A DYNAMIC SIMULATION MODEL FOR LONG-TERM HYPERTENSION PROGRESSION

by

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ABSTRACT

A DYNAMIC SIMULATION MODEL FOR LONG-TERM HYPERTENSION PROGRESSION

Dynamics of blood pressure over the life span of human beings demonstrates a growth path. The most significant theories which aim to explain this trend adopt a kidney-dependent approach. Structural reductions in the size of renal arterioles (vascular remodeling) and loss of nephrons are considered to be primarily responsible for the progressive increase in blood pressure. Dynamics of progression of blood pressure can most suitably be modeled by conceptualizing the problem as a long-term control of fluid excretion capacity.

The goal of this thesis is to construct a dynamic simulation model that can realistically reproduce the long-term progression of blood pressure in healthy and in hypertensive subjects. For this purpose, a system dynamics model is built which focuses on systemic interactions that result in vascular remodeling in renal arterioles and loss of nephrons. These hypertensive mechanisms are integrated with a blood pressure control mechanism responsible for functional vasodilation of renal arterioles. For both normal and hypertensive subjects the model realistically reproduces the behavior of blood pressure, fluid volume, plasma renin and distribution of normal and remodeled nephrons. The reference behaviors of the model point out a number of important characteristics that differentiate blood pressure progression in essential-hypertensive and normal subjects. Experiments demonstrate that management of the number of remodeled arterioles over time should be an essential task in long-term blood pressure progression control. With proper control of remodeled arterioles, blood pressure of essential hypertensive subjects can be reduced back to normal and the longevity of adequate fluid excretion capacity can be greatly improved. Scenario runs with the simulation model help distinguish such successful policies from the ineffective interventions.

ÖZET

UZUN DÖNEMDE YÜKSEK TANSİYON İLERLEMESİ ÜZERİNE BİR DİNAMİK SİMULASYON MODELİ

Tansiyon insanın yaşam süreci boyunca bir yükselme dinamiği göstermektedir. Bu davranışı açıklamaya çalışan en belli başlı teoriler böbrek bazlı bir bakış açısından konuya yaklaşmaktadırlar. Renal arterioldeki yapısal daralmalar ya da nefron kaybı bu büyüme davranışına sebep olduğu düşünülen başlıca etkenlerdir. Tansiyonun büyüme dinamiklerini modelleyebilmenin en uygun yolu konuyu uzun dönemli bir kapasite kontrol problemi olarak kavramsallaştırmaktır.

Bu tezin amacı, tansiyonun sağlıklı ve hipertansif hastalarda uzun dönemde gelişimini gerçekçi bir biçimde üreten bir dinamik benzetim modeli kurmaktır. Bu amaçla arteriollerde yapı değişimi ve nefron kaybına sebep olan sistemik ilişkilere odaklanan bir sistem dinamiği modeli kurulmuştur. Bu hastalıklı süreçler ile, renal arteriollerdeki fonksiyonel değişimleri yöneterek kan basıncını kontrol eden geri besleme mekanizması entegre edilmiştir. Model, normal tansiyonlu ve yüksek tansiyonlu denekler için tansiyon, vücud sıvısı, kandaki renin, normal ve yapısı değişmiş nefronların dağılımı gibi değişkenlerin davranışını gerçekçi bir şekilde üretebilmektedir. Modelin ürettiği referans davranışlar, hipertansif ve sağlıklı örneklerde tansiyonun ilerlemesini farklı kılan özellikleri göstermektedir. Yapılan benzetim deneyleri göstermiştir ki, yapısı değişmiş arteriollerin sayısının zaman içindeki gelişimini denetlemek, uzun dönemli tansiyon ilerlemesini kontrol etmenin ana unsurlarından biri olmalıdır. Yapısı değişmiş arteriol sayısının iyi denetlenmesi durumunda primer hipertansif hastalarda tansiyonun normal seviyelere indirilebildiği ve yeterli sıvı atımı kapasitesine sahip olma ömrünün uzadığı görülmüştür. Model ile yapılmış olan senaryo benzetimleri, böyle etken stratejilerle, başarısız olanların farklarını ortaya çıkarmaktadır.

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LIST OF ABBREVIATIONS

1K1C	One Kidney One Clip Goldblatt Hypertension model
2K1C	Two Kidney One Clip Goldblatt Hypertension model
Ang II	Angiotensin II
BP	Blood Pressure
FV	Fluid Volume
FV-RAS	Fluid Volume-Renin Angiotensin System
GFR	Glomerular Filtration Rate
MAP	Mean Arterial Pressure
N.N.	Normal Nephrons
NPR	Normal Plasma Renin
NRpN	Normal Renin per Nephron
R.M.	Remodeled Nephrons
RAS	Renin Angiotensin System
RpN	Renin per Nephron
snGFR	Single Nephron Glomerular Filtration Rate
snRen sec	Single Nephron Renin Secretion
WI	Water Intake

1. INTRODUCTION

Homeostasis, the ability of the body to maintain a stable internal environment, is an essential need of the body in order to sustain its proper function. Maintenance of normal Fluid Volume (FV) and Blood Pressure (BP) is a primary goal in providing this stable environment. The stability of FV in long-term depends on the capability of water excretion function of kidneys. Hypertension can be regarded as body's response according to homeostatic principle to achieve necessary water excretion from the kidneys when water excretion function is significantly compromised (Guyton, 1980).

There are multiple negative feedback loops governing the excretion function in different time horizons. With respect to long-term control of excretion function, one of the most significant control mechanisms takes place over Angiotensin II (Ang II) hormone and Fluid Volume. The Renin-Angiotensin System (RAS) accomplishes control of FV by changing water retention of the body through regulation of renal arterioles and reabsorption from renal tubules. Any changes that lead to reduction in excretion function or any changes in Water Intake (WI) levels will be counterbalanced by RAS to maintain FV near normal levels (Guyton and Hall, 2000; Laragh, 2002).

On the other hand, there are positive feedback mechanisms that affect proper control of FV. Two mechanisms, the first one mediated over loss of nephrons and the second one mediated over structural narrowing of renal arterioles (vascular remodeling), lead to reduced capability of excretion function. In the case of nephron loss, remaining nephrons compensate for loss in excretion by increasing their own filtration. Increased filtration makes nephrons more susceptible to experience injuries and become obsolete. This thesis involves a further hypothesis that remodeled arterioles trigger an alternative positive feedback mechanism over RAS that undermine control of FV. The mechanism involves nephrons coupled with remodeled arterioles secreting very high amounts of renin. Unsuppressed secretion of renin leads to high Angiotensin levels in the blood. Over time the state of vasoconstriction caused by higher than normal angiotensin levels lead to remodeling of healthy nephrons. Proliferation of remodeling decreases total filtration capacity and increases global renin levels further. Moreover, high angiotensin levels impair filtration of remaining healthy nephrons through functional constriction of renal arterioles.

The interaction of the above feedback loops provides a good framework to understand the long-term progression of BP in conjuncture with structural and functional changes in the kidneys. Progression of BP in healthy and hypertensive subjects can be demonstrated by testing different pathways of interactions among these mechanisms. This study aims to put forward a dynamic model for the structure responsible for long-term progression of BP and to underline the difference between normal progression of BP under normal physiological conditions and under kidney-dependent essential hypertension.

In the following section, a review of hypertension with special emphasis on kidney based mechanisms and theories on pathogenesis and progression of essential hypertension will be given. Next, the system dynamics model will be presented with emphasis on its structure. In following chapters, progression dynamics of prototypical cases of normal and hypertensive subjects will be demonstrated. In scenario analysis section, alternative progression dynamics will be explored, and findings will be summarized in the conclusion chapter.

2. LITERATURE SURVEY ON HYPERTENSION AND KIDNEY DAMAGE

Hypertension, chronic elevated levels of blood pressure, is such a prevalent condition in modern societies that most people will eventually develop hypertension during their lifetime (Kaplan, 1998). Although normal level of blood pressure (BP) and its variation is endemic for each person, the medical world has reached some kind of consensus on the levels of BP which will be considered in the hypertensive range. People who have systolic and diastolic BP above 140 and 90 mmHg, respectively, are considered hypertensive. Yet, the diagnosis of hypertension requires a much more careful evaluation of other characteristics of the patient, such as genetic history, obesity, stress level, smoking-habits and state of target organ damage (Kaplan, 1998).

In clinical practice, hypertension is classified with respect to its severity and its underlying cause. However, most cases of hypertension are of an *unknown cause*, i.e. there is not a specific identifiable cause which is responsible for chronic elevation of BP. This type of hypertension is called essential or primary (since hypertension is not secondary to another condition, such as renal artery stenosis, obesity, stress or pregnancy). The difficulty in establishing the cause of hypertension lies in the *dynamic systemic nature of blood pressure*. This systemic nature of blood pressure is well described in an editorial in Lancet:

> "Blood Pressure is a measurable end product of an exceedingly complex series of factors including those which control blood vessel calibre and responsiveness, those which control fluid volume within and outside the vascular bed, and those which control cardiac output. None of these factors is independent: they interact with each other and respond to changes in blood pressure. It is not easy, therefore to dissect out cause and effect. Few factors which play a role in cardiovascular control are completely normal in hypertension: indeed, normality would require explanation since it would suggest a lack of responsiveness to increased pressure."
>
> **(**Editorial, Lancet in Kaplan, 1998)

According to Poiseuille's Law, BP equals cardiac output times total peripheral resistance (Guyton and Hall, 2000). In theory, a permanent change affecting either one or

both of the variables on the right hand side could cause an increase in long-term level of BP. Despite the practical impossibility of identifying the original cause of essential hypertension, most theories emphasize its renal-dependent nature. They suggest that a sustained increase in fluid volume (FV), which determines cardiac output is responsible for hypertension. Accordingly, increased FV is a result of inadequate excretion of salt and water (Guyton and Hall, 2000). Renal-based hypotheses predominantly suggest that excess water retention is primarily due to structural lesions in kidney which increase total renal resistance (Sealey et al. 1988, Johnson et al. 2005a,b). There is an ongoing debate whether these lesions are initiated by hypertension or whether they cause hypertension themselves. Regardless of the initial cause and the effect, it is widely accepted that these renal pathological changes are responsible for maintenance of hypertension.

Uncontrolled high levels of blood pressure is not a life-threatening condition in itself, however; it eventually progresses to other diseases which have high mortality. The target organ damage caused by hypertension may lead to cardiac failure or infarction, cerebral ischemia, nephrosclerosis, renal failure or end-stage renal disease (Kaplan, 1998). In this respect, theories connecting initial origins of essential hypertension with its progression are of great value as they might explain the causal structure responsible for different BP dynamics observed in normal and hypertensive people.

Long-term blood pressure and fluid volume levels are regulated around a normal value according to the homeostatic principle. There are two major long-term control mechanisms of FV and BP. The first one is the Pressure Natriuresis mechanism whose workings was postulated by Guyton in his elaborate system analysis model (Guyton, 1980). This mechanism operates over FV, BP and water filtration from kidneys. If for some reason water intake is increased or water excretion is decreased, FV rises over its normal level because of the positive water balance over time. As FV rises, it increases arterial pressure. Subsequently, increased perfusion pressure causes higher excretion of water from kidneys, bringing FV back to its normal level. This negative feedback mechanism controls FV around a set level perfectly, if there are no structural impediments affecting water excretion.

The other mechanism, whose importance in controlling BP has been elucidated by Laragh and associates, is the renin-angiotensin-system (RAS). According to them, the kidney-based plasma renin system is the servocontrol for blood pressure and sodium balance (Laragh, 2002). The two main components of this system are renin and salt, which are indicators of volume and vasoconstrictor factors of blood pressure, respectively. In essence, plasma renin determines the amount of Angiotensin II (Ang II) in the blood which determines the level of vasoconstriction of arterioles. On the other hand, amount of salt determines the amount of water in the body. According to Laragh, the normal function of renin system is to ensure that kidneys have sufficient perfusion pressure to accomplish appropriate filtration of blood. Thus, in the cases of high pressures, low amounts of renin will be secreted in order to avoid constriction of arterioles. Thereby, BP will be reduced through lowered total peripheral resistance in the short-term and reduced water retention in the kidneys in the long-term (Laragh, 2002).

Despite these efficient control mechanisms, blood pressure is expected to follow a growth path over time. Medical world agrees on the existence of the growth path. This growth path is supported by population-wide data from longitudinal studies on blood pressure (Figure 2.1). There are many theories that explain this growth by some kind of a positive feedback loop. In its most generic form, this loop connects structural changes in blood vessels, vascular hypertrophy, and blood pressure (Lever and Harrap, p.70 in Kaplan, 1998).

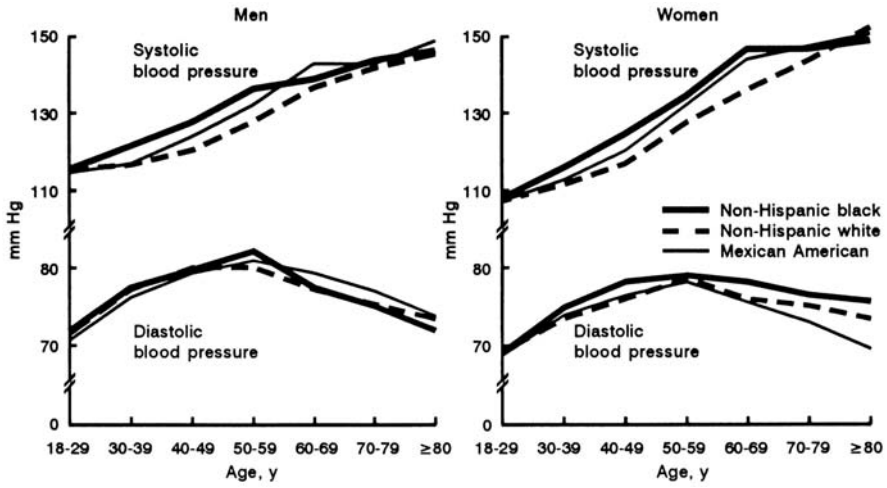

Figure 2.1. Mean systolic and diastolic blood pressures for US population (Vicki et al., 1995)

The reinforcing relationship between remodeling and BP is demonstrated by the growth of media to lumen ratio (M/L), which is the indicator of the extent of remodeling, over the degree of hypertension and age (Figure 2.2). According to a widely accepted view, a positive feedback mechanism takes place between hypertension and vascular lesions (Wilson 1939, 1941; Byrom, 1948; Beilin, 1977 in Guyton, 1980). In this view, high levels of blood pressure cause vascular damage in the kidneys. Increased resistance due to remodeling causes further increases in blood pressure. Although this is the most traditional view for the positive feedback loop between vascular damage and hypertension, this thesis adopts a different approach. This thesis takes the view that a positive feedback mechanism between renal arteriole remodeling and plasma Ang II levels is involved in the progression of blood pressure in essential hypertension. The deviation from the standard vascular damage approach is due to the increasing emphasis given on Ang II for mediating eutrophic remodeling, the kind of remodeling which is predominates initial stages of essential hypertension (Schiffrin, 2004; Mazzali et al., 2002). Moreover, as Mazzali et al. point out, remodeling can occur independent of BP. The positive feedback mechanism modeled in this thesis operates in the following way: High levels of Ang II hormone in circulation cause powerful constriction of renal arterioles. Persistant constriction via Ang II leads to structural reductions in the diameter of renal arterioles which reduces blood flow to the glomeruli. Reduced blood flow through arterioles further stimulates Ang II in circulation through increased secretion of renin. A similar positive feedback loop between high circulating Ang II levels leading to vascular damage was put forward by Guyton as a possible mechanism for driving malignant hypertension (Guyton, 1980).

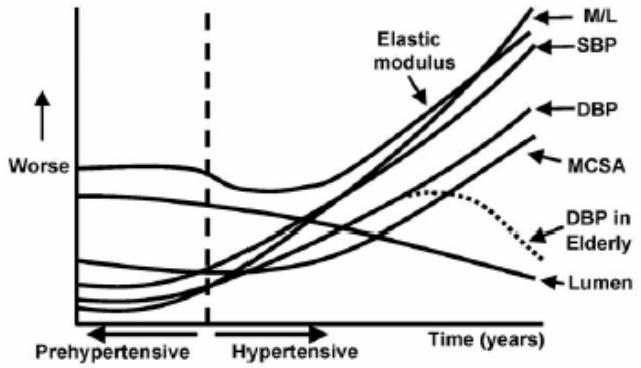

FIG. 4 Changes in morphologic and mechanical aspects of resistance arteries as hypertension evolves in time. DBP = diastolic blood pressure; MCSA = minimal cross-sectional area; M/L = media–lumen ratio; SBP = systolic blood pressure.

Figure 2.2. Time path of remodeling progression (Schiffrin, 2004)

Another positive feedback mechanism on structural changes in kidneys involves elevated levels of blood pressure which engage in a vicious cycle with the number of nephrons, the smallest self-sufficient water excretory unit of kidneys. Persistantly elevated blood pressure causes increased filtration by remaining nephrons. Increased filtration leads to futher loss of nephrons. Consequently, long-term blood pressure rises further as total kidney water excretion capacity will be insufficient to get rid of excess water in the body (Brenner and Chertow, 1994).

A recent hypothesis based on two stages of hypertension put forward by R.J. Johnson and associates provides a solid framework for how different theories on progression of kidney damage relate to each other (Johnson et al., 2005a). According to this hypothesis, essential hypertension occurs via two phases. In the first phase, arterial pressure is elevated from its normal value because of frequent renal vasoconstriction induced by any of extra-renal pressor mechanisms of arterial pressure. Over time, vascular remodeling (structural changes in the size of vascular smooth cells) occurs in kidneys because of the hypertophic effects of these extra-renal pressor mechanisms. After significant remodeling of arterioles has occured in kidneys, hypertension proceeds into the second phase where the vicious circle of blood pressure and glomerular hypertrophy leads to further progression of hypertension. Both these phases are defined by different pathologic and hemodynamic features. In the first phase, the kidney is mildly damaged or undamaged; and there is intermittent or constant vasoconstriction induced most likely by stimuli originating from outside of kidneys. Extra-renal stimuli may be due to conditions such as an overactive sympathetic nervous system or hyperuricemia. Hypertension in the first phase is salt-resistant. Second phase is characterized by persistent renal vasoconstriction, non-uniform remodeling in afferent arterioles, diverging glomerular filtration rates and renin secretion from remodeled and normal nephrons. Hypertension in the second phase is maintained by intra-renal dynamics; it is volume-dependent and salt-sensitive (Johnson et al., 2005a,b).

In this thesis, an intermediary phase was introduced in order to conceptualize progression of hypertension on a continuous scale. A combined volume-loading and vasoconstrictor-type of hypertension similar to the two kidney one clip (2K1C) Goldblatt hypertension is expected to follow the initial phase, which is characterized by intermittent vasoconstrictor type of hypertension (For comprehensive description of these hypertension

types, please refer to Guyton, 1980). Eventually, this intermediary phase would lead to volume-loading hypertension due to accelerated nephron loss caused by ineffective autoregulation of remodeled nephrons. The defining features of this conceptual framework is summarized below (Table 2.1):

Table 2.1. Phases of hypertension progression

Phases of Progression	1.Phase	Intermediary Phase	2.Phase
Hypertension type	Vasoconstrictor	2K1C Goldblatt	Volume-loading
Nephron Number	Normal	Normal	Low
Plasma Renin	High	High-Normal	Low
Remodeling Tendency	High	High-Normal	Low

Heterogeneous distribution of nephrons observed in the intermediary phase results in high plasma renin levels consistent with Sealey et al.'s nephron heterogeneity hypothesis (Sealey et al., 1988; also see 4.2.2 for a detailed recap of this hypothesis). Consequently, remodeling positive feedback loop becomes effective after significant remodeling has occured in the first phase. Progression from high to low renin constitutes one of the many possible pathways. An alternative progression from high-normal to high renin case is also a viable possibility (Personal communication with Sealey and Laragh).

There are many examples of dynamic physiological models which represent the compensating feedback relationships between hemodynamic variables involved in BP and FV regulation (Guyton, 1980; Coleman and Hall, 1992, Karaaslan 2005). There exists also a model which partially focuses on malignant hypertension and growth of BP (Guyton and Coleman, 1969). However, none of these models focuses on the distribution of different types of nephrons over the life span of a person.

3. RESEARCH OBJECTIVES AND OVERVIEW OF THE MODEL

The purpose of this study is to develop a dynamic model which would demonstrate long-term dynamics of blood pressure with specific focus on essential hypertensive people. In each section features of both normotensive and hypertensive kidney-dependent blood pressure progression dynamics will be investigated. Since causal mechanisms for progression are similar in both groups, the difference in behavior of prototypical cases of hypertensive and normotensive will be demonstrated by experimentation with initial conditions and parameters of the model.

In healthy subjects, the water balance of the body between water intake and water excretion is kept at zero without a significant increase in the long-term set level of blood pressure (BP). There are many mechanisms responsible for achieving this balance; the most significant one is the kidney-blood volume-pressure servocontrol mechanism (Guyton, 1980). Blood pressure will fluctuate day in and out around a set value to ensure that water excreted from the body equals water coming into the body. By these short-term fluctuations total Fluid Volume(FV) and BP will be kept stable around their set values.

This daily regulation of FV and BP can be compromised if there are impediments to excretory function of kidneys. *Remodeling* (narrowing) of renal afferent arterioles commonly observed in essential hypertensive subjects constitutes a structural impediment to regulation of FV. Additionally, loss of nephrons due to aging or prolonged hypertension also reduces excretion capacity of kidneys. In both cases, the body takes adaptive measures to ensure that balance between intake and excretion is achieved. The daily or short-term response to loss of filtration would be more frequent elevations in blood pressure (exaggerated natriuresis). However, over long-term, in a matter of weeks or months, other measures will be taken that replace these short-term responses. These measures include hypertrophic changes in the glomerulus of nephrons, vasodilalation of arterioles and other changes which increase excretion efficiency.

From a long-term perspective, control of BP can be viewed as a capacity control problem. FV and BP will be controlled at their normal levels by adaptive increases in excretion capacity, which counterbalance loss of filtration due to remodeling of renal

arterioles and/or nephron loss. This thesis adopts the view that functional regulation of renal arteriole resistance by angiotensin II hormone plays a significant role in the compensation of these structural losses in filtration capacity. The main difference between normotensive and hypertensive subjects in a long-term model mainly lies in the extent of adaptive changes that can be taken against losses in filtration capacity. Inappropriately high levels of plasma Angiotensin observed in essential hypertensives is the primary factor that interferes with adaptive responses and exacerbates the subject's already compromised filtration capacity.

This research focuses on progression of the deteriorative mechanisms of remodeling, nephron loss and the compensatory mechanism of functional adjustments via Renin-Angiotensin System. Whereas other adaptive measures such as hypertrophy and increased excretion efficiency also play a role in the long-term compensatory response, Renin-Angiotensin response was investigated in isolation because of its significant role in pathogenesis and progression of essential hypertension (Sealey et al. 1988, Johnson et al. 2005a,b)

The causal loop diagram in Figure 3.1 demonstrates the relationships among these mechanisms and stocks of the model. Loops 1 and 2 represent control of FV via Renin Angiotensin-Single Nephron Glomerular Filtration Rate (snGFR) and water excretion for both nephron/arteriole subpopulations. Feedback loop 3 demonstrates the positive feedback mechanism between *Remodeled Arterioles*, total remodeled nephron renin secretion (*Renin Secretion R.M.*), plasma renin (PRA) and functional resistance of normal nephrons (Functional Resistance N.N.) which is primarily responsible for progression of remodeling. Loop 4 demonstrates the positive feedback mechanism between remodeled nephron renin secretion, *PRA*, snGFR of remodeled arterioles (snGFR R.M.). and *Remodeled Arterioles*. Feedback loop 5 displays the compensating relationship between *Normal Arterioles*, renin secretion from normal nephron, plasma renin and Functional Resistance N.N.. Lastly, loop 6 demonstrates the positive feedback between *Normal Arterioles*, water excretion, fluid volume, renin secretion from normal nephrons and *snGFR N.N.*

The model is composed of two sectors corresponding to FV and Nephrons. First sector encapsulates FV control structure for a given nephron subpopulation. Nephron

sector includes the two nephron subpopulations, normal and remodeled, and structure necessary to represent nephron loss and remodeling phenomena.

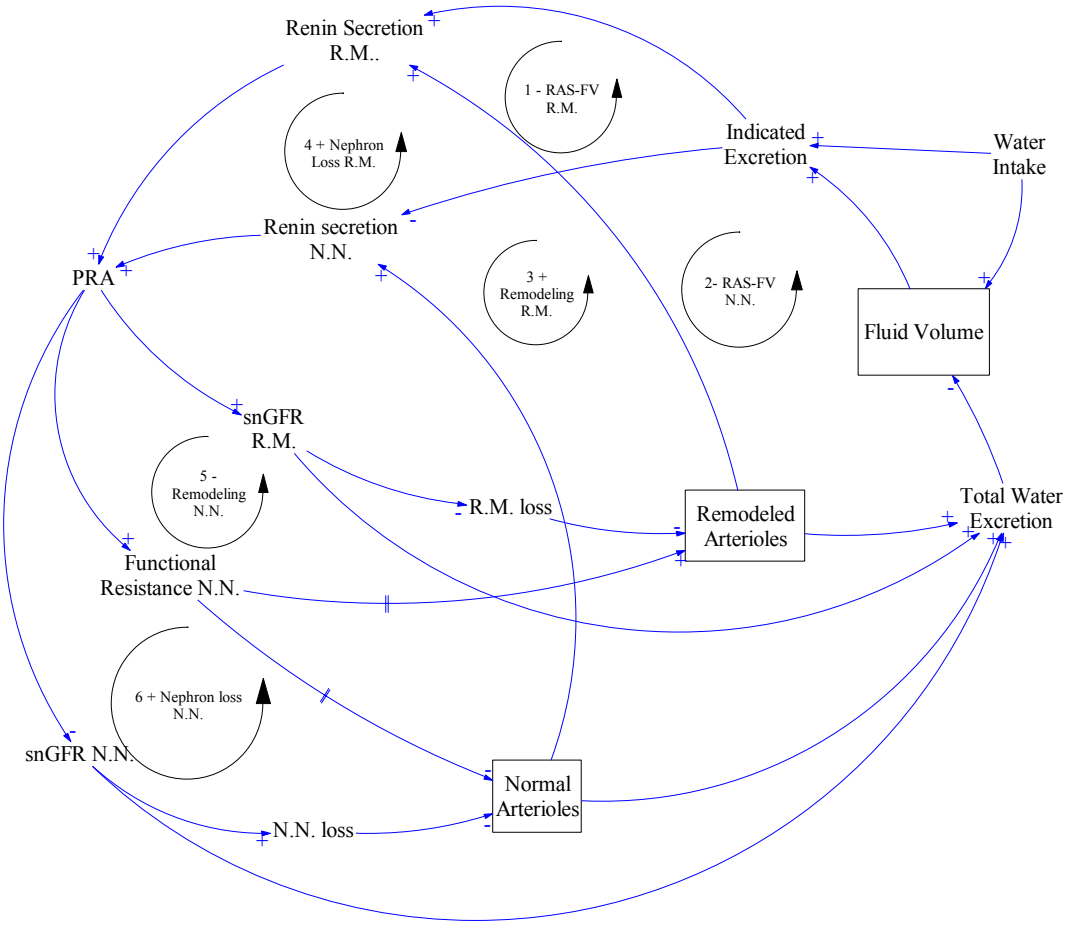

Figure 3.1. Causal-Loop diagram of the model

4. DESCRIPTION OF THE MODEL

4.1. Fluid Volume Sector

4.1.1. Background Information

Fluid Volume refers to the volume of water in the body which is composed of extracellular and intracellular components. Extracellular fluid volume (ECFV) relates to blood pressure over blood volume (BV). The normal physiological value of ECFV in a 70 kg man is about 15 L, where 5L of this amount corresponds to BV. The regulation of ECFV and BV in the body is very tight, thus over longer periods of time they can assumed to be proportional. ECFV will be referred to as fluid volume (FV) throughout this thesis, since intracellular component is outside the boundary of the model. FV changes through evaporation, fluid intake and fluid excretion, namely through urination.

Blood pressure is given by *BP = Total Peripheral Resistance (TPR) * Cardiac Output (CO)*, where *Cardiac Output = f (BV)* . Therefore, when resistance of blood vessels in the body is taken as a constant, FV can be considered as the main determinant of long-term levels of BP. Throughout the rest of the thesis, mean arterial pressure (MAP) will be used to represent BP.

4.1.2. Fundamental Approach and Assumptions

According to homeostasis principle, it is imperative to maintain a balance between water intake and water excretion, otherwise it would be impossible to keep a stable internal environment for the body.

Water intake of human beings are governed by complex feedback mechanisms involving water, osmolality and ADH-hormone. These mechanisms are beyond the boundary of a model which focuses on progression of blood pressure w.r.t. long-term fluid excretion capacity.

Water intake will be modeled as an exogenous variable reflecting the average weekly water intake. Since there is tight control of osmolality in the body that equilibrates water

intake to sodium intake in the short-term, average water intake should be seen as an indicator of average weekly sodium intake. The detrimental effect of excess sodium intake for hypertensive subjects is well known. It causes elevation of BP since it puts additional pressures on the already-compromised excretion function of kidneys. Exogenous water intake can therefore be regarded as a decision parameter to test policies of blood pressure management. Under normal physiological conditions, the body operates in such a way to ensure FV fluctuates very little despite significant changes in water intake. In this model, this homeostatic principle is accomplished by controlling water excretion by FV and water intake levels.

Long-term control of water excretion is accomplished by Renin-Angiotensin System (RAS), which is primarily responsible for controlling the functional constriction and vasodilalation of arterioles. Amount of Ang II in blood is adjusted to respond to different water excretion levels necessary to match water intake. In the model this negative feedback loop will be referred as FV-RAS mechanism.

4.1.2.1.Renin-Angiotensin System: Renin is an enzyme responsible for increasing the secretion rate of Angiotensin I (Ang I) hormone. Ang I is then converted to Ang II which is a powerful constrictor for all arteries and arterioles. The site of renin secretion is near the Juxtaglomerular Appratus of each nephron. Renin secretion is controlled by each nephron individually according to its single nephron glomerular filtration rate (snGFR) and renal arterial pressure. Although renin is produced locally, global Ang II will be consumed in each individual nephron. This means that although nephrons may contribute different amounts of renin to the circulation, they will all benefit from the same concentration of Ang II (Sealey et al., 1973).

The impact of Ang II to renal hemodynamics is mostly through water retention. Ang II affects water retention in the kidneys via three significant ways. Firstly, Ang II increases secretion of aldosterone, a hormone responsible for increasing water reabsorption. Secondly, Ang II itself causes water reabsorption in renal tubules. Thirdly, Ang II has direct and indirect effects on renal afferent and efferent arterioles, which are involved in determining single nephron GFR. Ang II's effects on aldosterone secretion will not be considered in this thesis as they constitute less than 1/3 of Ang II's effects on water

retention. Ang II's effects on reabsorption can not be distinguished from its effects on snGFR, as these two variables are tightly regulated via tubuloglomerular balance mechanism. This thesis will focus only on Ang II's effects on renal arteriolar resistance and autoregulation of snGFR .

4.1.2.2.Renal Arterioles, Afferent and Efferent Resistance: Each nephron has an afferent arteriole and an efferent arteriole. The blood coming from renal artery enters first the afferent arteriole then the glomerulus of nephron and finally the efferent arteriole. The resistance of each arteriole is involved in determining the blood flow through the nephron. The resistance of an arteriole depends on its structure and functional state. The structural state of the arteriole varies over longer time period (weeks/months/years). Thus, there may be multiple nephron groups which can be classified according to the structural size of arteriole diameter. The functional state of the arteriole is constantly regulated by short-term mechanisms in order to respond to the current needs of the body or the local tissue (Autoregulation). Control of afferent and efferent arterioles is achieved via both sympathetic nerve activity and Ang II. It is not quite clear whether Ang II causes vasoconstriction directly at afferent arterioles or whether it causes afferent vasoconstriction over some other mechanisms (Coleman and Hall, 1992). However, its vasoconstrictive effect on efferent arteriole is well-established (Guyton and Hall, 2000). There are many vasoconstrictor and vasodilalative hormones which alter the diameter of the arteriole. However, only one of these hormones, Ang II, is within the boundary of this thesis. This model does not deal with the intricate control of afferent and efferent resistances involving direct and indirect control of Ang II or other hormones. The regulation of these resistances are modeled implicitly as they relate to global Ang II levels. The approach taken in this thesis is that Ang II has a negative effect on both afferent and efferent arteriole resistance.

4.1.2.3. Regulation of Glomerular Filtration Rate: Efferent and afferent resistance are crucially important for regulation of blood flow through the nephrons and glomerular filtration rate. Glomerular filtration rate is a function of ultrafiltration coefficient (kf) and glomerular pressure (Pgc), which in return is determined by arterial pressure.

$$GFR = kf * f(Pgc) \tag{4.1}$$

Pgc is controlled via autoregulation mechanism which involves coordinated vasoconstriction and vasodilalation of afferent and efferent arterioles. The goal of autoregulation mechanism is to provide a stable Pgc, as high pressures can be destructive for the glomerulus. For a fixed arterial pressure, different combinations of arteriolar resistance may increase or decrease Pgc. The relationship between Pgc, afferent resistance and efferent resistance are analogous to a series connection of resistors which has arterial pressure as the voltage across the series and Pgc as the voltage between two resistances. Consequently, while increased resistance at afferent arteriole decreases Pgc, increased resistance at efferent arteriole increases Pgc. However, Pgc is also affected by renal blood flow, which is determined by the total resistance of afferent and efferent arterioles, and arterial pressure. To what extent a sustained reduction in renal blood flow decreases Pgc depends on the individual resistances of afferent and efferent arterioles.

Since Pgc directly determines GFR, the relationship between Ang II and renal arteriolar resistances plays an important role in the control of GFR. Certain aspects of this intricate control mechanism have been clarified. Guyton suggests that in normal physiological regulation afferent arteriole resistance affects GFR negatively with a relationship which can be estimated by a hyperbolic function f=(k/Afferent Arteriolar Resistance).

The normal physiological relationship between efferent arteriole resistance and GFR is more complex and it is suggested to be biphasic. An increase in efferent arteriole resistance from its minimum level initially increases GFR. However, beyond a certain resistance level, further increase in efferent resistance does not increase GFR anymore, but decreases it slightly (Guyton and Hall, 2000).

The relationship between Ang II and GFR levels will be modeled in congruence with these basic relationships. Ang II's effects on each arteriole will not be modeled explicitly. Instead a single relationship between Ang II and GFR will be used bypassing the relationship between Ang II and resistance. Despite the intricacies of renal autoregulation with respect to afferent and efferent arterioles, there is consensus in medical world that under normal physiological conditions sustained high levels of Ang II would increase water retention by constricting arterioles and increasing reabsorption in tubules. Modeling

approach taken in this study is consistent with this view: *Under normal physiological conditions an increase in Ang II decreases GFR.*

Yet, the biphasic relationship between efferent resistance and GFR poses an alternative way to experiment with this relationship. This possibility is based on a hypothesis developed by Sealey et al. on heterogeneity of nephrons (Sealey et al., 1988). To recap Sealey's hypothesis in a nutshell, Sealey et al. suggest that in essential hypertensive patients renin secretion from remodeled nephron subpopulation will be extremely high as these nephrons would try to increase their efferent resistance to increase their compromised snGFR. On the other hand, normal nephrons try to decrease their renin secretion in order to have maximum vasodilalation of afferent and efferent arterioles and thus increase renal blood flow. Although both subpopulations want to increase their snGFR, they have quite opposite renin secretion needs. Consequently, high renin secretion from remodeled and low renin secretion from normal arterioles result in a weighted sum of Ang II in circulation that is inappropriate for both subpopulations. In the presence of significant remodeled nephron subpopulation in the kidney, the steady state level of global plasma Ang II is higher than required renin per normal nephron and lower than the required renin per remodeled nephron. As a result of high renin, excretion function of normal arterioles will be compromised and fluid volume will rise. Based on this hypothesis two different reference relationships with opposite causalities between renin-Ang II and GFR of remodeled nephrons can be adopted.

In the model, plasma renin levels are modeled not as accumulation of renin secretion over time but as aggregation of renin contributed by normal and remodeled nephron populations. Desynthesis rate of renin is proportional to the amount of renin in the blood; and in the absence of a pathological problem in the liver, which is the main site of desynthesis, plasma renin is determined by renin secretion in the kidneys (Sealey et al., 1973). For clinical purposes, plasma renin levels are measured as plasma Renin Activity (PRA) in Ang I concentration in blood per hour of incubation period (in ng/mL/h). In the renal hemodynamics model of Coleman and Hall, log of Ang II concentration is used to model effects of Ang II on arteriole resistances (Coleman and Hall, 1992). However, their model is a short-term model, with a time unit of minutes/hours, where concentration of Ang II is endogeneously modeled. This long-term model does not deal with explicit

modeling of Ang II concentration. This model takes the approach that each nephron would secrete the necessary amount of renin corresponding to its snGFR needs. The total amount of renin in the blood will be calculated as the sum of renin secretion by all nephrons. Subsequently, snGFR of each nephron will be affected by the average renin per nephron. The term "renin" will be used as the indicator of Ang II throughout this thesis.

4.1.2.4. Parameter Calibration: Macro level parameters for the model are the number of nephrons, FV, BP, plasma renin levels, water excretion, water intake and GFR for a representative person. Normal physiological values were used for these parameters (Guyton and Hall, 2000). Micro level parameters are single nephron GFR and the magnitude of possible functional change in snGFR w.r.t. levels of plasma renin. A top-down approach is used to estimate these micro-level parameters from macro parameters. SnGFR is calculated by dividing GFR to the number of nephrons. The magnitude of effects of functional changes on snGFR by average renin per nephron is estimated from the physiological range of snGFR and arteriole resistance values mentioned in literature (Guyton and Hall, 2000). The constants used in the model are summarized in Table 4.1.

4.1.2.5.Fundamental Approach to Fluid Volume sector: In reality, FV control is managed by an integrated system of at least three main separate systems of water intake control, water excretion control, and evoporation control. Long-term FV of the body is kept pretty much around a target level, through constant feedbacks between these mechanisms. In other words, daily mechanisms such as ADH thirst system adjusts the level of water intake, whereas other mechanims such as pressure natriuresis adjusts the level of water excretion to ensure that FV of the body is not significantly changed day in day out. This model is not concerned with the daily fluctuations of FV. The weekly/monthly long-term perspective of the model renders modeling of these short-term mechanisms unnecessary. Nevertheless, the end result of daily interactions of thirst mechanism will be used in the model as average weekly water intake. The model takes into account reasonable variations in water intake and excretion. The hypothetical person in this model cannot sustain extreme variations in water intake over a number of weeks. For example, a 10 times increase in normal weekly value would be unrealistic. Since the integrated short-term system responding to such excess variations are not modeled, such scenarios would be irrelevant to this model. That being said, the model can be tested against reasonable

changes in water intake to verify whether it passes structural validity tests and to conduct experiments with salt-intake policies.

The basic approach taken in this model can be summarized as following: FV changes through water intake or water excretion. The FV control system initiates adaptive responses in excretion function of kidneys in the case of a change in water intake or any changes that affect current water excretion. The body determines desired water excretion level based on average weekly intake and current level of FV. For example, if FV is above its target level, desired water excretion increases and vice versa..

At any point in time, there is a certain number of nephrons in the body which have to supply this water excretion level in order to appropriately control FV. Any reduction in the number of nephrons increases the necessary excretion each remaining nephron has to achieve in order to maintain FV. Nephrons only loose a small fraction of their snGFR as urine; most of filtered water is reabsorped back into the body. However, when snGFR and single nephron reabsorption are tightly regulated, a fixed fraction of snGFR can be used to determine water excretion from the body. Under normal physical conditions, the *tubuloglomerularbalance mechanism* ensures that glomerular filtration and reabsorption by the nephron are tightly regulated (Guyton and Hall, 2000). With the assumption that this mechanism remains intact while kidney undergoes structural changes, the desired excretion will be converted to desired snGFR per nephron using a fixed fraction..

In addition to this desired snGFR which is dictated by the goal-seeking mechanism for control of FV, there is a normal snGFR which is dictated by BP. Since BP is considered to be mainly as a function of FV, any changes in FV affect normal snGFR. In other words, when FV is high, normal snGFR and therefore water excretion from the body will also be high. However, this second negative feedback loop does not have an explicit target that for FV. On the other hand, when FV or water intake are different from their normal levels adaptive changes initiated by Renin-Angiotensin System ensures that FV is maintained exactly at its target level.

When there is a difference between desired snGFR and normal snGFR, each nephron adjusts its actual snGFR to desired snGFR by regulating its own renin secretion. This

regulation works in the following way: For example, as desired snGFR increases, renin secretion from normal arterioles is reduced below its normal level. Under steady-state conditions, the renin amount in the blood is directly proportional to the rate of renin secretion by all nephrons (Sealey et al., 1973). So, when there is higher desired snGFR there will be lower renin and Ang II in the blood since, as mentioned previously, renin is the main determinant of Ang II in the blood. Low levels of Ang II in blood will decrease resistance of renal arterioles. This will increase the actual snGFR above the current level of normal snGFR and thus actual water excretion will meet desired water excretion.

4.1.3. Description of the Fluid Volume Sector Structure

This sector has one stock, *FV,* which is changed by its inflow *Water Intake* and outflow *Water Excretion.* The body regulates *FV* stock by changing excretion rate based on the current value of *FV* and *Water Intake.* If there are any deviations from normal *Water Intake* of the body, *Desired Excretion* changes by an amount equal to the extent of deviation from normal *Water Intake*. Similarly, if there are any deviations from the target level of FV for the body, *Target FV, Desired Excretion* changes proportionally to the ratio of actual FV over the target level of FV (*FV/Target FV).* Whether *Desired Excretion* can be achieved or not depends on the capability of renin system and the current level of *normal snGFR* dictated by *FV.* If desired corrective actions are within max and min capacity constraints of *renin secretion* and snGFR, this structure ensures that *Water Excretion* will always be equal to *Desired Excretion.* This means that when *FV* is at its target level, *Desired Excretion* will be equal to *Normal Water Intake.* On the other hand, when *FV* deviates from its *Target FV, Desired Excretion* will equal *Normal Water Intake* times the ratio of *FV/Target FV* plus any deviations of *Water Intake* from *Normal Water Intake.* The maximum formulation guarantees that *Desired Excretion* never falls below 0. *Target FV* is set to 15 L, whereas *Normal Water Intake* is set to 10.08 L/week.

$$Desired\ Excretion = max(0,(Normal\ Water\ Intake*FV/Normal\ FV + Additional\ Desired\ Excretion)) \quad (4.2)$$

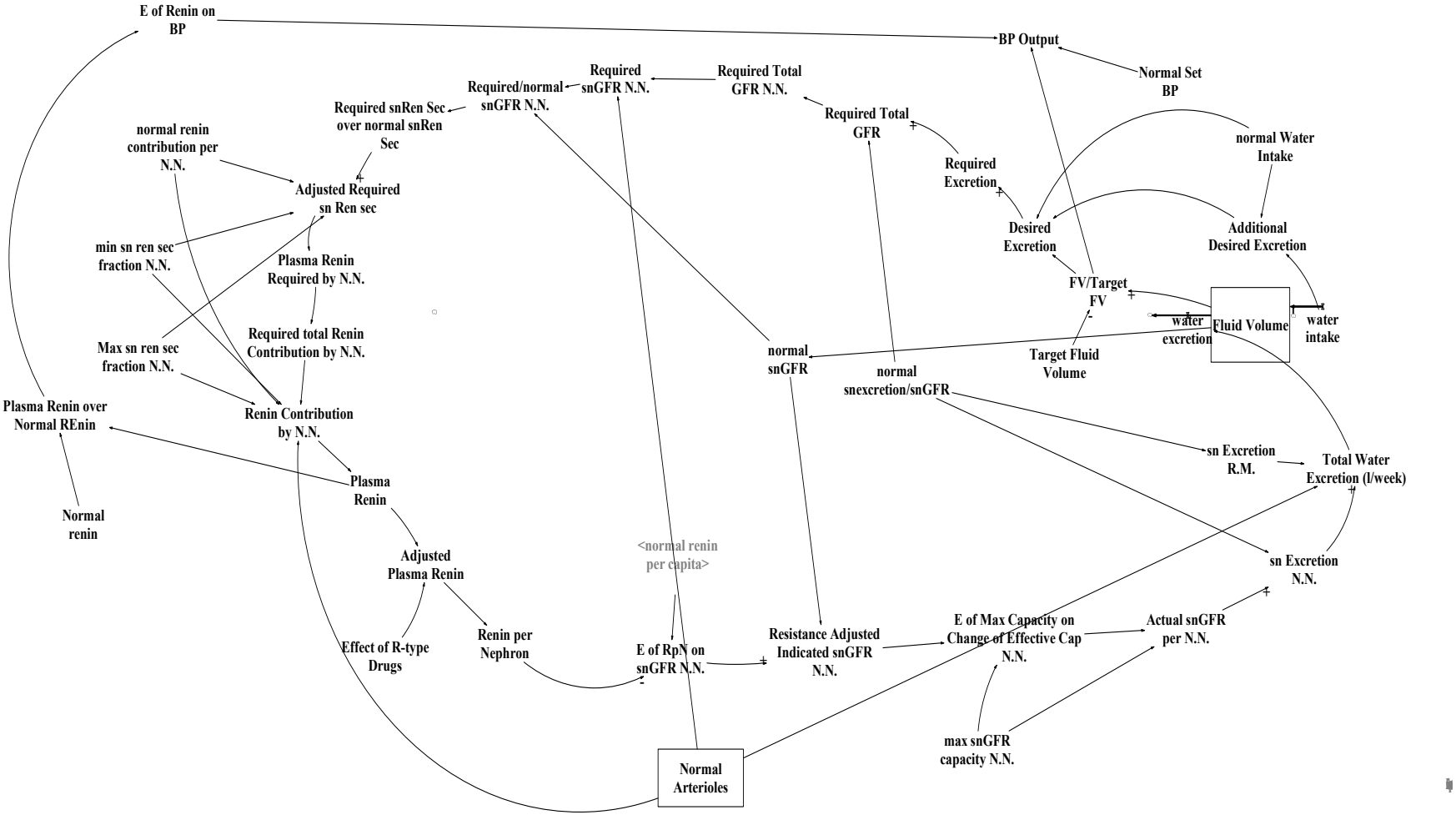

Figure 4.1. Stock-Flow diagram for FV sector

$$Additional\ Desired\ Excretion = Water\ Intake - Normal\ Water\ Intake \quad (4.3)$$

Any deviation of *FV* or *Water intake* from normal levels prompts corrective action via *Desired Excretion*, renin secretion and subsequent changes in snGFR.

Desired Excretion is constrained by absolute levels of minimum and maximum water excretion the body must conduct. Therefore, *Desired Excretion* is converted to Required Excretion by an effect function (Figure 4.2).

$$Required\ Excretion = E\ of\ Desired\ Excretion\ on\ Required\ Excretion * Normal\ Excretion \quad (4.4)$$

$$E\ of\ Desired\ Excretion\ on\ Required\ Excretion = f\left(\frac{Desired\ Excretion}{Normal\ Water\ Intake}\right)$$

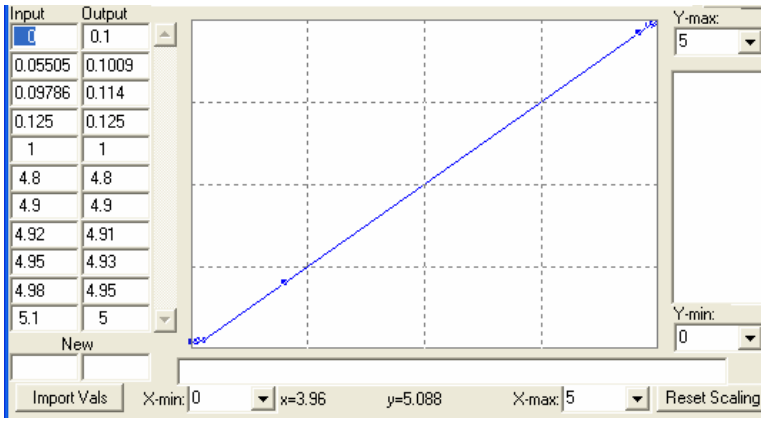

Figure 4.2. E of Desired Excretion on Required Excretion

Required Total GFR (ml/day) is calculated from *Required Excretion* (L/week) by dividing it to three different conversion fractions, namely, *normalsnexcretion/snGFR,* a conversion fraction between excretion and glomerular filtration rate; a *time unit conversion* which converts weeks to days and a *volume unit conversion* which converts liters to milliliters (The latter two variables are excluded from the stock-flow diagram to avoid visual overload) . Through these conversions, average daily GFR value corresponding to *Required Total GFR* (ml/day) is found.

Required Total GFR is compared to current *Total Normal GFR* which is dictated by *normal snGFR* and the number of nephrons. *Normal snGFR* refers to snGFR proportional

to the pressure *FV* applies to renal arterioles when they are at their normal resistance levels. Therefore, *Normal snGFR* is given by a fraction of *FV, normal snGFR fraction* which equals 0.006 (ml/day)/L.

$$normal\ snGFR = normal\ snGFR\ fraction * FV \tag{4.5}$$

Under normal physiological conditions, when *FV* is at its Target level of 15L, *normal snGFR* is equal to 15 L*0.006 (ml/day)/L = 0.09 ml/day. When *FV* is at its target level of 15 L, this *normal snGFR* value is calibrated to 0.09 ml/day, because normal physiological GFR equals 180000 (ml/day) and there are initially 2000000 nephrons. Thus, normal glomerular filtration per nephron equals the division of normal physiological GFR to normal number of nephrons.

Required/Normal GFR gives by what proportion each nephron has to adjust its *normal snGFR* in order to reach *Required snGFR.* Based on the ratio of *Required snGFR* and *normal snGFR,* corrective action will be taken by adjusting renin secretion if necessary. *Required sn Ren Sec over normal snRen Sec* ratio returns the desired single nephron renin secretion in proportion to normal renin secretion per nephron. This function would return the necessary level of renin per nephron circulating in the blood, which would result in the adjustment of *normal snGFR* to *Required snGFR* (Figure 4.3)

Required sn Ren Sec over normal snRen sec = f (Required/Normal snGFR N.N.)

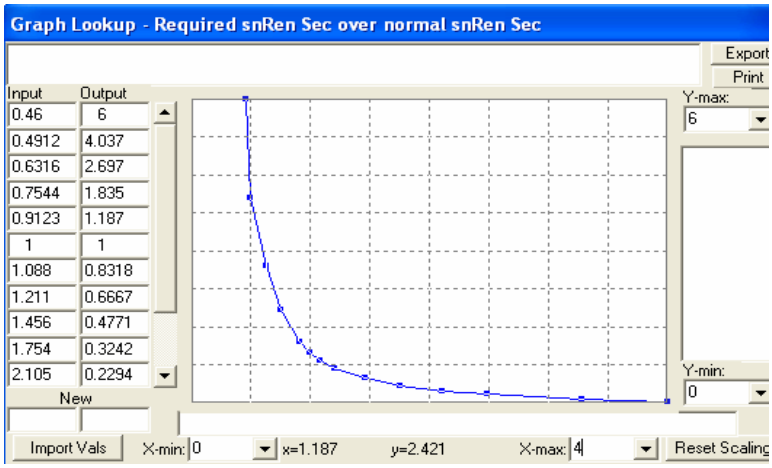

Figure 4.3. Required sn Ren Sec over normal snRen sec

In reality, each single nephron tries to reach its *Required snGFR* by functionally changing their afferent and efferent arteriole resistances. For the right combination of afferent and efferent resistances the *Actual snGFR* will be equal to *Required snGFR*. There is a right amount of plasma renin, which would return this required combination of afferent and efferent resistance values. In the case of single nephron subpopulation, it can be assumed that nephrons can exactly achieve this *Required snGFR*, as long as the desired renin amount is within the min/max limits of renin secretion. This exact match between required snGFR and resistance adjusted snGFR may seem unrealistic. However, considering that renin secretion is a short-term mechanism, it is reasonable that steady-state levels of plasma renin will be reached within a week. Since there are no other variables affecting renin secretion within system boundary, an exact match between desired renin secretion and actual renin secretion should be considered to be reasonable.

Required single nephron renin secretion over normal single nephron renin secretion, *Required sn Ren Sec over normal snRen sec,* multiplied by *normal renin contribution per nephron* and number of nephrons gives the total renin contribution by nephron subpopulation. In the presence of two nephron subpopulations, the renin contribution for each nephron group is added together to give *Plasma Renin*. Since renin is produced locally but global Ang II is consumed by each nephron, the weighted average for renin per nephron will be calculated by dividing *Plasma Renin* to total number of alive nephrons. This renin per nephron will be the input for effect of renin per nephron on snGFR, *E of RpN on snGFR* (Figure 4.4.).

E of RpN on snGFR N.N. =f (Renin per nephron/normal renin per nephron)

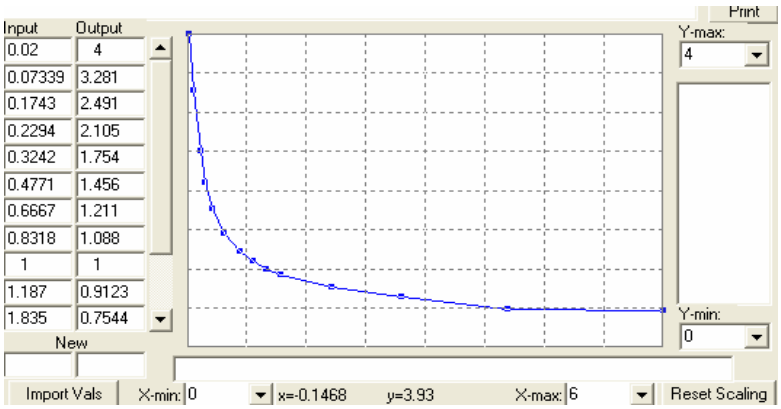

Figure 4.4. E of RpN on snGFR N.N.

E of RpN on snGFR N.N. represents the relationship between *Renin per Nephron* values and *normal snGFR* of each nephron. As *Renin per Nephron* increases, *Actual snGFR* decreases. *Actual snGFR* falls down to its minimum possible value for maximum renin per nephron. This value corresponds to the resistance combination of afferent and efferent arteriole where snGFR will be lowest for the current *normal snGFR*. The maximum and minimum output values of *E of RpN on snGFR N.N.* are estimated from information on limits of snGFR (Guyton and Hall, 2000). Input values are estimated from Sealey et al.'s conceptual model, by following their model's assumptions and theory (Sealey et al., 1988).

Resistance Adjusted Indicated snGFR is found by multiplication of *E of RpN on snGFR N.N* and *normal snGFR*. This value is checked against a maximum possible value given by *Max snGFR capacity*. As long as *Resistance Adjusted Indicated snGFR* is within maximum and minimum limits of snGFR, it will determine *Actual snGFR*. The relationship between *Resistance Adjusted snGFR* and *Max snGFR* can best be formulated by a fuzzy min fomulation (Figure 4.5). The approach of *Actual snGFR* to maximum GFR capacity of the nephron is expected to be non-linear, since nephrons can be assumed to be reluctant to operate at their max capacity. A similar structure for remodeled nephron is introduced in Nephron sector.

$$E\ of\ max\ Capacity\ on\ snGFR\ N.N. = f\left(\frac{Resistance\ Adjusted\ Indicated\ snGFR\ N.N}{max\ snGFR\ capacity\ N.N.}\right)$$

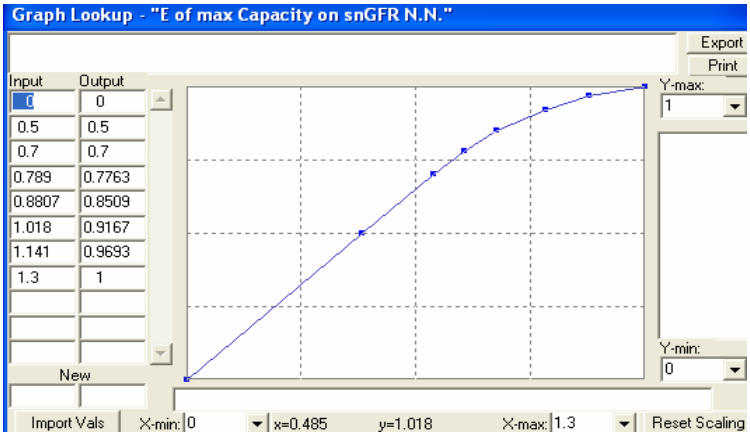

Figure 4.5. E of Max Capacity on snGFR N.N.

Single nephron water excretion, *sn Excretion N.N.,* will be calculated from *Actual snGFR* by multiplication with *normalsnexcretion/snGFR. Total Water Excretion* is equal to the sum of excretion of all nephrons.

There are two variables related to BP in the model. The first one is *Indicated BP* which represents BP level indicated by current *FV.* This constitutes the average BP caused by volume-loading or water retention.

$$Indicated\ BP = Normal\ Set\ BP*FV/Target\ FV \tag{4.6}$$

The other BP related variable is *BP Output,* which also takes into account the effects of plasma renin levels on other blood vessels in the body. This parameter is a better representation of measured BP. Therefore, only *BP Output* will be reported in the analysis section.

$$BP\ Output = Normal\ Set\ BP*\ FV/Target\ FV*E\ of\ Renin\ on\ BP \tag{4.7}$$

E of Renin BP is an s-shaped function which has a positive relationship with *Plasma Renin* over *Normal Renin,* which corresponds to normal renin secretion level of 6.4 g/day. Renin effect is allowed to affect BP only minorly, since long-term BP is to a great extent determined by water excretion function of the kidney and therefore by the level of *FV* (Figure 4.6).

E of Renin BP= f (Plasma Renin/Normal Renin)

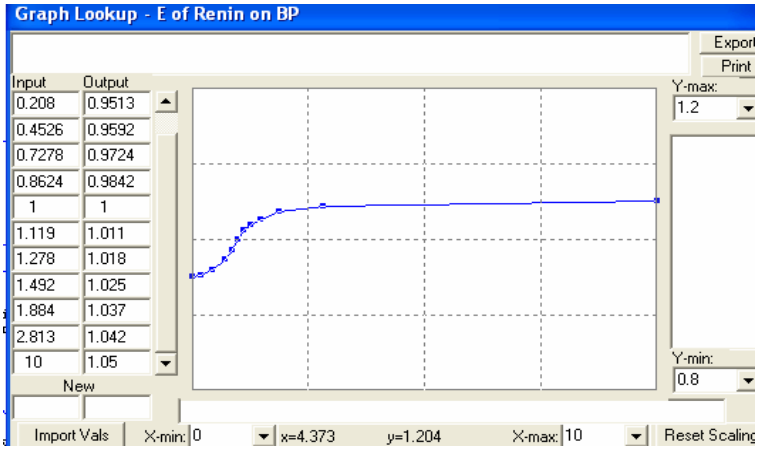

Figure 4.6. E of Renin on BP

In summary, there are two (-) feedback loops in FV sector. The first one, RAS-FV loop, controls FV around the Target FV. It prompts corrective action via renin secretion when *Required snGFR* is different from *normal snGFR* dictated by current *FV. Actual snGFR* will be found based on the effects of actual renin secreted on *normal snGFR*. When actual renin per nephron exactly matches desired renin per nephron this feedback loop ensures that *Required snGFR* is reached at each time unit. The second (-) feedback loop, *FV-Normal snGFR* adjusts *normal snGFR* to changes in *FV* level. Current parameter values of *Normal Water Intake,* initial FV and *normalsnGFR fraction* are set such that when *FV* changes from its initial level because of a change in water intake, this loop alone would bring *FV* back to its *Target FV* without causing any changes in renin secretion.

4.1.4. Dynamics of Fluid Volume Sector in Isolation

In this section, a number of tests will be conducted to verify that FV structure works properly. In order to verify the proper functioning of FV volume sector, experiments with initial FV values and sudden increases in water intake will be conducted. The behavior of key variables such as FV, BP, water excretion, plasma renin and renin per nephron will be demonstrated for a simulation period of 50 weeks.

In the first experiment, it will be tested whether the current structure controls FV volume around its target level of 15 L. At simulation start FV is initiated at 30 L (See Figure 4.7 on the next page). The results demonstrate that both FV and BP return back to their target values of 15 L and 100 mmHg, respectively. While Actual snGFR adjusts itself through the FV normal snGFR mechanism to Required snGFR, FV-RAS control is not involved in the establishment of equilibrium. Required single nephron renin over normal single nephron renin (Required snRenin over NsnR) remains at one, indicating that normal renin contribution will not be changed. Plasma renin also stays at the level of normal plasma renin (Figure 4.7).

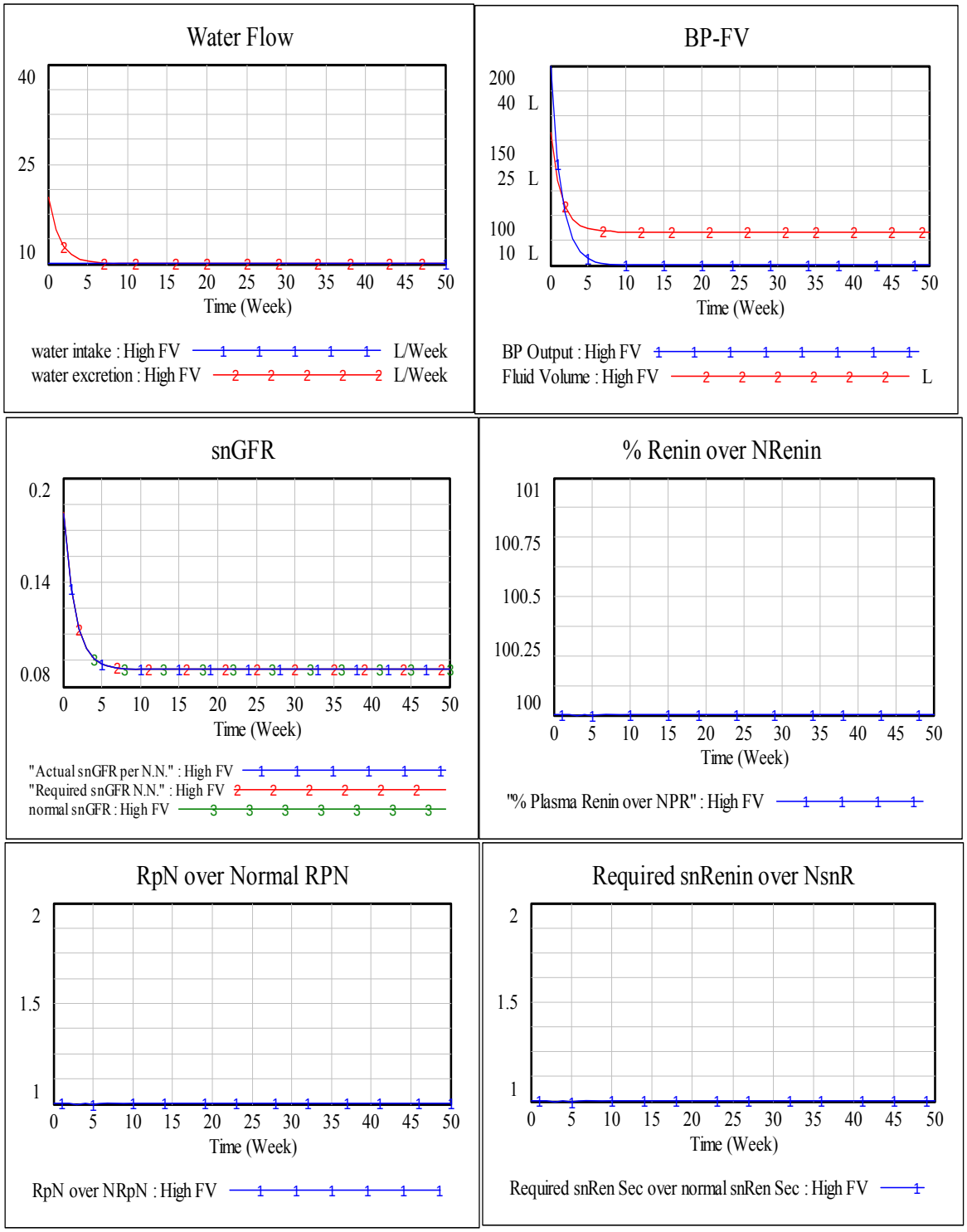

Figure 4.7. Dynamics of FV sector for high FV initially

The next experiment tests FV sector's response to an increase in water intake by 50 per cent at time 10. Required single nephron renin over normal single nephron renin secretion (Required snRenin over NsnR) decreases in order to decrease the renal arteriole resistances. Renin per nephron follows Required snRenin over NsnR. FV does not move

from its target level. BP output falls slightly because of the reduction in renin levels (Figure 4.8).

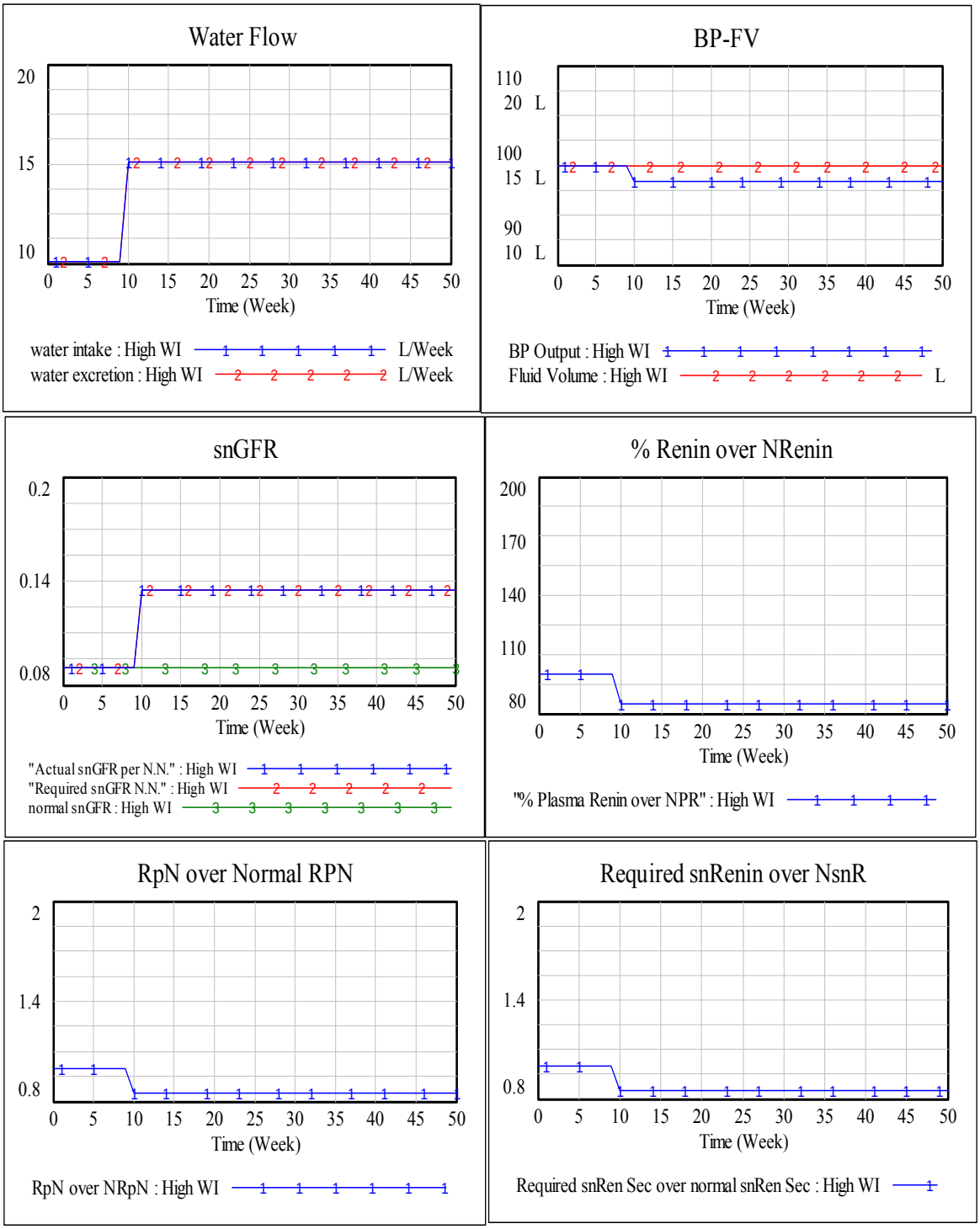

Figure 4.8. Dynamics of FV for increased WI

Next, FV sector's response to high initial FV and high water intake will be tested. Initial FV is set to 30 L and Water Intake is set to 15.08 L/week. Both BP and FV return to their target levels, through the adjustments in renin levels made by FV-RAS mechanism (Figure 4.9). The three experiments conducted so far, demonstrate that the structure for FV control is valid.

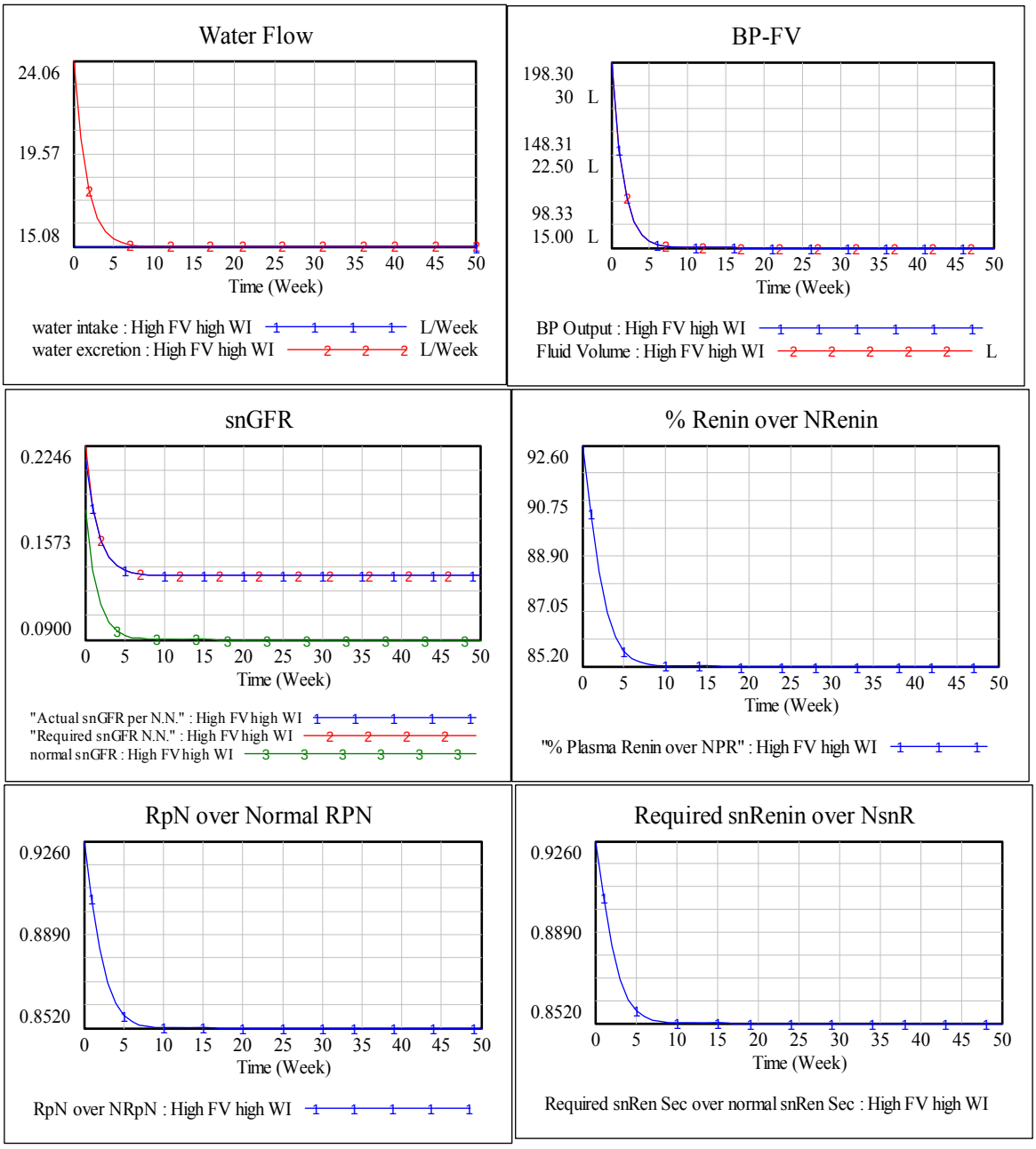

Figure 4.9. Dynamics of FV sector for high FV and high WI

In the final experiment, FV sector's response for an extreme initial FV level will be tested. FV is initialized at 150 L and Water intake set to 15 L. FV and BP return back to Target Value. However, return to target takes a longer time since max snGFR capacity constrains Actual snGFR (see snGFR graph, Figure 4.10).

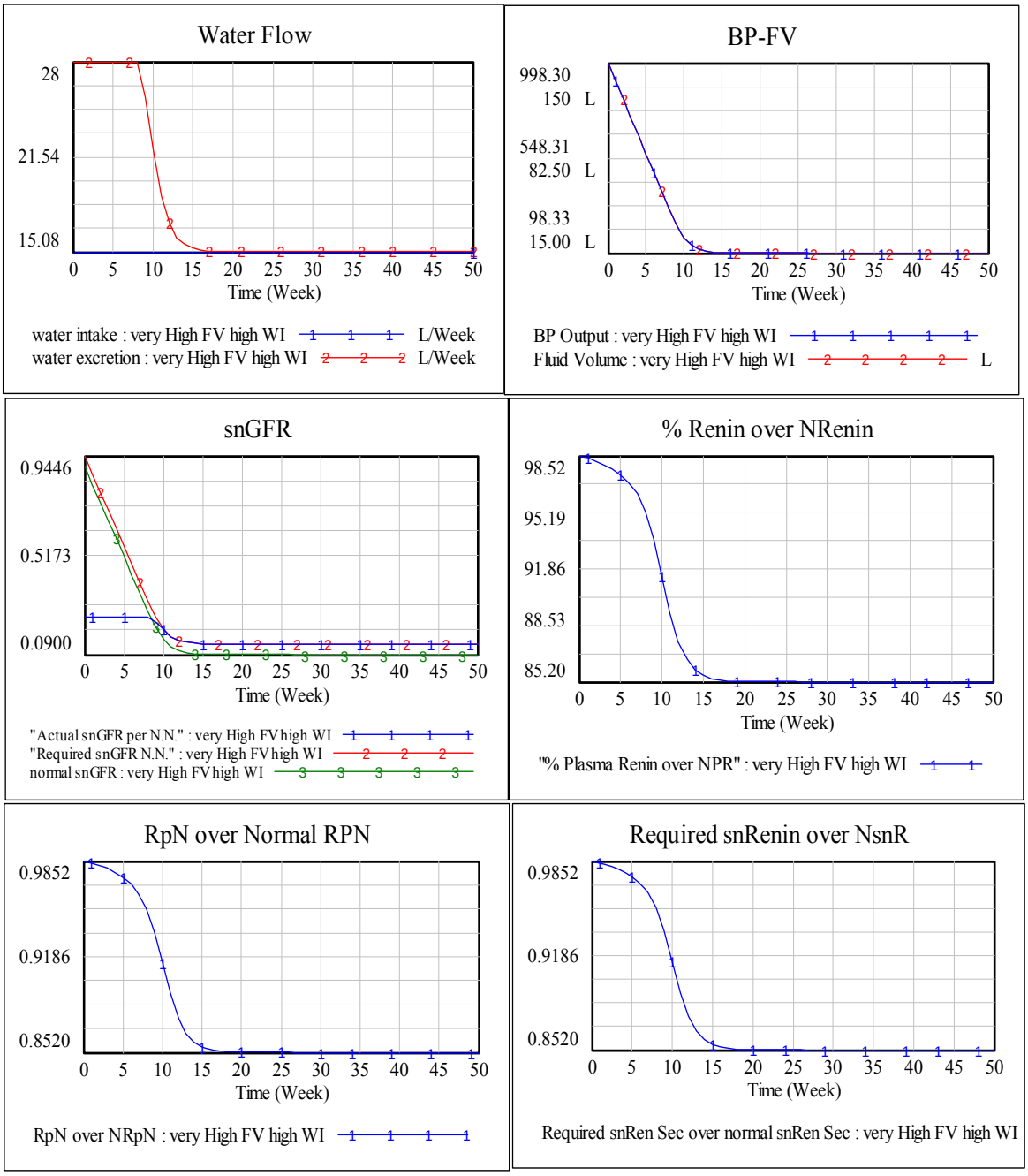

Figure 4.10. Dynamics of FV sector for very high FV and high WI

4.2. Nephron Sector

4.2.1. Background Information

Most hypotheses on pathogenesis of hypertension originate from experimental hypertension models such as one kidney one clip (1K1C) and two kidney one clip (2K1C) Goldblatt models. The distribution of nephrons over time, especially, over the lifespan of a human being is rather continuous than discrete as it's usually characterized in these experimental models. The nephron distribution approach of this thesis facilitates a more appropriate framework for representation of continuous phenomena such remodeling and nephron loss.

Human beings are born with a fixed number of nephrons (approximately 2 million nephrons); nephrons do not regenerate after birth. Therefore, the number of nephrons at birth and their filtration capacities can to a large extent predetermine the effectiveness of a person's excretory function and his/her predisposition to develop hypertension (Brenner and Chertow, 1994).

Healthy functioning of nephrons necessitates a stable environment. Too high or too low Glomerular Pressures are dangerous for nephrons as both conditions may destroy the nephron. Loss of nephrons would decrease excretion capacity of a person. Autoregulation is to a great extent responsible for providing this stable environment by its regulation of afferent and efferent arteriole resistances. Remodeling constitutes the other structural mechanism by which the excretion capability of nephrons can be reduced. In most cases, remodeling occurs at the afferent arteriole leading to glomerulus. Therefore, "remodeled nephron" term will be used interchangebly with "remodeled arteriole" term throughout this study (Similarly, normal nephron and normal arteriole will also be used interchangebly).

4.2.2. Fundamental Approach and Assumptions

In Nephron Sector, the FV-RAS structure which controls FV via functional changes will be integrated with other structural change mechanisms of remodeling and nephron loss.

4.2.2.1.Remodeling: The remodeling of afferent arteriole is one of the characteristics of essential hypertension. The initiation of remodeling may be due to many reasons; however, there seems to be consensus on the notion that chronic vasoconstriction is responsible for thickening of the arteriole, especially, eutrophic type of remodeling (Schiffrin, 2004, Johnson et al., 2005a). Thus, any vasoconstrictor substance in abnormally high blood concentrations could be responsible for initiation of remodeling. Ang II seems to be an especially important substance in mediating remodeling. In animal experiments, it has been demonstrated that high doses of Ang II infusion causes remodeling. Although in smaller magnitude than in Ang II infusion experiments, Ang II is also present in high concentrations in some essential hypertensive patients. Essential hypertensive cases similar to 2K1C experimental model which have high plasma renin may especially provide a suitable venue for causing Ang II mediated remodeling. This likelihood of Ang II's involvement in remodeling brings about the interesting possibility that there may be a high renin-remodeling-high renin loop in essential hypertension. This possibility is supported by the theory on different renin levels in essential hypertension (Sealey et al., 1988). Sealey et al. explain the pathway responsible for high plasma renin in the presence of an ischemic subpopulation of nephrons by an analogy to 2K1C experimental model. In 2K1C model, one of the renal arteries is constricted. It is observed that BP and plasma renin levels rise until normal excretion from the kidneys is achieved. The hypertension dissappears once constriction of arteriole is removed. The basic notion is that ischemic kidney secretes high amounts of renin which interferes with the subject's water excretion capability. This conclusion follows from the fact that one kidney alone can achieve normal excretion without any rise in BP. Sealey et al. suggest that a major subgroup essential hypertension cases (about 30 per cent) are affected by similar phenomenon to 2K1C model. There are significant number of ischemic nephrons which are underperfused. Therefore they have unsuppressed renin secretion. Subsequently, global renin levels rise. High levels of renin interferes with the excretion of remaining healthy nephrons. Other than Sealey's hypothesis, there may be other alternative explanations as to why ischemic nephrons secrete excess renin and why global renin levels can not be suppressed. Based on current medical knowledge there are a number of observations/fact that will be used in this model:

1) Remodeled nephrons secrete more renin than normal nephrons given the same global conditions, i.e. BP level
2) There are different possible explanations for their behavior:

- Nephrons try to increase their efferent resistance and thus increase their snGFR (Sealey et al., 1988).
- Nephrons try to increase global BP and provide for themselves a constant source for achieving normal perfusion (Guyton, 1980).
- They cannot turn off their renin secretion because of a deficiency caused by remodeling. For example, according to Sealey, they cannot sense arteriolar pressure at the afferent arteriole.
- They do not need to consider renin's direct or indirect effects on their own afferent arteriole, since it has lost its distensibility and cannot constrict any futher. Thus, they stop suppressing their renin secretion.
- They have distorted autoregulation because of remodeled afferent arteriole. Therefore they cannot estimate the effects of secreted renin amount on their snGFR.

3) Normal Nephrons compensate for the lack of filtration/water excretion caused by the presence of remodeled nephrons by increasing their own filtration.
4) Normal Nephrons try to achieve compensation via RAS-mechanism by lowering their own renin production (Laragh, 2002).
5) The global renin level is inadequate for needs of either subpopulation. It is too high for normal subpopulation's desired level and too low for remodeled nephrons' desired level.

Based on these five points the following framework was developed for modeling plasma renin and remodeling relationship.

- Under normal physiological conditions, i.e. when there are no remodeled nephrons, normal nephrons secrete approximately the right amount of renin which would give them the desired snGFR to control FV.
- Presence of remodeled nephrons somehow distorts the proper control of this Normal nephrons' RAS mechanism, and leads to inappropriate levels of plasma renin which would increase FV above target level.

The view adopted in this model is as follows: Normal nephrons control their renin secretion to satisfy their individual needs after taking into account renin production by remodeled nephrons. Thus, normal nephrons would secrete renin at rate which would result in a global renin level that provides the necessary amount of renin per time unit per nephron to achieve the required snGFR dictated by FV and Water Intake.

4.2.2.2.Nephron Loss: Death of nephrons is determined by natural aging process and the level of glomerular pressure. Sustained high or low glomerular pressures decrease a nephron's lifespan. As discussed in the fundamental approach section of FV sector, in this model glomerular pressure per nephron is not modeled explicitly. However, relative value of Actual snGFR over normal snGFR provides a good measure for modeling effects of glomerular pressure on the death rate of nephrons.

Nephron subpopulations differ with respect to their average snGFR values. Whereas normal nephrons have normal or high snGFR values as remodeling or nephron loss progresses, remodeled nephrons have low snGFR values. Therefore the death rate of normal nephrons are affected by effects of high glomerular pressures; whereas the death rate of remodeled nephrons are affected by low glomerular pressures.

Both remodeling and nephron loss increase the required excretion by remaining nephrons. Only normal nephrons can undertake corrective actions in their snGFR over RAS-FV control mechanism. Remodeled nephrons are incapable of taking such corrective actions since their renin secretion function is considered to be distorted. Although remodeled nephrons are incapable of taking any corrective action, they still contribute to filtration through their FV-normal snGFR mechanism. Thus, the structure of the model will represent a mechanism in which only normal nephrons would try to increase their filtration to compensate for losses in filtration capacity which may result from conversion to low capacity remodeled nephrons or reduction in nephron number. While doing so normal nephrons will also take into account any loss in their filtration rates due to increased levels of plasma renin, and they will adjust their renin secretion accordingly.

4.2.3. Description of the Nephron Sector Structure

This thesis tries to represent long-term control of fluid volume like a capacity management problem. Nephrons, each self-sufficient unit of kidneys, may be seen as members of workforce responsible for achieving delivery of goods from an inventory stock (Fluid Volume) while maintaining a target level of inventory (ideal blood pressure). The workforce cannot be increased above its initial level because there is not a viable pool of other candidates. As time goes by, people depart from the workforce (loss of nephrons) or become handicapped (remodeling of nephrons). Either way, the total delivery rate of the workforce decreases. In response, the management provides incentives to increase individual delivery rate of each remaining healthy member of the workforce (reduction in renin secretion of normal nephrons). However, these incentives are hampered by the negative effects of growing handicapped group (high renin secretion from remodeled nephrons). Handicapped workers still contribute to total delivery rate; therefore, their presence is initially beneficial for the company ("body"). However, as the relative distribution of handicapped worker per healthy worker increases above a critical threshold value, handicapped workers get in the way of healthy workers. This causes a decrease in healthy workers' delivery rate, or worse, it causes work-related injuries in healthy workers. Thus, the task of the management is to control the relative distribution of members of this workforce in the best possible way to ensure that the company meets its incoming requests (water intake) and maintains an inventory near target levels (Target FV).

To represent this workforce management problem in the context of kidneys, Nephron Sector is composed of two identical stocks: *Normal Arterioles* and *Remodeled Arterioles*. These stocks change through their outflows *N.N. Loss rate* and *R.M. Loss rate*, respectively. Furthermore, these stocks are connected to each other via *Arteriolar Conversion* flow which converts Normal Arterioles to Remodeled Arterioles.

Nephron loss rates are controlled by first-order control of nephron stocks. They are composed from nephron loss fractions and effects of low or high Blood flow on nephron loss rates.

Nephron Sector is connected to FV-RAS mechanism in the following way. *Required Total GFR N.N.* is adjusted based on the difference of *Required Total GFR* and *Total Normal GFR R.M.*. The latter is a function of *normal snGFR R.M.* and *Remodeled Arterioles*. *Required snGFR N.N.* is calculated by dividing *Required Total GFR N.N.* to *Normal Arterioles.*

The ratio of *Required snGFR* and *Normal snGFR N.N.* is used as an input to *Required snRen Sec over normal snRen Sec*. Based on this value and minimum and maximum possible single nephron renin secretion rates, adjusted required single nephron renin secretion is calculated.

Adjusted Required sn Ren sec = normal renin contribution per N.N. min(Max sn ren sec fraction N.N., max(min sn ren sec fraction N.N.,Required snRen Sec over normal snRen Sec)* (4.8)

Normal renin contribution per N.N. is set to 3.2 e-6 (g/day). This constant is determined by dividing normal plasma renin secretion to normal nephron number (6.4 (g/day)/ 2000000 (nephrons)). It is assumed that normal nephrons expect a similar renin secretion from all alive nephrons. Therefore *Plasma Renin Required by N.N*. is set to *Adjusted Required sn Ren sec* times total number of alive nephrons. Renin Contribution from remodeled nephrons will be subtracted from *Plasma Renin Required by N.N.* to find out the final required total renin contribution by normal nephrons.

Required total Renin Contribution by N.N. = Plasma Renin Required by N.N. – Renin Contribution from R.M. (4.9)

Renin Contribution from R.M. is composed of *normal renin contribution per R.M.* and *Remodeled Arterioles.* The value of *Normal renin contribution per R.M.* will be set to different values to demonstrate progression dynamics of different types of subjects.

Required total Renin Contribution by N.N. is again constrained by the maximum and minimum possible renin secretion rates of individual normal nephrons.

*Renin Contribution by N.N.= min(normal renin contribution per N.N.*Max sn ren sec fraction N.N.*Normal Arterioles, max(normal renin contribution per N.N.* min sn ren sec fraction N.N.*Normal Arterioles, Required total Renin Contribution by N.N.))* (4.10)

Plasma Renin equals the sum of actual renin contributions from normal and remodeled subpopulations. *Plasma Renin* is divided by the number total alive nephrons to calculate the weighted average of renin secretion per nephron from both subpopulations. This weighted average, *Renin per Nephron*¸ corresponds to consumption rate of Ang II by each alive nephron. Thus, *Renin per Nephron* determines the adjustment in snGFR of normal nephrons over *E of RpN on snGFR N.N.(*see Figure 4.4*).*

Renin per Nephron(RpN) is also the variable which determines the conversion rate of normal arterioles to remodeled arterioles. When *RpN* is above *remodeling threshold RpN*, *Effect of RpN on Functional Afferent Resistance N.N.* will instigate remodeling through chronic vasoconstriction of afferent arteriole (Figure 4.11).

$$\textit{Effect of RpN on Functional Afferent Resistance N.N.} = f\left(\frac{RpN}{\textit{Remodeling Threshold } RpN}\right)$$

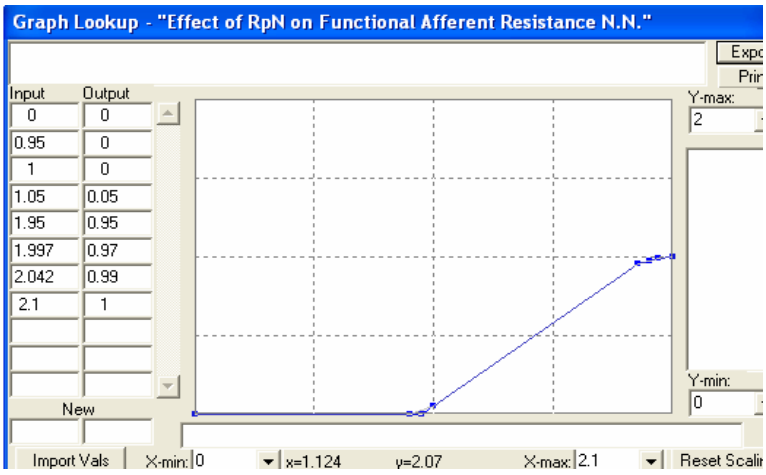

Figure 4.11. Effect of RpN on Functional Afferent Resistance N.N.

Effect of RpN on Functional Afferent Resistance N.N. represents the relationship between renin per nephron and average arteriolar resistance adjustment. When *RpN* is high, afferent arteriole resistance will be high. However, there is a threshold renin per nephron necessary to cause strong enough vasoconstriction that would initiate remodeling stimuli. Currently, the relationship between RpN and remodeling stimuli is modeled linearly with a

saturation effect. When RpN is equal or smaller than *threshold RpN*, no remodeling stimuli will be initiated. When *RpN* is approximately twice as great as *threshold RpN,* this function returns the maximum possible remodeling stimuli which would correspond to maximum arteriolar conversion rate (Figure 4.11).

Effect of RpN on Functional Afferent Resistance N.N. updates the *Average Remodeling Stimuli N to M* stock. This stock accumulates past remodeling stimuli and updates *Arteriolar Conversion* rate with an average delay of two weeks.

$$Arteriolar\ Conversion = Normal\ Arterioles * max\ conversion\ fraction\ N\ to\ M * Average\ Remodeling\ Stimuli\ N\ to\ M \quad (4.11)$$

Max conversion fraction N to M represents the estimated time necessary for an arteriole to become remodeled under maximum remodeling stimuli. In animal experiments, significant remodeling was initiated in a couple of weeks under extremely high Ang II infusion (Franco et al., 2001). There is a significant difference between Ang II infusion experiments and normal physiological conditions. Even the highest Ang II levels under normal physiological conditions for spontaneously hypertensive rat (SHR), which characterizes essential-hypertensive subjects, are much lower than Ang II levels attained in infusion experiments. Thus, a significant upshot of animal experiments is that without a high extra-renal infusion of Ang II, remodeling of arterioles takes a much longer time in essentially-hypertensive subjects. Since there are no experiments on human subjects, conversion fraction, i.e. remodeling delay, of the model for circulating Ang II is highly uncertain parameter. Nevertheless, based on hypothesized reference behavior of progression and based on the notion that physiological circulating Ang II levels are less likely to cause remodeling, the max conversion fraction (mimimum remodeling delay) in the model is estimated at 0.005 /weeks (200 weeks).

Renin per nephron also indirectly affects the behavior of N.N stock in this sector by its effects on Actual snGFR N.N.. Changes in Actual snGFR affect nephron loss rates of normal nephrons. For each nephron subpopulation, there is a pair of effect functions *Effect of High Blood Flow on Nephron Loss Rate, Effect of Low Blood Flow on Nephron Loss Rate*. These functions are formulated to represent the destructive effects of glomerular

pressure on nephrons. As mentioned previously in section 4.2.1.3, an increased Actual snGFR via adjustment of afferent and efferent arterioles corresponds to a high glomerular pressure. Therefore, when *Actual snGFR* is above its normal physiological snGFR value, i.e. 0.09 ml/day, the normal loss Rate is multiplied by a monotonically increasing function of Actual snGFR (Figure 4.12). On the other hand, *Effect of Low Blood Flow on Nephron Loss Rate* represents the detrimental effects of low glomerular pressures on nephrons (Figure 4.13). Although these effect functions are formulated for both stocks, only *Effect of High Blood Flow on Nephron loss* is applicable for normal nephrons for actual operating ranges of the model (Figure 4.12). Remodeled nephrons, on the other hand, mostly loose their nephrons because of low actual snGFR (Figure 4.13).

Effect of High Blood Flow on Nephron Loss Rate = f (Actual snGFR N.N. /Normal snGFR)

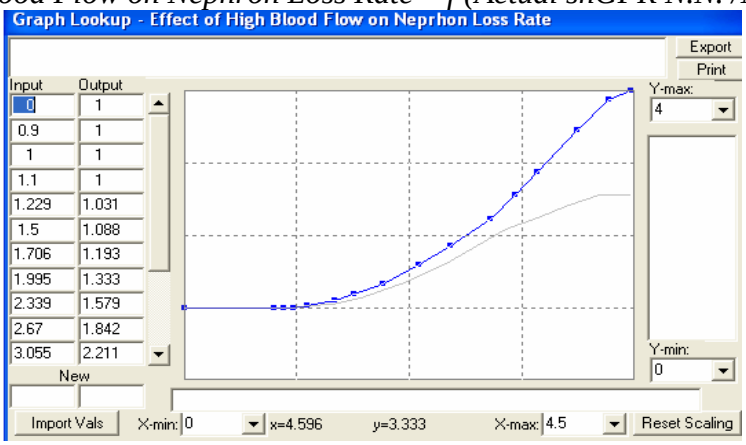

Figure 4.12. Effect of High Blood Flow on Nephron Loss Rate

Effect of Low Blood Flow on Nephon Loss Rate R.M. $= f\left(\frac{\textit{Actual snGFR R.M.}}{\textit{normal snGFR R.M.}}\right)$

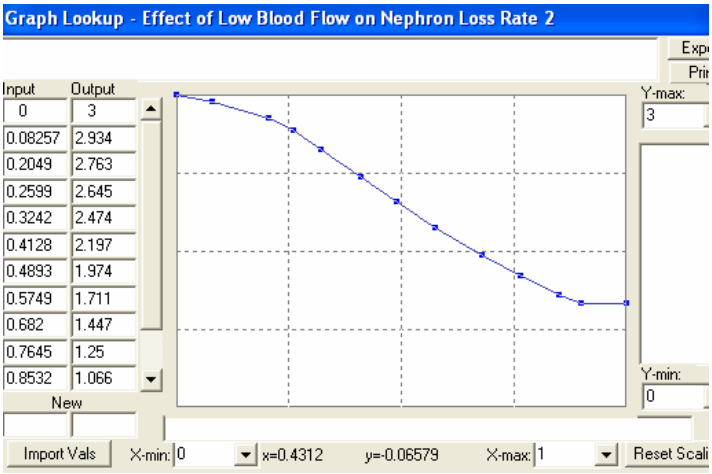

Figure 4.13. Effect of Low Blood Flow on Nephron Loss Rate R.M.

In addition to these functions which update nephron loss rate with according to actual snGFR, there is a normal nephron loss fraction which represents average lifespan of a normal nephron, as part of physiological aging processes. In normal subjects, under healthy conditions initial nephron number is to a great extent preserved up until 4th decade of life. After 30's people start loosing their nephrons at a rate of approximately 1 per cent per year (Guyton and Hall, 2000). Thus, *normal nephron loss fraction* is set to 0.0005/week. On the other hand, *Remodeled nephron loss fraction* is set to 0.001/week; because compared to normal arterioles, remodeled arterioles are considered to be more susceptible to die due to high pressures, and more susceptible to become obsolote due to low pressures. The uncertainty regarding these parameters will be explored in scenario analysis section.

Significant dynamics of this sector are driven by the positive Remodeling loop between *Remodeled arterioles*, *Renin Contribution from R.M.*, and *arteriolar conversion* and through the positive nephron loss loop involving *Normal Arterioles, Required snGFR N.N.* and *Actual snGFR N.N.*.

Table 4.1. Constants used in the model

Constant Name	Value	Units
Effect of R-type Drugs	0	Unitless
max conversion fraction N to M	0.005	1/week
Max sn ren sec fraction N.N.	10	Unitless
max snGFR capacity N.N.	0.25	ml/day
max snGFR capacity R.M.	0.09	ml/day
min sn ren sec fraction N.N.	0.02	unitless
min snGFR threshold N.N.	0.09	ml/day
min snGFR threshold R.M.	0.09	ml/day
normal nephron loss fraction	0.0005	1/week
Normal Renin	6.4	g/day
normal renin contribution per N.N.	3.20E-06	g/day
normal renin contribution per R.M.	6.00E-06	g/day
Normal Set BP	100	mmHG
normal snexcretion/snGFR	0.008	unitless
normal sngfr fraction	0.006	(ml/day)/L
normal snGFR R.M. fraction	0.003	(ml/day)/L
normal Water Intake	10.08	L/week
remodeled nephron loss fraction	0.001	1/week
remodeling delay N to M	2	weeks
remodeling threshold RpN	3.20E-06	g/day
Target Fluid Volume	15	L
time unit conversion	7	day/week
Total Nephrons	2.00E+06	nephrons
volume unit conversion	0.001	L/ml
water intake	10.08	L/week

Table 4.2. Parameters and initial conditions which will be modified in experiments

Parameter Name / Initial Condition	Base Value	Values used in Experiments	Units
Effect of R-type Drugs	0	(-0.1, -0.2, -0.3)	unitless
normal nephron loss fraction	0.0005	(0.0004, 0.0001)	1/week
normal renin contribution per R.M.	6.00E-06	(1.8 E-05)	g/day
remodeled nephron loss fraction	0.001	(0.0005, 0.002, 0.0025)	1/week
remodeling threshold RpN	3.20E-06	2.24E-06	g/day
water intake	10.08	12.08	L/week
Normal Arterioles	2000000	(1800000, 1600000)	nephrons
Remodeled Arterioles	0	(200000, 400000)	nephrons

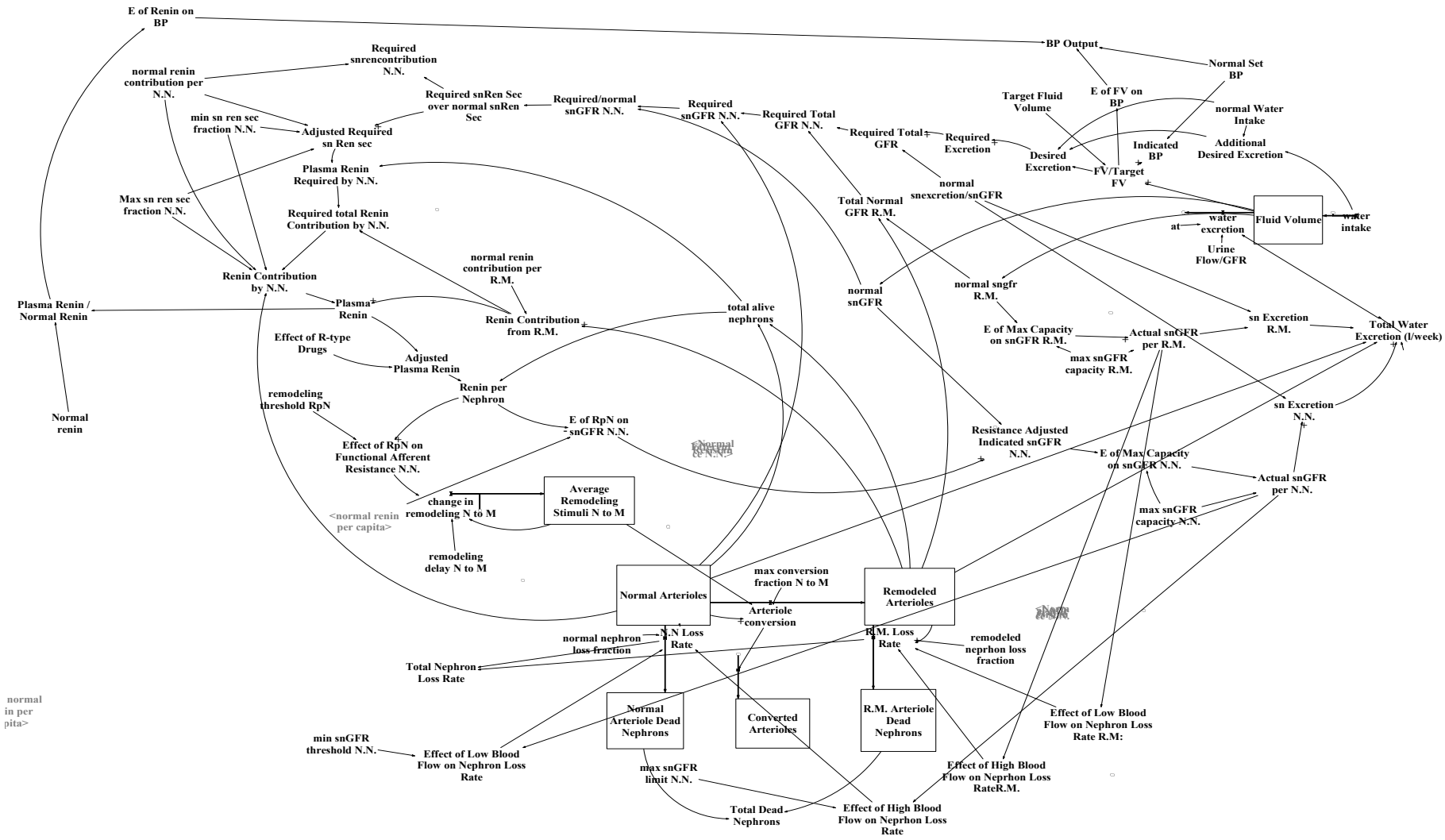

Figure 4.14. Stock-Flow diagram of complete model

4.2.4. Nephron Sector Dynamics

In this section a number of runs will be conducted on nephron sector dynamics. Initial set of runs belong to steady-state dynamics of different nephron distributions. The purpose is to demonstrate different levels of BP and FV that arise from nephron distributions and important parameters.

4.2.4.1.Steady state with different nephron distributions: First run is initialized with the following conditions: 1.8 million Normal Nephrons and 0.2 million Remodeled Nephrons, normal renin contribution per R.M. = 6 e-6 g/day/nephron. This run demonstrates that for heterogeneous distribution of nephrons BP can be controlled at target BP, by adaptive reduction in renin levels. The presence of remodeled nephrons increases the required snGFR of normal nephrons. Normal nephrons respond to this increased snGFR request by decreasing their renin secretion as evidenced by Renin per Nephron (RpN) which is slightly below 1. The effect of reduction in renin levels is a slight increase in E of RpN on snGFR, which increases Actual snGFR to 0.095 slighlty above its normal value of 0.09 (Figure 4.15).

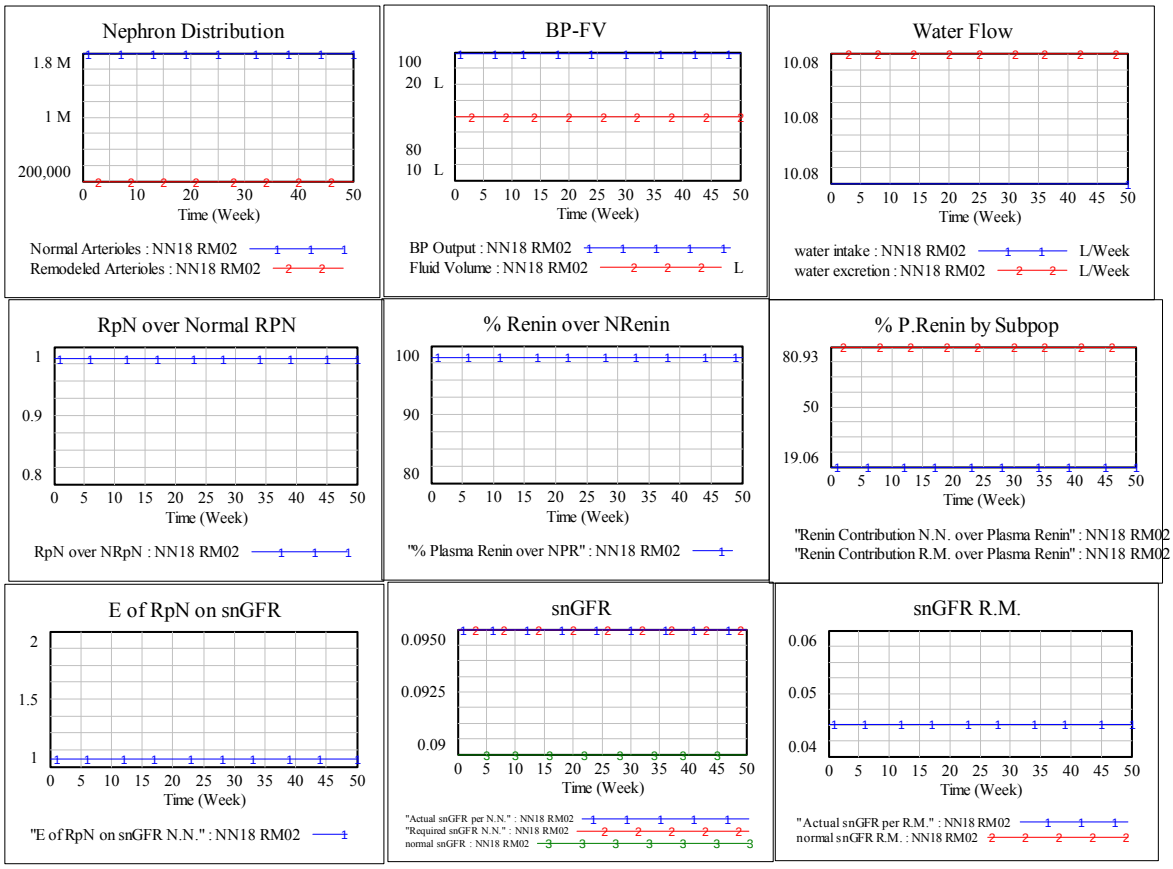

Figure 4.15. Steady-state dynamics with normal and remodeled nephrons

Second run is initialized with 1.6 million Normal Nephrons, 0.4 million Remodeled Nephrons and with high *normal renin contribution per R.M.*= 1.8 e-5 (g/day/nephron). This run demonstrates dynamics of key variables for a heterogeneous distribution with high renin contribution from remodeled nephrons. The run also represents the characteristic features of high-renin type of essential hypertension. There is a significant remodeled subpopulation which secretes high amounts of renin. Excess renin decreases affects Actual snGFR negatively, as demonstrated by the E of RpN of snGFR which is below 1.

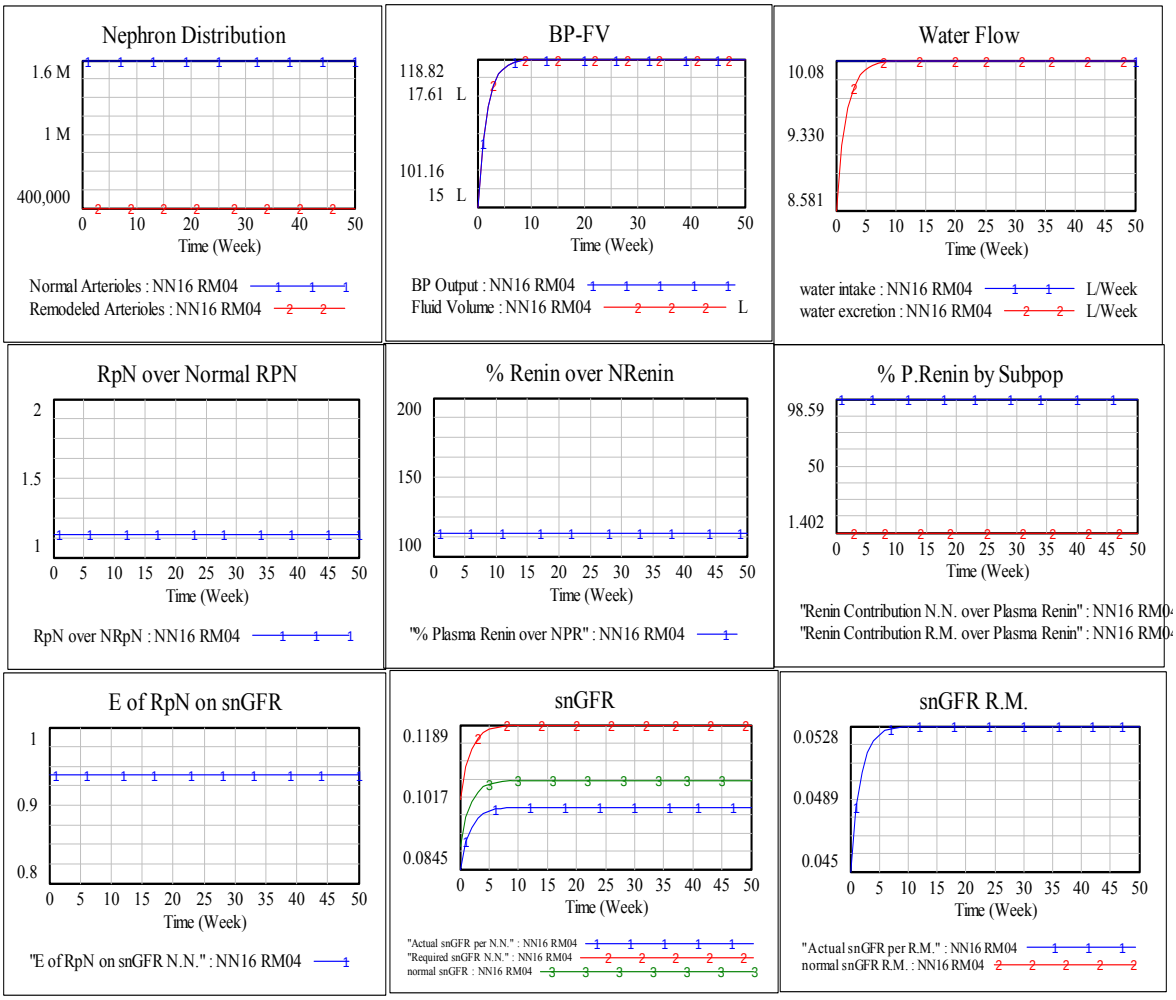

Figure 4.16. Steady-state dynamics with normal and remodeled nephrons and high renin

In the previous experiment, it was demonstrated that normal nephrons have to increase their Actual snGFR in order for the kidney to achieve water excretion that equals water intake when there are remodeled nephrons present. To achieve zero water balance, normal nephrons lower their renin secretion such that plasma renin per nephron falls below normal. However, in the presence of high renin secreting remodeled nephrons, even though

normal nephrons reduce their renin secretion to minimum possible levels, plasma renin levels stay above normal levels (see % Renin over Nrenin in Figure 4.16). This means that the FV-RAS mechanism of normal nephrons is overridden by the high renin contribution from remodeled nephrons. Since normal nephrons cannot increase their snGFR, there is initially a positive water balance between water intake and water excretion. Consequently, FV rises in order to increase snGFR of normal and remodeled nephrons. This behavior is demonstrated by the increase of FV from 15 to stabilize at level 17.61. Comparison of this run with the next experiment reveals the defining features of essential hypertension.

Third run is also initialized with 1.6 million Normal Nephrons, 0.4 million Remodeled Nephrons, but with a normal renin contribution per R.M. that is equal to 6 e-6 (g/day/nephron). BP and FV remain at their target levels. Single nephron GFR of normal nephrons is increased; however, the increase is due to reductions in renin per nephron levels as seen in RpN over Normal RpN graph (Figure 4.17).

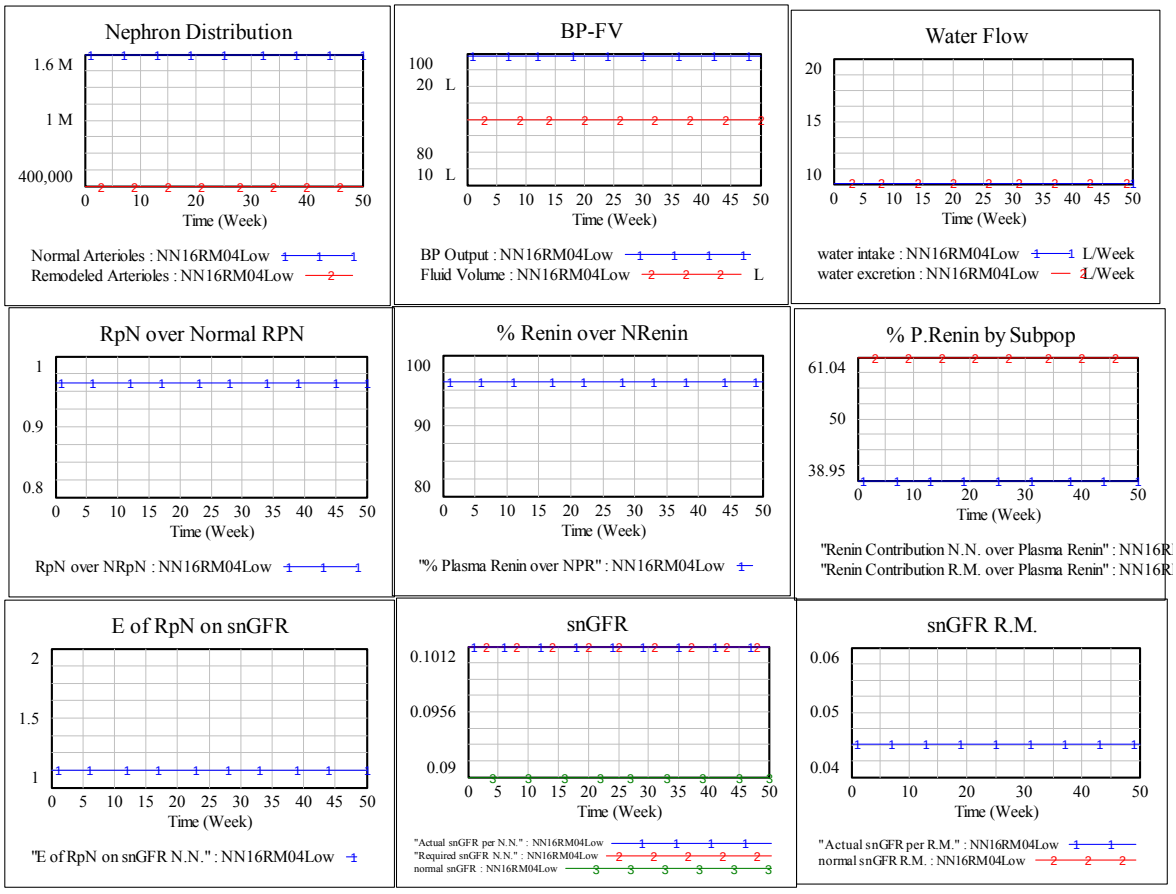

Figure 4.17. Steady-State dynamics with normal and remodeled nephrons and low renin

Whereas in the previous run there is a positive water balance and FV rises to zero that balance, there is no positive balance in this run. The proper control of FV can be achieved over FV-RAS mechanism of normal nephrons. The difference in behavior of FV and BP between the two runs demonstrate that in essential hypertension *FV-RAS control is distorted and zero water balance can only be achieved at the expense of higher FV and BP*.

4.2.4.2.Nephron loss Dynamics: First run demonstrates nephron loss dynamics on a uniform distribution of normal nephrons. Initial conditions are 2 million Normal Nephrons with a normal nephron loss fraction of 0.0005.

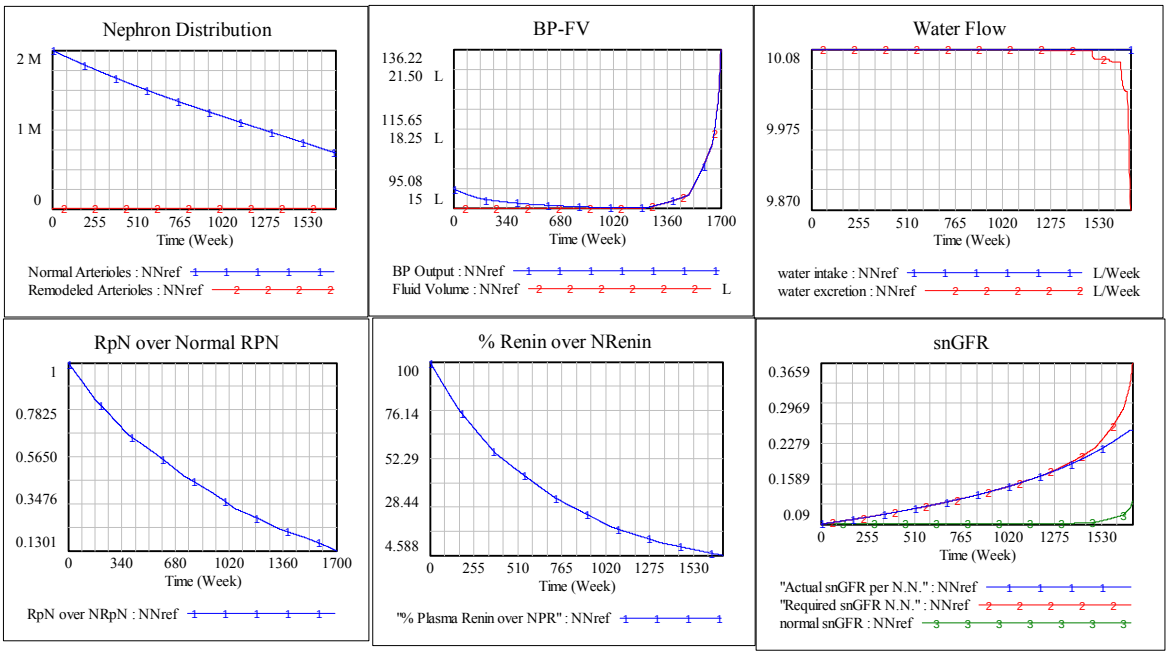

Figure 4.18. Dynamics under normal nephron loss

Dynamics under nephron loss on normal nephrons demonstrate initially stable levels of BP and FV. Loss of nephrons is compensated by increases in snGFR. Water balance is zero up until the later stages of simulation. Renin levels keep declining both because of the reduction in nephron number and the reduction in individual renin contribution of each remaining nephron (Figure 4.18).

Second run demonstrates isolated nephron loss phenomena in an essential hypertension case whose steady-state dynamics were shown in the previous section (Figure 4.16). Renin per nephron (RpN) is initially above 1. On the other hand, required snRenin over normal single nephron renin is below 1 and keeps decreasing throughout the simulation. This discrepancy between desired and actual levels of available renin per nephron results in excess fluid accumulation as demonstrated by BP-FV graph (Figure 4.19).

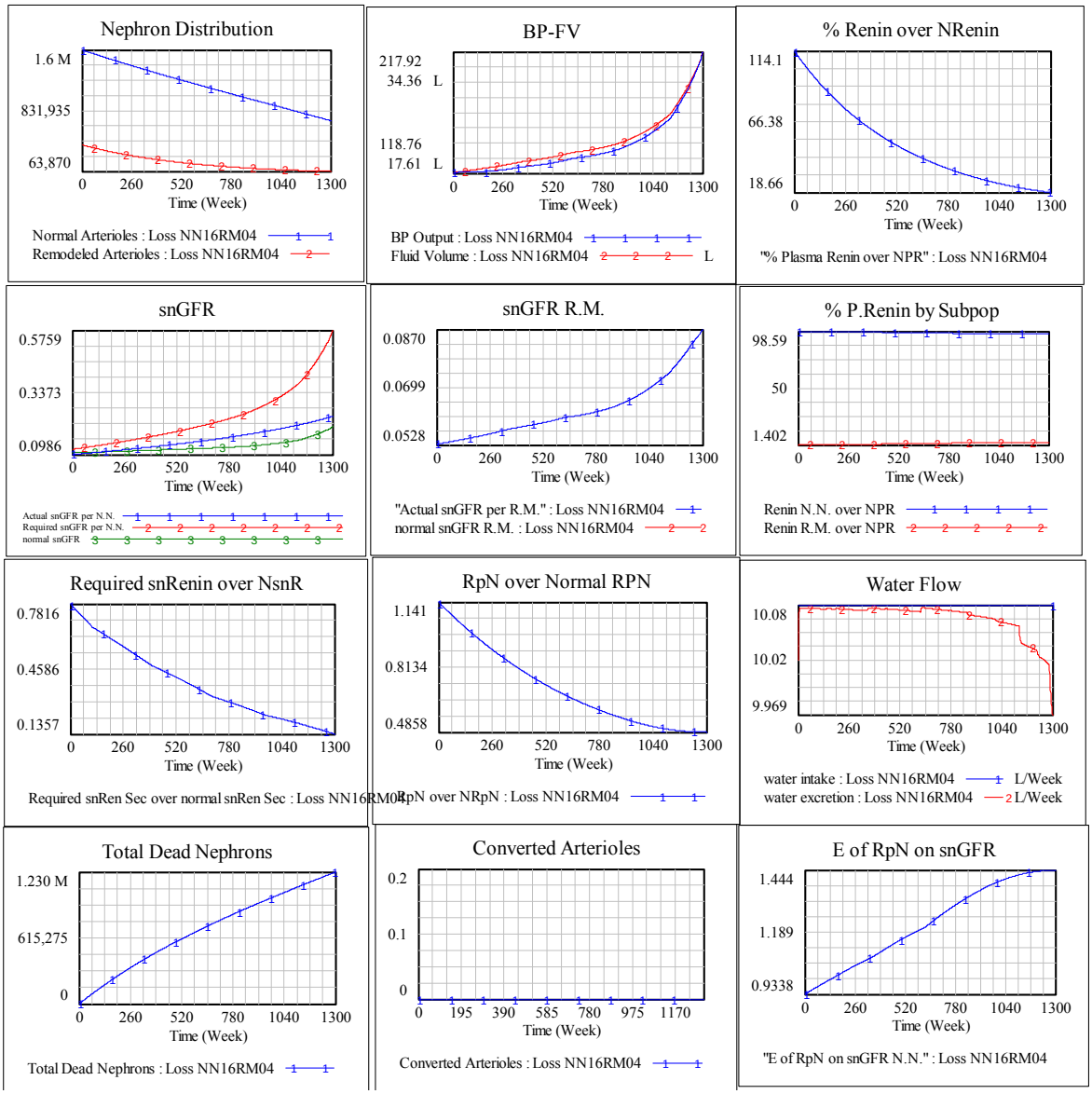

Figure 4.19. Dynamics with heterogeneous nephron distribution and high renin

In the third run, same initial distribution of nephrons will be run with lower normal renin contribution per R.M. = 6e-6 (g/day/nephron). This experiment also represents the nephron loss on a heterogeneous distribution. However, the dynamics of key variables are quite different from the previous essential hypertension isolated nephron loss case. Both nephron subpopulations exhibit a decline path. After normal nephron number falls below a certain number, FV cannot be controlled at its target level any more; since all remaining nephrons have reached their maximum snGFR levels. This is demonstrated by the growing discrepancy difference between water intake and water excretion. Plasma renin and RpN levels keep declining throughout the simulation (Figure 4.20). Unlike the essential hypertension case high levels of BP are not caused by high renin levels which distort FV-RAS mechanism. On the contrary, this FV-RAS mechanism is intact up until late stages of simulation and hypertension develops because remaining nephrons reach their max snGFR capacity.

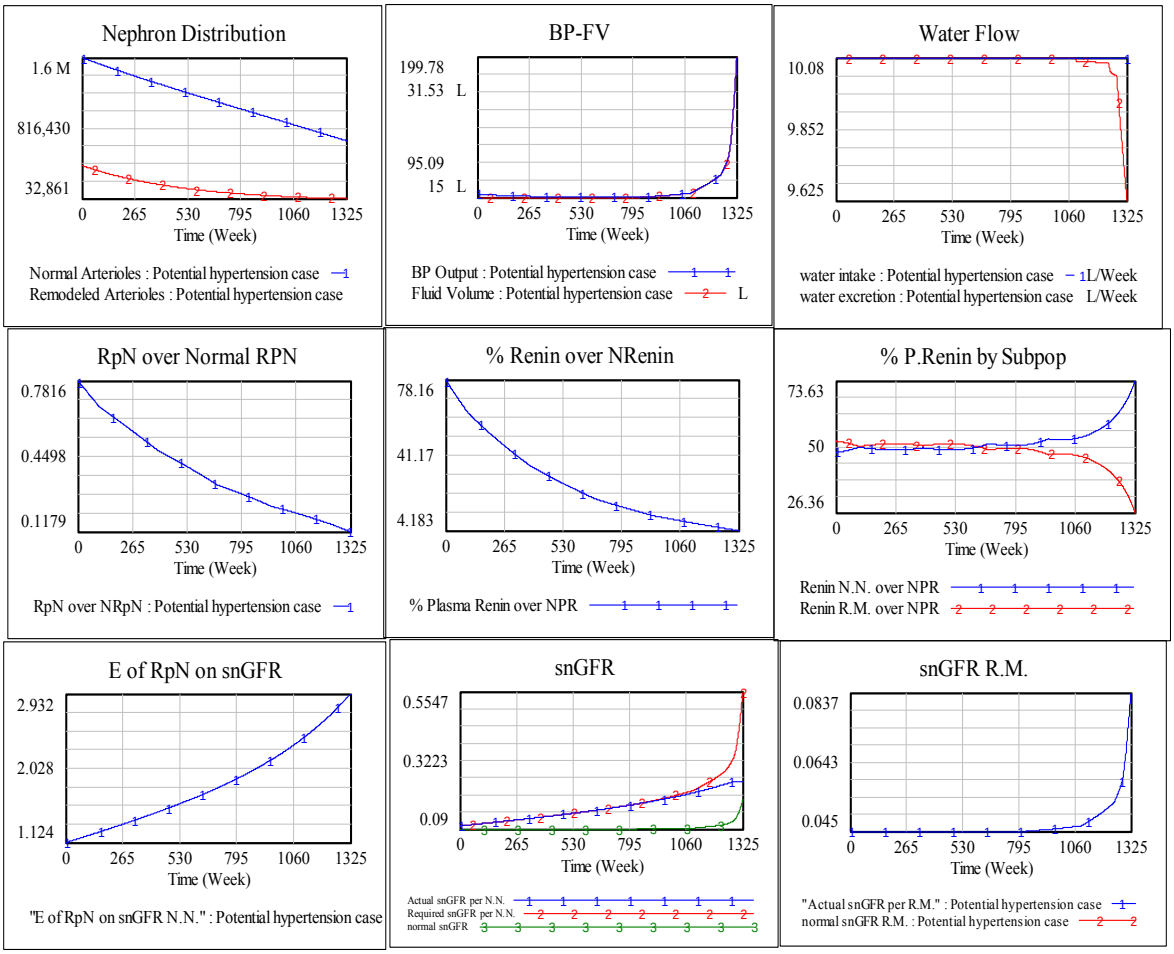

Figure 4.20. Dynamics with heterogeneous nephron distribution and low renin

4.2.4.3.Remodeling Dynamics: In this experiment, dynamics of remodeling will be demonstrated without loss of nephrons. The run is initialized with a heterogeneous distribution and high renin secreting remodeled nephrons. Initial Conditions are 1.6 million Normal Nephrons, 0.4 million Remodeled Nephrons and maximum conversion fraction equals 0.005/week and high normal renin contribution R.M. is 1.8 e-5 (g/day/nephron)

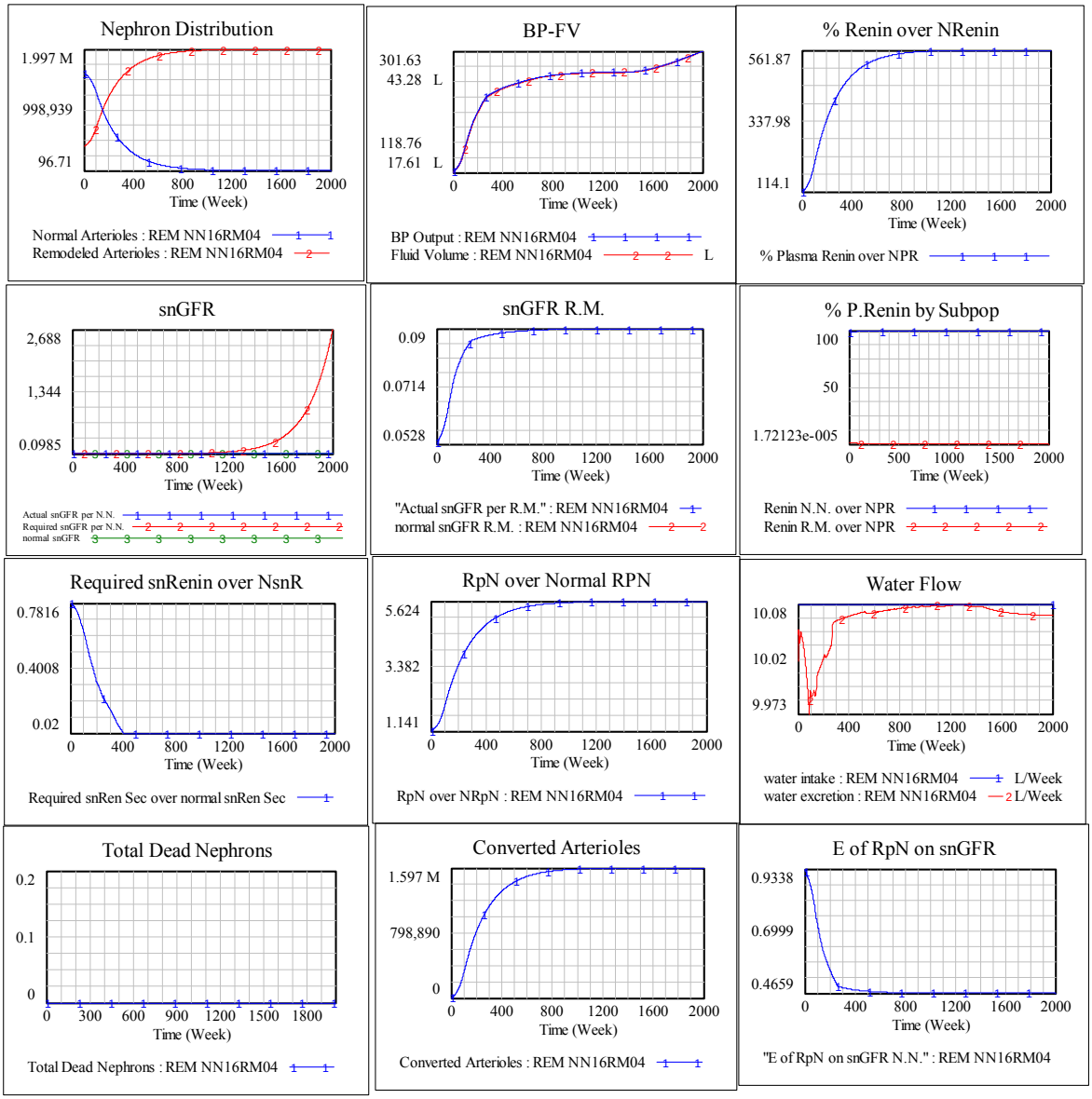

Figure 4.21. Dynamics of nephron remodeling

The key feature of the isolated remodeling run is the conversion of all normal nephrons to remodeled nephrons over time. As the number of high renin secreting remodeled nephrons increases, plasma renin rises to maximum possible levels. Since max

snGFR capacity of remodeled arterioles is set at normal snGFR (0.09 ml/day), when all arterioles are remodeled, stable BP can be achieved. However, the level of BP necessary to achieve zero water balance is above the MAP level of 200 mmHG, which is too high for a subject to survive over longer periods of time.

The graph below demonstrates a hypothesized progression of arterial pressure caused by increasing afferent arteriolar resistance over time (Guyton, 1980; see Figure 4.22.). In the isolated remodeling run, the dynamics of blood pressure and total afferent arteriolar resistance, which is demonstrated by number of remodeled arterioles, behave similarly to Guyton's model output. On the other hand, renin levels in Guyton's model are normal up until later stages of simulation when the subject enters heart failure stage. The difference in behavior originates from the difference in assumptions on renin secretion from remodeled nephrons. Guyton assumes that high blood pressure would suppress renin secretion from all nephrons. However, this thesis adopts a different view on renin secretion in line with Sealey's nephron heterogeneity hypothesis (Sealey et al., 1988), as discussed in section 4.2.2.1..

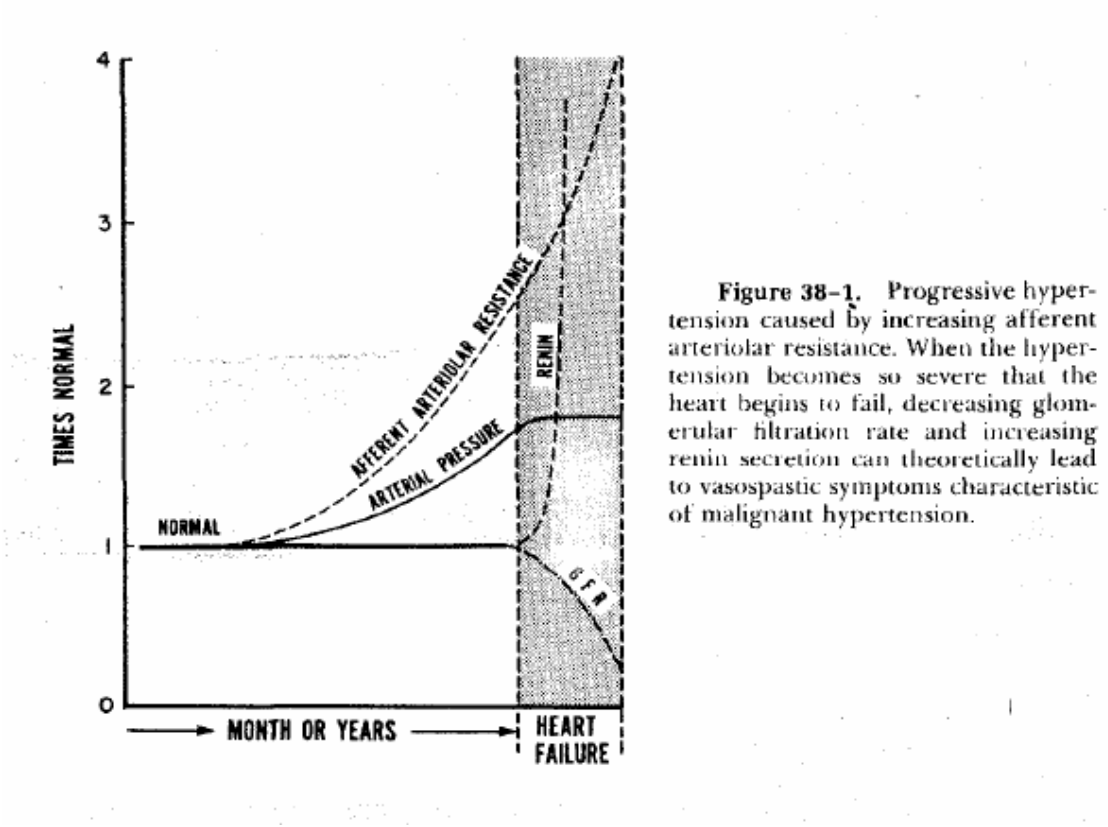

Figure 38–1. Progressive hypertension caused by increasing afferent arteriolar resistance. When the hypertension becomes so severe that the heart begins to fail, decreasing glomerular filtration rate and increasing renin secretion can theoretically lead to vasospastic symptoms characteristic of malignant hypertension.

Figure 4.22. Arteriolar resistance and blood pressure progression (Guyton, 1980)

In summary, the experiments conducted so far serve to verify that the model behaves reasonably with respect to key variables under a number of isolated conditions. Steady-state runs demonstrate that the model returns reasonable values for key variables such as BP, FV and Plasma Renin under different nephron distribution . Isolated nephron loss runs verify the operation of nephron loss positive feedback loop. Similarly, isolated remodeling run demonstrates that the model behaves as expected with respect to number of remodeled arterioles and renin dynamics.

The main novelty of this study with respect to progression of essential hypertension is coexistence of remodeling and nephron loss (+) feedback loops. Reinforcement of nephron loss by remodeling phenomena is suggested in the unifying hypothesis on pathogenesis of essential hypertension (Johnson et al., 2005a,b); however, a dynamic approach demonstrating interaction between the two processes is not readily available. Remodeling of arterioles may not only explain high levels of FV and BP, but also provide another explanation for increased susceptibility of essential-hypertensive patients for accelerated progression of BP and plasma renin as seen in the case of *malignant hypertension.* Such a case was demonstrated in the isolated remodeling run (Figure 4.21).

In the next section, the reference behaviors for progression of BP in normal and hypertensive subjects will be introduced. The behavior validity of the model will also be established by comparing the behavior of key variables in normal subjects to quantitive data. The reference runs on the integrated model with nephron loss and remodeling verify that both versions can be used in scenario analysis for long-term progression dynamics of BP, FV and structural changes in the kidneys.

5. BASE BEHAVIOR OF THE MODEL

The start of simulation for base runs, week zero, represents a 30 year old subject who has not experienced any significant loss from his/her inborn nephrons. The fundamental distinction between normal subjects and hypertensive subjects is based on the number of remodeled nephrons initially. The presence of an initial remodeled population might be the result of a short-term injury or may be due to congenital narrowing. However, causal pathway leading initiation of remodeling depends on chronic vasoconstriction which may be due to many vasoconstrictive mechanisms (Johnson et al., 2005a; Schiffrin, 2005). A potent vasoconstrictor, Ang II, which is common in high concentrations in both acquisition and later in developed stages of essential hypertension may be involved in initiation and progression of further structural injury. To demonstrate the proposed positive feedback loop of remodeling in essential hypertensive patients, hypertensive subjects will start simulation with a significant number of remodeled nephrons at the age of 30.

Normal subjects will be assumed not to have any significant remodeled nephron population at simulation start time. The progression dynamics of normal subjects will solely be driven by loss of nephrons because remodeling cannot be initiated endogenously in the model for the current set of initial conditions, i.e. when all nephrons are normal. In this chapter, first the dynamics of an idealized normal subject will be demonstrated which would also serve to establish the behavioral validity of the model. The behavior will be compared to final values of key variables which are given in medical literature. The table below summarizes the differences in initial conditions among base cases.

Table 5.1. Initial conditions and parameters of base cases

Different Base Cases:	Initial Normal Arterioles	Initial Remodeled Arterioles	normal Renin Contribution per R.M.
Normal Subjects	2000000	0	6.00E-06
Potential-Hypertensive	1600000	400000	6.00E-06
Essential-Hypertensive	1600000	400000	1.80E-05

5.1. Normal Subjects

People after 4th decade of life are estimated to loose 10 per cent of their nephrons in every ten years because of aging of nephrons and other conditions such as benign nephrosclerosis (Guyton and Hall, 2000). The reference run of normal subjects represents a similar scenario. In the reference case, the subject looses about 65 per cent of nephrons over 35 years (Figure 5.4). Interestingly, fluid does not start accumulating in the body until after week 1500 (30 years) when nephron number is reduced by almost 60 per cent (Figure 5.3 and Figure 5.4). This is consistent with real observations since people who have lost as much as 70 per cent of nephrons can maintain normal excretion of water (Guyton and Hall, 2000). The subject in the first run demonstrates a normal subject who has developed hypertension over 35 years as a result of significant nephron loss (Figure 5.1). The subject in the second run represents an alternative, a slower progression of nephron loss (Figure 5.4). The second subject does not experience any rise in BP within the time frame of simulation.

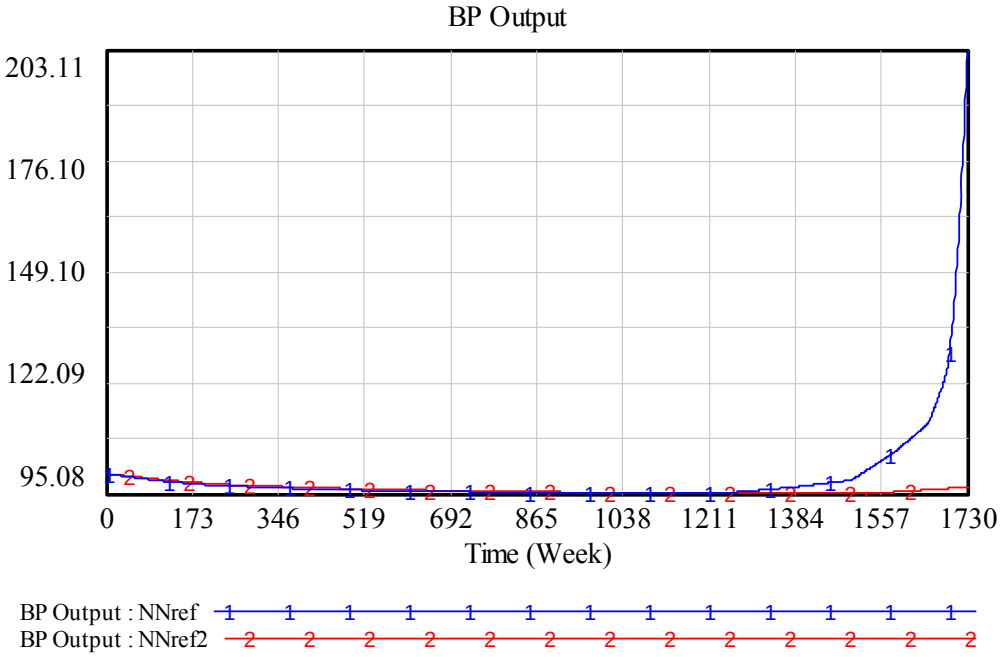

Figure 5.1. Dynamics of blood pressure

The stable dynamics of FV up until week 1500 is due to the fact that remaining nephrons excrete increased amount of water to compensate for excretion capacity lost by death of nephrons (Figure 5.3). However, as nephrons approach their max snGFR capacity

their compensation becomes imperfect and BP rises to hypertensive levels within 200 to 300 weeks (4-6 years) as demonstrated by the behavior of BP after week 1500, after 55 years of age (Figure 5.2).

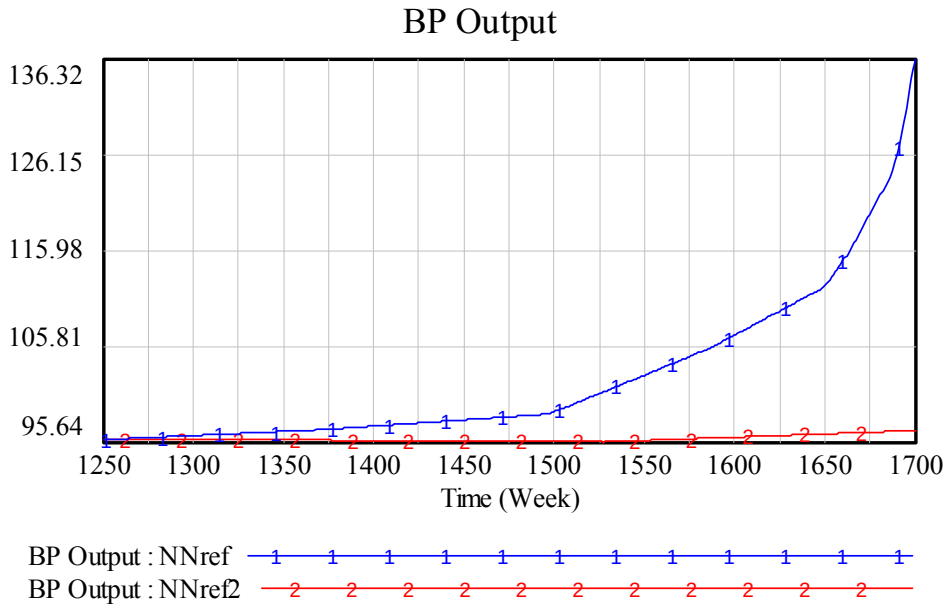

Figure 5.2. Progression dynamics of blood pressure

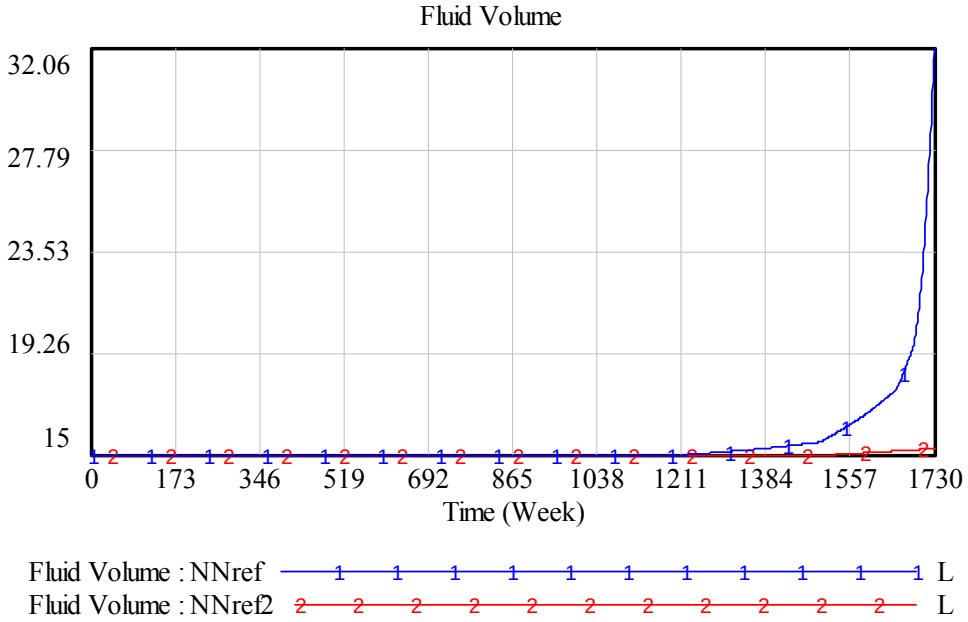

Figure 5.3. Dynamics of fluid volume

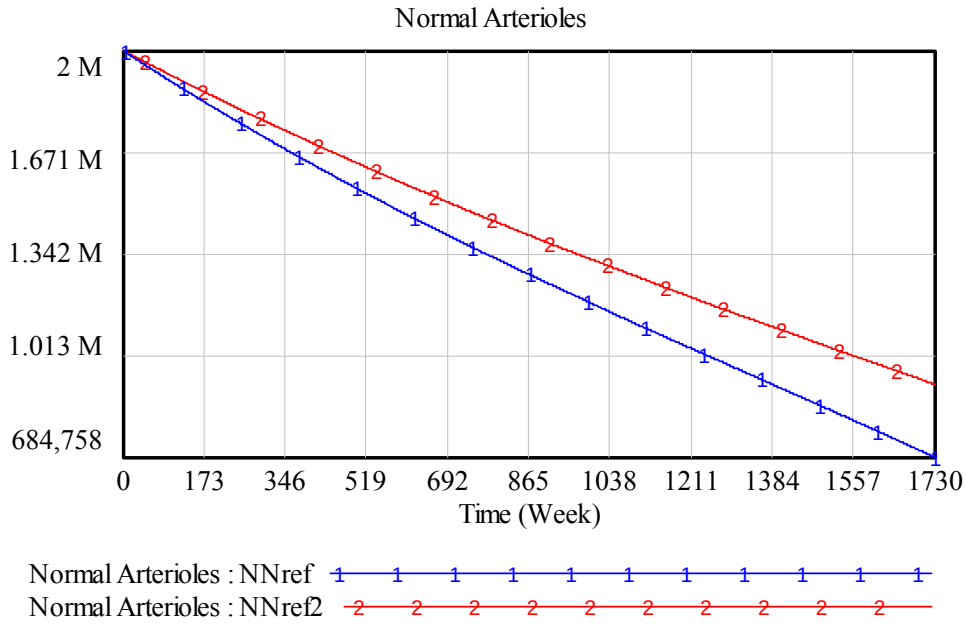

Figure 5.4. Dynamics of Normal Arterioles

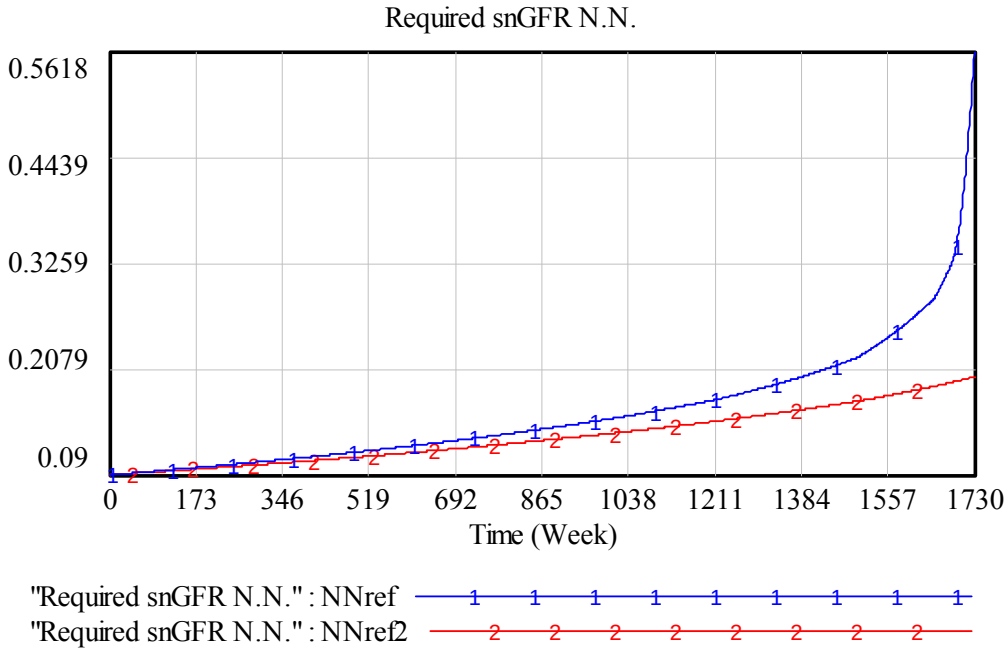

Figure 5.5. Dynamics of required single nephron glomerular filtration rate N.N.

The growth path of Required snGFR from onset of nephron loss demonstrates the increasing need for higher snGFR by remaining nephrons (Figure 5.5). Nephrons respond to this increasing need by decreasing their renin secretion which allows them to increase their actual snGFR at the current level of BP and FV (Figure 5.7,Figure 5.8 and Figure 5.10).

Nephrons can increase their filtration by regulating afferent and efferent resistances. The exact measurement of long-term snGFR increase is not available. However, a reasonable estimate would be that nephrons raise their max snGFR up to 2-3 times of their normal snGFR, which is equal to 0.09 ml/day when BP is at its target level. Therefore, maximum capacity for normal nephrons is set at 0.25 ml/day.

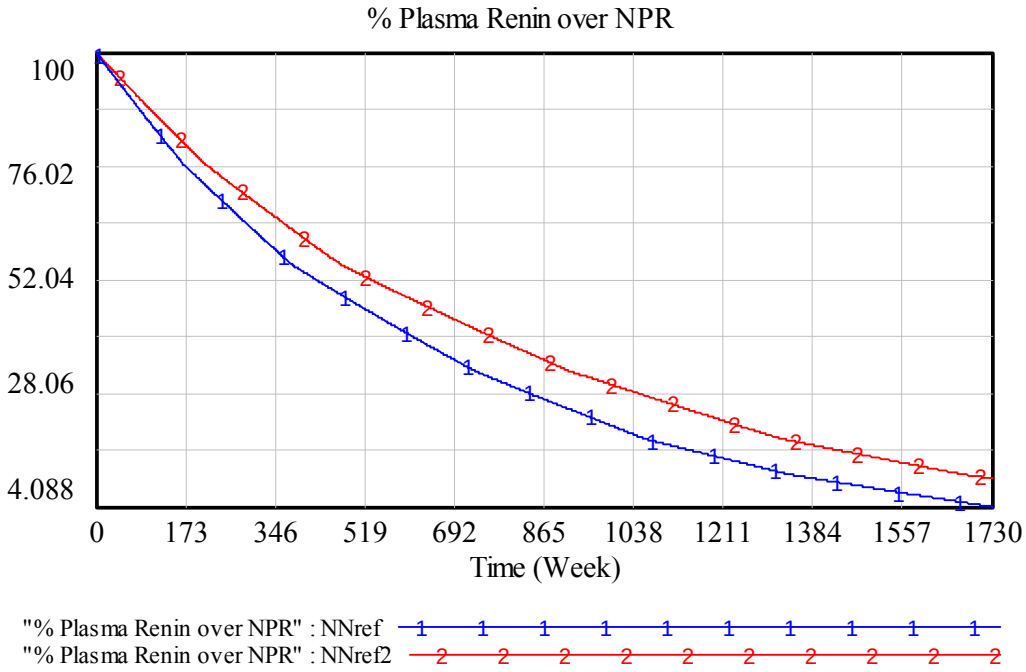

Figure 5.6. Dynamics of plasma renin over normal plasma renin

The decline in Plasma Renin with age is a consequence of reduced nephron number (Figure 5.6, Figure 5.4). However, individual renin secretion of nephrons decreases in addition to this reduction due to loss of nephrons (Figure 5.7). Consequently, plasma renin per nephron which determines the resistances of afferent and efferent arterioles decreases as well (Figure 5.8).

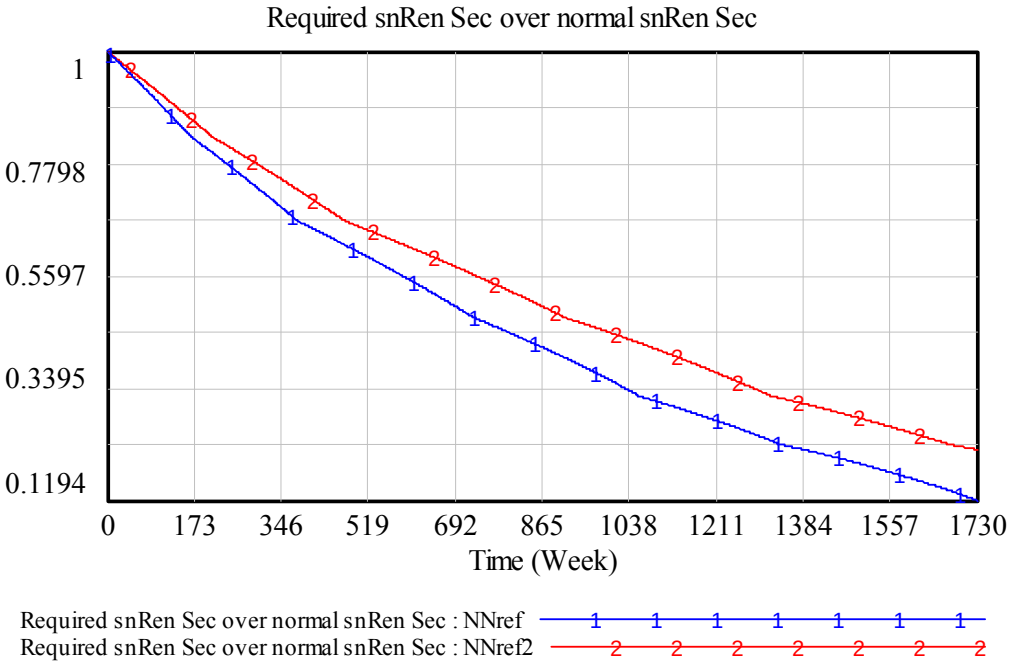

Figure 5.7. Dynamics of Required snRen Sec over normal snRen Sec

A key observation is that there is an exact match between Required snRen sec over normal snRen Sec and renin per nephron (Figure 5.7 and Figure 5.8). The tight regulation of required and actual renin is not always the case as it will be demonstrated in the run for essential hypertension.

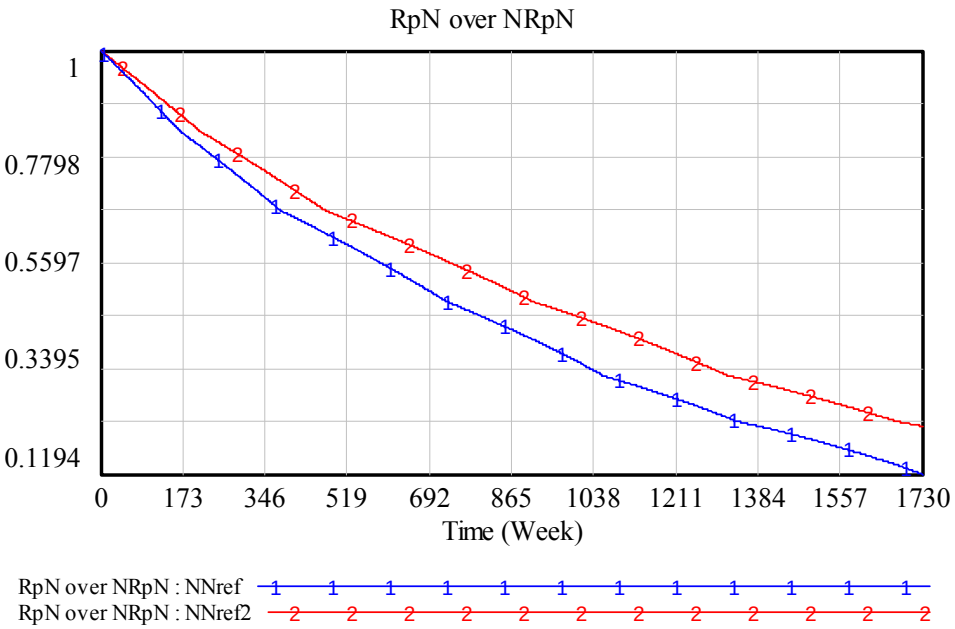

Figure 5.8. Dynamics of renin per nephron

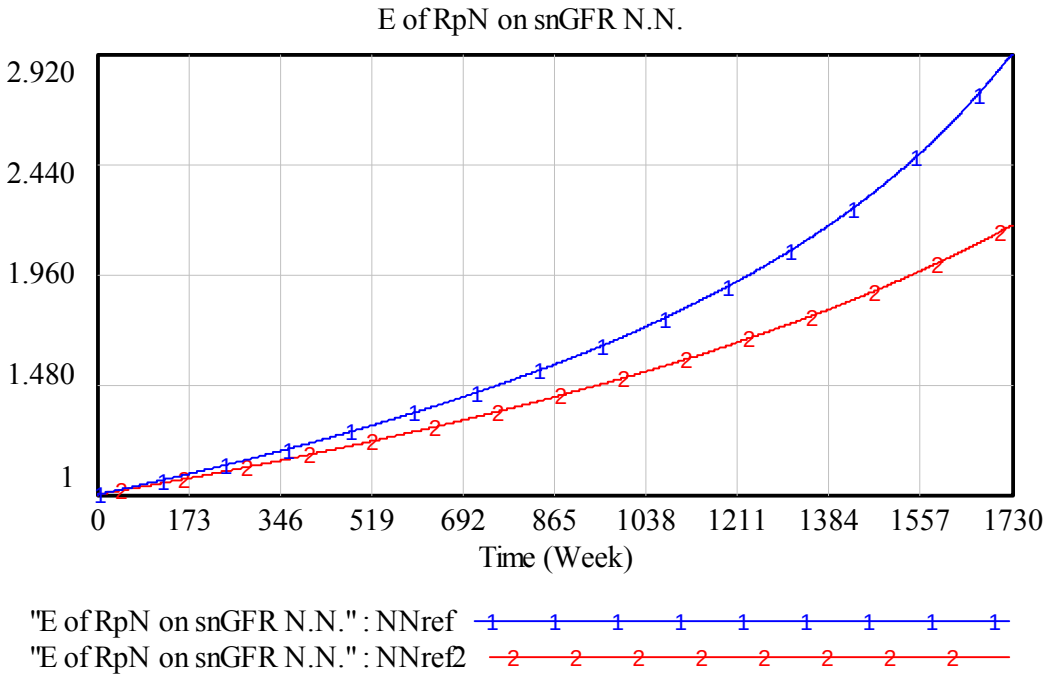

Figure 5.9. Dynamics of Effect of Renin on snGFR

The decline path of RpN affects snGFR in the opposite direction (Figure 5.8 and Figure 5.9). E of Renin per nephron is capable of increasing Resistance Adjusted Indicated snGFR N.N. up to multiple times of current normal snGFR (Figure 5.10).

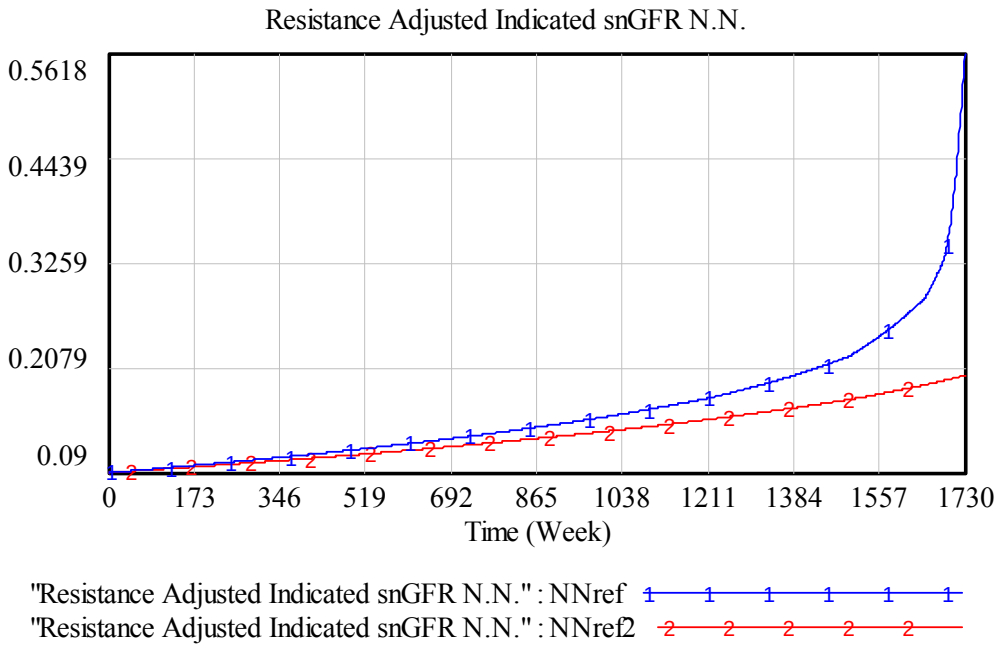

Figure 5.10. Dynamics of resistance adjusted snGFR

The progression dynamics of BP with nephron loss is characterized by initially stable, well-controlled BP and compensation by remaining nephrons through functional vasodilalation mediated over FV-RAS control mechanism. With further loss of nephrons, either renin per nephron approaches its minimum limit or Actual snGFR approaches maximum snGFR Capacity. Either way, water balance between water intake and water excretion becomes positive as capacity is approached and FV starts accumulating in the body.

5.2. Hypertensive Subjects

As mentioned in introduction, in this thesis, hypertensive subjects are characterized by the presence of an significant number of remodeled nephrons initially. It must be noted right away that presence of remodeled nephrons does not necessitate the subject to have increased levels of BP.

The prerequisite for high BP at a heterogeneous nephron distribution is that remodeled nephrons secrete high enough renin such that the control of FV by normal nephrons cannot be performed. The dynamics of BP and FV in steady-state runs of heterogeneous nephron distributions demonstrate the impact of high and normal renin secretion from remodeled nephrons (Figure 4.15, Figure 4.16, Figure 4.17). When total renin secretion from remodeled nephrons is too high, normal nephrons cannot achieve their desired renin per nephron even if they reduce their renin secretion to minimum possible levels. Thus, the control of FV by normal nephrons will be distorted because they can not overcome the negative effects of remodeled nephrons on their filtration.

If there is a remodeled subpopulation but such a distortion FV control is not present, progression of BP will be similar to the case of normal subjects. FV would start increasing when the maximum excretion capacity by remaining normal nephrons is approached. Nevertheless, high blood pressures would manifest itself much earlier in such potential hypertensive subjects than in normal subjects who loose their nephrons with aging process. This is because normal nephrons would already be working close to their maximum capacity to compensate for lack of filtration by remodeled nephrons. Moreover, subjects with such remodeled subpopulations could exhibit high levels of BP for shortened periods of time during which their water intake may be excessive. Such subjects resemble the real

life cases which are characterized as “borderline hypertensive” in medical literature (Kaplan, 1998).

The progression of BP in essential-hypertensives differs from normal subjects in two main ways. Firstly, uncontrolled high renin levels originating from remodeled nephrons could decrease snGFR of normal nephrons and cause a positive water balance which would increase BP right away. Secondly, high renin levels present in essential-hypertensive patients could possibly trigger a remodeling loop which would convert more normal nephrons to remodeled nephrons. Consequently, blood pressure would rise further since nephrons with high snGFR’s would be converted to nephrons with low snGFR’s. These two main possible pathways will be demonstrated for progression of BP in essential hypertensive patients. In scenario analysis section, other possible progression scenarios will be investigated. It must be noted that the pathway for progression of BP is not fully comprehended and there may be infinite number of different paths. Therefore, the reference behaviors presented in this chapter should be considered as two of the many reasonable and possible characteristic progression paths, some of which will be presented in scenario analysis section.

5.2.1. Potential-hypertensive subjects

Course of progression for potential-hypertensive subjects is primarily driven by nephron loss from normal and remodeled nephrons rather than remodeling. Reduction in filtration capacity is compensated by increase in snGFR of remaining normal nephrons. In order to increase their snGFR, remaining nephrons try to influence plasma renin by reducing their own renin contribution. The progression dynamics of key variables are similar to the case of normal subjects. FV and BP are maintained near target values for long periods of time. The only difference from normal subjects is the coexistence of a remodeled subpopulation. Dynamics of the reference case of normal subjects will be presented along with the dynamics potential-hypertensives to demonstrate these differences.

The following initial conditions will be used to demonstrate dynamics of potential hypertension: Normal renin contribution per R.M. = normal (6E-6 g/day), normal snGFR

R.M.= 0.045 (ml/day), Max snGFR Capacity R.M. = 0.09 (ml/day), Max conversion fraction = 0.005 (1/week), remodeling threshold RpN = Normal renin contribution N.N.(3.2e-6 g/day). There will be initially 1.6 million normal and 0.4 million remodeled nephrons.

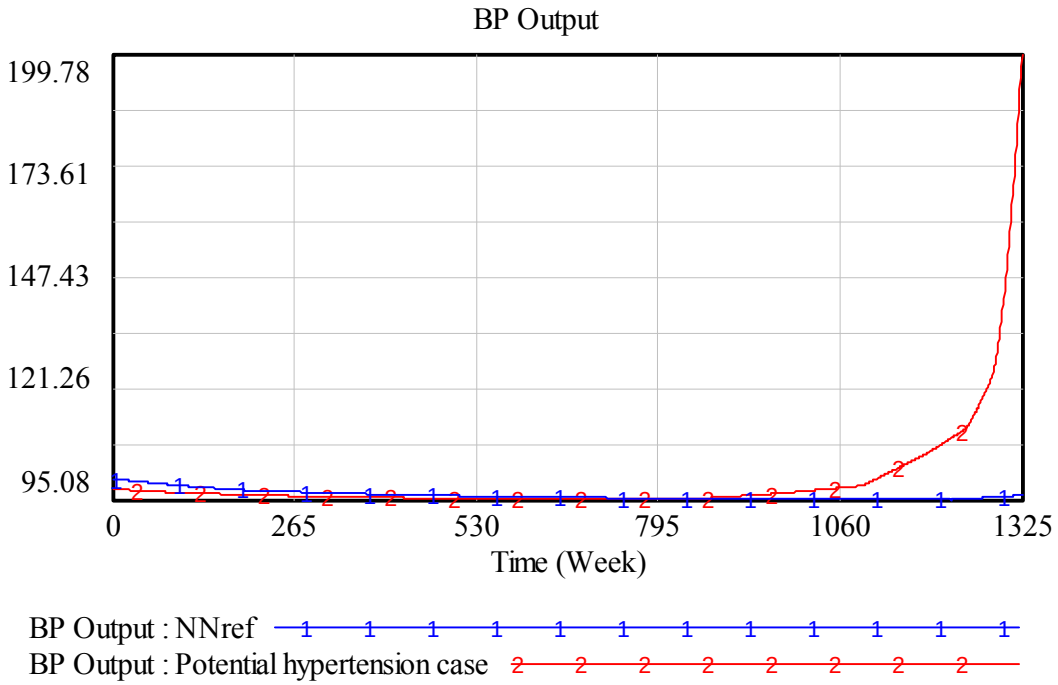

Figure 5.11. Dynamics of blood pressure-potential hypertension

Blood pressure behaves around its normal level for up until week 1060 (Figure 5.11). The dynamics of potential-hypertensives are indistinguishable from normal subject for the first 20 years. However, throughout these 20 years potential-hypertensives loose a significant amount of normal nephrons (Figure 5.12).

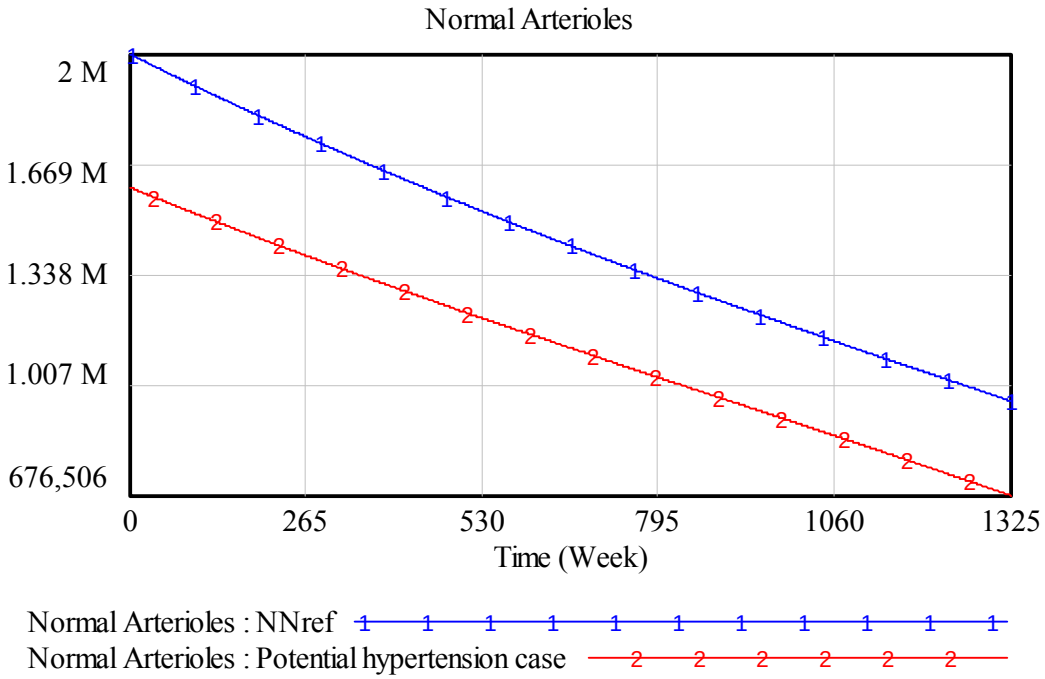

Figure 5.12. Dynamics of normal nephrons-potential hypertension

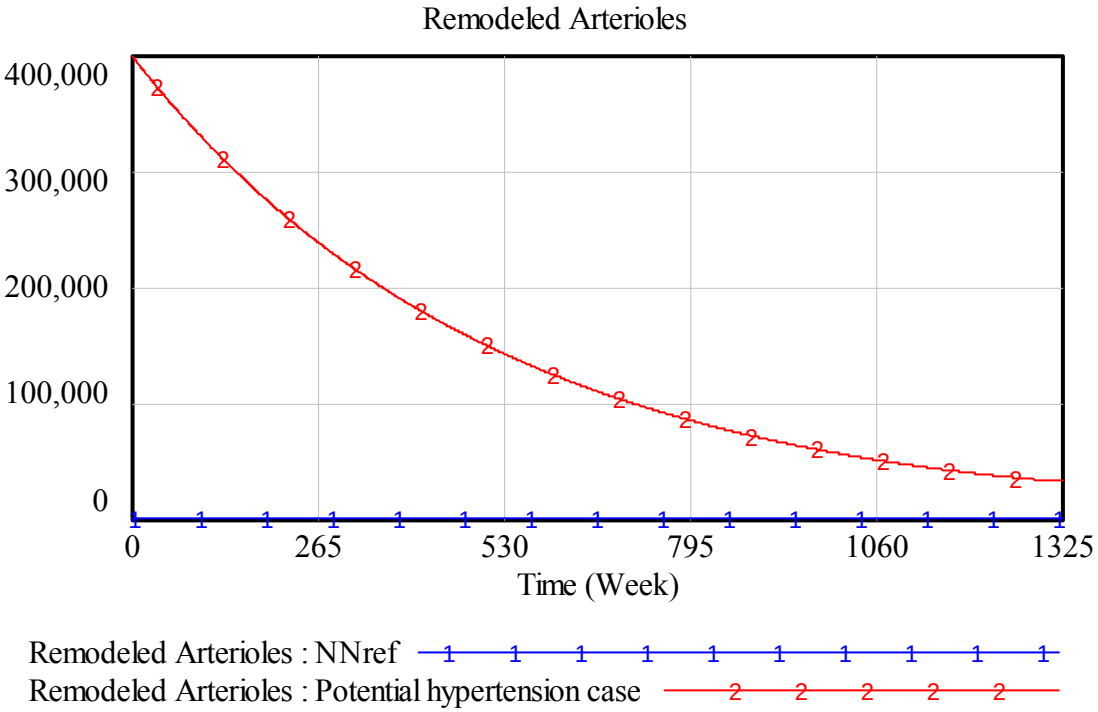

Figure 5.13. Dynamics of remodeled nephrons-potential hypertension

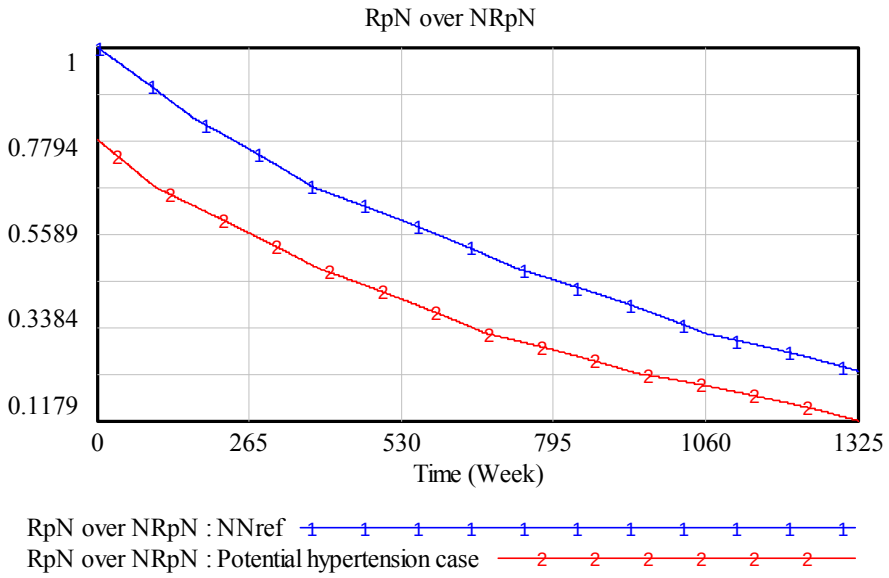

Figure 5.14. Dynamics of renin per nephron-potential hypertension

Renin per nephron is an indicator of how much Ang II will be consumed by each remaining nephron per unit time. Lower levels of renin per nephron is due to the fact that in potential hypertensives normal nephrons need to compensate for greater loss of filtration than in the case of normal subjects (Figure 5.14 and Figure 5.15). The increased suppression of renin secretion is normal nephrons' adaptive response to increased required snGFR (Figure 5.15).

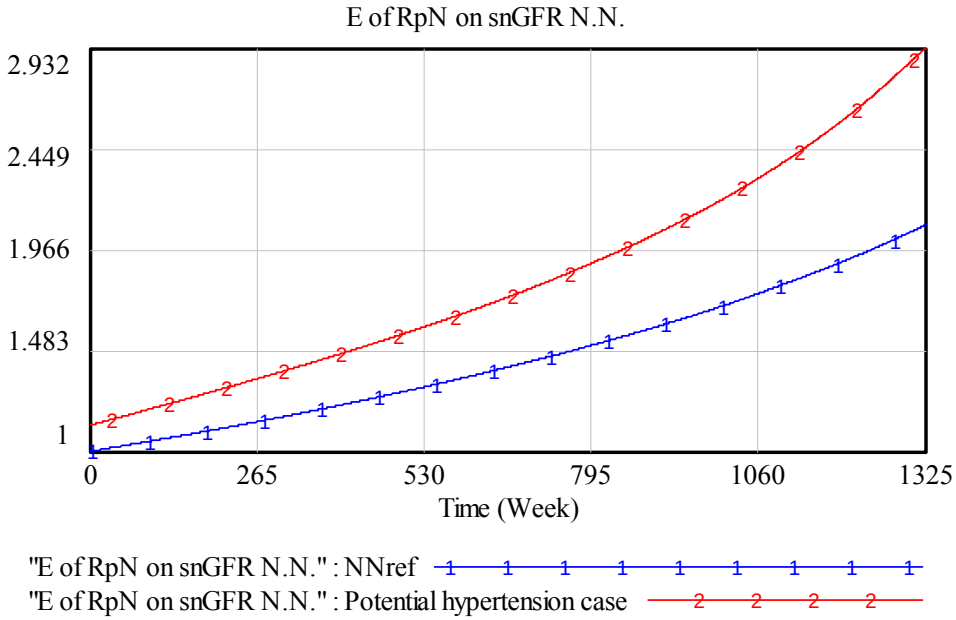

Figure 5.15. Effect of Renin on snGFR-potential hypertension

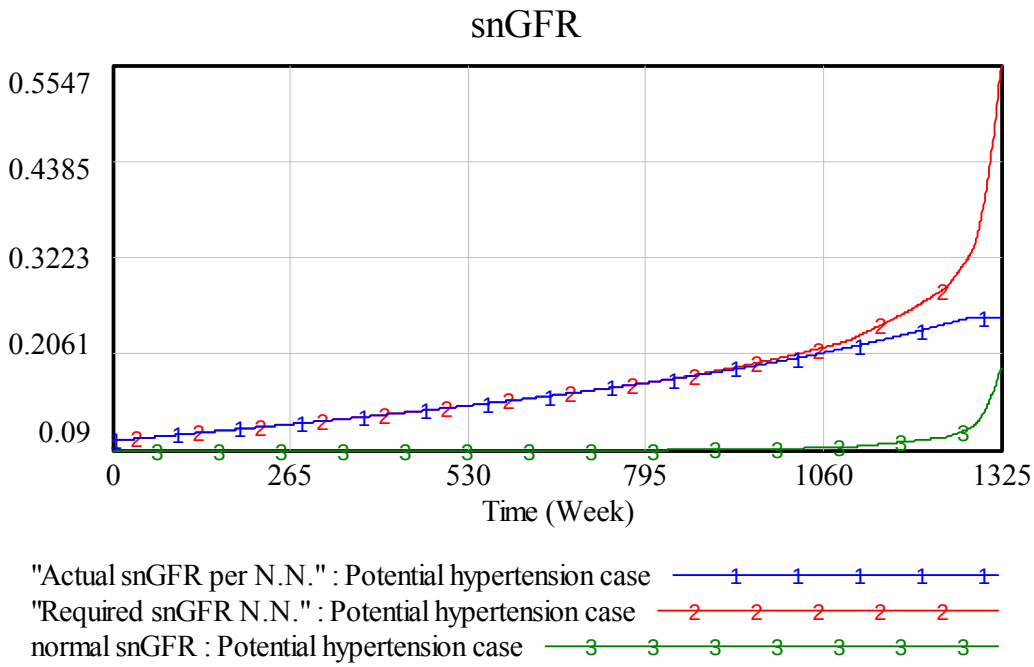

Figure 5.16. Comparative dynamics of snGFR-potential hypertension

In potential-hypertensives, Actual snGFR can exactly match required snGFR up until late stages because normal nephrons adjust their own renin secretion according to global level of renin (Figure 5.16). Even though remodeled nephrons secrete higher amounts of renin, this poses no problem for normal nephrons. The high renin contribution from remodeled nephrons can be counterbalanced by reductions in their own renin contribution. However, as it will be demonstrated in essential hypertension case, there is no guarantee that normal nephrons can always decrease their renin secretion to sufficiently low levels. This is because that renin secretion by remodeled nephrons may be so high that even zeroing of normal nephrons' renin secretion may not be sufficient to increase Actual snGFR to match required snGFR.

When Actual snGFR approaches max snGFR capacity it becomes more difficult for nephrons to match Resistance adjusted snGFR. As max capacity is approached actual outflow starts falling short of meeting desired outflow (Figure 5.16).

The dynamics of growth are essentially similar to the case of normal subjects. Nevertheless, subjects with significant remodeled nephron subpopulation can be called "potential" hypertensive, because their excretion capacity will be approach earlier. Thus,

they will develop hypertension earlier in life. Potential-hypertensives are also more vulnerable for developing further remodeling in the case of an overactivated RAS system which can be observed in the case of salt deprivation over extended periods of time.

5.2.2. Essential-hypertensive subjects

The reference case for essential hypertension has also initially 1.6 million normal and 0.4 million remodeled arterioles. People with normal nephron number who have a remodeled nephron subpopulation will only exhibit hypertension if renin secretion from remodeled nephrons is so high that FV-RAS control mechanism of normal nephrons is distorted. This reference case demonstrates the dynamics of such a subject.

To demonstrate dynamics of essential-hypertensives, normal contribution R.M. is set to 1.8e-5 g/day, 3 times of normal renin contribution R.M. of the potential-hypertension case. Max conversion fraction is set to 0.005/week. Other parameters are kept the same (normal snGFR R.M.= 0.045 ml/day, Max snGFR Capacity R.M.= 0.09 ml/day, Remodeling threshold RpN= 3.2e-6 g/day).

The dynamics of essential hypertension (run 1) will be presented in comparison to dynamics of potential hypertension case (run 2).

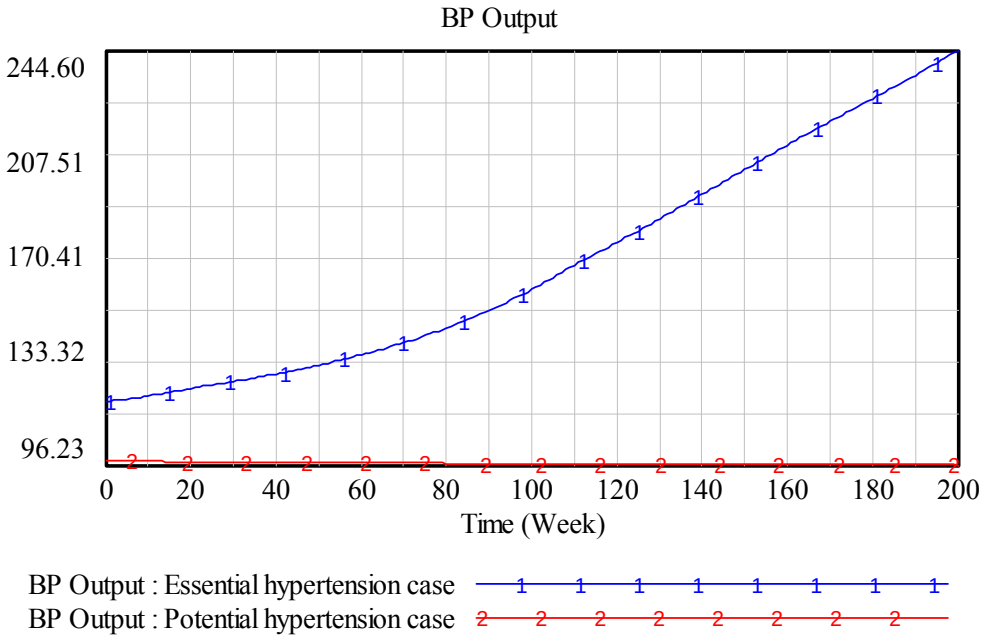

Figure 5.17. Dynamics of blood pressure-essential hypertension

BP of essential hypertensive patient (run1) progresses to lethal stages within 160 weeks (Figure 5.17). This case demonstrates a severe hypertension patient who has passed the development stages of hypertension and who is not treated with any medication.

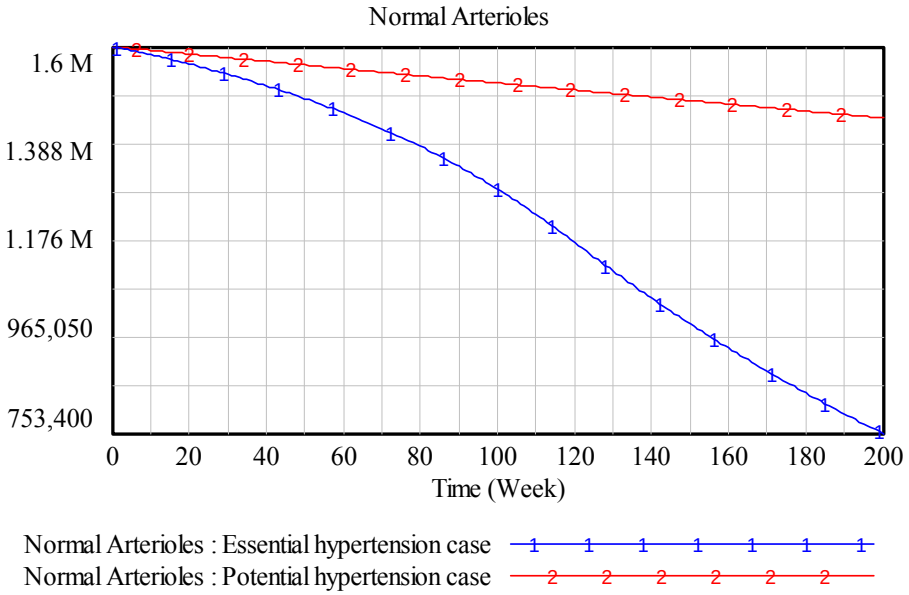

Figure 5.18. Dynamics of Normal Arterioles-essential hypertension

The precipitous fall in Normal Arterioles does not result from loss of nephrons as it does in the potential hypertension case. It results predominantly from conversion of normal arterioles to remodeled arterioles (Figure 5.18, Figure 5.19 and Figure 5.20).

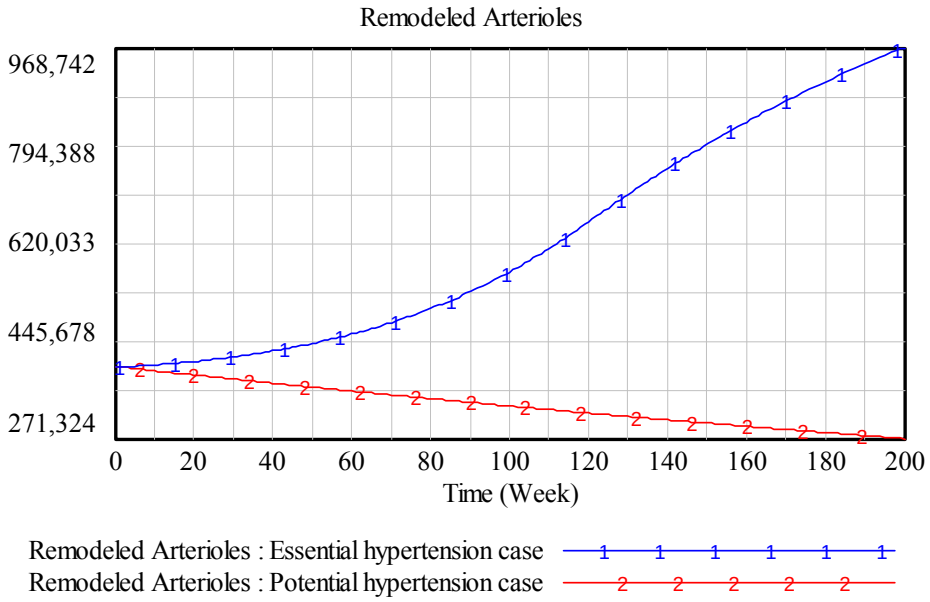

Figure 5.19. Dynamics of Remodeled Arterioles-essential hypertension

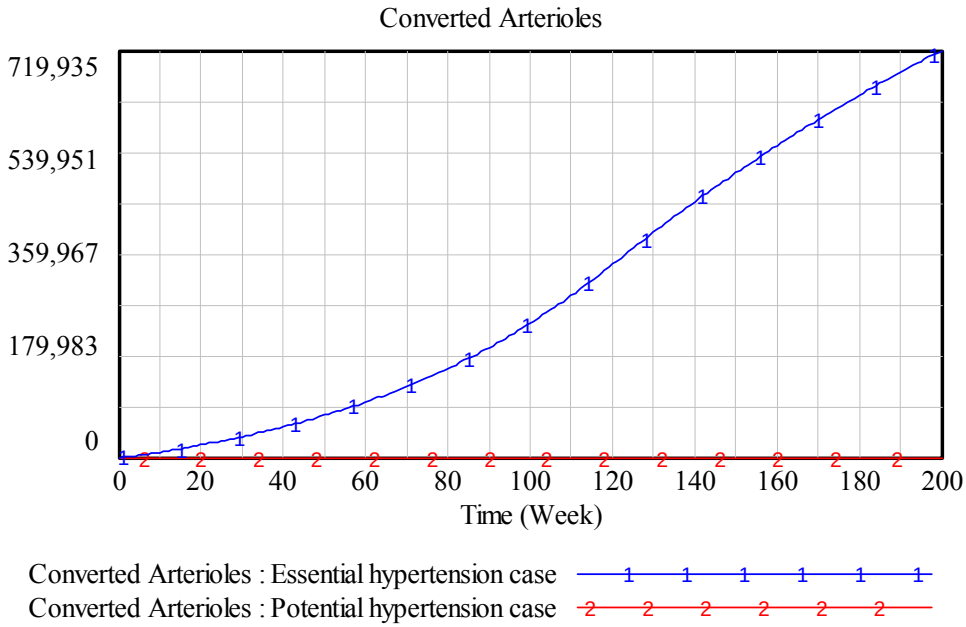

Figure 5.20. Dynamics of Converted Arterioles-essential hypertension

The behavior of BP in this reference case of essential hypertension is dominated by remodeling rather than nephron loss as demonstrated by difference between total conversions and deaths from normal nephrons (Figure 5.20 vs. Figure 5.21).

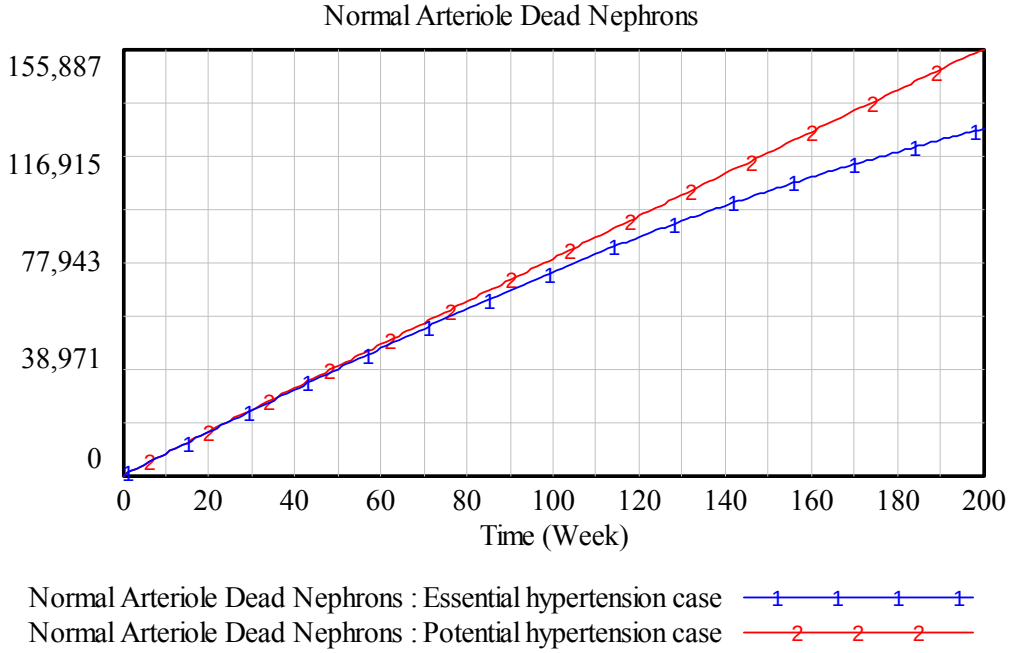

Figure 5.21. Dynamics of normal nephron deaths-essential hypertension

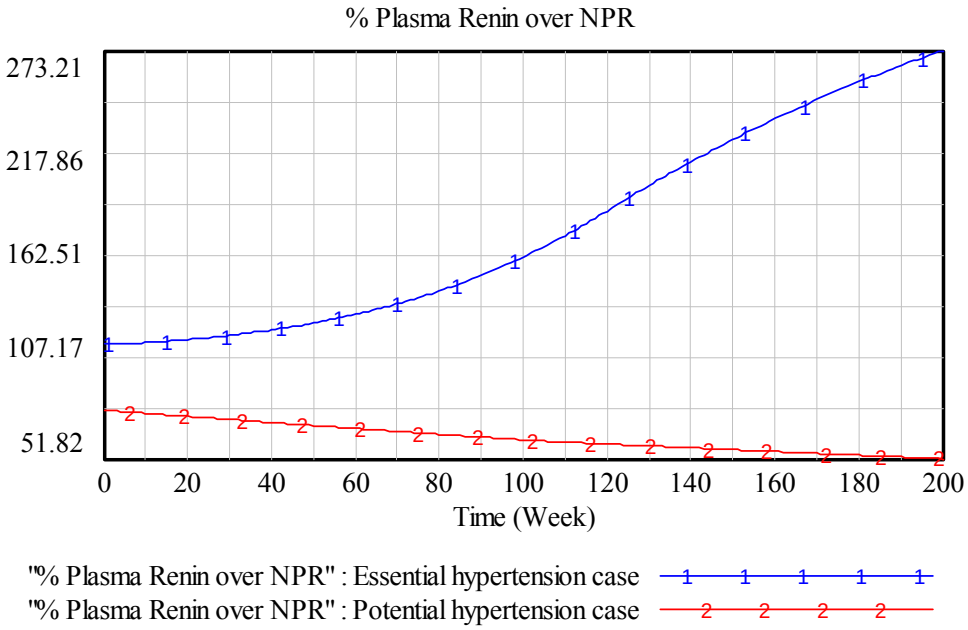

Figure 5.22. Dynamics of plasma renin-essential hypertension

In essential hypertension case, plasma renin levels and renin per nephron (RpN) demonstrate growth behavior (Figure 5.22, Figure 5.23). The growth is caused by the positive remodeling loop. The increase in RpN means that afferent and efferent arteriole of normal nephrons will be vasoconstricted above their normal states. Thus, more blood flow would be necessary to achieve the same amount of water excretion.

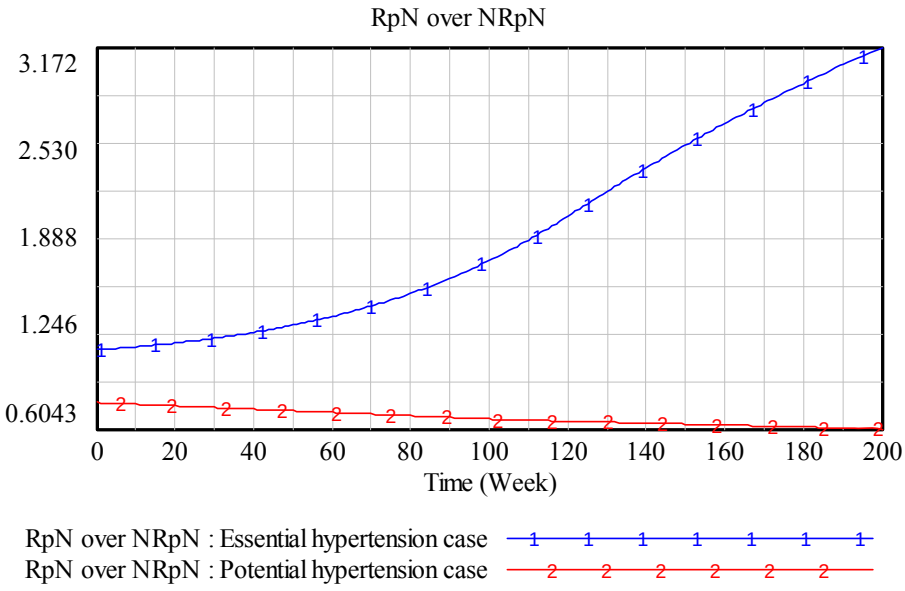

Figure 5.23. Dynamics of renin per nephron-essential hypertension

The discrepancy in goal-seeking FV-RAS control mechanism of normal nephrons is best demonstrated by the difference between the Actual snGFR, run1, and Required snGFR, run2 (Figure 5.24). Throughout the simulation, Actual snGFR is below Required snGFR.

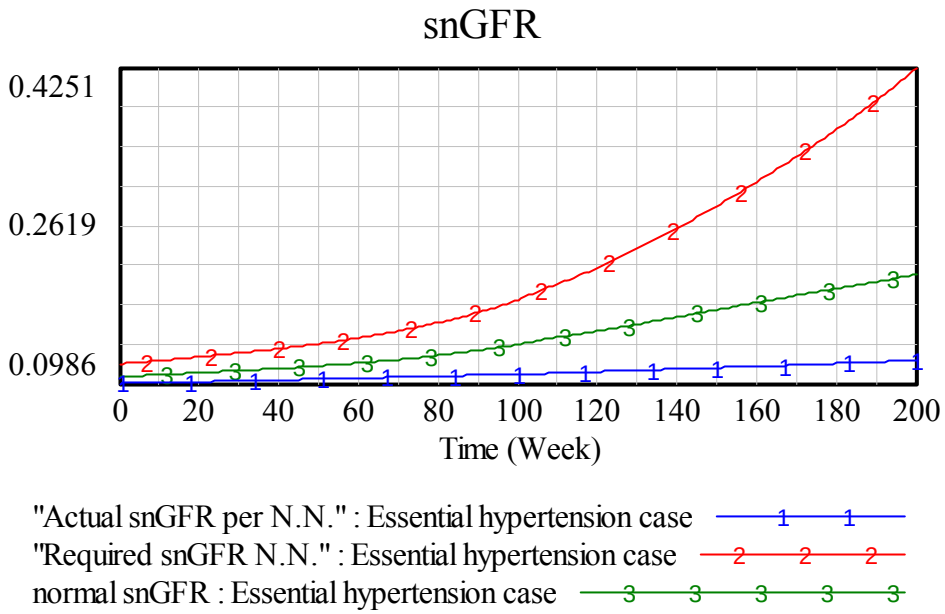

Figure 5.24. Dynamics of snGFR-essential hypertension

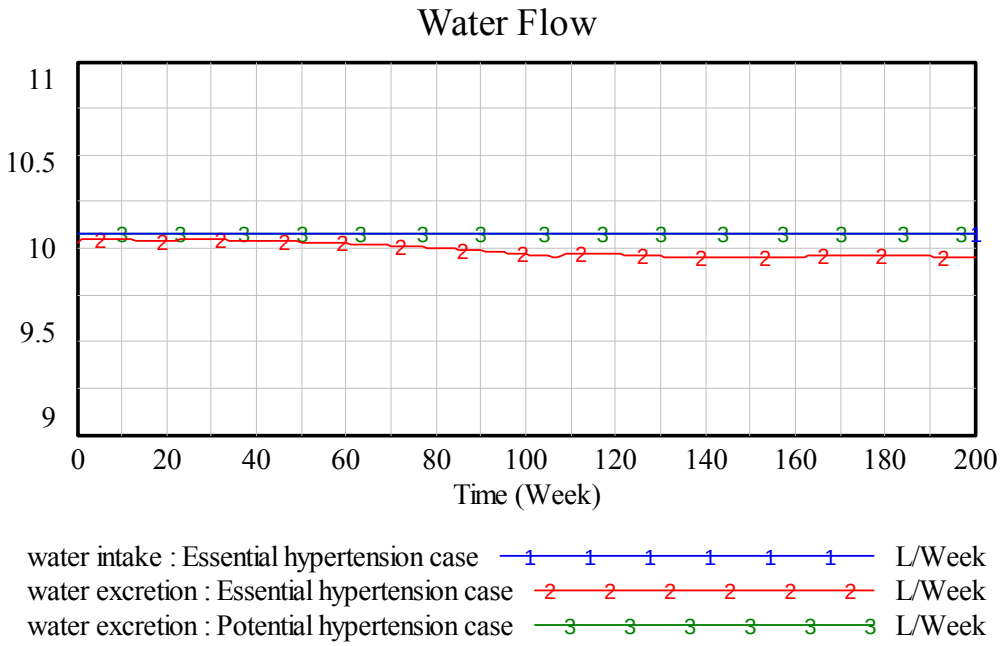

Figure 5.25. Dynamics of Water Balance-essential hypertension

Actual snGFR must equal required snGFR to bring FV back to its target level and achieve excretion that equals intake. The persistent difference between required and actual snGFR over weeks results in the gap between water intake and water excretion throughout out the life span of the subject. Note that the horizontal line in Figure 5.25 denotes the water intake and that 2nd run denotes water excretion of essential hypertension case. The positive water balance between the two flows results in accumulation of FV over time. On the other hand, Water Excretion of Potential hypertension case (3rd run, Figure 5.25) perfectly matches water intake.

In the next section, scenario analysis on normal subject and hypertensive subjects will be conducted to find out whether there are different possible modes of behavior for key variables which could significantly change the progression dynamics of blood pressure.

6. SCENARIO ANALYSIS

6.1. Low Remodeling Threshold Renin per Nephron in Normal Subjects

In this experiment, remodeling threshold RpN for normal subjects is reduced by 30 per cent from its normal level. This case represents a scenario where the arterioles of a person are especially susceptible to become remodeled even for lower average levels of Ang II in blood. At the simulation start, all nephrons are normal. The behavior will be compared against normal subject's reference case.

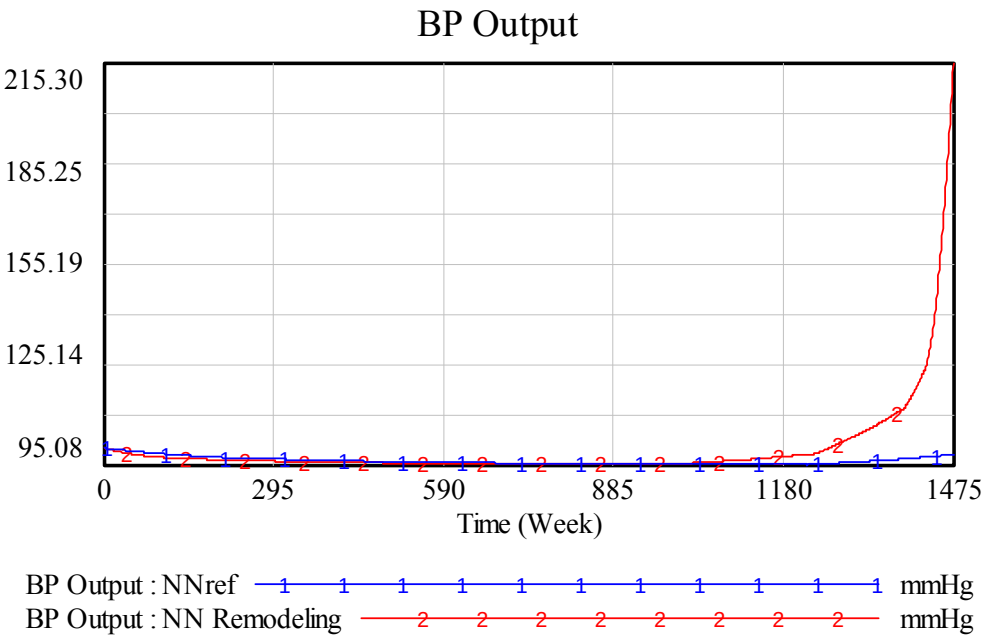

Figure 6.1. Dynamics of blood pressure-1

The behavior of BP demonstrates the expected exponential growth behavior (see run 2, NN Remodeling in Figure 6.1). However, unlike the reference case of normal subjects the initiation of growth is much earlier, around week 1200, 20 years. (see run 1, NN ref, vs. run 2, NN Remodeling in Figure 6.1).

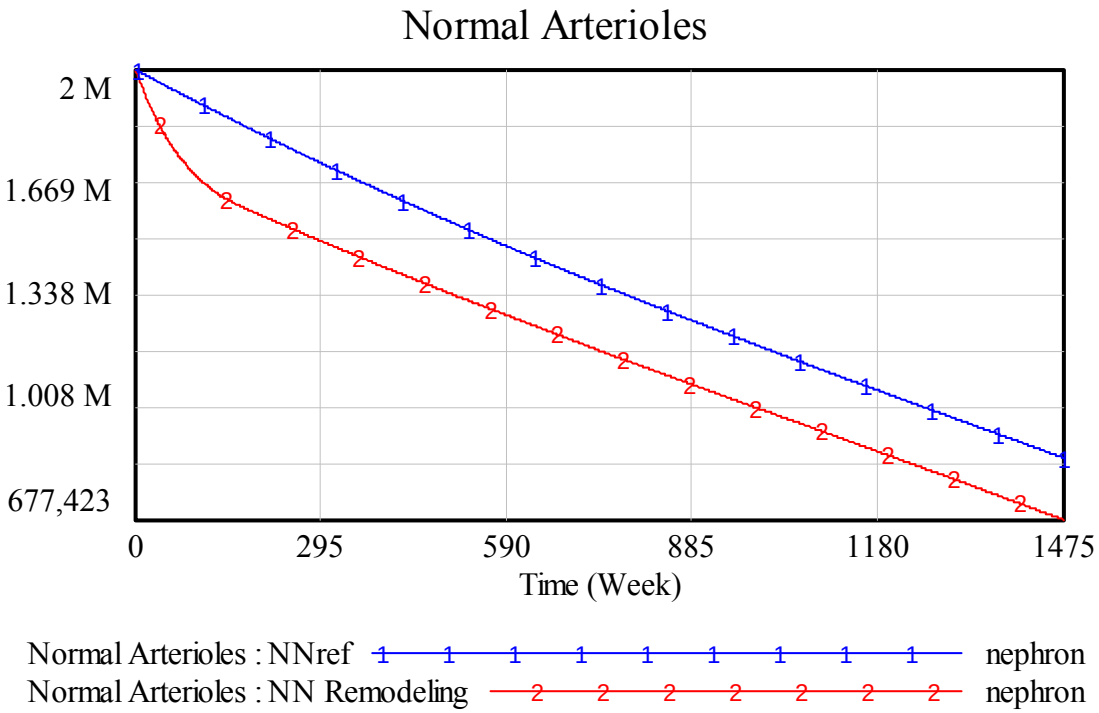

Figure 6.2. Dynamics of Normal Arterioles-1

Normal Arterioles decline over time (Figure 6.2). The decline is due to both nephron loss and arteriolar conversion. Remodeled Arterioles initially grow then decline to lower levels (Figure 6.3).

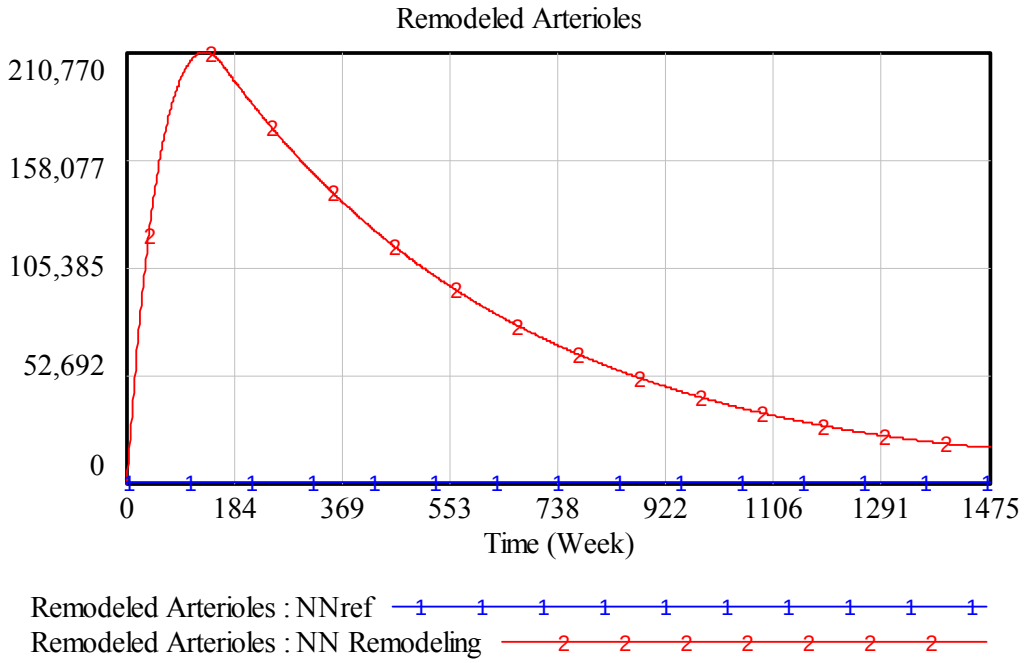

Figure 6.3. Dynamics of Remodeled Arterioles-1

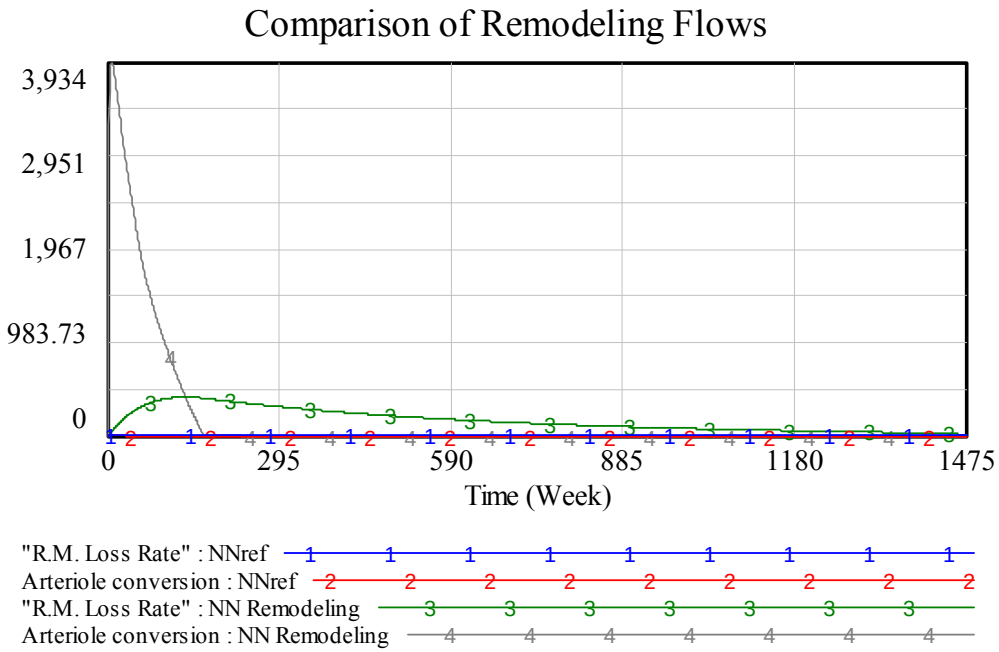

Figure 6.4. Dynamics of flows of remodeled arterioles-1

The growth then decline behavior of remodeled arterioles is due to the fact that initially, arteriolar conversion is much greater than nephron loss from remodeled nephrons (run 4 vs. run 3 in Figure 6.4). However, arteriolar conversion decreases over time and nephron loss remains high enough levels such that remodeled arterioles start declining after around week 150 (Figure 6.3).

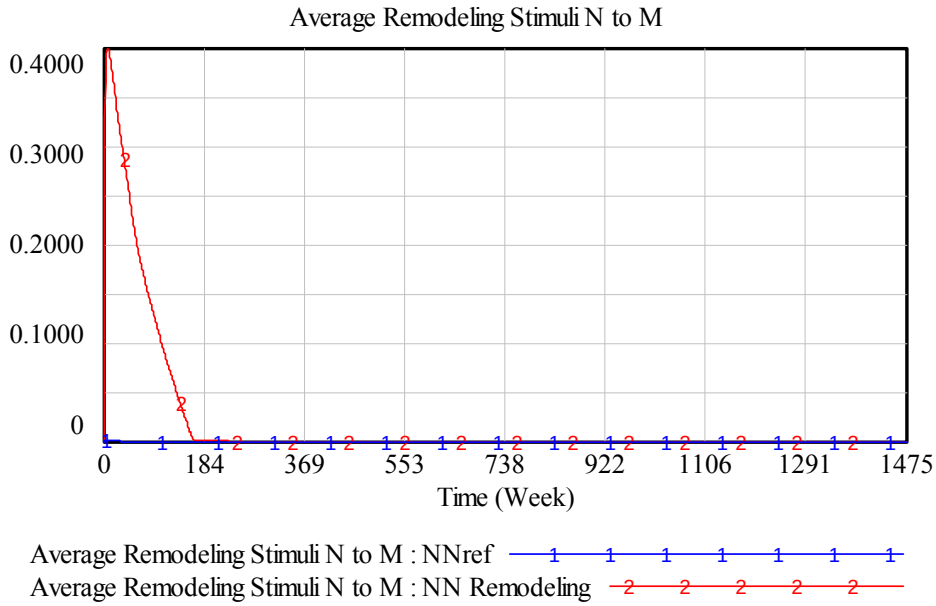

Figure 6.5. Dynamics of remodeling stimuli-1

The fall of arteriolar conversion is due to the fact that renin per nephron eventually falls below threshold RpN below which there is no remodeling stimuli (Figure 6.6, Figure 6.5).

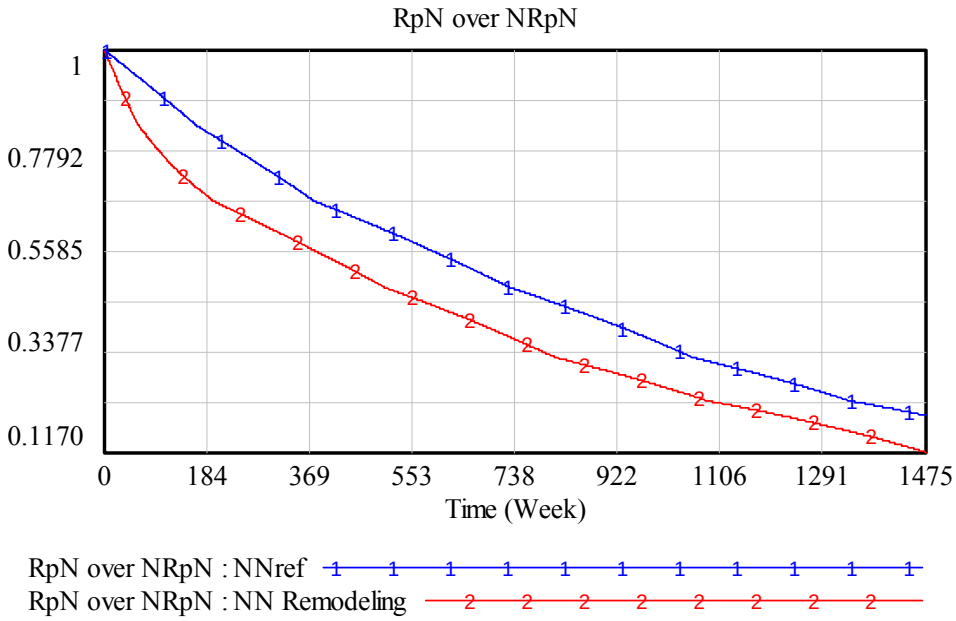

Figure 6.6. Dynamics of renin per nephron-1

Renin per nephron demonstrates a decline path throughout most of the simulation (Figure 6.6). This is in contrast to the case of essential hypertension where remodeling and elevation of BP happen simultaneously. The difference in progression of BP in normal subjects results from the fact that renin secretion from remodeled nephrons is not as high as in the case of essential hypertension. Thus, although there is ongoing conversion to remodeled nephrons, the FV-RAS control mechanism of normal nephrons remains intact. Normal nephrons can achieve the required snGFR by adaptive reductions in their renin secretion. Accordingly, resistance adjusted snGFR matches required snGFR perfectly throughout the simulation. On the other hand, the behavior of Actual and Required snGFR demonstrate a growing discrepancy, as Actual snGFR approaches max snGFR capacity (Figure 6.7). This growing discrepancy is responsible for the rise in BP after week 1200.

In summary, progression of remodeling in normal subjects constitutes a different type of BP progression than progression of remodeling in essential hypertension (Figure 5.17 vs. Figure 6.1). In essential hypertension, BP levels are already high because of the problem in FV-RAS control mechanism. In normal subjects, this mechanism is still intact.

Rise in BP is due to the fact that remaining nephrons approach their maximum snGFR limits. The difference between the two types of hypertension is best demonstrated by the behavior of water flows (Figure 6.8 vs. Figure 6.9). Although there is a perfect match between water intake and excretion in normal subjects up until late stages of simulation, the water balance is positive in the essential hypertension case throughout the simulation.

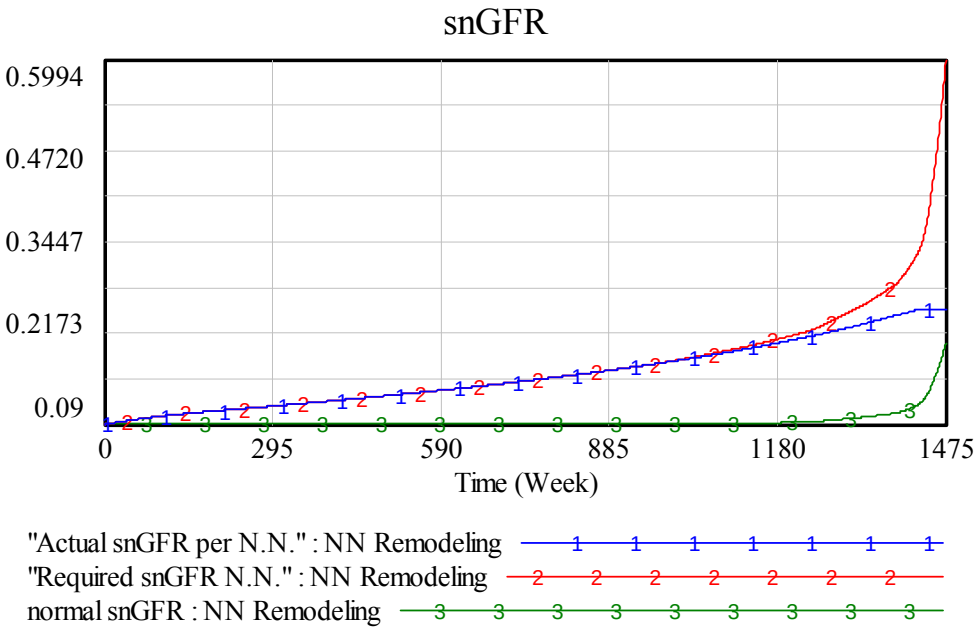

Figure 6.7. Dynamics of required and actual single nephron glomerular filtration rate-1

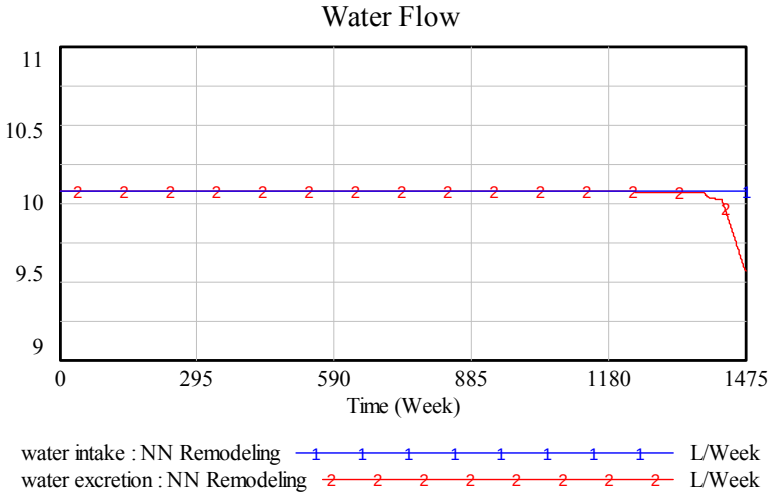

Figure 6.8. Dynamics of fluid volume flows -1

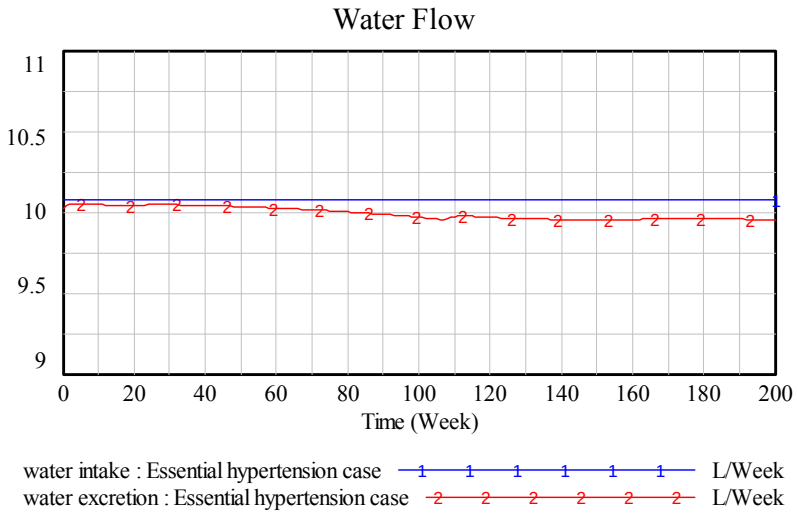

Figure 6.9. Dynamics of fluid volume flows in essential hypertension

6.2. Increased Water Intake in Potential-hypertensives

In this experiment, the potential hypertensive subject increases his/her water intake by 20 per cent at week 10. In real life this could represent a person who eats a lot of salty food or whose short-term osmolality-water intake mechanism does not work properly. The behavior of increased water intake in potential-hypertensives scenario will be compared to the potential hypertension base case.

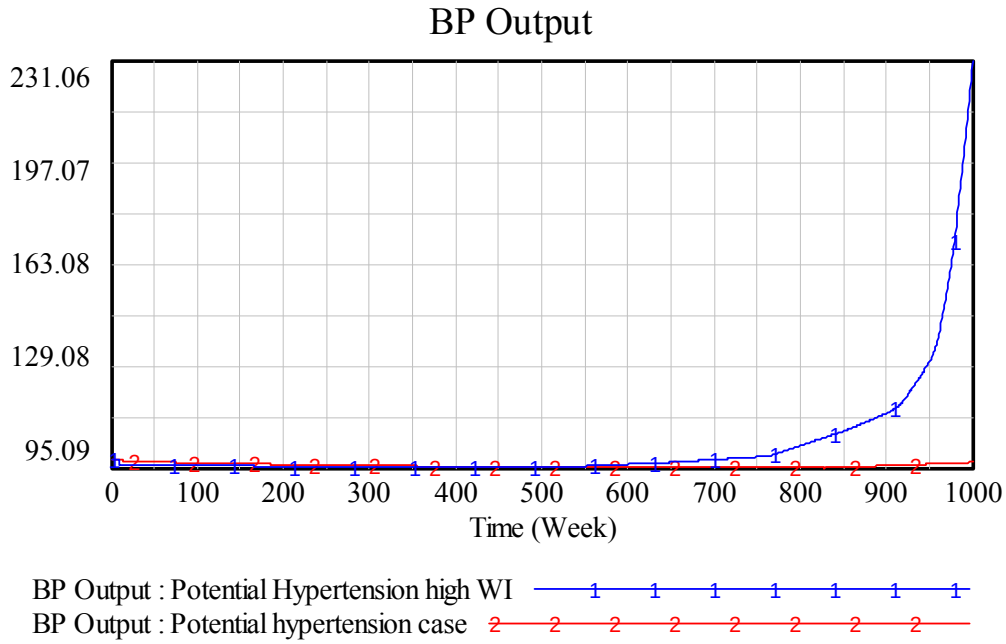

Figure 6.10. Comparitive dynamics of blood pressure-2

BP of the subject with high water intake starts increasing from the normal value of BP much earlier than the potential-hypertensive subject who has normal water intake (Figure 6.10).

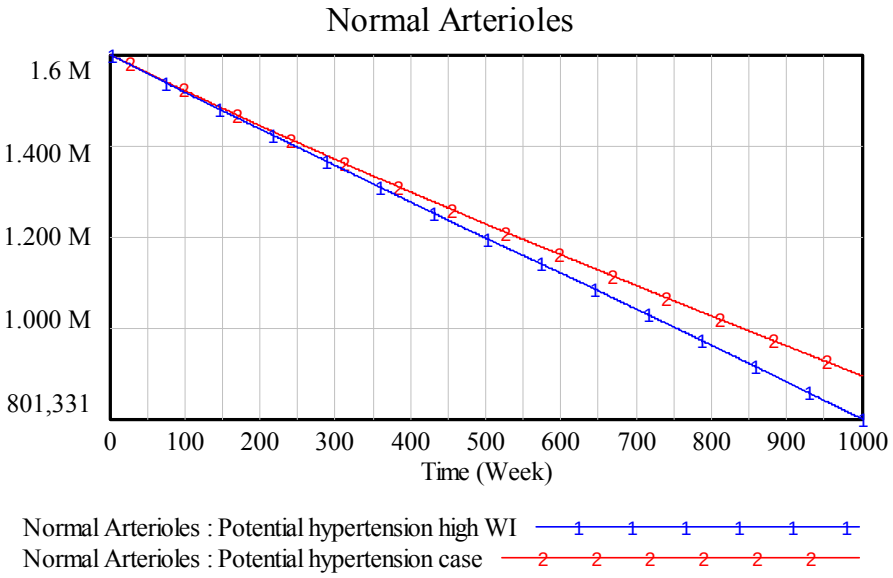

Figure 6.11. Dynamics of Normal Arterioles-2

There is no remodeling in the high WI case since normal renin contribution from remodeled arterioles is low. Thus, the observed difference in BP dynamics originates from differences in nephron loss. The nephron loss rate of normal arterioles is higher in the subject with high water intake (Figure 6.11). Since N.N. nephrons must have higher filtration in order to get rid off excess fluid, their Actual snGFR will be higher (Figure 6.12). Consequently, the effect of high glomerular pressure on nephron loss rate is higher in the high water intake scenario (Figure 6.13)

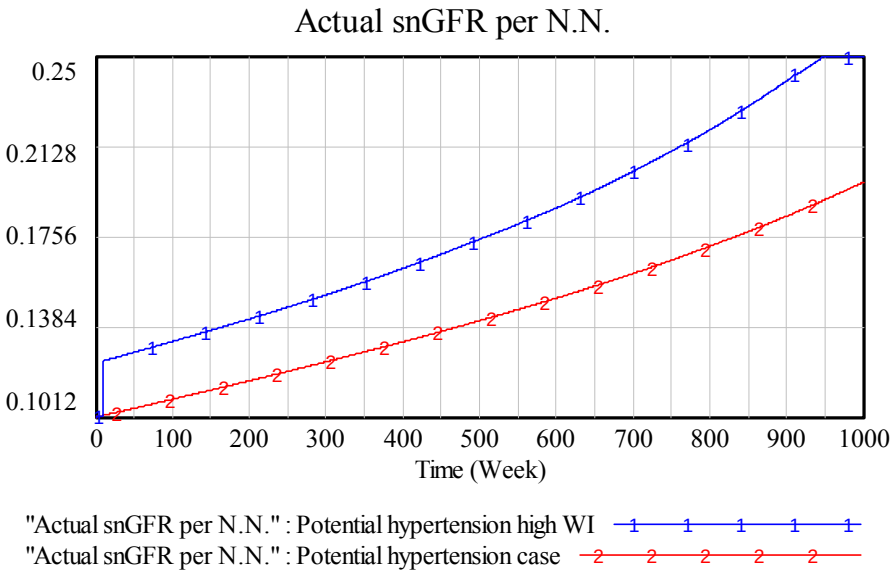

Figure 6.12. Dynamics of Actual snGFR-2

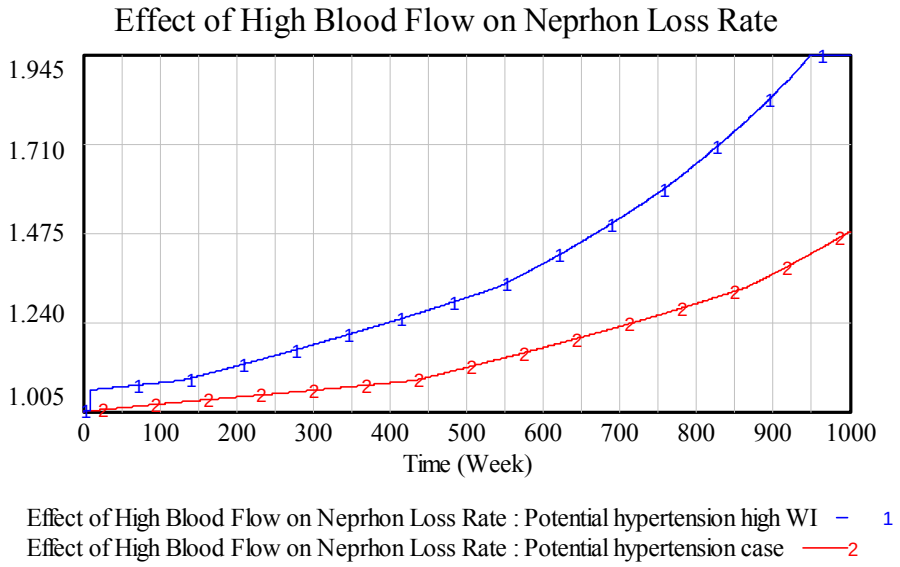

Figure 6.13. Dynamics of effects of glomerular pressure on Nephron loss-2

Remodeled arterioles demonstrate similar dynamics with normal water intake case. This is due to the fact that BP only starts to increase during late stages of simulation (Figure 6.14). Therefore, Actual snGFR R.M. and Effect of Low Blood Flow on Nephron loss rate will be similar for both runs throughout most of the simulation.

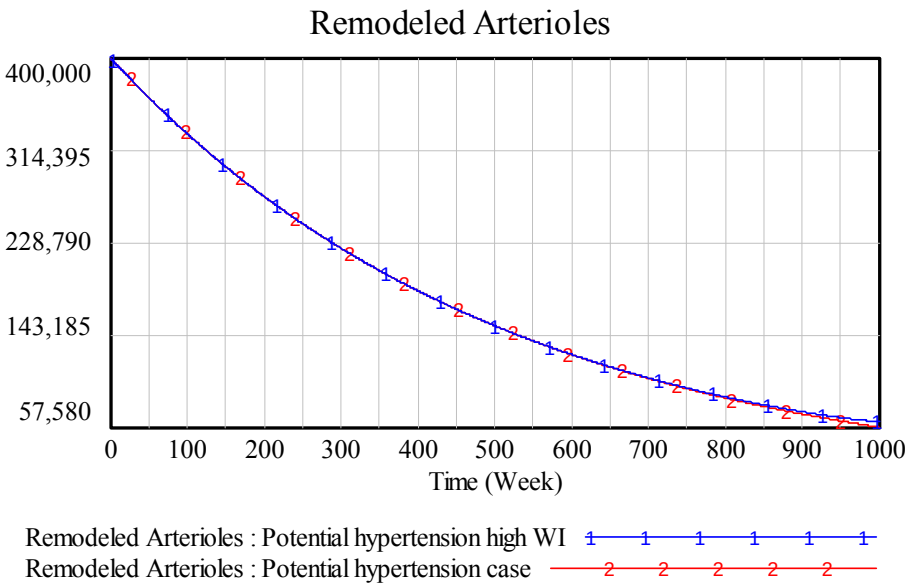

Figure 6.14. Dynamics of Remodeled Arterioles-2

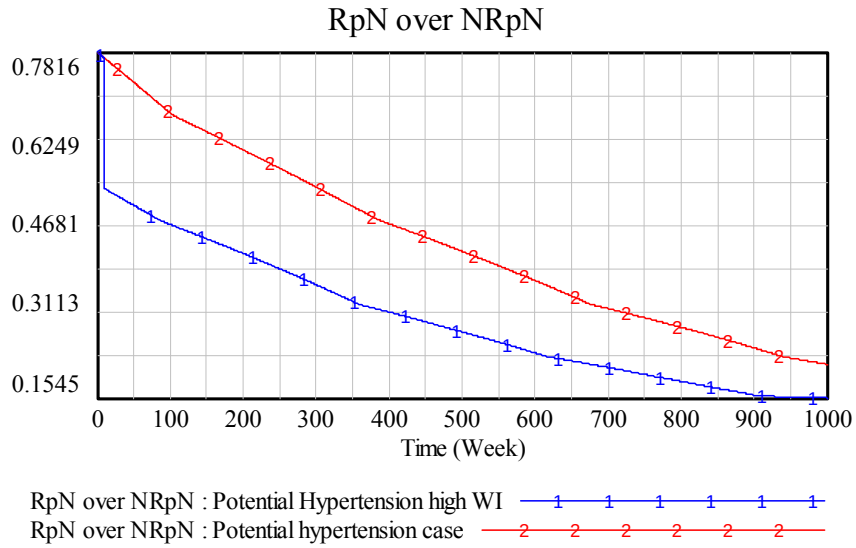

Figure 6.15. Dynamics of renin per nephron-2

Renin per nephron declines throughout the simulation (Figure 6.15). The decline is due to the fact that normal arterioles decrease their renin secretion in order to compensate for the increased Required snGFR caused by loss of nephrons and high water intake (Figure 6.16). The difference in renin per nephron levels between the two runs results from the fact that higher water intake necessitates higher Required snGFR, i.e. greater need for compensation by FV-RAS. Nevertheless, a discrepancy between Required and Actual

snGFR only occurs during late stages of simulation, in a similar manner to the case of normal and potential hypertensive subjects.

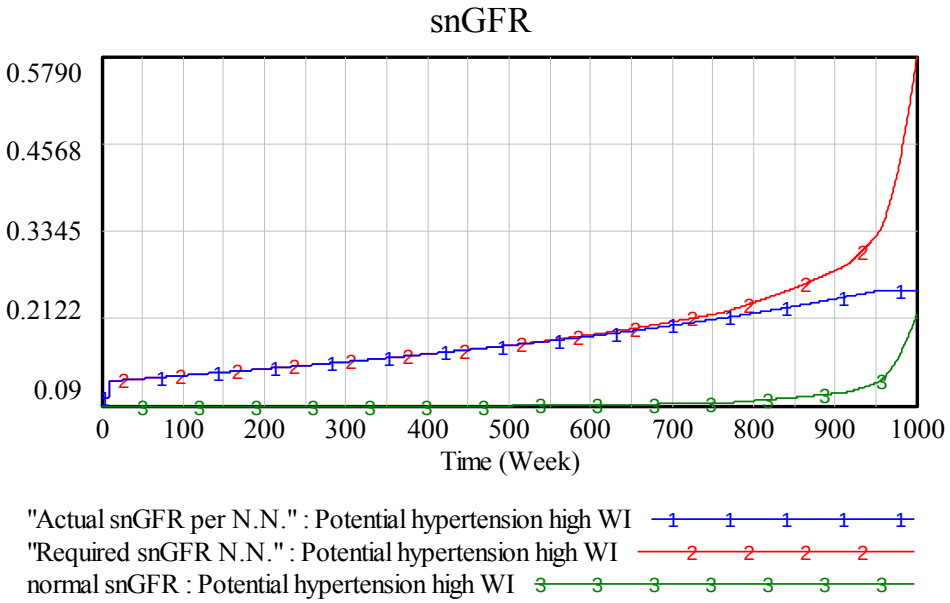

Figure 6.16. Dynamics of single nephron glomerular filtration rate-2

6.3. Different Combinations of Nephron Loss Fractions in Essential-hypertensives

6.3.1. Low Normal Nephron Loss Fraction and Low Remodeled Nephron Loss Fraction

The base case of essential hypertension corresponds to normal values of nephron loss fractions. In this experiment, normal nephron loss fraction will be decreased by 80 per cent from 0.0005 to 0.0001 and remodeled nephron loss fraction will be decreased by 50 per cent from 0.001 to 0.0005.

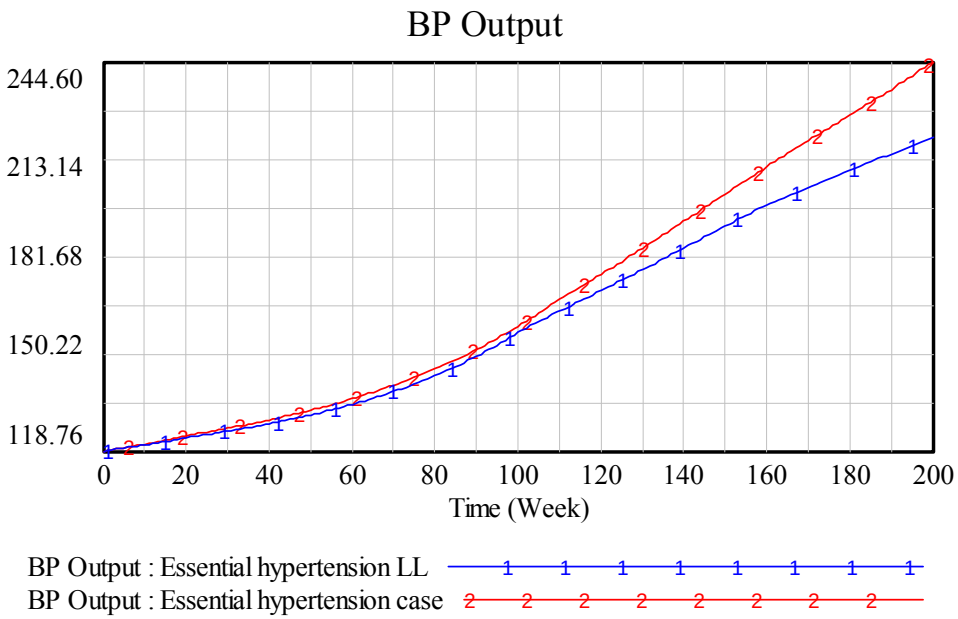

Figure 6.17. Dynamics of blood pressure-3; early phases

The behavior of BP is not significantly different from the reference case despite significant reductions in nephron loss fractions (see run 1 vs. run 2 in Figure 6.17).

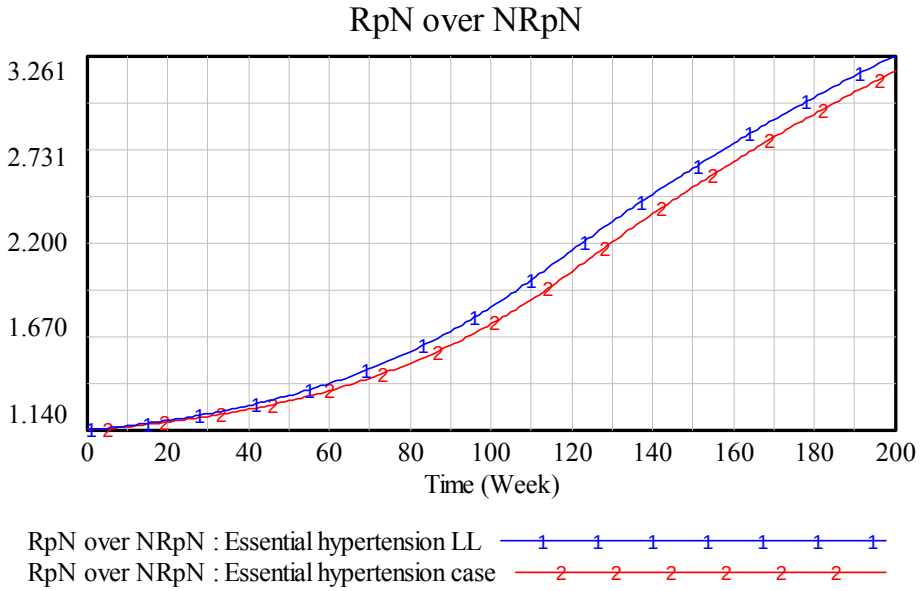

Figure 6.18. Dynamics of RpN over NRpN-3

Renin per nephron levels are above the reference case as a result of higher remodeled population (Figure 6.18). The number of remodeled nephrons increases consistent with expectations from a lower nephron loss fraction (Figure 6.19).

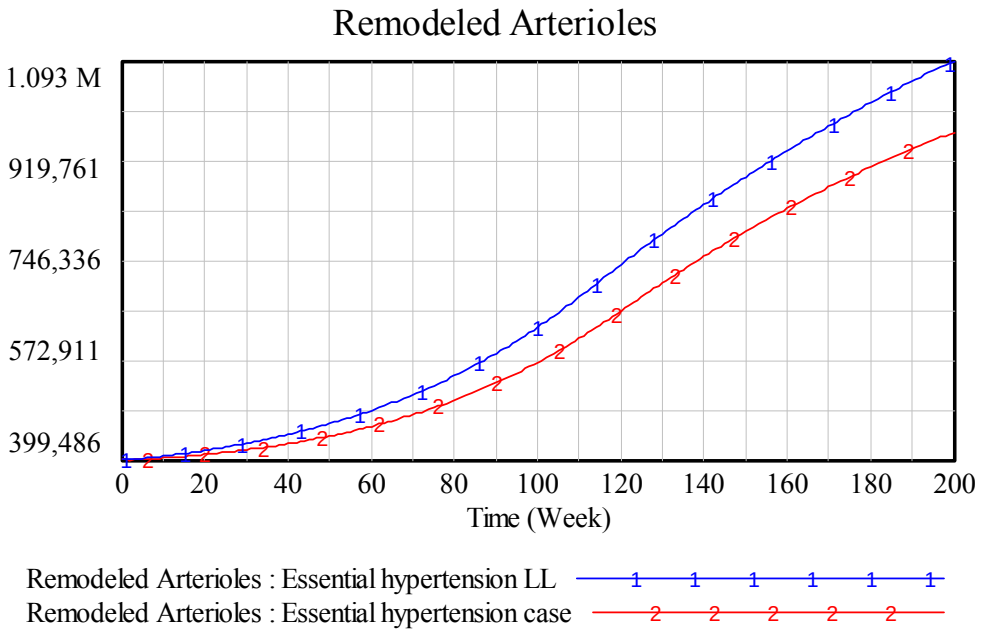

Figure 6.19. Dynamics of Remodeled Arterioles-3

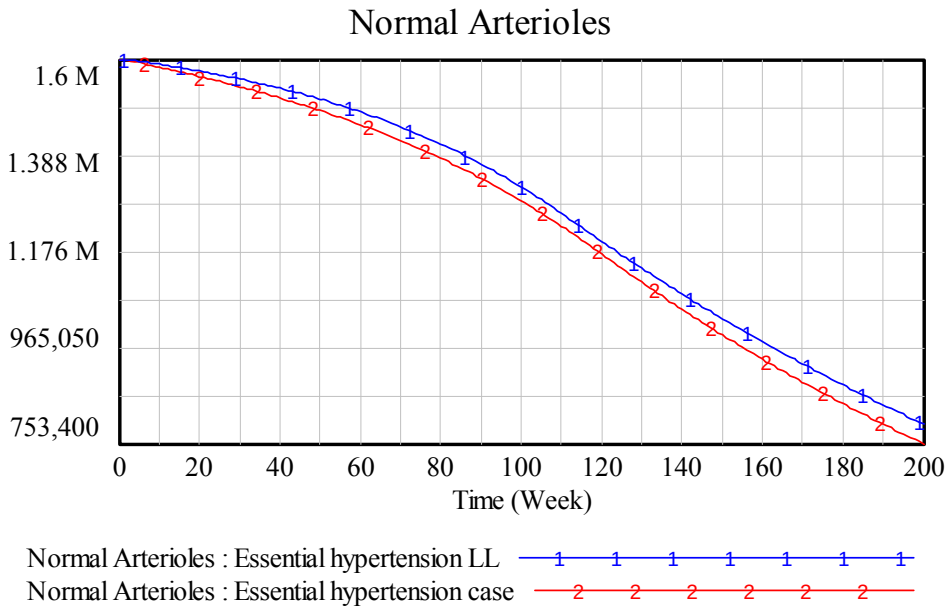

Figure 6.20. Dynamics of Normal Arterioles-3

The number of normal nephrons and remodeled nephrons are higher, consistent with expectations, but the general behavior pattern of BP and FV in essential hypertension does not change by reductions in both nephron loss fractions (Figure 6.19, Figure 6.20).

6.3.2. 100 per cent Increase in Remodeled Nephron Loss Fraction only

Normal nephron loss fraction is kept at its normal level of 0.0005 and remodeled nephron loss fraction is increased by 100 per cent, from 0.001 to 0.002. The general behavior pattern for BP dynamics does not change; however, higher death fraction from remodeled nephron results in a slower progression of BP over time (Figure 6.21).

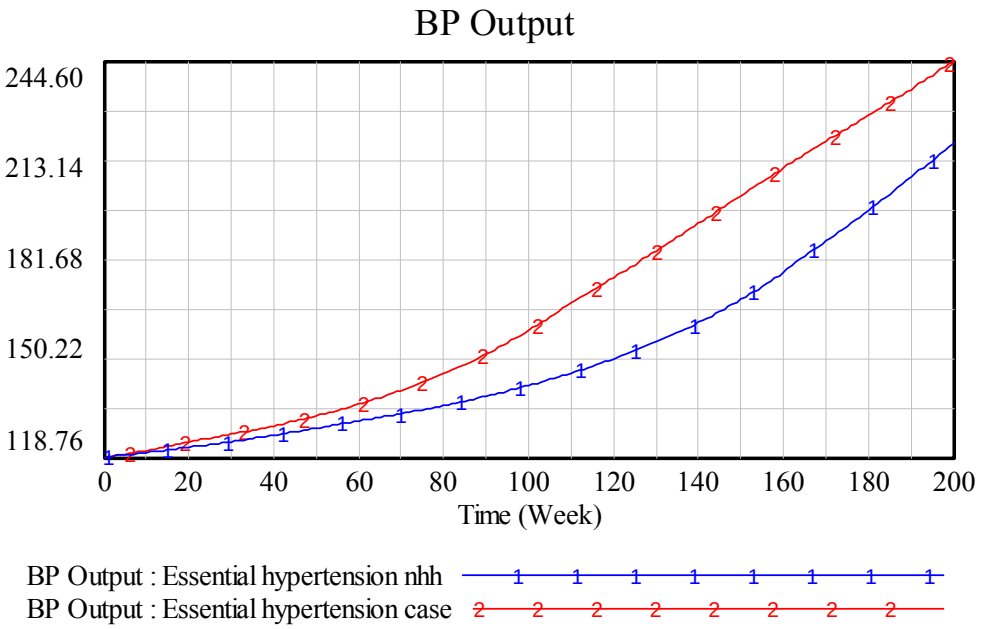

Figure 6.21. Dynamics of blood pressure–4; early phases

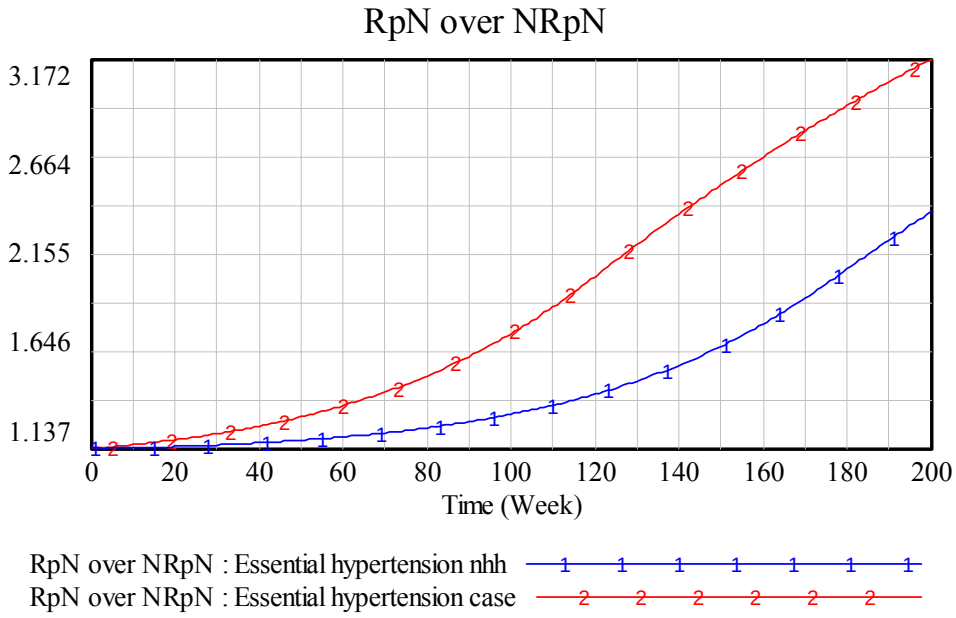

Figure 6.22. Dynamics of renin per nephron-4

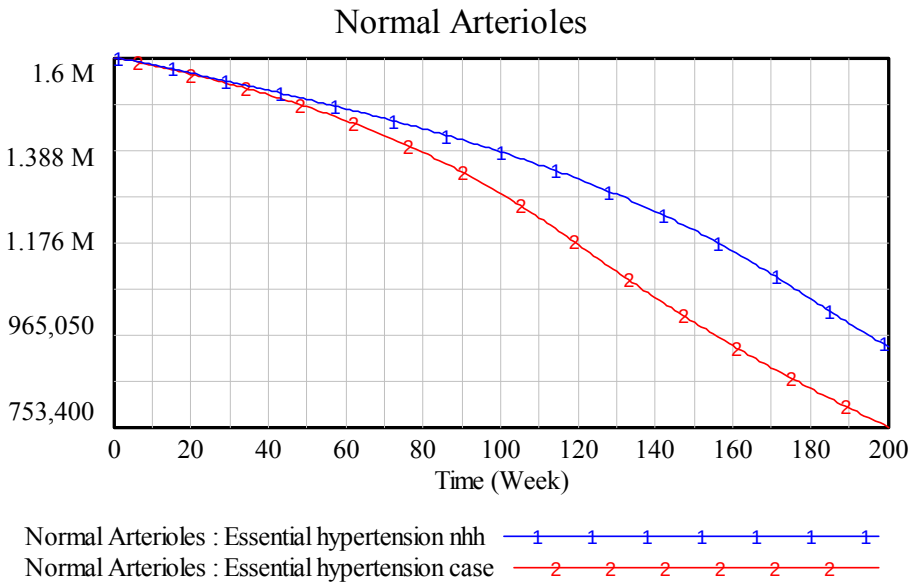

Figure 6.23. Dynamics of Normal Arterioles-4

The reduction path of Normal Arterioles starts deviating from that of reference essential hypertension case after about thirty weeks (Figure 6.23). Remodeled Arterioles maintain a stable level initially, then start increasing only after about week 60 (Figure 6.24).

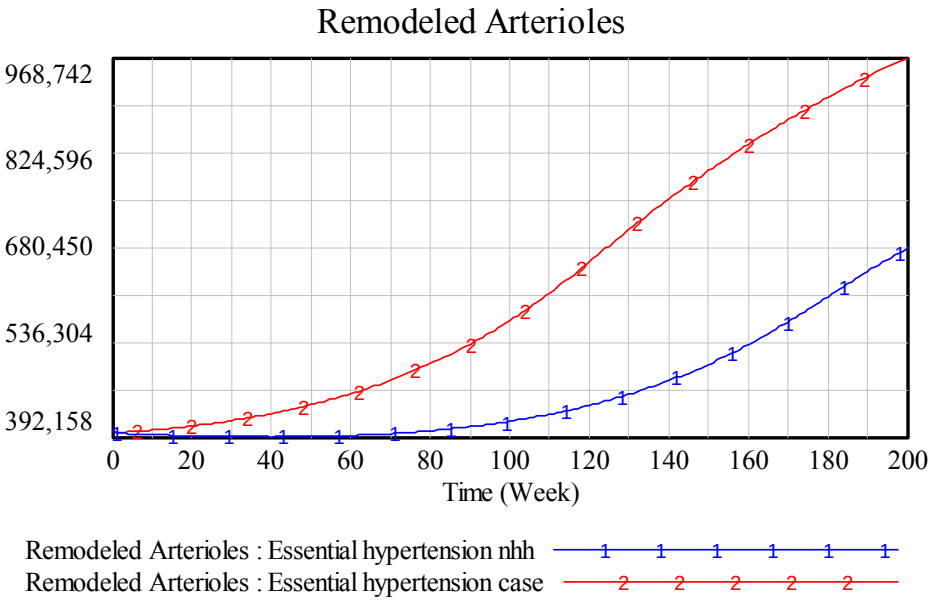

Figure 6.24. Dynamics of Remodeled Arterioles-4

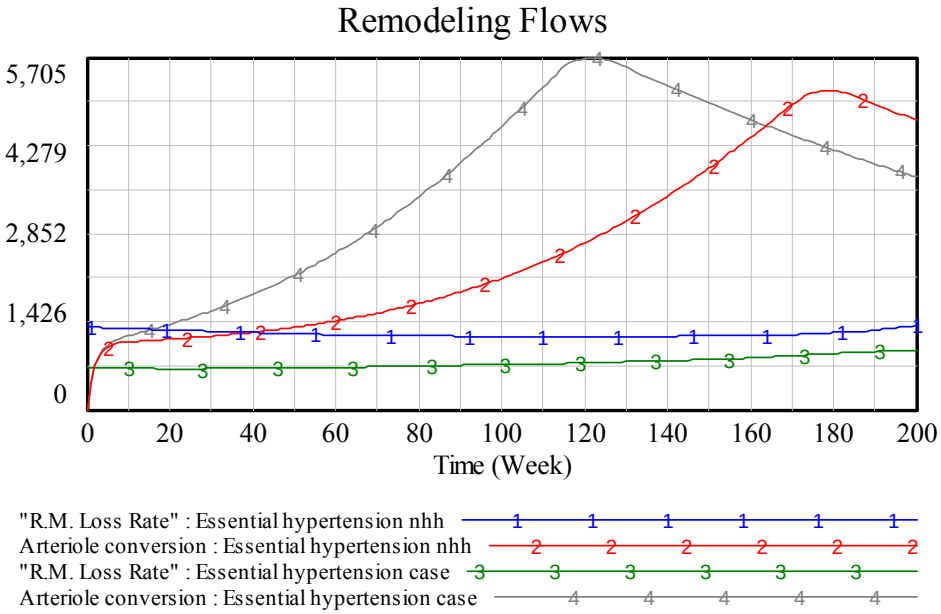

Figure 6.25. Dynamics of flows of remodeled nephrons-4

The delayed rise in remodeled arterioles compared to the case of essential hypertension is due to the fact that arteriolar conversion is below the remodeled nephron loss rate up until week 40 (Figure 6.24, Figure 6.25). Increased remodeled nephron loss fraction delays dominance of arteriole conversion over remodeled nephron loss. The slower progression of BP for increased nephron loss fraction suggests that improved progression paths of BP may be possible for higher values of this fraction. Such an example will be demonstrated in the next scenario where remodeled nephron loss fraction will be increased by 150 per cent.

6.3.3. 150 per cent Increase in Remodeled Nephron Loss Fraction only

Normal nephron loss fraction is kept at its normal level of 0.0005, whereas remodeled nephron loss fraction is increased by 150 per cent from 0.001 to 0.0025. This change has a very significant impact on the behavior. *Higher loss from remodeled nephrons leads to normalization of BP*. In this respect, behavior of BP in reference essential hypertension case (see 5.2.2) and in the case with similar reduction in both of nephron loss fractions (see 6.3.1) are in stark contrast to BP of this run. In both of those cases, the subject reaches lethally high levels of blood pressure within about 160 weeks. In the current scenario, BP decreases from its initially high levels and demonstrates a stable

behavior around its normal value of 100 between week 500 and 800 (Figure 6.26). The progression of blood pressure to dangerous levels takes place over a longer period of time. The subject does not experience any significant increase in BP up until week 1000.

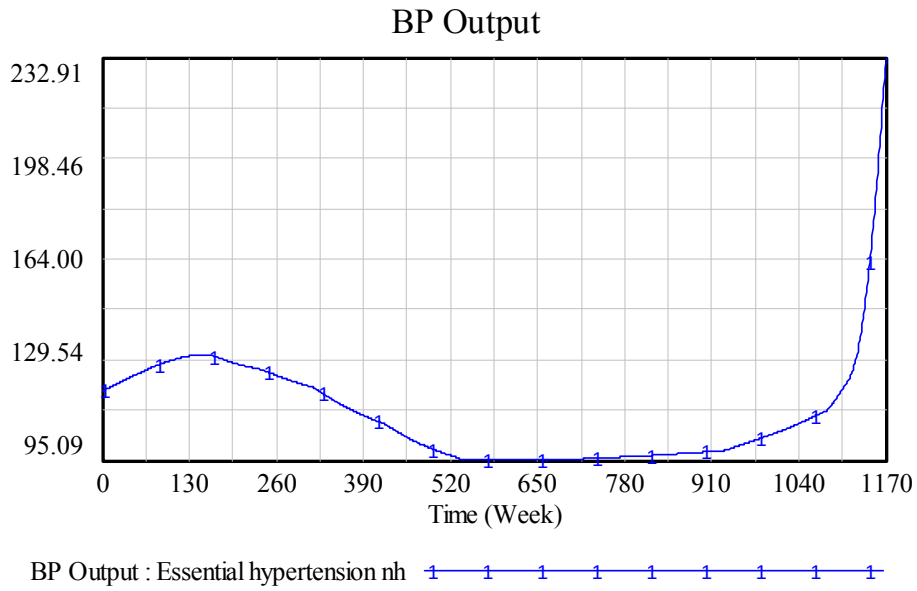

Figure 6.26. Dynamics of blood pressure-5

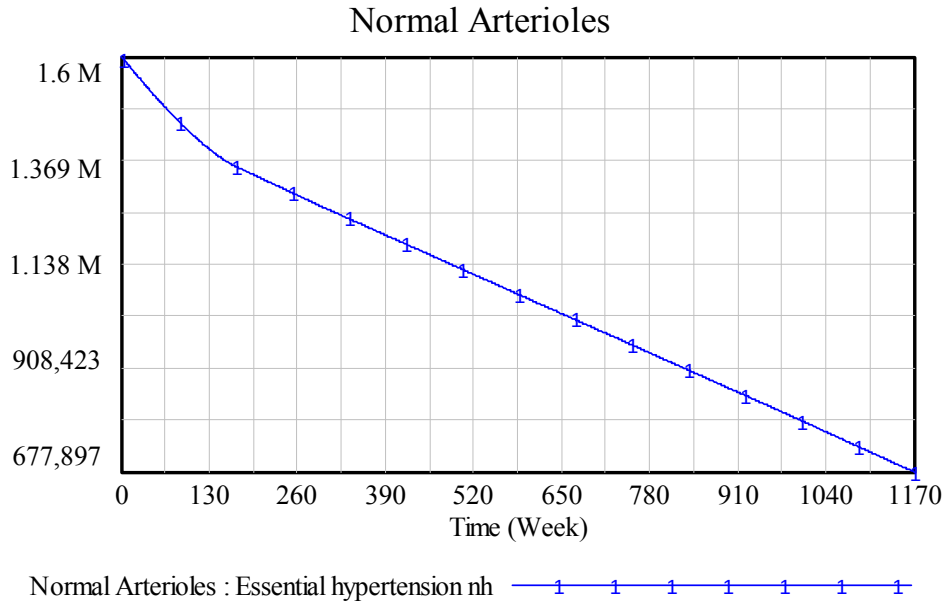

Figure 6.27. Dynamics of Normal Arterioles-5

Despite decline path of both Normal and Remodeled Arterioles, BP manages to return to its normal levels (Figure 6.27 and Figure 6.28).

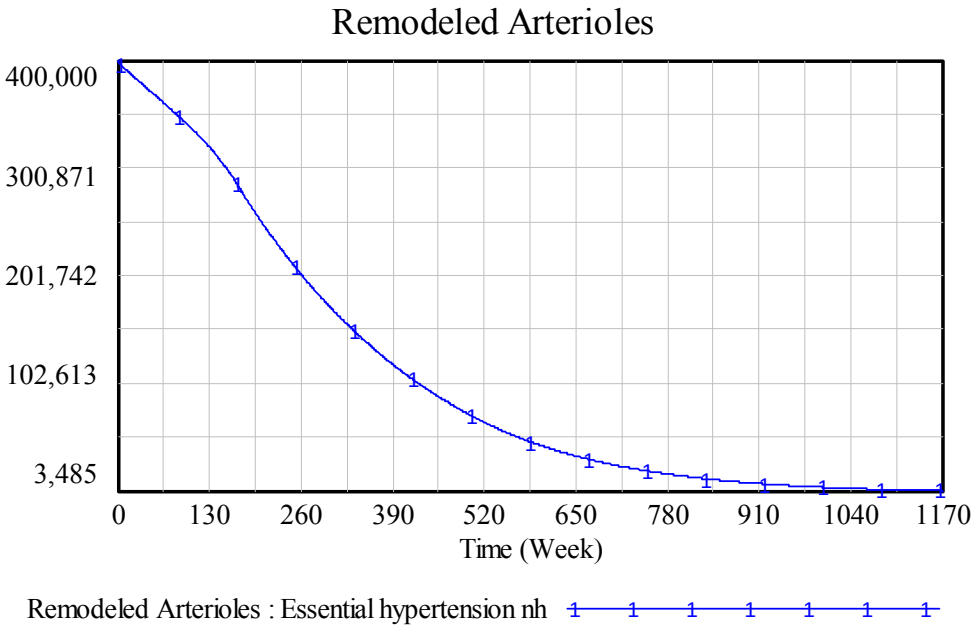

Figure 6.28. Dynamics of Remodeled Arterioles-5

The return of BP to its normal level suggests that FV-RAS control mechanism of normal Arterioles has become intact after the distribution of remodeled nephrons among all nephrons has fallen below a critical point. The recovery of FV-RAS is due to the elimination of high renin secreting remodeled nephrons over time. Nephron loss rate from remodeled nephrons is above the arteriolar conversion rate which drives the number of remodeled nephrons (Figure 6.29).

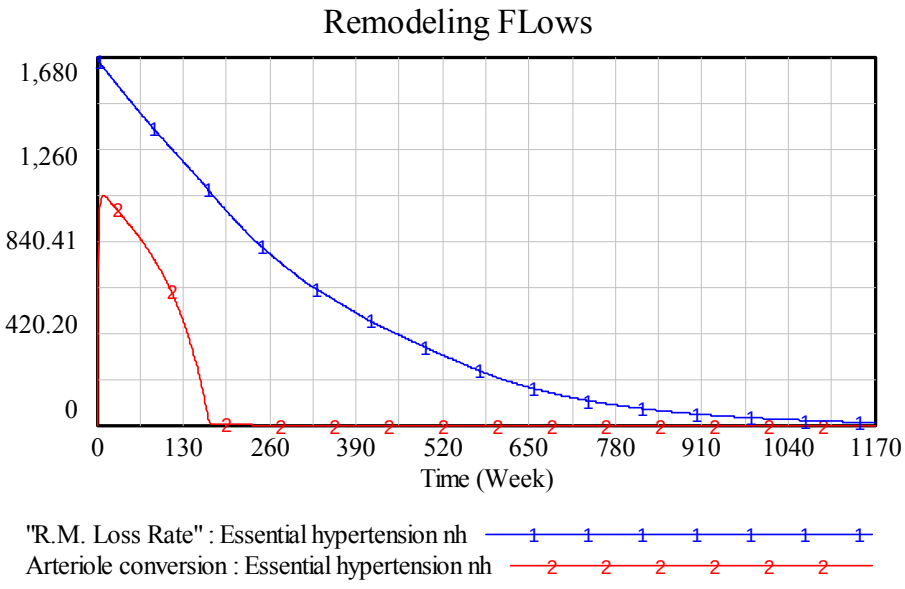

Figure 6.29. Dynamics of flows of Remodeled Arterioles-5

The behavior of renin per nephron demonstrates a decline path which is responsible for the recovery of FV-RAS mechanism (Figure 6.30).

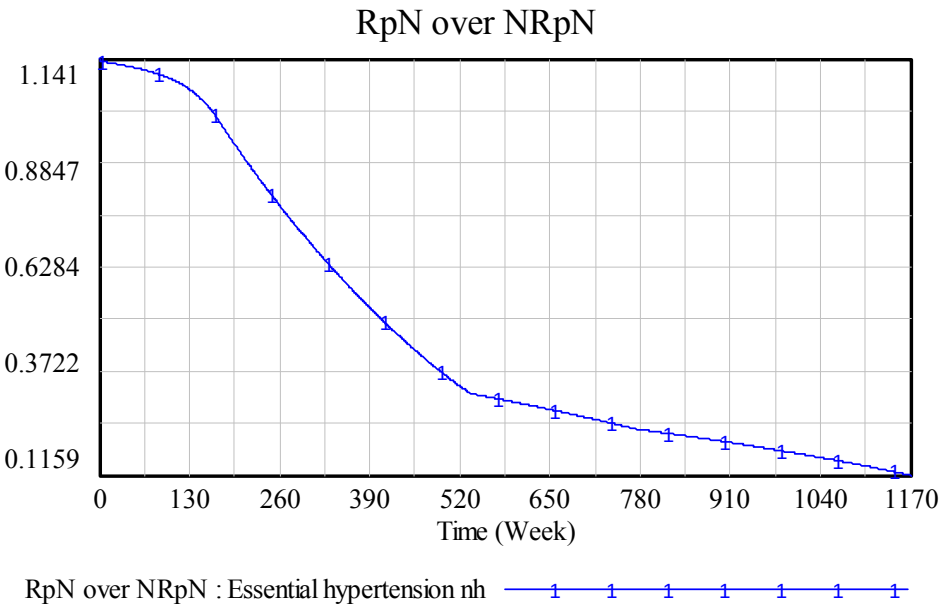

Figure 6.30. Dynamics of renin per nephron-5

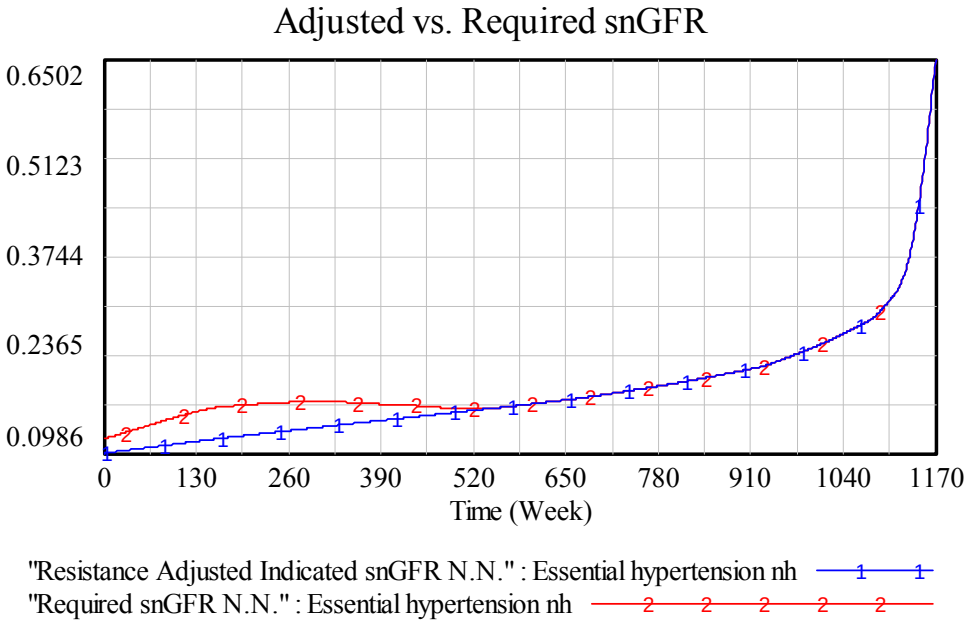

Figure 6.31. Dynamics of Required and Resistance Adjusted snGFR-5

The exact match between Required and Resistance Adjusted snGFR after week 520 demonstrates that normal nephrons can achieve the required snGFR necessary to keep FV at its target level (Figure 6.31). When FV eventually starts rising after week 900, the rise is

due to the fact that Actual snGFR of normal nephrons approach their max snGFR capacity. The progression of BP happens through insufficient capacity of remaining normal nephrons in a way similar to the progression of BP in normal subjects (Figure 6.32).

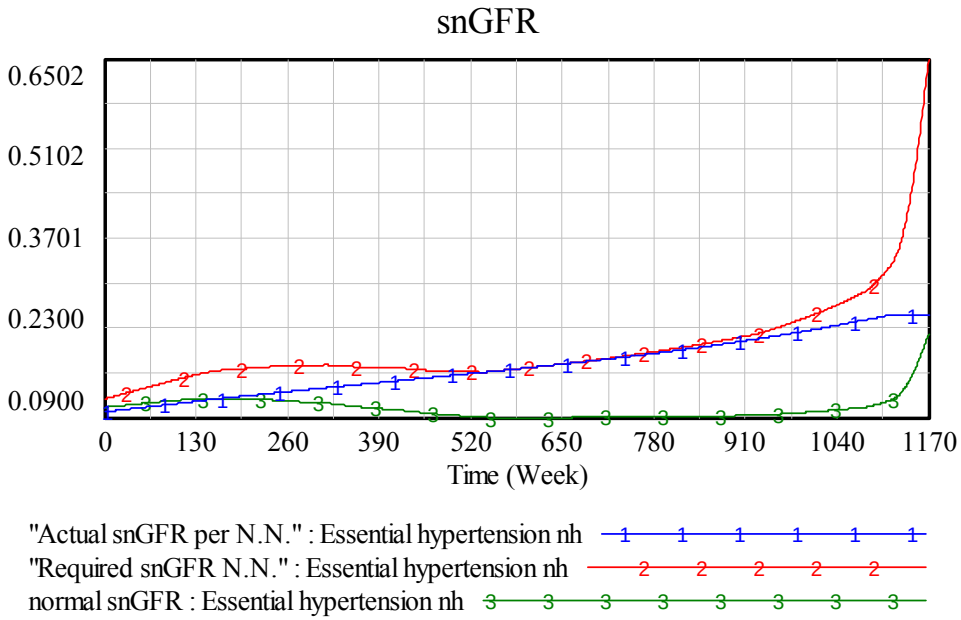

Figure 6.32. Dynamics of Actual and Required snGFR-5

The behavior of the model in this high remodeled nephron loss fraction scenario seems counterintuitive at first. Nephrons die faster, yet the survival time of the patient increases. This is due to the fact that the patient is able to quickly get rid of deleterious, high renin secreting remodeled nephrons. Consequently, remodeling loop will cease to be effective since renin per nephron levels fall below the remodeling threshold RpN. Additionally, once remodeled nephrons fall below levels where they would not interfere with the control of FV-RAS mechanism of normal nephrons, proper FV control can be maintained over a long period of time. This is because the number of normal nephrons is still high enough to compensate for remodeled nephrons and dead nephrons. The graph of BP over the initial 200 weeks reemphasizes the difference in the behavior of reference essential hypertension case and 150 per cent increase in remodeled nephron loss fraction only scenario (Figure 6.33).

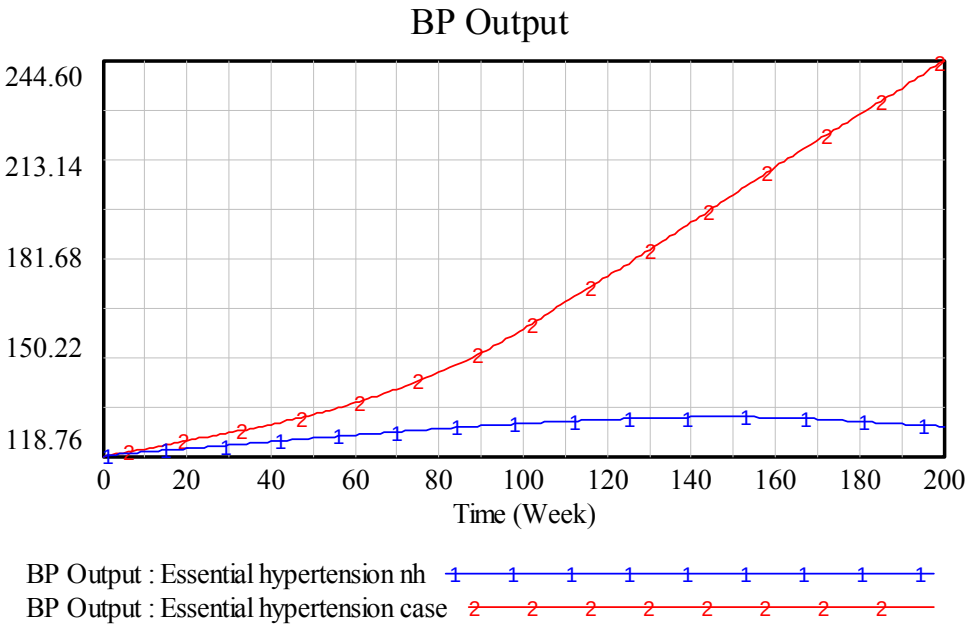

Figure 6.33. Comparative dynamics of blood pressure; early phases

The subject in this scenario experiences both kinds of hypertension. He/she initially has an essential type of hypertension where water balance is positive and FV has to rise in order to overcome vasoconstriction of arterioles caused by excess renin per nephron (Figure 6.34). However, after a significant reduction in remodeled nephrons, water balance becomes negative and the body gets rid of excess fluid (Figure 6.34). The body does not retain FV again up until the number of normal nephrons decrease to significantly low levels and water excretion falls below water intake during the late stages of patients' life span (Figure 6.35).

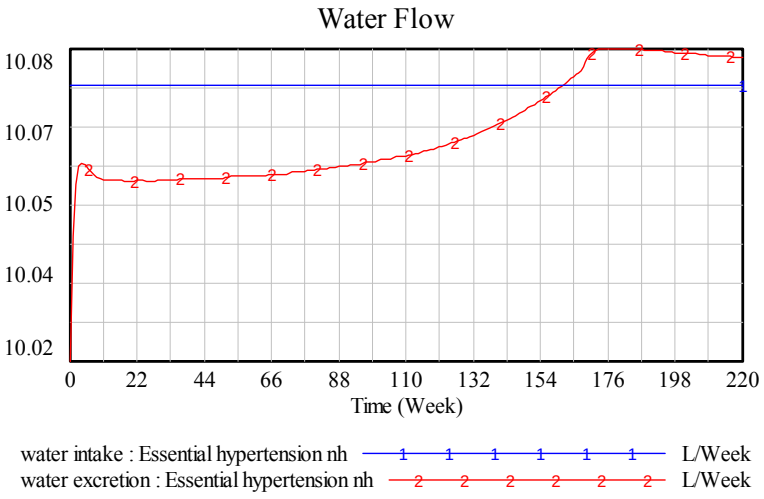

Figure 6.34. Dynamics of FV flows; early phases

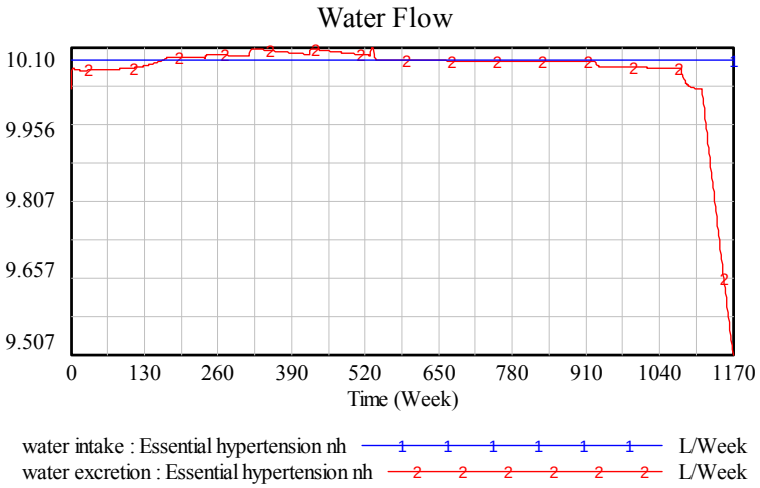

Figure 6.35. Long-term dynamics of FV flows

6.4. Drug Intervention in Essential Hypertension

This scenario represents a drug intervention to an essential hypertension patient. New variables *Effect of R-type Drug* and *Adjusted Renin* are defined. "R-type" denotes a cluster of drugs that affect renin-angiotensin system (Laragh, 2002). *Adjusted Renin* equals *Plasma Renin + Effect of R-Type Drug*Plasma Renin*. In this experiment different parameters for *Effect of R-Type Drug* were tested. Drug therapy with different doses of anti-Renin drugs is initiated at week 30. Effect of R-type drugs were set to -0.1, -0.2, -0.3, respectively. A comparison of BP verifies that any R-type drug affects progression of BP favorably (Figure 6.36).

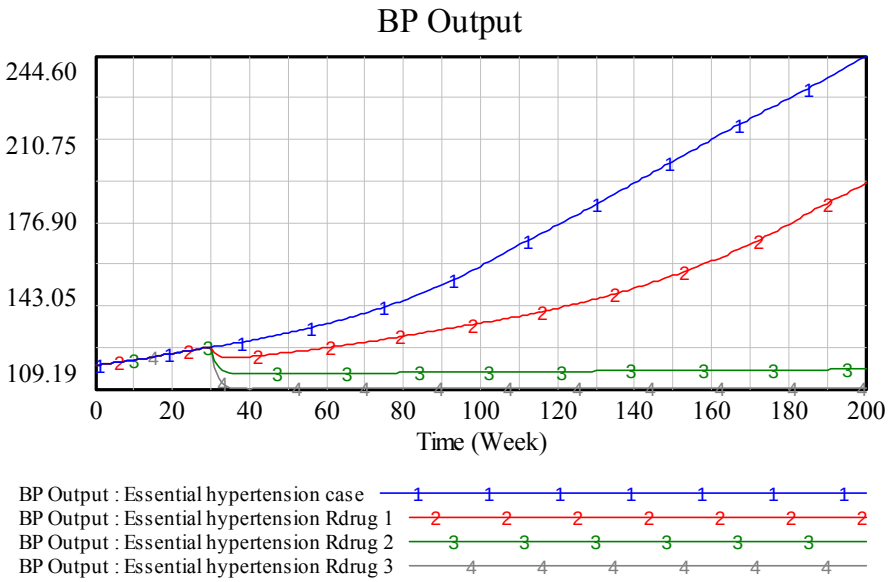

Figure 6.36. Comparitive dynamics of BP- drug intervention

The drug intervention has a short- and a long-term affect on the blood pressure of the patient. The immediate effect of drug intervention is a fall in plasma renin (Figure 6.37). The magnitude of reduction depends on the dose of the drug. Higher doses cause more reduction in plasma renin than lower doses.

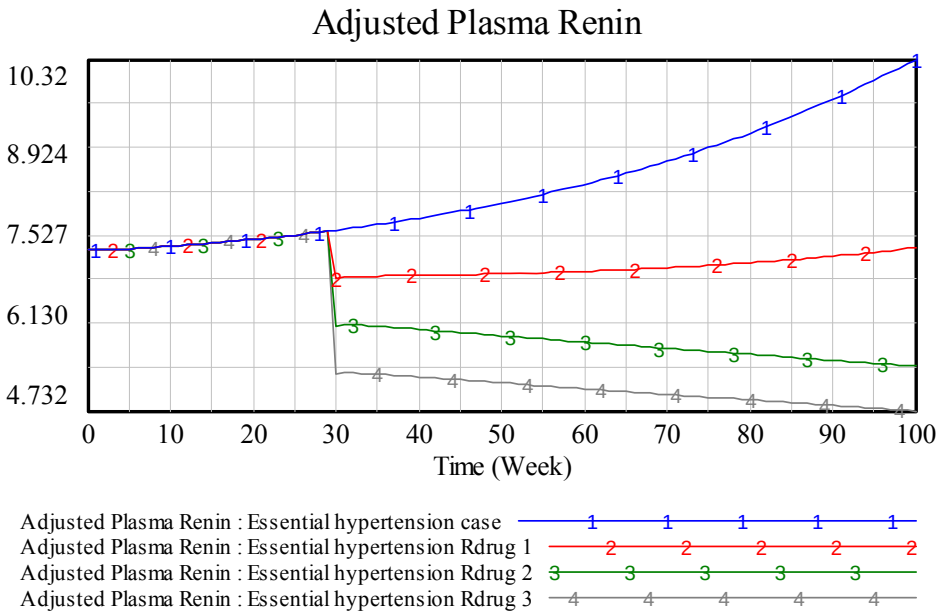

Figure 6.37. Comparative dynamics of renin-drug intervention; early phases

The long-term impact of reducing plasma renin and renin per nephron can be much more significant. If the initial reduction achieved in plasma renin levels is great enough, remodeling stimuli may be reduced to zero (Figure 6.38).

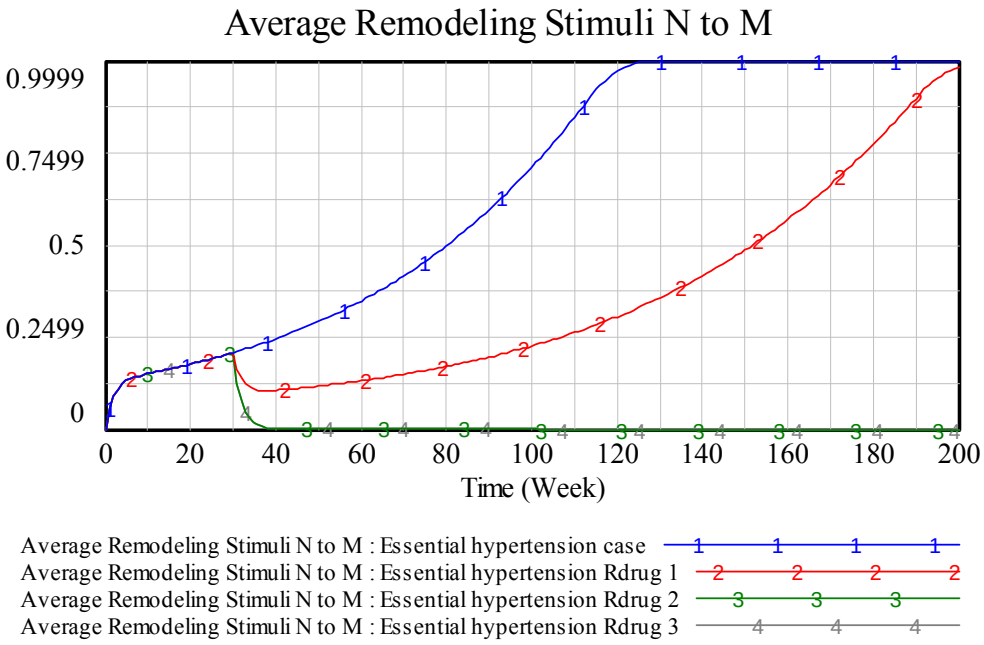

Figure 6.38. Long-term dynamics of Average Remodeling Stimuli-drug intervention

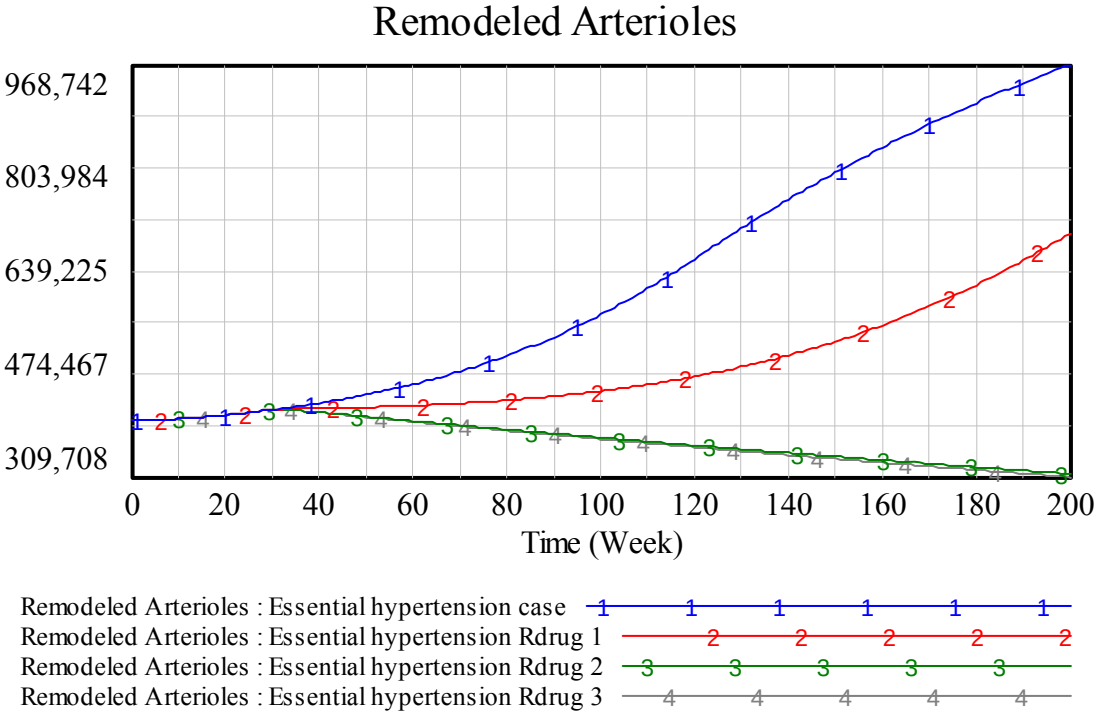

Figure 6.39. Dynamics of Remodeled Arterioles-drug intervention

If remodeling stimuli is reduced to zero as in the case of Rdrug 2 and Rdrug3 runs, the growth path of remodeled arteriole population can be reversed (Figure 6.39). The

graphs of remodeled nephron flows for Rdrug 1 and Rdrug 2 demonstrate the difference between low and high doses of drug intervention (Figure 6.40).

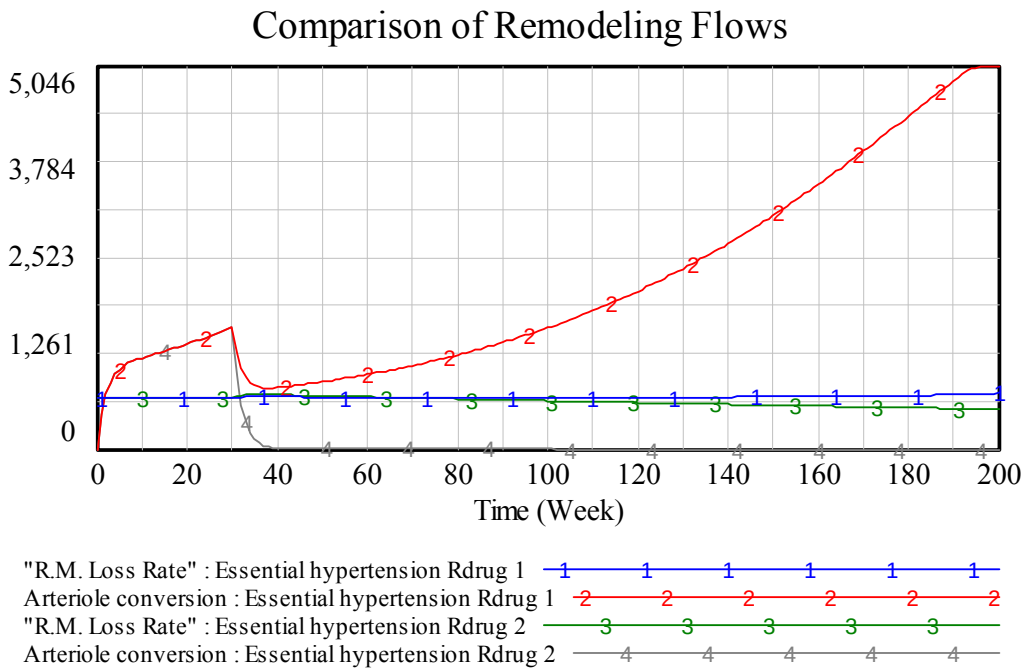

Figure 6.40. Comparative dynamics of remodeled nephron flows of Rdrug 1 and Rdrug 2 scenarios

If arteriolar conversion is reduced to zero as in the case of Rdrug2, remodeled nephrons start declining (see run 4 in Figure 6.40). In later years, the behavior of remodeled nephrons demonstrates a similar behavior to the potential hypertension case where dynamics are driven by nephron loss only.

The simple drug intervention policy of decreasing plasma renin by a constant proportion of itself represents a very simple decision rule and a crude abstraction of reality. Management of hypertension over time is a dynamic problem and it necessitates that an iterative, adaptive approach should be taken in the determination of the doses and types of drugs. Implementing structures that facilitate experimentation with different hypertension management policies for choice and doses of drugs can be the next step for advancing this research.

7. CONCLUSION AND FURTHER RESEARCH

There exist comprehensive dynamic simulation models on circulation and control of arterial pressure. However, most of these models deal with short-term dynamics of arterial pressure control. A long-term dynamic model of structural changes in kidneys and kidney-dependent blood pressure could facilitate a framework to test many different pathways for progression of essential hypertension. Structural reductions in the size of renal arterioles (vascular remodeling) and loss of nephrons are considered to be primarily responsible for the progressive increase in blood pressure. A modeling approach that clusters different nephron types into separate groups would be especially beneficial, as essential hypertension is characterized by heterogeneous distribution of nephrons.

In a nutshell, our model tries to represent long-term control of fluid volume like a capacity management problem. Nephrons, each self-sufficient unit of kidneys, may be seen as members of workforce responsible for achieving delivery of goods from an inventory stock (Fluid Volume) while maintaining a target level of inventory (ideal blood pressure). The body ("company") faces a similar problem in long-term control of its blood pressure (inventory). Some nephrons die (leave workforce) or some become remodeled (become injured during work). Fluid Volume-Renin-Angiotensin (FV-RAS) mechanism fulfills this control-task by adapting remaining normal nephrons' filtration rate ("delivery rate") to changes in the composition of nephrons (workforce). FV-RAS mechanism is effective in achieving desired water excretion ("delivery rate") as long as the relative distribution of remodeled arterioles does not rise too high or as long as the number of normal nephrons does not decrease too low.

The reference run of the model for normal subject demonstrates an idealized version of inevitable progression of structural damage with aging. The subject does not significantly suffer from high blood pressure up until the later stages of his life. The reference cases for potential and essential hypertensive subjects demonstrate two different types of progression. In the potential hypertension case the progression is driven by nephron loss due to aging, similar to the case of normal subjects. On the other hand, in essential hypertension, progression is reinforced with vascular remodeling in addition to

nephron loss. Therefore, blood pressure (BP) progresses faster to lethal levels. Moreover, the interference of high plasma renin with FV-RAS control of normal nephrons decreases the effectiveness of this mechanism in responding to required water excretion need of the body. Water balance becomes positive and fluid volume rises. Consequently, normal filtration from all nephrons rise and required water excretion can only be achieved at a steady-state FV and BP that are higher than their target levels. In other words, not only will BP progress faster in essential-hypertensives, it will also be higher than in potential hypertensives for the same distribution of nephrons.

The results of scenario runs hint at possible policies to deal with the nephron capacity management problem. Whereas reducing the loss fractions of both types of nephron subpopulations has little effect on slowing down the progression of blood pressure, *increasing the loss fraction of remodeled nephrons has significant positive impact* on the performance of the kidneys and longevity of healthy functioning of the body. As matter of fact, there is reason to believe that the body might employ such an implicit rule in the control of structural changes in kidneys. Remodeled arterioles are known for their inability to engage in functional autoregulation which makes them vulnerable to variations in BP (Johnson et al., 2005a, 2005b). In their hypothesis, Johnson and associates argue strongly that loss of nephron over time is responsible for the transition of essential hypertensive subjects from vasoconstrictor to volume-loading hypertension. Our simulation with 150 per cent increase in remodeled nephron loss fraction only demonstrates a possibility where the patient progresses from Goldblatt hypertension (combined vasoconstrictor and volume-loading hypertension) to a healthy state and then to volume-loading hypertension). In the context of "workforce" management, higher loss fraction of remodeled arterioles corresponds to higher firing fraction of unproductive labor force which gets in the way of productivity of healthy workers. For future work, further scenario analysis concentrating on nephron loss fractions and arteriolar conversion can be conducted to demonstrate different progression paths from vasoconstrictor to volume-loading hypertension.

Drug interventions could also be employed to improve excretion capacity of nephrons. For example, in essential hypertension, a simple heuristic such as constantly reducing a fraction of plasma renin, would both lower the level of blood pressure and stop

the progression of remodeling. Scenario runs with the simulation model help distinguish such successful policies from ineffective interventions.

The model used in this study can be used as a building block for more comprehensive models of long-term structural management of kidney. Recognizing that kidney is the site of excretion of multiple critical electrolytes and waste products, a viable addition could be inclusion of an explicit control of filtration rate along with control of FV. However, a more urgent step would be to verify the model with data from longitudinal studies which focus on the number and distribution of nephrons and plasma renin levels over time. Those experiments are very difficult to conduct in real life; therefore, acquisition of appropriate experimental data may be a mirage. Nevertheless, such experiments are imperative in order to build full confidence in the model.

Another possible direction for advancing the model would be to include a structure to endogenously control the remodeled nephron's renin secretion. Finally, the introduction of a drug intervention structure could facilitate experimentation with different policies of long-term blood pressure management. The complete model can be transformed to an interactive gaming version for hypertension management.

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APPENDIX: LIST OF EQUATIONS

Variables used in the model are listed below:

Stocks:

Average Remodeling Stimuli N to M= INTEG (change in remodeling N to M, 0)
Units: unitless

Converted Arterioles= INTEG (Arteriole conversion,0)
Units: nephron

Fluid Volume= INTEG (+water intake-water excretion,17.61)
Units: L

Normal Arteriole Dead Nephrons= INTEG ("N.N Loss Rate",0)
Units: nephron

Normal Arterioles= INTEG (-Arteriole conversion-"N.N Loss Rate",Total Nephrons-Remodeled Arterioles)
Units: nephron

"R.M. Arteriole Dead Nephrons"= INTEG ("R.M. Loss Rate",0)
Units: nephron

Remodeled Arterioles= INTEG (Arteriole conversion-"R.M. Loss Rate", 400000)
Units: nephron

Flows and Auxiliary Variables:

"% Adjusted Renin over NPR"= 100*Adjusted Plasma Renin/Normal renin
Units: unitless

"% Plasma Renin over NPR"= 100*Plasma Renin/Normal renin
Units: **undefined**

"% Renin N.N. over normal PRA N.N."= ZIDZ("Plasma Renin Required by N.N.","Normal Renin N.N.")
Units: **undefined**

"Actual snGFR per N.N."="E of Max Capacity on snGFR N.N."*"max snGFR capacity N.N."
Units: ml/day

"Actual snGFR per R.M."= "E of Max Capacity on snGFR R.M."*"max snGFR capacity R.M."
Units: ml/day

Additional Desired Excretion= water intake-normal Water Intake
Units: L/Week

Adjusted Plasma Renin= Plasma Renin+"Effect of R-type Drugs"*Plasma Renin
Units: g/day

Adjusted Required sn Ren sec= "normal renin contribution per N.N."*min("Max sn ren sec fraction N.N.",max ("min sn ren sec fraction N.N.",Required snRen Sec over normal snRen Sec))
Units: g/day/nephron

Arteriole conversion= Normal Arterioles*max conversion fraction N to M*Average Remodeling Stimuli N to M
Units: **undefined**

BP Output= Normal Set BP*E of FV on BP*E of Renin on BP
Units: mmHg

change in remodeling N to M= ("Effect of RpN on Functional Afferent Resistance N.N."-Average Remodeling Stimuli N to M)/remodeling delay N to M
Units: **undefined**

Dead and Alive Normal= Normal Arterioles+Normal Arteriole Dead Nephrons
Units: **undefined**

Desired Excretion= max (0,normal Water Intake*"FV/Target FV"+Additional Desired Excretion)
Units: L/Week

E of FV on BP="FV/Target FV"
Units: unitless

E of Indicated Excretion on Required Excretion= WITH LOOKUP (Desired Excretion/normal Water Intake, ([(0,0)-(5,5)], (0,0.1), (0.0550459,0.100877), (0.0978593,0.114035), (0.125,0.125), (1,1), (4.8,4.8), (4.9,4.9), (4.92,4.91), (4.95,4.93),(4.98,4.95),(5.1,5)))
Units: **undefined**

"E of Max Capacity on snGFR N.N."= WITH LOOKUP ("Resistance Adjusted Indicated snGFR N.N."/"max snGFR capacity N.N.", ([(0,0)-(1.3,1), (0,0), (0.5,0.5), (0.7,0.7), (0.788991,0.776316), (0.880734,0.850877), (1.01774,0.916667), (1.14098,0.969298), (1.3,1)], (0,0), (0.5,0.5), (0.7,0.7), (0.788991,0.776316), (0.880734,0.850877), (1.01774,0.916667), (1.14098,0.969298), (1.3,1)))
Units: **undefined**

"E of Max Capacity on snGFR R.M."= WITH LOOKUP ("normal sngfr R.M."/"max snGFR capacity R.M.", ([(0,0)-(1.2,1),(0,0),(0.5,0.5),(0.651988,0.652),(0.850765,0.815789),(0.962079,0.881579),(1.02966,0.921053),(1.1211,0.960526),(1.21651,0.986842),(1.29602,1)],(0,0),(0.5,0.5),(0.651988,0.652),(0.850765,0.815789),(0.962079,0.881579),(1.02966,0.921053),(1.1211,0.960526),(1.21651,0.986842),(1.29602,1)))
Units: **undefined**

"E of min ren sec on Actual Renin Contriubution N.N."= WITH LOOKUP ("Required total Renin Contribution by N.N."/"min sn ren sec fraction N.N."*Normal Arterioles, ([(0,0)-(2,2)],(0,1),(0.88685,1),(0.98471,1.01754),(1.03364,1.05263),(1.1,1.1),(10,10)))
Units: **undefined**

"E of min sn ren sec on Ren Con N.N."= WITH LOOKUP ("Required total Renin Contribution by N.N."/"Min Ren sec N.N.", ([(-1,0)-(5,5)],(-1,1), (-0.0825688,1.09649), (0.59633,1.29386), (1.56881,1.6886), (2.33945,2.2807), (5,5), (10,10), (50,50)))
Units: unitless

E of Renin on BP= WITH LOOKUP ("Plasma Renin / Normal Renin", ([(0,0.8)-(10,1.2)], (0,0.95), (0.207951,0.951316), (0.452599,0.959211), (0.727829,0.972368), (0.862385,0.984211), (1,1), (1.11927,1.01053), (1.27829,1.01842), (1.49235,1.025),(1.88379,1.03684),(2.81346,1.04211),(10,1.05)))
Units: unitless

"E of RpN on snGFR N.N."= WITH LOOKUP (Renin per Nephron/normal renin per capita, ([(0,0)-(6,4)],(0.02,4),(0.0733945,3.2807),(0.174312,2.49123),(0.229358,2.10526),(0.324159,1.75439),(0.477064,1.45614),(0.666667,1.21053),(0.831804,1.08772),(1,1),(1.187,0.9123),(1.83486,0.754386),(2.69725,0.631579),(4.0367,0.491228),(6,0.46)))
Units: **undefined**

Effect of High Blood Flow on Neprhon Loss Rate= WITH LOOKUP ("Actual snGFR per N.N."/"max snGFR limit N.N.", ([(0,0)-(4.5,4), (0,1), (0.9,1), (1,1), (1.1,1), (1.22936,1.0307), (1.48624,1.05263), (1.76147,1.12281), (2.23853,1.35088), (2.58716,1.57895), (2.88073,1.82456), (3.21101,2.07018), (3.52294,2.24561), (3.85321,2.42105), (4.14679,2.54386), (4.45872,2.5614)], (0,1), (0.9,1), (1,1), (1.1,1), (1.22936,1.0307), (1.5,1.08772), (1.70642,1.19298), (1.99541,1.33333), (2.33945,1.57895), (2.66972,1.84211), (3.05505,2.21053), (3.31651,2.54386), (3.52294,2.87719), (3.92202,3.4386), (4.25229,3.85965), (4.45872,4)))
Units: **undefined**

"Effect of High Blood Flow on Neprhon Loss RateR.M."= WITH LOOKUP ("Actual snGFR per R.M."/"max snGFR limit R.M.", ([(0,0)-(3,3), (0,0), (0.5,0), (1,0), (1.3,0), (1.5,0.1), (1.7,0.3), (1.9,0.55), (2.04587,0.675439), (2.21101,0.789474),(2.37615,0.890351), (2.72477,0.97807), (3,1)], (0,1), (0.9,1), (1,1), (1.1,1), (1.2419,1.05263), (1.5263,1.26316), (2,1.63377), (2.26606,1.84211), (2.62385,2.12719), (2.83486,2.3136), (2.99083,2.36842)))
Units: **undefined**

Effect of Low Blood Flow on Nephron Loss Rate= WITH LOOKUP ("Actual snGFR per N.N."/"min snGFR threshold N.N.", ([(0,0)-(2,3), (0,1), (0.0366972,1), (0.0917431,0.951754), (0.174312,0.789474), (0.232416,0.587719), (0.327217,0.350877), (0.394495,0.201754), (0.501529,0.0964912), (0.681957,0.0219298), (0.8,0), (0.9,0), (1,0)], (0,3), (0.0825688,2.93421), (0.204893,2.76316), (0.259939,2.64474), (0.324159,2.47368), (0.412844,2.19737), (0.489297,1.97368), (0.574924,1.71053), (0.681957,1.44737), (0.764526,1.25), (0.853211,1.06579), (0.9,1), (1,1), (1.1,1)))
Units: **undefined**

"Effect of Low Blood Flow on Nephron Loss Rate R.M:"= WITH LOOKUP ("Actual snGFR per R.M."/"min snGFR threshold R.M.", ([(0,0)-(2,3), (0,3), (0.0825688,2.93421), (0.204893,2.76316), (0.259939,2.64474), (0.324159,2.47368), (0.412844,2.19737), (0.489297,1.97368), (0.574924,1.71053), (0.681957,1.44737), (0.764526,1.25), (0.853211,1.06579), (0.9,1), (1,1)], (0,3), (0.0825688,2.93421), (0.204893,2.76316), (0.259939,2.64474), (0.324159,2.47368), (0.412844,2.19737), (0.489297,1.97368), (0.574924,1.71053), (0.681957,1.44737), (0.764526,1.25), (0.853211,1.06579), (0.9,1),(1,1),(1.2,1),(2,1)))
Units: **undefined**

"Effect of RpN on Functional Afferent Resistance N.N."= WITH LOOKUP (Renin per Nephron/remodeling threshold RpN, ([(0,0)-(2.1,0.5), (0,0), (0.873394,0), (0.963303,0.0175439), (1.03394,0.0438596), (1.1,0.1), (1.95,0.95), (1.99725,0.97), (2.0422,0.99), (2.1,1)], (0,0), (0.873394,0), (1,0), (1.05,0.05), (1.1,0.1), (1.95,0.95), (1.99725,0.97), (2.0422,0.99), (2.1,1)))
Units: **undefined**

"FV/Target FV"= Fluid Volume/Target Fluid Volume
Units: **undefined**

Indicated BP= Normal Set BP*"FV/Target FV"
Units: mmHg

"Initial N.N. Nephrons"= Total Nephrons-Initial MR nephrons
Units: **undefined**

input e of pra=Renin per Nephron/normal renin per capita
Units: **undefined**

max possible Effective snGFR= "max capacity adjustment N.N."*"Resistance Adjusted Indicated snGFR N.N."
Units: **undefined**

"Min Ren sec N.N."= "min sn ren sec fraction N.N."*Normal Arterioles*"normal renin contribution per N.N."
Units: **undefined**

"N.N Loss Rate"= Normal Arterioles*normal nephron loss fraction*Effect of High Blood Flow on Neprhon Loss Rate*Effect of Low Blood Flow on Nephron Loss Rate
Units: **undefined**

"Normal Renin N.N."= Normal Arterioles*"normal renin contribution per N.N."
Units: g/day

normal renin per capita= Normal renin/Total Nephrons
Units: g/(day*nephron)

"Normal Renin R.M."= "normal renin contribution per R.M."*Remodeled Arterioles
Units: **undefined**

normal snGFR= normal sngfr fraction*Fluid Volume
Units: **undefined**

"normal sngfr R.M."= "normal snGFR R.M. fraction"*Fluid Volume
Units: **undefined**

Plasma Renin= "Renin Contribution by N.N."+"Renin Contribution from R.M."
Units: g/day

"Plasma Renin / Normal Renin"= Plasma Renin/Normal renin
Units: unitless

"Plasma Renin Required by N.N."= Adjusted Required sn Ren sec*total alive nephrons
Units: g/day

"R.M. Loss Rate"= remodeled nephron loss fraction*Remodeled Arterioles*"Effect of Low Blood Flow on Nephron Loss Rate R.M:"*"Effect of High Blood Flow on Neprhon Loss RateR.M."
Units: **undefined**

"Renin Contribution by N.N."= min("normal renin contribution per N.N."*"Max sn ren sec fraction N.N."*Normal Arterioles,max("normal renin contribution per N.N."*"min sn ren sec fraction N.N."*Normal Arterioles,"Required total Renin Contribution by N.N."))
Units: g/day

"Renin Contribution from R.M."= "normal renin contribution per R.M."*Remodeled Arterioles
Units: **undefined**

"Renin Contribution N.N. over Plasma Renin"= 100*"Renin Contribution from R.M."/Plasma Renin
Units: **undefined**

"Renin Contribution R.M. over Plasma Renin"= 100*"Renin Contribution by N.N."/Plasma Renin
Units: **undefined**

Renin per Nephron= Adjusted Plasma Renin/total alive nephrons
Units: g/(day*nephron)

"REnin R.M. over normal PRa R.M."= 100*ZIDZ("Renin Contribution from R.M.","Normal Renin R.M.")
Units: **undefined**

Required Excretion= Desired Excretion
Units: L/Week

"Required snGFR N.N."= ZIDZ("Required Total GFR N.N.",Normal Arterioles)
Units: ml/day/nephron

Required snRen Sec over normal snRen Sec= WITH LOOKUP ("Required/normal snGFR N.N.", ([(0,0)-(8,11)], (0.46,6), (0.491228,4.0367), (0.631579,2.69725), (0.754386,1.83486), (0.9123,1.187), (1,1), (1.08772,0.831804), (1.21053,0.666667), (1.45614,0.477064), (1.75439,0.324159), (2.10526,0.229358), (2.49123,0.174312), (3.2807,0.0733945),(4,0.02)))
Units: unitless

"Required snrencontribution N.N."= "normal renin contribution per N.N."*Required snRen Sec over normal snRen Sec
Units: g/day

Required Total GFR= Required Excretion/"normal snexcretion/snGFR"/time unit conversion/volume unit conversion
Units: ml/day

"Required Total GFR N.N."= Required Total GFR-"Total Normal GFR R.M."
Units: ml/day

"Required total Renin Contribution by N.N."= "Plasma Renin Required by N.N."-"Renin Contribution from R.M."
Units: g/day

"Required/normal snGFR N.N."= "Required snGFR N.N."/normal snGFR
Units: unitless

"Required/normal snGFR Ratio"= "Required snGFR N.N."/normal snGFR
Units: **undefined**

"Resistance Adjusted Indicated snGFR N.N."= "E of RpN on snGFR N.N."*normal snGFR
Units: ml/day

Resistance Adjusted Total GFR= (Normal Arterioles*"Resistance Adjusted Indicated snGFR N.N."+"normal sngfr R.M."*Remodeled Arterioles)
Units: **undefined**

RpN over NRpN= (Renin per Nephron/normal renin per capita)
Units: unitless

"sn Excretion N.N."= "normal snexcretion/snGFR"*"Actual snGFR per N.N."*"Effect of V-type Drug on Excretion"
Units: ml/day

"sn Excretion R.M."= "normal snexcretion/snGFR"*"Actual snGFR per R.M."*"Effect of V-type Drug on Excretion"
Units: ml/day

total alive nephrons= (Remodeled Arterioles+Normal Arterioles)
Units: **undefined**

Total Dead Nephrons= Normal Arteriole Dead Nephrons+"R.M. Arteriole Dead Nephrons"
Units: **undefined**

"Total Excretion N.N."= volume unit conversion*time unit conversion*("sn Excretion N.N."*Normal Arterioles)
Units: **undefined**

"Total Excretion R.M."= volume unit conversion*time unit conversion*("sn Excretion R.M."*Remodeled Arterioles)
Units: **undefined**

"Total GFR by N.N."= Normal Arterioles*"Actual snGFR per N.N."
Units: **undefined**

"Total GFR by R.M."= Remodeled Arterioles*"Actual snGFR per R.M."
Units: **undefined**

Total GFR Filtration="Total GFR by N.N."+"Total GFR by R.M."
Units: ml/day

Total GFR weekly= time unit conversion*volume unit conversion*("Total GFR by R.M."+"Total GFR by N.N.")
Units: **undefined**

Total Normal GFR= "Total Normal GFR N.N."+"Total Normal GFR R.M."
Units: **undefined**

"Total Normal GFR N.N."= normal snGFR*Normal Arterioles
Units: **undefined**

"Total Normal GFR R.M."= "normal sngfr R.M."*Remodeled Arterioles
Units: **undefined**

"Total Water Excretion (l/week)"= volume unit conversion*time unit conversion*("sn Excretion N.N."*Normal Arterioles+"sn Excretion R.M."*Remodeled Arterioles)
Units: L/Week

water excretion= "Total Water Excretion (l/week)"
Units: L/Week

Constants:

"Effect of R-type Drugs"= 0
Units: **undefined**

"Effect of V-type Drug on Excretion"= 1
Units: **undefined**

FINAL TIME = 2000
Units: Week

INITIAL TIME = 0
Units: Week

max conversion fraction N to M= 0.005
Units: 1/Week

"Max sn ren sec fraction N.N."=10
Units: unitless

"max snGFR capacity N.N."=0.25
Units: ml/day

"max snGFR capacity R.M."=0.09
Units: ml/day

"max snGFR limit N.N."=0.09
Units: ml/day

"max snGFR limit R.M."= 0.09

Units: ml/day

"min sn ren sec fraction N.N."= 0.02
Units: unitless

"min snGFR threshold N.N."= 0.09
Units: ml/day

"min snGFR threshold R.M."= 0.09
Units: ml/day

normal nephron loss fraction= 0.0005
Units: 1/Week

Normal renin=6.4
Units: g/day

"normal renin contribution per N.N."= 3.2e-006
Units: g/day

"normal renin contribution per R.M."= 6e-006
Units: g/(day*nephron)

Normal Set BP= 100
Units: mmHg

"normal snexcretion/snGFR"= 0.008
Units: unitless

normal sngfr fraction= 0.006
Units: (ml/day)/L

"normal snGFR R.M. fraction"= 0.003
Units: (ml/day)/L

normal Water Intake=10.08
Units: L/Week

remodeled nephron loss fraction= 0.001
Units: 1/Week

remodeling delay N to M= 2
Units: 1/Week

remodeling threshold RpN= 3.2e-006
Units: g/(day*nephron)

SAVEPER = 1
Units: Week

Target Fluid Volume=15
Units: L

TIME STEP = 0.0078125
Units: Week

time unit conversion= 7
Units: day/Week

Total Nephrons= 2e+006
Units: nephron

volume unit conversion= 0.001
Units: L/ml

water intake= 10.08
Units: L/Week