typically calibrated in human subjects through the use of a known step change in volume. This change is typically produced by having subjects breathe into and out of an 800 ml Spirobag (Ambulatory Monitoring Systems Inc., Model 10-4026). Since this calibration is unavailable in the animal model, the following procedure was used to calibrate ILV. From each recording, one or more periods of resting spontaneous breathing were identified. The mean tidal volume for the segment was calculated in terms of A/D units and was equated to 350 ml, a reasonable tidal volume for a 30 kg sheep\textsuperscript{4} [70]. This calibration constant was then applied to the entire data segment.

An instantaneous heart rate signal sampled synchronously with the other signals, was generated at each sampling rate according to the technique first described by Berger et al. [22]. The technique is schematically illustrated in Figure 3-2. First, R wave peaks were detected in the ventricular electrogram (sampled at 360 Hz) and their time locations recorded. Next, a sampling rate, $f_r$, for the heart rate (HR) signal was chosen (3.0, 0.5 or 0.1 Hz), and a local window was defined at each sample point to include the time between the previous and the next sample. Finally, the number of RR intervals, $n_i$, within the $i$th local window, including any fractions of RR intervals, was determined and HR was given by

$$\text{HR}[t_i] = f_r \frac{n_i}{2}$$  \hspace{1cm} (3.1)

A beat series of estimates of stroke volume (SV) was derived from the CO recordings (sampled at 360 Hz) by integrating the cardiac output signal over the duration of each beat, That is

$$SV_i = \frac{1}{60 \cdot 1000} \sum_{t=t_i}^{t_{i+1}} \text{CO}(t)$$  \hspace{1cm} (3.2)

where $i$ is an index of beats, $t_i$ and $t_{i+1}$ are the occurrence times of sequential R waves, and the scale factors provide stroke volume in units of milliliters. A continuous stroke

\textsuperscript{4}An approximation of a mammal tidal volume may be given as 10–20 mL/kg of body weight [162].
Figure 3-2 (a) A segment of electrocardiogram (ECG). (b) The heart rate samples corresponding to the ECG signal in (a). The number of RR intervals within the local window centered at $t_1$ is $a/I_2$ and at $t_2$ is $b/I_3 + c/I_4$. The value of the heart rate at each sample point is taken to be the number of intervals that fell within the local window centered at that point divided by the width of the window. (c) The corresponding instantaneous heart rate signal. The value held during each interval is the reciprocal of the duration of that interval. The sample values in (b) are equivalent to those of the signal that would result from convolution of the signal in (c) with a rectangular window that is two sample intervals wide. (from [22])

volume signal sampled synchronously with the other signals was then computed by splining and resampling the beat series. A similar approach has been described for estimating a systolic and diastolic blood pressure time series [5,24,153].

Each data segment was both automatically and manually reviewed for the presence of spike noise ("glitches"), non-sinus beats, or loss of signal on any channel. Consecutive data loss of greater than two minutes on any channel was criterion for exclusion of the data set. Shorter losses of data were repaired by linear spline. The merits of this approach have been discussed previously [4]. Such splines may cause a small reduction in high frequency bands of the power spectrum but do not alter other spectral components. Short segments of missing data relative to the length of
the data segment have no significant effect on the system identification algorithms.

3.3.2 Power Spectral Estimation

Power spectra were computed from the entire length of each HR, CO, SV, and ABP data segment. Power spectra were computed as the unwinned, discrete Fourier transform (DFT) of an estimate of the autocorrelation function of the data segment [19,138]. That is, for a signal \( x[t] \), the power spectrum \( S_{xx}(f) \) is given by

\[
S_{xx}(f) = T_s \text{DFT}(\hat{R}_{xx}[\ell])
\]  

(3.3)

where the autocorrelation function, \( \hat{R}_{xx}(\ell) \) is estimated as

\[
\hat{R}_{xx}[\ell] = \frac{1}{N - |\ell|} \sum_{n=0}^{N-|\ell|-1} x[n]x[n + |\ell|]
\]  

(3.4)

The autocorrelation estimates were zero-padded to provide a greater spectral resolution such that the lowest decade of frequency in the power spectrum was represented by at least 60 samples as required by the slope and intercept estimation procedure (see Section 3.3.3). Despite zero-padding, the spectrum was considered accurate only above the reciprocal length of the data segment. For example, for a two hour data segment in this study, the lowest frequency considered was \( 1.4 \times 10^{-4} \text{ Hz} \), while for a four hour data segment frequencies as low as \( 7 \times 10^{-6} \text{ Hz} \) were considered. The unwinned (unsmoothed) power spectral estimate has a larger variance than a windowed estimate but achieves the maximum effective resolution and a minimum (zero) bias for the given data length. All spectra were then log transformed and smoothed in the logarithmic domain prior to graphical or numerical analyses.

3.3.3 Estimation of Power Spectral Slope and Intercept

Power spectra, \( S(f) \), were smoothed in the log domain by integrating power in logarithmically spaced frequency bins. Bins were spaced at 60 per decade (\( i.e., 0.167 \))
log(Hz) wide). Since each decade has ten times the number of points of the adjacent lower frequency decade, bins at higher frequencies represent averages of a greater number of points than bins at lower frequencies. The slope and intercept of the linear (1/f) region of the log-smoothed power spectrum were calculated by linear regression. The regression was performed on spectral estimates in the range between $10^{-2}$ and $10^{-4}$ Hz (or the inverse length of the data segment whichever was greater). The intercept was calculated at $10^{-3}$ Hz. For each point in the regression frequency range, an upper and lower 90% confidence limit was calculated.\(^5\) This method of spectral smoothing and identification of spectral slopes and intercepts is the same as that described in [34].\(^6\) An alternate approach for estimating spectral slope and intercept is described in Appendix A.

Group average regression slopes and intercepts were calculated as the means of the slopes and intercepts of the individual regression lines in the group. For each point in the regression frequency range, a mean upper and a mean lower 90% confidence limit was computed from the individual upper and lower confidence limits in each group. Once again this method of formulating group averages was selected to match that used in [34]

### 3.3.4 System Identification

#### Simplified Model

The data were analyzed according to a system identification algorithm designed to characterize the simplified model depicted as a block diagram in Figure 3.3.4. This model is similar to that of Figure 2-6 but is augmented to include the two new signals: CO and SV. The new model includes physiologically reasonable couplings between the

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\(^5\) Estimates of regressions slope intercept and confidence limits were calculated according to techniques described in [54].

\(^6\) Bigger et al. calculated the intercept at $10^{-4}$ Hz rather than $10^{-3}$ Hz because it was farthest from the nonlinear region of the spectrum. However, estimates at $10^{-3}$ Hz are made with higher statistical confidence due to the data range [54].
Figure 3-3 Simple model of cardiovascular regulation incorporating signals derived from measured electrocardiogram, arterial blood pressure, instantaneous lung volume and cardiac output.

five signals and omits those that are redundant or expected to be physiologically less important. It includes seven transfer couplings, \( \text{ILV} \rightarrow \text{HR} \), \( \text{ILV} \rightarrow \text{SV} \), \( \text{ILV} \rightarrow \text{ABP} \), \( \text{HR} \rightarrow \text{SV} \), \( \text{ABP} \rightarrow \text{SV} \), \( \text{HR BAROREFLEX} \) and \( \text{PERIPHERAL IMPEDANCE} \) and three perturbing noise sources, \( N_{\text{ABP}} \), \( N_{\text{SV}} \), and \( N_{\text{HR}} \). The physiological interpretations of the transfer couplings and noise sources will be discussed in Section 5.3.1. Each data set was used to determine all transfer couplings and noise sources in the model with one exception. Since heart rate variability was effectively eliminated by atrial pacing, data recorded during this intervention was used to evaluate only those transfer couplings not associated with heart rate, \( \text{ILV} \rightarrow \text{SV} \), \( \text{ILV} \rightarrow \text{ABP} \), \( \text{ABP} \rightarrow \text{SV} \), and \( \text{PERIPHERAL IMPEDANCE} \) and the two noise sources \( N_{\text{SV}} \) and \( N_{\text{ABP}} \).
**ARMA Model Structure**

For the purposes of system identification, the model is represented by a set of linear-time-invariant autoregressive moving-average (ARMA) difference equations [105, 147, 161] of the form

\[
\begin{align*}
\text{HR}(t) &= \sum_{i=1}^{A} a_i \text{HR}(t - i) + \sum_{i=1}^{B} b_i \text{ABP}(t - i) + \sum_{i=C}^{C} c_i \text{ILV}(t - i) + W_{\text{HR}}(t) \quad (3.5a) \\
\text{ABP}(t) &= \sum_{i=1}^{Q} q_i \text{ABP}(t - i) + \sum_{i=1}^{R} r_i \text{CO}(t - i) + \sum_{i=1}^{S} s_i \text{ILV}(t - i) + W_{\text{ABP}}(t) \quad (3.5b) \\
\text{SV}(t) &= \sum_{i=1}^{K} k_i \text{SV}(t - i) + \sum_{i=1}^{M} m_i \text{ABP}(t - i) \\
&\quad + \sum_{i=1}^{N} n_i \text{HR}(t - i) + \sum_{i=1}^{O} o_i \text{ILV}(t - i) + W_{\text{SV}}(t). \quad (3.5c)
\end{align*}
\]

Equation (3.5a) characterizes the effects of the inputs, ILV and ABP, on the output, HR. The ARMA structure expresses the current value of the output as a weighted sum of the previous values of the output and inputs. In Equation (3.5a), the sets of weights or parameters, \(\{a_i\}, \{b_i\} \text{ and } \{c_i\}\), are estimated from the data and fully determine the transfer couplings \([\text{ILV} \Rightarrow \text{HR}]\) and \([\text{HR BAROREFLEX}]\). The term \(W_{\text{HR}}\) in Equation (3.5a) is referred to as the equation error or residual and is the difference between the true HR and the HR predicted from the other terms. The perturbing noise \(N_{\text{HR}}\) in the model of Figure 3.3.4 is calculated from \(W_{\text{HR}}\) as

\[
N_{\text{HR}}(t) = \sum_{i=1}^{A} a_i N_{\text{HR}}(t - i) + W_{\text{HR}}(t). \quad (3.6)
\]

It represents the actual noise perturbation added to the HR signal and accounts for HR variability not attributable to the coupling mechanisms.

Similarly, Equation (3.5b) characterizes the effects of ILV and CO on ABP and the sets of parameters, \(\{q_i\}, \{r_i\}\) and \(\{s_i\}\), are estimated from the data and determine the transfer couplings \([\text{ILV} \Rightarrow \text{ABP}]\) and \([\text{PERIPHERAL IMPEDANCE}]\). The residual term
\( W_{\text{ABP}} \) in Equation (3.5b) is used to compute \( N_{\text{ABP}} \) as

\[
N_{\text{ABP}}(t) = \sum_{i=1}^{Q} q_i N_{\text{ABP}}(t - i) + W_{\text{ABP}}(t).
\] (3.7)

Finally, Equation (3.5c) characterizes the effects of ILV, HR and ABP on SV and the identified sets of parameters, \( \{k_i\}, \{m_i\}, \{n_i\} \) and \( \{o_i\} \), determine the transfer couplings \( \text{ILV} \rightarrow \text{SV} \), \( \text{HR} \rightarrow \text{SV} \) and \( \text{ABP} \rightarrow \text{SV} \). The residual term \( W_{\text{SV}} \) is used to compute \( N_{\text{SV}} \) as

\[
N_{\text{SV}}(t) = \sum_{i=1}^{K} k_i N_{\text{SV}}(t - i) + W_{\text{SV}}(t).
\] (3.8)

It should be noted that for strict causality, the lower limits of the summations in Equations (3.5) must all be greater than or equal to one. Loose causality may be achieved with a lower limit equal to zero which indicates that although future values of the input do not effect the output, there is immediate throughput of the current value of the input. In this study, strict causality was enforced except in the case of the \( \text{ILV} \rightarrow \text{HR} \) transfer coupling. This coupling has been previously established to be noncausal [127]. That is, fluctuations in HR induced by fluctuations in ILV actually slightly precede the associated ILV fluctuations. This noncausal behavior may be accounted for in Equation (3.5a) by allowing \( i \) to range from a negative value of \( C' \) to \( C \) in the summation of ILV terms in Equation (3.5a). We selected \( C' \) (dependent on sampling rate) to allow fluctuations in ILV to precede corresponding changes in HR by between one and two seconds. The upper limits on all summations determine the model order and are selected to optimize the model within the constraints of an information criterion. Estimation of the model parameters and determination of the appropriate model order are the two major steps of the system identification process [105, 161].
ARMA Parameter Estimation and Order Selection

The basic ARMA model structure may be conveniently expressed in vector-product form. Consider, for example, Equation (3.5a) which may be expressed in vector-product form as:

$$HR(t) = \phi^T(t)\theta + W_{HR}(t) \quad (3.9)$$

where

$$\phi(t) = \begin{bmatrix} HR(t - 1) \\ \vdots \\ HR(t - A) \\ ABP(t - 1) \\ \vdots \\ ABP(t - B) \\ ILV(t - C') \\ \vdots \\ ILV(t - C) \end{bmatrix}, \quad \text{and} \quad \theta = \begin{bmatrix} a_1 \\ \vdots \\ a_A \\ b_1 \\ \vdots \\ b_B \\ c_{C'} \\ \vdots \\ c_C \end{bmatrix}.$$ 

The current output, HR, is expressed as the weighted sum of past values of itself and of the inputs, ABP and ILV, which are grouped in the data vector, $\phi(t)$. The sets of weights or parameters, $\{a_i\}$, $\{b_i\}$, and $\{c_i\}$, are grouped in the parameter vector, $\theta$.

To allow for identification of the system parameters, a long time segment of data is collected so that for each time, $t$, an equation similar to Equation (3.9) may be written. The set of such equations may be conveniently expressed in matrix form as:

$$Y = \Phi \theta + \epsilon \quad (3.10)$$

---

<sup>7</sup>For the following discussion, I use Equation (3.5a) as an example. Equations (3.5b) and (3.5c) are analogous and are solved by the same methods.
where

\[
Y = \begin{bmatrix}
HR(t) \\
HR(t-1) \\
\vdots \\
HR(t-D+1)
\end{bmatrix}, \quad \Phi = \begin{bmatrix}
\phi^T(t) \\
\phi^T(t-1) \\
\phi^T(t-2) \\
\vdots \\
\phi^T(t-D+1)
\end{bmatrix}
\]

and \[\epsilon = \begin{bmatrix}
W_{HR}(t) \\
W_{HR}(t-1) \\
\vdots \\
W_{HR}(t-D+1)
\end{bmatrix}.
\]

If the number of equations (the length of the data vectors), \(D\), is equal to the number of parameters \(P = A + B + C - C' + 1\), then \(\Phi\) is a square matrix and if it is nonsingular, the set of linear equations may be solved uniquely for the parameters, \(\theta\), based on the input and output data (and the residuals are zero). However, more commonly, the number of equations is significantly larger than the number of parameters, and the set of equations becomes over-determined or inconsistent. An exact solution in general does not exist. One must choose a criterion for selecting the “best” solution. This “best” solution is typically determined based on an evaluation of the remaining residual error terms.

The residual error may be expressed as the difference between the true value of the output and the predicted value of the output at each time. The estimated residual error vector is thus given by

\[
\epsilon = \hat{y} - \Phi \hat{\theta}
\]  \hspace{1cm} (3.11)

where \(\hat{\theta}\) is the estimate of the parameter vector.
<table>
<thead>
<tr>
<th>INFORMATION CRITERION</th>
<th>EQUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akaike Information Criterion (AIC)</td>
<td>$AIC = D \log V(\hat{\theta}) + 2P$</td>
</tr>
<tr>
<td>Final Prediction Error (FPE)</td>
<td>$FPE = V(\hat{\theta})\frac{1 + P/D}{1 - P/D}$</td>
</tr>
<tr>
<td>Minimum Description Length (MDL)</td>
<td>$MDL = V(\hat{\theta}) + P \log \frac{D}{P}$</td>
</tr>
</tbody>
</table>

Table 3.1: Examples of commonly used information criteria used in selecting model order. $\hat{\theta}$ is the estimated parameter vector; $V$ is the loss function, $D$ is the data length and $P$ is the number of parameters. Additional discussion regarding information criteria may be found in [105, 161].

The most common approach to selecting the "best" solution is the least squares method. The least squares solution is defined to be the solution which minimizes the loss function, $V(\hat{\theta})$, defined as the sum of squares of the residual errors:

$$V(\hat{\theta}) = \frac{1}{2} \sum_{i=1}^{D} \epsilon^2(t) = \frac{1}{2} \epsilon^T \epsilon = \frac{1}{2} \| \epsilon \|_2^2$$  \hspace{1cm} (3.12)

This loss function has a unique minimum (provided that $\Phi^T \Phi$ is nonsingular or equivalently $\Phi$ is full column rank) when

$$\hat{\theta} = (\Phi^T \Phi)^{-1} \Phi^T Y.$$  \hspace{1cm} (3.13)

This is the least squares solution to Equation (3.10) [105, 161, 165].

For a given model order, Equation (3.13) provides an estimate of the system parameters. However, in the general system identification problem, the model order or structure (determined by the upper limits of the summations) is not known. To identify the appropriate model structure, one can re-compute the model parameter estimates for a varied set of model orders and compare the models to select the best choice. A standard system identification approach is to calculate the least-squares estimate for a low order model using Equation (3.13). Then, the order is incrementally increased, and new parameter estimates are computed in the same way for the higher order model. This process is repeated and an information criterion is used to select the preferred order. Examples of some common information criteria are given in Table 3.1. Typically, the model structure which minimizes the information criterion
is selected as the model of choice. Note that each information criterion provides a “reward” for reducing the loss function (decreasing the mean squared error) and a “penalty” for increasing the model order. Therefore, information criteria provide some means of determining the smallest model order that still provides a good description of the dynamics of the system. Further discussion of system identification, ARMA models and information criteria may be found in [105,161].

It would seem that Equation (3.13) must be solved a number of times as part of the system identification procedure. From a computational standpoint, the equation may be solved in a number of ways. It may be solved, for example, directly by a matrix inversion, by use of cross-correlation functions, by Gaussian elimination or via a QR decomposition. The matrix inversion is computationally expensive. It is also subject to errors associated with finite arithmetic. Gaussian elimination suffers similarly. Solution via cross-correlation functions is also a relatively computationally intensive option which is susceptible to rounding errors — but does overcome the large memory requirements of the matrix inversion. QR decompositions and other orthogonalization procedures provide a more computationally efficient and accurate approach.

Korenberg has developed a fast orthogonal search algorithm for automatic estimation of model orders and concurrent estimation of model parameters [98–102]. The procedure is similar to the QR decomposition approach in that it is based on orthogonalizing the data matrix, \( \Phi \). It has significant advantages in that the model order may be increased and additional terms added without the need to recompute all previous parameters. Furthermore, because of the orthogonalization, the newly added terms may immediately be evaluated for their potential benefit in reducing residual errors.

Korenberg recognized that the Gram-Schmidt procedure allows the data matrix, \( \Phi \), to be transformed to a new matrix, \( \tilde{\Phi} \), in which all \( P \) columns are mutually
orthogonal. Let \( \Phi_p \) be the \( p \)th column of \( \Phi \). Then, the transformation is completed as follows:

\[
\tilde{\Phi}_p = \Phi_p - \sum_{i=0}^{p-1} \lambda_{pi} \tilde{\Phi}_i \quad p = 0, \ldots, P - 1
\]  

(3.14)

where

\[
\lambda_{pi} = \frac{\Phi_i^T \tilde{\Phi}_i}{\tilde{\Phi}_i^T \tilde{\Phi}_i}.
\]

Equation (3.10) may therefore be rewritten as

\[
\mathbf{Y} = \tilde{\Phi} \hat{\mathbf{\theta}} + \epsilon
\]

(3.15)

where \( \tilde{\Phi} \), the transformed data matrix, is now composed of columns which are mutually orthogonal and \( \hat{\mathbf{\theta}} \) is a vector of new parameters associated with the new \( \tilde{\Phi} \).

Because \( \tilde{\Phi} \) is composed of mutually orthogonal columns, \( (\tilde{\Phi}^T \tilde{\Phi})^{-1} \) is a diagonal matrix and the least squares estimate of \( \hat{\mathbf{\theta}} \) is

\[
\tilde{\mathbf{\theta}}_{LS} = (\tilde{\Phi}^T \tilde{\Phi})^{-1} \tilde{\Phi}^T \mathbf{Y}
\]

\[
= \begin{bmatrix}
\frac{1}{\Phi_0^T \Phi_0} & 0 & \cdots & 0 \\
0 & \frac{1}{\Phi_1^T \Phi_1} & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & \frac{1}{\Phi_{P-1}^T \Phi_{P-1}}
\end{bmatrix}
\begin{bmatrix}
\tilde{\Phi}_0^T \mathbf{Y} \\
\tilde{\Phi}_1^T \mathbf{Y} \\
\vdots \\
\tilde{\Phi}_{(P-1)}^T \mathbf{Y}
\end{bmatrix}
\]

(3.16)

Each of the new parameters in the \( \tilde{\mathbf{\theta}}_{LS} \) vector is therefore given by

\[
\tilde{\theta}_{LS}(p) = \frac{\tilde{\Phi}_p^T \mathbf{Y}}{\tilde{\Phi}_p^T \tilde{\Phi}_p} \quad p = 0, \ldots, P - 1
\]

(3.17)

The parameters may be estimated recursively from Equations (3.14) and (3.17). As the model order is incremented and consequently additional columns are added to \( \Phi \), the new orthogonal columns of \( \tilde{\Phi} \) may be computed without recomputing all previous
columns. Thus, each new parameter in $\tilde{\theta}_{LS}$ may be estimated without the need to recompute the other parameters. Furthermore, the potential effect of a new model term on the residual error may be immediately estimated. In fact, two candidate model terms may be compared based on their potential to reduce the mean square error. Korenberg shows that the reduction in the mean square error due to a particular term is given by

$$\tilde{\theta}^2(p) \frac{\tilde{\Phi}_p^T \tilde{\Phi}_p}{D}$$

(3.18)

where D is the number of data points (length of each $\tilde{\Phi}_p$). It should be noted that without the orthogonalization of the data vectors, estimation of new parameters and evaluation of a term’s effect on the residual error would require recomputing all parameters and the resultant mean square error.

The original parameters in $\theta$ may be calculated from the new parameters as

$$\tilde{\theta}(p) = \sum_{i=p}^{P} \tilde{\theta}_{LS}(i)v_{ip}, \quad p = 0, \ldots, P-1$$

(3.19)

where

$$v_{ip} = \begin{cases} 1 & \text{if } i = p, \text{ for all } i \\ -\sum_{j=p}^{i-1} \lambda_{ij}v_{jp} & i = m + 1, \ldots, P - 1 \end{cases}$$

In summary, Equations (3.14) and (3.17) are used to estimate the parameters in the orthogonalized model and Equation (3.19) is then used to convert these parameters to the parameters of the original model.\(^8\)

The Korenberg algorithm may be used to add candidate terms to the model based on their effect in reducing the mean square error and the mean square error may be monitored as a criterion for deciding when the model order has reached an appropriate level. Korenberg suggests a number of simple but effective criteria

---

\(^8\)It should be noted that in practice, the orthogonalized $\Phi$ matrix is not calculated and the orthogonal coefficients are calculated using an efficient factorization algorithm described in detail in [98].
for determining an appropriate model order. These techniques have been applied effectively to other physiological systems [98,101]. For example, one may choose to terminate the parameter search once a predetermined percentage of the variance of the output has been described—that is, once the mean-square error is reduced to a small enough percentage of the variance of the output [102]. Other criteria, such as the information criteria in Table 3.1, may also be used to terminate the addition of model terms.

In this study, model terms were considered in groups which included the shortest lag of each autoregressive and moving average term in the given equation. For example, in Equation (3.5a) the terms HR(t – 1), ABP(t – 1), and ILV(t – C’r) were considered first, and the one which provided the greatest reduction in mean square error was incorporated into the model. Next, if HR(t – 1) was selected as the first term, then HR(t – 2), ABP(t – 1), and ILV(t – C’r) were considered as candidates for the second term. Similarly, if the ABP(t – 1) term was selected, then the candidates for the next term included HR(t – 1), ABP(t – 2), and ILV(t – 1) and if the ILV(t – C’r) term was selected, then the candidates for the next term included HR(t – 1), ABP(t – 1), and ILV(t – (C’r + 1)). This process was repeated at each stage by replacing the selected term in the candidate list with the next lag of the same term. The search was ended when no candidate term reduced the mean square error by more than 0.05%.

Model Representation

The transfer function estimates determined by the system identification algorithm are presented in their time domain form of impulse responses and step responses. The squared magnitude of each coupling mechanism’s frequency response is also presented. The squared magnitude of the frequency response is calculated directly from the model parameters. For example, the squared magnitude of the **HR BAROREFLEX** coupling
is given by

\[ |H(f)|^2 = \left| \frac{\sum_{k=1}^{B} b_k e^{-j2\pi f k T}}{1 + \sum_{k=1}^{A} a_k e^{-j2\pi f k T}} \right|^2 \]  

(3.20)

The squared magnitude of other couplings are calculated from analogous expressions.

Group average impulse responses were calculated on a point by point basis and represent the mean of all impulse responses in the group. Ninety percent confidence intervals on the mean were calculated as \( \mu \pm 1.65 \times \sigma_{\mu} \) where \( \mu \) is the mean and \( \sigma_{\mu} \) is the standard error of the mean. Group average step responses and squared transfer function magnitudes and corresponding 90% confidence intervals were calculated analogously.

The power spectra of the noise sources, \( N_{HR} \), \( N_{ABP} \), and \( N_{SV} \), were computed by the methods described in Section 3.3.2, and linear regressions of the 1/f portion of the spectra were performed as described in Section 3.3.3.

### 3.4 Simulated system with 1/f power transfer

In order to verify the capability of the ARMA model to accurately characterize a 1/f shaped transfer function, numerical simulations were performed. A system with a 1/f power transfer was developed by frequency sampling design [142]. A white noise input was applied to the system to produce an output with a 1/f spectral character. The simulated input and output signal were used to identify the system using the same algorithm applied to the physiological data. The simulation was repeated for different realizations of the white noise input.
Chapter 4

Results

4.1 Experimental Results

Five animals were studied. One animal was disqualified due to the development of a post-operative ventricular arrhythmia. Table 4.1 indicates the number of complete full-duration experiments for each of the four remaining animals and each experimental intervention. Animal A provided limited data due to chronic respiratory ailments post-operatively compounded by a loss of patency of arterial and pulmonary catheters after recovery. The α-Sympathetic Blockade was successfully completed and maintained in only one animal and therefore comparisons of other conditions to this condition must be made with particular caution.

Table 4.2 presents the mean and standard errors of HR, ABP, CO, and SV for

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>ANIMAL A</th>
<th>ANIMAL B</th>
<th>ANIMAL C</th>
<th>ANIMAL D</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>ACE Blockade</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Atrial Pacing</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>β Blockade</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>α Blockade</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 4.1: Number of complete experimental data records. ACE Blockade = Angiotensin Converting Enzyme Blockade, α-Blockade=α-Sympathetic Blockade, β-Blockade=β-Sympathetic Blockade
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>HEART RATE (bpm)</th>
<th>BLOOD PRESSURE (mmHg)</th>
<th>CARDIAC OUTPUT (L/min)</th>
<th>STROKE VOLUME (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>95.8 ± 8.3</td>
<td>106.9 ± 3.6</td>
<td>4.3 ± 0.2</td>
<td>38.5 ± 2.1</td>
</tr>
<tr>
<td>ACE Blockade</td>
<td>87.1 ± 9.8</td>
<td>103.8 ± 3.0</td>
<td>4.3 ± 0.4</td>
<td>42.2 ± 1.8</td>
</tr>
<tr>
<td>Atrial Facing</td>
<td>—</td>
<td>109.8 ± 4.4</td>
<td>3.7 ± 0.8</td>
<td>21.9 ± 6.5</td>
</tr>
<tr>
<td>β Blockade</td>
<td>87.9 ± 9.1</td>
<td>111.6 ± 2.9</td>
<td>5.4 ± 1.7</td>
<td>47.5 ± 10.6</td>
</tr>
<tr>
<td>α Blockade</td>
<td>91.0 ± 20.0</td>
<td>99.4 ± 0.9</td>
<td>3.4 ± 0.3</td>
<td>33.7 ± 3.9</td>
</tr>
</tbody>
</table>

Table 4.2: Mean hemodynamic values for each experimental condition. β Blockade=β-Sympathetic Blockade, α Blockade=α-Sympathetic Blockade

Each of the experimental conditions. SV was significantly ($p < 0.05$) reduced during Atrial Pacing relative to Baseline. Such a decrease might be expected at the higher heart rates associated with pacing. No other changes were statistically significant.

### 4.2 Power Spectral Analyses

Figures 4-1–4-4 illustrate, on a log-log scale, the power spectra of HR, ABP, CO, and SV for each experimental condition. The figure legend keys are defined as follows: The first letter in the key specifies the animal (a, b, c, or d), the remaining letters indicate the experimental condition (b=Baseline, a=ACE Blockade, s=β-Sympathetic Blockade, r=α-Sympathetic Blockade and pb=Atrial Pacing) and the trailing number specifies the repetition. The group average regression lines with 90% confidence intervals are plotted for each signal and each condition in Figure 4-5.

The group average and standard errors of slopes and intercepts (at $10^{-3}$ Hz) of the linear regressions of the spectra are given in Table 4.3. The slope of the HR spectrum was made significantly less steep (less negative) by ACE blockade and by β-sympathetic Blockade. Atrial pacing led to a relative flattening of the slope of the ABP spectrum. The slope of the CO spectrum was made significantly steeper by atrial pacing and less steep by β-blockade. The slope of the SV spectrum was also made more steep by atrial pacing. The CO and SV intercepts were significantly
decreased by ACE Blockade and by Atrial Pacing. These differences are also evident in the plots of group average regressions presented in Figure 4-5. The slopes of the ILV spectra are all significantly less steep than the other signals, do not exhibit a 1/f pattern and do not exhibit significant changes from one condition to the other.
Figure 4-1 Power spectra of HR from each experimental condition. Legend keys: first letter specifies animal (a,b,c,d), subsequent letters indicate experimental condition (b=baseline, a-ACE Blockade, s=β-Sympathetic Blockade, r=α-Sympathetic Blockade, bp=Atrial Pacing), and trailing number specifies repetition.
Figure 4-2 Power spectra of ABP from each experimental condition. For legend key definitions see Figure 4-1
Figure 4-3 Power spectra of CO from each experimental condition. For legend key definitions see Figure 4-1.
Figure 4-4 Power spectra of SV from each experimental condition. For legend key definitions see Figure 4-1
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>ACE Blockade</th>
<th>Atrial Pacing</th>
<th>β Blockade</th>
<th>α Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart Rate (bpm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.97 ± 0.02</td>
<td>-0.65 ± 0.04‡</td>
<td>—</td>
<td>-0.62 ± 0.03‡</td>
<td>-0.77 ± 0.08</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.66 ± 0.03</td>
<td>3.63 ± 0.05</td>
<td>—</td>
<td>3.75 ± 0.02</td>
<td>4.24 ± 0.16‡</td>
</tr>
<tr>
<td><strong>Arterial Blood Pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.94 ± 0.02</td>
<td>-1.09 ± 0.03</td>
<td>-0.66 ± 0.04‡</td>
<td>-0.84 ± 0.08</td>
<td>-1.16 ± 0.02</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.71 ± 0.05</td>
<td>3.90 ± 0.03</td>
<td>3.59 ± 0.05</td>
<td>3.94 ± 0.1</td>
<td>3.70 ± 0.06</td>
</tr>
<tr>
<td><strong>Cardiac Output (L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.99 ± 0.01</td>
<td>-0.97 ± 0.06</td>
<td>-1.20 ± 0.04†</td>
<td>-0.67 ± 0.06‡</td>
<td>-0.94 ± 0.01</td>
</tr>
<tr>
<td>Intercept</td>
<td>1.51 ± 0.05</td>
<td>0.83 ± 0.05‡</td>
<td>0.68 ± 0.07†</td>
<td>1.2 ± 0.26</td>
<td>0.88 ± 0.03†</td>
</tr>
<tr>
<td><strong>Stroke Volume (mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.99 ± 0.02</td>
<td>-0.98 ± 0.05</td>
<td>-1.21 ± 0.05†</td>
<td>-0.96 ± 0.06</td>
<td>-0.96 ± 0.12</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.32 ± 0.06</td>
<td>2.78 ± 0.04†</td>
<td>2.40 ± 0.08‡</td>
<td>3.20 ± 0.24</td>
<td>3.14 ± 0.02</td>
</tr>
</tbody>
</table>

Table 4.3: Average signal spectral slopes and intercepts (10^{-3} Hz) for each experimental condition (mean ± standard error). Significant differences from Baseline: † indicates p < 0.1, ‡ indicates p < 0.05
Figure 4-5 Group average regression of HR, ABP, CO, and SV power spectra from each experimental condition.
4.3 System Identification

The group average system identification results from Baseline, ACE Blockade, $\beta$-Sympathetic Blockade and $\alpha$-Sympathetic Blockade conditions are presented in Figures 4-6-4-20. These identification results were computed from data sampled at 0.5 Hz. First, the group average impulse responses of each of the seven coupling mechanisms, \( \text{ILV} \rightarrow \text{ABP} \), \( \text{PERIPHERAL IMPEDANCE} \), \( \text{ILV} \rightarrow \text{HR} \), \( \text{HR} \rightarrow \text{BAROREFLEX} \), \( \text{ILV} \rightarrow \text{SV} \), \( \text{ABP} \rightarrow \text{SV} \), \( \text{HR} \rightarrow \text{SV} \) are plotted with associated 90% confidence intervals (Figures 4-6-4-10). The impulse response represents the response of the system to an input of unit area and vanishingly small duration applied at time zero. Next, the corresponding group average unit step responses of each coupling mechanism with 90% confidence intervals are plotted (Figures 4-11-4-15). The step response illustrates the response of the system to an input of unit amplitude beginning at time zero. Finally, the group average squared magnitude of each transfer function are presented with 90% confidence intervals (Figures 4-16-4-20).

Figures 4-21-4-23 display, on a log-log scale, the power spectra of the perturbing noise sources, \( N_{HR} \), \( N_{SV} \), and \( N_{ABP} \), for each experimental condition. The figure legend keys are defined in the same fashion as in Figures 4-1-4-4: The first letter in the key specifies the animal (a, b, c, or d), the remaining letters indicate the experimental condition (b=Baseline, a=ACE Blockade, s=$\beta$-Sympathetic Blockade, r=$\alpha$-Sympathetic Blockade and pb=Atrial Pacing), and the trailing number specifies the repetition. The group average and standard errors of slopes and intercepts (at \( 10^{-3} \) Hz) of the linear regressions of the noise power spectra are given in Table 4.4. The group average regression lines with 90% confidence intervals are plotted for each signal and each condition in Figure 4-24.
Figure 4-6 Group average system identification results for the Baseline experimental Condition. Solid lines are average impulse responses. Dashed lines are 90% confidence intervals.
Figure 4-7 Group average system identification results for the ACE Blockade experimental condition. Solid lines are average impulse responses. Dashed lines are 90% confidence intervals.
Figure 4-8 Group average system identification results for the Atrial Pacing experimental condition. Solid lines are average impulse responses. Dashed lines are 90% confidence intervals.
Figure 4-9 Group average system identification results for the β-Sympathetic Blockade experimental condition. Solid lines are average impulse responses. Dashed lines are 90% confidence intervals.
Figure 4-10 Group average system identification results for the α-Sympathetic Blockade experimental condition. Solid lines are average impulse responses. Dashed lines are 90% confidence intervals.
Figure 4-11 Group average system identification results for the Baseline experimental condition. Solid lines are average step responses. Dashed lines are 90% confidence intervals.
Figure 4-12 Group average system identification results for the ACE Blockade experimental condition. Solid lines are average step responses. Dashed lines are 90% confidence intervals.
Figure 4-13 Group average system identification results for the Atrial Pacing experimental condition. Solid lines are average step responses. Dashed lines are 90% confidence intervals.
Figure 4-14 Group average system identification results for the $\beta$-Sympathetic Blockade experimental condition. Solid lines are average step responses. Dashed lines are 90% confidence intervals.
Figure 4-15 Group average system identification results for the α-Sympathetic Blockade experimental condition. Solid lines are average step responses. Dashed lines are 90% confidence intervals.
Figure 4.16: Group average system identification results for the Baseline experimental condition. Solid lines are average squared transfer function magnitudes. Dashed lines are 90% confidence intervals.
Figure 4-17 Group average system identification results for the ACE Blockade experimental condition. Solid lines are average squared transfer function magnitudes. Dashed lines are 90% confidence intervals.
Figure 4-18 Group average system identification results for the Atrial Pacing experimental condition. Solid lines are average squared transfer function magnitudes. Dashed lines are 90% confidence intervals.
Figure 4-19 Group average system identification results for the β-Sympathetic Blockade experimental condition. Solid lines are average squared transfer function magnitudes. Dashed lines are 90% confidence intervals.
Figure 4-20 Group average system identification results for the α-Sympathetic Blockade experimental condition. Solid lines are average squared transfer function magnitudes. Dashed lines are 90% confidence intervals.
Figure 4-21 Power spectra of HR noise source ($N_{HR}$) from each experimental condition. Legend keys: first letter specifies animal (a,b,c,d), subsequent letters indicate experimental condition (b=baseline, a-ACE Blockade, s=$\beta$-Sympathetic Blockade, r=$\alpha$-Sympathetic Blockade, bp=Atrial pacing), and the trailing number specifies repetition.
Figure 4-22 Power spectra of ABP noise source ($N_{ABP}$) from each experimental condition. For legend key definitions see Figure 4-21.
Figure 4-23 Power spectra of SV noise source ($N_{SV}$) from each experimental condition. For legend key definitions see Figure 4-21.
<table>
<thead>
<tr>
<th>Noise</th>
<th>Baseline</th>
<th>ACE Blockade</th>
<th>Atrial Pacing</th>
<th>β Blockade</th>
<th>α Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>( N_{HR} ) (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.97 ± 0.02</td>
<td>-0.68 ± 0.04‡</td>
<td>—</td>
<td>-0.85 ± 0.08</td>
<td>-1.43 ± 0.01‡</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.76 ± 0.02</td>
<td>3.58 ± 0.07</td>
<td>—</td>
<td>3.40 ± 0.09†</td>
<td>4.36 ± 0.24‡</td>
</tr>
<tr>
<td>( N_{ABP} ) (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-0.85 ± 0.02</td>
<td>-0.97 ± 0.03</td>
<td>-0.76 ± 0.03</td>
<td>-0.97 ± 0.10</td>
<td>-1.16 ± 0.06†</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.44 ± 0.04</td>
<td>3.77 ± 0.04†</td>
<td>3.48 ± 0.04</td>
<td>3.65 ± 0.09</td>
<td>3.64 ± 0.1</td>
</tr>
<tr>
<td>( N_{SV} ) (mL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>-1.11 ± 0.04</td>
<td>-0.96 ± 0.06</td>
<td>-1.07 ± 0.05</td>
<td>-1.04 ± 0.16</td>
<td>-0.81 ± 0.14</td>
</tr>
<tr>
<td>Intercept</td>
<td>2.90 ± 0.04</td>
<td>2.75 ± 0.04</td>
<td>2.30 ± 0.09‡</td>
<td>2.82 ± 0.13</td>
<td>2.71 ± 0.04</td>
</tr>
</tbody>
</table>

Table 4.4: Average noise source \( (N_{HR}, N_{ABP}, N_{SV}) \) spectral slopes and intercepts \( (10^{-3} \text{ Hz}) \) for each experimental condition \( (\text{mean ± standard error}) \). Significant differences from Baseline: † indicates \( p < 0.1 \), ‡ indicates \( p < 0.05 \).
Figure 4-24 Group average linear regressions of $N_{HR}$, $N_{ABP}$, and $N_{SV}$ power spectra from each experimental condition.
4.4 1/f Simulations

Representative results from applying the ARMA system identification techniques to input-output data sets from a simulated system with 1/f power transfer are given in Figure 4-25. Note that the ARMA approach produces accurate estimates of the 1/f characteristic across 2–3 decades of frequency. Accurate fit requires only 20–40 parameters.
Chapter 5

Discussion

5.1 Experiment

The surgical protocol was successful, and despite its complexity, the surgical survival rate was 100%. It is, however, unclear whether the post-operative arrhythmia developed by the excluded animal was related to the placement of instrumentation.

Post-operatively, each animal’s hemodynamic status remained within normal ranges. The mean cardiovascular values presented in Table 4.2 are reasonable mean values for 30 kg sheep. A collection of previously reported measurements in sheep are gathered in [71]. Typical values of heart rate for sheep range from 80–160 bpm, typical values of mean arterial blood pressure range from 70–110 mmHg, and typical values of stroke volume range from 30–50 ml. Mean values of these cardiovascular parameters were not statistically altered by any experimental interventions with the exception of a decrease in stroke volume associated with atrial pacing. This decrease in stroke volume may be attributed to a shorter filling time associated with the pacing protocol.
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>ACE Blockade</th>
<th>Atrial Pacing</th>
<th>( \beta ) Blockade</th>
<th>( \alpha ) Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart Rate (bpm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>(-0.97 \pm 0.02)</td>
<td>(-0.65 \pm 0.04)†</td>
<td>—</td>
<td>(-0.62 \pm 0.03)†</td>
<td>(-0.77 \pm 0.08)</td>
</tr>
<tr>
<td>Intercept</td>
<td>(3.66 \pm 0.03)</td>
<td>(3.63 \pm 0.05)</td>
<td>—</td>
<td>(3.75 \pm 0.02)</td>
<td>(4.24 \pm 0.16)†</td>
</tr>
<tr>
<td><strong>Arterial Blood Pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>(-0.94 \pm 0.02)</td>
<td>(-1.09 \pm 0.03)</td>
<td>(-0.66 \pm 0.04)†</td>
<td>(-0.84 \pm 0.08)</td>
<td>(-1.16 \pm 0.02)</td>
</tr>
<tr>
<td>Intercept</td>
<td>(3.71 \pm 0.05)</td>
<td>(3.90 \pm 0.03)</td>
<td>(3.59 \pm 0.05)</td>
<td>(3.94 \pm 0.1)</td>
<td>(3.70 \pm 0.06)</td>
</tr>
<tr>
<td><strong>Cardiac Output (L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>(-0.99 \pm 0.01)</td>
<td>(-0.97 \pm 0.06)</td>
<td>(-1.20 \pm 0.04)†</td>
<td>(-0.67 \pm 0.06)†</td>
<td>(-0.94 \pm 0.01)</td>
</tr>
<tr>
<td>Intercept</td>
<td>(1.51 \pm 0.05)</td>
<td>(0.83 \pm 0.05)†</td>
<td>(0.68 \pm 0.07)†</td>
<td>(1.2 \pm 0.26)</td>
<td>(0.88 \pm 0.08)†</td>
</tr>
<tr>
<td><strong>Stroke Volume (mL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>(-0.99 \pm 0.02)</td>
<td>(-0.98 \pm 0.05)</td>
<td>(-1.21 \pm 0.05)†</td>
<td>(-0.96 \pm 0.06)</td>
<td>(-0.96 \pm 0.12)</td>
</tr>
<tr>
<td>Intercept</td>
<td>(3.32 \pm 0.06)</td>
<td>(2.78 \pm 0.04)†</td>
<td>(2.40 \pm 0.08)†</td>
<td>(3.20 \pm 0.24)</td>
<td>(3.14 \pm 0.02)</td>
</tr>
<tr>
<td><strong>Lung Volume (L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slope</td>
<td>(-0.20 \pm 0.02)</td>
<td>(-0.30 \pm 0.09)</td>
<td>(0.23 \pm 0.03)</td>
<td>(-0.28 \pm 0.05)</td>
<td>(-0.32 \pm 0.01)</td>
</tr>
<tr>
<td>Intercept</td>
<td>(0.13 \pm 0.06)</td>
<td>(-0.20 \pm 0.13)</td>
<td>(-0.24 \pm 0.10)</td>
<td>(0.24 \pm 0.06)</td>
<td>(0.29 \pm 0.01)</td>
</tr>
</tbody>
</table>

Table 5.1: Average signal spectral slopes and intercepts \(10^{-3}\) Hz for each experimental condition (mean ± standard error). Significant differences from Baseline: † indicates \(p < 0.1\), ‡ indicates \(p < 0.05\)

### 5.2 Power Spectra of Cardiovascular Variables

The first investigation was of the power spectra of HR, ABP, SV, and CO. It is well established that the heart rate power spectrum demonstrates a \(1/f\) character below approximately \(10^{-2}\) Hz \([82,97,139,151,166,179]\). It is also well established that the blood pressure spectrum demonstrates a \(1/f\) character \([117,139,172,173]\) although studies disagree as to whether there is a change of slope within the \(1/f\) range \([172]\).

The HR and ABP power spectra computed in this study are illustrated in Figure 4-1 and 4-2, respectively. In the resting condition with no experimental interventions, both the HR and ABP power spectra exhibit a \(1/f^\alpha\) characteristic with \(\alpha \approx 1\) in the frequency band below \(10^{-2}\) Hz. The slopes were given in Table 4.3 and repeated here in Table 5.1.

The slope of the HR power spectrum was significantly decreased in magnitude with both ACE blockade and \(\beta\)-blockade. It may be argued that \(\beta\)-blockade results in a decreased level of low frequency sympathetic modulation of heart rate and therefore,
the relative power in lower frequency bands was reduced. It is more difficult to understand how ACE blockade alters the heart rate power spectrum in the absence of changes in blood pressure fluctuations. One would expect the alteration in the direct influence of angiotensin II on blood pressure to be the major effect of ACE blockade. However, the slope and intercept of the ABP power spectrum remain unchanged during all interventions except atrial pacing. It is recognized that angiotensin II may have both central nervous and direct cardiac effects. As discussed in Section 2.1.1, angiotensin II may alter cardiac output by increasing central sympathetic drive and by direct action on cardiac muscle [103]. Perhaps ACE blockade leads to a decrease in central sympathetic drive which might account for the reduced low frequency heart rate variability seen during ACE blockade.

The slope and intercept of the ABP power spectrum remained unchanged during all interventions except that of atrial pacing. Atrial pacing eliminated all heart rate variability and one could argue that the loss of a $1/f$ pattern to the heart rate power fluctuations led to the alteration of the blood pressure fluctuations – specifically to a reduction in low frequency blood pressure variability. That is, one could argue that the $1/f$ pattern in blood pressure is due to the $1/f$ pattern in heart rate. However, as we will see in Section 5.3.2, this conclusion is not well supported by the system identification results. Furthermore, blood pressure does maintain its $1/f^\alpha$ character; only the magnitude of the slope, $\alpha$, is reduced.

Fluctuations in both CO and SV were also found to have a $1/f$ spectral distribution below $10^{-2}$ Hz. Although it has been previously established that fluctuations in renal blood flow in rats follows a $1/f$ frequency distribution [117], the fact that fluctuations in CO itself have a $1/f$ spectral character has not been previously reported. The slope of the $1/f$ region of the cardiac output spectrum was made less steep by $\beta$-blockade. The decrease in low frequency cardiac output variability occurs without a similar decrease in stroke volume variability. Thus, it seems likely that the decrease is
associated with a decrease in low frequency heart rate variability due to the decrease in sympathetic modulation. Both cardiac output and stroke volume show an increase in the magnitude of the $1/f$ spectral slope during atrial pacing. They also both exhibit a significant decrease in the spectral intercept. Thus, there is a reduction in the total variability in both signals but a more dramatic decrease in high frequency than in low frequency fluctuations. These findings may be explained by the elimination of fluctuations in heart rate. The more dramatic effect on higher frequency fluctuations may be attributed to the fact that the largest effects of heart rate on stroke volume are experienced within the time scale of 1-2 beats.

It is interesting to note by way of contrast that ILV fluctuations are not $1/f$ in character. In fact, even when attempts are made to estimate a linear fit to the ILV power spectra as presented in Table 5.1, it is clear that the spectra are more nearly flat than sloped.

5.3 System Identification

The data were used to characterize all of the coupling mechanisms and noise sources in the model presented in Figure 3.3.4 and reproduced here in Figure 5.3.

One issue which arose in the system identification process was that of selecting the appropriate sampling rate for the data. In ARMA modeling, the sampling rate is a critical determinant of the effective signal to noise ratio [105]. In particular, if the sampling rate is chosen to be too high relative to the passband of the system being identified, then the result is an effective reduction in signal to noise ratio. That is, the high frequency components which are not coupled through the system act to corrupt the system estimates. The system identification in this study was performed on the data from the baseline condition at three sampling frequencies, 3.0, 0.5, and 0.1 Hz. In each case, the input signals were then individually applied to the appropriate
coupling mechanism in order to simulate the effects of each input on the output. For example, the effect of CO on ABP was simulated as

\[ \text{ABP}_{\text{CO}}(t) = \sum_{i=1}^{Q} q_i \text{ABP}(t - i) + \sum_{i=1}^{R} r_i \text{CO}(t - i) \]  

This is simply Equation (3.5b) with the ILV and N\text{ABP} terms set to zero. Analogous equations were used to simulate the other individual effects, and the process was repeated for models derived from data sampled at 3.0, 0.5 and 0.1 Hz. The relative effect of each input on the output may be quantified as a percentage of the total output variance\(^1\). The average percentage of variability in the output signals

\(^1\)Note that the variances due to each input signal will not be expected to sum to the total output variance but the analysis does provide some insight nevertheless.
<table>
<thead>
<tr>
<th>Sampling Frequency</th>
<th>ABP from CO</th>
<th>ABP from ILV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>22.3667</td>
<td>1.8515</td>
</tr>
<tr>
<td>0.5</td>
<td>21.2199</td>
<td>5.7702</td>
</tr>
<tr>
<td>3.0</td>
<td>16.3950</td>
<td>0.8000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling Frequency</th>
<th>HR from ABP</th>
<th>HR from ILV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>22.3667</td>
<td>1.8515</td>
</tr>
<tr>
<td>0.5</td>
<td>22.6640</td>
<td>12.3867</td>
</tr>
<tr>
<td>3.0</td>
<td>12.8559</td>
<td>8.3382</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sampling Frequency</th>
<th>SV from HR</th>
<th>SV from ABP</th>
<th>SV from ILV</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>6.8060</td>
<td>11.0210</td>
<td>1.1567</td>
</tr>
<tr>
<td>0.5</td>
<td>21.5450</td>
<td>33.2238</td>
<td>1.3100</td>
</tr>
<tr>
<td>3.0</td>
<td>6.8060</td>
<td>11.0210</td>
<td>1.1567</td>
</tr>
</tbody>
</table>

Table 5.2: Average percentages of total Baseline ABP, HR and SV variability accounted for by each of their respective inputs as a function of sampling frequency.

explained by each input signal at each sampling rate are given in Table 5.2. Note that the performance, in terms of total variability explained, tends to decrease with both lower and higher sampling frequencies. The sampling rate of 0.5 Hz was not selected to be an optimum for describing variability, and in fact, a slightly higher rate of 1.0 or 1.5 Hz (as used in [127]) may be closer to optimal for capturing all of the model dynamics. A sampling rate in this range corresponds closely to the typical heart rate frequency which is reasonable since in many ways, the rate of new information available from the cardiovascular system is linked to the heart rate. Further discussion of this concept is given in Section 5.5. In the present study, the lower sampling rate of 0.5 Hz was selected since the low frequency 1/f fluctuations were of primary interest.

Complete group average system identification results computed from data sampled at 0.5 Hz are presented in Figures 4-6 through 4-20. Individual noise source power spectra are presented in Figures 4-21 through 4-23.
5.3.1 Physiological Interpretation

The first task in interpreting the system identification results is to determine whether the coupling mechanisms are physiologically reasonable. The group average impulse responses from the Baseline condition are reproduced in Figure 5-2. Each of the coupling mechanisms is represented in this Figure by its time domain response to an arbitrarily narrow, unit area pulse input at time zero. The group average step responses from the Baseline condition are reproduced in Figure 5-3. Each of the coupling mechanisms is represented in this Figure by its time domain response to a unit step input at time zero.

The \[ \text{ILV} \rightarrow \text{ABP} \] impulse response in Figure 5-2 is characterized by a rapid increase followed by a return to baseline within 5-10 seconds (beats). It is quite similar to the response identified in human subjects from short duration recordings [127]. The increase in ABP associated with inspiration has been attributed to an increase in diastolic filling associated with the decrease in intrathoracic pressure. In the human study [127], an immediate small decrease in ABP was noted which was followed by the rapid increase seen in the present study. This decrease was attributed to the decrease in intrathoracic pressure being transmitted to arterial structures leading to a rapid transient decrease in ABP. In the present study, since the sampling rate was 0.5 Hz rather than 1.5 Hz, this transient decrease is presumably filtered out of the data. The plateau of the \[ \text{ILV} \rightarrow \text{ABP} \] step response is approximately 5 mmHg/L which is within a physiologically reasonable range [148].

The \[ \text{ILV} \rightarrow \text{HR} \] impulse response also demonstrates a rapid and immediate increase. This response is consistent with the observation that on inspiration there is an increase in heart rate. Furthermore, this increase begins to assume positive values at times less than zero indicating that heart rate rises in anticipation of corresponding changes in ILV. This response is similar to that found in human subjects [127] although the return to baseline is slightly slower than in the human response. The
Figure 5-2 Group average system identification results for the Baseline experimental condition. Solid lines are average impulse responses. Dashed lines are 90% confidence intervals.
**Figure 5-3** Group average system identification results for the Baseline experimental condition. Solid lines are average step responses. Dashed lines are 90% confidence intervals.
ILV → HR step response has a plateau amplitude of approximately 10 bpm/liter which is a physiologically reasonable level [77, 155].

The PERIPHERAL IMPEDANCE impulse response reflects an immediate increase in blood pressure associated with an increase in cardiac output. Physiologically such a response is expected since the increase in blood flow in the face of an unchanged resistance must lead to an increase in pressure. It is possible that the underdamped nature of the response reflects the reflexive adjustments in peripheral resistance but this idea is highly speculative. The step response has a plateau amplitude of approximately 5 mmHg/(L/min) which, based simply on estimates of peripheral resistance [148], seems to be a physiologically reasonable response level.

The HR BAROREFLEX impulse response demonstrates a rapid negative deflection followed by a very rapid return to baseline. Once again this response is analogous to that found previously in humans [127] and the decrease in heart rate associated with an increase in blood pressure is well established. The HR BAROREFLEX step response reaches a plateau at approximately -0.5 bpm/mmHg. This is a reasonable value for typical baroreflex sensitivity [35, 71, 160].

The ILV → SV impulse response shows an immediate decrease followed by an increase, but these changes are not significantly different than zero. It was expected that inspiration would lead to an increase in stroke volume associated with the decrease in intrathoracic pressure and increased diastolic filling. It is possible that the 0.5 Hz sampling rate was not sufficiently high to capture the anticipated effects.

The HR → SV impulse response shows a small but significant decrease in stroke volume associated with an increase in heart rate. The decrease seen in the step response is on the order of 30 μL/bpm which means a step increase of 10 bpm would be expected to decrease stroke volume by about 1%. Such a change in heart rate decreases the ventricular filling time by approximately 10% (dependent on heart rate). However, the majority of ventricular filling happens during the rapid filling phase [28].
so that, at normal heart rates, the magnitude of the the identified response seems physiologically reasonable.

The $\text{ABP} \Rightarrow \text{SV}$ impulse response is not significantly different than zero. An increase in arterial blood pressure might be expected to decrease stroke volume in the absence of other regulatory function. However, as discussed in Section 2.1.2, in the healthy heart, stroke volume is normally not altered by changes in afterload and therefore we expect this coupling to be minimal. This coupling mechanism, however, may be expected to be a more important component in the evaluation of patients with diseases such as hypertension or heart failure.

The group average impulse responses from the ACE Blockade, Atrial Pacing, $\beta$-Sympathetic Blockade and $\alpha$-Sympathetic Blockade are presented in Figures 4-7 through 4-10. The step responses are given in Figures 4-12 through 4-15. The response characteristics during the ACE blockade condition were not significantly altered with the exception of the $\text{HR BAROREFLEX}$ impulse response which was slightly diminished. Although this difference was not quite statistically significant, such a decrease in the heart rate baroreflex might be explained by the central and cardiac interactions of angiotensin II as discussed in Section 2.1.1. The group average impulse responses from the atrial pacing intervention were significantly altered in that the $\text{ILV} \Rightarrow \text{ABP}$ impulse response was markedly reduced and the $\text{ABP} \Rightarrow \text{SV}$ impulse response showed a more significant initial decrease. The reduction in the $\text{ILV} \Rightarrow \text{ABP}$ impulse response may be associated with the reduced filling time during atrial pacing. Since filling time is reduced, the effect of a decrease in intrathoracic pressure may be reduced as well. The elimination of the respiratory sinus arrhythmia during atrial pacing may also reduce $\text{ILV} \Rightarrow \text{ABP}$. The larger magnitude of the initial $\text{ABP} \Rightarrow \text{SV}$ impulse response may be due to a reduced capacity of the paced heart to overcome increases in afterload. It should also be noted that the $\text{PERIPHERAL IMPEDANCE}$ impulse response is significantly altered during atrial pacing. However, since HR
is fixed, the quality of the estimate of this coupling is somewhat suspect. During 
$\beta$-sympathetic blockade, the $\text{ILV} \rightarrow \text{HR}$ and $\text{HR BAROREFLEX}$ group average step response plateau magnitudes are slightly diminished. This change is expected since the $\text{ILV} \rightarrow \text{HR}$ and $\text{HR BAROREFLEX}$ couplings are largely autonomically mediated [127]. As one would expect, the effect of $\beta$-sympathetic blockade on these couplings is significantly less dramatic than combined blockade of the parasympathetic and $\beta$-sympathetic systems [127]. The $\alpha$-sympathetic blockade was completed in only one animal and only two repetitions were completed so it is not possible to make reliable statistical comparisons with this condition.

5.3.2 Occurrence of $1/f$

As discussed in Section 5.2, fluctuations in heart rate, blood pressure, cardiac output and stroke volume all exhibit a $1/f^\alpha$ frequency distribution below $10^{-2}$ Hz. The major objective of this investigation was to determine whether the $1/f$ pattern is due to one or more of the model transfer couplings or originates in one or more noise sources of the model. The group average squared magnitudes of the identified transfer functions are presented in Figures 4-16 through 4-20. The power spectra of the individual noise spectra are presented in Figures 4-21 through 4-23.

The squared magnitude of the transfer function represents the power transfer as a function of frequency. If the system is responsible for producing an output with a $1/f$ power spectral distribution when given a random, white input perturbation, then it is expected to have a $1/f$ shaped squared transfer function magnitude. None of the coupling mechanisms from the baseline condition (Figure 4-16) demonstrate a $1/f$ shape in their squared transfer function magnitudes. Therefore, it seems that the $1/f$ character of fluctuations in hemodynamic variables cannot be attributed to the linear couplings investigated in our model.

If the model transfer couplings cannot account for the $1/f$ distribution of hemody-
Table 5.3: Average noise source (N_{HR}, N_{ABP}, N_{SV}) spectral slopes and intercepts (10^{-3} Hz) for each experimental condition (mean ± standard error). Significant differences from Baseline: † indicates $p < 0.1$, ‡ indicates $p < 0.05$

Table 5.3: Average noise source (N_{HR}, N_{ABP}, N_{SV}) spectral slopes and intercepts (10^{-3} Hz) for each experimental condition (mean ± standard error). Significant differences from Baseline: † indicates $p < 0.1$, ‡ indicates $p < 0.05$

Dynamic fluctuations, then it must be accounted for by one or more of the noise sources. In fact, each of the noise sources in the model demonstrates a 1/f spectrum. The slopes and intercepts of the noise source power spectra are repeated in Table 5.3. The slopes of N_{HR}, N_{ABP}, and N_{SV} are all 1/f^{\alpha} with $\alpha \approx 1$. Thus, the source of the 1/f fluctuations in our model is not a single noise source or a single coupling mechanism but rather all of the noise sources. Furthermore, when considering the fluctuations from all interventions, it seems that the noise sources remain quite consistently 1/f.

Since each of the noise source power spectra demonstrate a 1/f shape, it is interesting to determine whether these noises are correlated or not. A significant correlation might suggest a common source of the noise or a single perturbative mechanism that influences each of the noise spectra. To verify that these noise sources are linearly independent, correlation coefficients between pairs of the three noise sources, N_{HR}, N_{ABP} and N_{SV}, were calculated as

$$r_{n_1n_2} = \frac{s_{n_1n_2}}{s_{n_1}s_{n_2}} = \frac{\sum(n_1(t) - \bar{n}_1)(n_2(t) - \bar{n}_2)}{\sqrt{\sum(n_1(t) - \bar{n}_1)^2 \sum(n_2(t) - \bar{n}_2)^2}}$$

(5.2)

where $r_{n_1n_2}$ is the correlation coefficient between noise sources $n_1$ and $n_2$, the sums are computed over the length of the data, and the overbar indicates the mean value. The group average correlation coefficients between each pair of noise sources for each
<table>
<thead>
<tr>
<th>SIGNALS</th>
<th>BASELINE</th>
<th>ACE BLOCKADE</th>
<th>ATRIAL PACING</th>
<th>β-BLOCKADE</th>
<th>α-BLOCKADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N_{SV} to N_{HR}</td>
<td>-0.07</td>
<td>-0.22</td>
<td>—</td>
<td>-0.12</td>
<td>-0.33</td>
</tr>
<tr>
<td>N_{ABP} to N_{HR}</td>
<td>0.27</td>
<td>0.31</td>
<td>—</td>
<td>0.19</td>
<td>0.43</td>
</tr>
<tr>
<td>N_{SV} to N_{ABP}</td>
<td>-0.21</td>
<td>-0.15</td>
<td>0.186</td>
<td>-0.21</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

Table 5.4: Average correlation coefficients of noise sources (N_{SV}, N_{ABP} and N_{HR}) in each experimental condition.

Experimental condition are given in Table 5.4. The correlation coefficients between any pair of noise spectra are small under all experimental conditions. Thus, the 1/f perturbations seen in N_{HR}, N_{ABP}, and N_{SV} seem to be linearly independent of one another which suggests that there may be more than one mechanism for the production of 1/f fluctuations in hemodynamic variables.

The finding that the 1/f fluctuations arise from the noise sources and that none of the transfer couplings in the model exhibited a 1/f character might be taken as an indication that the ARMA identification approach does not accurately identify a system with a 1/f power transfer characteristic. To demonstrate that the identification protocol would indeed accurately identify such a system, a simulation was performed as described in Section 3.4. The identification procedure was applied to the input-output data of a simulated system with 1/f shape power transfer. Representative simulation results are presented in Figure 5-4. Provided that the model is not under-parameterized, an accurate identification of the 1/f transfer characteristic may be achieved across multiple decades of frequency. An accurate identification required only 20–40 parameters. Furthermore, the Korenberg algorithm used in this investigation performs well in automatically selecting the model order of 18 autoregressive and 18 moving-average terms.

It may also be argued that the simplified model depicted in Figure 5.3 eliminates important couplings between the signals. As discussed in Section 3.3.4, the model was developed to omit couplings which seemed redundant or relatively unimportant. To investigate the possibility that important couplings were omitted, a larger model
Figure 5-4 System Identification of a simulated system with $1/f$ power transfer. The straight solid line is the true squared magnitude of the transfer characteristic of the simulated system. The Korenberg algorithm used in this investigation automatically selected 18 AR and 18 MA coefficients and produced the long-dashed transfer characteristic.
<table>
<thead>
<tr>
<th></th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
<th>Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>-0.93 ± 0.04</td>
<td>-0.82 ± 0.04</td>
<td>-1.04 ± 0.04</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.67 ± 0.07</td>
<td>3.55 ± 0.04</td>
<td>4.2 ± 0.02</td>
</tr>
</tbody>
</table>

Table 5.5: Average slopes and intercepts (10^{-3} Hz) of noise source (N_{HR}, N_{ABP}, and N_{SV}) power spectra from the maximal interactions model in the Baseline condition.

Based only on the heart rate, blood pressure, lung volume, and cardiac output was identified and the noise source spectra were inspected for the presence of 1/f distribution. The new model considered all possible interactions between heart rate, blood pressure, and cardiac output and also allowed lung volume to affect each of these signals. Stroke volume was not included in this model since all inputs to stroke volume were considered in the original model. Only the data from the Baseline experimental condition were studied. The slopes and intercepts of the resulting heart rate, blood pressure, and cardiac output noise sources are given in Table 5.5. Note that the slopes of the heart rate and blood pressure noise source spectra in this “maximal model” retain the 1/f shape and the slopes are largely unchanged from those in the original model. Also note that the cardiac output noise spectrum exhibits a 1/f distribution. Therefore, to the extent that we are able to identify an alternative model from the same data set, we find that the alternative model also isolates the 1/f pattern of fluctuations in the model noise sources.

Finally, it may be argued that the linear modeling does not permit the possibility that nonlinear couplings between the measured signals may explain the origin of the 1/f fluctuations. To test this hypothesis, a nonlinear autoregressive moving average (NARMA) model structure was used. The NARMA formulation differed from the ARMA formulation in Equation (3.5) in that all possible second- and third-order nonlinear interactions were permitted between the inputs and outputs in the model. The nonlinear terms are simply considered as new inputs to the ARMA model. For a two input linear model such as that describing HR in Equation (3.5a), a total of
<table>
<thead>
<tr>
<th></th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
<th>Stroke Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slope</td>
<td>-0.98 ± 0.03</td>
<td>-0.75 ± 0.04</td>
<td>-0.87 ± 0.04</td>
</tr>
<tr>
<td>Intercept</td>
<td>3.99 ± 0.07</td>
<td>3.96 ± 0.11</td>
<td>3.25 ± 0.10</td>
</tr>
</tbody>
</table>

Table 5.6: Average slopes and intercepts (10^-3 Hz) of noise source (N_{HR}, N_{ABP} and N_{SV}) power spectra from nonlinear model in the Baseline condition.

six possible second-order terms, and ten possible third-order terms were included to arrive at the full third-order nonlinear model. All of these terms were considered as new potential inputs in the NARMA formulation. Each of the baseline data sets was used to characterize the third-order NARMA model and the noise spectra were observed for the presence of 1/f fluctuations. The group average slopes and intercepts of the noise sources in the nonlinear model are given in Table 5.6. Despite the addition of second- and third-order nonlinear terms, the spectra of the noise sources all retain their 1/f shape and the slopes remain near one.

It is also interesting to note that, in the Baseline condition, the linear model explains on average 75% of heart rate variability, 87% of blood pressure variability and 72% of stroke volume variability. The addition of nonlinear terms provides only a small improvement in these percentages. The nonlinear model explains 78% of heart rate variability, 88% of blood pressure variability, and 73% of stroke volume variability. It is conceivable that a more complex nonlinear model may capture a 1/f-type coupling between hemodynamic parameters, but the investigation of such models is beyond the scope of this thesis.

Based on these results, it appears that none of the model transfer functions account for the production of the 1/f^α fluctuations in hemodynamic variables. The 1/f^α fluctuations originate in each of three model noise sources impinging on heart rate, blood pressure, and stroke volume. Augmenting the model to include additional linear relationships between the variables did not alter the 1/f nature of the model noise sources. The addition of second- and third-order nonlinear terms to the model also
did not alter the shape of the model noise sources. Furthermore, none of the experimental interventions eliminated the \(1/f^\alpha\) pattern of fluctuations (except atrial pacing, which trivially eliminated the \(1/f^\alpha\) pattern in heart rate), although some significant changes in the exponent, \(\alpha\), were observed in some signals during the interventions.

Therefore, we conclude that the \(1/f^\alpha\) fluctuations seen in hemodynamic signals such as heart rate, blood pressure, stroke volume, and cardiac output are not due to linear or low-order nonlinear regulatory mechanisms coupling the signals. Rather, the \(1/f^\alpha\) appears to arise from unmeasured perturbations to heart rate, blood pressure, and stroke volume. These perturbations appear in the model noise source \(N_{SV}, N_{ABP}\), and \(N_{HR}\).

### 5.4 What causes the \(1/f\) noise source fluctuations?

Although this investigation cannot provide direct evidence as to the specific mechanisms underlying the \(1/f\) fluctuations seen in the noise sources, it is interesting to speculate on some potential mechanisms.

In Section 2.3.3, a simple model of one dimensional diffusion is shown to produce \(1/f\) fluctuations when driven by a white noise. Consider the situation in which a solute is dripped or released in small quantities at a point and is allowed to diffuse in one dimension away from that point. If the concentration of solute as a function of time at the origin \((x = 0)\) is a white noise, then the spectrum of concentration at a point \(x\), away from the origin, is given by

\[
S(x, f) = \frac{e^{-2\sqrt{16Dx}}}{128D\pi f} \quad \text{for} \quad x > 0
\]

(5.3)

where \(D\) is the diffusion coefficient, \(f\) is frequency, and \(x\) is the distance from the origin.\(^2\) At low frequencies or for small distances from the origin, this spectrum is

---

\(^2\)This equation follows directly from Equations (2.13) and (2.14) with a white system input and the substitution \(\omega = 2\pi f\).
Figure 5-5 Spectrum of solute concentration at a point 10 microns from the origin in a one-dimensional diffusion model for a range of diffusion constants.

approximately $1/f$. Figure 5-5 displays the spectrum of concentration at a distance ten microns from the origin for a range of diffusion constants. The diffusion coefficients of many electrolytes, neurotransmitters, or autacoids are within the range of values selected. It is interesting to note that the $1/f$ region extends over much of the same frequency band as the hemodynamic parameters examined in this investigation. Perhaps the $1/f$ behavior exhibited by heart rate, blood pressure, and stroke volume is attributable to $1/f$ diffusive mechanisms related to neural or hormonal control of cardiac rate, cardiac contractility, and peripheral resistance.

Another mechanism which has been proposed by Machlup [107] and by Montroll and Shlesinger [122] is a simple statistical model. This model was presented in Section 2.3.3. Essentially, the model asserts that if an ensemble of random processes has a scale invariant distribution of relaxation times, then the power spectrum of the
ensemble is distributed as $1/f$. Montroll and Shlesinger assert that a type of central limit theorem applies to a product of random variables so that the limiting distribution is the log-Normal distribution. They also demonstrate that the log-Normal distribution is scale invariant across a wide range. For example, in a system in which an outcome is dependent on a sequence of probabilistic events, then the probability of the outcome is the product of the individual probabilities of each event. Montroll and Shlesinger assert that the probability distribution of the outcome will approach the log-Normal distribution and therefore exhibit scale invariance across a considerable range [122]. Thus, if a system is affected by a range of potential random noise sources and the distribution of relaxation times of these noise sources is dependent on a sequence of events, then the system may exhibit $1/f$ noise as a result.

In the cardiovascular system it is not difficult to envision a collection of processes influenced by random variability that is due to a series of control steps. Montroll and Shlesinger discuss, as an example, the $1/f$ fluctuations in the level of the river Nile at its mouth. An analogous situation may apply, for example, in the generation of $1/f$ fluctuations in stroke volume. Consider that each drop of blood must proceed from the arterial to venous circulation and be delivered to the ventricle. First, the drop of blood must be delivered to the arterial tree, then, the progress of the drop is determined by the peripheral resistance, gravitational effects, changes in intrathoracic pressure, alterations in cardiac contractility and so on. The conditions must all be right for the drop to proceed to the venous circulation and into the ventricle. Thus, the flow rate of blood into the ventricle might be expected to demonstrate a log-Normal distribution and thus the volume of blood delivered from the ventricle may demonstrate $1/f$ noise.

This statistical model is speculative and applying it to cardiovascular variability is even more so. However, the model does have the advantage that it may explain the presence of $1/f$ noise in the diverse range of systems in which it is seen. It is not
dependent, as the diffusion model is, on a specific physical mechanism. Since the range of physical systems displaying $1/f$ noise is so diverse, it is often difficult to imagine that so many different physical mechanisms might lead to $1/f$ noise. Therefore, many may find that a statistical model such as this one which might provide a single explanation is somehow satisfying.

5.5 Recommendations

A number of recommendations for future studies stem from the present research. The first recommendation is that further investigation of the source of $1/f$ fluctuations in hemodynamic variables focus on fluctuations in neural and hormonal regulatory systems.

A second recommendation is that studies of cardiovascular variability be conducted on a beat-to-beat basis rather than a second-to-second basis unless a specific need mandates otherwise. This recommendation applies particularly when the objective is to study hemodynamic parameters such as cardiac contractility or peripheral resistance. The present challenge in advancing the clinical utility of cardiovascular variability is to develop techniques for quantifying such physical control parameters from variability data.

A third recommendation is to consider the role of alternative model structures in the identification of cardio-regulatory systems. Since it seems clear that $1/f$ noise is ubiquitous in the cardiovascular system, model structures which more easily handle the presence of $1/f$ noise may be advantageous. The ARMAX structure was tested briefly and informally during this thesis work. It did not alter the findings in that the model results were similar. However, the ARMAX model provides a better parameterization for the $1/f$ noise since it provides both autoregressive and moving average parameters for characterizing the noise sources. The additional computational com-
plexity associated with identifying the ARMAX model may be justified by a more parsimonious model.

Finally, it is recommended that the effects of $\alpha$-sympathetic blockade be further investigated. The blockade is difficult to achieve and maintain in sheep due to the occurrence of spontaneous large oscillations in blood pressure and heart rate. Some of the fluctuations in blood pressure were at 0.1 Hz, the Mayer wave frequency, but were quite large and often included deflections on the order of 10-20 mmHg. It would be interesting to determine to what extent instabilities in blood pressure control are induced by complete $\alpha$-sympathetic blockade.
Chapter 6

Summary and Conclusions

Since the discovery in the early 1980's that heart rate variability provides a "window" for investigating autonomic nervous regulation of cardiovascular function [2], there has been an explosion of interest in the study of short-term (minutes) cardiovascular variability [167]. The analysis of variability is often undertaken with the objective of identifying markers of clinical events or conditions. Researchers look, for example, for power spectral indices which distinguish normal autonomic function from abnormal or predict the risk of sudden death.

In recent years we have developed a system identification approach which offers the advantage of providing a quantitative means for examining the couplings between fluctuations in different hemodynamic variables and for quantifying the regulatory mechanisms. We have successfully applied this approach to analyze short-term fluctuations in arterial blood pressure, heart rate and instantaneous lung volume [127] so as to quantify such important regulatory mechanisms as the respiratory sinus arrhythmia and heart rate baroreflex. The system identification approach allows for the study of intact regulatory function.

Relatively fewer investigations of long-term (hours to days) hemodynamic variability have been undertaken. However, these investigations have revealed an interesting
pattern in the low frequency fluctuations of heart rate. The power spectral density of heart rate fluctuations, over many decades of frequency below $10^{-2}$ Hz, is approximately inversely proportional to frequency ($1/f^\alpha$, where $\alpha$ is close to 1). Such $1/f$ distributions are ubiquitous in nature but the mechanisms leading to such fluctuations remain unknown. Interestingly, the exponent $\alpha$ has been found to change significantly and consistently in cardiac disease states and in some cases is a better predictor of clinical outcomes than any parameter based on analyses of short-term heart rate fluctuations. The origin of the $1/f^\alpha$ fluctuations seen in hemodynamic variables such as heart rate remains unknown.

The general goal of this investigation was to extend the system identification approach to the study of cardiovascular regulation over a longer time scale and to incorporate measurement of cardiac output (CO) into a model relating fluctuations in hemodynamic signals. Using the augmented model, the specific objective was to determine whether the $1/f^\alpha$ spectral pattern seen in hemodynamic variables is due to one or more of the transfer function couplings or originates in the model noise sources. A secondary objective was to determine whether pharmacological interventions or fixed-rate atrial pacing altered the $1/f^\alpha$ pattern seen in spectra or transfer couplings.

A conscious sheep model was employed. Each animal was surgically instrumented for measurement of heart rate, arterial blood pressure, and cardiac output. Lung volume was monitored non-invasively. After surgical recovery, two to four hour recordings of these signals were made, on separate days, under resting conditions, during fixed-rate atrial pacing, and after administration of an angiotensin converting enzyme inhibitor (captopril), a $\beta$-sympathetic blocking agent (propranolol), and an $\alpha$-sympathetic blocking agent (phentolamine).

As in previous studies, we found that, under resting conditions, heart rate and blood pressure fluctuations did indeed demonstrate a $1/f$ spectral pattern at frequencies below $10^{-2}$ Hz. In addition, we found that resting cardiac output and stroke
volume fluctuations also exhibited a $1/f$ spectral pattern in this same low frequency band.

We applied the system identification approach to a simplified model relating heart rate, blood pressure, cardiac output, stroke volume and lung volume and found that none of the model transfer functions accounted for the production of the $1/f^\alpha$ fluctuations. The $1/f^\alpha$ fluctuations originated in each of three model noise sources impinging on heart rate, blood pressure and stroke volume. We also found that the addition of second- and third- order nonlinear terms to the model did not alter the $1/f^\alpha$ nature of the model noise sources. Furthermore, none of the experimental interventions eliminated the $1/f^\alpha$ pattern of fluctuations (except atrial pacing which trivially eliminated the $1/f^\alpha$ pattern in heart rate), although some significant changes in the exponent, $\alpha$, were observed in some signals during the interventions.

Therefore, we conclude that the $1/f^\alpha$ fluctuations seen in hemodynamic signals such as heart rate, blood pressure, stroke volume and cardiac output are not due to linear or low-order nonlinear regulatory mechanisms coupling the signals. Rather, the $1/f^\alpha$ appears to arise from unmeasured perturbations to heart rate, blood pressure and stroke volume. We speculate that these perturbations may be related to diffusive mechanisms associated with neural or local hormonal regulatory processes.
Appendix A

An Alternate Approach for Spectral Slope Estimation

This appendix presents an alternative, computationally efficient means for estimating the power spectral slope and intercepts. A similar approach was presented by Taratura [166].

Assume the following form for the power spectrum, $S(f)$:

$$ S(f) = \frac{f_1}{f_\alpha}. \quad (A.1) $$

Then,

$$ \log S(f) = \log f_1 - \alpha \log f \quad (A.2) $$

and if $b = \log f_1$ then,

$$ \log S(f) = b - \alpha \log f. \quad (A.3) $$

The slope, $\alpha$, and intercept, $b$, are the parameters of interest and may be estimated from measures of the total power in two frequency bands, $A_c$ and $A_d$, as illustrated in Figure A-1.
We can calculate the total power with a given band of frequencies as

\[ A_c = \int_{10^c}^{10^{c+d}} S(f) \, df = f_1 \int_{10^c}^{10^{c+d}} \frac{1}{f^\alpha} \, df \]  \hspace{1cm} (A.4)

\[ A_c = \begin{cases} f_1 (10^{c+d}(1-\alpha) - 10^c(1-\alpha)) & \alpha \neq 1 \\ f_1 (\ln 10^{c+d} - \ln 10^c) & \alpha = 1. \end{cases} \]  \hspace{1cm} (A.5)

First, taking the case of \( \alpha \neq 1 \), we can substitute for \( f_1 = 10^b \) and rearrange to find

\[ A_c = \frac{10^b}{1 - \alpha} 10^c(1-\alpha)(10^{b(1-\alpha)} - 1) \]  \hspace{1cm} (A.6)

We may choose a second frequency band of equal logarithmic width, \( \delta \) such that

\[ A_d = \int_{10^d}^{10^{d+d}} S(f) \, df \]  \hspace{1cm} (A.7)

or

\[ A_d = \frac{10^b}{1 - \alpha} 10^d(1-\alpha)(10^{d(1-\alpha)} - 1) \]  \hspace{1cm} (A.8)
where \( d \neq c \) and typically the two frequency bands are chosen so that they do not overlap.

If the areas, \( A_c \) and \( A_d \), are calculated from the measured spectrum, we can treat these two equations with two unknowns, \( \alpha \) and \( b \). We can solve for \( \alpha \):

\[
\frac{A_c}{A_d} = 10^{(c-d)(1-\alpha)} \quad (A.9)
\]

and therefore

\[
\alpha = 1 - \frac{\log(A_c/A_d)}{c-d} \quad (A.10)
\]

We can solve\(^1\) for \( b \)

\[
b = \log\frac{A_c(1-\alpha)}{10^c(1-\alpha)(10^d(1-\alpha) - 1)} \quad (A.11)
\]

Note that \( A_c \) and \( A_d \) will be equal if and only if \( \alpha = 1 \), and the second case of the solution to the integral applies. We can solve for the intercept, \( b \), in this case as:

\[
b = \log\left(\frac{A_c}{\ln(10^{c+d}) - \ln(10^c)}\right) \quad (A.12)
\]

\(^1\)Taratura et al. [166] solve for \( b \) using the expression for \( A_cA_d \) and then substitute \( \alpha \) into this more complicated expression: \( b = \log\left(\frac{\sqrt{A_cA_d}(1-\alpha)}{10^c(1-\alpha)}\right) - \frac{(c+d)(1-\alpha)}{2} \)
Bibliography


