A Mathematical Model of Neurally-Mediated Angiotensin II-Salt Hypertension

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Dedication

To my family
Abstract

This thesis presents a mathematical model of long-term blood pressure control that explains how latent activation of the sympathetic nervous system in the AngII-salt model of hypertension can lead to chronic blood pressure elevation without modifying renal ability to excrete sodium. Previous mathematical models of hypertension were built on the assumption that such modification is necessary. The model integrates four major systems of body fluid and solute control: the cardiovascular system, kidneys, microvascular exchange between extracellular and intracellular compartments, and the sympathetic nervous system. The model excludes two major hypotheses used in previous mathematical models: the chronic pressure-natriuresis mechanism and the whole-body autoregulation mechanism; the model adds a hypothesis of slow long-term activation of the sympathetic nervous system, which acts to increase pressure via increased non-renal arterial resistances and venous tone. Despite the difference in assumptions, the model’s predictions agree well with all major classical observations associated with AngII-salt hypertension, including the pressure-natriuresis phenomenon. Analysis of the model demonstrates that the pressure-natriuresis curves are projections of a three-dimensional dynamics driven by both renal and neural control and reflect an additive impact of both controls on blood pressure. Thus, the current interpretation of pressure-natriuresis curves as the result only of a direct mechanistic impact of arterial pressure on renal function may not be warranted in some cases of hypertension. The presented model conclusively demonstrates that AngII-salt hypertension can be maintained without the sole renal dominance.
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Chapter 1

Introduction

Chronically elevated arterial blood pressure, or hypertension, is a major risk factor in the development of cardiovascular diseases such as heart failure and stroke. About a third of the U.S. population and a quarter of the world’s population have hypertension. An exaggerated rise in blood pressure in response to increased salt intake, so-called salt-sensitivity of blood pressure, is of particular clinical importance. About 25% of the normotensive population, and over 50% of the hypertensive population, are salt-sensitive, which has been shown to be a stronger predictor of death and cardiovascular risk, even more than arterial pressure alone [108]. Despite improvements in medical therapies over the years, normalization of blood pressure is still not achievable in almost 50% of hypertensive patients. This poor control rate is partially due to the patient’s medication noncompliance, but is also due to an incomplete understanding of the mechanisms that lead to the development of hypertension. Because of the sheer number of physiological factors involved in blood pressure regulation, mathematical modeling plays an important role in identifying which of these factors are significant.

Existing mathematical models are of limited scientific and clinical impact as they are incapable of identifying pathways that do not include kidney dysfunction. Recent efforts have been focused almost exclusively on designing an accurate and detailed model of kidney function, since kidneys were believed to be the sole culprit of hypertension. However, the latest experimental and clinical findings have shown that targeting neural
pathways can be successful in treating hypertension, independent of kidney function. Since the current models dramatically limit the ability to model the influence of alternate pathways in the development of hypertension, we build a novel framework for a mathematical model that includes neural pathways as an independent long-term controller of blood pressure.

1.1 Basics of blood pressure control

There are many mechanisms by which arterial blood pressure may eventually be raised, but there are only two immediate factors: cardiac output and total peripheral resistance. Cardiac output, the amount of blood pumped by the heart each minute, creates a pressure gradient between arteries and veins that drives the flow through circulatory system. By averaging the above variables across a cardiac cycle, Ohm’s law representation of this phenomenon can be expressed as:

\[
\text{Mean Arterial Pressure - Mean Venous Pressure} = \text{Total Peripheral Resistance} \times \text{Cardiac Output}.
\]

Since mean venous pressure is near zero, changes in arterial pressure are determined by peripheral resistance and cardiac output.

Total peripheral resistance and cardiac output are under the control of a larger number of factors. Activation of the sympathetic nervous system\(^1\) and circulating hormones can increase peripheral resistance by constricting the vascular walls. The sympathetic nervous system can increase heart rate and cardiac contractility, causing an elevation in cardiac output. An increase in blood volume and venous tone cause expansion of the stressed blood volume\(^2\), delivering more blood to the heart, stretching the heart muscle further, resulting in more vigorous contractions, and thus also increasing cardiac output.

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1 The sympathetic nervous system is one of the divisions of the nervous system, influencing many factors of blood pressure control such as heart rate, vascular tone, and sodium excretion.
2 Blood vessels contain a certain volume of blood at a zero transmural pressure, called unstressed volume. The unstressed volume depends on the diameter of the vessels and thus is modified by vessel tone, primarily venous tone. The remaining portion of the total blood volume is called stressed volume.
output. Blood volume can be increased by moving fluid from the extravascular space or by retention of water and sodium. A schematic view of this basic control cascade is shown in Figure 1.1. A complete list of all factors and mechanisms involved in blood pressure control is large, with entire books dedicated to the discussion [38, 60]. A summary based on the diagram proposed by Page [79] is shown in Figure 1.2, with relevant portions covered in later sections of this dissertation highlighted.

Figure 1.1: Basic sequence of changes leading to an elevation of mean arterial pressure.

1.2 Salt-sensitive hypertension

1.2.1 Direct observations

Studying hypertension in humans is complicated not only because most variables are experimentally inaccessible, but also because the disease progression usually spans decades and often goes undiagnosed for years. Thus, hypertension research is often performed in animals. One of the common rodent models of salt-sensitive hypertension is a chronic infusion of angiotensin II (AngII) in combination with a high salt diet (AngII-salt). Angiotensin II is a hormone which plays an important role in blood pressure control and has a wide range of effects on the vasculature, kidneys, and brain, leading to vasoconstriction, renal sodium retention and an elevation of sympathetic nerve activity. The magnitude of chronic blood pressure response in the AngII-salt animal model is

3 "Renal" means pertaining to kidney.
directly related to the level of salt intake.

A typical arterial pressure response to AngII-salt protocol is shown in Figure 1.3. In this example, chronic infusion of angiotensin II caused minimal increase in mean arterial pressure in rats on a low salt diet. However, when animals were placed on normal or high salt diet, blood pressure progressively increased.

A similar observation has been made in a study performed in dogs by Krieger et al [62]. After several days of intravenous infusion of angiotensin II, daily salt intake was increased and the corresponding changes in blood pressure, cardiac output, and total body weight were measured. Total body weight was assumed to correlate with the total blood volume; total peripheral resistance was computed as the ratio of arterial

---

4 Salt is composed primarily of sodium chloride (NaCl). Sodium is the principal osmole in extracellular fluid and chloride is its primary anion. The ions are transported in equivalent amounts in most cases, thus in hypertension literature the terms “salt” and “sodium” are often used interchangeably.
pressure to cardiac output. As shown in Figure 1.4,A, the combination of high salt and angiotensin II resulted in the elevation of blood pressure. Initially the elevation in blood pressure was accompanied by an increase in blood volume and cardiac output (the onset phase). At the later stage, however, the cardiac output returned to control levels and only total peripheral resistance was elevated (the maintenance phase). This temporal pattern of arterial pressure, cardiac output, blood volume, and total peripheral resistance has been observed in several similar studies, and was stylized by Guyton as shown in Figure 1.4,B. It is referred to as the hemodynamic profile of AngII-salt hypertension.

In human hypertension a similar hemodynamic profile has been observed, albeit over much longer period of time (years) than that which is observed in the animal models. In mild hypertension, cardiac output is elevated while resistance is normal. In moderate to severe hypertension, cardiac output is normal but resistance is elevated. Unlike in Krieger’s and Guyton’s studies, however, blood volume in hypertensive humans is reported to be normal or slightly below normal levels.

The mechanisms behind the hemodynamic profile of AngII-salt hypertension have been debated for decades, in part because angiotensin II has renal, vascular, and neural
actions, all of which can raise blood pressure via multiple pathways. There are two main theories that have been proposed to explain the hemodynamic profile: the renocentric theory and the neurocentric theory.

1.2.2 The renocentric theory

Hypotheses

The renocentric theory was introduced by Guyton in early 1970’s. It relies on two hypothetical mechanisms: chronic pressure-natriuresis mechanism and whole-body autoregulation mechanism.
The chronic pressure-natriuresis hypothesis states that the renal ability to excrete salt (natriuresis) over long-term is directly determined by the arterial pressure: the higher the pressure the more salt is excreted. The evolution of this hypothesis is shown in Figure 1.5. Isolated kidney studies from the 1950’s demonstrated that an acute (within minutes) rise of renal perfusion pressure\(^5\) leads to an acute rise in sodium excretion in an isolated kidney [96, 97, 103]. The dependence of acute sodium excretion on renal perfusion pressure is known as an acute renal function curve, or acute pressure-natriuresis curve (Figure 1.5,A). This relationship, however, does not hold long term [38].

The classical experiment that measured chronic relationship between pressure and natriuresis was performed by DeClue et al [23] (Figure 1.5,B). In this experiment, two groups of dogs were studied. In one group, plasma AngII was elevated 2.5 times via continuous infusion. The other group was used as control. In both groups chronic sodium and water intake was varied via infusions over the period of few weeks. Arterial blood pressure and urinary sodium excretion were measured at three day intervals until these variables reached steady state, and sodium excretion matched the new level of sodium intake. The results were first plotted as blood pressure versus sodium intake and a correlation was noted: an almost zero slope in the control group and a non-zero slope in the other group. Since sodium intake and excretion were the same at the time of the measurements, the authors proposed that the correlation could be the sign of a direct long-term causal relationship between the arterial pressure and sodium excretion. The axes of the plot were reversed and relabeled (Figure 1.5,C). The resulting curve is known as the chronic pressure-natriuresis curve, and is used to describe the direct functional dependence of sodium excretion on arterial pressure in Guyton’s theory.

The whole body autoregulation mechanism of peripheral resistance was proposed by Guyton and his colleagues to help explain the rise in total peripheral resistance during the maintenance phase of the hemodynamic profile. Guyton did not believe that the sympathetic nervous system was involved in the long-term regulation of blood pressure

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\(^5\) Renal perfusion pressure is the pressure in the renal arteries. It is measured further away from the heart than the arterial pressure and thus lower in magnitude, but can be assumed to be linearly dependent on the arterial pressure.
and thus hypothesized that the observed constriction of vessels is due to over-perfusion.

This mechanism is similar to a well-known acute response, called the myogenic response, where vascular tone is rapidly adjusted within seconds. There is sparse experimental evidence for the long-term autoregulation mechanism proposed by Guyton, and its existence remains highly debated [59].

**Explanation of AngII-salt hemodynamic profile**

Under the above assumptions the hemodynamic profile of AngII-salt hypertension shown in Figure 1.4 can be explained as follows. The chronic pressure-natriuresis mechanism
implies that in normal conditions it takes only a small increase in pressure to produce a large change in excretion, but a disturbance such as the infusion of AngII may reduce the slope and thus the hemodynamic profile of AngII-salt hypertension would ensue as follows. At the onset of high salt intake, when arterial pressure is still at a normal level, the sodium excretion is relatively low which leads to an accumulation of salt and expansion of blood volume. The latter increases cardiac output (the onset phase) followed by the over-perfusion of systemic organs which triggers whole body autoregulation mechanism and a rise in peripheral resistance (the maintenance phase). Thus the arterial pressure rises and continues to rise until it reaches a level necessary to match salt excretion with salt intake (Figure 1.6).

Additional experimental evidence

There are two often-cited arguments of indirect evidence for chronic dependence of blood pressure on renal ability to excrete sodium:

1. **Hypertension follows transplanted kidney:** Several studies of kidney cross-transplantation between normotensive and hypertensive subjects show that hypertension often follows the kidney [21, 32]. That is, transplantation of kidneys from normotensive subjects reduces the blood pressure of the hypertensive recipients and transplantation of kidneys from hypertensive subjects increases the blood pressure in the normotensive recipients.

2. **Natriuresis may be insufficient if perfusion pressure is fixed:** In a study by Hall et al [44] two groups of dogs received chronic AngII infusion over a couple of weeks and daily measurements of arterial blood pressure and sodium excretion were collected. In one group of dogs renal perfusion pressure was clamped, i.e. fixed at a constant normal level, effectively buffering the kidney from changes in the arterial pressure. The other group of dogs was used as a control. The authors showed that clamping of the renal perfusion pressure led to a severe reduction in sodium excretion and excessive fluid retention, which was resolved only after renal perfusion pressure was unclamped. It was concluded that a rise in renal perfusion
Figure 1.6: Basic renocentric concept of chronic blood pressure response to AngII-salt protocol. The onset phase is due to a shift of the renal function curve in response to AngII which leads to an insufficient sodium excretion for the new elevated level of sodium intake. This results in blood volume accumulation and increase in cardiac output. The maintenance phase is sustained by the whole body autoregulation mechanism which increases peripheral resistance in response to high cardiac output. The system reaches an equilibrium when arterial pressure is high enough to generate sodium excretion equal to sodium intake via the renal function curve determined by AngII concentration.

pressure is essential in allowing kidneys to attain sodium balance.

The direct mechanisms governing chronic pressure-natriuresis have not yet been identified [28, 46]. The kidneys excrete sodium and water by first filtering large amounts of fluid and solutes and then reabsorbing the majority of them back into the circulation. Thus there are three fundamental ways by which sodium excretion may change: change in renal blood flow, change in filtration rate and change in reabsorption rate. It has been demonstrated that both renal blood flow and filtration rate are efficiently regulated against changes in arterial pressure [89]. So most of the recent studies have been focused
on the control of the reabsorption rate [20, 33, 68]. However, the question of how the kidney is able to sense arterial pressure remains unanswered.

1.2.3 The neurocentric theory

Hypotheses

The neurocentric theory has been around for as long as the renocentric theory, but only recent technological advancements have enabled collection of robust evidence in its support. The theory relies on two hypotheses: 1) sympathetic nerve activity is elevated by a combination of high AngII with high sodium intake, and 2) sodium excretion within a physiologically relevant concentrations does not need to be regulated by the arterial pressure. The latter hypothesis is a key to distinguishing neurocentric theory from the renocentric one. Without this hypothesis, Guyton’s renocentric theory can be invoked by claiming that the abnormal sympathetic activity ”must in the end somehow modify the kidney’s ability to excrete salt and water for a given level of [blood pressure]” [71]. The neurocentric theory also does not rely on the existence of whole body autoregulation mechanism.

The neurocentric theory does not state that sodium excretion is entirely independent of pressure, but rather that the kidney’s function is regulated by a variety of hormonal and physical factors which are capable of regulating sodium excretion with little to no reliance on arterial pressure within a certain physiological range of sodium intake and circulating AngII. In the absence of abnormal renal function, hypertension is driven primarily by elevated sympathetic activity via non-renal pathways. The arterial pressure, however, can become an important controller of sodium excretion in more extreme conditions when sodium intake is significantly elevated, other control mechanisms are overwhelmed, or if the pressure itself is very high.

Explanation of AngII-salt hemodynamic profile

Under the above assumptions, the AngII-salt hemodynamic profile can be explained as follows. The onset phase is a combination of normal responses to AngII and to salt
intake, seen in normotensive and hypertensive subjects alike. Increase in salt intake is
matched by renal excretion via hormonal responses, hydrostatic and osmotic forces, but
is somewhat delayed by the elevated AngII which opposes excretion. The 2-3 day delay
of the renal response to sodium intake is thus accompanied by a minor salt and water
accumulation, an increase in blood volume, cardiac output and arterial pressure. This
eyearly rise of blood pressure triggers an acute transient decrease in sympathetic activity
known as the baroreflex response. The vasodilation associated with the baroreflex masks
the vasoconstriction caused by AngII. Thus total peripheral resistance remains largely
unchanged during the onset phase of AngII-salt hypertension. The maintenance phase
is triggered by a latent chronic activation of the sympathetic nerve activity initiated
by the brain’s cardiovascular control center in response to elevated circulating levels
of salt and AngII. The elevated sympathetic nerve activity increases venous tone and
constricts vessels in non-renal vascular beds elevating total peripheral resistance, along
with now unopposed vasoconstrictor effect of AngII.

Experimental evidence

The following experimental evidence is used in support of the neurocentric theory:

1. Elevated sympathetic nerve activity (SNA) has been observed via direct
   and indirect measurements of sympathetic activity [29, 34, 57, 104].

2. Increased SNA is not uniformly distributed: splanchnic\(^6\) SNA is elevated
   [63, 84], renal SNA is decreased [113], and skeletal muscle SNA remains fairly
   unchanged [112]. Moreover, renal denervation does not affect the development of
   AngII-salt hypertension [58] while splanchnic denervation attenuates its develop-
   ment [57, 58].

3. Blocking cardiovascular centers in the brain attenuates AngII-salt hy-
   pertension: Lesions of sites in the brain responsive to changes in AngII and

\(^6\) Splanchnic is a term used when referring to a subset of systemic circulation consisting of gastric,
small intestinal, colonic, pancreatic, hepatic, and splenic circulations. Splanchnic organs are responsible
for a majority of the total venous capacity.
Figure 1.7: Basic neurocentric concept of chronic blood pressure response to AngII-salt protocol. The onset phase is due to the renal component and the maintenance phase is due to the neural component. Renal mechanisms match sodium excretion to sodium intake via a complex interaction of intra-renal and extra-renal feedbacks. The delay in response causes blood volume and thus cardiac output to increase. Neural mechanisms are activated by a combination of AngII-salt with a several day delay. Elevated sympathetic nerve activity increases peripheral resistance and venous tone.

plasma sodium were shown to attenuate hypertension [19, 77]. Chronic administration of a sodium channel blocker directly into the brain completely reverses the maintenance phase of AngII-salt hypertension [78].

4. **Sodium excretion may not be regulated by arterial blood pressure.**

Studies with acute, modest increase of sodium intake either by isotonic or hypertonic solutions showed that natriuresis happens without changes in arterial blood pressure [3, 11, 85]. A study by Seeliger et al [95] showed that clamping renal perfusion pressure does not prevent increased natriuresis following isotonic saline infusion. Furthermore, a study by Reinhardt et al [86] showed that clamping renal
perfusion pressure in an AngII-salt model of hypertension does not prevent the
needed increase in natriuresis and thus the natriuresis is regulated by factors other
than arterial pressure. The study by Reinhardt is in direct contradiction with the
study by Hall et al [44] used to support the renocentric theory.

5. There is no evidence of renal dysfunction in most cases of human hyper-
tension, in fact renal abnormality is usually observed only after years of exposure
to high blood pressure [60].

1.2.4 Mathematical models

Mathematical modeling can be useful to hypertension research in at least three ways.
First, it offers a single framework in which all relevant physiological mechanisms and
hypotheses are expressed and allows identification of various pathways leading to the
same set of experimentally observed variables. Second, it generates new hypotheses
that may not be apparent from the experimental data. Third, it provides a tool for
designing future experiments. The latter characteristic also determines future revisions
of the model’s hypotheses, in particular if its predictions contradict new experimental
evidence.

The renocentric theory is supported by the mathematical model designed by Guyton
and Coleman. The basic concept described in Figure 1.6 consisted of just a handful of
equations and was first published in the late 1960’s [39], followed by a more extensive
model with more detailed organ function description in the early 1970’s [41]. A full
mathematical description of the Guyton-Coleman model (GC model) and parameter
identification has never been published and instead a flowchart of the entire system was
provided (Figure 1.8). However, this has not prevented publications of the improvements
to the model’s various elements over the years [47, 49, 55].

The improvements and increasing complexity of later versions of the GC model have
not changed the basic premise of the theory, i.e. the chronic pressure-natriuresis is still
the key mechanism which controls the emergence of hypertension in the model. The
model was created not just for the study of hypertension but of other diseases (e.g.
Figure 1.8: Guyton-Coleman’s mathematical model of long-term blood pressure control as published in 1972 [41].
heart failure) and responses to various stimuli (e.g. temperature, exercise), thus many of its details are unimportant for the discussion of hypertension onset. In fact, most of the current publications with references to the GC model still describe it via its basic, simplest form similar to the one shown in Figure 1.6 [49, 71].

Even though the renocentric theory heavily relies on the existence of the pressurerenatriuresis mechanism, its description in the GC model has not withstood the test of time. In the version published in 1972 (Figure 1.8) the arterial pressure increases renal blood flow and filtration rate in order to increase sodium excretion. As mentioned previously, it has been shown experimentally that both renal blood flow and filtration rate are efficiently regulated against changes in arterial blood pressure. Thus, changes in sodium excretion cannot be modeled in such a direct manner and should be instead controlled via renal reabsorption rate, if they are dependent on arterial pressure at all.

This weakness in the model has focused most of the recent work on the improvement of the GC’s renal function description [47, 48, 55, 72, 100]. The new models can be roughly divided into two categories: models of renal function alone, and integrative models where renal function interfaces with the circulation and the sympathetic nervous system. The former models describe renal processes in great physiological detail, but lack clear explanation on the direct role of arterial pressure. The latter models have a simpler representation of renal function and assume that either the arterial pressure or renal sympathetic activity triggered by changes in the arterial pressure directly modify renal reabsorption rate. However, this assumption still needs to be vetted by direct experimental evidence and more detailed mathematical models.

Integrating a physiologically-based model of renal function with a model of the circulatory system is a big challenge, which explains why the two renal model categories above exist. The kidneys sense changes in sodium and water intake indirectly, via changes in the extra-renal responses to dietary inputs (such as osmotic pressures, plasma composition and circulating hormones). At the same time, the kidneys modify those responses by modifying total body water and sodium. This complex interaction is difficult to model, requiring either a simple renal model or a simple representation of sodium sensing. A more detailed discussion can be found in Chapter 2, Section 2.5.
All existing mathematical models of long-term blood pressure control are based on
the GC model. No mathematical models in support of the neurocentric theory, which
we are aware of, have been proposed prior to publications based on our work [6, 7, 75].

1.3 Thesis aims

The goal of the current research was to build a mathematical model of long-term blood
pressure control consistent with the neurocentric theory, that is able to explain the
hemodynamic profile of AngII-salt hypertension in rats by chronic activation of the
sympathetic nervous system in the absence of a chronic pressure-natriuresis mechanism.
It is a significant effort to incorporate all known mechanisms of blood pressure control
(Figure 1.2). The first version of Guyton’s model took several years and an effort of at
least three people. Improvements to the model have been made over several decades, by
dozens of scientists working in teams. The model presented in this dissertation aims not
to compete in size and detail to the GC model but to complement it with a qualitatively
different framework which allows study of non-renal causes under the assumption of a
normal renal function. This framework can serve as a foundation for future work which
can extend these findings, much as the GC model has done for the renocentric research
for more than 5 decades.

The assumption of pressure-natriuresis dependence in the GC model is often incor-
correctly interpreted as mathematical evidence that the hemodynamic profile of AngII-salt
hypertension cannot occur unless the pressure-natriuresis mechanism exists. We have
recently demonstrated that this is not true. Natriuresis can be controlled independently
of arterial pressure, and yet hypertension can still develop [6]. This was an important
step toward the overall goal of developing a neurocentric model of hypertension, but it
has also raised a question of how the kidney is able to sense changes in sodium intake
in the absence of pressure dependence. The answer to this question requires a more de-
tailed mathematical model which includes renal function and key physiologic pathways
affected by sodium and AngII.

The choice of physiological mechanisms and variables to be included in the model
was driven by identifying the strongest known contributors to blood pressure control and their known physiological impact. The simplest possible representation was preferred to keep the size of the model manageable. This approach led to the identification of four major modules of the model, representing circulatory system, fluid-solute exchange between vascular and extravascular spaces, renal function, and the sympathetic nervous system (Figure 1.9). The first two modules (Chapter 2, Sections 2.2 and 2.4) were based on the previously existing models used in simulations of acute responses. The model of chronic activation of the sympathetic nervous system (Chapter 2, Section 2.3) was based on the experimental evidence and the hypotheses of the neurocentric theory. One important note is that a portion of the sympathetic module acts on a slow time scale due to known latent activation (Figure 1.7), while the rest of the system acts on a faster time scale.

Figure 1.9: A schematic representation of the overall model representing four physiological contributors to blood pressure control: circulation, extravascular space, kidneys, and the sympathetic nervous system (blocks with white background). Direct interactions are shown by arrows. All interactions are on the fast time scale (solid lines) except for those with the sympathetic nervous system which acts on a slow time scale (dashed line). The AngII and sodium intake directly affect only the circulatory system. They cause changes in plasma composition, hydrostatic pressures, and flows which then impact the other three systems. In return, each of them can change parameters of the circulatory system (e.g. blood volume or resistance) and thus impact the mean arterial blood pressure.
The renal function module (Chapter 2, Section 2.5) is the most complex and novel module of the entire model. What makes it unique is that it combines the following features: it represents renal sodium and water excretion in moderate detail, it works together with the circulatory module and fluid-solute exchange module to adjust sodium excretion to sodium intake, and it does not rely on arterial pressure or a direct sensing of sodium intake to modify the excretion. Thus it addresses the challenge currently faced by the current models of renal function, as described in the section above.

Simulations in Chapter 3 show that the new model produces a hemodynamic profile of AngII-salt studies consistent with the experimental observations. The pressure-natriuresis relationship still exists in the new model but as a correlation of two largely independent variables responding to physiological stimuli by way of two different control pathways. Pressure is raised via a neural pathway in response to the combined stimuli of AngII and salt, and natriuresis is raised via a renal response to increased salt intake. A simple mathematical example of this behavior can be demonstrated via the following system of two variables $x_1$ (mean arterial pressure) and $x_2$ (sodium excretion) with an input parameter $p$ (sodium intake):

$$\frac{dx_1}{dt} = f(p) - x_1$$
$$\frac{dx_2}{dt} = p - x_2$$

While the two variables are determined independently by $p$, one can express a dependence using their steady state values: $x_1 = f(x_2)$. Figure 1.10 demonstrates the concept behind pressure-natriuresis in the new model in its extreme, when the two controls are decoupled.

Model parameters were chosen based on the available experimental data. Not all mechanisms can be assessed experimentally, and in particular, the specific measurements of responses to AngII-salt protocol are limited, so some of the parameters were fit using the best available information on directional change or other mathematical models. This approach resembles the approaches by other researchers in this field [41, 47, 55]. However, we have added global sensitivity analysis given the large uncertainty in many
Figure 1.10: An illustration of how the pressure-natriuresis phenomenon emerges under the assumptions of the neurocentric theory. Steady state values of mean arterial pressure and sodium excretion are plotted in response to sodium intake and AngII. Sodium intake and excretion are shown in normalized units (n.u.). Two of the three orthogonal planes represent physiological mechanisms of control: sodium excretion is matched to sodium intake by renal mechanisms and arterial pressure is driven by the sympathetic nervous system sensitive to sodium intake and AngII, where AngII affects the slope of the curve. The projection of the resulting 3-D curve onto the plane of mean arterial pressure versus sodium excretion is the pressure-natriuresis phenomenon observed experimentally. The plane itself does not reflect a direct mechanistic relationship between sodium excretion and pressure.

of the parameters. It helped identify key parameters and mechanisms responsible for arterial pressure control in this model. The results of this analysis are shown in Chapter 3.

Finally, in Chapter 4, conclusions from model’s analysis and future directions are discussed. One of the main contributions of this work is the creation of a framework for testing and comparing various pathways, renal or non-renal, which may be involved in AngII-salt hypertension. As of today, a number of experimental and clinical efforts have been used to target the neural component of blood pressure regulation. Yet in
mathematical modeling, virtually all current work is focused on improving models of renal function to be fit into the framework of the GC model. However, no matter how accurately one models an organ’s function, if its interactions with the rest of the system are limited by a narrow assumption such as the pressure-natriuresis mechanism, all conclusions may be of questionable scientific and clinical merit. And if renal dysfunction is not the single culprit of hypertension, or if arterial pressure does not drive sodium excretion, then there are missed opportunities to look for treatments outside of the kidneys with the help of a mathematical model. The outcome of the presented research addresses this limitation and provides mathematical modeling support for the neurocentric theory. This neurocentric mathematical model may in turn yield future clinical benefit by providing a tool for clinicians and scientists to better understand the important physiologic factors that regulate long-term blood pressure levels.
Chapter 2

Mathematical model of long-term blood pressure control

The diagram in Figure 2.1 shows the "big-picture" view of how arterial pressure is controlled by the mathematical model presented in this chapter. The system consists of four major control modules: a circulatory module, a neural module, a renal-hormonal module, and a whole-body exchange module. Arterial pressure is the output of the Circulatory Module, which describes how total blood volume is circulated and partitioned by the vasculature. It has four key parameters that regulate arterial blood pressure: heart rate, extra-renal resistance, venous capacitance, and total blood volume. The first three parameters are driven by the Neural Module, which senses circulating plasma osmolality and angiotensin II. The fourth parameter, total blood volume, is determined by the Whole-Body Exchange Module; this module defines how total body water, sodium chloride, and proteins are distributed across cells, interstitium, and vascular spaces and is based on fundamental laws of microvascular transport and lymphatic mechanisms. The Whole-Body Exchange Module also generates key inputs for the Renal and Hormonal Module, such as plasma protein concentration, plasma osmolality, and hematocrit. Together with arterial and venous pressure these inputs control sodium and water excretion, as well as plasma angiotensin II, closing the loop between the modules.

The Renal Module is designed to generate urinary excretion rates via an indirect
Figure 2.1: Modular flowchart of the entire system. The four modules (white background, large bold italics) are indicated with their main inputs and outputs (grey, bold font). There are three inputs to the system: sodium intake, water intake, and angiotensin II infusion (grey, plain font).
sensing of sodium and water intakes and does not rely exclusively on vascular pressures. This module is a novel contribution to the field both as a stand-alone model and as a part of the entire system, as it allows a new framework for studying arterial blood pressure control.

The Neural Module consists of two controls: the traditionally known baroreflex control which acts on the same time scale as the rest of the system and the hypothesized latent control which acts on a much slower scale. Thus, for simulations and analysis (Chapter 3) the entire system is split into a fast and slow subsystems by way of time scale separation technique. The fast system contains all but one equation ((2.14)) and represents the early, onset phase of AngII-salt hypertension. The slow activation presented by Equation (2.14) acts on the steady states of the fast subsystem by modifying three key parameters of the Circulatory Module: resistance, venous tone and heart rate. The dynamics of the slow subsystem simulates the maintenance phase of AngII-salt hypertension (see Figure 1.4).

2.1 Notation and parameters

The approach to parameter identification used in this model resembles the approaches of others in the field [47, 55, 41, 107]. Experimental findings collected from experimental literature are combined with functions borrowed from parts of the existing models. Data from non-rodent species was used if no other sources available, after proper scaling.

The description of all system variables is given in Table 2.1 (names) and Table 2.2 (subscripts). Table 2.5 shows normal steady-state values of key system variables and parameters as well as their source (e.g. a reference or the equation used to compute it). The normal steady-state value is denoted by subscript 0. For example, cardiac output’s normal value is \( \text{CO}_0 = 74 \text{ ml/min} \).

The system has a fair number of parameters many of which have either a common notation or describe a specific physiological quantity. However, the model contains many phenomenological relationships for which parameters were fitted to experimental data or adopted from previously published models. Due to a large number of parameters of
the latter type, and, to avoid cumbersome notation we reuse the same notation \((p_1, p_2\) and so on) in each equation and list the parameter values in a corresponding row of the Table 2.3. The units of these parameters are not explicitly shown, but were matched to the units of the corresponding variables in the equation (see Table 2.5).

For example, equation (2.5) describes cardiac output as follows:

\[
CO = HR \cdot SV = HR \cdot (p_1 - \frac{p_1}{1 + e^{p_2(P_V - p_3)}})
\]

where \(HR\) is heart rate, \(SV\) is stroke volume, \(P_V\) is venous pressure, and \(p_i\)'s are parameters describing a phenomenological relationship between venous pressure and stroke volume, known as the Frank-Starling law. From Table 2.3 and units of \(P_V\) and \(CO\) one can find that \(p_1 = 0.5\) ml, \(p_2 = 0.8\) mmHg\(^{-1}\), and \(p_3 = 0.665\) mmHg. The parameters are also consistent with the normal steady-state values of the variables, that is

\[
CO_0 = HR \cdot (p_1 - \frac{p_1}{1 + e^{p_2(P_{V,0} - p_3)}})
\]

where \(HR = 400\) beats per minute (Table 2.4), \(CO_0 = 74\) ml/min, and \(P_{V,0} = 0\) mmHg (as listed in Table 2.5).

When it is necessary to distinguish among parameters of several functions which use the above notation, the expanded notation is used by appending the variable’s name (first column of Table 2.3) to subscript of that parameter, for example \(p_{CO,1}\).
\([X]_Y\)  Concentration of substance X in compartment Y
Ald  Aldosterone
AngII  Angiotensin II
ANP  Atrial natriuretic peptide
AVP  Vasopressin
BF  Blood flow
C  Vessel compliance
CO  Cardiac output
d  Arteriolar diameter
GFR  Glomerular filtration rate
h  Half-life constant
H  hematocrit
HR  Heart rate
\(J_{X,Y - Z}\)  Transmembrane flow of substance X from Y into Z
\(\dot{J}_{X,Y - Z}\)  Luminal flow of substance X from Y into Z
K  Permeability surface-area product coefficient
M  Rate of hormone secretion
\(N_n\)  Total number of nephrons
NaCl  Sodium chloride content
Osm  Total small ion content
P  Hydrostatic pressure
Q  Protein content
R  Vessel resistance
SNA  Sympathetic nervous activity
V  Volume
\(\alpha\)  Sensitivity of sympathetic nerve activity
\(\eta\)  Fraction of reabsorbed NaCl
\(\mu\)  Relative apparent blood viscosity
\(\nu\)  Fraction of reabsorbed water
\(\pi\)  Oncotic pressure
\(\sigma\)  Reflection coefficient
\(\tau\)  Time constant

Table 2.1: Variable and parameter names.
A  afferent, or arterial
AL  ascending limb
AngII  angiotensin II
Av  available
B  blood
b  basal
C  capillary (extra-renal)
d  delay
DL  descending limb
DN  distal nephron
E  efferent
exc  excitatory
G  glomerular
I  intake
IF  interstitial fluid space
inh  inhibitory
NaCl  sodium chloride
P  plasma
PT  proximal tubule
Q  protein
R  renal, or reabsorption (for $K_R$)
RBC  red blood cells
S  extra-renal
Str  stressed
T  total
TC  tissue cells
U  urine
Unstr  unstressed
V  fluid, or venous (depending on the context)

Table 2.2: Variable and parameter subscripts.
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<th>$p_3$</th>
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<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$M_{AVP}$</td>
<td>(2.78)</td>
<td>27.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{IF}$</td>
<td>(2.32)</td>
<td>6</td>
<td>12</td>
<td>4</td>
<td>66.48</td>
<td></td>
</tr>
<tr>
<td>$R_{VR}$</td>
<td>(2.70)</td>
<td>2.3456</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{IF,Av}$</td>
<td>(2.35)</td>
<td>47.9</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_{Unstr}$</td>
<td>(2.8)</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\eta_{AL}$</td>
<td>(2.63)</td>
<td>0.8</td>
<td>0.4</td>
<td>-0.5</td>
<td>21.87</td>
<td></td>
</tr>
<tr>
<td>$\eta_{DN}$</td>
<td>(2.64)</td>
<td>0.98</td>
<td>0.48</td>
<td>-3.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\nu_{DN}$</td>
<td>(2.62)</td>
<td>0.5</td>
<td>0.38</td>
<td>0.12</td>
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<td></td>
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Table 2.3: Generic parameters of the system’s phenomenological functions.
<table>
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<th>Parameter</th>
<th>Value</th>
<th>Units</th>
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<tr>
<td>$\nu_{DL}$</td>
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<tr>
<td>$\pi_{R,IF} - P_{R,IF}$</td>
<td>5.197</td>
<td>mmHg</td>
</tr>
<tr>
<td>$\sigma_Q$</td>
<td>0.988</td>
<td></td>
</tr>
<tr>
<td>$\text{Osm}_{TC}$</td>
<td>24.4886</td>
<td>mOsm</td>
</tr>
<tr>
<td>$\text{Osm}_{RBC}$</td>
<td>1.8737</td>
<td>mOsm</td>
</tr>
<tr>
<td>$C_A$</td>
<td>0.0092</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_R$</td>
<td>0.1473</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_S$</td>
<td>0.2062</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$C_V$</td>
<td>0.313</td>
<td>ml/mmHg</td>
</tr>
<tr>
<td>$HR$</td>
<td>400</td>
<td>beats/min</td>
</tr>
<tr>
<td>$h_{\text{AngII}}$</td>
<td>40</td>
<td>min</td>
</tr>
<tr>
<td>$h_{\text{ANP}}$</td>
<td>250</td>
<td>min</td>
</tr>
<tr>
<td>$h_{\text{Ald}}$</td>
<td>250</td>
<td>min</td>
</tr>
<tr>
<td>$h_{\text{AVP}}$</td>
<td>20</td>
<td>min</td>
</tr>
<tr>
<td>$K_C$</td>
<td>0.0083</td>
<td>ml/mmHg/min</td>
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<tr>
<td>$K_G$</td>
<td>$3.3 \cdot 10^{-6}$</td>
<td>ml/min/mmHg</td>
</tr>
<tr>
<td>$K_Q$</td>
<td>0.005</td>
<td>ml/min</td>
</tr>
<tr>
<td>$K_R$</td>
<td>$3.3 \cdot 10^{-6}$</td>
<td>ml/min/mmHg</td>
</tr>
<tr>
<td>$K_S$</td>
<td>25</td>
<td>ml/min</td>
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<td>$N_n$</td>
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<td>$P_{PT}$</td>
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</tr>
<tr>
<td>$Q_T$</td>
<td>2.3342</td>
<td>g</td>
</tr>
<tr>
<td>$R_{AS,b}$</td>
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<td>mmHg.min/ml</td>
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<td>$R_{CS}$</td>
<td>0.0206</td>
<td>mmHg.min/ml</td>
</tr>
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<td>$R_{VR}$</td>
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<td>mmHg.min/ml</td>
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<tr>
<td>$R_{VS}$</td>
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<td>mmHg.min/ml</td>
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<td>$R_{A,b}$</td>
<td>87849</td>
<td>mmHg.min/ml</td>
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<tr>
<td>$R_{E,b}$</td>
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<td>mmHg.min/ml</td>
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Table 2.4: Other parameters of the system equations.
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<tr>
<th>Variable</th>
<th>Value</th>
<th>Source</th>
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</thead>
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<tr>
<td>Ald, pg/ml</td>
<td>5</td>
<td>[70]</td>
</tr>
<tr>
<td>AngII, pg/ml</td>
<td>18</td>
<td>[14]</td>
</tr>
<tr>
<td>ANP, pg/ml</td>
<td>100</td>
<td>[54]</td>
</tr>
<tr>
<td>AVP, pg/ml</td>
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<td>[88]</td>
</tr>
<tr>
<td>$d_{AS}$, µm</td>
<td>40</td>
<td>[12]</td>
</tr>
<tr>
<td>CO, ml/min</td>
<td>74</td>
<td>[22]</td>
</tr>
<tr>
<td>$H_A$</td>
<td>0.45</td>
<td>[22]</td>
</tr>
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<td>$[\text{NaCl}_P]$, mOsm/ml</td>
<td>0.282</td>
<td>[22]</td>
</tr>
<tr>
<td>$\pi_F$, mmHg</td>
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<td>[37]</td>
</tr>
<tr>
<td>$[Q]_P$, g/ml</td>
<td>0.0693</td>
<td>[22]</td>
</tr>
<tr>
<td>$Q_F$, g</td>
<td>2.33</td>
<td>[22]</td>
</tr>
<tr>
<td>$J_{\text{NaCl}_I-P}$, mOsm/min</td>
<td>0.0011 (1.6 mOsm/day)</td>
<td>[78]</td>
</tr>
<tr>
<td>$J_{V,I-P}$, ml/min</td>
<td>0.0208 (30 ml/day)</td>
<td>[22]</td>
</tr>
<tr>
<td>SNA, n.u.</td>
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<td>Assumed</td>
</tr>
<tr>
<td>$P_A$, mmHg</td>
<td>100</td>
<td>[22]</td>
</tr>
<tr>
<td>$P_G$, mmHg</td>
<td>45</td>
<td>[73]</td>
</tr>
<tr>
<td>$P_V$, mmHg</td>
<td>0</td>
<td>[22]</td>
</tr>
<tr>
<td>$\text{NaCl}_{IF}$, mOsm</td>
<td>18.93</td>
<td>[22]</td>
</tr>
<tr>
<td>RBF, ml/min</td>
<td>9.2</td>
<td>[22]</td>
</tr>
<tr>
<td>$V_B$, ml</td>
<td>15</td>
<td>Equation (2.7)</td>
</tr>
<tr>
<td>$V_{IF}$, ml</td>
<td>66.4</td>
<td>[22]</td>
</tr>
<tr>
<td>$V_{TC}$, ml</td>
<td>85.2</td>
<td>[22]</td>
</tr>
<tr>
<td>$V_{RBC}$, ml</td>
<td>6.57</td>
<td>[22]</td>
</tr>
<tr>
<td>$V_{Unstr}$, ml</td>
<td>8</td>
<td>[80]</td>
</tr>
</tbody>
</table>

Table 2.5: Normal values; n.u., normalized units. See Tables 2.1, 2.2 and text for definition and explanation of terms.
2.2 The circulatory module

2.2.1 Modeling objectives

Understanding the long-term dynamics of arterial pressure requires a model of the controlled circulatory system. Thus, the mathematical model of circulatory system is required to meet at least the following conditions:

1. It represents sufficient detail of the controlled systemic circulation of a normal, resting, conscious, rat suitable for the study of long-term hemodynamics.

2. It reflects fluid volume exchange with external environments via filtration into interstitial space and lymphatic return, dietary fluid intake, and renal excretion.

3. It allows study of the overall effects of AngII and sympathetic nervous system on arterial pressure.

2.2.2 Model formulation

The model of circulatory system which fits the modeling objectives is based on the lumped-parameter windkessel approach widely used in cardiovascular modeling. This approach is especially useful for designing a model of the entire circulation as it combines moderate accuracy of system representation with the relatively small set of parameters that can be identified from experimental data. The lumped-parameter models are used on both short-time scales, such as the response to hemorrhage, baroreceptor stimulation, and postural change [74, 106, 105], and long-term scales such as the Guyton-Coleman model [40].

Our previously published circulatory model [6] is adapted to represent the interactions of the Circulatory Module with other modules and ensure the correct mass balance for the entire system (Figure 2.1). The total blood volume is distributed among four capacitive vascular compartments: the arteries, the renal vascular bed, the extra-renal vascular beds, and the large veins such as inferior and superior vena cava (Figure 2.2).

1 The lymphatic system is a network of vessels that carry a clear fluid called lymph extracted from the interstitial spaces back into great veins of the circulatory system.
Each of the two vascular beds is preceded by a capillary bed where fluid filtration into the interstitial space (extra-renal bed) or the bladder (renal bed) occurs. The pulmonary circulation is omitted and the heart is represented by a continuous non-pulsatile pump which moves blood from the venous to the arterial side of systemic circulation.

The chosen compartment partition allows for the simplest representation of the circulatory dynamics of the vascular space and fluid volume exchange with the extra-vascular spaces. The renal vascular bed represents the vasculature structure of the Renal Module and accounts for the loss of water from the system by modeling glomerular filtration and tubular reabsorption (see Section 2.5). The extra-renal compartment represents all other vascular beds of the circulation lumped into one. It is much larger than the renal compartment in its contribution to total compliance, resistance, and volume, and all of the water intake and exchange with interstitial space is assumed to occur in the extra-renal compartment only. The major veins receive the lymphatic return from the Whole-Body Exchange Module as well as the ingested water intake. Thus, the extra-renal and venous compartments interface with the Whole-Body Exchange Module (see Section 2.4) to account for the remaining fluid shifts to and from vascular space.

We arrive at the model by requiring that the change of volume in each compartment is equal to the difference of its total inflow and outflow. Volume of each compartment ($V$) is assumed to be linearly dependent on its pressure ($P$): $V = V_U + C \cdot P$ where $V_U$ is the unstressed volume of the compartment and $C$ is its compliance. The flow ($F$) between vascular compartments is driven by the pressure gradient and impeded by the resistance ($R$) between the compartments: $F = \frac{\Delta P}{R}$. The only exception to the above is cardiac output, the flow from the venous to the arterial compartment generated by the heart. Thus, the following equations represent the circulatory module dynamics:

\[
\begin{align*}
C_A \cdot \frac{dP_A}{dt} &= CO - \frac{P_A - P_C}{R_{AS}} - RBF \\
C_S \cdot \frac{dP_S}{dt} &= \frac{P_C - P_S}{R_{CS}} - \frac{P_S - P_V}{R_{VS}} \\
C_V \cdot \frac{dP_V}{dt} &= \frac{P_S - P_V}{R_{VS}} + \tilde{J}_{V,IF-P} + J_{V,I-P} + RBF - J_{V,P-U} - CO \\
V_{Str} &= C_A \cdot P_A + C_S \cdot P_S + C_R \cdot P_R + C_V \cdot P_V
\end{align*}
\]
Figure 2.2: Fluid flow (arrows) in the Circulatory Module and the interactions with the other modules of the system. Total blood volume is distributed among four systemic vascular reservoirs. Blood is circulated via a cardiac pump modeled as a nonlinear Frank-Starling relationship between venous pressure and cardiac output. $P$, pressures; $R$, hydraulic resistances; $C$, compliances; $CO$, cardiac output; $A$, arteries; $V$, veins; $C$, capillaries; $G$, glomerulus; AS, extra-renal arteries; CS, extra-renal capillaries; VS, extra-renal veins; AR, renal afferent arterioles; ER, renal efferent arterioles; VR, renal veins. The pulmonary circulation is omitted. The Circulatory Module exchanges fluid flow with the Renal Module via glomerular filtration and tubular reabsorption and with the Whole-Body Exchange Module via capillary filtration rate, water intake, and lymphatic return.

where $C_A$, $C_R$, $C_S$, and $C_V$ are the compliances of arterial, renal, extra-renal, and venous compartments, respectively; $P_A$, $P_S$, $P_R$, and $P_V$ are the hydrostatic pressures in the above compartments; $P_C$ is the extra-renal capillary pressure; $R_{AS}$, $R_{CS}$, and $R_{VS}$ are the extra-renal arterial, capillary, and venous resistances; $R_{VR}$ is the renal venous
resistance; \( V_{\text{Str}} \) is the total stressed blood volume; and \( J_{V,I-P} \), \( J_{V,P-U} \), and \( \tilde{J}_{V,IF-P} \) are the water intake, urinary water excretion, and lymphatic return, respectively (see Section 2.4 for details).

The cardiac output (CO) is a product of heart rate (HR) and stroke volume where stroke volume is expressed as a logistic function of venous pressure, according to the Frank-Starling law ([36, 91]):

\[
CO = HR \cdot (p_1 - \frac{p_1}{1 + e^{p_2 \cdot (P_V - p_3)}})
\]  

(2.5)

where \( p_1 \) is the maximal stroke volume, \( p_2 \) and \( p_3 \) describe cardiac contractility.

A portion of the total blood volume (\( V_B \)) which fills the circulatory system to maximum capacity without increasing transmural pressure is called the total unstressed blood volume (\( V_{\text{Unstr}} \)). The remaining portion is called the total stressed blood volume:

\[
V_{\text{Str}} = V_B - V_{\text{Unstr}}
\]  

(2.6)

where the total blood volume \( V_B \) is the sum of plasma volume \( V_P \) and red blood cell volume \( V_{\text{RBC}} \) (see Section 2.4):

\[
V_B = V_P + V_{\text{RBC}}
\]  

(2.7)

The total unstressed blood volume, or venous capacitance, of the system is modulated by the sympathetic nerve activity via change in venous tone:

\[
V_{\text{Unstr}} = V_{\text{Unstr},0} - p_1 \cdot \text{SNA}
\]  

(2.8)

where \( p_1 \) is the sensitivity of venous smooth muscle to sympathetic stimulation and its value chosen based on data from [99].

Note that the difference between inflow and outflow from the extra-renal capillary bed \( \frac{P_A - P_C}{R_{AS}} - \frac{P_C - P_V}{R_{GS}} \) is the capillary filtration rate \( J_{V,P,IF} \) driven by capillary perfusion pressure \( P_C \) as well as other forces described in detail in Section 2.4.
The renal blood flow (RBF) is the net sum of all individual nephron blood flows:

\[ \text{RBF} = \text{BF}_A \cdot N_n \]  \hspace{1cm} (2.9)

and the urinary water excretion \( (J_{V,P-U}) \) is the net outflow from all renal distal tubules:

\[ J_{V,P-U} = J_{V,DN} \cdot N_n \]  \hspace{1cm} (2.10)

(see Section 2.5 for details).

Note, that we avoid expressing renal blood flow as \( \frac{P_A - P_R}{R_{AR}} \) where \( R_{AR} \) is an arterial renal resistance. In the renal bed, the resistance to flow is the result of glomerular filtration out of the circulation followed by tubular reabsorption back into the circulation, thus combining vascular and membrane transports (Figure 2.2). See Section 2.5 for details on the modeling of fluid transport through the kidneys.

Arteriolar resistances in the model are modeled via Hagen-Poiseuille’s law:

\[ R = \frac{8\mu l}{\pi r^4} \]

where \( l \) is the length of the arteriole, \( r \) is its radius, and \( \mu \) is blood viscosity which is hematocrit\(^2\) dependent. At low-vessel diameter, blood viscosity becomes strongly dependent on the hematocrit of the local blood flow, known as a Fahraeus-Lindqvist effect [83]. The phenomenon is called relative apparent blood viscosity. Thus, the extra-renal arteriolar resistance is modeled as

\[ R_{AS} = R_{AS,b} \cdot \frac{\mu(H_A, d_{AS})}{\mu(0, d_{AS,0})} \cdot \frac{d_{AS,0}^4}{d_{AS}^4} \]  \hspace{1cm} (2.11)

where \( d_S \) is the average arteriolar diameter, \( H_A \) is the arterial hematocrit, and \( R_{AS,b} \) is the total resistance at basal arteriolar diameter \( d_{AS,0} = 40\mu m \) and zero hematocrit. The details on the modeling of the relative apparent blood viscosity \( \mu \) as well as renal afferent and efferent arteriolar resistances can be found in Section 2.5.3.

\(^2\) Hematocrit is the ratio of the volume of red blood cells to the total volume of blood.
The extra-renal arteriolar diameter ($d_{AS}$, in microns) is assumed to be controlled by the plasma angiotensin II concentration (AngII) and sympathetic nerve activity (SNA). Sympathetic nerves in a normal state exert certain tonic vasoconstriction which can be withdrawn or further activated by lessening or increasing SNA, thus we assume a linear dependence of the diameter on SNA. Normal levels of AngII exert almost no vasoconstrictive effect on the vessels, so that further decrease of AngII has little to no effect on arteriolar diameter. Doubling of AngII plasma concentration exerts maximal vasoconstrictive effect. Thus we assume a logistic function form of arteriolar diameter dependence on AngII:

$$d_{AS} = p_1 - \frac{p_2}{1 + e^{p_3(AngII - p_4)}} - p_5 \cdot SNA \tag{2.12}$$

where the coefficients are derived from the overall qualitative behavior described above and assuming that the effect on resistance $R_{AS}$ is limited by about 50-200% of its normal value, given general experimental observations of hemodynamic behaviors.
2.3 The neural module

2.3.1 Modeling objectives

The neurocentric theory assumes that the sympathetic nerve activity is comprised of a long-term slow time scale component and a transient fast scale component. The sympathetic nerve activity (SNA) affects parameters of the circulatory system and therefore modifies arterial blood pressure. While SNA is capable of modifying renal excretion as well, its role in the development of AngII-salt hypertension has been refuted by the experimental evidence (see Chapter 1). Thus, the mathematical model of SNA is required to meet at least the following conditions:

1. Activation of the sympathetic nerve activity is triggered by long-term (several days) elevation of plasma sodium and AngII.

2. The well-known short-term (minutes) neural control of circulation via baroreflex is represented.

3. Long-term and short-term sympathetic nerve activity modifies the parameters of the circulatory system only.

2.3.2 Model formulation

According to the neurogenic theory, the control of the sympathetic nerve activity is comprised of two major mechanisms acting on different time scales: baroreflex mechanism and long-term activation mechanism. Baroreflex is a well-known sympathetic response to arterial pressure elevation and is a mechanism that acts on the time scale of minutes to hours. The other mechanism is a proposed hypothetical mechanism based on the indirect evidence suggesting activation of sympathetic response after days of elevated plasma sodium and AngII (see Chapter 1). Both responses are merged by a group of neurons in the brain into a set of neural responses sent to the body organs via different neural projections in the spinal cord.

A simplified depiction of the neural pathways thought to be involved in the generation of the sympathetic nerve outflow of AngII-salt hypertension is shown in Figure 2.3.
Clusters of nerve cell bodies within the brain form specialized centers for processing inputs from external sources or other clusters. Mapping all neuronal interactions between all known central cardiovascular brain centers is an area of on-going investigation.

Figure 2.3: Hypothetical neural pathways involved in the generation of sympathetic nerve control of three circulatory parameters via four major brain cardiovascular centers: NTS - nucleus tractus solitarius; PVN - paraventricular nucleus; RVLM - rostral ventrolateral medulla; and SFO - subfornical organ. Excitatory signals are shown as solid lines, inhibitory signals are shown as dashed lines. See text for details.

The generation of both fast and slow sympathetic responses occurs via at least four cardiovascular brain centers: NTS - nucleus tractus solitarius; PVN - paraventricular nucleus; RVLM - rostral ventrolateral medulla; and SFO - subfornical organ. Changes in mean arterial pressure are continuously monitored by various sensors in the body, primarily by mechanical stretch receptors in the carotid arteries and aorta, termed baroreceptors. The sensory information from the baroreceptors enters NTS, which converts an excitatory input into an inhibitory signal to RVLM. RVLM generates a sympathetic outflow via several parallel neuronal projections into the spinal cord and then body organs. Inhibitory pattern of RVLM response includes a decreased arteriolar resistance, venous tone, and heart rate. The excitatory pattern of RVLM response yields changes in the opposite direction. Long-term exposure to elevated pressure leads to reduced
sensitivity of baroreceptors, such that the excitatory signal to the NTS disappears after 1-2 days of elevated blood pressure. This phenomenon is known as the baroreceptor resetting.

Circulating AngII and sodium are sensed by several cardiovascular brain centers, which have a weak blood-brain barrier. One of them is the subfornical organ (SFO). It is believed that a combination of both elevated AngII and plasma sodium are needed in order to trigger a response of SFO [77]. The neurons from SFO relate the signal to PVN and then RVLM. Activation of RVLM neurons is delayed and need a sustained elevation of the excitatory inputs from PVN. When all three inputs to the brain (plasma sodium, AngII and mean arterial pressure) are elevated during AngII-salt protocol, the inhibitory pattern of RVLM response is initially dominated by the baroreflex pathway. After the baroreflex mechanism resets the excitatory pattern of RVLM response emerges.

In the Neural Module the sympathetic nerve activity is modeled as the net sum of the two responses:

\[ SNA = SNA_{\text{exc}} + SNA_{\text{inh}} \]

where \( SNA_{\text{exc}} \) is the slow excitatory response and \( SNA_{\text{inh}} \) is the fast inhibitory response, with both responses expressed in dimensionless units.

The sympathetic nerve activity modifies two parameters of the Circulatory Module: venous capacitance (\( V_{\text{INSTR}} \)) and the arteriolar diameter of the extra-renal bed (\( d_{\text{AS}} \)), shown in equations (2.8) and (2.12), respectively. We assume that each of the two parameters responds instantaneously and linearly to the sympathetic input.

Baroreceptor reflex is a mechanism that provides short-term regulation of blood pressure via sensing arterial pressure by sensory receptors, translating it to the NTS center of the brain, where it is then formed into the efferent sympathetic nerve activity (\( SNA_{\text{inh}} \)). According to the experimental evidence [61], the baroreflex response is activated within a few minutes of elevation of the mean arterial pressure (\( P_A \)) and then resets within 48 hours if the elevation is sustained. The relationship between the sympathetic nerve activity and arterial pressure is well approximated by a sigmoid curve. During resetting, the center of this curve shifts toward new level of sustained arterial
pressure (Figure 2.4). This dynamics can be modeled as:

$$SNA_{inh} = 1 - \frac{2}{1 + e^{-0.5(P_A - x)}}$$  \hspace{1cm} (2.13)$$

with

$$\frac{dx}{dt} = \frac{P_A - x}{240}$$

Here, SNA is expressed in dimensionless units, ranging between -1 and 1, with $SNA_{inh} = 0$ at the steady state arterial pressure.

![Figure 2.4: An illustration of baroreceptor reflex resetting. Originally the baroreceptor reflex leads to sympathetic nerve activity according to the sigmoid relationship centered at $P_A = 100$ (solid line). After arterial pressure has been elevated to 130 mmHg and sustained at that level, the curve shifts to the right (dashed line).](image)

Chronic activation of the slow excitatory response can be modeled as a first-order delayed response to a simultaneous elevation of circulating plasma angiotensin II and sodium:

$$\tau_{exc} \frac{dSNA_{exc}}{dt} = \alpha \cdot \left(1 - \frac{1}{1 + e^{5 \cdot (x(t-\tau_d) - 3)}}\right) - SNA_{exc}$$  \hspace{1cm} (2.14)$$

with $x(t-\tau_d) = \frac{[NaCl]_P(t-\tau_d) - [NaCl]_P0}{0.001 \cdot \frac{AngII(t-\tau_d) - AngII0}{AngII0}}$ is a dimensionless quantity, where $\tau_{exc}$ is the time constant of the response, $\tau_d = 5 \cdot 24 \cdot 60$ minutes is the time delay of the response [78], $\alpha$ is the sympathetic sensitivity to the stimulus; $[NaCl]_P$ is
plasma osmolarity (see Section 2.4), and AngII is plasma angiotensin II (see Section 2.5). Figure 2.5 shows an example of the chronic SNA response.

Figure 2.5: Solution (slow activation of the sympathetic nerve activity, SNA_{exc}) of (2.14) in response to a sustained elevation of plasma osmolarity and AngII.
2.4 The whole-body exchange module

2.4.1 Modeling objectives

The understanding of volume dynamics within the vascular space is incomplete without a model of the whole-body transport of fluid and solutes. Ingestion of extra water and sodium upsets osmotic and hydrostatic balances with the interstitial fluid and cells, causing fluid, solutes, and protein shifts in and out of the vascular space. Thus, a mathematical model of whole-body fluid, protein, and sodium chloride distribution is needed. The following model is based on the published model of acute fluid-solute transport in the human body [43] with the following modifications: solute exchange with cellular compartments, the Donnan effect and and small ion osmotic pressures are assumed to be insignificant; of all small ion solutes only sodium chloride dynamics is represented; descriptions of lymphatic flow, interstitial pressure, protein transport rate, and oncotic pressure are corrected; the parameters were fitted or scaled to represent the fluid-solute dynamics in a rat.

2.4.2 Model formulation

Figure 2.6 shows the division of the body water, proteins, and sodium chloride content across four major compartments connected either by a membrane or a lumen. The four compartments are tissue cells (TC), interstitial fluid (IF), plasma (P), and red blood cells (RBC). The plasma compartment also exchanges the water and sodium chloride with external compartments. Intake of water and sodium chloride is considered to be through ingestion or infusion (I). Loss of water and sodium chloride is considered to be through urinary excretion into the bladder (B) only and other losses such as through perspiration are not considered. Each compartment is considered to be well mixed with spatially constant descriptive parameters. Total protein content is assumed to be constant at all times.

The transcapillary transport of fluid from the plasma into the interstitium is driven by the Starling law, which states that the bulk movement of fluid across the capillary
Figure 2.6: Schematic of exchange of three substances (V, water; Q, protein, and NaCl, sodium chloride) between four body compartments: tissue cells (TC), interstitial fluid (IF), plasma (P), and red blood cells (RBC). Transport rate of a substance X from compartment A to compartment B across a membrane is denoted as $J_{X,A\rightarrow B}$ (shown as a black arrow) and via lymphatic vessels is denoted as $\hat{J}_{X,A\rightarrow B}$ (shown as a shaded wide arrow). The only intake (I) of water and sodium chloride from an external source is considered to be through the plasma compartment, as well as the only loss into the bladder (B) via urinary excretion. Compartments are drawn to scale, with area roughly proportional to volume. The process of urinary excretion (star) is discussed in detail in Section 2.5.

membrane is proportional to the net sum of filtration driven by the transmembrane hydrostatic pressure gradient and reabsorption is driven by transmembrane oncotic pressure gradient. The transport of proteins and sodium chloride is governed by diffusive-convective mechanisms. The substances are returned back into the circulation via the lymphatics by convective mechanisms. It is assumed that only fluid (no solute or protein) exchange happens across the cellular membranes, which are governed by osmotic gradient.

Nearly 80% of total osmolarity of the interstitial fluid and plasma and 10% of intracellular space is produced by sodium and chloride ions. Transport of small ions other than sodium and chloride is not of major significance for the study of long-term blood
pressure control. Thus the following assumptions are made to simplify the model: small ion content of cells remains constant at all times and small ion content of interstitium and plasma as well as its transport is proportional to that of the sodium chloride content.

**Sodium chloride content balance equations**

The sodium chloride content (NaCl) balances are:

\[
\frac{d\text{NaCl}_{IF}}{dt} = J_{\text{NaCl,IF-P}} - \hat{J}_{\text{NaCl,IF-P}} \tag{2.15}
\]

\[
\frac{d\text{NaCl}_P}{dt} = J_{\text{NaCl,P-U}} - J_{\text{NaCl,P-IF}} + \hat{J}_{\text{NaCl,IF-P}} \tag{2.16}
\]

where the sodium chloride intake flow \(J_{\text{NaCl,P}}\) is given and urinary excretion flow \(J_{\text{NaCl,P-U}}\) is the net sum of all distal nephron sodium chloride outflows (see Section 2.5 for details):

\[
J_{\text{NaCl,P-U}} = N_n \cdot J_{\text{NaCl,DN}} \tag{2.17}
\]

The total small ion content (Osm) of extracellular compartments (plasma and interstitium) is assumed to be proportional to their respective sodium chloride contents:

\[
\text{Osm}_P = 1.14 \cdot \text{NaCl}_P \tag{2.18}
\]

\[
\text{Osm}_{IF} = 1.14 \cdot \text{NaCl}_{IF} \tag{2.19}
\]

while the total small ion content of intracellular compartments (tissue cells and red blood cells) has a different proportionality coefficient and is constant at all times:

\[
\text{Osm}_{\text{TC}} = 24.17 \cdot \text{NaCl}_{\text{TC}} = \text{Constant} \tag{2.20}
\]

\[
\text{Osm}_{\text{RBC}} = 24.17 \cdot \text{NaCl}_{\text{RBC}} = \text{Constant} \tag{2.21}
\]
Fluid mass balance equations

The fluid mass balances are:

\[
\frac{dV_P}{dt} = J_{V,I-P} - J_{V,P,U} + J_{V,RBC-P} - J_{V,P-IF} + \tilde{J}_{V,IF-P} \tag{2.22}
\]

\[
\frac{dV_{IF}}{dt} = J_{V,P-IF} + J_{V,TC-IF} - \tilde{J}_{V,IF-P} \tag{2.23}
\]

\[
\frac{dV_{TC}}{dt} = -J_{V,TC-IF} \tag{2.24}
\]

\[
\frac{dV_{RBC}}{dt} = -J_{V,RBC-P} \tag{2.25}
\]

where the intake flow \( J_{V,I-P} \) is given and urinary excretion flow \( J_{V,P,U} \) is the net sum of all distal nephron fluid outflows (see Section 2.5 for details):

\[
J_{V,P,U} = N_n \cdot J_{V,DN} \tag{2.26}
\]

The fluid shift across the cellular membrane is driven by the osmotic gradient, and the cellular water permeability is very high compared to other transport coefficients. Thus, the above system can be simplified by assuming that the water shift in and out of cells is instantaneous, dropping differential equations for \( V_{TC} \) and \( V_{RBC} \), and adjusting all volumes by the shift instantly, independent of the terms on the right hand side of the above equations:

\[
\Delta V_{RBC-P} = \frac{Osm_P \cdot V_{RBC} - Osm_{RBC} \cdot V_P}{Osm_{RBC} + Osm_P} \tag{2.27}
\]

\[
\Delta V_{TC-IF} = \frac{Osm_{IF} \cdot V_{TC} - Osm_{TC} \cdot V_{IF}}{Osm_{TC} + Osm_{IF}} \tag{2.28}
\]

Protein content balance equations

A small portion of plasma proteins leaks across capillary membrane into the interstitial space where it is collected by the lymphatic vessels and returned into the blood pool via emptying into a large vein near the heart. Protein transport is an important contributor to the model of fluid transport as it creates oncotic gradient across the capillary membrane. The dynamics of protein synthesis has not been fully characterized [8]. However,
it has been observed that plasma protein remains constant despite various disturbances due to water, solute or protein infusion.

The protein content \((Q)\) balances are:

\[
\frac{dQ_{IF}}{dt} = J_{Q,P,IF} - \tilde{J}_{Q,IF,P} \tag{2.29}
\]

\[
Q_P + Q_{IF} = Q_T = \text{Constant} \tag{2.30}
\]

**Transcapillary transport equations**

Transcapillary fluid filtration is driven by Starling forces due to hydrostatic and oncotic gradient across the capillary membrane:

\[
J_{V,P,IF} = K_C \cdot (P_C - P_{IF} - \sigma_Q \cdot (\pi_C - \pi_{IF})) \tag{2.31}
\]

where \(K_C\) is the hydraulic permeability coefficient; \(\sigma_Q\) is the reflection coefficient for proteins; \(P_C\) and \(P_{IF}\) are the hydrostatic pressures in the capillary and interstitium, respectively; \(\pi_C\) and \(\pi_{IF}\) are the oncotic pressures in the capillary and interstitium, respectively. Note, that the contribution of sodium chloride to the osmotic pressures is omitted since the diffusion happens quickly and does not affect capillary filtration in an appreciable way. Capillary hydrostatic pressure is determined by the arterial perfusion pressure and myogenic response of the arterioles to buffer the pressure and calculated via Circulatory Module (see Section 2.2).

Interstitial hydrostatic pressure \(P_{IF}\) is a highly nonlinear function of the interstitial volume \(V_{IF}\) since the compliance of the interstitium varies significantly with hydration state. Interstitial pressure also varies from tissue to tissue, ranging from -5 mmHg in subcutis to +6 mmHg in kidneys [1, 37]. No distinction among tissues is made in the model, thus the interstitial pressure is presented phenomenologically, as an average value across all major tissues, using experimental curves to derive the rate of change around its normal value:

\[
P_{IF} = p_1 - \frac{p_2}{1 + e^{p_3(V_{IF} - p_4)}} \tag{2.32}
\]
The oncotic pressure $\pi(c)$, also referred to as colloid osmotic pressure, is expressed as a second order polynomial of protein concentration $c_A$ ([24], expressed in grams per liter):

$$\pi_C = \frac{Q_P}{V_P} \cdot (0.0029 \cdot \frac{Q_P}{V_P} + 0.1631) \quad (2.33)$$

$$\pi_{IF} = \frac{Q_{IF}}{V_{IF,Av}} \cdot (0.0029 \cdot \frac{Q_{IF}}{V_{IF,Av}} + 0.1631) \quad (2.34)$$

Note, that the protein concentration in the interstitial space is based on the available interstitial volume $V_{IF,Av}$. The extracellular matrix behaves as a porous structure with pores of about 20-25nm in diameter, due to the presence of a collagen structure and negatively-charged hyaluronan and proteoglycans. This results in macromolecular crowding of the interstitial space, excluding a portion of the total interstitial volume for the protein diffusion. The exclusion properties depend on the hydration state of the interstitium. Based on data presented in [111], [43], and [5] we assume linear dependence of the available interstitial volume on the total interstitial volume ($V_{IF}$):

$$V_{IF,Av} = p_1 + p_2 \cdot (V_{IF} - V_{IF,0}) \quad (2.35)$$

Transcapillary solute filtration is dominated by diffusive mechanism with the rate of diffusion is about 1000 times faster than that of convection:

$$J_{NaCl,P-IF} = K_{NaCl} \cdot ([NaCl]_P - [NaCl]_{IF}) \quad (2.36)$$

where $K_{NaCl}$ is the capillary permeability-surface area product for sodium chloride and $[NaCl]_P$ and $[NaCl]_{IF}$ are the concentrations of sodium chloride in plasma and interstitial fluid, respectively:

$$[NaCl]_P = \frac{NaCl_P}{V_P}, \quad [NaCl]_{IF} = \frac{NaCl_{IF}}{V_{IF}}$$
Transcapillary protein filtration has to take both diffusion and convection mechanisms into account as they are of relatively similar magnitude:

\[ J_{Q,P,IF} = (1 - \sigma_Q) \cdot J_{V,P,IF} \cdot [Q]_P + K_Q \cdot ([Q]_P - [Q]_{IF}) \]  (2.37)

where \( K_Q \) is the capillary permeability-surface area produce for protein and \([Q]_P\) and \([Q]_{IF}\) are the concentrations of protein in plasma and interstitial fluid, respectively:

\[ [Q]_P = \frac{Q_P}{V_P}, \quad [Q]_{IF} = \frac{Q_{IF}}{V_{IF}} \]

**Lymphatic transport equations**

The lymphatic return of water is often described phenomenologically as a piecewise-linear function of interstitial pressure ([15, 26, 43]), since the mechanisms by which lymph vessels collect and propel fluid have not been studied extensively. We model lymphatic flow as a logistic function, using the experimental data reported in [87] and [9]:

\[ \tilde{J}_{V,IF-P} = p_1 - \frac{p_1}{1 + e^{p_2(P_{IF} - p_3)}} \]  (2.38)

The lymphatic return of protein and sodium chloride is dominated by convection:

\[ \tilde{J}_{Q,IF-P} = \tilde{J}_{V,IF-P} \cdot [Q]_{IF} \]  (2.39)

\[ \tilde{J}_{NaCl,IF-P} = \tilde{J}_{V,IF-P} \cdot [NaCl]_{IF} \]  (2.40)
2.5 The renal and hormonal module

2.5.1 Modeling objectives

The whole-body model of pressure and volume control requires that a dietary change of water or sodium intakes lead to matching renal excretion of water and sodium. According to AngII-salt experimental data, such renal response occurs under various conditions of renal perfusion pressure and circulating angiotensin II. Thus, the mathematical model of renal function is required to meet at least the following conditions:

1. It represents major renal anatomical features and physiological phenomena of filtration, reabsorption, and hormonal response in a normal, resting, conscious rat.

2. Renal excretion of water and sodium matches dietary intake (normal physiological range) within several days.

3. Accumulated or lost water and sodium are in agreement with experimentally observed values.

4. Renal perfusion pressure and renal venous pressure have little to no effect on renal excretion.

5. Externally fixed level of circulating angiotensin II does not prevent proper renal response to dietary changes.

2.5.2 Literature review

Mathematical models of renal function can be classified into three categories by the level of detail in representation of renal physiology. Models with a high level of detail represent specific vascular and tubular structure and function in vast detail but focus on a specific aspect of renal physiology rather than the entire phenomenon of sodium and water excretion. There are models for studying renal autoregulation response [4, 66], glomerular filtration [50], nephron interaction [65], transport properties of a portion of
a tubule [109], medullary concentration [64], and so on. The effort of combining results of these models into one is still ongoing [102].

Low-level-of-detail models ignore most of the structural and functional properties and represent excretion phenomenologically [41, 51, 101]. The limitation of these models lies with oversimplifying controlling factors which are either too limiting (e.g. renal excretion is driven by arterial pressure [39]) or not detailed enough (e.g. renal excretion is assumed to be driven by sodium intake directly [6]).

The third category is comprised of models which represent some physiological and structural detail but with significant simplification of both renal anatomy and regulatory mechanisms, in order to maintain the ability to simulate overall regulation of water and sodium excretion. These models are usually built on a lumped-nephron representation of tubular anatomy but vary greatly in the amount of attention paid to glomerular filtration control, number of representative nephrons, medullary interstitium, reabsorption control, hormonal regulatory effects, etc. For the purposes of the modeling objectives presented here, a mid-level-of-detail model is deemed appropriate. There are several published models of renal function of mid-level detail [47, 56, 55, 72]. However, all three models are based on the assumption that arterial pressure strongly influences glomerular filtration and/or tubular reabsorption which directly contradicts the modeling objective #4.

A significant modeling challenge is determining how to interface the renal model with the extra-renal ones, especially the circulatory and fluid-solute shift models. Kidneys sense sodium and water intake indirectly, via changes in the extra-renal responses to dietary inputs (e.g. hydrostatic and osmotic pressures, plasma composition, and hormonal input) and at the same time kidneys modify those responses by varying total body sodium and water. This complex interaction seems to be the main reason why many renal models are standalone [72, 102]. For all other models, without exception, the problem has been addressed by assuming that the arterial pressure is the sole controller of glomerular filtration and/or tubular reabsorption [40, 47, 51, 55]. This assumption, however, limits the utility of the model for two reasons, 1) because it contradicts experimental studies which show that renal excretion can be varied without changes in
arterial pressure ([10, 86]) and 2) because it asserts an exclusive mechanistic link between sodium intake and arterial pressure. Mathematical models relying on such a link are not suitable for the investigation of non-renal causes of hypertension.

A novel model of renal excretion is presented in the following sections. When combined with the circulatory and fluid-solute shift models, it produces a correct response to various dietary change in sodium and water intakes under both naturally varying and clamped angiotensin II. The model does not rely on perfusion pressure for modulation of sodium excretion. Two features of the model, the ability to match excretion despite changes in arterial pressure or angiotensin II, make it a novel contribution to the field.

2.5.3 Model formulation

Figure 2.7 shows the division of the renal excretory function into three subsystems: the vascular, tubular, and hormonal subsystems. It also shows the main internal subsystem variables and external control variables: renal arterial and venous pressures, hematocrit, plasma osmolarity, and plasma protein concentration. The kidneys are modeled as a set of 60,000 identical filtering units, each one is represented by a nephro-vascular module composed of a glomerulus with afferent and efferent arterioles and a renal tubule.

Afferent and efferent arterioles are modeled as cylindrical tubes. Both arteriolar resistances are functions of local hematocrit and vessel diameter (Figure 2.8). The size of the afferent arteriole is driven by the myogenic response to perfusion pressure and angiotensin II. The size of the efferent arteriole is under control of angiotensin II. The glomerular filtration rate is determined by the gradient of hydrostatic and oncotic pressures across glomerular capillary membrane and a filtration coefficient (Figure 2.9). The tubular system consists of four segments representing proximal tubule, descending limb of Henle, ascending limb of Henle, and distal nephron which combines distal tubule and collecting duct combined (Figure 2.10). Fluid and sodium reabsorption in

---

3 Hematocrit is the ratio of the volume of red blood cells to the total volume of blood.
4 Plasma osmolarity is a measure of the body’s electrolyte-water balance, expressed in number of osmoles of solute per liter of solution (Osm/L).
5 Plasma protein concentration, measured in grams per liter, is the major determinant of the osmotic pressure.
6 Oncotic pressure is the osmotic pressure exerted by blood proteins.
each segment is governed by various physical and hormonal controls. In particular, the proximal tubule isotonic reabsorption is determined by the gradient of hydrostatic and oncotic pressures across the peritubular capillary membrane, rather than specific transport across the tubular wall. The reabsorption of water is varied by vasopressin effects on the distal nephron. The reabsorption of sodium is modulated by angiotensin II effect on the ascending limb of Henle and effects of aldosterone and atrial natriuretic peptide on the distal tubule. Tubuloglomerular feedback and the effect of renal sympathetic activity are not included in the model since neither is critical to sodium excretion control. Other substances such as potassium, glucose, urea, etc are assumed to be in constant balance.

The hormonal response of the system consists of vasopressin, angiotensin II, aldosterone, and atrial natriuretic peptide (ANP). Vasopressin is assumed to be controlled by plasma osmolality, ANP release is stimulated by angiotensin II and venous pressure, angiotensin II concentration varies in response to sodium flow senses by the macula densa, and aldosterone response is driven by angiotensin II for low to moderate levels of angiotensin II and by ANP for high values of angiotensin II. Medullary interstitium is not explicitly represented but reabsorption due to changes in medullary osmolality gradient is incorporated via overall vasopressin’s effects on the distal nephron.

Time-dependent processes in the glomerular capillaries and nephron tubules are very rapid (several seconds) compared to hormonal regulation and dynamics of other modules. Thus, the glomerular and tubular subsystems are assumed to be in a quasi steady-state with respect to the rest of the system. Hormonal dynamics is described via ordinary differential equations. Each subsystem is modeled in the simplest manner possible while reflecting the most important characteristics of fluid and sodium transport in the kidney. For a detailed description of renal physiology refer to Appendix A.
Figure 2.7: Structure of the renal module. The module is comprised of three subsystems: vascular, tubular, and hormonal subsystems. In each subsystem internal variables are highlighted in white and outputs are highlighted in grey. Inputs from other modules are highlighted by thick outlines. Renal module outputs that influence other modules are highlighted in grey with thick outlines. Some of the complex internal dependencies (e.g. those for the glomerular pressure) are omitted and their outputs are shown in hexagon shapes. Excitatory connections are shown by solid-ended arrows and inhibitory connections are shown by flat-ended arrows.
Glomerular filtration

Blood, composed of plasma, proteins and red blood cells, is delivered via an afferent arteriole to a glomerulus. A portion of the protein-free fluid is filtered into the Bowman’s capsule of the nephron and the rest of the blood flows through the efferent arteriole to the peritubular capillaries where it merges with the fluid and solutes reabsorbed from the nephron and then flows into systemic veins.

The model structure of glomerulus is shown in Figure 2.8.

In this section the following inputs are assumed to be known: arterial pressure ($P_A$), venous pressure ($P_V$), proximal tubule pressure ($P_{PT}$), peritubular capillary pressure ($P_R$), afferent hematocrit ($H_A$), afferent plasma protein concentration ($[Q]_A$), afferent arteriolar resistance ($R_A$), efferent arteriolar resistance ($R_E$), and glomerular filtration coefficient ($K_G$). Using these inputs the following expressions are derived: afferent arteriolar blood flow ($BF_A$), efferent arteriolar blood flow ($BF_E$), efferent plasma protein concentration ($[Q]_E$), efferent hematocrit ($H_E$), glomerular pressure ($P_G$), and glomerular filtration rate (GFR).

Blood flow across the afferent arteriole, $BF_A$, is determined by the difference between arterial pressure $P_A$ and glomerular pressure $P_G$ and afferent arteriolar resistance $R_A$:

$$BF_A = \frac{P_A - P_G}{R_A} \quad (2.41)$$

Note, that the sum of all individual blood flows gives the total renal blood flow (RBF)
used in the Circulatory Module (same as equation (2.9)): \( \text{RBF} = \text{BF}_A \cdot N_n \).

Blood flows across the efferent arteriole \( \text{BF}_E \) and the renal venule \( \text{BF}_V \) are:

\[
\begin{align*}
\text{BF}_E &= \frac{P_G - P_R}{R_E} \\
\text{BF}_V &= \frac{P_R - P_V}{R_V}
\end{align*}
\]

(2.42) \hspace{1cm} (2.43)

where \( P_R \) is peritubular capillary pressure, \( P_V \) is renal venous pressure, \( R_E \) is the efferent arteriolar resistance and \( R_V \) is the resistance of peritubular capillaries.

Note that \( \text{BF}_V \) does not account for all of the renal venous blood flow as it only includes efferent blood flow and the proximal reabsorption rate. The third component is the tubular reabsorption from the descending limb of Henle and distal nephron (see the section below) which is returned via vasa recta, not explicitly represented in this renal model but is accounted for in the circulatory model (Section 2.2, Figure 2.1). The total renal venous blood flow can be also expressed as \( \text{BF}_A - J_{V, DN} \), where \( J_{V, DN} \) is the urinary water excretion rate.

Protein and red blood cells are not filtered into the nephron and thus their afferent
and efferent flows are equal:

\[ \text{BF}_A \cdot (1 - H_A) \cdot [Q]_A = \text{BF}_E \cdot (1 - H_E) \cdot [Q]_E \]  \hspace{1cm} (2.44)

\[ \text{BF}_A \cdot H_A = \text{BF}_E \cdot H_E \]  \hspace{1cm} (2.45)

where \([Q]_A\) and \([Q]_E\) are protein concentration at the afferent and efferent arteriole, respectively; \(H_A\) and \(H_E\) are the afferent and efferent hematocrit, respectively. The afferent hematocrit is the same as the arterial hematocrit and is computed as a ratio of red blood cell volume (\(V_{\text{RBC}}\)) to the sum of red blood cell and plasmas (\(V_P\)) volumes (i.e. the total blood volume \(V_B\)):

\[ H_A = \frac{V_{\text{RBC}}}{V_P + V_{\text{RBC}}} = \frac{V_{\text{RBC}}}{V_B} \]  \hspace{1cm} (2.46)

Similarly, the afferent protein concentration is the same as the plasma protein concentration: \([Q]_A = [Q]_P\).

By the conservation of mass, the single nephron glomerular filtration rate (GFR) is the difference between flows:

\[ GFR = \text{BF}_A - \text{BF}_E \]  \hspace{1cm} (2.47)

Glomerular filtration along the glomerular capillaries is governed by the gradient of hydrostatic pressures in the glomerulus and the Bowman capsule of the nephron along with oncotic pressure in the glomerular capillary. As the blood flows through the glomerular capillaries, water is filtered into the nephron and thus the protein concentration rises, reducing pressure gradient needed for filtration (see Figure 2.9 and detailed description for Figure A.4 in Appendix A).

To model glomerular filtration, a spatially-distributed model is used as described in [24]. The glomerular capillary bed is presented as a permeable tube of fixed length, radius and permeability. The equation for volumetric flow rate of plasma (\(F\)) within the glomerular capillaries can be derived using conservation of mass:

\[ \frac{dF}{dx} = -K_G \cdot (P_G - P_{\text{PT}} - \pi(c)), \quad F(0) = \text{BF}_A \cdot (1 - H_A) \]  \hspace{1cm} (2.48)
where $x$ is the dimensionless distance along the glomerular capillary so that $F(1) = BF_E \cdot (1 - H_E)$; \(c\) is protein concentration, \(K_G\) is filtration coefficient of the glomerular membrane, \(P_G\) is the hydrostatic glomerular pressure, \(P_{PT}\) is the hydrostatic Bowman’s pressure (assumed to be the same as proximal tubule pressure), and \(\pi\) is the oncotic pressure. The protein concentration can be calculated using conservation of protein equation (2.44):

\[
c(x) = \frac{[Q]_A \cdot BF_A \cdot (1 - H_A)}{F(x)}
\]

There is no significant change in \(P_G\) along the length of the capillary, although the assumption of a small gradient allows for a more precise model of filtration equilibrium often observed in rat experiments [24]. Such precision is not necessary for the purposes of the renal excretion model here, thus \(P_G\) is assumed to be spatially constant.

The oncotic pressure \(\pi(c)\) is expressed as a second order polynomial (per [24], also used in Section 2.4):

\[
\pi(c) = c \cdot (0.0029 \cdot c + 0.1631)
\] (2.49)

where \(c\) is protein concentration, expressed in grams per liter.

Bowman’s pressure is assumed constant since GFR is tightly controlled and the filtration is dominated by oncotic pressure gradient.

The model of glomerular filtration described by equations (2.41)-(2.49) can be solved by an iterative method, using Matlab’s fzero function. An initial guess for \(P_G\) is made and the model is solved without invoking (2.42) which is used as the exit condition.

**Tubular reabsorption**

As the filtrate of water and solutes flows through the renal tubule it undergoes a sequential and selective reabsorption before exiting into the bladder. The model structure of renal tubule is shown in Figure 2.10. For detailed description of renal tubule anatomy and reabsorption processes see Appendix A.

The tubule is assumed to be rigid and divided into four consecutive compartments representing proximal tubule (PT), descending limb of Henle (DL), ascending limb of Henle (AL), and distal nephron (DN) consisting of distal tubule and collecting ducts.
Figure 2.10: Structure of renal tubule and reabsorption process. Luminal flows through the tubule are shown by thick grey arrows. The fraction of luminal flow reabsorbed back into circulation is shown by thin black arrows.

In each compartment a fraction of water inflow ($\nu$) and/or a fraction of sodium chloride inflow ($\eta$) is removed. The water outflow from a compartment $X$ is denoted as $J_{V,X}$ and the sodium chloride outflow as $J_{\text{NaCl},X}$.

Glomerular filtration into the proximal tubule and the reabsorption from the proximal tubule into the peritubular capillaries is isoosmotic with plasma. Thus the luminal flows of water and sodium chloride from the proximal tubule into the descending limb of Henle are:

\[
J_{V,\text{PT}} = (1 - \nu_{\text{PT}}) \cdot \text{GFR} \quad (2.50)
\]
\[
J_{\text{NaCl},\text{PT}} = (1 - \eta_{\text{PT}}) \cdot \text{GFR} \cdot [\text{NaCl}]_P \quad (2.51)
\]

where $[\text{NaCl}]_P$ is plasma sodium chloride concentration and

\[
\nu_{\text{PT}} = \eta_{\text{PT}} \quad (2.52)
\]
In the descending limb of Henle only water is reabsorbed, thus the water and sodium chloride outflows into the ascending limb of Henle are:

$$J_{V,DL} = (1 - \nu_{DL}) \cdot (1 - \nu_{PT}) \cdot GFR$$  \hspace{1cm} (2.53)

$$J_{NaCl,DL} = J_{NaCl,PT}$$  \hspace{1cm} (2.54)

In the ascending limb of Henle only sodium chloride is reabsorbed, thus the outflows are:

$$J_{V,AL} = J_{V,DL}$$  \hspace{1cm} (2.55)

$$J_{NaCl,AL} = (1 - \eta_{AL}) \cdot (1 - \eta_{PT}) \cdot GFR \cdot [NaCl]_P$$  \hspace{1cm} (2.56)

In the distal nephron both sodium and water are reabsorbed before the filtrate enters the bladder. Thus renal excretion of water and sodium chloride are:

$$J_{V,DN} = (1 - \nu_{DN}) \cdot (1 - \nu_{DL}) \cdot (1 - \nu_{PT}) \cdot GFR$$  \hspace{1cm} (2.57)

$$J_{NaCl,DN} = (1 - \eta_{DN}) \cdot (1 - \eta_{AL}) \cdot (1 - \eta_{PT}) \cdot GFR \cdot [NaCl]_P$$  \hspace{1cm} (2.58)

Note, that the sum of all individual renal excretion fluid flows gives the total renal excretion of volume used in the Circulatory Module and Whole-Body Exchange Module (equations (2.10) and (2.26)):

$$J_{V,P-U} = J_{V,DN} \cdot N_n.$$  

Similarly, the total sodium excretion used in the Whole-Body Exchange Module is the net sum of all individual nephron sodium excretion flows (equation (2.17)):

$$J_{NaCl,P-U} = J_{NaCl,DN} \cdot N_n$$

Models for each of the tubular reabsorption coefficients are presented below. For detailed description of physiology see Appendix A.
Most models of proximal reabsorption are based on the transport across the renal tubule, rather than the uptake by the peritubular capillaries. However, proximal reabsorption is dominated by the physical forces similar to those governing glomerular filtration (see Figure 2.9). The forces favor movement of the isoosmotic fluid from the proximal tubule into the peritubular capillaries. A model based on the physical force description has been shown to agree with the experimental data [25]. Moreover, it allows an elegant explanation of glomerulotubular balance and the changes in its efficiency under varying inputs.

Similarly to (2.48), the volumetric flow of plasma \( F \) through peritubular capillaries is described as:

\[
\frac{dF}{dx} = -K_R \cdot (P_R - P_{R,IF} + \pi_{R,IF} - \pi(c(x))) \quad F(0) = B F_E \cdot (1 - H_E) \quad (2.59)
\]

where \( x \) is the dimensionless distance along the capillary, \( K_R \) is the reabsorption coefficient, \( P_R \) is the peritubular capillary pressure, \( P_{R,IF} \) is the renal interstitial pressure, and \( \pi_{R,IF} \) is the renal interstitium osmotic pressure. Renal interstitial pressures \( P_{R,IF} \) and \( \pi_{R,IF} \) are assumed constant. Protein concentration \( c(x) \) can be calculated using conservation of protein mass:

\[
c(x) = \frac{[Q]_E \cdot BF_E \cdot (1 - H_E)}{F(x)} \quad (2.60)
\]

The proximal tubule reabsorption rate is then computed as the difference of peritubular plasma outflow and efferent arteriolar plasma flow so that the reabsorption coefficient for the proximal tubule is a ratio of the reabsorption rate to glomerular filtration rate:

\[
\eta_{PT} = \nu_{PT} = \frac{F(1) - F(0)}{GFR} \quad (2.61)
\]

Water reabsorption in the descending limb of Henle is due to water permeable tubular walls and osmotic concentration gradient of the medulla. Although the medullary osmolality varies the reabsorption in the descending limb is limited by the constant tubular permeability. Thus, \( \nu_{DL} \) is assumed constant.
Water reabsorption in the distal nephron is strongly dependent on varying permeability driven by vasopressin concentration. Vasopressin inserts aquaporin channels in the tubular membrane of collecting ducts, thus increasing water reabsorption and medullary osmolality gradient. Since the concentrating mechanism of mammalian medulla is not well-understood [64], the distal water reabsorption is modeled as a function of vasopressin concentration ([AVP]_P) which indirectly incorporates both effects:

\[ \nu_{DN} = p_1 + p_2 \cdot [AVP]_P \]  

(2.62)

Sodium reabsorption in the ascending limb is inhibited by angiotensin II concentration (AngII):

\[ \eta_{AL} = p_1 - \frac{p_2}{1 + e^{p_3 \cdot (AngII - p_4)}} \]  

(2.63)

Sodium reabsorption in the distal nephron is driven by aldosterone (Ald), which regulates the number of sodium channels in the tubular membrane:

\[ \eta_{DN} = p_1 - \frac{p_1}{1 + e^{p_2 \cdot (AVP - p_3)}} \]  

(2.64)

Regulation of arteriolar resistances

The expression for the resistance \( R \) of an arteriole is based on Poiseuille’s law:

\[ R = \frac{8\mu l}{\pi r^4} \]

where \( \mu \) is blood viscosity, \( l \) is the arteriolar length, and \( r \) is the arteriolar radius.

At low vessel diameter, blood viscosity becomes strongly dependent on the hematocrit of the local blood flow, known as a Fahraeus-Lindqvist effect [83]. The phenomenon is called relative apparent blood viscosity. Since afferent arteriolar diameter is about 15 \( \mu m \) and efferent arteriolar diameter is about 12 \( \mu m \), and these diameters are affected by various controls, the hematocrit effect cannot be ignored. Thus, the afferent arteriolar...
resistance ($R_A$) and the efferent arteriolar resistance ($R_E$) are modeled as:

$$R_A = R_{A,b} \cdot \frac{\mu(H_A, d_A)}{\mu(0, d_{A,0})} \cdot \frac{d_{A,0}^4}{d_A^4}$$

(2.65)

where $d_A$ is the afferent arteriolar diameter, $H_A$ is the hematocrit of the afferent blood flow, and $R_{A,b}$ is the afferent resistance at basal diameter $d_{A,0}$ and zero hematocrit.

Similarly, the expression for the efferent arteriolar resistance ($R_E$) is:

$$R_E = R_{E,b} \cdot \frac{\mu(H_E, d_E)}{\mu(0, d_{E,0})} \cdot \frac{d_{E,0}^4}{d_E^4}$$

(2.66)

where $d_E$ is the efferent arteriolar diameter, $H_E$ is the hematocrit of the efferent blood flow, and $R_{E,b}$ is the efferent resistance at basal diameter $d_{E,0}$ and zero hematocrit.

An empirical equation for the variation of relative apparent blood viscosity $\mu$ was derived by [83] based on the comprehensive analysis of extensive experimental data:

$$\mu = \left[ 1 + (\mu^* - 1) \cdot \frac{(1 - H)^C - 1}{(1 - 0.45)^C - 1} \cdot \left( \frac{D}{D - 1.1} \right)^2 \cdot \left( \frac{D}{D - 1.1} \right)^2 \right]$$

(2.67)

with

$$C = (0.8 + e^{-0.075D}) \cdot \left( -1 + \frac{1}{1 + 10^{-11}D^{12}} \right) + \frac{1}{1 + 10^{-11}D^{12}}$$

and

$$\mu^* = 220 \cdot e^{-1.3D} + 3.2 - 2.44 \cdot e^{-0.06D^{0.645}}$$

where $D = 0.84 \cdot d$ with $d$ being the vessel diameter expressed in microns. The coefficient of 0.84 is required to make an adjustment for the rodent model, since mean corpuscular volume of rodent blood cells is smaller than that of human red blood cells, for which the above formulas were derived.

The afferent vascular diameter is controlled by a myogenic response to an increased arterial pressure and angiotensin II while the efferent vascular diameter is passively increased by distending pressure and reduced by angiotensin II:

$$d_A = d_{A,0} + p_1 \cdot (P_A - P_{A,0}) + p_2 \cdot (\text{AngII} - \text{AngII}_0)$$

(2.68)
where both diameters are expressed in microns and parameters are chosen based on general directional and relative change experimental observations [14]. The effect of AngII on the efferent arteriolar diameters ceases below normal values of AngII.

After the fluid is reabsorbed into peritubular capillaries it is carried back into the veins. The resistance of the peritubular capillaries is modulated by AngII [53]. We do not model individual resistances of peritubular capillaries $R_V$ per nephron and instead represent the total renal venous resistance $R_{VR}$ to the flow:

$$R_{VR} = N_n \cdot R_V = p_1 + p_2 \cdot (\text{AngII} - \text{AngII}_0)$$  \hspace{1cm} (2.70)

where the effect of AngII ceases below normal values of AngII.

**Hormone response**

The hormone concentrations included in this model are: angiotensin II, aldosterone, atrial natriuretic peptide, and vasopressin. All four hormones exert control on renal reabsorption processes as discussed above. The following section describes the control of hormone response in the model. A detailed description of the physiology can be found in Appendix A.

In general, plasma hormone concentration ($X$) can be described by the rates of the hormone secretion ($M_X$) and clearance which is proportional to the hormone concentration and has a known half-life constant ($h_X$):

$$\frac{dX}{dt} = \tilde{M}_X - \frac{\ln 2}{h_X} X$$

where the rate of secretion is a function of one or more control factors so that $\tilde{M}_X = \frac{\ln 2}{h_X} X_0$ when all controls are quiescent. However, experimental measurements of the hormone concentration, not the rate of secretion are usually available and thus the
following form for expressing hormone concentration dynamics is used:

\[
\frac{dX}{dt} = \ln 2 \cdot \frac{h}{h_X} \cdot (M_X - X)
\]

where \( M_X = X_0 \) when all control of secretion are quiescent.

Plasma angiotensin II concentration is determined by the renin production by the juxtaglomerular cells in response to an increased sodium chloride flow at macula densa \( J_{NaCl,AL} \) and is inhibited by own concentration:

\[
\frac{d\text{AngII}}{dt} = \ln 2 \cdot \frac{h}{h_{\text{AngII}}} \cdot (M_{\text{AngII}} - \text{AngII}) \tag{2.71}
\]

where

\[
R_{\text{AngII}} = J_{\text{AngII},I-P} + \left( p_1 - \frac{p_1}{1 + e^{p_2(x - p_3)}} \right) \cdot \left( 1 - \frac{1}{1 + e^{p_4 - [\text{AngII}]_p}} \right) \tag{2.72}
\]

where \( J_{\text{AngII},I-P} \) is the infusion rate of exogenous angiotensin II and \( x = J_{NaCl,AL} \cdot N_n \).

Atrial natriuretic peptide, or ANP, is a hormone secreted by cardiac muscle cells in response to angiotensin II and elevated venous pressure \( P_V \), among other stimuli [54]:

\[
\frac{d\text{ANP}}{dt} = \ln 2 \cdot \frac{h}{h_{\text{ANP}}} \cdot (M_{\text{ANP}} - \text{ANP}) \tag{2.73}
\]

where

\[
M_{\text{ANP}} = p_1 - \frac{p_2}{1 + e^{p_2(\text{AngII} - p_4)}} + p_5 \cdot P_V \tag{2.74}
\]

Plasma aldosterone concentration (Ald) is proportional to the concentration of angiotensin II for low to moderate values of angiotensin II (AngII). At high levels of angiotensin II (about twice the normal value) and especially in the presence of elevated plasma osmolality aldosterone production dissociates from angiotensin II [62]. The mechanism behind this dissociation is not well studied. At high levels of angiotensin II production of aldosterone may be inhibited by elevated plasma osmolality [70] or atrial natriuretic peptide [16]. The physiological effect of the hormones on the distal nephron is delayed by 1-2 hours as changes in gene expression and protein synthesis need to take
place in order to insert active sodium transport channels into the tubular membrane. This delay is included into the time constant of the hormone dynamics:

$$\frac{dAld}{dt} = \frac{\ln 2}{h_{Ald}} \cdot (M_{Ald} - Ald) \tag{2.75}$$

where

$$M_{Ald} = (p_1 - p_2 \cdot ANP) \cdot (p_3 - \frac{p_3}{1 + e^{p_4 \cdot (AngII - p_5)}}) \tag{2.76}$$

Vasopressin, also known as arginine vasopressin (AVP), is released in response to increased plasma osmolality ([NaCl]_P) and the responsiveness is sensitized by the circulating angiotensin II [13]:

$$\frac{dAVP}{dt} = \frac{\ln 2}{h_{AVP}} \cdot (M_{AVP} - AVP) \tag{2.77}$$

where

$$M_{AVP} = p_1 \cdot AngII \cdot ([NaCl]_P - [NaCl]_{P,0}) + AVP_0 \tag{2.78}$$

truncated at 0, with the slope of the response derived from the data presented in [88] and truncated at 1 when angiotensin II is below its normal value.
Chapter 3

Analysis

The objective of this chapter is to demonstrate the validity of the model and to analyze its steady-state behavior. We are particularly interested in elucidating the causal factors behind pressure-natriuresis phenomenon in the model. We show that the multifactorial control of arterial pressure necessitates a multidimensional view of all of the control mechanisms, renal and non-renal. Pressure-natriuresis curves are the lower-dimension observations and reflect a mix of controls within the system, rather than simply renal control. To establish our argument, we structure the chapter in the following way:

1. The reduction technique using time scale separation is applied to the model. It separates out its fast and slow dynamics. The fast subsystem represents all major established physiological controls in the model and is responsible for the early onset phase of hypertension (see Figure 1.4). The slow subsystem consists of the hypothetical slow activation of the sympathetic nervous system and is responsible for the maintenance phase of hypertension.

2. The steady state response of the fast subsystem is validated by comparing its predictions to the available experimental data in three scenarios, where either plasma AngII levels, sodium intake, or both AngII and sodium are elevated.

3. A global sensitivity analysis demonstrates a multifactorial nature of blood pressure control and identifies some of the key factors which can affect steady state of
arterial pressure in the fast subsystem.

4. The steady state response of the complete system is approximated by the reduced (degenerate) system. Two of the key factors from the global sensitivity analysis, the unstressed volume and extra-renal arteriolar diameter, are assumed to be the variables of this subsystem, driven by the slow sympathetic activation. This allows an explanation of the maintenance phase of AngII-salt hypertension which is validated against experimental observations.

5. The long-term response of arterial pressure to varying salt intake levels generates a surface in a three-dimensional space, with axes of renal and sympathetic control. The projections of this surface generate the curves of the pressure-natriuresis phenomenon which reflect a combination of the two controls.

All simulations were performed in Matlab. The results of the analysis will be discussed in Chapter 4.

3.1 Time scale separation

All of the dynamic equations of the model have time scale of minutes to hours, except for the hypothetical latent activation dynamics, which is assumed to act on the scale of days to weeks. This suggests that the analysis of the model can be simplified via singular perturbation theory. In particular, we will use the outer solution to approximate the slow manifold in the discussion of the effects of the slow activation of the sympathetic nervous system and generation of the pressure-natriuresis curves.

We first express the entire system as:

\[
\frac{dy}{dt} = f(y, z, t), \quad y(0) = y_0
\]

\[
\epsilon \frac{dz}{dt} = g(y, z, t), \quad z(0) = z_0
\]

where \(0 < \epsilon \ll 1\), \(t\) is the time variable of the slow phenomena, \(y\) is a vector of two slow variables, the unstressed blood volume (\(V_{Unstr}\)) and extra-renal arteriolar diameter
(\(d_{AS}\)), and \(z\) is a vector of all remaining variables of the system (fast variables), in particular, arterial pressure \(P_A\).

The system has to be nondimensionalized and rescaled in order to express \(\epsilon\). We have done such derivation only for a simplified system shown in Appendix C and believe this could be expanded in a straightforward way to the rest of the system. However, this remains to be verified.

The system (3.1) is:

\[
\begin{align*}
C_A \cdot \frac{dP_A}{dt} &= CO - \frac{P_A - PC}{R_{AS}} - RBF \\
C_S \cdot \frac{dP_S}{dt} &= \frac{PC - PS}{R_{CS}} - \frac{PS - PV}{R_{VS}} \\
C_V \cdot \frac{dP_V}{dt} &= \frac{PS - PV}{R_{VS}} + \hat{J}_{V,IF-P} + J_{V,I-P} + RBF - J_{V,P-U} - CO \\
\frac{dNaCl_{IF}}{dt} &= J_{NaCl,P-IF} - \hat{J}_{NaCl,IF-P} \\
\frac{dNaCl_{IF}}{dt} &= J_{NaCl,P-IF} - \hat{J}_{NaCl,IF-P} \\
\frac{dNaCl_P}{dt} &= J_{NaCl,P-IF} - J_{NaCl,P-U} \\
\frac{dNaCl_U}{dt} &= J_{NaCl,P-IF} - J_{NaCl,P-U} \\
\frac{dV_T}{dt} &= J_{V,IF-P} - J_{V,P-U} \\
\frac{dV_P}{dt} &= J_{V,IF-P} - J_{V,P-U} + J_{V,RBC-P} - J_{V,P-IF} + \hat{J}_{V,IF-P} \\
\frac{dQ_P}{dt} &= \hat{J}_{Q,IF-P} - J_{Q,P-IF} \\
\frac{dAngII}{dt} &= \frac{\ln 2}{h_{AngII}} \cdot (R_{AngII} - AngII) \\
\frac{dANP}{dt} &= \frac{\ln 2}{h_{ANP}} \cdot (R_{ANP} - ANP) \\
\frac{dAld}{dt} &= \frac{\ln 2}{h_{Ald}} \cdot (R_{Ald} - Ald) \\
\frac{dAVP}{dt} &= \frac{\ln 2}{h_{AVP}} \cdot (R_{AVP} - AVP) \\
\frac{dy}{dt} &= \frac{P_A - (y + x)}{10} \\
\frac{dx}{dt} &= \frac{P_A - x}{240}
\end{align*}
\]

with supporting algebraic equations as described in Chapter 2.
The system (3.2) is:

$$\tau_{\text{exc}} \frac{dS_{\text{NA exc}}}{dt} = \alpha \cdot \left(1 - \frac{1}{1 + e^{5 \cdot (x(t-\tau_d)-3)}}\right) - S_{\text{NA exc}}$$

where $x(t-\tau_d) = \frac{[\text{NaCl}]_{P(t-\tau_d)}-[\text{NaCl}]_{P0}}{0.01} \cdot \frac{\text{AngII}(t-\tau_d)-\text{AngII}_0}{\text{AngII}_0}$ with

$$d_{AS} = p_1 - \frac{p_2}{1 + e^{p_3(\text{AngII}-p_4)}} - p_5 \cdot (S_{\text{NA exc}} - S_{\text{NA inh}})$$

and

$$V_{\text{Unstr}} = V_{\text{Unstr},0} - p_1 \cdot (S_{\text{NA exc}} - S_{\text{NA inh}})$$

as described in Chapter 2.

The outer solution is obtained via the degenerate system by taking the limit of (3.1)-(3.2) as $\epsilon \to 0$:

$$\frac{dy_s}{dt} = f(y_s, z_s, t), \quad y_s(0) = y_0 \quad (3.3)$$

$$0 = g(y_s, z_s, t) \quad (3.4)$$

This system is referred to as the slow subsystem in the following sections.

The inner solution is obtained via the adjoined system. We rewrite (3.1)-(3.2) in the fast time scale $\tau$

$$\frac{dy}{d\tau} = \epsilon f(y, z, \epsilon \tau) \quad \epsilon \to 0 \Rightarrow \frac{dy}{d\tau} = 0 \quad (3.5)$$

$$\frac{dz}{d\tau} = g(y, z, \epsilon \tau) \quad \epsilon \to 0 \Rightarrow \frac{dz}{d\tau} = g(y, z, 0) \quad (3.6)$$

This system is referred to as the fast subsystem in the following sections.

The inner solution is an approximation of the exact solution within a neighborhood (boundary layer) of the initial condition. In our case the inner solution coincides with the exact solution during first 5 days of the simulation since the activation of the sympathetic system is assumed to be delayed by 5 days. The match between the inner and the outer solutions in the region where their time scales overlap has to be verified. In the simpler
case we have shown that the adjoined system has a single stable root and thus the quasi-steady states approximate the steady states of the original system. Since for the full system we do not have the explicit solutions and since our practical focus lies with the long-term behavior we will focus on the outer solution.

3.2 The onset phase of hypertension

The response of the fast subsystem to changes in AngII and sodium intake is of central importance to the analysis of the model’s long term behavior. The available experimental data falls into three categories: plasma AngII levels are modified without changes to sodium intake, sodium intake is modified while AngII is controlled by normal physiological mechanisms, or both plasma AngII and sodium are elevated. In the latter scenario, a latent activation of slow mechanisms (such as the sympathetic activation) can be involved, thus only the data from the first few days of the response (the onset phase) can be used for the validation of the fast subsystem. The latent response has not be shown to occur in the other two scenarios.

To represent typical experimental conditions, the following three input scenarios to the system were simulated and validated: "High AngII + Normal Salt", "Normal AngII + High Salt", and "High AngII + High Salt", where "High AngII" means an infusion of AngII is administered so that plasma AngII is elevated two-fold, "Normal AngII" means plasma AngII is regulated by normal physiological processes, and "High Salt" means that sodium intake is increased 5-fold from normal salt intake.

Since the experimental studies typically report measurements after an initial stabilization period, only the steady states of the fast subsystem are validated. This is deemed acceptable given the overall focus of the model on the long-term blood pressure control. The experimental data were scaled to match the initial steady-state values of the corresponding simulation to compare the relative changes in the responses.

The main simulation results are combined into a hemodynamic profile panel; i.e. the responses of arterial pressure, cardiac output, total blood pressure and total peripheral resistance to changes in plasma AngII and/or sodium intake. One panel per each of the
three simulations is created. More detailed simulation results are provided in Section 3.2.4 in an additional three plots per each scenario. These simulation panels contain key variables of each of the three system modules: the Circulatory Module panel, the Whole-Body Exchange Module, and the Renal-Hormonal Module. All results are presented on the same scale to allow quick comparison across scenarios. Normal steady-state (i.e. values under "Normal AngII + Normal Salt") is shown as a dotted line on each plot and relative change of the new steady state as a percentage of normal is shown on Day 6 for ease of data interpretation.

3.2.1 High AngII, normal salt intake

Consider the scenario "High AngII + Normal Salt", when sodium intake is normal, but AngII infusion is administered starting on Day 2 so that the plasma AngII is elevated two-fold within several hours. The hemodynamic profile of the system’s response is shown in Figure 3.1, left panel. More detailed results can be found in Section 3.2.4, Figures 3.4, 3.5, and 3.6.

Table 3.1 shows that the model predictions are in good agreement with the experimental data collected from several studies. There is a considerable variation in cardiac output values reported in different studies, but it appears that the model predicts lower than expected cardiac output response. Blood volume is also somewhat lower than observed experimentally but within the experimental measurement error of 10%.

3.2.2 Normal AngII, high salt intake

Consider the scenario "Normal AngII + High Salt", when sodium intake is increased 5-fold either by a change in salt diet or infusion, but AngII is under normal physiological control. The hemodynamic profile of the system’s response is shown in Figure 3.1, middle panel. More detailed results can be found in Section 3.2.4, Figures 3.7, 3.8, and 3.9.

Table 3.2 shows that model predictions are in good agreement with the experimental data collected from several studies. The behavior of arterial pressure in our model is
Figure 3.1: Simulated hemodynamic profiles of three scenarios: "High AngII + Normal Salt" (left panel), "Normal AngII + High Salt" (middle panel), "High AngII + High Salt" (right panel). Simulated response is shown in black; sodium input on the top plots is shown in light grey; relative change on Day 7 as compared to the normal steady state (dashed line) is shown as a percentage of normal.
Table 3.1: "High AngII + Normal Salt" scenario: Comparison between model predictions and available experimental data from various studies. Relative changes as a fraction of control conditions of each study are shown. \( P_A \), mean arterial pressure; CO, cardiac output; TPR, total peripheral resistance; \([\text{NaCl}]_P\), plasma osmolarity; \( V_B \), blood volume; GFR, glomerular filtration rate; RBF, renal blood flow; Ald, plasma aldosterone concentration; ANP, plasma atrial natriuretic peptide concentration.

3.2.3 High AngII, high salt intake

Consider the scenario "High AngII + High Salt", when the animal began receiving AngII infusion to elevate plasma AngII levels about 2-fold, after already being on a high sodium intake (5 times normal) for several days prior to the infusion. As discussed at length in Chapter 1, this is the scenario of AngII-salt hypertension, where the animal is expected to develop hypertension at a later stage. The acute response to this protocol representing the onset phase of the hypertension only is shown in Figure 3.1, right panel. More detailed results can be found in Section 3.2.4 (Figures 3.10, 3.11, 3.12, 3.13, 3.14, and 3.15).

The results of the simulations can be validated against two experimental studies discussed in Chapter 1: the study by Osborn and Fink [76] in rats (only arterial pressure...
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Table 3.2: "Normal AngII + High Salt" scenario: Comparison between model predictions and available experimental data from various studies. Relative changes from normal condition (control) are shown. \( P_A \), mean arterial pressure; CO, cardiac output; TPR, total peripheral resistance; [NaCl]_P, plasma osmolarity; \( V_B \), blood volume; GFR, glomerular filtration rate; RBF, renal blood flow; AngII, plasma angiotensin II concentration; Ald, plasma aldosterone concentration; ANP, plasma atrial natriuretic peptide.

was measured) and the study by Krieger et al [62] in canines.

Figure 3.2 shows good agreement between the simulated mean arterial pressure and the pressure collected in rats on 2% NaCl diet (about 5 times the normal diet) that began receiving AngII infusion which doubled their plasma AngII levels [76]. No scaling of data was performed. Note that we focus here only on the onset phase of the profile shown in Panel B; the maintenance phase of this experimental response is the subject of the following section.
Figure 3.2: Arterial pressure during the onset phase of the "High AngII + High salt" protocol (panel A) as compared to experimental data from [76] (panel B). In Panel A the data from rats on 2% NaCl diet (white squares) is overlayed on top of the simulated arterial pressure response (black line).

Figure 3.3 shows the comparison of the hemodynamic profile reported by Krieger et al [62]. In this study, the order of AngII and sodium perturbation was reversed: the animals were first put on a continuous infusion of AngII and after a stabilization period the sodium intake was increased. The simulation of this scenario is shown in Figure 3.3, A. Note that the steady states of the response are the same as in Figure 3.1, right panel, but the initial conditions are different, due to the change in the order of AngII and salt intake perturbations. The experimental data (except for arterial pressure) is re-scaled to the initial states when overlayed on top of the simulated data in Panel A. Krieger’s study did not report daily changes in blood volume due to technical difficulties of measuring it sequentially. However, the change in blood volume was measured on Day 2 of the experiment as an 11% increase from normal, which corresponded to 500 g weight increase on that day. We have assumed that this relationship applies for the other days of the study and re-scaled the data to rodent values using the initial state of the simulation as normal.

The model prediction and data agree well for arterial pressure. For cardiac output and blood volume the model predicts higher than observed values. For total peripheral resistance the prediction disagrees with the data: Krieger observes continuous rise in
Figure 3.3: Hemodynamic profile during the onset phase of the AngII-salt hypertension ("High AngII + High salt" scenario). Simulated response (Panel A, black lines) is compared to the experimental data from [62] (panel B). The data is also overlaid on top of the simulated responses (Panel A, white squares).

resistance, while the model predicts transient decline and lower steady state. Note first, that resistance is not a measured but a calculated value in experiments (ratio of arterial pressure to cardiac output), thus the disparity in the results for resistance and cardiac output are related. Note also, that the disagreement is driven by the difference in the initial states between the simulation and the experiment. High level of AngII has been shown to increase total peripheral resistance by 40% both in our simulation ("High AngII + Normal Salt", Figure 3.1, left panel) and experimental studies (see Table 3.1). However, in Krieger’s experiment no vessel constriction response to the infusion
of AngII was reported. It is possible that an exaggerated cardiac output response in our simulation may be due to the model of Frank-Starling law we used. On the other hand, our predicted profile for all four variables agree with Guyton’s stylized summary of studies like Krieger’s (see Figure 1.4, Panel B). Thus, additional experimental data may be needed to explain the disparity in the results.

3.2.4 Auxillary simulation data

The following figures provide additional simulation results for the acute system response to the three scenarios discussed earlier. See Section 3.2 for details.
Figure 3.4: Response of the key variables of the Circulatory Module to "High AngII + Normal salt" scenario. See Section 3.2 for details.
Figure 3.5: Response of the key variables of the Whole-Body Exchange Module to "High AngII + Normal salt" scenario. See Section 3.2 for details.
Figure 3.6: Response of the key variables of the Renal Module to "High AngII + Normal salt" scenario. See Section 3.2 for details.
Figure 3.7: Response of the key variables of the Circulatory Module to "Normal AngII + High salt" scenario. See Section 3.2 for details.
Figure 3.8: Response of the key variables of the Whole-Body Exchange Module to "Normal AngII + High salt" scenario. See Section 3.2 for details.
Figure 3.9: Response of the key variables of the Renal Module to "Normal AngII + High salt" scenario. See Section 3.2 for details.
Figure 3.10: Response of the key variables of the Circulatory Module to "High AngII + High salt" scenario, with AngII infusion started after the change of sodium intake. See Section 3.2 for details.
Figure 3.11: Response of the key variables of the Whole-Body Exchange Module to "High AngII + High salt" scenario, with AngII infusion started after the change of sodium intake. See Section 3.2 for details.
Figure 3.12: Response of the key variables of the Renal Module to "High AngII + High salt" scenario, with AngII infusion started after the change of sodium intake. See Section 3.2 for details.
Figure 3.13: Response of the key variables of the Circulatory Module to "High AngII + High salt" scenario, with AngII infusion started before the change of sodium intake. See Section 3.2 for details.
Figure 3.14: Response of the key variables of the Whole-Body Exchange Module to "High AngII + High salt" scenario, with AngII infusion started before the change of sodium intake. See Section 3.2 for details.
Figure 3.15: Response of the key variables of the Renal Module to “High AngII + High salt” scenario, with AngII infusion started before the change of sodium intake. See Section 3.2 for details.
3.3 Global sensitivity analysis

The early response of the system which does not include any of the competing hypotheses of either renocentric or neurocentric theory, shows at most a modest elevation in arterial pressure. Thus, some of the variables could be modified slowly and over a long-term so that further elevation of arterial pressure is observed. One way to identify such variables is to consider the Circulatory Module, the module which directly determines arterial pressure, and find which of its inputs and parameters have the largest impact on its steady state. Global sensitivity analysis (GSA) is a well-suited technique for this purpose, capable of addressing the uncertainty of model parameters and identifying key parameters and interactions which influence the model outcome the most. To apply the technique, a specific feature of the model’s solutions (the output factor) has to be chosen and all parameters and inputs that may affect the feature (the input factors) listed along with their uncertainty ranges. For further details on the method and a simple example see Appendix B.

The steady state solutions of the Circulatory Module are the solutions of the following system of implicit algebraic equations derived from (2.1)-(2.4):

\[\begin{align*}
\text{CO} - \frac{P_A - P_C}{R_{AS}} - \text{RBF} &= 0 \\
\frac{P_C - P_S}{R_{CS}} - \frac{P_S - P_V}{R_{VS}} &= 0 \\
\frac{P_S - P_V}{R_{VS}} + \hat{J}_{V,IF-P} + \text{RBF} - \text{CO} &= 0 \\
C_A \cdot P_A + C_S \cdot P_S + C_R \cdot P_R + C_V \cdot P_V &= V_{Str}
\end{align*}\]

where \(V_{Str} = V_B - V_{Unstr}\) is the stressed volume of the vascular system and other variables as introduced in Section 2.2.

The system can be solved for the following variables: \(P_A, P_V, P_S,\) and \(P_C,\) so that the rest of the variables can be considered input factors which affect these solutions. However, only two of the pressures, \(P_A\) and \(P_V,\) influence other modules of the system (see Figure 2.1). Thus we denote them as the output factors for the global sensitivity
analysis below.

The input factors to the Circulatory Module are comprised of the internal parameters and inputs from other modules (Table 3.3). All distributions are assumed to be normal distributions with a default 20% deviation from the input’s normal value. The deviation is then adjusted if there are available experimental measurements in animals or humans with hypertension under two conditions: acute stimulation of neural control (e.g. electrical stimulation of carotid baroreceptors, infusion of epinephrine); or natural variation with age or time of day.

<table>
<thead>
<tr>
<th>Input factor</th>
<th>Distribution</th>
<th>Deviation from normal</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_A$</td>
<td>$\mathcal{U}(0.007,0.01)$</td>
<td>(-20%, +10%)</td>
<td>[98], [90]</td>
</tr>
<tr>
<td>$C_R$</td>
<td>$\mathcal{U}(0.103,0.162)$</td>
<td>(-30%, +10%)</td>
<td>[98], [90], [60]</td>
</tr>
<tr>
<td>$C_S$</td>
<td>$\mathcal{U}(0.165,0.289)$</td>
<td>(-20%, +40%)</td>
<td>[98], [90], [60]</td>
</tr>
<tr>
<td>$C_V$</td>
<td>$\mathcal{U}(0.188,0.344)$</td>
<td>(-40%, +10%)</td>
<td>[98], [90], [60]</td>
</tr>
<tr>
<td>HR</td>
<td>$\mathcal{U}(320,480)$</td>
<td>(-10%, +15%)</td>
<td>[57], [60]</td>
</tr>
<tr>
<td>$\hat{J}_{V,IF-P}$</td>
<td>$\mathcal{U}(0.006,0.009)$</td>
<td>(-20%, +20%)</td>
<td>default</td>
</tr>
<tr>
<td>$p_{CO,1}$</td>
<td>$\mathcal{U}(0.4,0.6)$</td>
<td>(-20%, +20%)</td>
<td>[30], [31], [35], [60]</td>
</tr>
<tr>
<td>$p_{CO,1}$</td>
<td>$\mathcal{U}(0.64,0.96)$</td>
<td>(-20%, +20%)</td>
<td>[30], [31], [35], [60]</td>
</tr>
<tr>
<td>$p_{CO,2}$</td>
<td>$\mathcal{U}(0.532,0.798)$</td>
<td>(-20%, +20%)</td>
<td>[30], [31], [35], [60]</td>
</tr>
<tr>
<td>$P_R$</td>
<td>$\mathcal{U}(18.8,28.2)$</td>
<td>(-20%, +20%)</td>
<td>default</td>
</tr>
<tr>
<td>$R_{AS}$</td>
<td>$\mathcal{U}(1.197,1.796)$</td>
<td>(-10%, +35%)</td>
<td>[30], [60]</td>
</tr>
<tr>
<td>$R_{CS}$</td>
<td>$\mathcal{U}(0.017,0.025)$</td>
<td>(-20%, +20%)</td>
<td>default</td>
</tr>
<tr>
<td>$R_{VS}$</td>
<td>$\mathcal{U}(0.149,0.223)$</td>
<td>(-20%, +20%)</td>
<td>default</td>
</tr>
<tr>
<td>RBF</td>
<td>$\mathcal{U}(5.06,10.12)$</td>
<td>(-45%, +10%)</td>
<td>[60]</td>
</tr>
<tr>
<td>$V_{Str}$</td>
<td>$\mathcal{U}(5.76,9.6)$</td>
<td>(-10%, +50%)</td>
<td>[80], [81], [35]</td>
</tr>
</tbody>
</table>

Table 3.3: Inputs to the Circulatory Module and their distributions.

The results of the GSA are shown in Table 3.4 and lead to the following conclusions:

1. There are no significant interactions between the factors since the main and the total effects are almost equal for each factor.

2. Arterial pressure is most sensitive to stressed blood volume and venous compliance.
as well as the extra-renal resistance and pressure in renal peritubular capillaries. 
In particular, this implies that unstressed blood volume and extra-renal arteriolar 
diameter are among the top impact factors for the arterial pressure.

3. Venous pressure is sensitive to the above factors, and also to the parameters of 
governing cardiac output.

4. All other factors do not play a significant role in altering pressures.

<table>
<thead>
<tr>
<th>Input factor</th>
<th>Arterial Pressure, $P_A$</th>
<th>Venous Pressure, $P_V$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Main effect, $S_i$</td>
<td>Total effect, $S_T$</td>
</tr>
<tr>
<td>$V_{StF}$</td>
<td>0.54</td>
<td>0.55</td>
</tr>
<tr>
<td>$C_V$</td>
<td>0.26</td>
<td>0.27</td>
</tr>
<tr>
<td>$P_R$</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>$R_{AS}$</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>$R_{VS}$</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>$k_1$ (CO)</td>
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<td>0</td>
</tr>
<tr>
<td>$k_2$ (CO)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$k_3$ (CO)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$C_A$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$C_R$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$C_S$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$\hat{J}_{V,IF-P}$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RBF</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>$R_{CS}$</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sum</td>
<td>0.99</td>
<td>1.02</td>
</tr>
</tbody>
</table>

Table 3.4: Global sensitivity results for the Circulatory Module: Main and total effects ordered roughly in the descending order of significance.
3.4 The maintenance phase of hypertension

Out of the three scenarios considered in the previous section, only "High AngII + High Salt" scenario generates the trigger to the slow increase in the sympathetic nerve activity: simultaneous elevation of plasma AngII and plasma osmolarity. The unstressed blood volume and the extra-renal arteriolar diameter are among top factors which impact the steady state arterial pressure in the fast subsystem. These two variables were chosen as the two slow variables of the model, driven by the sympathetic activation, based on indirect experimental evidence (see Chapter 1). The following section demonstrates the impact of changes in the unstressed blood volume and extra-renal arteriolar diameter on the maintenance phase of the hemodynamic profile of AngII-salt hypertension.

Most experimental studies collect daily data only for a few days, due to experimental difficulties in making measurements in conscious animals for a prolonged period of time. However, there are two experimental studies in rats on AngII-salt protocol which have collected daily data for duration of about 3 weeks. They show an additional rise in arterial pressure of about 20 mmHg during the maintenance phase, i.e. after the first 4-5 days of the protocol (Figure 3.16). This rise cannot be explained by the fast subsystem which settles to a steady state by Day 5 or so (see Figure 3.3). We hypothesized that the rise in arterial pressure is due to a slow decrease in extra-renal arteriolar diameter alongside a slow decrease in the unstressed blood volume, both of which are driven by the sympathetic nervous system.

These studies did not measure any other components of the hemodynamic profile and we are not aware of other studies that reported those values in rodents. However, a qualitative behavior during the maintenance phase of AngII-salt hypertension was summarized by Guyton based on sparse measurements in canines (Chapter 1, Figure 1.4) shown here again for reference (Figure 3.17). Since the dynamics of the maintenance phase is not well known due to technical difficulties of long-term measurements in conscious animals we focus on model predictions of the steady state behavior of the hemodynamic profile.
Figure 3.16: Arterial pressure response to AngII-salt hypertension in rats on various sodium diets. Panel A shows data from King and Fink [57], Panel B shows data from Osborn and Fink [76]. In animals on high salt diet (black squares in both panels) a latent increase in arterial pressure of about 20 mmHg is observed between Day 5 and Day 20 of the protocol.
The simulated response of our model is shown in Figure 3.18. It assumes that the latent sympathetic activation decreases the unstressed volume by 1.1 ml (86% of normal) and extra-renal arteriolar diameter by 12 microns (30% of normal). The results show the expected directional change in all hemodynamic variables: cardiac output and blood volume return back to normal values, total resistance increases further, and arterial pressure reaches levels observed in the studies by Osborn and Fink. The differences with the intermediate values of Guyton’s stylized profile (i.e. the values at the end of the onset phase) are due to the differences between the fast subsystem and Guyton’s observations. The latent phase, however, agrees well with the expected behavior.
Figure 3.18: Hemodynamic profile of the system to "High AngII + High Salt" scenario, including latent activation of the sympathetic nervous system (SNS). The relative change from normal at the end of the onset phase and the end of the maintenance phase are stated and denoted by black-filled circles. The dynamics of the maintenance phase is omitted, changes in quasi-steady states of the fast subsystem due to sympathetic drive are shown by arrows.
The magnitude of the decreases in the unstressed volume and arteriolar diameter were chosen based on two principles: 1) they are within the expected range of change based on the indirect experimental data; 2) change in both variables is needed in order to explain why cardiac output returns to normal levels. Let us explain this in more detail.

The expected range of change in the extra-renal resistance is derived from the following: 1) total peripheral resistance has to increase; and 2) renal denervation does not disrupt the hypertensive response thus the increase is mostly due to the extra-renal vessels. If one is to expect a 155% increase from normal arterial pressure (in rodent experiments mentioned above) and a minimal change in cardiac output (Guyton’s observation) and assuming all other variables remain roughly the same, then the extra-renal resistance would have to increase by about 155%. In our model, this would translate to a decrease in extra-renal arteriolar diameter by about 15 microns.

The decrease in the unstressed blood volume due to increased venous tone is hypothesized based on the experimental observations of increased mean circulatory filling pressure in AngII-salt protocol as reported in [57]. The mean circulatory filling pressure (MCFP) is defined as the mean pressure in the vascular system at zero cardiac output. When flow through the system stops, the volume redistributes across all vascular compartments so that all pressures are equalized. It can be expressed as:

\[ \text{MCFP} = \frac{V_B - V_{Unstr}}{C_T} \]

where \( V_B \) is the total blood volume, \( V_{Unstr} \) is the unstressed blood volume, and \( C_T \) is the total vascular compliance. Thus, if total compliance and blood volume is unchanged, the increase in MCFP implies a decrease in the unstressed blood volume.

In the study by King and Fink [57] conducted in rats on the AngII-salt protocol, it was observed that by Day 14 the total blood volume remained normal but MCFP had increased by about 50%, from 6.5 to 9.8 mmHg. In the current model, assuming that all other variables are unaffected, that would translate into a 60% decrease in the unstressed volume, from 8 to 4.7 ml.
The ranges derived above are only rough estimates and do not consider the concomitant effect of changes in other variables of the system. To derive the values for the simulation in Figure 3.18 we have simulated responses across a range of changes in the unstressed blood volume and arteriolar diameter. The summary of these results are shown in Figures 3.19 and 3.20 which show the same data in two different views for ease of interpretation.

Figure 3.19: Steady state responses of the hemodynamic profile variables. Each curve represents values across a range of the unstressed blood volume $V_{Unstr}$ changes for a fixed decrease in the extrarenal arteriolar diameter ($\Delta d_{AS}$, microns). The black diamond shows the state of the system at the end of the onset phase of AngII-salt hypertension. Horizontal dashed grey line indicates the expected values of each of the hemodynamic variables by the end of the maintenance phase (level for arterial pressure is taken from studies of Osborn and King, and the rest are chosen from Guyton’s studies (see text for detail).

A decrease in either unstressed volume or extrarenal arteriolar diameter leads to a similar directional change in the three of the four hemodynamic responses: an increase
Figure 3.20: Steady state responses of the hemodynamic profile variables. Each curve represents values across a range of the decrease in extrarenal arteriolar diameter ($\Delta d_{AS}$) for a fixed value of the unstressed blood volume ($V_{Unstr}$, ml). The black diamond shows the state of the system at the end of the onset phase of AngII-salt hypertension. Horizontal dashed grey line indicates the expected values of each of the hemodynamic variables by the end of the maintenance phase (level for arterial pressure is taken from studies of Osborn and King, and the rest are chosen from Guyton’s studies (see text for detail).

In arterial pressure and total resistance, and a decrease in blood volume. However, cardiac output is affected in the opposite directions: a decrease in the unstressed blood volume elevates it, and a decrease in the diameter lowers it. While a decrease in the diameter drives expected qualitative changes in all four hemodynamic variables, it does not have a sufficient impact expected from experimental data. Thus, a decrease in both unstressed volume and extrarenal arteriolar diameter is needed based on experimental and mathematical considerations.
3.5 Pressure-natriuresis phenomenon

The pressure-natriuresis phenomenon was observed experimentally by varying salt intake and measuring long-term changes in arterial blood pressure and sodium excretion (Figure 3.21, Panel A; see also Chapter 1, Figure 1.6). For the measurements done in animals without affecting their plasma AngII the curves look almost flat, but when plasma AngII is maintained at higher levels the curves have a significant slope.

Figure 3.21: Pressure-natriuresis relationship observed in a study by DeClue et al [23] (Panel A) and via model simulations (Panel B). The x-axis on the left plot was relabeled assuming that 5 mEq/kg/day is a normal intake. On both panels, the response of arterial pressure to salt intake is shown for normally controlled AngII (black line) and when plasma AngII is elevated (dashed line). On Panel B a further distinction is added: the response with the latent activation of the sympathetic nervous system, SNS (dashed line) is compared to the response in the absence of the SNS activation (dotted line). The arrow shows the incremental change in slope due to the SNS activation.

We simulate this experiment by generating the quasi-steady states of the system by varying sodium intake from normal to a 5-fold increase. Since plasma osmolarity is dependent on the level of sodium intake, we assume there is a linear dependence of the magnitude of the latent sympathetic activation on sodium intake. It can be expressed as follows:

$$f_{SI} = \frac{J_{NaCl-I-P}}{J_{NaCl-I-P,0}}$$
$$SNA = \alpha \cdot (fSI - 1) \cdot (\frac{\text{AngII}}{\text{AngII}_0} - 1)$$

$$V_{\text{Unstr}} = 8 - 1.1 \cdot SNA$$

$$\Delta d_{AS} = 12 \cdot SNA$$

where $fSI$ is the fractional increase in sodium intake, $SNA$ is the sympathetic nerve activity, $J_{\text{NaCl,I-P}}$ is the current sodium intake and $J_{\text{NaCl,I-P,0}}$ is the normal sodium intake, AngII and AngII$_0$ are the current and normal plasma AngII levels respectively, $V_{\text{Unstr}}$ is the unstressed blood volume, and $\Delta d_{AS}$ is the decrease in extrarenal arteriolar diameter. The coefficient $\alpha$ is the sensitivity of sympathetic activation to its triggers of elevated plasma AngII and sodium intake.

Figure 3.22 shows the three-dimensional surface of the arterial pressure steady states in "High AngII + salt" scenario where salt intake ranges between 1- and 5-fold normal and the sensitivity of sympathetic activation $\alpha$ ranges between 0 and $\frac{1}{4}$.

Figure 3.22: Three-dimensional view of the steady state arterial pressure as a function of sodium intake and sensitivity of the sympathetic system. The left panel shows results of assuming 2-fold elevation of plasma AngII and the right panel shows results under the assumption of normally controlled AngII levels. Here, the sympathetic system is not activated and thus the gradient of arterial pressure is zero in its plane. Sodium excretion which is equal to the sodium intake in steady state is expressed as a fraction of normal sodium intake. Sympathetic sensitivity, $\alpha$, is shown on the other axis. See text for details on line plots.
In Figure 3.22 three specific solutions are shown. First solution (Panel A, dashed line) is obtained by taking $\text{AngII} = 2 \cdot \text{AngII}_0$ and $\alpha = \frac{1}{4}$. Note that when $f_{SI} = 5$, $V_{\text{Unstr}} = 6.9$ and $\Delta d_{AS} = 12$ which were the values chosen for our hemodynamic profile simulation of AngII-salt hypertension (Figure 3.18). Second solution (Panel A, dotted line) is obtained by taking $\text{AngII} = 2 \cdot \text{AngII}_0$ and $\alpha = 0$. It represents the system’s response if the latent activation of SNS does not occur. Finally, the third solution (Panel B, solid line) is obtained by taking $\text{AngII} = \text{AngII}_0$ ($\alpha$ is assumed 0). It represents the normal system response to changes in sodium intake.

When these three solutions are projected on the plane of sodium excretion versus arterial pressure, they depict the pressure-natriuresis phenomenon similar to the one obtained in DeClue’s study (Figure 3.21, Panel B - the line marking is kept the same). The added distinction between pressure-natriuresis curves under the assumptions of present versus absent latent activation of the sympathetic nervous system (dashed vs dotted lines in Panel B) show that the change in slope of the pressure-natriuresis curve cannot be fully attributed to a direct renal control. In other words, pressure-natriuresis curves are a two-dimensional reflection of a complex higher-dimensional dynamics and thus reflect a combination of various direct controls involved in blood pressure regulation. We will discuss the implication of this result in further detail in Chapter 4.
Chapter 4

Conclusions

This thesis presents a mathematical model of long-term blood pressure control which explains how activation of the sympathetic nervous system in AngII-salt model of hypertension can lead to chronic blood pressure elevation without modifying renal excretory function. Prior to the completion of this work and its associated publications, mathematical models of hypertension were built on the assumption that such modification is necessary. These old models stem from work by Guyton and Coleman in 1970’s (GC model) which postulated that there is a direct control of sodium excretion by arterial pressure via complex intra-renal processes, the so-called chronic pressure-natriuresis mechanism. The construct of the GC model is based on two key observations: 1) chronic arterial pressure and sodium excretion are positively correlated, and 2) artificially reducing renal perfusion pressure while simultaneously infusing AngII leads to the development of hypertension. The correlation between pressure and sodium excretion has been observed to have different slopes under various conditions. The GC interpretation of these observations has been that the resulting change in blood pressure must be due to those conditions directly affecting renal ability to excrete sodium and unless renal ability is disabled, hypertension cannot occur. The GC model is built to operate under the assumption of sole renal dominance, i.e. that there is a direct mechanistic effect of arterial pressure on renal sodium excretion.
and this effect must be modified in order to cause all types of hypertension. In order to explain the long-term elevation in peripheral resistance associated with hypertension, the GC model also added a hypothesis that there is a whole-body autoregulation mechanism which converts early elevation of cardiac output into chronic elevation of peripheral resistance.

Our model is based on a different assumption, that renal ability remains unaffected beyond its normal response to AngII, but sympathetic nervous system activity is slowly amplified over time and ultimately drives hypertension via non-renal influences. This assumption represents recent experimental evidence which demonstrates the findings in AngII-salt induced hypertension: 1) sympathetic activity is chronically elevated; 2) blocking sympathetic activity leads to attenuation of hypertension, and 3) renal sympathetic activity is not involved in altering chronic blood pressure. In particular, the new evidence implicates long-term sympathetically-mediated increase in extra-renal resistance and decrease in venous capacitance as the main drivers of hypertension.

These observations are modeled by first representing major well-known physiological mechanisms involved in blood pressure and fluid volume control by incorporating detailed functions of sodium excretion, fluid and solute exchange across tissues, circulatory dynamics, and short-term neural control. This representation is similar to that of the GC model or its later variations, except that it does not include its two key mechanisms: chronic pressure-natriuresis and whole-body autoregulation. In particular, the present model demonstrates renal function which is capable of sensing sodium intake without relying on a single controller. This renal model describes excretory function in a combination of physiologically-based and phenomenological descriptions based on the available experimental knowledge. It is affected by several external controllers, such as hematocrit, plasma protein concentration, plasma osmolarity and arterial pressure. The only direct impact that arterial pressure has on the renal function is modulation of renal blood flow which is buffered by myogenic constriction of afferent arterioles. There are no other effects of arterial blood pressure on renal filtration or reabsorption. The model also includes latent activation of sympathetic nervous system triggered by
increased plasma AngII and sodium. The sympathetic nervous system does not impact renal function directly, but instead modifies two non-renal parameters: extra-renal resistance and venous capacitance.

**Despite the differences in assumptions with the GC model, our model’s predictions agree well with all major classical observations associated with AngII-salt hypertension, including the pressure-natriuresis phenomenon.** The model predicts correct responses to AngII infusion and to sodium intake increases. It produces key qualitative behavior of the hemodynamic profile of salt-sensitive hypertension: a chronic elevation in blood pressure and peripheral resistance, with transiently increased blood volume and cardiac output, both of which later return to near-normal values (Figure 3.18). Finally, the model reproduces the pressure-natriuresis phenomenon. Specifically, it shows that the steady state values of arterial pressure and sodium excretion in the model are positively correlated, and the slope of the correlation is modified by an infusion of AngII just as it is experimentally observed. But we go further to show that these slopes are also affected by the degree of sympathetic activation (see Figure 3.21, Panel B), even though there is no direct control of renal excretory function by the sympathetic nervous system in the model.

**This newly proposed model conclusively demonstrates that AngII-salt hypertension can be maintained without the sole dominance of renal ability to excrete sodium.** This disputes the hypothesis that has been prevailing for more than 50 years. If one were to consider the new model predictions from the standpoint of the GC theory, one would conclude that chronically elevated sympathetic activity is directly affecting renal excretory function. However, this conclusion is inconsistent with our model which excludes renal sympathetic activity contribution. Thus, one has to accept that there is another independent contributor to blood pressure elevation, namely, the sympathetic nervous system.

It is important to note, that **the above observations do not entirely exclude renal involvement in the model.** Only about a half of the total blood pressure response in AngII-salt protocol is due to latent sympathetic activation, while the other
half is due to mechanisms involved during the onset phase of hypertension. Administration of AngII, acting in the opposite of the normal renal function control, does affect renal ability to excrete sodium during the onset phase leading to volume expansion and pressure increase. Yet, even then the kidney is not the sole determinant of blood pressure, as AngII constricts all vessels and thus contributes to the elevation of pressure via a non-renal pathway.

The conclusion that **there are several independently important contributors, such as renal and neural controls, to hypertension development** is not surprising from either physiological or mathematical perspectives. The multifactorial nature of blood pressure control is widely accepted in physiology. Experimental treatments of non-renal pathways, such as baroreflex stimulation, splanchnic denervation, atrial-venous shunts, and weight loss, have been shown to be effective in hypertensive subjects. From a mathematical perspective the conclusion is also natural if one is to expand from the two-dimensional view of hypertension in the pressure-natriuresis plane to a larger-dimensional view of several controllers of blood pressure. The newly proposed model has provided an example of such an approach by showing that the steady state of arterial pressure in our model can viewed as a 3-D function of sodium intake and sympathetic activity shown in Figure 3.22. For a chosen level of sympathetic sensitivity, one can generate a solution from this 3-D surface which projects onto the pressure-natriuresis plane as a pressure-natriuresis curve shown in Figure 3.21. The slope of this curve is only partially explained by AngII effects on renal function during the onset phase of hypertension, while the rest of the change is dependent on the level of sympathetic sensitivity during the maintenance phase. Thus, in our model the **pressure-natriuresis curve, and any other plane projections, is a reflection of a combination of independent control mechanisms and does not imply dominance of any single control.**

This multidimensional view of blood pressure control does not exclude a possibility of a single control mechanism dominating all the others. The GC model and its associated experiments have argued that disrupting renal ability to excrete sodium can cause hypertension. For example, the study by Hall et al. [46] showed
severe blood pressure elevation when renal perfusion pressure was fixed at a constant level and AngII was infused. Another example is the kidney transplantation studies showing that blood pressure often follows kidney. However, what the GC model shows in combination with the present work is that renal dysfunction is sufficient for hypertension development, but is not necessary and experimental studies are supportive. Despite extensive research over several decades, it remains to be shown that renal dysfunction is responsible for the majority of hypertension cases. Instead, several non-renal causes such as sympathetic activation, inflammation, and arterial stiffening, have gathered solid experimental evidence in their support [60, 17, 52, 82, 94].

In its current implementation the model is designed and validated for a specific type of salt-sensitive hypertension, AngII-salt hypertension, and thus is limited in its direct application to a more general discussion of hypertension. AngII-salt protocol is one among many protocols for studying hypertension, including infusion of aldosterone-like substance (DOCA-salt), reduction of renal mass, or by weight-gain (obesity). Moreover, pathways other than neural have also been implicated in hypertension. Thus the model might need be revised, improved, or expanded to reflect the hypotheses of a particular theory. Phenomenological descriptions of renal processes have been used, and thus the short-term dynamics (within minutes of a stimulus such AngII infusion) needs further validation. More detailed and sophisticated renal models already exist in the literature as described in Chapter 3 and could be incorporated into the framework of this model. The model also explicitly excludes sympathetic control of the renal function. This was a fair assumption for studies of AngII-salt protocol, where renal denervation did not impact the outcome and it allowed a more clear emphasis on the extra-renal role of the sympathetic nervous system. However, in other models of hypertension renal sympathetic activity may play an important role and should be added to the model. Finally, improvements can be made even for AngII-salt hypertension. For example, venous compliance, not just the capacitance, is likely to also be diminished as the consequence of the overall increase of sympathetic stimulation of veins. The dynamics of the slow sympathetic response and specific neural signaling pathways require further description but await additional experimental observations.
Future improvements to the model should address the above limitations and perform full global sensitivity analysis of the model which can point to specific critical pathways that should be considered in further expansion of the model. We have illustrated a simple example toward this approach by performing a global sensitivity analysis on the circulatory sub-model. This analysis shows that the key factors which impact blood pressure are stressed volume, venous compliance, extra-renal resistances, and pressure in renal peritubular capillaries. All of these factors can be modulated by renal and neural influences, and some can be affected by other controls such as inflammatory processes and vessel stiffening. This finding means that the control of these factors must be included in the modeling.

Hypertension is a multifactorial disease with a host of factors that can influence its development and maintenance. In this dissertation, effort was focused on specific neural pathways, and thus this mathematical model does not address many of the larger clinical questions surrounding the mechanisms of hypertension. However, the model demonstrates how the integrative nature of blood pressure control can be elucidated in a model if the hypothesis of the chronic pressure-natriuresis mechanism is omitted. Relaxing this hypothesis does not deny renal involvement in hypertension, but allows equal representation of other important regulatory mechanisms. This finding may be of particular interest, for example, to the on-going efforts of multi-scale modeling of body fluid homeostasis and blood pressure regulation. The aim of these ongoing efforts is to "provide an open-source multi-resolution modeling environment that will permit, at a practical level, a plug-and-play construction of integrated systems models using lumped-parameter components at the organ/tissue level while also allowing focus on cellular- or molecular-level detailed sub-models embedded in the larger core model" [101]. The core model is largely based on the GC model, which has now been shown to limit the ability of these extensive efforts to identify non-renal pathways of hypertension. A mathematical model which is able to distinguish between pathways depending on the experimental data to which it is applied, is a more accurate representation of the complex regulation of long-term blood pressure control, and will enable future scientists, clinicians, and mathematicians to pursue novel therapeutic
strategies to treat patients with hypertension.
References


[47] KM Hallow, A Lo, J Beh, M Rodrigo, S Ermakov, S Friedman, H de Leon, A Sarkar, Y Xiong, and R Sarangapani. A model-based approach to investigating


[94] MP Schlaich, MD Esler, GD Fink, JW Osborn, and DE Euler. Targeting the


Appendix A

Renal physiology

A.1 Renal functions

The kidneys are some of the most complex organs in the body. They possess an intricate anatomical structure, and are under precise physiological control by an astounding number of various factors. The kidneys play the central role in regulating balance of water and solutes, and the removal of waste products from the blood. Table A.1 shows average daily values of sodium and water gains and losses in human adults, under normal physiological conditions. However, these averages can fluctuate dramatically as a result of changes in diet, water intake, exercise, and the environment. This can disrupt total body sodium and water balance which is fundamental to basic cellular processes, and ultimately impacts many organ functions. The kidneys serve to prevent these fluctuations from happening by matching gains and losses over an extremely wide range and doing so quickly and precisely. For example, in human adults urinary water excretion can match intakes ranging between 0.4 L/day to 25 L/day. Urinary sodium excretion can adjust to sodium intakes ranging from 0.05 g/day to 25 g/day. The goal of this chapter is to describe the key anatomical and physiological features underlying renal control of sodium and water excretion.

Human kidneys receive about 20% of the cardiac output (at rest) and filter about 120
ml/min of plasma which amounts to about 170 l/day. Such large filtration rate necessitates almost complete reabsorption of key solutes back into circulation. Human kidneys reabsorb about 99% of filtered water and sodium. Most of the filtered water, ~ 85%, is reabsorbed passively due to active reabsorption of sodium, while the remaining portion is under independent control. In humans, the urine flow rate varies between 0.5 to 2.5 L/day and the urine osmolality varies between 300 mOsm/L and 1400 mOsm/L. The variation of urine flow rate and osmolality are the key features that allow independent maintenance of both water and sodium homeostasis over wide range of intakes.

Description of the human renal anatomy and physiology will be the focus of the discussion. However, some rodent anatomy and physiology will also be provided because much of the experimental data was collected in that animal model, and there are important differences between human and rodent renal functions.

### A.2 Anatomic structure of the kidneys

#### A.2.1 Gross features

The two kidneys lie in the back of the abdominal wall, outside the abdominal cavity. The adult human kidney weigh about 150 grams and is approximately 11 cm by 6 cm by 3 cm.

<table>
<thead>
<tr>
<th>Total intake</th>
<th>Sodium</th>
<th>Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>10.5 g</td>
<td>1000 ml</td>
</tr>
<tr>
<td>Liquids</td>
<td>-</td>
<td>1200 ml</td>
</tr>
<tr>
<td>Metabolically produced</td>
<td>-</td>
<td>350 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total loss</th>
<th>10.5 g</th>
<th>2550 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and lungs</td>
<td>-</td>
<td>900 ml</td>
</tr>
<tr>
<td>Sweat</td>
<td>0.25 g</td>
<td>50 ml</td>
</tr>
<tr>
<td>Feces</td>
<td>0.25 g</td>
<td>100 ml</td>
</tr>
<tr>
<td>Urine</td>
<td>10 g</td>
<td>1500 ml</td>
</tr>
</tbody>
</table>

Table A.1: Average daily gains and losses of sodium and water for an average human [110]. A portion of the sodium may also be stored in inactive form in skin and bones, which represents another means of sodium loss.
in size. The kidney is surrounded by a tough fibrous capsule and is supplied by a single renal artery, a renal vein, the lymphatics, and a nerve plexus. There are two distinct regions of the kidney (Figure A.1): an outer region (the cortex) and an inner region (the medulla). In humans, the medulla is divided into 8-18 conical masses (the renal pyramids), with the apexes extended toward the renal pelvis to form a papilla. The cortex forms a cap over a base of each renal pyramid and extends downward between the pyramids. The ureters originate from the lower portion of the renal pelvis and descend into the bladder. In rats, the medulla has a single renal pyramid.

At the top of each kidney sits the adrenal gland which is mainly responsible for releasing several hormones: aldosterone, cortisol, androgens, epinephrine, and norepinephrine. These hormones regulate various functions, but aldosterone in particular plays a major role in regulating renal sodium excretion and will be discussed more in detail in a later section of this chapter.

A.2.2 Nephron structure

There are several anatomical structures that play an important role in urine formation: vasculature, renal corpuscle, renal tubule, collecting duct system, interstitium, and two types of nephrons. The functional unit of the kidney is the nephron. A human kidney contains about a million nephrons; a rat kidney contains about 30,000 nephrons. Each nephron consists of a filtering component called the renal corpuscle, and a renal
Figure A.2: Basic structure of a nephron and renal interstitium.

tubule (Figure A.2). The renal corpuscle forms a filtrate from blood, free from blood cells and proteins. The filtrate then flows through the renal tubule, where water, sodium, and substances are judiciously reabsorbed back into the circulation. All nephron tubules eventually merge into the collecting duct system which drains the remaining filtrate into the bladder.

The blood is supplied to the kidney via a renal artery which arises off the side of the abdominal aorta, immediately below the superior mesenteric artery. The blood is carried away via a renal vein into the ascending vena cava. Once the artery enters the kidney near the renal pelvis it branches off into segmental arteries which travel up towards the cortex in the space between renal pyramids (Figure A.1) and then branch into arcuate arteries which run between the cortex and medulla. They further branch off at right angles into interlobular arteries which rise into the cortex and continually
branch off into the afferent arterioles that supply the renal corpuscles (Figure A.2). The venous structure is similar and lies adjacent to the arterial structure.

Each renal corpuscle is supplied with blood via an **afferent arteriole**, which feeds into a compact cluster of capillaries, called the **glomerular capillaries**, or **glomerulus** (Figure A.3). The blood is then filtered into the renal tubule via a **Bowman capsule**, which is a fluid-filled capsule surrounding the glomerulus. The remaining blood then flows through another arteriole, called the **efferent arteriole**, and then another set of capillaries, called **peritubular capillaries**, and into the venous system. The peritubular capillaries wind around the renal tubule and receive the reabsorbed quantities back into the general circulation.

The renal tubule consists of three major components (Figure A.2): the **proximal tubule**, the **loop of Henle**, and the **distal tubule**. The proximal and distal tubules lie in the cortex and are connected by the loop of Henle which is a hairpin-like tubule diving down into the medulla. The loop of Henle can be further subdivided into the **descending limb of Henle**, the **thin ascending limb of Henle**, the **thick ascending limb of Henle**. The end of the thick ascending limb on Henle of each renal tubule passes between the afferent and efferent arterioles of that same nephron. At that location there is a specialized patch of cells in the wall of the ascending limb called **macula**
densa (Figure A.3), and a patch of cells in the wall of the afferent arteriole called juxtaglomerular (JG) cells. The combination of these two groups of cells is known as the juxtaglomerular apparatus (JGA). Renal nerve endings innervate smooth muscle of the afferent arteriole and juxtaglomerular cells. The JGA plays an important role in control of sodium excretion which will described in a later section.

Once the filtrate passes through the distal tubule it flows into the collecting duct system and gradually merges with filtrates from other nephrons. The collecting ducts continue to merge and pass through the medulla to deliver the filtrate to the renal pelvis (Figure A.2). The renal pelvis is continuous with the ureter draining the kidney into the bladder.

A.2.3 Two populations of nephrons

The renal corpuscles of all nephrons are located in the renal cortex, but the loop of Henle of each nephron descends into renal medulla at varying depths. The length of the loop of Henle allows to differentiate two major populations of nephrons in the kidney: those with short loops of Henle, termed cortical or superficial nephrons, and those with long loops of Henle, termed juxtamedullary nephrons (see Figure A.2). Some of the cortical nephrons have loops of Henle which remain fully in the cortex. About 85% of nephrons are cortical. This proportion of cortical to juxtamedullary nephrons, as well as the distribution of blood flow between them, might be playing an important role in control of sodium excretion. In short, cortical nephrons carry the majority of bulk reabsorption while juxtamedullary nephrons play a key role in concentrating inner medulla and thus allow fine-tuning of reabsorption.

There are two more important features that differentiate cortical and juxtamedullary nephrons. First, cortical nephrons do not have the thin ascending limb, so that the descending limb transitions directly into the thick ascending limb; their renal corpuscles are also located in the upper cortex, while juxtamedullary corpuscles are located in the lower cortex, near the medulla. Second, the peritubular capillaries of a cortical nephron surround its proximal and distal tubular segments, so that the capillaries remain
entirely within the cortex. In contrast, the peritubular capillaries of a juxtamedullary nephron, called the **vasa recta**, dive into the medulla following the nephron’s loop of Henle. Efferent arterioles of juxtamedullary nephrons are larger in diameter and possess thicker walls and smooth muscle layer than the efferent arterioles of cortical nephrons. The substances reabsorbed from the proximal and distal segments of a juxtamedullary nephron are picked up by the peritubular capillaries of the nearby cortical nephrons.

Sometimes a third population of nephrons is defined, the midcortical nephrons. The glomeruli of these nephrons are located in midcortex, their renal tubules are similar to those of juxtamedullary nephrons (i.e. contain the thin ascending limb), although they do not dive as deep into the medulla. However, the peritubular capillaries of the midcortical nephrons reside in the cortex only, similar to the cortical nephrons.

### A.2.4 Interstitium

The cortex and the medulla regions of the kidney have different osmolar properties. The cortex has constant osmolality approximately equal to that of plasma. The medulla has a significant osmolality gradient so that osmolality is about 4 times higher at the papillae in humans (9 times in rats). This osmotic gradient is the key factor in kidney’s ability to regulate water and sodium loss. The gradient is maintained even in diuresis, although it is diminished in magnitude relative to anti-diuresis.

The boundary between the renal cortex and medulla is difficult to identify, but is usually associated with the location of the branching of interlobular arteries (Figure A.2). The renal medullary interstitium contains fluid, microfibrils, extracellular matrix, and interstitial cells. The renal medulla can be segmented into an **inner medulla** and **outer medulla**, and the outer zone can be further subdivided into an **inner stripe** and an **outer stripe**. This segmentation is based on the types of nephron segments that can be found in each zone. The inner medulla contains both descending and ascending thin limbs and large collecting ducts. In the inner stripe of the outer medulla, thick ascending limbs are present as well. The outer stripe of the outer medulla contains the terminal segments of proximal tubules. The remaining portions of the nephron
(the renal corpuscle, the proximal and distal tubules) lie in the cortex. As will become evident later, this subdivision of the medulla into zones that contain a subset of tubules with specific permeability and transport features allows understanding of the processes that lead to the creation and maintenance of medullary osmolality gradient.

The blood supply of the medulla is derived only from the vasa recta, while the blood supply of the cortex is derived from the peritubular capillaries of cortical nephrons. The cortex contains abundant peritubular capillaries and receives a high effective blood flow, so that the reabsorbed water and solutes are immediately returned to the general circulation. However, in the medulla, capillaries are more sparse and arranged in a parallel fashion. It provides a means of reducing the effective blood flow to the medulla while maintaining a high absolute perfusion rate. It slows down the removal of reabsorbed solutes from the medulla and thus enables its osmotic gradient, the essential feature of urine concentration discussed below. Medullary blood flow constitutes only 10-15% of total renal blood flow and is derived from 7-18% of glomeruli (depending on the species). The capillary plexus in the outer medulla is considerably more dense and much better perfused than the plexus in the inner medulla and the inner stripe of the outer medulla receives the largest portion of the medullary flow.

Fluid and plasma proteins can leave the renal interstitium via either capsular lymphatics or hilar lymphatics. Knowledge of the distribution of the lymphatics within the kidney is limited. The lymphatics drain mostly the cortical interstitium and are embedded in the loose connective tissue around the renal arteries and travel along the interlobular and arcuate arteries. The medullary interstitium may not have intramedullary lymphatics at all and drain either directly into ascending vasa recta or to the interlobar lymphatics. The role of the lymphatics is usually not considered in the discussions of renal function.

A.3 Basic renal processes

In healthy people, urinary sodium excretion changes to match sodium intake within 1 to 3 days. The response is so precise that the total body sodium varies just a few percent
despite wide fluctuations in sodium intake and occasional non-renal losses, e.g. sweating. However, there are no known receptors of total body sodium. The understanding and search for particular sodium sensors is an area of active research. Currently it is believed that renal control of sodium excretion is the result of an indirect sensing of effects of sodium. Most well-understood control signals to the kidney are triggered by changes in extracellular fluid (ECF) and their effect on cardiovascular pressures, as well as changes in cell and plasma osmolalities. Since NaCl constitutes nearly 90% of ECF and is important to many cellular and organ functions, it seems reasonable to assume that the precise control of NaCl is likely to be tied to the accurate sensing of ECF and osmolality changes.

Urine formation begins with the glomerular filtration of protein-free, cell-free fluid into the renal tubules. As the filtrate flows through the tubules it is reabsorbed back into the circulation. The process is called tubular reabsorption and it varies for each segment of the tubule as well as the substance being reabsorbed. Some substances are also secreted into the filtrate or metabolized by the tubular cells. Thus, the amount of water and sodium excreted in the urine is the amount filtered minus the amount reabsorbed (neither substance is secreted). The kidney’s ability to maintain total body water and sodium balance is determined by its urine concentrating ability which is driven by the medullary interstitial gradient. The next few sections describe each of the three key renal processes in detail.

A.3.1 Glomerular filtration

The glomerular filtrate contains no blood cells or proteins, but contains all other plasma substances in essentially the same concentration as in plasma. The cells and proteins are excluded for two reasons. First, the fenestrations in the walls of glomerular capillaries are not large enough for high-molecular-weight substances to pass through. Second, the filtration pathways are negatively charged and thus oppose the movement of the negatively charged plasma proteins. The exclusion of proteins creates an osmotic gradient.
across glomerular membrane, which becomes crucial for proper filtration and reabsorption of substances.

Figure A.4: A: Summary of glomerular and peritubular dynamics with representative values for humans. Arrows show direction and relative amount of water moved across capillary membranes. While the hydrostatic glomerular capillary pressure remains relatively constant, the colloid osmotic pressure increases from the afferent to the efferent end, as the protein concentration increases. The increased osmotic pressure in the peritubular capillaries creates necessary pressure gradient for water reabsorption from the interstitium. The osmotic pressure returns to almost normal plasma values at the terminal end of the peritubular capillaries, since almost all filtered water is reabsorbed. B: Two cases of colloid osmotic pressure profiles along glomerular capillaries. Filtration equilibrium (Π, solid line) can be achieved at low plasma flow rate, while at high plasma flow rates filtration pressure remains positive at the efferent end (Π, dashed line). Notation: Π, colloid osmotic pressure; P, hydrostatic pressure; G, glomerular capillaries; B, Bowman space; C, peritubular capillaries; I, cortical interstitium.

Filtration across the glomerular capillary walls, called the **glomerular filtration rate (GFR)**, is determined by the opposing hydrostatic and osmotic forces and the filtration coefficient of the glomerular membrane (Figure A.4):

\[
GFR = K_G(P_G - P_B - \Pi_G)
\]  
(A.1)

where \(K_G\) is the glomerular filtration coefficient, \(P_G\) is the glomerular hydrostatic pressure, \(P_B\) is the opposing hydrostatic pressure in Bowman’s capsule, and \(\Pi_G\) is the average osmotic pressure in the glomerular capillaries. In humans, filtration continues
throughout the entire length of the glomerular capillaries and there remains a positive net filtration pressure at the efferent end of the glomerular capillaries. In rats, filtration equilibrium maybe achieved before the efferent end so the equation (A.1) has to be revised to include plasma flow rate which affects the distance to the filtration equilibrium.

The hydrostatic glomerular capillary pressure is controlled via independent adjustments of the afferent and efferent arteriolar resistances. As the fluid is filtered out, the plasma protein concentration and, hence, the osmotic force, increases toward the efferent end. The hydraulic permeability of the glomerular membrane may also affect the filtration although there is no clear consensus on its physiological regulation.

Similarly, reabsorption of water by the peritubular capillaries from the surrounding interstitium is determined by the opposing hydrostatic and osmotic forces and the filtration coefficient of the peritubular walls:

\[ PRR = K_R(P_I - P_C - (\Pi_I - \Pi_G)) \]  

where \( PRR \) is the peritubular reabsorption rate, \( K_R \) is the reabsorption coefficient, \( P_C \) is the peritubular hydrostatic pressure, \( P_I \) is the opposing hydrostatic pressure in the surrounding interstitial, \( \Pi_G \) is the average osmotic pressure in the peritubular capillaries, and \( \Pi_I \) is the opposing interstitial osmotic pressure.

While the reabsorption of water and solutes from the interstitium into the peritubular capillaries happens by bulk flow driven by Starling forces (i.e. the movement of fluid due to hydrostatic and oncotic forces), the reabsorption from the renal tubules into the interstitium is more complex and described in detail in the following section.

A.3.2 Tubular reabsorption

One of the major functions of the kidney is to eliminate waste products from the blood. Thus the filtered load is enormous compared to the total body values. Since the filtration happens by bulk flow it would lead to the loss of the important substances, unless reabsorption rates were almost equally high. The reabsorption of most useful plasma
components such as water and sodium is almost complete, so that only a very small fraction of the filtered load is excreted in the urine. Thus, the reabsorption of filtrate components, termed **tubular reabsorption**, plays a critical role in urine formation.

Unlike glomerular filtration, tubular reabsorption does not happen by bulk flow, as there are inadequate pressure differences and permeability of the tubular membranes. Instead, the reabsorption happens either by diffusion or mediated transport. Once a reabsorbed substance moves from the tubular lumen to the interstitial fluid it is picked up by the peritubular capillaries. This movement occurs by a combination of diffusion and bulk flow, driven by the capillary Starling forces (Figure A.4).

The majority of reabsorption of both water and solutes happens in the proximal tubule (Table A.2 and Figure A.5). Henle’s loop also reabsors relatively large quantities of major ions, and some water. Thus the proximal portion of the tubule (near macula densa) does the major reabsorption work, removing about equal portion of water and sodium so that the filtrate is nearly isosmotic when it arrives to the distal portion of the tubule. The distal segments of the nephron (distal tubule and collecting ducts) perform fine-tuning of the reabsorption of most substances. Thus, most homeostatic controls act upon the distal segments of the tubule.

<table>
<thead>
<tr>
<th>Segment</th>
<th>Inflow ml/min</th>
<th>Reabsorbed flow as a fraction of GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>The proximal tubules</td>
<td>125</td>
<td>0.64</td>
</tr>
<tr>
<td>The descending limb of Henle</td>
<td>45</td>
<td>0.16</td>
</tr>
<tr>
<td>The ascending limb of Henle</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>The distal tubules</td>
<td>25</td>
<td>0.10</td>
</tr>
<tr>
<td>The collecting ducts</td>
<td>12</td>
<td>0.08 (0.02..0.09)</td>
</tr>
<tr>
<td>The bladder</td>
<td>1 (10..0.4)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table A.2: Normal reabsorption rates within a human nephron (based on [42] and [2]). Values in parentheses reflect the range of values in diuresis (large water loss) and anti-diuresis (restricted water loss). Note that the adjustment of water loss happens almost entirely in the final tubular segments - the collecting ducts.

Tubules may also move substances directly from peritubular capillaries into the tubular lumen by a process termed **tubular secretion**. It is usually coupled in some way to the reabsorption of sodium. The most important substances secreted by the
tubules are hydrogen ions, potassium, and creatinine. Secretion helps improve the filtering efficiency of the kidney. However, since it plays a minor role compared to other mechanisms at play, it will not be discussed further.

The water and solutes can be transported across a tubular wall by either tight junctions between the cells or through the epithelial cells themselves. They first move from the tubular lumen into the cell across its **luminal membrane**, and then from the cell into the interstitium across its **basolateral membrane**. In all sodium-reabsorbing tubular segments, sodium reabsorption happens via the active transport of sodium out of the epithelial cells into the interstitial fluid. This transport is achieved by Na/K-ATPase pumps in the basolateral membrane of the cells. Active transport also ensures low sodium concentration within the cells and thus encourages sodium diffusion from the tubular lumen into the cells across their luminal membrane. The mechanism of sodium movement across the luminal membrane, however, varies from segment to segment. For example, in the proximal tubule it occurs either by cotransport with an organic molecule (such as glucose) or by countertransport with hydrogen ions. In the cortical collecting duct, the diffusion occurs through sodium channels. Different types of transport allow reabsorption of various substances and flexibility in sodium excretion control.

As sodium and other solutes are removed from the tubular lumen, the local (near the epithelial cell) osmolality in the lumen lowers and local osmolality of the interstitial fluid rises. Water diffuses passively by osmosis from the lumen into the interstitial fluid either across the epithelial cells or tight junctions. Water movement can happen only if the epithelium is permeable to water. The water permeability varies across different tubular segments and depends largely on the presence of **aquaporins**, which are the water channels in cell membranes. The last portions of renal tubules, the cortical and medullary collecting ducts, have varying water permeability which is controlled by **vasopressin** (also called antidiuretic hormone, or ADH), a peptide hormone secreted by the posterior pituitary. Vasopressin stimulates the insertion of aquaporins into the luminal membrane of epithelial cells.
A.3.3 Urine concentration

The human kidney can produce urine of varying osmolality, as high as 1400 mOsm/L, but it is typically around 600 mOsm/L. This is 2-5 times higher than the plasma osmolality of 290 mOsm/L. The kidney's ability to create an interstitial fluid osmolality gradient from cortex to the inner medulla is the key to urine concentration and maintenance of total body water and sodium balance. Let us for now assume that the interstitial gradient is maintained and consider how the reabsorption of sodium and water is handled along different tubular segments. Two extreme cases of large water loss (diuresis) and restricted water loss (anti-diuresis) will be considered to illustrate the importance and contribution of various segments. Water and sodium permeabilities of all renal tubule segments as well filtrate osmolality and interstitial osmolality gradient are schematically shown in Figure A.5. Table A.2 shows relative reabsorption rates of water in each tubular segment.

As mentioned earlier, tubular segments prior to macula densa site are responsible for bulk water and sodium reabsorption, while the distal segments fine tune the excretion rates. Thus, the earliest site along the nephron where differences in tubular fluid osmolality between diuresis and anti-diuresis can be detected is towards the end of the distal tubule. Here, the tubular fluid is isosmotic with plasma during anti-diuresis and hypotonic during diuresis. In the final segment of the inner medullary collecting duct the tubular fluid osmolality remains hypotonic during diuresis, and rises to levels above plasma osmolality during anti-diuresis. The chief site for water dilution is the loop of Henle and this dilution process happens in either diuresis or anti-diuresis. Further urine dilution or concentration occurs in the collecting ducts, where it is mostly controlled by vasopressin. Sodium and water permeability properties of each tubular segment are briefly described below.

The proximal tubule is a site of major isosmotic reabsorption; it actively reabsorbs about 60-70% of sodium and a similar portion of water by osmosis. The descending limb of the loop of Henle is almost completely impermeable to sodium and allows passive reabsorption of water only as it descends into the medullary regions of progressively
Figure A.5: Summary of water and sodium transport in a juxtamedullary nephron. The filtrate osmolality at the proximal end of each tubular segment is shown in white boxes. The interstitial osmolality gradient is shown in the axis on the left. Two scenarios, of a diuresis (large water loss) and anti-diuresis (restricted water loss) are shown. Majority of water control is done in medullary collecting ducts and is closely linked to the inner medullary osmolality. See also Table A.2.

Increasing osmolality. On average, by the end of the loop about 15% of filtrate fluid is reabsorbed in this segment and the filtrate osmolality is increased about 4-fold. The permeability properties depend on the depth of the limb in the inner medulla and whether it belongs to a superficial or a long-looped nephron. The permeability is mostly driven by the presence of aquaporin water channels, which are expressed along the length of the descending limb in gradually decreasing numbers. The epithelium of descending limbs in the outer medulla has the highest aquaporin content and thus highest water permeability. The water permeability of descending thin limbs in the middle part of the inner medulla is about 42% that of outer medullary thin descending limbs. These changes in water permeability are accompanied by a progressive increase in sodium permeability, although it is considerably less than that of the ascending thin limb. Superficial nephrons have a short descending limb within the inner stripe of the outer
medulla. A segment of the descending limb right before it joins the thick ascending limb has no aquaporin channels and its water permeability is essentially zero.

The thin ascending limb has very high permeability to NaCl and almost zero water permeability. Passive reabsorption of Na happens mostly via paracellular Na transport, and Cl is reabsorbed via transcellular transport. Active transport of Na is almost nonexistent, adding up to only about 2% of Na reabsorption by all thin ascending limbs. The thick ascending limb (TAL) is water impermeable and reabsorbs about 30% of filtered sodium via active transport. This is a critical component of the renal countercurrent multiplication system, a specific mechanism which creates and maintains the required medullary concentration gradient. The TAL begins after the ascending limb of long-looped nephrons and after the aquaporin-poor segment of short-looped nephrons. The TAL reaches into the renal cortex, near the parent glomerulus, and joins the distal tubule.

The distal convoluted tubule (DCT) provides the final fine-tuning of urinary sodium excretion. The DCT is located in the cortex and continues to actively transport sodium with minimal loss of water (in the absence of vasopressin). Its regulation of sodium reabsorption plays a critical role in controlling the amount of sodium excretion. It reabsorbs about 7-10% of filtered NaCl. Eventually the hypotonic filtrate enters the collecting duct which starts to descend into the hyper-concentrated medulla once again where the final fine-tuning of water excretion is done. The duct walls are impermeable to sodium and their permeability to water is strongly influenced by vasopressin, allowing for a wide range of water reabsorption control. Water is passively drawn out into the medullary interstitium via aquaporin channels. The medullary collecting duct is always slightly permeable to water, even in the absence of vasopressin.

Although the previous sections have adequately described how the kidney regulates sodium and water excretion and absorption, it is important to understand that tubular wall permeabilities and transport properties can be adjusted via various mechanisms. These include mechanistic, hormonal, or neural factors and are described in more detail in later sections. The next few sections deal with the mechanisms behind the interstitial osmolality gradient which ultimately controls urine concentration.
Table A.3: Composition on plasma, papilla, and urine during diuresis and anti-diuresis in rats (in mmol/L) [93].

<table>
<thead>
<tr>
<th>Component</th>
<th>Plasma</th>
<th>Papilla</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuresis (urine flow ≃ 192µL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>138</td>
<td>159</td>
<td>5</td>
</tr>
<tr>
<td>Urea</td>
<td>4.5</td>
<td>34</td>
<td>23</td>
</tr>
<tr>
<td>Osmolality</td>
<td>304</td>
<td>572</td>
<td>59</td>
</tr>
<tr>
<td>Anti-diuresis (urine flow ≃ 5µL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>145</td>
<td>417</td>
<td>148</td>
</tr>
<tr>
<td>Urea</td>
<td>4.4</td>
<td>605</td>
<td>946</td>
</tr>
<tr>
<td>Osmolality</td>
<td>314</td>
<td>1832</td>
<td>1805</td>
</tr>
</tbody>
</table>

A.3.4 Interstitial osmolality gradient

The axial osmolality gradient in the renal medulla is composed of gradients of several solutes, mostly NaCl and urea. In the outer medulla the gradient is primarily maintained by the increase in NaCl concentration. In the inner medulla the gradient is mostly due to the increase in urea concentration. In the steady state there is mass balance for every substance that enters and leaves the medulla via tubules or blood vessels. However, during physiological perturbations the medullary osmotic gradient can change due to transient accumulation or washout of solutes (e.g. see differences between diuresis and anti-diuresis shown in Figure A.5 and Table A.3). In the following, we discuss the well-understood mechanisms contributing to the development of the medullary osmotic gradient (see summary in Figure A.6) and then briefly address remaining open questions.

Generation of NaCl gradient in the renal outer medulla

The renal outer medulla contains descending and thick ascending portions of juxtamedullary nephrons, entire loops of Henle of the cortical nephrons, and segments of collecting ducts and vasa recta (see Figure A.2). Thick ascending limbs actively pump sodium into interstitium, while descending limbs and collecting ducts allow only water movement across their walls. The vasa recta is highly permeable to both sodium and water. These varying permeability properties and parallel arrangement of vessels play an important role as described below (see also to Figure A.6).
Figure A.6: Water, NaCl, and urea transport responsible for the creation of the medullary osmolality gradient during anti-diuresis. In the outer medulla the gradient is created by the active NaCl transport (green/gray solid arrows) from thick ascending limbs to interstitium. Most of the sodium is trapped via a countercurrent exchange in the vasa recta (green striped arrows). In the inner medulla gradient can be further enhanced by urea accumulation. During anti-diuresis, vasopressin-induced water reabsorption in the collecting ducts leads to a significant increase in filtrate’s urea concentration and urea diffusion into the interstitium (purple-dotted arrows). Most of the urea is recycled through the distal portion of the nephron and some is trapped via a countercurrent exchange in the vasa recta. While solutes can accumulate in the interstitium without significant impact on volume, water outflow (solid black arrows) is tightly matched to inflow to prevent excessive swelling or shrinking of the kidney. The tight water balance allows to reduce solute washout from the interstitium.

The NaCl gradient in the renal outer medulla is developed due to the deposition of NaCl in excess of water. The solute is delivered by the water impermeable thick ascending limb which actively pumps NaCl into the interstitium. At slow enough rates of medullary blood flow the solute is not fully removed and thus starts to accumulate in the medulla. The parallel arrangement of vasa recta also allows sodium re-circulation. The descending blood flow is concentrated by diffusive influx of NaCl and blood flowing toward the cortex in ascending vasa recta is diluted by diffusive efflux so that NaCl is trapped and recycled in the medulla. This movement from ascending to descending limbs is called countercurrent exchange.
The interstitium is also being diluted with water drawn from descending limb, collecting duct, and descending vasa recta via osmosis. However, while solutes can accumulate in the interstitium without a major effect on renal volume, water amount changes could cause significant swelling or shrinking. Thus water movement into the interstitium is closely matched by water removal via vasculature. This minimizes dilution of the hyperosmotic interstitium. Loss of water from the descending vasa recta results in higher osmolality of blood delivered to the inner medulla and reduced volume flow which reduces the tendency to dilute the inner medullary interstitium. The ascending vasa recta picks up water from the interstitium due to its high osmolality and high oncotic pressure (see Figure A.4). Thus the countercurrent exchange of water prevents blood from diluting the inner medulla.

The osmotic gradient might be further optimized by shunting of water from descending to ascending vasa recta in vascular bundles and further reducing blood flow rate to the deep medulla. The short loops of superficial nephrons, which make a turn in the outer medulla may also contribute additional concentrating power. The final segment of the descending limb of short-looped nephrons lacks water channels and thus do not dilute nearby interstitium while its nearby thin ascending limb continues to concentrate the interstitium by actively pumping out NaCl.

**ACCUMULATION OF UREA IN THE RENAL INNER MEDULLA**

As indicated above, the inner medullary osmolality can almost double during antidiuresis (Table A.3). The inner renal medulla contains only thin portion of the ascending limbs of long-looped nephrons. They have little to no capacity for active NaCl transport, thus it cannot account for the inner medullary osmolality gradient. Instead, the gradient is driven by urea accumulation which is also achieved by a process of solute recycling with the help of parallel flows in the vasa recta.

Normal plasma concentration of urea is small (about 5 mmol/L) and the main purpose of urea is to transport and excrete excess nitrogen. Thus, once urea is filtered into the renal tubules, a large portion of it is excreted with urine and another significant portion may be trapped in the inner medulla instead of being returned to the circulation.

The urea accumulation in the inner medulla is mainly due to a very high urea
permeability of the medullary collecting ducts and the bottom portion of the loop of Henle which allows its recycling within the distal portion of the nephron (Figure A.6).

Let us briefly describe how this phenomenon occurs. Urea is first filtered into the nephron at a low concentration equal to that of plasma (about 5 mmol/L). About half of the filtered load is reabsorbed in the proximal tubule and the rest flows down to the bottom of the loop of Henle. The urea concentration of the filtrate increases due to water loss in the urea-impermeable descending limb (about 15 mmol/L). At the bottom of the loop of Henle the interstitial urea concentration is significantly higher luminal one (about 500 mmol/L) which together with high wall permeability leads to urea secretion into the loop of Henle. This results in restoring almost all of the filtrate’s urea content. The remaining portion of the nephron is fairly impermeable to urea until the very last segment, the inner medullary collecting duct, where it arrives at very high concentrations, especially during anti-diuresis and thus significant water reabsorption in the collecting ducts. When the luminal urea concentration exceeds that of the surrounding interstitium passive reabsorption from the inner medullary collecting ducts raises interstitial gradient and drives urea secretion in the thin limbs. Thus, a large portion of the urea load is recycled within the nephron. Normally about 15-30% of the originally filtered urea is excreted in the urine.

Vasa recta is also highly permeable to urea and thus has a potential of washing out the inner medullary gradient. The washout is mitigated via several pathways. First, some of the urea is recycled between the descending and the ascending vasa recta limbs. The blood flow to the region (the descending recta flow) is reduced by the osmotic gradient in the outer medulla as well as shunting of water through vascular bundles. The ascending vasa recta flow, however, is higher, especially during anti-diuresis when water reabsorption is elevated. High urea permeability of the vasa recta equalizes the concentration between the two limbs and thus traps some of the urea (Figure A.6). Second, a portion of urea is picked up from the ascending vasa recta by the thick ascending limbs. Third, in the outer stripe of the medulla high urea permeability of thick ascending limbs and relatively attenuated effective blood flow allow urea transfer to neighboring proximal tubules. Finally, a portion of the urea may be extracted from
vasa recta in the outer medulla by the descending limbs of the short loops of Henle. The importance of this last pathway is still being debated.

**Remaining open questions**

While the mechanisms behind outer medullary interstitial gradient have been confirmed via modeling and experimental data, the urine concentrating mechanism in the inner medulla remains controversial despite decades of investigation [64]. The passive mechanism as described above is critically dependent on tubular permeabilities to NaCl and urea. However, mathematical predictions based on measured values of urea permeabilities have been unable to predict a significant osmolality gradient. Several alternative hypotheses have been proposed, such as the impact of anatomical proximity of different tubular segments and vasculature, the effect of muscular contractions of pelvic wall, and the role of other solutes. Another not completely understood phenomenon is the origin of the small NaCl gradient in the inner medulla. The mathematical modeling of inner medullary interstitial gradient remains an area of active research.

### A.4 Control of filtration rate

As described above, sodium excretion is the net difference of sodium filtration and sodium reabsorption, both of which can be varied via intrinsic and extrinsic controls. In the following sections we discuss major known controls of sodium and water reabsorption. Later, we will combine these pathways of sodium control into one picture of the cascade of the events triggered in response to an increased sodium intake. The first step in sodium and water excretion process is the glomerular filtration rate (GFR). As discussed in A.3.1, it has four primary determinants: transcapillary hydrostatic pressure difference \((P_G - P_B)\), glomerular filtration coefficient, colloid osmotic pressure \((\Pi)\) at the afferent end, and the renal blood flow (Figure A.7). The effect of the latter is seen in cases of low flow rate when the filtration equilibrium is achieved. It can be understood by deriving GFR from the following facts. First, protein is conserved during filtration and thus \(Q_A \cdot c_A = Q_E \cdot c_E\), where \(Q\) and \(c\) are the plasma flow rate and protein concentration at the afferent (A) and efferent (E) ends of glomerular capillaries,
respectively. Second, colloid osmotic pressure is almost linearly proportional to protein concentration: $\Pi \simeq ac$. Third, at filtration pressure equilibrium $\Pi_E = P_G - P_B$. Thus, we get

$$GFR = Q_A(1 - \frac{c_E}{c_A}) \simeq Q_A(1 - \frac{\Pi_A}{P_G - P_B})$$

GFR varies linearly with the plasma flow rate only at low values of flow, when the filtration equilibrium is achieved, which is often observed in rat kidneys or severe cases of renal dysfunction in human kidneys.

![Diagram of controls of glomerular filtration rate (GFR)](image)

Figure A.7: Controls of glomerular filtration rate (GFR). Note that the resistance control on both ends of the filtration process allows for a flexible control of perfusion pressure and blood flow. Positive feedback is shown by solid-ended arrows, negative feedback is shown by flat-ended arrows.

Out of the four determinants of GFR, the perfusion pressure $P_{GC}$ and renal blood flow (RBF) have the most potential to affect it. They in turn can be modulated by changing afferent and efferent arteriolar resistances. Vasoconstriction of afferent arterioles is mediated via an increase of intracellular calcium concentration, which happens in response to gating of mechanosensitive channels producing membrane depolarization and activation of calcium-dependent channels. There is a multitude of mechanical, neural, extrinsic and local hormonal vasoconstrictor and dilators, which may affect one
or both arterioles as well as excite or inhibit other pathways of control. Some of the controllers are shown in Figure A.8. Such vast number of controllers allows kidney to regulate both flow and perfusion pressure over a large range of renal arterial pressures. Additional flexibility may come from the unequal response of the cortical versus medullary arterioles to the same stimulants [68]. Thus, despite large variations in arterial pressure, sodium and water intake, and volume fluctuations, GFR and RBF remain within narrow limits in most physiological circumstances, and in particular in early hypertension.

Figure A.8: Major controls of renal arteriolar resistances. Many pathways, especially the role of endothelial factors such as prostaglandins, endothelin, and nitric oxide, are not shown due to complexity. They can, however, play an important role. For example, angiotensin II activates endothelial release of prostaglandin PGE_2 and nitric oxide in the afferent but not the efferent arteriole, which blunt the vasoconstriction caused by the angiotensin II. Thus angiotensin II-mediated vasoconstriction of the efferent arteriole is 10-100 stronger than that of afferent arteriole. Positive feedback is shown by solid-ended arrows, negative feedback is shown by flat-ended arrows.
Glomerular membrane permeability is also under neurohumoral control. Mesangial cells covering the glomerular capillaries can relax or constrict based on the input from atrial natriuretic peptide, sympathetic stimulation, angiotensin II, or tubuloglomerular feedback. Changes in the contraction of the mesangial cells lead to changes in the membrane permeability. However, the significance of membrane permeability control is still being debated.

A.4.1 Renal autoregulation

The kidney is one of the most efficient organs (along with brain and heart) in its autoregulation ability - the ability to maintain relatively constant blood flow across a wide range of perfusion pressures. In addition to blood flow, the kidney also autoregulates glomerular filtration rate which is a consequence of the autoregulation of flow and glomerular capillary pressure. Autoregulation of blood flow requires parallel changes in resistance with changes in perfusion pressure. When perfusion pressure is increased, the predominant resistance change comes from the constriction of the afferent arterioles and slight dilation of the efferent arterioles. Together these changes dampen the increase in blood flow and glomerular capillary pressure responses.

Autoregulation is mostly present in the cortical circulation only. The medullary circulation shows little autoregulatory response as was demonstrated in studies by Cohen et al [18] and Mattson et al [69]. Autoregulation of renal blood flow is intrinsic to the kidney and is largely independent of circulating hormonal or neurogenic factors, as it persists in an isolated and a denervated preparations. There are two major components of the renal autoregulation: the myogenic mechanism and the tubuloglomerular feedback mechanism. The two components are not mutually exclusive and are capable of modulating each other as they act on the same effector site, the afferent arteriole.

The ability of smooth muscle around a vessel to contract and relax in response to vascular wall tension is termed a myogenic response. The constricting force has passive and active components, the latter sensitive to the stretch of the vessel. A myogenic response of autoregulation occurs very rapidly, with full response in 3-10 seconds. It is
observed in the afferent arteriole, as well as arcuate and interlobular arteries. The efferent arterioles seem to have only passive component as they dilate in response to increase perfused pressure (in the absence of other competing mechanisms). The autoregulatory threshold can be reset in response to various conditions. In particular, in some animal models of hypertension much higher pressures are required to invoke vasoconstrictor response in the afferent arteriole.

The **tubuloglomerular feedback (TGF)** mechanism alters the afferent arteriolar resistance in response to sensed sodium flow (often termed as "sodium delivery") at the macula densa site of the same nephron. The main purpose of TGF is to maintain relatively constant sodium flow to the distal tubule. The increased sodium perfusion of the macula densa causes reduction in nephron’s glomerular blood flow and GFR, as well as the release of renin which initiates longer term hormonal response (see the following section). Certain substances such as nitric oxide and angiotensin II affect sensitivity of TGF. Over the long term exposure to a new sodium delivery rate TGF system resets to a new operating point.

**A.5 Control of sodium reabsorption**

There are two major steps to tubular sodium reabsorption. First step is the bulk reabsorption which happens in the proximal tubule and thick ascending limb. It reabsorbs nearly 90% of filtered sodium. Second step is the fine-tuning of reabsorption which happens in the distal tubule and collecting ducts. Control of sodium reabsorption is complex and involves a variety of interdependent neural and hormonal factors [14]. The summary of all reabsorption steps and their major controllers are given in Table A.4, the details are discussed below.

The major factor determining the rate of tubular sodium reabsorption is the hormone **aldosterone**. It stimulates the sodium reabsorption by the distal tubule and collecting ducts. When aldosterone is completely absent, approximately 2% of the filtered sodium is excreted. In contrast, when the plasma aldosterone is high, essentially all the sodium reaching the distal tubule and collecting ducts is reabsorbed. Aldosterone’s effect on
sodium transport is delayed by a few hours since there is a sequence of events (changes in gene expression and protein synthesis) that needs to take place in order to insert active sodium transport channels into the tubular membrane.

The production of aldosterone is a part of the hormonal complex termed the renin-angiotensin-aldosterone system (RAAS) (see Figure A.9). As the name implies it is a sequential hormone production, starting from the secretion of renin, which is also the limiting factor in the entire chain. Renin is an enzyme secreted by the juxtaglomerular cells. Once in the blood stream, it undergoes several conversions that lead to the production of angiotensin II, which then stimulates aldosterone production by the adrenal cortex. In addition to the systemic circulating RAAS, there are separate organ-specific renin-angiotensin systems in tissues such as the kidneys, brain, and the heart.

There are at least four distinct inputs that modulate renin production: the renal sympathetic nerves, intrarenal baroreceptors, the macula densa, and angiotensin II. The renal sympathetic nerves directly innervate the juxtaglomerular cells, and an increase in their activity stimulates renin secretion. Since the juxtaglomerular cells are located in the walls of the afferent arterioles, they can sense wall stretch due to changes in pressure and thus function as intrarenal baroreceptors. An increase in blood pressure leads to a reduction renin secretion. The juxtaglomerular cells also receive input from

<table>
<thead>
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<th>Segment</th>
<th>Reabsorbed sodium, % of the filtered load</th>
<th>Major controllers</th>
</tr>
</thead>
<tbody>
<tr>
<td>The proximal tubules</td>
<td>60%</td>
<td>SNS(+), AngII(±)</td>
</tr>
<tr>
<td>The ascending limb of Henle</td>
<td>30%</td>
<td>Vasopressin(+), AngII(-)</td>
</tr>
<tr>
<td>The distal tubules and collecting ducts</td>
<td>8–10%</td>
<td>Aldosterone(+), Vasopressin(+)</td>
</tr>
</tbody>
</table>

Table A.4: Sodium reabsorption rates within a human nephron and factors that stimulate (+) or inhibit (-) the reabsorption. Ranges of values show variation between natriuresis (large sodium loss) and anti-natriuresis (restricted sodium loss). Note that the control of reabsorption resides in the distal nephron where the fine-tuning is performed. AngII, angiotensin II; GFR, glomerular filtration rate; GTB, glomerulotubular balance; SNS, sympathetic nerve stimulation
the macula densa so that an increased sodium concentration at the macula densa results in a reduction of renin secretion. Angiotensin II (either systemic or intrarenal) reduces renin secretion, providing a negative feedback to RAAS.

Figure A.9: Summary of the major components of the renin-angiotensin-aldosterone system. Positive feedback is shown by solid-ended arrows, negative feedback is shown by flat-ended arrows.

Angiotensin II (AngII) exerts many effects on both the entire cardiovascular system and the renal function. AngII is produced not only in plasma but also within kidneys themselves. The concentration of intrarenal AngII might exceed the plasma concentration and play a more significant role in the regulation of renal function. We have already described the AngII effect on the stimulation of the secretion of aldosterone and the constriction of arterioles. AngII also has a potent and complex effect on proximal sodium reabsorption. At high doses of AngII the reabsorption in the proximal tubule is inhibited, and at low doses it is stimulated. AngII also blunts sodium reabsorption in the thick ascending limb.

Changes in sympathetic input and the RAAS are the most important means of regulating sodium reabsorption. However, there are many other modulators, some of which are outlined below:

- Independently of the neurohumoral control, there is an intrarenal phenomenon of **glomerulotubular balance** wherein changes in glomerular filtration rate are
balanced by equivalent changes in proximal reabsorption. This results in a constant fractional reabsorption of fluid and NaCl over a wide range of filtration rates. The mechanisms responsible for this phenomenon are subject of active research.

- **Vasopressin** is one of the strongest modulators of transepithelial NaCl transport in the thick ascending limb. It activates apical Na-K-Cl co-transport, apical K+ channels and basolateral Cl channels within minutes. It also increases sodium channel presence in the distal nephron by slowing down their natural removal and degradation processes. Sustained increases in circulating vasopressin result in a long-term effect of cell hypertrophy and almost doubling of active NaCl transport. Vasopressin also exerts an anti-natriuretic effect on collecting ducts and has a synergistic effect on sodium transport when combined with aldosterone.

- Intrarenal production of **dopamine** plays an important role in inhibition of proximal sodium reabsorption. The mechanisms are still not clear but it seems to both reduce the reabsorption itself and blunt the stimulating effect of AngII.

- **Atrial natriuretic peptides** inhibit release of renin, inhibit actions of AngII that promote sodium reabsorption, and inhibit sodium reabsorption in the medullary collecting duct.

### A.6 Control of water reabsorption

Water is reabsorbed passively by osmosis until distal portions of the nephron where water permeability of the tubular walls is controlled independently of sodium. The major determinant of this permeability is vasopressin. It stimulates the insertion of aquaporin channel into the luminal membrane of the collecting ducts. It also vasoconstricts the descending vasa recta, limiting the medullary blood flow and thus limiting the washout of the medullary osmolality gradient. Thus, in the presence of a high plasma concentration of vasopressin water reabsorption is increased both due to high permeability and high osmotic gradient drawing the water into the interstitium, resulting in water conservation.
Vasopressin is a peptide synthesized by neurons in the hypothalamus. There are two main triggers of vasopressin secretion. First is the osmoreceptor signal which monitors cell volume and thus changes in plasma osmolality. Second trigger comes from the cardiopulmonary baroreceptors which monitor venous, atrial, and arterial pressures.

Figure A.10 shows an example of vasopressin-related pathways triggered in response to an increased plasma osmolality, which may occur, for instance, during high sodium intake. All mechanisms involved in this diagram are fast acting which explains why changes in plasma osmolality are almost impossible to observe experimentally. An increase in plasma osmolality causes osmotic water shift out of the cells, restoring the osmolality to normal, but shrinking the cells and increasing the extracellular fluid volume. Both of the effects trigger vasopressin release which leads to reduced water excretion and increased sodium excretion. This causes a reverse osmotic shift of water back into cells, restoring the homeostatic balance. Note, that vasopressin’s control of sodium excretion is fairly limited and would be further attenuated if a large amount of sodium is ingested in equal portions with water.
Figure A.10: Vasopressin-related pathways by which plasma osmolality and extracellular fluid volume are restored in response to high sodium intake. Positive feedback is shown by solid-ended arrows, negative feedback is shown by flat-ended arrows.
Appendix B

Sensitivity analysis

The hemodynamic pattern generated by a mathematical model of long-term blood pressure is affected by a high degree of uncertainty in both its structure and its parameters. This is due to the high inherent variability of a biological system, population variability, the complexity and unknown nature of the phenomena involved, and the experimental limitations. Therefore, any interpretation of the model’s predictions should acknowledge this uncertainty. Sensitivity analysis techniques are often employed for this purpose.

B.1 Local sensitivity analysis

Consider a dynamical system
\[
\frac{dZ}{dt} = F(Z(t), C)
\]
where \(Z\) is a state vector, \(C\) is a vector of parameters, and \(F\) is sufficiently continuous. The dynamical behavior of the system (B.1) in the vicinity of a solution \(Z^*\) can be studied via the linearization along this solution, which is given by the variational equation
\[
\frac{dZ}{dt} = D_Z F(Z(t), C) Z.
\]

Similarly, to study the impact of the change in a parameter \(C_j\) on the state \(Z_i\) one
can define a sensitivity measure \( S_{ij} \) as

\[
S_{ij}(t, C)|_{C=C_0} = \frac{\partial Z_i(t, C)}{\partial C_j}|_{C=C_0}
\]

where \( C_0 \) is the vector of original values parameters that is being perturbed. The sensitivity measures then can be computed by differentiating each equation of (B.1) with respect to each parameter:

\[
\frac{dS_{ij}}{dt} = \frac{\partial}{\partial C_j} F_i(Z, C)
\]  \hspace{1cm} \text{(B.2)}

and solving (B.2) together with the state equations (B.1).

In practice, the sensitivity measure is often normalized so that the relative sensitivity of the output could be assessed across model parameters:

\[
S_{ij} = \frac{\partial Z_i}{\partial C_j} \frac{C_j}{Z_i}.
\]

The derivative-based approach to sensitivity is an efficient approach in computational time and has been widely accepted in the literature. However, derivatives are only informative at the base point where they are computed and do not aid in the exploration of the rest of the parameter space. Thus this approach is of limited value when both the model inputs and outputs are uncertain and when the model is of unknown linearity. Even if variation in the model’s parameters and states can be taken into an account by defining \( S_{ij} = \frac{\partial Z_i}{\partial C_j} \frac{\sigma_{C_i}}{\sigma_{Z_j}} \) (where \( \sigma \)'s are the standard deviations), the approach remains local in the sense that the effect of variation in one parameter is studied while all others are fixed at their nominal values. Thus the nonlinear interactions between the parameters are not estimated in the derivative-based approach.
B.2 Global sensitivity analysis

Global approaches estimate the effect of a parameter when all the others are varying, enabling the identification of parameter interactions in nonlinear and non-additive models. These approaches are usually computationally more expensive. An elegant global sensitivity approach [92] is based on variance-based measures and has multiple uses for model simplification, identification of key parameters and model calibration.

Let us restate the original system (B.1) from a different perspective:

\[ Y = f(X) = f(X_1, \ldots, X_n) \]

where \( Y \) is the vector of model’s outputs and \( X \) is a vector of input variables. Both inputs and outputs have a wider meaning then the states and parameters in the above discussion. For example, \( Y \) can be defined as a maximum of the solution of (B.1) or its steady state or as any other feature of interest to a researcher. The model’s input factors consist of parameters with nonnull uncertainties and can include other entities, such as the initial values. The function \( f \) is usually not defined explicitly and in general refers to a procedure that one must do to obtain an output from the given inputs. The goal of the global sensitivity analysis is to apportion the uncertainty in the model’s output \( Y \) to the uncertainties in its input factors \( X \).

The function \( f(X) \) can be written as a sum of terms of increasing dimensionality, where each first-order term is a function of single variable, each second-order term is a function of two variables, etc:

\[
f(X) = f_0 + \sum_i f_i(X_i) + \sum_{i<j} f_{ij}(X_i, X_j) + \sum_{i<j<k} f_{ijk}(X_i, X_j, X_k) + \ldots \quad (B.3)
\]

where \( f_0 \) is a constant. This decomposition is not unique. However, if each term of (B.3) is chosen with zero average, then the decomposition is unique and the terms are pairwise orthogonal. Moreover, the terms are given by the conditional averages of \( f(X) \):

\[
f_i(X_i) = E(Y|X_i) - E(Y)
\]
\[ f_{ij}(X_i, X_j) = E(Y|X_i, X_j) - f_i(X_i) - f_j(X_j) \]

\[ ... \]

If the input factors are not correlated, then it is possible to decompose the variance of \( f(X) \) as \( V(Y) = \sum_i V_i + \sum_{i<j} V_{ij} + \sum_{i<j<k} V_{ijk} + \cdots + V_{12...n} \) where:

\[ V_i = V(f_i(X_i)) = V(E(Y|X_i)) \]
\[ V_{ij} = V(f_{ij}(X_i, X_j)) = V(E(Y|X_i, X_j)) - V_i - V_j \quad \text{(B.4)} \]

\[ ... \]

The \( f_i(X_i) \) are referred to as main effects of \( X_i \), and the higher order terms are referred to as interactions.

### B.2.1 Main effects

The main effect of \( X_i \) is a measure of sensitivity of \( Y \) to an individual input \( X_i \). An intuitive way to define it would be to say that it is \( V(E(Y|X_i)) \), the expected amount of variance that would be removed from the output if \( X_i \) is fixed at some value (within its range of uncertainty). A more rigorous approach starts by considering how the uncertainty of \( Y \) would be affected in the factor \( X_i \) is fixed at a particular value \( x \). Then the conditional variance \( V(Y \mid X_i = x) \) could be considered as a measure of the remaining variance in \( Y \), or the relative importance of \( X_i \), in relation to the total unconditional variance in the output \( V(Y) \). This measure can be further improved by taking the average over all possible values of \( x \): \( E_{X_i}(V(Y \mid X_i)) \). Moreover, by the law of total variance (see proof at the end of the section):

\[ E(V(Y \mid X_i)) + V(E(Y \mid X_i)) = V(Y). \]
Hence, a large $V(E(Y \mid X_i))$, will imply that $X_i$ is an important factor. Thus the first-order sensitivity index of $X_i$ on $Y$ is defined as:

$$S_i = \frac{V(E(Y \mid X_i))}{V(Y)}$$

$S_i$ is a number always between 0 and 1.

The first-order sensitivity index can indicate whether efforts at reducing uncertainty in $X_i$ can greatly reduce the uncertainty in the output. Thus this measure is useful prior to conducting a calibration experiment on a given input. The value $1 - S_i$ can be interpreted as the minimum value of the expected loss when $f(X)$ is approximated by $E(Y|X_i)$. The higher $S_i$, the better the approximation. However, the smaller values of $S_i$ do not necessarily imply the unimportance due to potential nonlinearities in the model.

Note, that the first-order sensitivity index also follows from (B.4). In a similar fashion, higher-order sensitivity indices can be defined for interaction terms:

$$S_{ij} = \frac{V_{ij}}{V(Y)}$$
$$S_{ijk} = \frac{V_{ijk}}{V(Y)}$$

\ldots

**Theorem 1.** The law of total variance: $V(Y) = E(V(Y|X)) + V(E(Y|X))$.

**Proof:**

We know that (a): $V(Y) = E(Y^2) - [E(Y)]^2$ by definition, (b) $E(Y) = E(E(Y|X))$ (the law of total expectation), and (c) $E(X + Y) = E(X) + E(Y)$ . Then we have

\[(a)\]
\[V(Y) = E(Y^2) - [E(Y)]^2\]

\[(b)\]
\[= E(E(Y^2|X)) - [E(E(Y|X))]^2\]

\[(a)\]
\[= E(V(Y|X)) + [E(Y|X)]^2) - [E(E(Y|X))]^2\]
\[ \begin{align*}
&\text{(c)} \Rightarrow E(V(Y|X)) + E([E(Y|X)]^2) - [E(E(Y|X))]^2 \\
&\text{(a)} \Rightarrow E(V(Y|X)) + V(E(Y|X))
\end{align*} \]

**B.2.2 Total effects**

While studying higher-order sensitivity measures for the input factors interactions (e.g., \( S_{ij} \)) can be of value, the second step after computing main effects is usually to compute total effects instead. The **total effect** of the input factor \( X_i \) is linked to \( E(V(Y|X_{\sim i})) \), which is the expected amount of output variance that would remain unexplained if only \( X_i \) is varying over its uncertainty range, while all other inputs are fixed. Thus the total sensitivity index (or total effect) is

\[ S_{T_i} = \frac{E(V(Y|X_{\sim i}))}{V(Y)}. \]

Another interpretation of the total sensitivity index \( S_{T_i} \) is that it is a sum total of all sensitivity indices involving \( X_i \) (assuming orthogonality), for example if there are total of three input factors:

\[ S_{T_i} = S_1 + S_{12} + S_{13} + S_{123}. \]

The total sensitivity indices are used in identifying input factors which are unessential either singularly or in combination with others. These input factors can thus be fixed at any value within their range and thus simplify the model. Also \( S_{T_i} - S_i \) measures how much \( X_i \) is involved in interactions with other input factors.

**B.3 An excitation-adaptation example**

Let’s consider an excitation-adaptation system:

\[ \begin{align*}
\dot{y}_1 &= \frac{I - (y_1 + y_2)}{\tau_E}, \quad y_1(0) = 0 \quad \text{(B.5)} \\
\dot{y}_2 &= \frac{I - y_2}{\tau_A}, \quad y_2(0) = 0
\end{align*} \]

where $\tau_A$ is the adaptation time constant, $\tau_E$ is the excitation time constant, and $I$ is the stimulus function which is assumed to be a step function: $I(t) = 0, t \leq 0$ and $I(t) = I_\infty, t > 0$.

The solutions and behavior of the system’s solutions are well-understood, so we will use them to compute sensitivities directly, even though in a general application one would have to solve the original system of differential equations numerically. The solutions of (B.5)-(B.6) are:

$$y_1 = \frac{I_\infty \tau_A}{\tau_A - \tau_E} (e^{-t/\tau_A} - e^{-t/\tau_E}) \quad (B.7)$$
$$y_2 = I_\infty (1 - e^{-t/\tau_A}) \quad (B.8)$$

One can observe that the steady state of $y_1$ is 0, i.e. after a short period of excitation it returns to its initial state. The magnitude of the deviation is influenced by the system’s parameters: $\tau_A$, $\tau_E$ and $I_\infty$ (see Figure B.1). Let’s employ both local and global sensitivity analysis techniques described above to the question of sensitivity of this deviation to system’s parameters.

Let’s assume the following uncertainties on the parameters $I_\infty \sim N(5, 0.5)$, $\tau_E \sim N(0.5, 0.1)$ and $\tau_A \sim N(1, 0.1)$. Let us also choose the following time points at which the global measures of sensitivities to be computed$^1$ : $t = 0.1, 0.2, 0.5, 0.7, 1, 2,$ and 4.

The results of the local sensitivity analysis are summarized in Figure B.2. We can distinguish roughly three time periods where sensitivities switch roles: the excitation period ($t < 0.5$), maximum ($0.5 < t < 1.6$) and the adaptation period ($t > 1.6$). During the excitation period $\tau_E$ is the most sensitive as compared to the other time intervals (Figure B.2, left panel). It is also relatively more sensitive than $\tau_A$ but less sensitive than $I_\infty$ during the excitation period and becomes the least important of all three parameters afterwards (Figure B.2, right panel). The stimulus magnitude $I_\infty$ is most sensitive up to the adaptation period during which the adaptation time constant $\tau_A$ takes the lead.

The results of the global sensitivity analysis are summarized in Figures B.3 and B.4. The total effects (Figure B.3) show that none of the parameters can be considered as

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$^1$ SimLab, version 2.2.1 was used for the computation of global sensitivity indices.
Figure B.1: Solution $y_1$ of (B.5)-(B.6) for $I_\infty \sim N(5, 0.5)$, $\tau_E \sim N(0.5, 0.1)$ and $\tau_A \sim N(1, 0.1)$ at their mean values. If a sample of parameters chosen from the parameter space, then the distribution of $y_1$ can be computed at a given time point. The error bars show the standard deviations of these distributions.

Noninfluential for the entire time period, but during the excitation period the adaptation time constant $\tau_A$ could be fixed if one wanted a simpler model of the solution at the early stage. Similarly, during the adaptation period total effect of the excitation time constant becomes small and thus it can be considered noninfluential. The main effects (Figure B.4) show that the stimulus signal $I_\infty$ makes the largest contribution to the uncertainty of the solution during the middle stage where it reaches its maximum. Small main effects for the time constants would not necessarily mean that they do not contribute as well. However, in this case the difference between total effects and main effects are small indicating that there are no significant interaction terms and thus the time constants indeed contribute little to the variation of the solution around its maximum. The conclusions of local and global sensitivity analysis agree well in this example.
Figure B.2: Left panel: Local sensitivity measures of $y_1$ (y-axis) as functions of time (x-axis): $\frac{\partial y_1}{\partial \tau_A}$ (solid line), $\frac{\partial y_1}{\partial \tau_E}$ (dashed line), and $\frac{\partial y_1}{\partial I_1}$ (dotted line). Right panel: Local normalized sensitivity measures of $y_1$: $\frac{\partial y_1}{\partial \tau_A \tau_A}$ (solid line), $\frac{\partial y_1}{\partial \tau_E \tau_E}$ (dashed line), and $\frac{\partial y_1}{\partial I_1 \tau_1}$ (dotted line).

Figure B.3: Total effects (y-axis) of parameters $\tau_A$ (diamond markers), $\tau_E$ (square markers), and $I_\infty$ (triangle markers) as functions of time (x-axis).

Figure B.4: Main effects (y-axis) of parameters $\tau_A$ (diamond markers), $\tau_E$ (square markers), and $I_\infty$ (triangle markers) as functions of time (x-axis).
Appendix C

Time scale separation example

Consider a highly simplified version of the model presented in Chapter 2: a circulatory model with two regulatory mechanisms, control of sodium excretion and arterial resistance, as we have described in [6]. The following analysis demonstrates the time scale separation technique for calculation of the quasi-steady states of the system.

The simplified system presented in [6] with the notation adjusted to the one presented in Chapter 2 is:

\[
\begin{align*}
C_A \frac{dP_A}{dt} &= CO - \frac{P_A - P_S}{R_{AS}} - \frac{P_A - P_R}{R_{AR}} \\
C_S \frac{dP_S}{dt} &= \frac{P_A - P_S}{R_{AS}} - \frac{P_S - P_V}{R_{VS}} \\
C_V \frac{dP_V}{dt} &= \frac{P_S - P_V}{R_{VS}} + \frac{P_R - P_V}{R_{VR}} - CO \\
\frac{dV_B}{dt} &= k_{VT}(F_{SI} - F_{SE}) \\
\tau_{SE} \frac{dF_{SE}}{dt} + F_{SE} &= F_{SI} \\
\tau_{N} \frac{dR_{AS}}{dt} + R_{AS} &= R_{AS,0}(1 + k_{N}(F_{SI} - F_{SI}(0))(a - 1))
\end{align*}
\]

where CO = \frac{F_{V} - p_0}{k_{FS}}, F_{SI} = J_{NaCl,L,P} is the sodium intake rate, F_{SE} is the sodium excretion rate, and a = \frac{AngII}{AngII_0} is the normalized AngII plasma concentration. See [6] for details on the parameters k_{FS}, k_{VT}, p_0, \tau_{SE}, \tau_{N}, and R_{AS,0}.

The conservation of total blood volume eliminates one of the pressure equations and
dictates:

\[ V_B - V_{\text{Unstr}} = C_A P_A + C_S P_S + C_R P_R + C_V P_V \]

The system can be simplified by defining \( V_{\text{Str}} = V_B - V_{\text{Unstr}} \) and replacing the equation for \( P_S \) by the one for \( P_R \):

\[
\begin{align*}
C_A \frac{dP_A}{dt} &= \text{CO} - \frac{P_A - P_S}{R_{AS}} - \frac{P_A - P_R}{R_{AR}} \\
C_r \frac{dP_R}{dt} &= \frac{P_A - P_R}{R_{AR}} - \frac{P_R - P_V}{R_{VR}} \\
C_v \frac{dP_V}{dt} &= \frac{P_S - P_V}{R_{VS}} + \frac{P_R - P_V}{R_{VR}} - \text{CO} \\
\frac{dV_{\text{Str}}}{dt} &= -\frac{V_{\text{Str}} - V_{\text{Str}}(0)}{\tau_{SE}} + k_{VT}(F_{SI} - F_{SI}(0)) \\
\frac{dR_{AS}}{dt} &= -\frac{1}{\tau_N}(R_{AS} + R_{AS,0}(1 + k_N(F_{SI} - F_{SI}(0))(a - 1)))
\end{align*}
\]

with

\[ V_{\text{Str}} = C_A P_A + C_S P_S + C_R P_R + C_V P_V. \]

The initial values for the variables in (C.1) are assumed to be their normal values:

\[
\begin{align*}
P_i(0) &= P_{i,0}, \quad i = A, S, V \\
V_{\text{Str}}(0) &= V_B(0) - V_{\text{Unstr}} = V_{\text{Str},0} \\
R_{AS}(0) &= R_{AS,0}
\end{align*}
\]

The goal is to rewrite the system (C.1) in the explicit form with two time scales.

Let us introduce dimensionless variables

\[
\begin{align*}
p_a &= \frac{C_S P_A}{V_{\text{Str},0}}, \quad p_r = \frac{C_S P_R}{V_{\text{Str},0}}, \quad p_v = \frac{C_S P_V}{V_{\text{Str},0}} \\
r_{as} &= \frac{R_{AS}}{R_{VR}}, \quad v = \frac{V_{\text{Str}}}{V_{\text{Str},0}}, \quad s = \frac{t}{\tau_{SE}}
\end{align*}
\]
and dimensionless parameters

\[
\hat{p}_0 = \frac{C_S p_0}{V_{Str,0}},
\]
\[
c_a = \frac{C_A}{C_S}, \quad c_r = \frac{C_R}{C_S}, \quad c_v = \frac{C_V}{C_S},
\]
\[
r_{ar} = \frac{R_{AR}}{R_{VR}}, \quad r_{vs} = \frac{R_{VS}}{R_{VR}}, \quad \rho = \frac{R_{AS,0}}{R_{VR}}, \quad \hat{k}_F = \frac{k_{FS}}{R_{VR}}.
\]
\[
\hat{k}_N = k_N F_{SI,0}, \quad \hat{k}_{VT} = \frac{k_{VT} F_{SI,0} \tau_{SE}}{V_{Str,0}}, \quad s_{in} = \frac{F_{SI}}{F_{SI,0}}.
\]
\[
\epsilon = \frac{C_R R_{VR}}{\tau_{SE}}, \quad \hat{\tau}_N = \frac{\tau_{SE}}{\tau_N}.
\]

Note that angiotensin II level, \(a(t)\) is already dimensionless.

Then we can rewrite (C.1) in dimensionless form as

\[
\begin{align*}
\epsilon \frac{dp_a}{ds} &= c_r \left( \frac{1}{k_{FS}} (p_a - \hat{p}_0) - \frac{1}{r_{as}} ((1 + c_a) p_a - v - c_r p_r - c_v p_v) - \frac{1}{r_{ar}} (p_a - p_r) \right) \nonumber \\
\epsilon \frac{dp_r}{ds} &= \frac{1}{r_{ar}} (p_a - p_r) - (p_r - p_v) \nonumber \\
\epsilon \frac{dp_v}{ds} &= c_r \left( \frac{1}{r_{sv}} (v - c_a p_a - c_r p_r - (c_v + 1) p_v) + p_r - p_v - \frac{1}{k_{FS}} (p_v - \hat{p}_0) \right) \quad (C.2) \\
\frac{dv}{ds} &= 1 - v + \hat{k}_{VT} (s_{in} - 1) \nonumber \\
\frac{dr_{as}}{ds} &= -\hat{\tau}_N (r_{as} - \rho (1 + \hat{k}_N (s_{in} - 1) (a - 1))) \nonumber 
\end{align*}
\]

It can be seen from Table C.1 that the functions on the right-hand side of the (C.2) are of approximately the same order.

<table>
<thead>
<tr>
<th>Variable (bold) or Parameter</th>
<th>Order</th>
</tr>
</thead>
<tbody>
<tr>
<td>(r_{as}, r_{ar}, \rho)</td>
<td>10</td>
</tr>
<tr>
<td>(v, p_a, c_v, r_{vs}, r_{ur}, k_{FS}, s_{in}, a)</td>
<td>1</td>
</tr>
<tr>
<td>(p_r, p_v, c_a, c_r, k_N, \hat{\tau}_N)</td>
<td>0.1</td>
</tr>
<tr>
<td>(\hat{p}<em>0, \hat{k}</em>{VT})</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table C.1: Estimated magnitudes of dimensionless parameters and variables.
Thus there are two groups of variables in the system: fast variables \( z = \begin{pmatrix} p_a \\ p_r \\ p_v \end{pmatrix} \) and slow variables \( y = \begin{pmatrix} v \\ r_{as} \end{pmatrix} \). And so (C.2) can be written as:

\[
\epsilon \frac{dz}{ds} = A_1(y)z + A_2(y), \quad z(0) = z_0
\]

\[
\frac{dy}{ds} = B_1y + B_2, \quad y(0) = y_0
\]

Setting \( \epsilon = 0 \) we obtain the quasi-steady states \( y_s \) and \( z_s \):

\[
0 = A_1(y_s)z_s + A_2(y_s)
\]

\[
\frac{dy_s}{dt} = B_1y_s + B_2, \quad y_s(0) = y_0
\]

Assuming that sodium intake and angiotensin input are constants we can obtain the quasi-steady states in the explicit form:

\[
y_s = \begin{pmatrix}
1 + \hat{k}_{VT}(s_{in} - 1)(1 - e^{-s}) \\
\rho(1 + \hat{k}_N(s_{in} - 1)(a - 1)(1 - e^{-\tau N s}))
\end{pmatrix}
\]

\[
z_s = -A_1^{-1}(y_s)A_2(y_s)
\]

In order to obtain the fast solutions, we rewrite system (C.3) in the fast time scale \( \tau = \frac{t}{\epsilon} \) and set \( \epsilon = 0 \):

\[
\frac{dz}{d\tau} = A_1(y)z + A_2(y) \quad \epsilon \to 0 \quad \frac{dz_f}{d\tau} = A_1(y_0)z_f(\tau), \quad z_f(0) = z_0 - z_s(0)
\]

\[
\frac{dy}{d\tau} = \epsilon(B_1y + B_2) \quad \epsilon \to 0 \quad \frac{dy_f}{d\tau} = 0
\]

Note that the fast subsystem is linear and thus has only one solution. It can be checked numerically that for the physiologically relevant parameters all eigenvalues of
$A_1(y_0)$ are negative and thus the fast solution is always stable. Therefore, the Tikhonov theorem applies and the long-term solutions of the original system (C.1) can be approximated by the quasi-steady states (C.6).