A Dynamic Simulation Model for Long-Term Hypertension Progression

Firat Incioglu

M.S. Graduate from Industrial Engineering Department

Bogazici University

Saral Sitesi D Blok 19 Gayrettepe 34349, Istanbul, Turkey

Telephone: +90 (532) 321-7850
E-mail: firat.incioglu@gmx.net

1 ABSTRACT

Dynamics of blood pressure over the life span of a human being demonstrates a growth path. The most significant theories which try to explain dynamics of blood pressure 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. A dynamic simulation model is constructed to realistically reproduce the long-term progression of blood pressure in healthy and in hypertensive people. It focuses on systemic interactions that result in vascular remodeling of renal arterioles and in loss of nephrons. These hypertensive mechanisms are integrated with fluid volume and blood pressure control mechanisms which are aimed to achieve homeostatis. This study suggests that progression of blood pressure can suitably be modeled by conceptualizing the problem as a long-term control of fluid excretion capacity. The reference behaviors for normal and hypertensive people underline alternative pathways in blood pressure progression. Experiments with the model demonstrate that management of the number of remodeled arterioles over time should be an essential task in long-term blood pressure progression control. Scenario runs with the simulation model help distinguish successful policies from the ineffective interventions.

2 INTRODUCTION

Sustained elevation in blood pressure (BP) above an average mean arterial pressure of 100 mmHg is considered as hypertension. Most cases of hypertension (95 per cent of cases) are estimated to be of an *unknown cause*, i.e. there is not a specific clinically 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 increase in blood pressure over the life span of a human being is an inevitable result of the aging process. As Arthur Guyton, the pioneer in applying control systems to physiology, wrote, *"presumably, if all persons lived to infinite age, everyone might eventually develop a consuming state of hypertension***.."** (Guyton, 1980, p. 471). The natural progression of BP to elevated levels does not pose a great threat to most people as they die of other causes prior to experiencing lethal consequences of hypertension. However, the accelerated growth behavior of BP observed in essential hypertension is a big threat to young and middle-aged people as it leads to target organ damage in vital organs such as heart, kidneys and brain.

The measured BP of a human being is the end result of interactions of a number of physiological control systems. Although BP is in a constant state of adjustment via these systems to respond to the current needs of the body, the long-term level of BP is proportional to the amount of water in the body. Thus, as Guyton convincingly demonstrated in his system analysis work, the long-term level of BP is to a great extent determined by kidneys' ability to excrete salt and water from the body (Guyton, 1980).

There is consensus in the field of hypertension that progression of BP over time is caused by structural changes in the kidneys which affect kidneys' salt and water excretion. These changes can best be understood by focusing on the nephron, the self-sufficient functional unit of the kidney. Each nephron undergoes structural changes that affect its excretion capacity. The most significant changes that take place in the nephron are the remodeling of its afferent arteriole, which reduces the cross-section of the blood vessel connecting the nephron to the circulatory system, and glomerularsclerosis, scarring incurred at the glomerulus of the nephron. Both of these changes lead to decreased filtration and excretion from the nephron. The loss in excretion due to structural changes is compensated by healthy nephrons which can increase their excretion by adaptive functional (i.e. non-structural) increases in the cross-section of their afferent arterioles. The compensation takes place over renin-angiotensin system by adjusting the amount of renin secreted from each healthy nephron. As long as the loss of excretion capacity can be compensated by the adaptive responses of healthy nephrons, long-term level of BP can be maintained at normal levels.

What causes these structural changes is still not exactly established, but in general there seems to be consensus that hypertension itself may be responsible (Lever and Harrap, p.70 in Kaplan, 1998). In the case of glomerularsclerosis, the glomerulus is scarred as a result of natural aging process and/or increased BP sustained over long periods. Remodeling of arterioles is also believed to be caused by elevated BP. However, recent work demonstrates that remodeling is caused by frequent or persistent

constriction of the afferent arteriole independent of BP (Johnson et al., 2005). In infusion experiments it was shown that a variety of vasoactive substances can lead to remodeling when their elevated levels are sustained over time.(Johnson et al., 2005). The renin-angiotensin system (RAS) which is responsible for functional regulation of arterioles by controling the concentration of such a vasocative substance, angiotensin II, is most likely to be involved in mediating remodeling (Schiffrin, 2004; Johnson et al., 2005).

In medical literature essential hypertension is characterized with remodeling of renal arterioles (Sealey et al., 1988). Yet, the increase in BP of a typical essential hypertensive case is not caused by healthy nephrons' insuffcient excretion capacity to compensate for decreased excretion of remodeled nephrons. It is rather caused by remodeling's effects on angiotensin II (Ang II) levels which interfere with healthy nephrons' ability to increase their excretion. The interference takes place over the renin-angiotensin system in the following way. Each nephron regulates its renin secretion in order to achieve a concentration of Ang II which is consistent with the nephron's own Ang II need. However, each nephron consumes an amount of Ang II proportional to global Ang II concentration, which is determined by the cumulative renin secretion of all nephrons. In a kidney that has a non-uniform composition with normal and remodeled nephrons, normal nephrons suppress their renin secretion, whereas remodeled nephrons secrete high amounts of renin. Thus, in a person with such kidneys, the long-term global renin may settle to a high level that inhibits normal nephrons' capability to achieve compensatory increase in their excretion. The sustained elevations in BP of essential hypertensive people are believed to be the result of such improper global renin levels interfering with adaptive functional changes of normal nephrons. (Sealey et al.,1988). Whether global renin reaches such disruptive levels depends on proliferation of remodeling in the kidney and on the severity of remodeling of each arteriole since renin secretion per remodeled nephron is inversely proportional with its remodeling grade.

3 KEY FEEDBACK RELATIONSHIPS OF BP PROGRESSION

Recent work which suggests that remodeling develops due to frequent vasoconstriction provides a possible alternative explanation for accelerated progression of BP in essential hypertensive people. High levels of global renin in people who have kidneys with non-uniform nephrons may intiate further remodeling of healthy nephrons. In other words, once the initial injury to a significant number of arterioles is acquired, further injury may be reinforced over renin-angiotensin system (RAS). A reinforcing mechanism involving RAS was previously proposed by Guyton as an attempt to explain fast progressing hypertension, *malignant* hypertension (Guyton and Coleman, 1969). However, their model focused on a short-term positive feedback between renin and functional constriction of arterioles, but not on the structural changes caused in the arterioles. Unable to maintain high levels of renin in a uniform kidney model Guyton commented that such a positive feedback was unlikely to be the primary cause of progression of BP (Guyton, 1980). However, he left the door open to the possibility that once structural changes occured such a positive feedback could be effective. This study explores the possibility of such a positive feedback in essential hypertension.

The proposed mechanism involves nephrons coupled with remodeled arterioles, denoted as remodeled nephrons, which secrete very high amounts of renin. Unsuppressed secretion of renin leads to high Ang II levels in the blood. Over time, the state of vasoconstriction caused by higher than normal Ang II levels leads to remodeling of healthy nephrons (Schiffrin, 2004; Johnson et al., 2005). Since renin secretion from remodeled nephrons is higher, the proliferation of remodeled nephrons increases global Ang II levels further (Please refer to (+) remodeling loop in Figure 3.1)

In the other positive feedback mechanism, healthy nephrons die due to the natural aging process. As a result water excretion capacity of kidneys decreases. As fluid volume increases, the pressure exerted upon remaining nephrons increases. Overload of pressure makes nephrons more susceptible to experience injuries and become obsolete. Hence, this positive feedback loops results in the reduction of number of alive nephrons. (Brenner and Chertow, 1994; please refer to (+) nephron loss loop in Figure 3.1)

Any changes that affect long-term control of excretion are compensated by functional regulation of renal arteriole over the renin-angiotensin system. The goal of this system is to maintain fluid volume at its normal physiological level. (Guyton and Hall, 2000; Laragh, 2002; please refer to (–) FV-RAS loop in Figure 3.1).

The model integrates the main long-term mechanisms involved in the progression and control of BP over the life span of a human being. The goal of this study is to demonstrate the differences between the dynamics of key variables of normal and essential hypertensive subjects. The study is also intended to facilitate experimentation for policies which can slown down the dangerous progression of BP in essential hypertensive subjects.

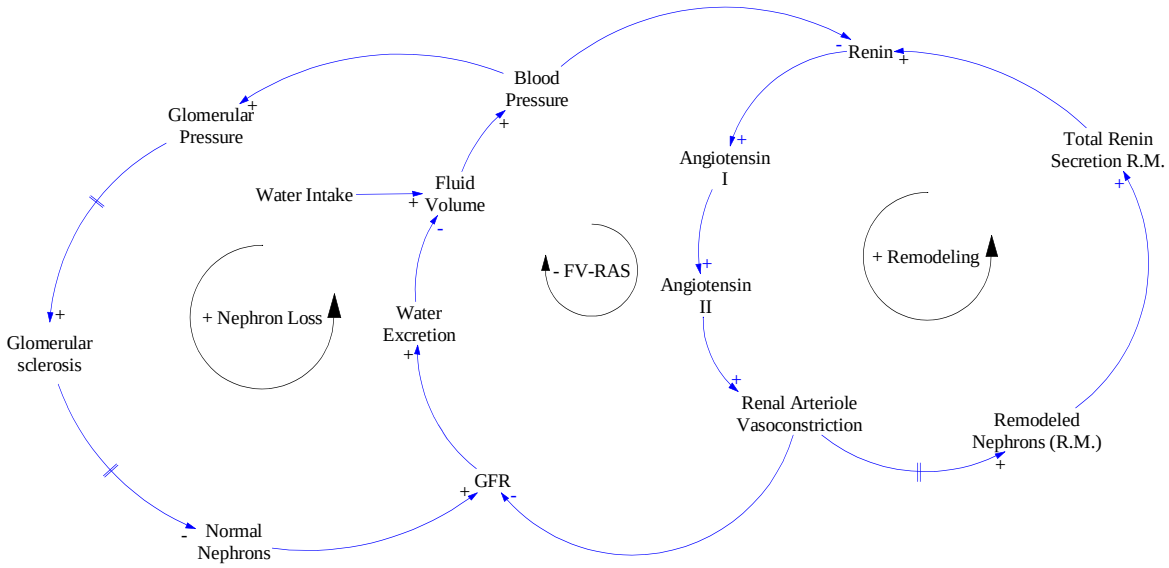

Figure 3.1.Integrated CLD of key feedback loops in the model

4 MODEL DESCRIPTION

The model is composed of three main stocks: Fluid Volume, Normal Arterioles and Remodeled Arterioles. The latter two are also denoted as normal and remodeled nephrons, respectively. Fluid Volume is the main determinant of long-term blood pressure. The model can be analyzed in two sectors, Fluid Volume and Nephron.

Normal physiological values from medical textbooks are used for normal values of constants (Guyton and Hall, 2000). The model represents a human being with two million nephrons who has not experienced any loss of nephrons due to aging.

4.1 Fluid Volume (FV) Sector

This sector has a single stock, *Fluid Volume*. Its inflow and outflow are the weekly water intake into the body and water excretion from the kidneys, respectively. Evaporation is considered to be negligible and water intake is taken as an exogenous variable in the model.

Normal filtration and excretion of each nephron is proportional to the amount of water in the body. For each nephron type, FV and water excretion are involved in a negative feedback loop over normal single nephron glomerular filtration rate (*normal snGFR),* which corresponds to filtration from a nephron for the current level of FV. This loop ensures that there be zero filtration when there is no water in the body.

FV is also involved in the goal-seeking FV-RAS loop of normal nephrons. The goal of this structure is to maintain FV at its normal physiological level despite changes in the number and type of nephrons as well as changes in water intake. *Normal snGFR* is compared to required snGFR of each normal nephron, single nephron filtration necessary to maintain FV at its normal level.

Renin-Angiotensin system is instrumental in adjusting actual single nephron filtration, *Actual snGFR*, to required single nephron filtration, *Required snGFR*, because of its role in the regulation of renal arteriole resistance. Glomerular filtration rate of each nephron is proportional to the size and inversely proportional to the resistance of its renal arterioles. Renal arteriole resistance can be adjusted by changing the amount angiotensin II consumed by the arteriole. Renin secretion of each nephron is determined by the nephron's own required Ang II consumption necessary to achieve the required arteriole resistance (Sealey et al., 1988). Based on this notion the model uses a sequence of equations that returns an actual renin degeneration rate per nephron for a given ratio of the required snGFR to normal snGFR. As part of this formulation there is a pair of graphical functions, required single nephron renin secretion over normal single nephron renin secretio*n (Required sn Ren Sec over normal snRen sec)*, and effect of renin per nephron on snGFR (*E of RpN on snGFR N.N.)* which are each other's inverse functions (Figure 4.1. and Figure 4.2). In the case of a single normal nephron population the output of the first function becomes the input of the second function as long as required snGFR is attainable within the maximum and minimum physiological limits of renin secretion. Thus, formulation pair ensures that indicated snGFR after adjustment by arteriole resistance equals the *Required snGFR.*

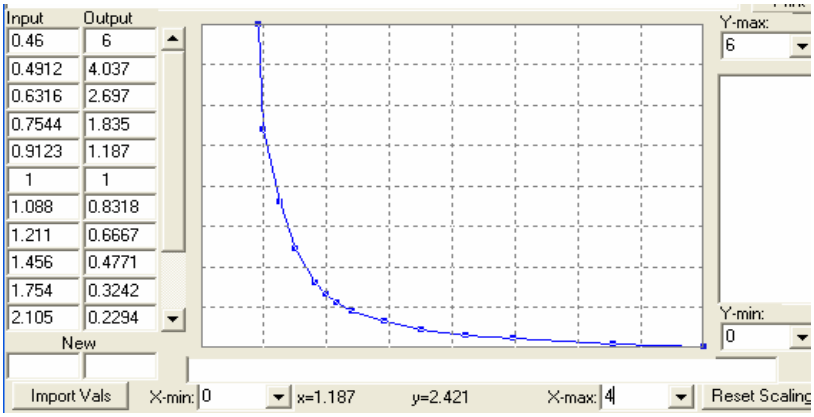

Figure 4.1. Required single nephron renin secretion over normal single nephron renin secretion as a function of required to normal snGFR ratio

Required single nephron renin secretion over normal single nephron renin secretion is checked against the minimum and maximum single nephron renin contribution factors. The result is then multiplied with normal renin contribution per normal nephron to give adjusted required single nephron renin secretion.

Total required renin secretion by normal nephrons is calculated by multiplying adjusted required single nephron renin secretion by total alive nephrons. In the presence of two nephron subpopulations, normal nephrons adjust their total renin secretion by taking into account the total renin secretion from remodeled nephrons. The renin contribution from 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 degeneration rate per nephron, *Renin per Nephron*, is calculated by dividing *Plasma Renin* to the total number of alive nephrons.

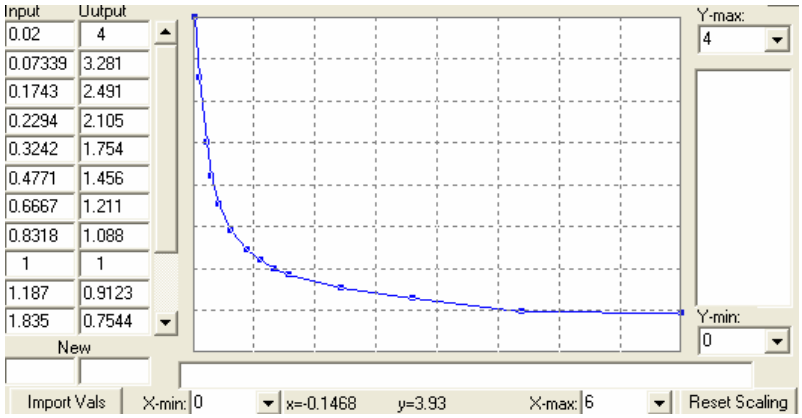

Figure 4.2 Effect of renin per nephron on single nephron glomerular filtration rate

Effect of renin per nephron on snGFR = f (Renin per nephron / normal renin per nephron)

*Resistance Adjusted Indicated snGFR = normal snGFR * Effect of renin per nephron on snGFR*

Resistance adjusted indicated snGFR represents the glomerular filtration rate of a normal nephron after the indicated adjustment by renal arteriole resistance. Its value is checked against the maximum physiologically possible snGFR, *Max snGFR capacity* (Figure 4.3).

*Actual snGFR = Max snGFR capacity * Effect of Capacity on snGFR*

Effect of Capacity on snGFR = f (Resistance Adjusted Indicated snGFR / Max snGFR capacity)

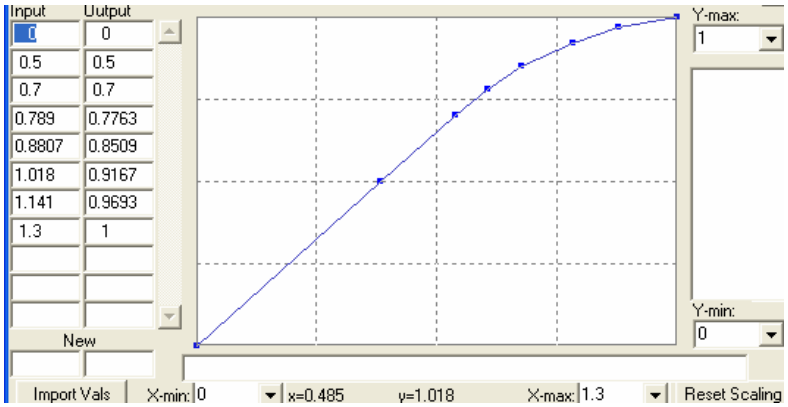

Figure 4.3 Effect of maximum renal arteriole capacity on snGFR

Single nephron water excretion, *sn Excretion*, for each nephron type will be calculated from Actual snGFR by multiplication with a constant that represents the normal physiological ratio between water excretion and glomerular filtration rate. *Total Water Excretion* is equal to the sum of water excretion from all nephrons.

The variable representing measured blood pressure, *BP Output*, is not involved in any of the feedback loops of the model. In reality, BP equals cardiac output times total peripheral resistance. BP output is formulated as a multiplicative effect formulation with FV over Target FV and effect of renin on BP. *Effect of Renin BP* is an s-shaped function which has a positive relationship with *Plasma Renin* over *Normal Renin*. This function represents the effect of Ang II on the resistance of other non-renal vessels in the body. However, effects of Ang II on peripheral resistance is allowed to affect BP only minorly, since long-term BP is to a great extent determined by the level of FV (Guyton, 1980)

BP Output = Normal Set BP FV/Target FV*Effect of Renin on BP*

Effect of Renin on BP= f (Plasma Renin/Normal Renin)

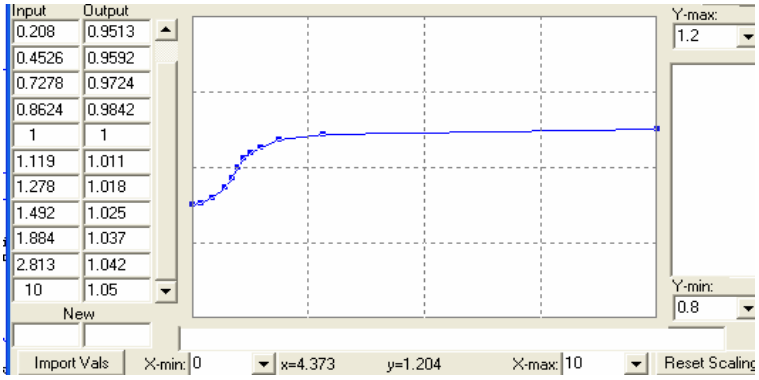

Figure 4.4.Effect of plasma renin on the resistance of non-renal vessels

4.2 Nephron Sector

Human beings are born with a fixed number of nephrons (approximately 2 million nephrons); nephrons do not regenerate after birth.

Nephron Sector is comprised of two stocks, *Normal Arterioles* and *Remodeled Arterioles.* In reality, various grades of remodeling would be present in a kidney. However, in this model remodeled nephrons are classified only with a single grade. Remodeled nephrons are considered to be incapable of regulating their renin secretion and excretion, whereas normal nephrons can adapt their excretion over FV-RAS loop. Thus, arteriole resistance and renin secretion is assumed to be constant for all remodeled nephrons. To account for excretion by remodeled nephrons, required total GFR by normal nephrons is set equal to the difference of required total GFR and total normal GFR from remodeled nephrons.

The presence of remodeled arterioles makes it possible for the positive remodeling feedback to be initiated. Renin per nephron is the variable responsible for initiating conversion of normal arterioles to remodeled arterioles. If *Renin per Nephron* rises above the threshold level, which correponds to normal physiological renin degeneration rate of normal arterioles, remodeling of normal arterioles will be initiated (Figure 4.5). There is a delay between functional constriction of a normal arteriole and its conversion to a remodeled arteriole. This delay is reflected by the *Average Remodeling Stimuli N to M* stock. This stock accumulates past remodeling stimuli and updates *Arteriole Conversion* rate with an average delay of two weeks.

*Arteriole Conversion = Normal Arterioles * max conversion fraction from normal to remodeled nephons * Average Remodeling Stimuli for conversion*

Change in Remodeling Stimuli = (Effect of renin per nephron on functional resistance - Average remodeling stimuli for conversion) / remodeling delay

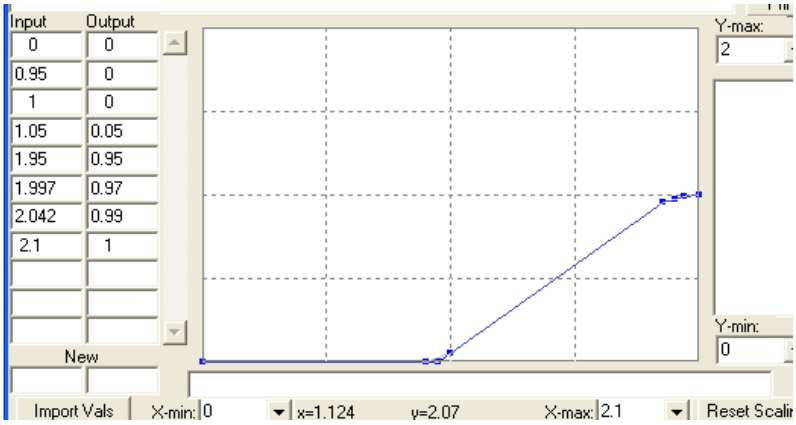

Figure 4.5. Effect of renin per nephron on functional afferent resistance

The effect function ensures that remodeling will only be initiated above the normal physiological level of constriction. When *Renin per Nephron* is approximately twice as great as the *remodeling threshold RpN*, this function returns the maximum possible remodeling stimuli which corresponds to maximum arteriole conversion rate.

Max conversion fraction from normal to remodeled nephrons represents the fraction of normal nephrons per week that would 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). However, 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. Since there are no experiments on human subjects, *max conversion fraction N to M* is a highly uncertain parameter.

The nephron stocks also decrease through their loss rates. For each nephron type there is a natural death fraction and a pair of effect functions which represent the effects of glomerular pressure on death rate. Actual snGFR of each nephron represents the glomerular pressure exerted upon the glomerulus. If *Actual snGFR* is above its normal physiological level, the normal loss rate is multiplied by a monotonically increasing function of Actual snGFR (Figure 4.6). On the other hand, *Effect of low blood flow on nephron loss rate* represents the detrimental effects of low glomerular pressures on nephrons (Figure 4.7). 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. On the other hand, remodeled nephrons mostly loose their nephrons because of low actual snGFR (Figure 4.7)

*Nephron loss rate = Arterioles * normal nephron loss fraction * Effect of high blood flow on nephron loss rate * Effect of low blood flow on nephron loss rate*

Effect of high blood flow on nephron loss rate = f (Actual snGFR /Normal snGFR)

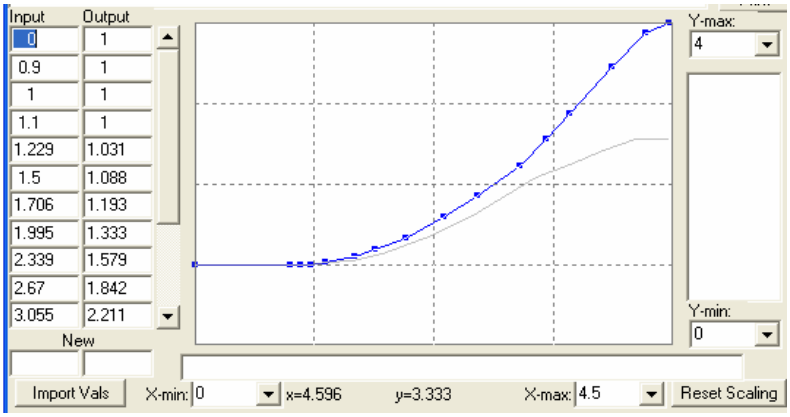

Figure 4.6. Effect of high blood flow on nephron loss rate of normal nephrons

Effect of low blood flow on nephron loss rate =f (Actual snGFR / Normal snGFR)

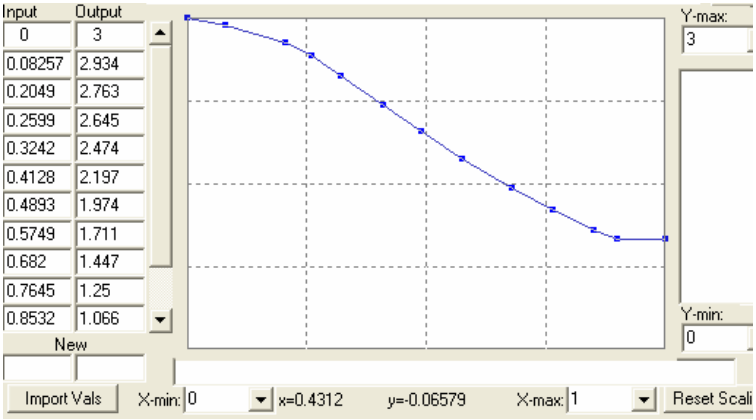

Figure 4.7. Effect of low blood flow on nephron loss of remodeled nephrons

Normal nephron loss fraction represents the average lifespan of a normal nephron. 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 nephrons have a higher normal physiological death rate. The difference is due to the fact that remodeled arterioles cannot achieve effective functional regulation that responds to short-term variations in glomerular pressure. As a result, remodeled nephrons are considered to be more vulnerable to high and low pressures (Johnson et al., 2005). *Remodeled nephron loss fraction* is set to two times of normal nephron loss fraction (0.001/week). The uncertainty regarding these parameters will be explored in scenario analysis section.

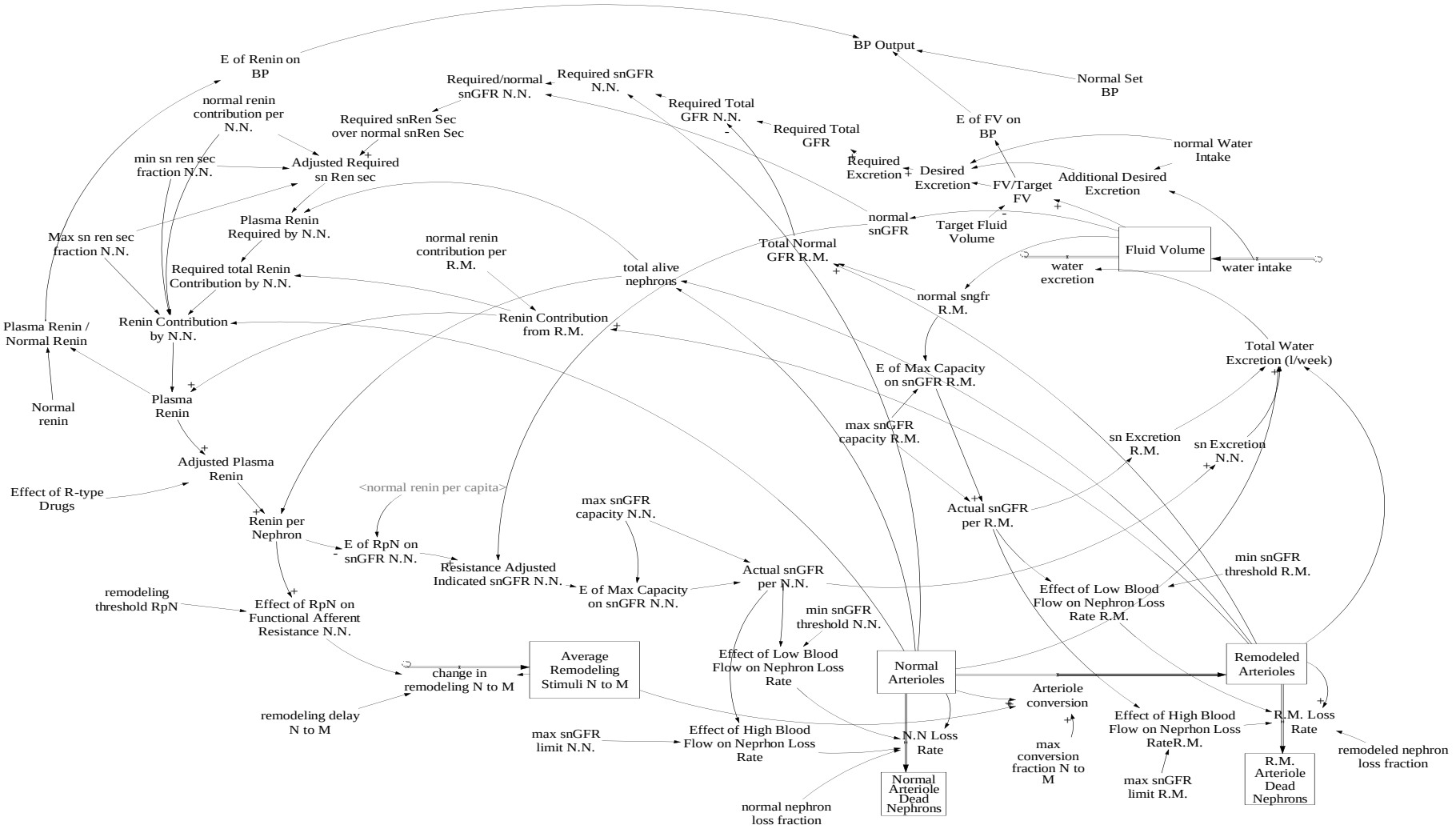

Figure 4.8. Stock-Flow Diagram

5 VALIDATION AND ANALYSIS OF THE MODEL

Verification and validation was carried out on the model using the standard procedures (Barlas, 1996). Structure-oriented behavior tests confirmed that each key loop, FV-RAS, remodeling and nephron loss operate as expected. Due to lack of availability of real data on progression of blood pressure over the course of years in either normal subjects or essential hypertensive categories, behavioral validation could only be conducted in comparison to described behavior in medical texts (Guyton and Hall, 2000). The base behavior for normal people also serves for the behavior validation test of the model.

Base cases for normal, potential-hypertensive and essential-hypertensive subjects are demonstrated to characterize different paths of progression. The difference between normal and hypertensive subjects arises from the initial presence of remodeled nephrons. In real life, the presence of an initial remodeled subpopulation may be the result of a short-term injury or it may be congenital (Johnson et al, 2005). Potential-hypertensives differ from essential-hypertensives only by the lower renin secretion from their remodeled nephrons.

Table 5-1. Initial conditions and parameters of base cases

Different Base Cases:	Initial Normal Arterioles	Initial Remodeled Arterioles	normal Renin Contribution per Remodeled Nephron
Normal Subjects	2000000	0	1.4* normal Renin Contribution per Normal Nephron
Potential-Hypertensive	1600000	400000	1.4* normal Renin Contribution per Normal Nephron
Essential-Hypertensive	1600000	400000	9.4* normal Renin per Normal Nephron

5.1 Base Behavior for 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 first run of normal subjects (NN ref) represents a similar scenario. The subject looses about 65 per cent of nephrons over 1730 weeks (35 years) (Figure 5.2). 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 5.2 and Figure 5.3). This is consistent with real examples 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 develops hypertension over 35 years as a result of significant nephron loss. The subject in the second run (NNref2) has a smaller normal nephron loss fraction and represents an alternative, a slower progression of nephron loss (Figure 5.2). The dynamics seen in normal subjects will be analyzed on the first run since the second subject does not experience any rise in BP within the time frame of simulation.

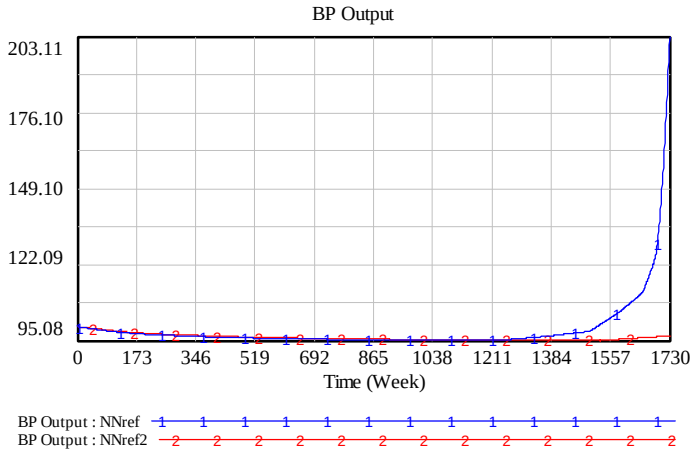

Figure 5.1. Dynamics of blood pressure

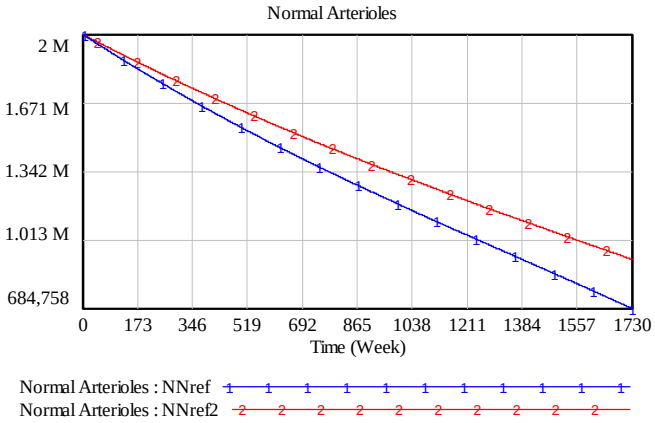

Figure 5.2. Dynamics of Normal Arterioles

The stable dynamics of FV up until week 1500 is due to the fact that remaining normal nephrons increase their excretion to compensate for excretion lost by each dying nephron (Figure 5.3). Only when surviving nephrons approach their maximum filtration capacity their compensation becomes imperfect and actual snGFR starts falling below required snGFR (Figure 5.7). Once maximum snGFR capacity (0.25 ml/day) is approached, 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 5.4).

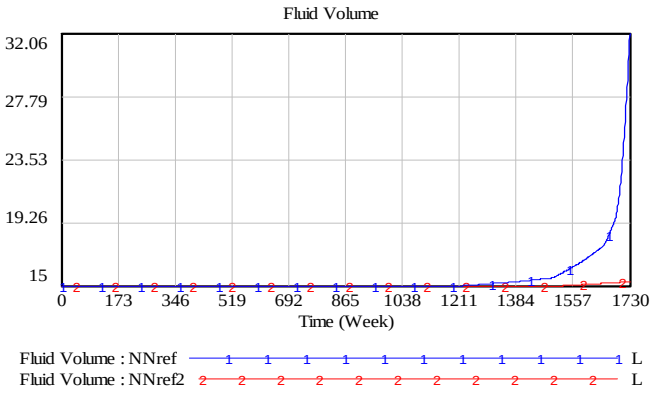

Figure 5.3. Dynamics of fluid volume

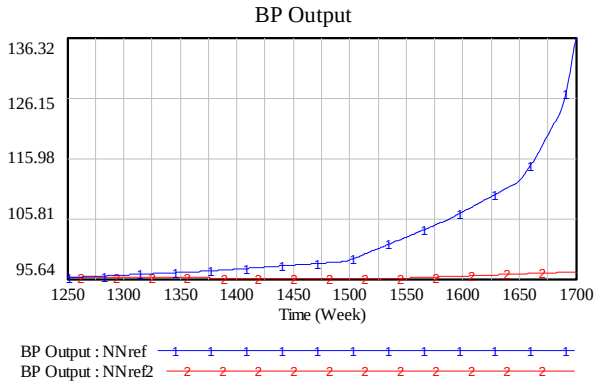

Figure 5.4. Progression dynamics of blood pressure

Nephrons respond to the need for higher snGFR by decreasing their renin secretion which allows them to increase their actual snGFR above their normal snGFR (Figure 5.5, Figure 5.6, Figure 5.7) A key observation is that there is an exact match between required single nephron renin secretion and renin per nephron (Figure 5.5 and Figure 5.6). The tight regulation of required and actual renin is not always the case as it will be demonstrated in the run for essential hypertension.

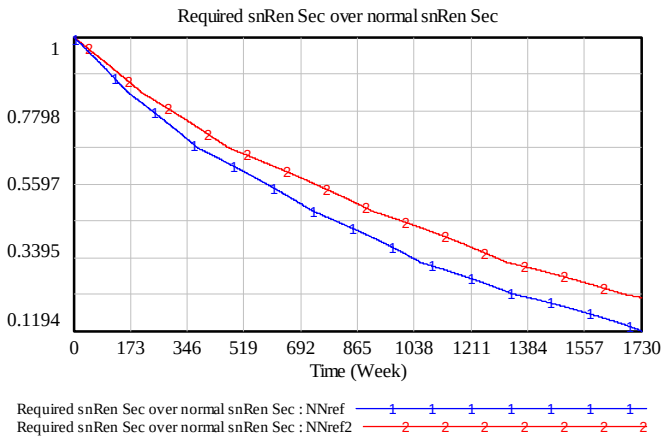

Figure 5.5. Dynamics of required single nephron renin secretion

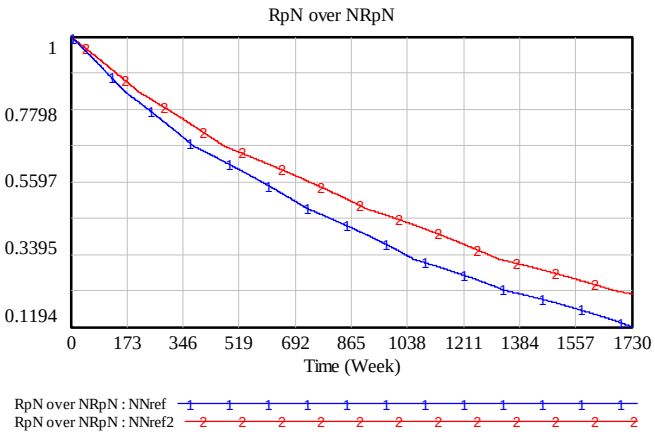

Figure 5.6. Dynamics of renin per nephron

Dynamics in normal subjects is characterized by initially stable, well-controlled BP and declining renin per nephron and compensation by remaining nephrons. Only after significant nephron loss does the water excretion fall below water intake (Figure 5.8.)

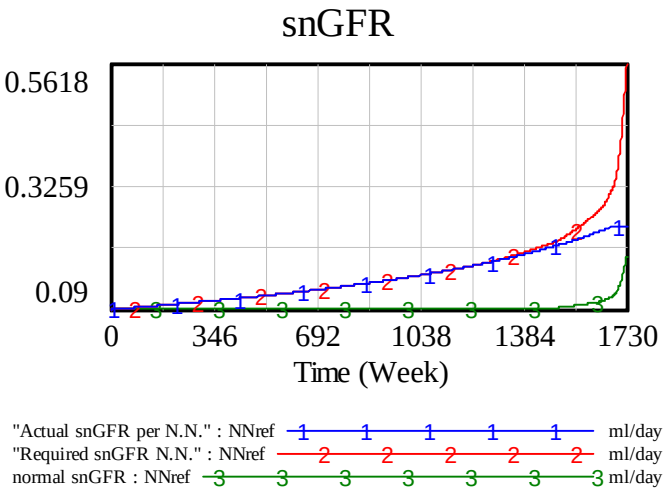

Figure 5.7. Comparative Dynamics of snGFR

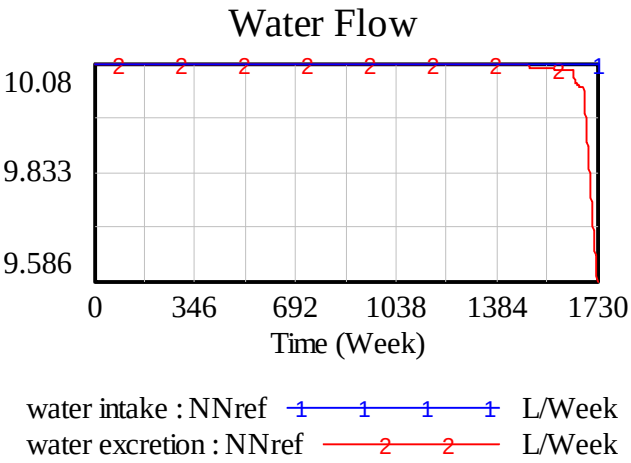

Figure 5.8. Water balance

5.2 Base Behavior for Potential-Hypertensives

The BP dynamics of potential-hypertensive subjects is primarily driven by nephron loss from normal and remodeled nephrons. Reduction in filtration capacity can be compensated by functional vasodilation of normal arterioles similar to the case of normal subjects. In order to increase their snGFR, remaining nephrons reduce their own renin contribution. The 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 decreasing remodeled subpopulation (Figure 5.11). Dynamics of the reference case of normal subjects (NNref) will be presented along with the dynamics of potential-hypertensives to demonstrate these differences.

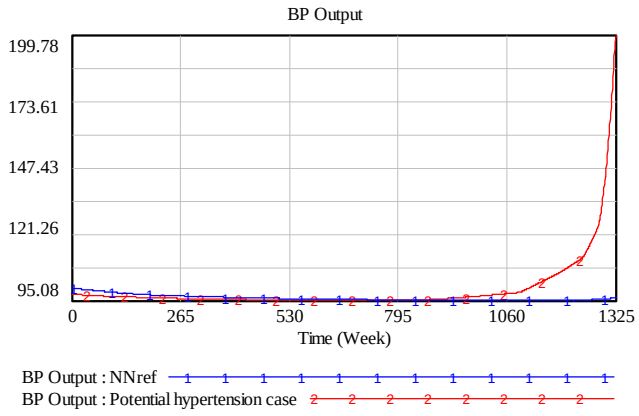

Figure 5.9. Dynamics of blood pressure-potential hypertension

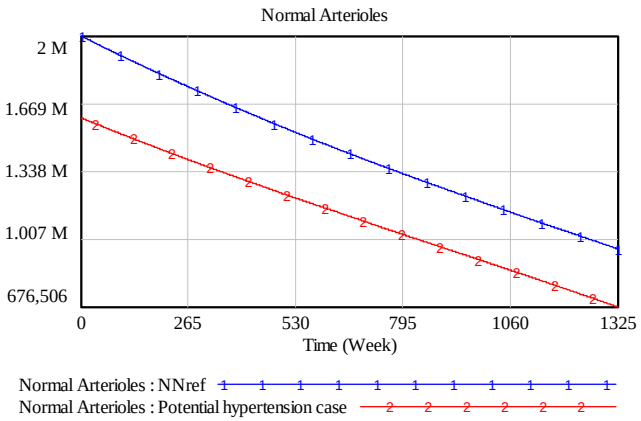

Figure 5.10. Dynamics of normal nephrons-potential hypertension

Blood pressure remains around its normal level for up until week 1060, 20 years (Figure 5.9). The dynamics of BP in potential-hypertensives are indistinguishable from normal subject for the first 20 years. However, since potential-hypertensives need to compensate for greater loss of filtration than normal subjects, their renin per nephron are lower throughout the simulation (Figure 5.12)

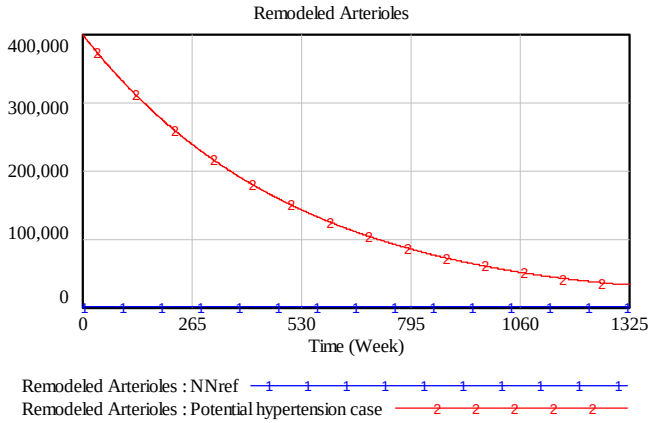

Figure 5.11. Dynamics of remodeled nephrons-potential hypertension

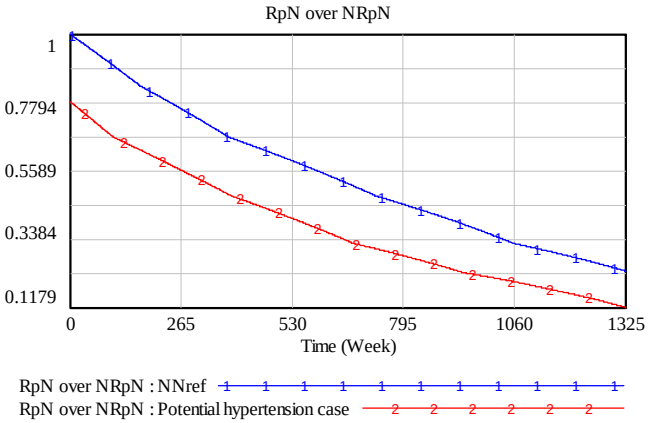

Figure 5.12. Dynamics of renin per nephron-potential hypertension

In potential-hypertensive subjects, actual snGFR can exactly match required snGFR up until week 1060 (Figure 5.13). Even though remodeled nephrons secrete higher amounts of renin, this poses no problem for normal arterioles' functional adjustment. The high renin contribution from remodeled nephrons can be counterbalanced by reductions in normal nephrons' own renin contribution. However, when renin secretion by remodeled nephrons is very high, even total elimination of normal nephrons' renin secretion may not be sufficient to increase Actual snGFR to match the required snGFR as it is the case in essential hypertension. The dynamics key variables and water balance are similar to the case of normal subjects. Nevertheless, subjects with significant remodeled nephron subpopulation are classified as "potential" hypertensive, because their excretion capacity will be approached earlier in life.

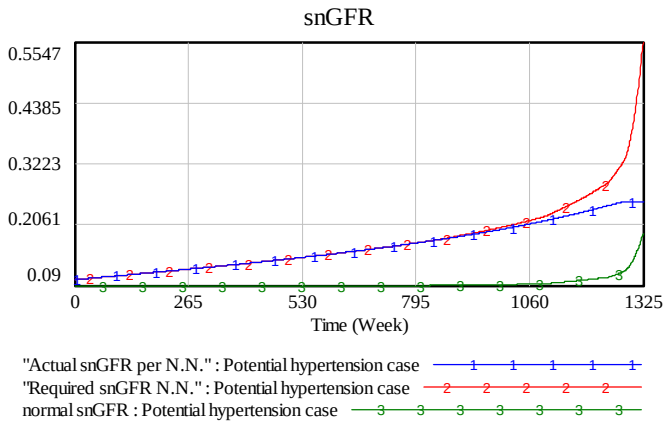

Figure 5.13. Comparative dynamics of snGFR-potential hypertension

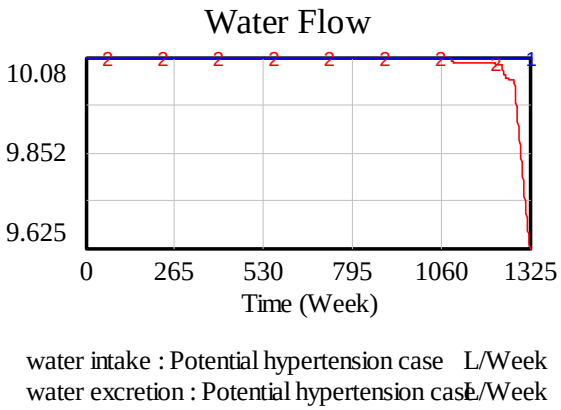

Figure 5.14 Water Balance-potential hypertension

5.3 Base Behavior for Essential-Hypertensives

Although the number of remodeled nephrons is the same for potential- and essential hypertension case, in essential hypetension the renin secretion from remodeled nephrons is high enough that FV-RAS control mechanism of normal nephrons is distorted at the beginning of simulation. The dynamics of key variables significantly differ between the two cases, because the initial levels of renin instigate the positive remodeling loop.

The BP of essential-hypertensive patient (run1) rises above the lethal level of 200 mmHg within 160 weeks (Figure 5.15). This case demonstrates a hypertension patient who starts in the incipient stages of essential hypertension and is treated with any medication.

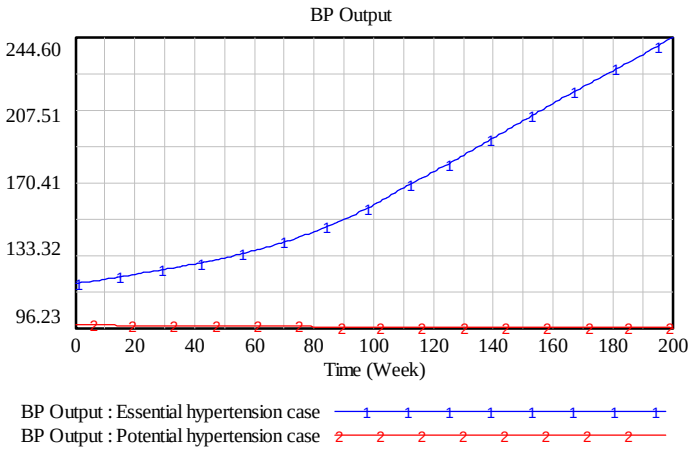

Figure 5.15. Dynamics of blood pressure-essential hypertension

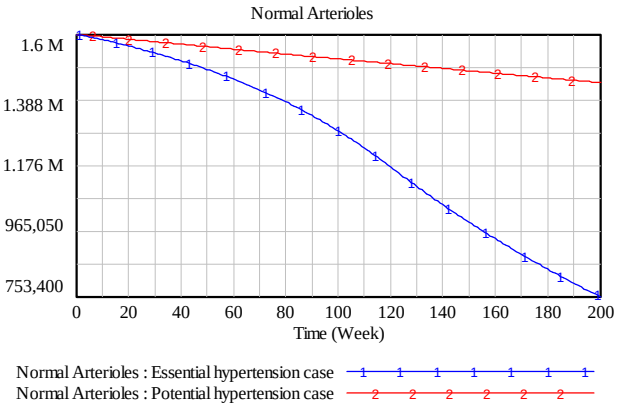

Figure 5.16. Dynamics of Normal Arterioles-essential hypertension

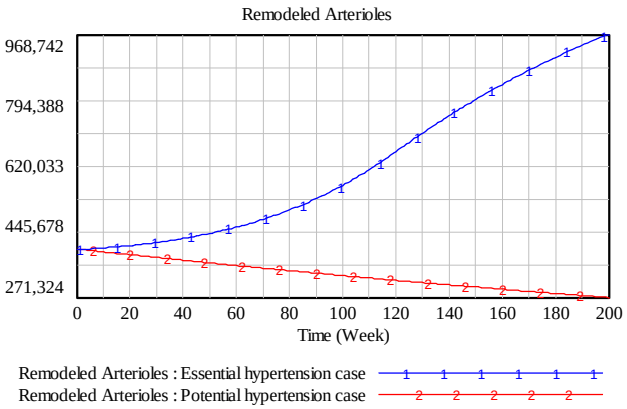

Figure 5.17. Dynamics of Remodeled Arterioles-essential hypertension

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 5.16, Figure 5.17 and Figure 5.18). Dynamics of the base case of essential hypertension is dominated by remodeling rather than nephron loss as demonstrated by the contrast between total conversions and deaths from normal nephrons (Figure 5.18 vs. Figure 5.19).

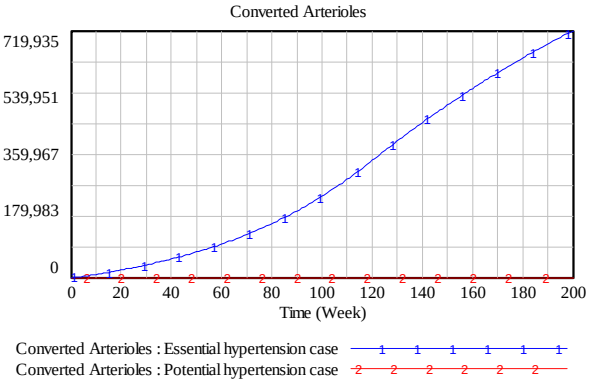

Figure 5.18. Dynamics of Converted Arterioles-essential hypertension

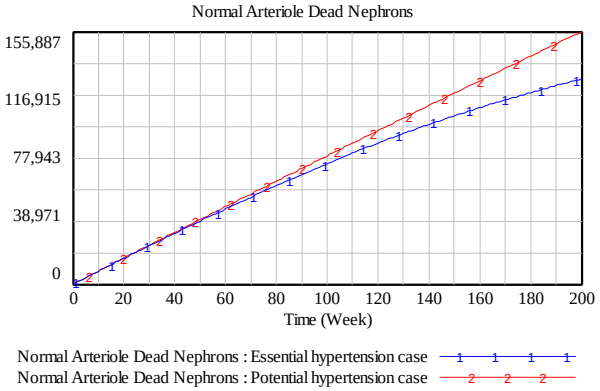

Figure 5.19. Dynamics of normal nephron deaths-essential hypertension

The increase in the number of remodeled arterioles drives up plasma renin levels and renin per nephron (RpN) (Figure 5.20 and Figure 5.21). The increase in RpN means that normal arterioles will be constricted more than their normal states. Thus, more blood flow would be necessary to achieve the same amount of water excretion. 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 5.23). Throughout the simulation, Actual snGFR is below Required snGFR in contrast to the previous two base cases.

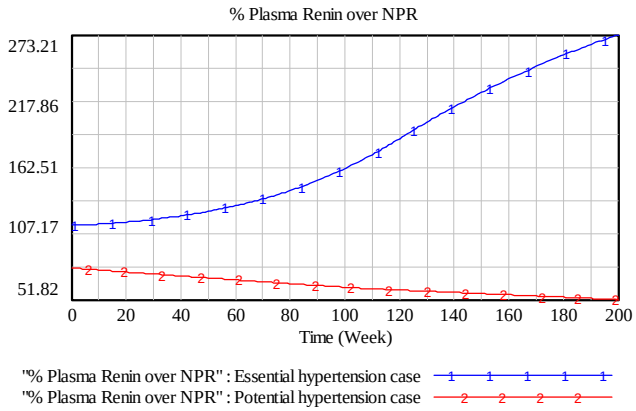

Figure 5.20. Dynamics of plasma renin-essential hypertension

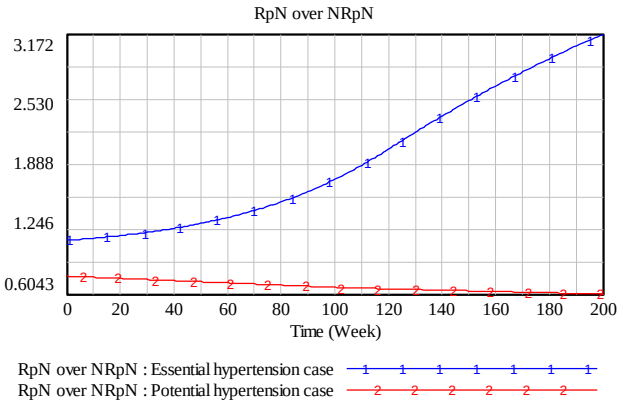

Figure 5.21. Dynamics of renin per nephron-essential hypertension

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 the life span of the subject. Note that the horizontal line in Figure 5.22, run 1, denotes the water intake and that run 2 denotes the water excretion in 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, run 3 perfectly matches water intake.

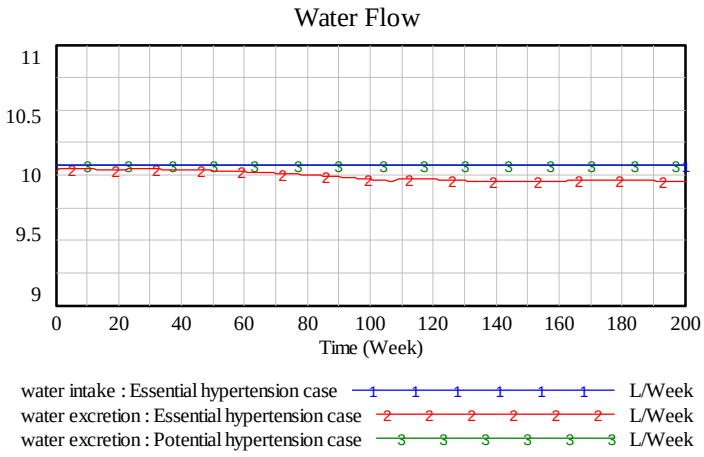

Figure 5.22. Dynamics of Water Balance-essential hypertension

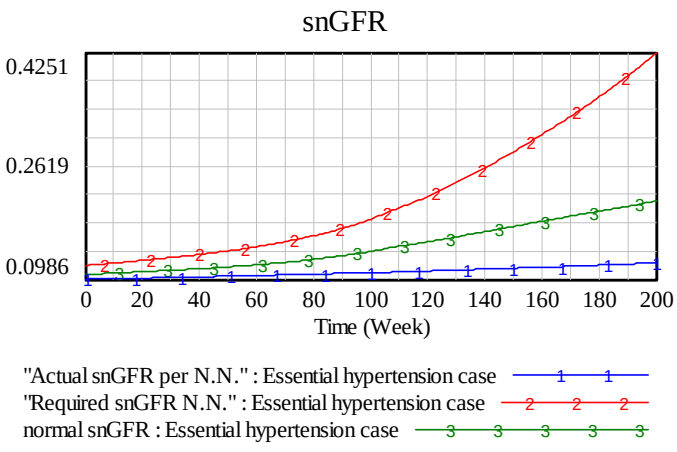

Figure 5.23. Dynamics of snGFR-essential hypertension

5.4 Scenario and Policy Analysis

A number of experiments were conducted on uncertain parameters in base cases. The scenarios below demonstrate experiments on essential hypertension base case.

5.4.1 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, nephron loss fraction for normal nephrons will be decreased to

20% of its normal value (from 0.0005 to 0.0001) and remodeled nephron loss fraction will be decreased to half of its normal value (from 0.001 to 0.0005). This scenario is demonstrated in run 1 (Essential hypertension LL) in comparison to the essential hypertension case, run 2.

.

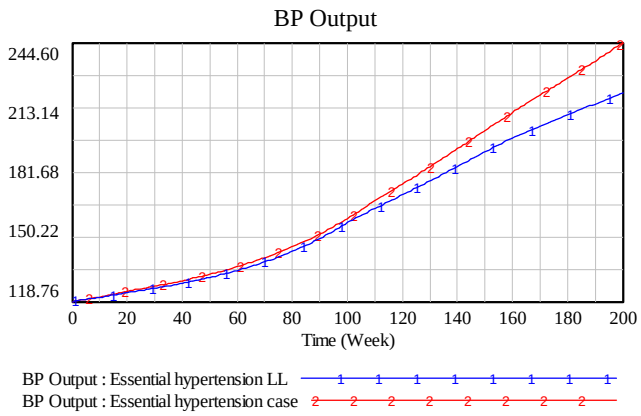

Figure 5.24. Dynamics of blood pressure for low nephron loss fractions

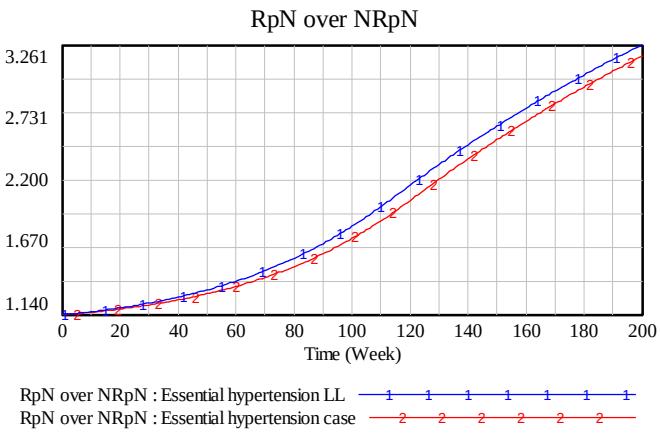

Figure 5.25. Dynamics of renin per nephron for low nephron loss fractions

The behavior of BP is not significantly different from the essential hypertension case despite significant reductions in nephron loss fractions. Renin per nephron levels are slightly higher as a result of higher remodeled population (Figure 5.25 and Figure 5.27). The number of normal nephrons and remodeled nephrons are higher, consistent with expectations, but the general behavior pattern of BP in essential hypertension does not change by reductions in nephron loss fractions.

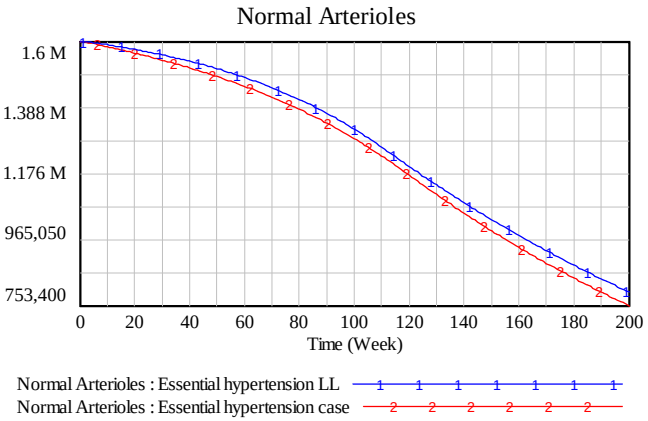

Figure 5.26. Dynamics of normal arterioles for low nephron loss fractions

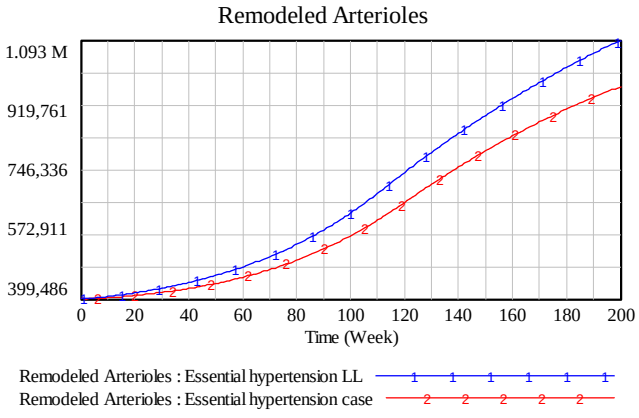

Figure 5.27. Dynamics of remodeled arterioles for low nephron loss fractions

5.4.2 150 per cent Increase in Remodeled Nephron Loss Fraction only

In this scenario, the normal nephron loss fraction is kept at its normal level of 0.0005, whereas remodeled nephron loss fraction is increased up to 2.5 times of its normal value (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*. The behavior of BP in the reference essential hypertension case and in the case with reduction in both of nephron loss

fractions (see 5.4.1) are in stark contrast to BP of this run (Figure 5.29). In both of those cases, the subject reaches lethally high levels of blood pressure within 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 5.28). 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.

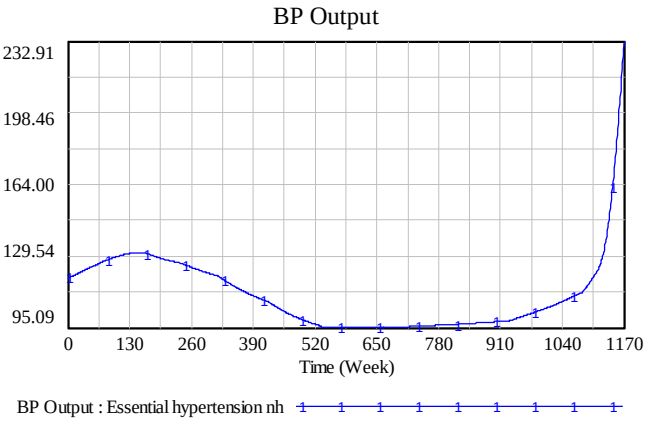

Figure 5.28. Dynamics of blood pressure - high remodeled nephron loss fraction

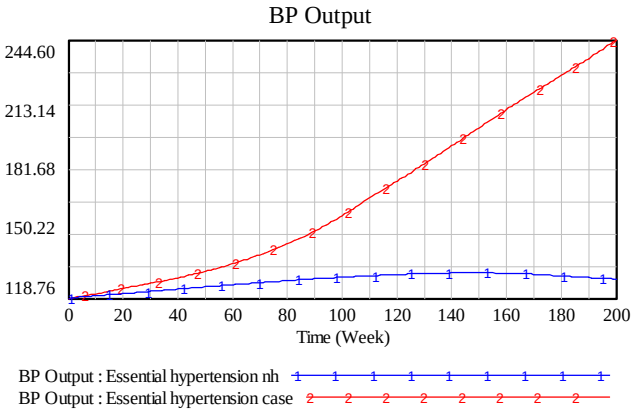

Figure 5.29. Comparative dynamics of blood pressure; early phase

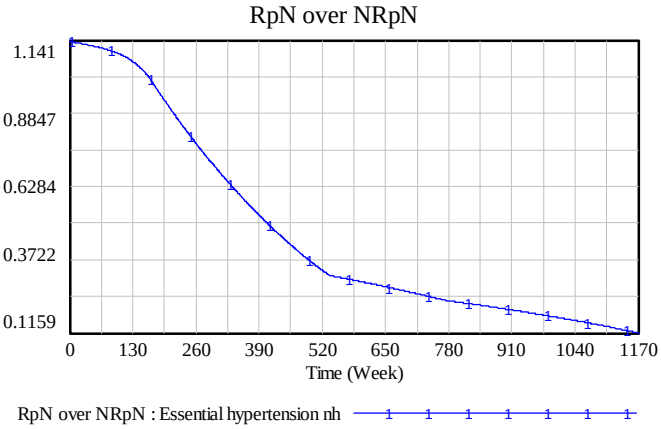

Figure 5.30. Dynamics of renin per nephron - high remodeled nephron loss fraction

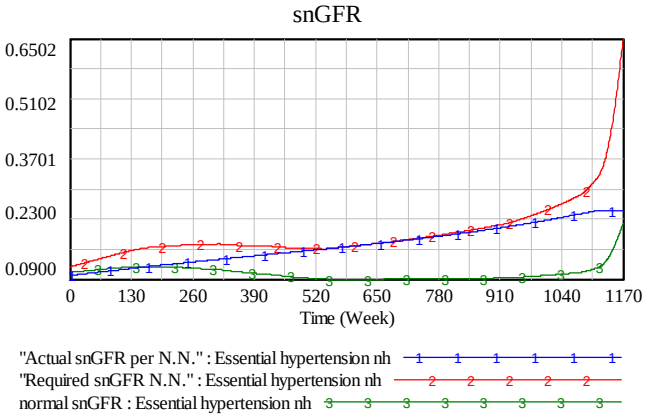

Figure 5.31. Comparative dynamics of actual and required snGFR

The exact match between Required and Resistance Adjusted snGFR after week 520 demonstrates that normal nephrons achieve the required snGFR necessary to keep FV at its target level (Figure 5.31). This means 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. When BP (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 and potential-hypertensive subjects.

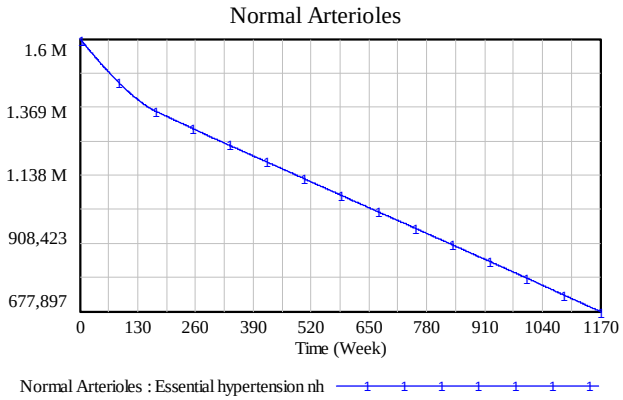

Figure 5.32. Dynamics of normal arterioles – high remodeled nephron loss fraction

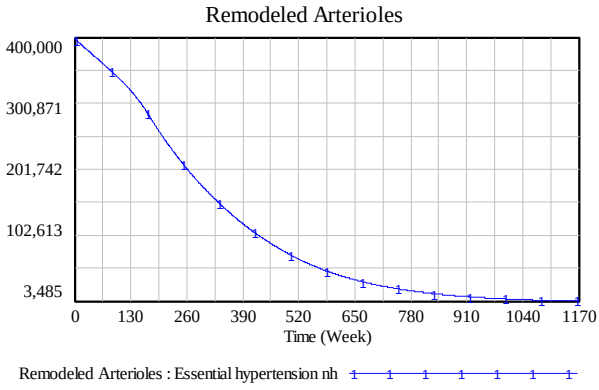

Figure 5.33. Dynamics of remodeled arteriole – high remodeled nephron loss fraction

The dynamics of BP in high remodeled nephron loss fraction scenario may initially seem counterintuitive given the theories relating nephron number and hypertension (Brenner et al., 1988). Nephrons die faster, yet the survival time of the patient increases. The critical point is that the patient is able to quickly get rid of deleterious, high renin secreting remodeled nephrons. Consequently, renin per nephron levels fall below the remodeling threshold renin per nephron and remodeling loop ceases to be effective. Once remodeled nephrons fall below levels where they would not interfere with the control of FV-RAS mechanism of normal nephrons, proper BP control can be maintained over a long period of time.

5.4.3 Drug Intervention in Essential Hypertension

This scenario represents a drug intervention to an essential hypertension patient. A new formulation that decreases plasma renin proportional to the dose of an R-type drug is introduced. “R-type” denotes a cluster of drugs that affect renin-angiotensin system (Laragh, 2002).

*Adjusted Renin = Plasma Renin + Effect of R-Type Drug*Plasma Renin.*

Drug therapy with different doses of R-type drugs is initiated at week 30. Effect of R-type drugs were set to -0.1, -0.2, -0.3, respectively. Comparisons with the reference essential hypertension case demonstrate that any R-type drug affects progression of remodeling and BP favorably (Figure 5.34 and Figure 5.35).

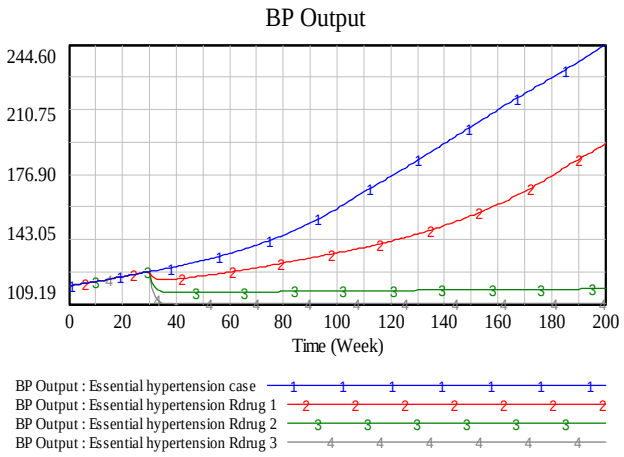

Figure 5.34. Comparative dynamics of BP

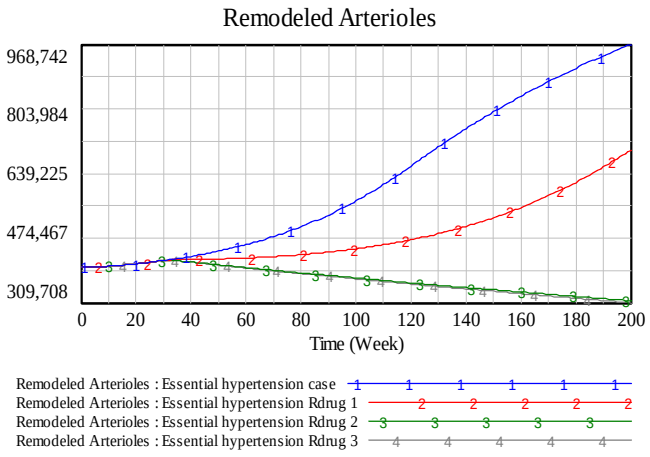

Figure 5.35. Dynamics of Remodeled Arterioles

6 CONCLUSION

The purpose of this research is to study the progression of blood pressure that results from structural changes in the kidneys. For this purpose a system dynamics model is built that focuses on systemic interactions among remodeling, nephron loss and renin-angiotensin system. Blood pressure progression dynamics of normal, potential-hypertensive and essential-hypertensive subjects are demonstrated in base runs and scenario analysis with respect to critical parameters are conducted.

The base cases reproduce the expected dynamic behavior for key variables. The normal subject case demonstrates how the inevitable progression of structural damage with aging is compensated by increased excretion from remaining healthy nephrons. Normal subject does not develop hypertension up until the later stages of his/her life. The reference cases for potential and essential hypertensive subjects underline 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 remodeling in addition to nephron loss. This reinforcing mechanism may be responsible for fast progression of BP observed in essential-hypertensive patients who subsequently experience malignant hypertension. Moreover, the distortion of fluid volume and renin angiotensin control of normal nephrons by inappropriately high plasma renin provides a realistic reproduction of renin-angiotensin system's involvement in essential hypertension.

The results of scenario runs hint at possible policies to control progression of BP in essential hypertension. 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 normalization of BP and its maintenance at normal levels. Drug interventions could also be employed to control hypertension. For example, in essential hypertension, drugs that affect renin-angiotensin system would both lower the level of blood pressure and stop the progression of remodeling.

The model can be used as a building block for more comprehensive models of long-term structural management of kidneys. An urgent step is to validate the model with data from longitudinal studies which focus on the number and distribution of nephrons and plasma renin levels. A possible direction for advancing the model would be to include a structure to control the remodeled nephrons' 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 long-term hypertension management.

7 REFERENCES

Bakker, Erik N.T.P., E.T. van den. Meulen, B.M van den Berg, V. Everts, J. A.E. Spaan, E Van Bavel, 2002, *Inward Remodeling Follows Chronic Vasoconstriction in Isolated Resistance Arteries,* J Vasc Res 2002;39:12–20.

Barlas, Y., 1996, *Formal Aspects of Model Validity and Validation in System Dynamics,* System Dynamics Review, Vol. 12, No. 3, pp. 183-210.

Brenner, B. M. and G.M. Chertow, 1994, *Congenital Oligonephropathy and the Etiology of Adult Hypertension and Progressive Renal Injury,* American Journal of Kidney Disease, 1994, 23:171-175.

Brenner, B. M., D.L. Garcia, S. Anderson, 1988, *Glomeruli and blood pressure—less of one, more of the other?,* American Journal of Hypertension, 1988; 1:355.

Coleman, T.G. and J.E. Hall, 1992, *A Mathematical model of Renal Hemodynamics and Excretory Function,* in S.S. Iyengar (ed.), *Structuring Biological Systems- A computer Modeling Approach,* CRC Press.

Franco M., E. Tapia, J. Santamaria, I. Zafra, R. Garcia-Torres, K.L. Gordon, 2001, *Renal cortical vasoconstriction contributes to development of saltsensitive hypertension after angiotensin II exposure,* J Am Soc Nephrol 12: 2263-2271.

Guyton, A.C., and J.E. Hall, 2000, *Textbook of Medical Physiology*, 10th edition, Saunders.

Guyton, A.C., 1980, *Circulatory Physiology III Arterial Pressure and Hypertension*, Saunders.

Guyton, A.C. and T.G. Coleman, 1969, *Quantitative Analysis of the Pathophysiology of Hypertension,* Circulation Research, 1969; Vol 24, No 5, Supp. 1.

Johnson R.J., Bernardo Rodriguez-Iturbe, Duk-Hee Kang, Daniel I. Feig, and Jaime Herrera-Acosta, 2005, *A Unifying Pathway for Essential Hypertension,* American Journal of Hypertension, 2005; 18:431–440.

Johnson R.J., Mark S. Segal, Titte Srinivas, Ahsan Ejaz, Wei Mu, Carlos Roncal, Laura G. Sánchez-Lozada, Michael Gersch, Bernardo Rodriguez-Iturbe, Duk-Hee Kang and Jaime Herrera Acosta, 2005, *Essential Hypertension, Progressive Renal Disease, and Uric Acid: A Pathogenetic Link?,* J Am Soc Nephrol, 2005, 16: 1909-1919.

Kaplan Norman, 1998, *Clinical Hypertension,* 7th edition, Williams&Wilkins.

Karaaslan, F, Y. Denizhan, A. Kayserilioglu, and H. O. Gulcur, 2005, *Long-Term Mathematical Model Involving Renal Sympathetic Nerve Activity, Arterial Pressure, and*

Sodium Excretion, Annals of Biomedical Engineering, Vol. 33, No. 11, November 2005 ,1607–1630.

Laragh, J., 2002, *Laragh's Lessons in Renin System Pathophysiology for Treating Hypertension and its Fatal Cardiovascular Consequences,* Elsevier.

Mazzali M, J. Kanellis, L. Han, L. Feng, Y.Y. Xia, Q. Chen, D.H. Kang, K.L. Gordon, S. Watanabe, T. Nakagawa, H.Y. Lan, R.J. Johnson, 2002, *Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure–independent mechanism,* Am J Physiol Renal Physiol 2002; 282:F991–F997.

Schiffrin, E., 2004, *Remodeling of Resistance Arteries in Essential Hypertension and Effects of Antihypertensive Treatment,* American Journal of Hypertension, 2004; 17:1192–1200.

Sealey J.E., J.D. Blumenfeld, G.M. Bell, M.S. Pecker, S.C. Sommers and J. Laragh, 1988, *On the renal basis for essential hypertension: nephron heterogeneity with discordant renin secretion and sodium excretion causing a hypertensive vasoconstriction–volume relationship*, J Hypertension, 1988;6:763–777.

Sealey J.E., F. Bühler, D. Vaughan and J. Laragh, 1973, *The Physiology of Renin Secretion in Essential Hypertension Estimation of Renin Secretion Rate and Renal Plasma Flow from Peripheral and Renal Vein Renin Levels,* Am Journal of Medicine, Sept 1973; 55: 391-401.