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1.1 Constants and Unit conversions

nL\_mL=1e+06

dl\_ml=0.01

L\_dL=10

L\_mL=1000

L\_m3=0.001

m3\_mL = 1000000

m\_mm = 1000

g\_mg=0.001

ng\_mg=1e-06

secs\_mins=60

min\_hr=60

min\_sec = 60

hr\_day=24

min\_day=1440

Pa\_mmHg = 0.0075 # (mmHg)

MW\_creatinine=113.12

Pi=3.1416

viscosity\_length\_constant=1.5e-09

gamma = 1.16667e-5; # viscosity of tubular fluid

water\_intake\_species\_scale = 1

1.2 Cardiac model parameters

1.2.1 Cardiovascular System

CO\_nom= 5 #L/min

BV = 0.005 # m\*\*3

P\_ven0 = 0

P\_art0 = 0

R\_per0 = 1.27e+008 # (Pa s /m\*\*3)

R\_ven0 = 5e+006 # (Pa s m\*\*-3)

R\_art0 = 5e+006 # (Pa s /m\*\*3)

R\_art\_pulm = 3e+006 # (Pa s m\*\*-3)

R\_ven\_pulm = 6.44e+006 # (Pa s m\*\*-3)

R\_r\_atrium = 1000000 # (Pa\*s/m3)

R\_left\_atrium = 1000000 # (Pa\*s/m3)

min\_flux = 5e-007 # (m3/s)

V\_art0 = 0.00045 # (m\*\*3)

V\_per0 = 0.00042 # (m3)

V\_ven0 = 0.0030 # (m\*\*3) [0.0020]

V\_pulm0 = 0.00015 # (m\*\*3)

V\_pulm\_art0 = 0.00004

V\_pulm\_ven0 = 0.00025

C\_art\_initial = 1.10e-008 # (m\*\*3 /Pa)

C\_per = 1.0e-008 # (m\*\*3 /Pa)

C\_ven0 = 1.8e-07 # (m\*\*3 /Pa) [2.0e-007]

C\_pulm\_ven = 1.65e-007 # (m\*\*3/Pa)

C\_pulm\_art = 2e-8

C\_pulm = 1.65e-7

C\_lv = 4e-008 #

L\_pulm = 60000

L\_art = 60000

LV\_V0\_baseline = 0.000052 # (m3) [0.000052]

LV\_V0\_min = 0.00001 # (m3)

V\_w\_0 = 0.00012 # (m3) [0.00017]

c\_r\_LV = 9

s\_r0 = 200

RV\_systolic\_time\_fraction = 0.3

RV\_V0\_min = 0.00001 # (m3)

RV\_V0 = 0.000075 # (m3)

contractility\_RV = 1 #

cf\_RV = 8 # (governs the shape of the passive fiber stress-stretch curve)'

s\_f0\_RV = 900 # (Pa)(governs the shape of the fiber passive stress-stretch curve)'

V\_w\_0\_RV = 0.0001 #

c\_r\_RV = 9 # ()

s\_r0\_RV = 200 # (Pa)

sigma\_ar\_RV = 55000 # (Pa)

ls\_a0\_RV = 0.0000015 # (m)

v0\_RV\_contraction\_velocity\_effect\_in\_RV = 0.00005 # (m/sec)

HR\_heart\_rate = 70 # (1/min)

cf = 11 # LV cardiac stiffness

s\_f0 = 900 # (Pa)(governs the shape of the fiber passive stress-stretch curve)'

sigma\_ar = 55000 # (Pa)

contractility = 1# 0.9 ## [0.75]

tau\_r\_LV\_twitch\_shape = 0.2 # originally = 0.1, changed to improve PV relationship

tau\_d\_LV\_twitch\_shape = 0.2

n\_r\_LV\_twitch\_shape = 2 # exponent for rise part of LV twitch

n\_d\_LV\_twitch\_shape = 4 # 4

ls\_a0 = 0.0000015 # (m)

ls\_ar\_sarcomere\_length\_effect\_in\_LV = 0.000002 # (m)

ls\_0\_passive\_LV\_sarcomere\_length = 0.0000019 # (m)

v0\_LV\_contraction\_velocity\_effect\_in\_LV = 0.000050 # (m/sec) #0.00005

Cv\_contraction\_velocity\_effect\_in\_\_LV = 0

### 1.2.2 Initial condition for stroke volume

SVnom = CO\_nom\*1000/HR\_heart\_rate

LV\_EDV\_nom = 110/1e6

LV\_ESV\_nom = (110 - SVnom)/1e6

### 1.2.3 Hypertrophy Parameters

Baseline\_Myocyte\_Number = 3.3e+9

Baseline\_Myocyte\_Length = 0.000115 # (m)

Baseline\_Myocyte\_Diameter = 0.000023313467 #(m)

Baseline\_Myocyte\_Volume = 4.909090909091e-014 # (m3)

max\_myocyte\_diameter\_increase = 1.5\*Baseline\_Myocyte\_Diameter #1x baseline diameter

max\_myocyte\_length\_increase = Baseline\_Myocyte\_Length

kD\_HYPERTROPHY = (2\*3e-8)/60 # 2e-08 - change in the run file

kL\_HYPERTROPHY = (8\*2e-9/60)# 1 # 2e-10 - change in the run file

hypertrophy\_Cf\_slope = 0.39

hypertrophy\_contractility\_slope = 0#.1

BNP\_factor = .0008 #change to manipulate slope of relationship between ln(BNP) and LVEDP

myo\_L\_scale = 1 # (scaling factor for myocyte lenght contribution to the change in volume)'

myo\_D\_scale = 0 #(scaling factor for myocyte diameter contribution to the change in volume)'

LV\_active\_stress\_threshhold = 49550 #49200# 54100 #53900

LV\_passive\_stress\_along\_fiber\_threshhold = 4500 #4550 #6000#11800

Baseline\_Interstitial\_Fibrosis = V\_w\_0\*0.02 # (m\*\*3) initial value for a healthy person, based on Betrami and Anversa 1994, assumes 2% initial interstitial fibrosis'

Baseline\_Replacement\_Fibrosis = V\_w\_0\*0.02 # (m\*\*3) initial value based on Betrami and Anversa 1994, assumes 2% initial replacement fibrosis)'

Baseline\_Interstitial\_Tissue = V\_w\_0\*0.22 # (m\*\*3)(data from olivetti and Anversa 1996. This value stays fairly constant across disease states)'

vascular\_responsiveness\_scale=1

TPR\_scale\_peripheral\_resistance = 1

compliance\_scale\_arterial\_compliance = 1

disease\_effect\_on\_TPR\_peripheral\_resistance = 1

contractility\_scale\_LV\_active\_stress = 1

c\_contr\_loss = 1

Kp\_CO = 0.1

Ki\_CO = 0.001

tissue\_autoreg\_scale=0.1 #3

venous\_autoregulation\_signal\_Km = 4; #Picked to be large enough so that there is no effect until the autoregulation signal becomes large (uncontrolled)

venous\_autoregulation\_signal\_scale = 0.5;

venous\_autoregulation\_signal\_slope = 0.75;

### 1.2.4 parameters governing the saturation of the tissue autoregulation signal

min\_tissue\_autoreg = 0.4

Vmax\_tissue\_autoreg = 2

Km\_tissue\_autoreg = 1.47

hill\_tissue\_autoreg = 2

### 1.2.5 BP effect on stiffness

Stiffness\_BP\_slope = 0.01 #0.03636364

C\_art\_scale = 1

stretch\_min\_LV\_passive\_stress\_along\_fiber = 1

stretch\_scale\_LV\_passive\_stress\_along\_fiber = 0

### 1.2.6 Initial volume calculations

venous\_volume\_0 = (V\_ven0 + C\_ven0 \* ((BV - LV\_V0\_baseline - V\_art0 - V\_per0 - V\_ven0 - RV\_V0 - V\_pulm0) / (C\_art\_initial + C\_per + C\_ven0 + C\_lv + C\_pulm)))

LV\_volume\_0 = LV\_V0\_baseline

arterial\_volume\_0 = (V\_art0 + C\_art\_initial \* ((BV - LV\_V0\_baseline - V\_art0 - V\_per0 - V\_ven0 - RV\_V0 - V\_pulm0) / (C\_art\_initial + C\_per + C\_ven0 + C\_lv + C\_pulm)))

peripheral\_circulation\_volume\_0 = (V\_per0 + C\_per \* ((BV - LV\_V0\_baseline - V\_art0 - V\_per0 - V\_ven0 - RV\_V0 - V\_pulm0) / (C\_art\_initial + C\_per + C\_ven0 + C\_lv + C\_pulm)))

RV\_volume\_0 = ((RV\_V0 + V\_w\_0\_RV / 3) \* (((1 / cf\_RV) \* np.log(((3 \* ((BV - LV\_V0\_baseline - V\_art0 - V\_ven0 - RV\_V0 - V\_pulm0) / (C\_art\_initial + C\_ven0 + C\_lv + C\_pulm)) / (np.log(1 + (V\_w\_0 / 0.000125))) + 2 \* (-0.193)) / s\_f0) + 1) + 1) \*\* 3) - V\_w\_0\_RV / 3)

pulmonary\_arterial\_volume\_0 = (V\_pulm\_art0 + C\_pulm\_art \* ((BV - LV\_V0\_baseline - V\_art0 - V\_per0 - V\_ven0 - RV\_V0 - V\_pulm\_art0 - V\_pulm\_ven0) / (C\_art\_initial + C\_per + C\_ven0 + C\_lv + C\_pulm\_art + C\_pulm\_ven)))

pulmonary\_venous\_volume\_0 = (V\_pulm\_ven0 + C\_pulm\_ven \* ((BV - LV\_V0\_baseline - V\_art0 - V\_per0 - V\_ven0 - RV\_V0 - V\_pulm\_art0 - V\_pulm\_ven0) / (C\_art\_initial + C\_per + C\_ven0 + C\_lv + C\_pulm\_art + C\_pulm\_ven)))

## 1.3 Renal Model Parameters

### 1.3.1 Systemic parameters

nominal\_map\_setpoint=85 #mmHg

IF\_nom = 15 #L

blood\_volume\_nom = 5 #L

Na\_intake\_rate=100/24/60 #mEq/min - 100mmol/day or 2300 mg/day

nom\_water\_intake = 2.1 #L/day

ref\_Na\_concentration=140 #mEq/L

glucose\_concentration = 5.5 #mmol/L

plasma\_albumin\_concentration= 35 #mg/ml

plasma\_protein\_concentration = 7 #g/dl

plasma\_urea = 0

nom\_serum\_uric\_acid\_concentration = 5.5 #mg/dl

equilibrium\_serum\_creatinine=0.92 #mg/dl

###Eventually should link this with P\_venous from cardiac model

P\_venous=4 #mmHg

### 1.3.2 Renal parameters

nom\_renal\_blood\_flow\_L\_min = 1 #L/min

baseline\_nephrons=2e6

nom\_Kf=3.9 #nl/min\*mmHg

nom\_oncotic\_pressure\_difference= 28 #mmHg

P\_renal\_vein=4 #mmHg

nom\_oncotic\_pressure\_peritubular= 28.05 #mmHg

interstitial\_oncotic\_pressure = 5 #mmHg

#### 1.3.2.1 Renal Vasculature

nom\_preafferent\_arteriole\_resistance= 14 #mmHg

nom\_afferent\_diameter=1.65e-5 #mmHg

nom\_efferent\_diameter=1.1e-05 #mmHg

#### 1.3.2.2 Renal Tubules

Dc\_pt\_nom = 27e-6 #m

Dc\_lh = 17e-6 #m

Dc\_dt = 17e-6 #m

Dc\_cd = 22e-6 #m

L\_pt\_s1\_nom = 0.005 #m

L\_pt\_s2\_nom = 0.005 #m

L\_pt\_s3\_nom =0.004 #m

L\_lh\_des = 0.01 #m

L\_lh\_asc = 0.01 #m

L\_dct = 0.005 #m

L\_cd= L\_lh\_des

tubular\_compliance = 0.2

Pc\_pt\_s1\_mmHg = 20.2#19.4#13.2 #15 #mmHg

Pc\_pt\_s2\_mmHg = 15

Pc\_pt\_s3\_mmHg = 11 #mmHg

Pc\_lh\_des\_mmHg = 8 #mmHg

Pc\_lh\_asc\_mmHg = 7 #mmHg

Pc\_dt\_mmHg = 6 #mmHg

Pc\_cd\_mmHg = 5 #mmHg

P\_interstitial\_mmHg = 5

nominal\_pt\_na\_reabsorption=0.7 #fraction # can change these 3 to

nominal\_loh\_na\_reabsorption = 0.8 #fraction # increase BP

nominal\_dt\_na\_reabsorption=0.5 #fraction

LoH\_flow\_dependence = 0.75

#### 1.3.2.3 Renal Glucose reabsorption

nom\_glucose\_reabs\_per\_unit\_length\_s1 = 5.4e-5

nom\_glucose\_reabs\_per\_unit\_length\_s2 = 0

nom\_glucose\_reabs\_per\_unit\_length\_s3 = 2.8e-5

diabetic\_adaptation = 1

maximal\_RTg\_increase = 0.3

T\_glucose\_RTg = 6000000

glucose\_natriuresis\_effect\_pt = 0

glucose\_natriuresis\_effect\_cd = 0

glucose\_diuresis\_effect\_pt = 0

glucose\_diuresis\_effect\_cd = 0

#### 1.3.2.4 Renal urea reabsorption

urea\_permeability\_PT = 0.5

#### 1.3.2.5 Renal albumin seiving

#### 1.3.2.6 Proteinuria

nom\_glomerular\_albumin\_sieving\_coefficient = 0.00062

SN\_albumin\_reabsorptive\_capacity = 1.4e-6

Emax\_seiving = 4

Gamma\_seiving = 3

Km\_seiving = 25

max\_PT\_albumin\_reabsorption\_rate = 0.1

nom\_albumin\_excretion\_rate = 3.5e-9

nom\_GP\_seiving\_damage = 65

c\_albumin = 0.0231 #min/nl, from Dean and Lazzara

seiving\_inf = 4.25e-4 #from Dean and Lazarra, calculated for seiving coeff =0.00062 when SNGFR = 50 nl/min

#### 1.3.2.7 RAAS Pathway parameters

concentration\_to\_renin\_activity\_conversion\_plasma = 61

nominal\_equilibrium\_PRA = 1000 #fmol/ml/hr

nominal\_equilibrium\_AngI = 7.5 #fmol/ml

nominal\_equilibrium\_AngII = 4.75 #fmol/ml

nominal\_renin\_half\_life = 0.1733 # (hr)

nominal\_AngI\_half\_life = 0.5/60 #(hr)

nominal\_AngII\_half\_life = 0.66/60 #(hr)

nominal\_AT1\_bound\_AngII\_half\_life = 12/60 #hr

nominal\_AT2\_bound\_AngII\_half\_life = 12/60 #hr

ACE\_chymase\_fraction = 0.95 #% of AngI converted by ACE. The rest is converted by chymase

fraction\_AT1\_bound\_AngII = 0.75 #assume AngII preferentially binds to AT1 vs AT2

## 1.4 The following parameters are calculated at equilibrium using the parameters above

#### 1.4.1 Pressure setpoint

#This pressure is the setpoint that determines the myogenic response of the preafferent vasculature

nom\_preafferent\_pressure = nominal\_map\_setpoint - nom\_renal\_blood\_flow\_L\_min\*nom\_preafferent\_arteriole\_resistance;

#This pressure is the setpoint that determines the myogenic response of the afferent vasculature

nom\_glomerular\_pressure = nom\_preafferent\_pressure - nom\_renal\_blood\_flow\_L\_min\*(L\_m3\*viscosity\_length\_constant/(nom\_afferent\_diameter\*\*4)/baseline\_nephrons);

#This pressure is the setpoint that determines the tubular pressure-natriuresis response

nom\_postglomerular\_pressure = nom\_preafferent\_pressure - nom\_renal\_blood\_flow\_L\_min\*(L\_m3\*viscosity\_length\_constant\*(1/(nom\_afferent\_diameter\*\*4)+1/(nom\_efferent\_diameter\*\*4))/baseline\_nephrons);

RIHP0 = 9.32 #nom\_postglomerular\_pressure

#### 1.4.2 Na and Glucose reabsorption rate

# The rate of sodium excretion must equal the rate of sodium intake. Sodium reabsorption rates vary along the tubule, but based on literature

# measurements we have a good, and literature data provides estimates for these rates. However, there is a precise

# rate of sodium reabsorption required to achieve the equilibrium defined by the parameters above.

# Assuming that reabsorption rates are known in all but one segment of the tubule, the exact rate

# of reabsorption of the remaining segment can be calculated. We chose to calculate the CD rate of reabsorpion based on estimates for

# PT, LoH, and DT reabsorption.

nom\_GFR = nom\_Kf\*(nom\_glomerular\_pressure - nom\_oncotic\_pressure\_difference - (Pc\_pt\_s1\_mmHg))/nL\_mL\*baseline\_nephrons;

nom\_filtered\_sodium\_load = nom\_GFR/L\_mL\*ref\_Na\_concentration;

#Reabsorption of Na through SGLT2 and SGLT1 at baseline

nom\_filtered\_glucose\_load = glucose\_concentration\*nom\_GFR/ 1000

nom\_glucose\_pt\_out\_s1 = max(0,nom\_filtered\_glucose\_load-nom\_glucose\_reabs\_per\_unit\_length\_s1\*L\_pt\_s1\_nom\*baseline\_nephrons)

nom\_glucose\_pt\_out\_s2 = max(0,nom\_glucose\_pt\_out\_s1-nom\_glucose\_reabs\_per\_unit\_length\_s2\*L\_pt\_s2\_nom\*baseline\_nephrons)

nom\_glucose\_pt\_out\_s3 = max(0,nom\_glucose\_pt\_out\_s2-nom\_glucose\_reabs\_per\_unit\_length\_s3\*L\_pt\_s3\_nom\*baseline\_nephrons)

nom\_glucose\_reabs\_per\_unit\_length\_s1

nom\_SGTL2\_Na\_reabs\_mmol\_s1 = nom\_filtered\_glucose\_load-nom\_glucose\_pt\_out\_s1;

nom\_SGTL2\_Na\_reabs\_mmol\_s2 = nom\_glucose\_pt\_out\_s1-nom\_glucose\_pt\_out\_s2;

nom\_SGTL1\_Na\_reabs\_mmol = 2\*(nom\_glucose\_pt\_out\_s2-nom\_glucose\_pt\_out\_s3);

nom\_total\_SGLT\_Na\_reabs = nom\_SGTL2\_Na\_reabs\_mmol\_s1+nom\_SGTL2\_Na\_reabs\_mmol\_s2+nom\_SGTL1\_Na\_reabs\_mmol; #mEq/min

nom\_SGLT\_fractional\_na\_reabs = nom\_total\_SGLT\_Na\_reabs/nom\_filtered\_sodium\_load

#calculate fractional reabsorption of Na through non-SGLT2 mechansims

nominal\_pt\_na\_reabsorption\_nonSGLT = nominal\_pt\_na\_reabsorption - nom\_SGLT\_fractional\_na\_reabs;

nom\_Na\_reabs\_per\_unit\_length = -np.log(1-nominal\_pt\_na\_reabsorption\_nonSGLT)/(L\_pt\_s1\_nom+L\_pt\_s2\_nom+L\_pt\_s3\_nom);

nom\_Na\_pt\_s1\_reabs = nom\_filtered\_sodium\_load\*(1-np.exp(-nom\_Na\_reabs\_per\_unit\_length\*L\_pt\_s1\_nom));

nom\_Na\_pt\_out\_s1 = nom\_filtered\_sodium\_load - nom\_Na\_pt\_s1\_reabs - nom\_SGTL2\_Na\_reabs\_mmol\_s1 ;

nom\_Na\_pt\_s2\_reabs = nom\_Na\_pt\_out\_s1\*(1-np.exp(-nom\_Na\_reabs\_per\_unit\_length\*L\_pt\_s2\_nom));

nom\_Na\_pt\_out\_s2 = nom\_Na\_pt\_out\_s1 - nom\_Na\_pt\_s2\_reabs - nom\_SGTL2\_Na\_reabs\_mmol\_s2;

nom\_Na\_pt\_s3\_reabs = nom\_Na\_pt\_out\_s2\*(1-np.exp(-nom\_Na\_reabs\_per\_unit\_length\*L\_pt\_s3\_nom));

nom\_Na\_pt\_out\_s3 = nom\_Na\_pt\_out\_s2 - nom\_Na\_pt\_s3\_reabs - nom\_SGTL1\_Na\_reabs\_mmol;

nom\_PT\_Na\_outflow = nom\_Na\_pt\_out\_s3;

nom\_Na\_in\_AscLoH = nom\_PT\_Na\_outflow/baseline\_nephrons;

AscLoH\_Reab\_Rate =(2\*nominal\_loh\_na\_reabsorption\*nom\_Na\_in\_AscLoH)/L\_lh\_des; #osmoles reabsorbed per unit length per minute. factor of 2 because osmoles = 2

nom\_LoH\_Na\_outflow = nom\_PT\_Na\_outflow\*(1-nominal\_loh\_na\_reabsorption);

nom\_DT\_Na\_outflow = nom\_LoH\_Na\_outflow\*(1-nominal\_dt\_na\_reabsorption);

nominal\_cd\_na\_reabsorption = 1-Na\_intake\_rate/nom\_DT\_Na\_outflow;

#RBF = (MAP - P\_venous)/RVR. Given MAP, P\_venous, RBF, and preafferent, afferent, and efferent resistances, the remaining peritubular resistance at steady state can be determined

nom\_RVR = (nominal\_map\_setpoint - P\_venous)/nom\_renal\_blood\_flow\_L\_min

nom\_peritubular\_resistance = nom\_RVR - (nom\_preafferent\_arteriole\_resistance + L\_m3\*viscosity\_length\_constant\*(1/(nom\_afferent\_diameter\*\*4)+1/(nom\_efferent\_diameter\*\*4))/baseline\_nephrons);

#Calculate the normal amount of sodium reabsorbed per unit surface area of the PT

PT\_Na\_reab\_perUnitSA\_0 = (nom\_filtered\_sodium\_load/baseline\_nephrons)\* nominal\_pt\_na\_reabsorption/(3.14\*Dc\_pt\_nom\*(L\_pt\_s1\_nom+L\_pt\_s2\_nom+L\_pt\_s3\_nom))

#### 1.4.3 baseline Total Peripheral Resistance (TPR)

#Given the values for baseline MAP and CO above, the baseline TPR required to maintain this MAP and CO can be calculated. Since TPR includes renal vascular resistance, the baseline systemic (non-renal) resistance

#can be calculated from this TPR and the values for baseline renal resistances defined above.

nom\_TPR = nominal\_map\_setpoint/CO\_nom

#### 1.4.4 Calculation of peritubular ultrafiltration coefficient

tubular\_reabsorption = nom\_GFR/1000 - nom\_water\_intake\*water\_intake\_species\_scale/60/24 #at SS, water excretion equals water intake

#Both RIHP and Kf are unknown, so we can either assume RIHP and calculate Kf, or vice versa. Since RIHP has been measured experimentally,

#it seems better to assume a normal value for RIHP and calculate Kf

nom\_peritubular\_cap\_Kf = - tubular\_reabsorption/(nom\_postglomerular\_pressure - RIHP0 - (nom\_oncotic\_pressure\_peritubular - interstitial\_oncotic\_pressure))

#### 1.4.5 Creatinine synthesisrate at equilibrium

creatinine\_synthesis\_rate = equilibrium\_serum\_creatinine \* dl\_ml \* nom\_GFR #Units: mg/min

#### 1.4.6 RAAS Pathway parameters

#Values for half lives and equilibrium concentrations of RAAS peptides available in the literature and

# defined above to calculate nominal values for other RAAS parameters not available in the literature:

#ACE activity

#Chymase activity

#AT1 receptor binding rate

#AT2 receptor binding rate

#equilibrium AT1\_bound\_AngII

#These values are then assumed to be fixed unless specified otherwise.

#Calculating these nominal parameter values initially in a separate file is required so that these parameters can then be varied independently in the main model

nominal\_equilibrium\_PRC = nominal\_equilibrium\_PRA/concentration\_to\_renin\_activity\_conversion\_plasma

nominal\_AngI\_degradation\_rate = np.log(2)/nominal\_AngI\_half\_life #/hr

nominal\_AngII\_degradation\_rate = np.log(2)/nominal\_AngII\_half\_life #/hr

nominal\_AT1\_bound\_AngII\_degradation\_rate = np.log(2)/nominal\_AT1\_bound\_AngII\_half\_life

nominal\_AT2\_bound\_AngII\_degradation\_rate = np.log(2)/nominal\_AT2\_bound\_AngII\_half\_life

#ACE converts 95% of AngI, chymase converts the rest

nominal\_ACE\_activity = (ACE\_chymase\_fraction\*(nominal\_equilibrium\_PRA - nominal\_AngI\_degradation\_rate\*nominal\_equilibrium\_AngI)/nominal\_equilibrium\_AngI)#Therapy\_effect\_on\_ACE

nominal\_chymase\_activity = (1-ACE\_chymase\_fraction)\*(nominal\_equilibrium\_PRA - nominal\_AngI\_degradation\_rate\*nominal\_equilibrium\_AngI)/nominal\_equilibrium\_AngI

#75% of bound AngII is AT1, the rest is AT2

nominal\_AT1\_receptor\_binding\_rate = fraction\_AT1\_bound\_AngII\*(nominal\_equilibrium\_AngI\*(nominal\_ACE\_activity+nominal\_chymase\_activity)-nominal\_AngII\_degradation\_rate\*nominal\_equilibrium\_AngII)/nominal\_equilibrium\_AngII

nominal\_AT2\_receptor\_binding\_rate = (1-fraction\_AT1\_bound\_AngII)\*(nominal\_equilibrium\_AngI\*(nominal\_ACE\_activity+nominal\_chymase\_activity)-nominal\_AngII\_degradation\_rate\*nominal\_equilibrium\_AngII)/nominal\_equilibrium\_AngII

nominal\_equilibrium\_AT1\_bound\_AngII = nominal\_equilibrium\_AngII\*nominal\_AT1\_receptor\_binding\_rate/nominal\_AT1\_bound\_AngII\_degradation\_rate

nominal\_equilibrium\_AT2\_bound\_AngII = nominal\_equilibrium\_AngII\*nominal\_AT2\_receptor\_binding\_rate/nominal\_AT2\_bound\_AngII\_degradation\_rate

## 1.5 The following parameters were determined indirectly from many different literature studies on the response

#various changes in the system (e.g. drug treatments, infusions of peptide, fluid, sodium, etc.....)

#### 1.5.1 Effects of AT1-bound AngII on preafferent, afferent, and efferent resistance, and aldosterone secretion

AT1\_svr\_slope = 0

AT1\_preaff\_scale = 0.8 #1

AT1\_preaff\_slope = 16

AT1\_aff\_scale=0.8 #0.5

AT1\_aff\_slope=16

AT1\_eff\_scale=0.8 #0.1

AT1\_eff\_slope=16

AT1\_PT\_scale = 0#.1

AT1\_PT\_slope = 16

AT1\_aldo\_slope = 0.02 # 0.05

AT1\_aff\_EC50 = 1e-9; #equilibrium AT1-bound AngII in Mol/L

AT1\_eff\_EC50 = nominal\_equilibrium\_AT1\_bound\_AngII\*1e-12; #equilibrium AT1-bound AngII in Mol/L

Emax\_AT1\_eff = 0

Emax\_AT1\_aff = 0

AT1\_hill = 15

AngII\_effect\_on\_venous\_compliance=1;

#### 1.5.2 Effects of Aldosterone on distal and collecting duct sodium reabsorption

nominal\_aldosterone\_concentration=85

aldo\_DCT\_scale=0

aldo\_DCT\_slope = 0.5

aldo\_CD\_scale=0.2 #0.35

aldo\_CD\_slope = 0.5

aldo\_renin\_slope = -0.4# 2.5#-0.7

#### 1.5.3 Effects of ANP

normalized\_atrial\_NP\_concentration = 1

nom\_ANP = 50 #pg/ml

ANP\_aff\_scale = 0.2

ANP\_aff\_slope = 1

ANP\_preaff\_scale = 0

ANP\_preaff\_slope = 1

ANP\_eff\_scale = 0

ANP\_eff\_slope = 1

anp\_CD\_scale =-0.1

anp\_CD\_slope = 2

ANP\_effect\_on\_venous\_compliance = 1

LVEDP\_ANP\_slope = 20 #Maeda 1998 ANP vs. LVEDP

ANP\_infused\_concentration = 0

ANP\_infusion = 0

#### 1.5.4 Effects of RSNA

renal\_sympathetic\_nerve\_activity = 1

nom\_rsna = 1

rsna\_preaff\_scale = 0.2

rsna\_preaff\_slope = 0.25

rsna\_PT\_scale=0

rsna\_PT\_slope=1

rsna\_CD\_scale = 0

rsna\_CD\_slope = 1

rsna\_renin\_slope=1

rsna\_svr\_slope = 0

rsna\_HR\_slope = 0

sna\_effect\_on\_contractility=1;

SNA\_effect\_on\_venous\_compliance=1;

B2sna\_effect\_on\_TPR = 1;

A1sna\_effect\_on\_TPR = 1;

#### 1.5.5 Osmolarity control of vasopressin secretion

Na\_controller\_gain=0.05

Kp\_VP = 2

Ki\_VP = 0.005

nom\_ADH\_urea\_permeability = .98

nom\_ADH\_water\_permeability = .98

#### 1.5.6 Effects of Vasopressin on water intake and reabsorption

nominal\_vasopressin\_conc=4

water\_intake\_vasopressin\_scale = 0.25#1.5

water\_intake\_vasopressin\_slope = -0.5

#### 1.5.7 Magnitude and Steepness of tubuloglomerular feedback

S\_tubulo\_glomerular\_feedback=0.7

F\_md\_scale\_tubulo\_glomerular\_feedback=6

MD\_Na\_concentration\_setpoint = 63.29 #60.8

#### 1.5.8 Effect of macula densa sodium flow on renin secretion

md\_renin\_A = 1

md\_renin\_tau = 1

#### 1.5.9 Responsiveness of renal vasculature to regulatory signals

preaff\_diameter\_range=0.25

afferent\_diameter\_range=1.2e-05

efferent\_diameter\_range=3e-06

preaff\_signal\_nonlin\_scale=4

afferent\_signal\_nonlin\_scale=4

efferent\_signal\_nonlin\_scale=4

#### 1.5.10 RAAS pathway (these parameters can be set to different values than used to calculate the equilibrium state above)

AngI\_half\_life=0.008333

AngII\_half\_life=0.011

AT1\_bound\_AngII\_half\_life=0.2

AT1\_PRC\_slope=-0.9

AT1\_PRC\_yint=0

AT2\_bound\_AngII\_half\_life=0.2

concentration\_to\_renin\_activity\_conversion\_plasma=61

fraction\_AT1\_bound\_AngII=0.75

nominal\_ACE\_activity=48.9

nominal\_AT1\_receptor\_binding\_rate=12.1

nominal\_AT2\_receptor\_binding\_rate=4.0

nominal\_chymase\_activity=1.25

nominal\_equilibrium\_AT1\_bound\_AngII=16.63

nominal\_equilibrium\_PRC=16.4

renin\_half\_life=0.1733

1.6 Transfer constants for ODEs - determine speed of processes

#### 1.6.1 timescale

C\_renal\_CV\_timescale = 60

#### 1.6.2 These constants govern the calculation of the cardiac cycle and subsequently calculation of CO and MAP

#They should NOT be scaled when the time scale between the renal and cardiac model is scaled.

C\_cycle = 50

C\_cycle2 = 100

C\_cycle3 = 100

C\_co = 0.1

C\_co\_delay = 0.25

C\_map = 0.25

time\_step = 1/C\_cycle;

#### 1.6.3 These parameters govern feedbacks between the cardiac and renal model, and ARE scaled when the time scale ebtween the cardiac and renal model is scaled

C\_co\_error=1

C\_vasopressin\_delay = 1 #1

#### 1.6.4 Na and water transfer between blood, IF

Q\_water = 1 ##\*60

Q\_Na = 1 ##\*60

Q\_Na\_store = 0

max\_stored\_sodium = 500

C\_Na\_error=1

C\_aldo\_secretion=100

C\_tgf\_reset=0

C\_md\_flow = 0.06 #Time delay between MD sodium flow and renin secretion

C\_tgf=1

C\_rbf=100

C\_serum\_creatinine = 1

C\_pt\_water=1

C\_rsna = 100

C\_postglomerular\_pressure = 1

## 1.7 Therapy effects

#### 1.7.1 Diuretic - Hydrochlorothiazide

HCTZ\_effect\_on\_DT\_Na\_reabs = 1 # Diuretic - Hydrochlorothiazide

HCTZ\_effect\_on\_renin\_secretion = 1 # Diuretic – Hydrochlorothiazide

#### 1.7.2 Calcium Channel Blocker

CCB\_effect\_on\_preafferent\_resistance = 1 # Calcium Channel Blocker

CCB\_effect\_on\_afferent\_resistance = 1 # Calcium Channel Blocker

CCB\_effect\_on\_efferent\_resistance = 1 # Calcium Channel Blocker

#### 1.7.3 Mineralocorticoid Receptor Antagonists

pct\_target\_inhibition\_MRA = 0 # Mineralocorticoid Receptor Antagonists

#### 1.7.4 Angiotensin Receptor Blocker

pct\_target\_inhibition\_ARB = 0 # Angiotensin Receptor Blocker

#### 1.7.5 ACE inhibitor

pct\_target\_inhibition\_ACEi = 0 # ACE inhibitor

#### 1.7.6 Direct Renin Inhibitor

pct\_target\_inhibition\_DRI = 0 # Direct Renin Inhibitor

#### 1.7.7 ARB (Angiotensin II Receptor Blocker)

ARB\_is\_on = 0

#### 1.7.8 Beta blocker

BB\_TPR\_effect = 1

BB\_cardiac\_relax\_effect = 0

BB\_venous\_compliance\_effect= 0

BB\_preafferent\_R\_effect = 1 # Beta Blocker

BB\_renin\_secretion\_effect = 1 # Beta Blocker

BB\_HR\_effect = 1 # Beta Blocker

BB\_contractility\_effect = 1 # Beta Blocker

BB\_is\_on = 0 #Turn on Beta Blocker

#### 1.7.9 Speed at which drug takes effect (important for heart rate changes w/BB)

k\_PD = 0.001 #Speed at which drug takes effect (important for heart rate changes w/BB)

#### 1.7.10 Normalized\_aldo\_secretion

K\_Na\_ratio\_effect\_on\_aldo = 1;

#### 1.7.11 Renal autoregulation of glomerular pressure and flow

gp\_autoreg\_scale=0

preaff\_autoreg\_scale = 0

myogenic\_steepness=2

RBF\_autoreg\_scale = 0

RBF\_autoreg\_steepness = 1

#### 1.7.12 Pressure natiuresis effect

Kp\_PN = 1

Kd\_PN = 0

Ki\_PN = 0#.0005

max\_pt\_reabs\_rate = 0.995

pressure\_natriuresis\_PT\_scale = 0.5#3, 1

pressure\_natriuresis\_PT\_slope = 1

pressure\_natriuresis\_LoH\_scale = 0 #3, 0

pressure\_natriuresis\_LoH\_slope = 1

pressure\_natriuresis\_DCT\_scale = 0 #3, 0

pressure\_natriuresis\_DCT\_slope = 1

max\_cd\_reabs\_rate = 0.995

pressure\_natriuresis\_CD\_scale = 0.5 #3, 1

pressure\_natriuresis\_CD\_slope=1

RBF\_CD\_scale = 1

RBF\_CD\_slope = 0.3

#### 1.7.13 Rate at which the tubular pressure natriuresis mechanism is lost in diabetes (should be zero or negative number)

CD\_PN\_loss\_rate = 0

water\_intake\_species\_scale = 1

CO\_species\_scale = 1

#### 1.7.14 Glomerular pressure effect on glomerular hypertrophy

maximal\_glom\_surface\_area\_increase = 0.5

T\_glomerular\_pressure\_increases\_Kf = 120000

#### 1.7.15 PT sodium reabsorption effects on tubular hypertrophy

maximal\_tubule\_length\_increase = 0#.5

maximal\_tubule\_diameter\_increase = 0#.25

T\_PT\_Na\_reabs\_PT\_length = (1e10)

T\_PT\_Na\_reabs\_PT\_diameter = (1e10)

#### 1.7.16 Reduce Kf due to glomerulosclerosis

disease\_effects\_decreasing\_Kf = 0

#### 1.7.17 Disease effects

disease\_effect\_on\_nephrons = 0

max\_s1\_Na\_reabs = 7.5e-6

max\_s2\_Na\_reabs = 2e-6

max\_s3\_Na\_reabs = 1

max\_deltaLoH\_reabs=0.75e-6

CD\_Na\_reabs\_threshold = 7e-7 #2.5e-7

#### 1.7.18 Treatment Parameters

SGLT2\_inhibition = 1

SGLT1\_inhibition = 1

C\_sglt2\_delay = 0.1\*60

C\_ruge = 0.0001\*60#.5

Anhe3 = 0

deltaCanp = 0 # To be used for modifying endogenous normalized ANP concentrations

ANP\_effect\_on\_Arterial\_Resistance = 0

loop\_diuretic\_effect = 1

#### 1.7.19 Aortic Stenosis Parameters

heart\_renal\_link = 1

aortic\_valve\_stenosis = 0

R\_art\_stenosis\_factor = 0

stenosis\_rate = 0.005

#### 1.7.20 Mitral Regurgitation Parameters

mitral\_regurgitation = 0

mitral\_regurgitation\_pressure\_diff = 1e10 #set really high so no regurgitation

max\_mitral\_diff = 19000

min\_mitral\_diff = 16500

k\_mitral\_diff = 0.05

#### 1.7.21 Aortic Regurgitation Parameters

aortic\_regurgitation = 0

aortic\_regurgitation\_pressure\_diff = 1e10 #set really high so no regurgitation

max\_aortic\_diff = 7000

min\_aortic\_diff = 5500

k\_aortic\_diff = 0.05

# 2. Model function.R

## 2.1 Drug Effects

ARB\_signal = ARB\_is\_on\*(1-np.exp(-k\_PD\*sim\_time));

BB\_signal = BB\_is\_on\*(1-np.exp(-k\_PD\*sim\_time));

BB\_venous\_effect = (1+BB\_venous\_compliance\_effect\*BB\_signal);

beta\_blocker\_effect\_on\_contractility = 1-(1-BB\_contractility\_effect )\*BB\_signal;

beta\_blocker\_effect\_on\_heart\_rate = (1-(1-BB\_HR\_effect)\*BB\_signal)

2.2 Disease Effects

### Aortic stenosis - approximate by increasing afterload resistance

if aortic\_valve\_stenosis == 1:

R\_art = R\_art0 \* (1 + R\_art\_stenosis\_factor \* (1 - np.exp(-stenosis\_rate \* sim\_time)))

# Uncomment the following line if you need the alternative calculation

# R\_art = R\_art0 \* (1 + R\_art\_stenosis\_factor \* (sim\_time / (365 \* 24)))

else:

R\_art = R\_art0

###Allow mitral regurgitation if pressure differential across mitral valve exceeds threshold (set threshold really high to eliminate any regurgitation)

if mitral\_regurgitation == 1:

#decrease threshold for leak gradually over time

mitral\_regurgitation\_pressure\_diff = min\_mitral\_diff + max\_mitral\_diff \* np.exp(-k\_mitral\_diff \* sim\_time)

else:

mitral\_regurgitation\_pressure\_diff = 1e10 # Set to a very large value

## 2.3 Heart Rate

rsna\_HR\_intercept = 1-rsna\_HR\_slope;

rsna\_effect\_on\_HR = rsna\_HR\_slope \* renal\_sympathetic\_nerve\_activity + rsna\_HR\_intercept;

heart\_rate = HR\_heart\_rate \*rsna\_effect\_on\_HR\*beta\_blocker\_effect\_on\_heart\_rate;

beat\_duration = min\_sec / heart\_rate ;

beat\_time = sim\_time/beat\_duration - np.floor(sim\_time/beat\_duration);

periods = np.floor(sim\_time/beat\_duration);

## 2.4 Mean Pressures

mean\_arterial\_pressure\_MAP = (systolic\_pressure/3+diastolic\_pressure\*2/3)\*Pa\_mmHg;

mean\_venous\_pressure = (systolic\_venous\_pressure/3+diastolic\_venous\_pressure\*2/3);

## 2.5 Vascular Autoregulation

#Local tissue autoregulation

tissue\_autoregulation\_sig1 = -tissue\_autoreg\_scale\*(Kp\_CO\*(CO\_delayed - CO\_nom\*CO\_species\_scale)+Ki\_CO\*CO\_error);

tissue\_autoregulation\_signal = 1/((0.2\*tissue\_autoregulation\_sig1 + 1)\*\*4);

#Venous autoregulation

#designed to only cause venous constriction when CO is decreased and can no longer be maintained by tissue autoregulation

venous\_autoregulation\_signal\_int = 1-venous\_autoregulation\_signal\_scale;

venous\_autoregulation\_signal = venous\_autoregulation\_signal\_int + venous\_autoregulation\_signal\_scale/(1+np.exp(((tissue\_autoregulation\_sig1 - venous\_autoregulation\_signal\_Km)-1)/venous\_autoregulation\_signal\_slope));

V\_ven0\_adjusted = V\_ven0\*venous\_autoregulation\_signal;

2.6 Volume unit conversions

LV\_volume\_mL = LV\_volume \* m3\_mL;

arterial\_volume\_mL = arterial\_volume \* m3\_mL;

peripheral\_volume\_mL = peripheral\_circulation\_volume \* m3\_mL;

RV\_volume\_mL = RV\_volume \* m3\_mL;

pulmonary\_arterial\_volume\_mL = pulmonary\_arterial\_volume \* m3\_mL;

venous\_volume\_mL = venous\_volume \* m3\_mL;

total\_blood\_volume\_mL = LV\_volume\_mL + arterial\_volume\_mL + peripheral\_volume\_mL + RV\_volume\_mL + pulmonary\_arterial\_volume\_mL + pulmonary\_venous\_volume \* m3\_mL + venous\_volume\_mL;

blood\_volume = blood\_volume\_L/1000;

## 2.7 Cardiac Sub-Model Non-ODE Equations

2.7.1 Cardiac tissue composition

baseline\_total\_myocyte\_volume = V\_w\_0 - Baseline\_Interstitial\_Fibrosis - Baseline\_Replacement\_Fibrosis - Baseline\_Interstitial\_Tissue; ## baseline myocyte volume determined by V\_w\_0

baseline\_single\_myocyte\_volume = baseline\_total\_myocyte\_volume/Baseline\_Myocyte\_Number;

#baseline myocyte diameter determined by V\_w\_0 & Baseline\_Myocyte\_Length, NOT by Baseline\_Myocyte\_Diameter

Baseline\_Myocyte\_Diameter = 2\*np.sqrt(baseline\_single\_myocyte\_volume/(Pi\*Baseline\_Myocyte\_Length));

myocyte\_length = Baseline\_Myocyte\_Length + change\_in\_myocyte\_length; ## change\_in\_myocyte\_length depends on passive stress levels

myocyte\_diameter = Baseline\_Myocyte\_Diameter + change\_in\_myocyte\_diameter; ## change\_in\_myocyte\_diameter depends on active stress levels - HYPERTROPHY

single\_myocyte\_volume = myocyte\_length \* Pi \* (myocyte\_diameter\*\*2) / 4; ## myocyte volume calculated as a cylinder

number\_of\_live\_myocytes = Baseline\_Myocyte\_Number;

total\_myocyte\_volume = single\_myocyte\_volume \* number\_of\_live\_myocytes;

total\_nonmyocyte\_volume = Baseline\_Interstitial\_Fibrosis + Baseline\_Interstitial\_Tissue + Baseline\_Replacement\_Fibrosis;

LV\_wall\_volume = total\_myocyte\_volume + total\_nonmyocyte\_volume;

## a measure of how much LV wall wolume has grown

level\_of\_hypertrophy = LV\_wall\_volume / (baseline\_total\_myocyte\_volume + total\_nonmyocyte\_volume);

pct\_change\_in\_myocyte\_diameter = 100 \* (change\_in\_myocyte\_diameter / Baseline\_Myocyte\_Diameter);

pct\_change\_in\_myocyte\_length = 100 \* (change\_in\_myocyte\_length / Baseline\_Myocyte\_Length ) ;

### 2.7.2 Cardiac Mechanics

## Muscle fiber stress and strain are approximately homogeneously distributed, so that they may be approximated by single values.

## Microscopic constitutive laws for fiber stress and radial stress are used to model active and passive fiber stress.

LV\_cavity\_volume = LV\_V0\_baseline \* ((1 + myo\_L\_scale \* change\_in\_myocyte\_length / Baseline\_Myocyte\_Length)\*\*3) \* ((1 - myo\_D\_scale \* change\_in\_myocyte\_diameter / Baseline\_Myocyte\_Diameter)\*\*2);

LV\_fiber\_stretch =((LV\_volume + (LV\_wall\_volume/3)) / (LV\_cavity\_volume + (LV\_wall\_volume / 3)))\*\*0.3333333;

outward\_growth = LV\_cavity\_volume / LV\_V0\_baseline; ## a measure of how much the LV chamber has grown in volume

LV\_sarcomere\_length = ls\_0\_passive\_LV\_sarcomere\_length \* LV\_fiber\_stretch;

LV\_sarcomere\_contraction\_velocity = (LV\_sarcomere\_length - LV\_sarcomere\_length\_delayed) / time\_step;

contraction\_velocity\_effect\_in\_LV = (1 - LV\_sarcomere\_contraction\_velocity / v0\_LV\_contraction\_velocity\_effect\_in\_LV) / (1 + Cv\_contraction\_velocity\_effect\_in\_\_LV \* LV\_sarcomere\_contraction\_velocity / v0\_LV\_contraction\_velocity\_effect\_in\_LV);

if LV\_sarcomere\_length > ls\_a0:

sarcomere\_length\_effect\_in\_LV = (LV\_sarcomere\_length - ls\_a0) / (ls\_ar\_sarcomere\_length\_effect\_in\_LV - ls\_a0)

else:

sarcomere\_length\_effect\_in\_LV = 0

chamber\_radius = ((LV\_cavity\_volume \* 3 / 4 / np.pi)\*\*0.3333333) \* m\_mm ; ## approximating the LV as a spherical shell

chamber\_diameter = 2 \* chamber\_radius;

outer\_radius = (((LV\_cavity\_volume + LV\_wall\_volume) \* 3 / 4 / np.pi)\*\*0.3333333) \* m\_mm ;

h\_wall = outer\_radius - chamber\_radius; ## wall thickness

h\_over\_r = h\_wall / chamber\_radius; ## a measure of the LV chamber growth; it's the ratio of wall thickness to chamber radius

EDV\_chamber\_radius = ((LV\_EDV \* 3 / 4 / np.pi) \*\* (1/3)) \* m\_mm;

EDV\_chamber\_diameter = 2\*EDV\_chamber\_radius;

EDV\_outer\_radius = (((LV\_EDV + LV\_wall\_volume) \* 3 / 4 / np.pi) \*\* 0.3333333) \* m\_mm;

EDV\_h\_wall = EDV\_outer\_radius - EDV\_chamber\_radius; ## wall thickness

EDV\_h\_over\_r = EDV\_h\_wall / EDV\_chamber\_radius;

LV\_mass = 1000000\*LV\_wall\_volume\*1.05 ; ##wall volume\*[(cm->m)\*\*3]\*density

LVID = ((6 \* LV\_EDV) / 3.14159) \*\* (1/3);

### 2.7.3 Cardiac excitation

###Generate justified sinusoidal activation signal - Left Ventricle

RV\_twitch\_duration = RV\_systolic\_time\_fraction \* beat\_duration;

t\_d = tau\_d\_LV\_twitch\_shape\*(1+BB\_cardiac\_relax\_effect\*BB\_signal);

t\_r = tau\_r\_LV\_twitch\_shape;

t\_twitch = t\_r + t\_d;

if beat\_time <= t\_r:

sin\_signal = (np.sin(np.pi \* beat\_time / t\_twitch)) \*\* n\_r\_LV\_twitch\_shape

else:

sin\_signal = (np.sin(np.pi \* beat\_time / t\_twitch)) \*\* n\_r\_LV\_twitch\_shape

LV\_twitch\_shape = sin\_signal;

# print("LV\_twitch\_shape",LV\_twitch\_shape)

# Left Ventricle Twitch Shape

# print("beat\_time",beat\_time)

# print("t\_twitch",t\_twitch)

if beat\_time < 0 or beat\_time > t\_twitch:

# print("beat\_time < 0 or beat\_time > t\_twitch")

LV\_twitch\_shape = 0

# print("LV\_twitch\_shape2",LV\_twitch\_shape)

###Generate justified sinusoidal activation signal - Right Ventricle

RV\_twitch\_shape = (np.sin(np.pi \* beat\_time / RV\_twitch\_duration)) \*\* 2

if beat\_time < 0 or beat\_time > RV\_twitch\_duration:

RV\_twitch\_shape = 0

### 2.7.4 Left Ventricle Stress Generation

LV\_active\_stress = contractility \* LV\_twitch\_shape \* sigma\_ar \* sarcomere\_length\_effect\_in\_LV \* contraction\_velocity\_effect\_in\_LV \* (beta\_blocker\_effect\_on\_contractility \* sna\_effect\_on\_contractility);

#Increase in left ventricle stiffness with increasing hypertrophy

hypertrophy\_effect\_on\_Cf = hypertrophy\_Cf\_slope\*max(0,(level\_of\_hypertrophy - 1));

C\_f = cf\*(1+hypertrophy\_effect\_on\_Cf);

#Unpressurized fiber stretch

stretch\_zero\_S = stretch\_min\_LV\_passive\_stress\_along\_fiber - stretch\_scale\_LV\_passive\_stress\_along\_fiber;

# LV Passive Stress Along Fiber

if LV\_fiber\_stretch >= stretch\_zero\_S:

LV\_passive\_stress\_along\_fiber = s\_f0 \* (np.exp(C\_f \* (LV\_fiber\_stretch - stretch\_zero\_S)) - 1)

else:

LV\_passive\_stress\_along\_fiber = 0

# LV Radial Stretch

LV\_radial\_stretch = 1 / (LV\_fiber\_stretch \* LV\_fiber\_stretch)

# LV Passive Radial Stress

if LV\_radial\_stretch >= 1:

LV\_passive\_radial\_stress = s\_r0 \* (np.exp(c\_r\_LV \* (LV\_radial\_stretch - 1)) - 1)

else:

LV\_passive\_radial\_stress = 0

#Total stress is sum of active and passive stresses

LV\_total\_stress = (LV\_active\_stress + LV\_passive\_stress\_along\_fiber - 2 \* LV\_passive\_radial\_stress);

if LV\_volume > LV\_V0\_min:

rel\_volume\_LV = 1 + LV\_wall\_volume / LV\_volume

else:

rel\_volume\_LV = 1 + LV\_wall\_volume / LV\_V0\_min

#LV Pressure depends on stress and relativ wall volume

LV\_pressure = LV\_total\_stress \* np.log(rel\_volume\_LV)/ 3;

### 2.7.5 Right Ventricle Stress Generation

RV\_Cavity\_Volume = RV\_V0;

RV\_wall\_volume = V\_w\_0\_RV;

RV\_fiber\_stretch = ((RV\_volume + V\_w\_0\_RV/3) / (RV\_Cavity\_Volume + RV\_wall\_volume/3))\*\*(0.333);

RV\_sarcomere\_length = ls\_a0\_RV \* RV\_fiber\_stretch;

if RV\_sarcomere\_length > ls\_a0\_RV:

sarcomere\_length\_effect\_in\_RV = (RV\_sarcomere\_length - ls\_a0\_RV) / (0.000002 - ls\_a0\_RV)

else:

sarcomere\_length\_effect\_in\_RV = 0

RV\_sarcomere\_contraction\_velocity = ((RV\_sarcomere\_length - RV\_sarcomere\_length\_delayed) / time\_step);

contraction\_velocity\_effect\_in\_RV = ((1 - RV\_sarcomere\_contraction\_velocity / v0\_RV\_contraction\_velocity\_effect\_in\_RV) / (1 + 0 \* RV\_sarcomere\_contraction\_velocity / v0\_RV\_contraction\_velocity\_effect\_in\_RV));

RV\_active\_stress\_multiplier = contractility\_RV\*sna\_effect\_on\_contractility;

RV\_active\_stress = (contractility\_RV \* RV\_twitch\_shape \* sigma\_ar\_RV \* sarcomere\_length\_effect\_in\_RV \* contraction\_velocity\_effect\_in\_RV \* sna\_effect\_on\_contractility);

RV\_radial\_stretch = 1/ (RV\_fiber\_stretch \* RV\_fiber\_stretch);

# RV Passive Radial Stress

if RV\_radial\_stretch >= 1:

RV\_passive\_radial\_stress = s\_r0\_RV \* (np.exp(c\_r\_RV \* (RV\_radial\_stretch - 1)) - 1)

else:

RV\_passive\_radial\_stress = 0

# RV Passive Stress Along Fiber

if RV\_fiber\_stretch >= 1:

RV\_passive\_stress\_along\_fiber = s\_f0\_RV \* (np.exp(cf\_RV \* (RV\_fiber\_stretch - 1)) - 1)

else:

RV\_passive\_stress\_along\_fiber = 0

# RV Total Stress

RV\_total\_stress = RV\_active\_stress + RV\_passive\_stress\_along\_fiber - 2 \* RV\_passive\_radial\_stress

# Relative Volume

if RV\_volume > RV\_V0\_min:

rel\_volume = 1 + RV\_wall\_volume / RV\_volume

else:

rel\_volume = 1 + RV\_wall\_volume / RV\_V0\_min

RV\_pressure = RV\_total\_stress \* np.log(rel\_volume) / 3;

### 2.7.6 LV Hypertrophy

if LV\_active\_stress\_peak > LV\_active\_stress\_threshhold:

# Myocyte diameter grows if peak active stress exceeds the threshold

kD\_HYPERTROPHY = (kD\_HYPERTROPHY \* C\_renal\_CV\_timescale) \* max(0, (max\_myocyte\_diameter\_increase - change\_in\_myocyte\_diameter) / max\_myocyte\_diameter\_increase)

else:

# Regression of hypertrophic growth

kD\_HYPERTROPHY = kD\_HYPERTROPHY \* C\_renal\_CV\_timescale

if LV\_EDS > LV\_passive\_stress\_along\_fiber\_threshhold:

# Myocyte length grows if passive stress along fiber exceeds the threshold

kL\_HYPERTROPHY = (kL\_HYPERTROPHY \* C\_renal\_CV\_timescale) \* max(0, (max\_myocyte\_length\_increase - change\_in\_myocyte\_length) / max\_myocyte\_length\_increase)

else: # adding a length threshhold to limit volumetric remodeling

# Myocyte length does not decrease once stretched

kL\_HYPERTROPHY = 0

## 2.8 Vascular Sub-Model Non-ODE Equations

### 2.8.1 Circulatory hemodynamics

peripheral\_pressure = P\_ven0 + (peripheral\_circulation\_volume - V\_per0) / C\_per;

venous\_compliance=(C\_ven0\*AngII\_effect\_on\_venous\_compliance\*(SNA\_effect\_on\_venous\_compliance\*BB\_venous\_effect));

venous\_pressure = (P\_ven0 +

(venous\_volume - V\_ven0) / venous\_compliance);

venous\_flow = (peripheral\_pressure - venous\_pressure) / R\_ven0;

##allow blood volume link between heart and kidney to be turned on/off

if heart\_renal\_link == 1:

venous\_volume\_target = (blood\_volume - LV\_volume - arterial\_volume - peripheral\_circulation\_volume - RV\_volume - pulmonary\_arterial\_volume - pulmonary\_venous\_volume)

else:

venous\_volume\_target = venous\_volume

tricuspid\_valve\_flow\_rate = max((venous\_pressure - RV\_pressure) / R\_r\_atrium,min\_flux);

pulmonary\_arterial\_pressure = ( pulmonary\_arterial\_volume - V\_pulm\_art0 )/(C\_pulm\_art) + P\_art0;

pulmonary\_venous\_pressure = P\_ven0 + (pulmonary\_venous\_volume - V\_pulm\_ven0 )/(C\_pulm\_ven\*BB\_venous\_effect);

pulmonary\_arterial\_blood\_flow = (pulmonary\_arterial\_pressure - pulmonary\_venous\_pressure )/ R\_ven\_pulm ;

dP = RV\_pressure - pulmonary\_arterial\_pressure;

Zn = L\_pulm + time\_step \* R\_art\_pulm;

pulmonary\_blood\_flow = (pulmonary\_blood\_flow\_delayed \* L\_pulm + dP \* time\_step) / Zn;

# Calculate mitral valve flow rate

if pulmonary\_venous\_pressure > LV\_pressure:

# Forward flow into ventricle

mitral\_valve\_flow\_rate = max((pulmonary\_venous\_pressure - LV\_pressure) / R\_left\_atrium, min\_flux)

else:

# If pressure difference is less than regurgitation limit, no regurgitation

if (LV\_pressure - pulmonary\_venous\_pressure) < mitral\_regurgitation\_pressure\_diff:

mitral\_valve\_flow\_rate = min\_flux

else:

# Allow negative flow back out of the ventricle

mitral\_valve\_flow\_rate = (pulmonary\_venous\_pressure - LV\_pressure) / R\_left\_atrium

# Calculate regurgitation rate

if mitral\_valve\_flow\_rate < 0:

mitral\_valve\_leak\_rate = mitral\_valve\_flow\_rate

else:

mitral\_valve\_leak\_rate = 0

pulmonary\_valve\_flow\_rate = max(pulmonary\_blood\_flow,min\_flux);

peripheral\_resistance\_multiplier = (disease\_effect\_on\_TPR\_peripheral\_resistance \* B2sna\_effect\_on\_TPR\*A1sna\_effect\_on\_TPR\*(1-(1-BB\_TPR\_effect)\*BB\_signal)\*tissue\_autoregulation\_signal);

peripheral\_resistance\_multiplier\_adjusted = 1+vascular\_responsiveness\_scale\*(peripheral\_resistance\_multiplier-1);

peripheral\_resistance = (R\_per0\* TPR\_scale\_peripheral\_resistance \* peripheral\_resistance\_multiplier\_adjusted);

## arterial\_pressure computed without taking account compliance

## arterial\_compliance = compliance\_scale\_arterial\_compliance \* (C\_art ) ;

## arterial\_pressure = (arterial\_volume - V\_art0) / arterial\_compliance + P\_art0 ;

## arterial\_pressure computed taking account compliance

## Constants taken from Safar, M. E., et al. Stiffness of carotid artery wall material and blood pressure in humans: application to antihypertensive therapy and stroke prevention. Stroke 31.3 (2000): 782-790.

## We assume a linear effect as follows.

## BP\_effect\_on\_stiffness = (arterial\_pressure - 85)\*Stiffness\_BP\_slope;

## Solving the following system

#When changing compliance, this will allow it to change gradually rather than instantaneously, preventing computational issues

C\_art = ((C\_art\_initial-C\_art\_initial\*C\_art\_scale)/np.exp(sim\_time/(24/2))+C\_art\_initial\*C\_art\_scale);

Stiffness0=1/C\_art;

arterial\_stiffness = (Stiffness0\*(1+ (mean\_arterial\_pressure\_MAP - nominal\_map\_setpoint)\*Stiffness\_BP\_slope));

arterial\_compliance = 1/arterial\_stiffness;

arterial\_pressure = (arterial\_volume - V\_art0) / arterial\_compliance + P\_art0 ;

peripheral\_pressure = (P\_ven0 + (peripheral\_circulation\_volume - V\_per0) / C\_per);

systemic\_blood\_flow = (arterial\_pressure - peripheral\_pressure) / peripheral\_resistance;

dP\_1 = LV\_pressure - arterial\_pressure;

Zn\_1 = L\_art + R\_art \* time\_step;

aortic\_blood\_flow = (aortic\_blood\_flow\_delayed \* L\_art + dP\_1 \* time\_step) / Zn\_1;

aortic\_valve\_flow\_rate = max(aortic\_blood\_flow,min\_flux);

### 2.8.2 Relating BNP and NTP to End Diastolic Stress

BNP = np.exp(BNP\_factor\*((LV\_EDS+1736)/5.094)+3.14);

NTP = np.exp((np.log(BNP)+1.4919)/1.0694);

LVEDP\_ANP\_effect = np.exp(max(0, LV\_EDP\*0.0075-10)/LVEDP\_ANP\_slope);

if heart\_renal\_link == 1:

if ANP\_infusion == 1:

ANP = ANP\_infused\_concentration

else:

ANP = nom\_ANP \* LVEDP\_ANP\_effect # pg/ml

normalized\_ANP = ANP / nom\_ANP

else:

ANP = nom\_ANP

normalized\_ANP = 1

## 2.9 Systolic / Diastolic Calculations

### 2.9.1 Capture End Diastolic Pressure, Volume, and Stress

if (1 - 0.01 / beat\_duration) <= beat\_time < 1:

LV\_pressure\_diastolic\_max = LV\_pressure

LV\_stress\_diastolic\_max = LV\_passive\_stress\_along\_fiber

LV\_volume\_maximum = LV\_volume

else:

LV\_pressure\_diastolic\_max = LV\_EDP

LV\_stress\_diastolic\_max = LV\_EDS

LV\_volume\_maximum = LV\_EDV

LV\_EDP\_old = LV\_pressure\_diastolic\_max;

LV\_EDS\_old = LV\_stress\_diastolic\_max;

LV\_EDV\_old = LV\_volume\_maximum;

### 2.9.2 Capture Systolic and Diastolic Pressures

## Method to find Systolic and Diastolic blood pressure

## use current and last two time steps to find local maxima and minima

##### 2.9.2.1 SBP and DBP

if arterial\_pressure\_delayed < arterial\_pressure\_bigger\_delay:

systemic\_pressure\_minimum\_1 = arterial\_pressure\_delayed

else:

systemic\_pressure\_minimum\_1 = diastolic\_pressure

if arterial\_pressure\_delayed < arterial\_pressure:

systemic\_pressure\_minimum = systemic\_pressure\_minimum\_1

else:

systemic\_pressure\_minimum = diastolic\_pressure

if arterial\_pressure\_delayed > arterial\_pressure\_bigger\_delay:

systemic\_pressure\_maximum\_1 = arterial\_pressure\_delayed

else:

systemic\_pressure\_maximum\_1 = systolic\_pressure

if arterial\_pressure\_delayed > arterial\_pressure:

systemic\_pressure\_maximum = systemic\_pressure\_maximum\_1

else:

systemic\_pressure\_maximum = systolic\_pressure

systolic\_pressure\_old = systemic\_pressure\_maximum

diastolic\_pressure\_old = systemic\_pressure\_minimum

##### 2.9.2.2 Venous Systolic and Diastolic Pressures

if venous\_pressure\_delayed < venous\_pressure\_bigger\_delay:

systemic\_venous\_pressure\_minimum\_1 = venous\_pressure\_delayed

else:

systemic\_venous\_pressure\_minimum\_1 = diastolic\_venous\_pressure

if venous\_pressure\_delayed < venous\_pressure:

systemic\_venous\_pressure\_minimum = systemic\_venous\_pressure\_minimum\_1

else:

systemic\_venous\_pressure\_minimum = diastolic\_venous\_pressure

if venous\_pressure\_delayed > venous\_pressure\_bigger\_delay:

systemic\_venous\_pressure\_maximum\_1 = venous\_pressure\_delayed

else:

systemic\_venous\_pressure\_maximum\_1 = systolic\_venous\_pressure

if venous\_pressure\_delayed > venous\_pressure:

systemic\_venous\_pressure\_maximum = systemic\_venous\_pressure\_maximum\_1

else:

systemic\_venous\_pressure\_maximum = systolic\_venous\_pressure

systolic\_venous\_pressure\_old = systemic\_venous\_pressure\_maximum

diastolic\_venous\_pressure\_old = systemic\_venous\_pressure\_minimum

##### 2.9.2.3 Find Peak systolic stress in the LV

if (t\_r \* 0.8) <= beat\_time < (t\_r \* 0.85):

LV\_peak\_stress = LV\_active\_stress

else:

LV\_peak\_stress = LV\_active\_stress\_peak

# Fixes a numerical computation problem

if LV\_active\_stress > 1:

LV\_active\_stress\_peak\_old = LV\_peak\_stress

else:

LV\_active\_stress\_peak\_old = LV\_active\_stress\_peak

## 2.10 Kidney Sub-Model Non-ODE Equations

number\_of\_functional\_glomeruli = baseline\_nephrons;

number\_of\_functional\_tubules = baseline\_nephrons\*(1-disease\_effect\_on\_nephrons);

### 2.10.1 Renal Vascular Resistance

##### 2.10.1.1 AT1-bound AngII constricts the preafferent, afferent, and efferent arterioles

AT1\_preaff\_int = 1 - AT1\_preaff\_scale/2;

AT1\_effect\_on\_preaff = AT1\_preaff\_int + AT1\_preaff\_scale/(1+np.exp(-(AT1\_bound\_AngII - nominal\_equilibrium\_AT1\_bound\_AngII)/AT1\_preaff\_slope));

AT1\_aff\_int = 1 - AT1\_aff\_scale/2;

AT1\_effect\_on\_aff = AT1\_aff\_int + AT1\_aff\_scale/(1+np.exp(-(AT1\_bound\_AngII

- nominal\_equilibrium\_AT1\_bound\_AngII)/AT1\_aff\_slope));

AT1\_eff\_int = 1 - AT1\_eff\_scale/2;

AT1\_effect\_on\_eff = AT1\_eff\_int + AT1\_eff\_scale/(1+np.exp(-(AT1\_bound\_AngII - nominal\_equilibrium\_AT1\_bound\_AngII)/AT1\_eff\_slope));

##### 2.10.1.2 ANP may dilate preafferent, afferent, and efferent arteriole

# ANP\_preaff\_int = 1 + ANP\_preaff\_scale/2;

# ANP\_effect\_on\_preaff = ANP\_preaff\_int - ANP\_preaff\_scale/(1+np.exp(-(normalized\_atrial\_NP\_concentration - 1)/ANP\_preaff\_slope));

# ANP\_aff\_int = 1 + ANP\_aff\_scale/2;

# ANP\_effect\_on\_aff = ANP\_aff\_int - ANP\_aff\_scale/(1+np.exp(-(normalized\_atrial\_NP\_concentration - 1)/ANP\_aff\_slope));

# ANP\_eff\_int = 1 + ANP\_eff\_scale/2;

# ANP\_effect\_on\_eff= ANP\_eff\_int - ANP\_eff\_scale/(1+np.exp(-(normalized\_atrial\_NP\_concentration - 1)/ANP\_eff\_slope));

##### 2.10.1.3 RSNA constricts the preafferent vasculature

rsna\_preaff\_int = 1 - rsna\_preaff\_scale/2;

rsna\_effect\_on\_preaff = rsna\_preaff\_int + rsna\_preaff\_scale/(1+np.exp(-(renal\_sympathetic\_nerve\_activity - nom\_rsna)/rsna\_preaff\_slope));

##### 2.10.1.4 Preafferent Resistance

#The resistance of the arcuate, interlobular arterioles, and other vasculature prior the afferent arterioles is represented by a single resistance - the preafferent arteriole resistance

#The preafferent arterioles respond myogenically to changes in pressure, and also responds to AT1-bound AngII, RSNA, and ANP

#The dilation/constriction of the arterioles is limited, and thus the total combined effect of all regulators must saturate

preaff\_arteriole\_signal\_multiplier = (AT1\_effect\_on\_preaff\*preafferent\_pressure\_autoreg\_signal\*CCB\_effect\_on\_preafferent\_resistance\*rsna\_effect\_on\_preaff\*(1-(1-BB\_preafferent\_R\_effect)\*BB\_signal));

preaff\_arteriole\_adjusted\_signal\_multiplier = (1/(1+np.exp(preaff\_signal\_nonlin\_scale\*(1-preaff\_arteriole\_signal\_multiplier)))+0.5);

preafferent\_arteriole\_resistance = (nom\_preafferent\_arteriole\_resistance\*preaff\_arteriole\_adjusted\_signal\_multiplier);

##### 2.10.1.5 Afferent Arteriole Resistance

#The afferent arteriole responses the tubuloglomerular feedback (calculated later), as well as to AT1-bound AngII and ANP.

#It may respond myogenically as well. Some studies suggest the upstream portion responds myogenically while the distal portion responds to TGF. Thus, one could consider the

#myogenically responsive portion as part of the preafferent resistance.

#The dilation/constriction of the arterioles is limited, and thus the total combined effect of all regulators must saturate

nom\_afferent\_arteriole\_resistance = (L\_m3\*viscosity\_length\_constant/(nom\_afferent\_diameter\*\*4));

afferent\_arteriole\_signal\_multiplier = (tubulo\_glomerular\_feedback\_effect \* AT1\_effect\_on\_aff \*glomerular\_pressure\_autoreg\_signal\* CCB\_effect\_on\_afferent\_resistance);

afferent\_arteriole\_adjusted\_signal\_multiplier = (1/(1+np.exp(afferent\_signal\_nonlin\_scale\*(1-afferent\_arteriole\_signal\_multiplier)))+0.5);

afferent\_arteriole\_resistance = (nom\_afferent\_arteriole\_resistance\*afferent\_arteriole\_adjusted\_signal\_multiplier);

##### 2.10.1.6 Efferent Arteriole Resistance

#The efferent arteriole responses to AT1-bound AngII and ANP.

#The dilation/constriction of the arterioles is limited, and thus the total combined effect of all regulators must saturate

nom\_efferent\_arteriole\_resistance = (L\_m3\*viscosity\_length\_constant/(nom\_efferent\_diameter\*\*4));

efferent\_arteriole\_signal\_multiplier = (AT1\_effect\_on\_eff \* CCB\_effect\_on\_efferent\_resistance);

efferent\_arteriole\_adjusted\_signal\_multiplier = (1/(1+np.exp(efferent\_signal\_nonlin\_scale\*(1-efferent\_arteriole\_signal\_multiplier)))+0.5);

efferent\_arteriole\_resistance = (nom\_efferent\_arteriole\_resistance\*efferent\_arteriole\_adjusted\_signal\_multiplier);

##### 2.10.1.7 Peritubular Resistance

#Autoregulation of peritubular resistance allows RBF to be autoregulated separately from GFR

#This is exploratory for now. By default, this effect is turned off by setting RBF\_autoreg\_scale to zero

RBF\_autoreg\_int = (1 - RBF\_autoreg\_scale/2);

peritubular\_autoreg\_signal = (RBF\_autoreg\_int + RBF\_autoreg\_scale/(1+np.exp((nom\_renal\_blood\_flow\_L\_min - renal\_blood\_flow\_L\_min\_delayed)/RBF\_autoreg\_steepness)));

autoregulated\_peritubular\_resistance = (peritubular\_autoreg\_signal\*nom\_peritubular\_resistance);

##### 2.10.1.8 Renal Vascular Resistance

renal\_vascular\_resistance = (preafferent\_arteriole\_resistance + (afferent\_arteriole\_resistance + efferent\_arteriole\_resistance) / number\_of\_functional\_glomeruli + autoregulated\_peritubular\_resistance);

##### 2.10.1.9 Renal blood flow

renal\_blood\_flow\_L\_min = (((mean\_arterial\_pressure\_MAP - (mean\_venous\_pressure\*0.0075-3.16) )/ renal\_vascular\_resistance));

renal\_blood\_flow\_ml\_hr = renal\_blood\_flow\_L\_min \* 1000 \* 60;

##### 2.10.1.10 Renal Vasculature Pressures

preafferent\_pressure = (mean\_arterial\_pressure\_MAP - renal\_blood\_flow\_L\_min\*preafferent\_arteriole\_resistance);

glomerular\_pressure = (mean\_arterial\_pressure\_MAP - renal\_blood\_flow\_L\_min \* (preafferent\_arteriole\_resistance + afferent\_arteriole\_resistance / number\_of\_functional\_glomeruli));

postglomerular\_pressure = (mean\_arterial\_pressure\_MAP - renal\_blood\_flow\_L\_min \* (preafferent\_arteriole\_resistance + (afferent\_arteriole\_resistance+efferent\_arteriole\_resistance) / number\_of\_functional\_glomeruli));

##### 2.10.1.11 Autoregulatory signals for preafferent and afferent resistances

preaff\_autoreg\_int = 1 - preaff\_autoreg\_scale/2;

preafferent\_pressure\_autoreg\_function = (preaff\_autoreg\_int+preaff\_autoreg\_scale/(1+np.exp((nom\_preafferent\_pressure - preafferent\_pressure)/myogenic\_steepness)));

gp\_autoreg\_int = (1 - gp\_autoreg\_scale/2);

glomerular\_pressure\_autoreg\_function = gp\_autoreg\_int+gp\_autoreg\_scale/(1+np.exp((nom\_glomerular\_pressure - glomerular\_pressure)/myogenic\_steepness));

### 2.10.2 Glomerular Filtration

#Glomerular hypertrophy resulting in increased surface area and thus increased Kf is assumed to occur

#in response to elevated glomerular pressure. A 2 mmHg buffer is built in (i.e. glomerular pressure must be at least 2 mmHg above normal for hypertrophy to begin

#The increase in Kf saturates and cannot exceed the fractional increase set by maximal\_glom\_surface\_area\_increase

GP\_effect\_increasing\_Kf = ((maximal\_glom\_surface\_area\_increase - disease\_effects\_increasing\_Kf) \* max(glomerular\_pressure/(nom\_glomerular\_pressure+2) - 1,0) / (T\_glomerular\_pressure\_increases\_Kf/C\_renal\_CV\_timescale));

glomerular\_hydrostatic\_conductance\_Kf = nom\_Kf\*(1+disease\_effects\_increasing\_Kf);

##### 2.10.2.1 Glomerular Fitlration Rate

net\_filtration\_pressure = (glomerular\_pressure - oncotic\_pressure\_difference - P\_bowmans);

if net\_filtration\_pressure <= 0:

SNGFR\_nL\_min = 0.001

else:

SNGFR\_nL\_min = glomerular\_hydrostatic\_conductance\_Kf \* net\_filtration\_pressure

#Unit conversion

GFR = (SNGFR\_nL\_min / 1000 / 1000000 \* number\_of\_functional\_tubules);

GFR\_ml\_min = GFR \* 1000;

filtration\_fraction = GFR/renal\_blood\_flow\_L\_min;

serum\_creatinine\_concentration = serum\_creatinine/blood\_volume\_L;

creatinine\_clearance\_rate = (GFR\_ml\_min \* dl\_ml \* serum\_creatinine\_concentration); #Units: mg/min

##### 2.10.2.2 Oncotic pressure

GPdiff = max(0, glomerular\_pressure - (nom\_GP\_seiving\_damage));

GP\_effect\_on\_Seiving = Emax\_seiving \* GPdiff\*\*Gamma\_seiving / (GPdiff\*\*Gamma\_seiving + Km\_seiving\*\*Gamma\_seiving);

#Dean and Lazzara 2006 - Seiving coefficient decreases as GFR increases

nom\_glomerular\_albumin\_sieving\_coefficient = seiving\_inf/(1-(1-seiving\_inf)\*np.exp(-c\_albumin\*SNGFR\_nL\_min));

glomerular\_albumin\_sieving\_coefficient = nom\_glomerular\_albumin\_sieving\_coefficient\*(1 + GP\_effect\_on\_Seiving);

SN\_albumin\_filtration\_rate = plasma\_albumin\_concentration\*SNGFR\_nL\_min\*1e-6\*glomerular\_albumin\_sieving\_coefficient; #mg/min

SN\_albumin\_excretion\_rate = max(0, SN\_albumin\_filtration\_rate - SN\_albumin\_reabsorptive\_capacity)+nom\_albumin\_excretion\_rate;

albumin\_excretion\_rate = SN\_albumin\_excretion\_rate\*number\_of\_functional\_tubules;

#Landis Pappenheimer equation used to calculate oncotic pressure at entrance and exit to glomerulus

#Oncotic pressure is approximated as varying linearly along the glomerulus. Oncotic pressure in the Bowman's space is zero

#Thus the average pressure difference is the average of the entrance and exit oncotic pressure

#We do not consider filtration equilibrium

Oncotic\_pressure\_in = (1.629\*plasma\_protein\_concentration+0.2935\*(plasma\_protein\_concentration\*\*2));

SNRBF\_nl\_min = (1e6\*1000\*renal\_blood\_flow\_L\_min/number\_of\_functional\_glomeruli);

plasma\_protein\_concentration\_out = ((SNRBF\_nl\_min\*plasma\_protein\_concentration-SN\_albumin\_filtration\_rate)/(SNRBF\_nl\_min-SNGFR\_nL\_min));

Oncotic\_pressure\_out = ((1.629\*plasma\_protein\_concentration\_out+0.2935\*(plasma\_protein\_concentration\_out\*\*2)));

oncotic\_pressure\_avg = (Oncotic\_pressure\_in+Oncotic\_pressure\_out)/2;

### 2.10.3 Plasma sodium concentration and vasopressin secretion

##### 2.10.3.1 Plasma sodium concentration

Na\_concentration = (sodium\_amount / blood\_volume\_L);

IF\_Na\_concentration = (IF\_sodium\_amount/interstitial\_fluid\_volume);

sodium\_storate\_rate = (Q\_Na\_store\*((max\_stored\_sodium - stored\_sodium)/max\_stored\_sodium)\*(IF\_Na\_concentration - ref\_Na\_concentration));

##### 2.10.3.2 Control of vasopressin secretion

#A proportional-integral controller is used to ensure there is no steady state error in sodium concentration

#Relative gains of the P and I controller must be chosen carefully.

#In order to permit a steady-state error, the integral controller can be removed. But care should be given then in choosing the proportional gain

Na\_water\_controller = (Na\_controller\_gain\*(Kp\_VP\*(Na\_concentration - ref\_Na\_concentration)+Ki\_VP\*Na\_concentration\_error));

normalized\_vasopressin\_concentration = (1 + Na\_water\_controller);

vasopressin\_concentration = (nominal\_vasopressin\_conc \* normalized\_vasopressin\_concentration);

#Effect of vasopressin on water intake

water\_intake\_vasopressin\_int = (1-water\_intake\_vasopressin\_scale/2);

water\_intake = (water\_intake\_species\_scale\*(nom\_water\_intake/60/24)\*(water\_intake\_vasopressin\_int + water\_intake\_vasopressin\_scale/(1+np.exp((normalized\_vasopressin\_concentration\_delayed-1)/water\_intake\_vasopressin\_slope))));

daily\_water\_intake = (water\_intake \* 24 \* 60);

### 2.10.4 Tubular Flow and Reabsorption

##### 2.10.4.1 Length of tubular segments

L\_pt\_s1 = L\_pt\_s1\_nom\*(1+tubular\_length\_increase);

L\_pt\_s2 = L\_pt\_s2\_nom\*(1+tubular\_length\_increase);

L\_pt\_s3 = L\_pt\_s3\_nom\*(1+tubular\_length\_increase);

Dc\_pt = Dc\_pt\_nom\*(1+tubular\_diameter\_increase);

L\_pt = L\_pt\_s1+L\_pt\_s2 + L\_pt\_s3;

SN\_filtered\_Na\_load = ((SNGFR\_nL\_min / 1000 / 1000000)\*Na\_concentration);

filtered\_Na\_load = (SN\_filtered\_Na\_load\*number\_of\_functional\_tubules);

##### 2.10.4.2 Regulatory effects on reabsorption

##### 2.10.4.3 Pressure natriuresis effects

pressure\_natriuresis\_signal = max(0.001, 1+Kp\_PN\*(postglomerular\_pressure - RIHP0) +Ki\_PN\*postglomerular\_pressure\_error +Kd\_PN\*(postglomerular\_pressure - postglomerular\_pressure\_delayed));

pressure\_natriuresis\_PT\_int = (1 - pressure\_natriuresis\_PT\_scale/2);

pressure\_natriuresis\_PT\_effect = max(0.001,pressure\_natriuresis\_PT\_int + pressure\_natriuresis\_PT\_scale / (1 + np.exp(pressure\_natriuresis\_signal-1)));

pressure\_natriuresis\_LoH\_int = (1 - pressure\_natriuresis\_LoH\_scale/2);

pressure\_natriuresis\_LoH\_effect = max(0.001,pressure\_natriuresis\_LoH\_int + pressure\_natriuresis\_LoH\_scale / (1 + np.exp((postglomerular\_pressure\_delayed - RIHP0) / pressure\_natriuresis\_LoH\_slope)));

pressure\_natriuresis\_DCT\_magnitude = max(0,pressure\_natriuresis\_DCT\_scale );

pressure\_natriuresis\_DCT\_int = (1 - pressure\_natriuresis\_DCT\_magnitude/2);

pressure\_natriuresis\_DCT\_effect = max(0.001,pressure\_natriuresis\_DCT\_int + pressure\_natriuresis\_DCT\_magnitude /(1 + np.exp((postglomerular\_pressure\_delayed - RIHP0) / pressure\_natriuresis\_DCT\_slope)));

pressure\_natriuresis\_CD\_magnitude = max(0,pressure\_natriuresis\_CD\_scale \*(1+disease\_effects\_decreasing\_CD\_PN));

pressure\_natriuresis\_CD\_int = (1 - pressure\_natriuresis\_CD\_magnitude/2);

pressure\_natriuresis\_CD\_effect = max(0.001,pressure\_natriuresis\_CD\_int + pressure\_natriuresis\_CD\_magnitude / (1 + np.exp(pressure\_natriuresis\_signal-1)));

RBF\_CD\_int = (1 - RBF\_CD\_scale/2);

RBF\_CD\_effect = max(0.001, RBF\_CD\_int + RBF\_CD\_scale/(1+np.exp((renal\_blood\_flow\_L\_min - nom\_renal\_blood\_flow\_L\_min)/RBF\_CD\_slope)));

##### 2.10.4.4 AT1-bound AngII effect on PT reabsorption

AT1\_PT\_int = (1 - AT1\_PT\_scale/2);

AT1\_effect\_on\_PT = (AT1\_PT\_int + AT1\_PT\_scale/(1+np.exp(-(AT1\_bound\_AngII - nominal\_equilibrium\_AT1\_bound\_AngII)/AT1\_PT\_slope)));

##### 2.10.4.5 RSNA effect on PT and CD sodium reabsorption

rsna\_PT\_int = (1 - rsna\_PT\_scale/2);

rsna\_effect\_on\_PT = 1;

rsna\_CD\_int = (1 - rsna\_CD\_scale/2);

rsna\_effect\_on\_CD= (rsna\_CD\_int + rsna\_CD\_scale/(1+np.exp((1 - renal\_sympathetic\_nerve\_activity)/rsna\_CD\_slope)));

##### 2.10.4.6 Aldosterone effect on distal and collecting duct sodium reabsorption

aldosterone\_concentration = (normalized\_aldosterone\_level\* nominal\_aldosterone\_concentration);

Aldo\_MR\_normalised\_effect = (normalized\_aldosterone\_level\* (1 - pct\_target\_inhibition\_MRA));

aldo\_DCT\_int = (1 - aldo\_DCT\_scale/2);

aldo\_effect\_on\_DCT = (aldo\_DCT\_int + aldo\_DCT\_scale/(1+np.exp((1 - Aldo\_MR\_normalised\_effect)/aldo\_DCT\_slope)));

aldo\_CD\_int = (1 - aldo\_CD\_scale/2);

aldo\_effect\_on\_CD= (aldo\_CD\_int + aldo\_CD\_scale/(1+np.exp((1 - Aldo\_MR\_normalised\_effect)/aldo\_CD\_slope)));

##### 2.10.4.7 ANP effect on collecting duct sodium reabsorption

anp\_CD\_int = (1 - anp\_CD\_scale/2);

anp\_effect\_on\_CD= (anp\_CD\_int + anp\_CD\_scale/(1+np.exp((1 - normalized\_ANP)/anp\_CD\_slope)));

##### 2.10.4.8 Effect of SGLT2/NHE3 coupling

NHE3inhib = Anhe3\*RUGE\_delayed;

pt\_multiplier = (AT1\_effect\_on\_PT \* rsna\_effect\_on\_PT \*pressure\_natriuresis\_PT\_effect\*(1-NHE3inhib));

e\_pt\_sodreab = min(1,nominal\_pt\_na\_reabsorption\_nonSGLT \* pt\_multiplier);

e\_dct\_sodreab = min(1,nominal\_dt\_na\_reabsorption \* aldo\_effect\_on\_DCT\*pressure\_natriuresis\_DCT\_effect \*HCTZ\_effect\_on\_DT\_Na\_reabs);

cd\_multiplier = (aldo\_effect\_on\_CD\*rsna\_effect\_on\_CD\*pressure\_natriuresis\_CD\_effect\*RBF\_CD\_effect);

e\_cd\_sodreab = min(0.9999,nominal\_cd\_na\_reabsorption\*cd\_multiplier\*anp\_effect\_on\_CD);

### 2.10.5 Proximal Tubule Reabsorption

##### 2.10.5.1 Glucose Filtration and reabsorption in PT

#Assume glucose reabsorption depends only on availability of SGLT1/2

#Assume constant amount of reabsorption per unit length through SGLT2 in convoluted PT

#Assume constant amount of reabsorption per unit length through SGLT1 in straight/recta PT

#Chosen so that UGE becomes non-zero for plasma\_glucose concentration ~8.5 mmol/l

glucose\_reabs\_per\_unit\_length\_s1 = (nom\_glucose\_reabs\_per\_unit\_length\_s1\*SGLT2\_inhibition\_delayed\*(1+RTg\_compensation));

glucose\_reabs\_per\_unit\_length\_s2 = (nom\_glucose\_reabs\_per\_unit\_length\_s2\*SGLT2\_inhibition\_delayed\*(1+RTg\_compensation));

glucose\_reabs\_per\_unit\_length\_s3 = (nom\_glucose\_reabs\_per\_unit\_length\_s3\*(1+RTg\_compensation)\*SGLT1\_inhibition);

SN\_filtered\_glucose\_load = glucose\_concentration\*SNGFR\_nL\_min / 1000 / 1000000; #mmol/min

glucose\_pt\_out\_s1 = max(0,SN\_filtered\_glucose\_load-glucose\_reabs\_per\_unit\_length\_s1\*L\_pt\_s1); #mmol/min

glucose\_pt\_out\_s2 = max(0,glucose\_pt\_out\_s1-glucose\_reabs\_per\_unit\_length\_s2\*L\_pt\_s2); #mmol/min

glucose\_pt\_out\_s3 = max(0,glucose\_pt\_out\_s2-glucose\_reabs\_per\_unit\_length\_s3\*L\_pt\_s3); #mmol/min

RUGE = glucose\_pt\_out\_s3\*number\_of\_functional\_tubules\*180; #RUGE in mg/min

excess\_glucose\_increasing\_RTg = ((maximal\_RTg\_increase - RTg\_compensation) \* max(RUGE,0) / (T\_glucose\_RTg/C\_renal\_CV\_timescale));

osmotic\_natriuresis\_effect\_pt = 1-min(1,RUGE \*glucose\_natriuresis\_effect\_pt);

osmotic\_natriuresis\_effect\_cd = 1-min(1,RUGE \*glucose\_natriuresis\_effect\_cd);

osmotic\_diuresis\_effect\_pt = 1-min(1,RUGE \*glucose\_diuresis\_effect\_pt);

osmotic\_diuresis\_effect\_cd = 1-min(1,RUGE \*glucose\_diuresis\_effect\_cd);

##### 2.10.5.2 PT Sodium filtration and reabsorption

# Sodium reabsorbed 1:1 with glucose in S1 and S2

# Sodium reabsorbed 2:1 with glucose in S3

# Assume for non-SGLT reabsorption, sodium reabsorbed at a constant RATE along the tubule

# (represents glomerulotubular balance)

SN\_filtered\_Na\_load = (SNGFR\_nL\_min / 1000 / 1000000)\*Na\_concentration; #mmol/min

SGTL2\_Na\_reabs\_mmol\_s1 = SN\_filtered\_glucose\_load- glucose\_pt\_out\_s1; #mmol/min

SGTL2\_Na\_reabs\_mmol\_s2 = glucose\_pt\_out\_s1- glucose\_pt\_out\_s2; #mmol/min

SGTL1\_Na\_reabs\_mmol = 2\*(glucose\_pt\_out\_s2-glucose\_pt\_out\_s3); #mmol/min

total\_SGLT\_Na\_reabs = SGTL2\_Na\_reabs\_mmol\_s1 + SGTL2\_Na\_reabs\_mmol\_s2 + SGTL1\_Na\_reabs\_mmol; #mmol/min

Na\_reabs\_per\_unit\_length = -np.log(1-e\_pt\_sodreab)/ (L\_pt\_s1+L\_pt\_s2+L\_pt\_s3); #non-SGLT2 reabs #mmol/min

Na\_pt\_s1\_reabs = min(max\_s1\_Na\_reabs, SN\_filtered\_Na\_load\* (1-np.exp(-Na\_reabs\_per\_unit\_length\*L\_pt\_s1)));

Na\_pt\_out\_s1 = (SN\_filtered\_Na\_load - Na\_pt\_s1\_reabs - SGTL2\_Na\_reabs\_mmol\_s1) ;

Na\_pt\_s2\_reabs = min(max\_s2\_Na\_reabs, Na\_pt\_out\_s1\*(1-np.exp(-Na\_reabs\_per\_unit\_length\*L\_pt\_s2)));

Na\_pt\_out\_s2 = (Na\_pt\_out\_s1 - Na\_pt\_s2\_reabs - SGTL2\_Na\_reabs\_mmol\_s2);

Na\_pt\_s3\_reabs = min(max\_s3\_Na\_reabs, Na\_pt\_out\_s2\*(1-np.exp(-Na\_reabs\_per\_unit\_length\*L\_pt\_s3)));

Na\_pt\_out\_s3 = (Na\_pt\_out\_s2 - Na\_pt\_s3\_reabs - SGTL1\_Na\_reabs\_mmol);

PT\_Na\_reabs\_fraction = (1-Na\_pt\_out\_s3/SN\_filtered\_Na\_load);

##### 2.10.5.3 PT Urea filtration and reabsorption

SN\_filtered\_urea\_load = (SNGFR\_nL\_min / 1000 / 1000000)\*plasma\_urea;

urea\_out\_s1 = (SN\_filtered\_urea\_load - urea\_permeability\_PT\*(SN\_filtered\_urea\_load/(0.5\*((SNGFR\_nL\_min / 1000 / 1000000)+water\_out\_s1\_delayed))-plasma\_urea)\*water\_out\_s1\_delayed); #For now, assuming only reabsorbed at the end

urea\_out\_s2 = (urea\_out\_s1 - urea\_permeability\_PT\*(urea\_out\_s1/(0.5\*(water\_out\_s1\_delayed+water\_out\_s2\_delayed))-plasma\_urea)\*water\_out\_s2\_delayed); #For now, assuming only reabsorbed at the end

urea\_out\_s3 = (urea\_out\_s2 - urea\_permeability\_PT\*(urea\_out\_s2/(0.5\*(water\_out\_s2\_delayed+water\_out\_s3\_delayed))-plasma\_urea)\*water\_out\_s3\_delayed); #For now, assuming only reabsorbed at the end

urea\_reabsorption\_fraction = (1-urea\_out\_s3/SN\_filtered\_urea\_load);

##### 2.10.5.4 PT Water Reabsorption

osmoles\_out\_s1 = 2\*Na\_pt\_out\_s1 + glucose\_pt\_out\_s1 + urea\_out\_s1;

water\_out\_s1 = ((((SNGFR\_nL\_min / 1000 / 1000000)/(2\*SN\_filtered\_Na\_load+SN\_filtered\_glucose\_load+ SN\_filtered\_urea\_load)))\*osmoles\_out\_s1);

osmoles\_out\_s2 = (2\*Na\_pt\_out\_s2 + glucose\_pt\_out\_s2 + urea\_out\_s2);

water\_out\_s2 = ((water\_out\_s1/osmoles\_out\_s1)\*osmoles\_out\_s2);

osmoles\_out\_s3 = (2\*Na\_pt\_out\_s3 + glucose\_pt\_out\_s3 + urea\_out\_s3);

water\_out\_s3 = ((water\_out\_s2/osmoles\_out\_s2)\* osmoles\_out\_s3);

PT\_water\_reabs\_fraction = (1-water\_out\_s3/(SNGFR\_nL\_min / 1000 / 1000000));

##### 2.10.5.5 Concentrations out of PT

Na\_concentration\_out\_s1 = Na\_pt\_out\_s1/water\_out\_s1;

Na\_concentration\_out\_s2 = Na\_pt\_out\_s2/water\_out\_s2;

Na\_concentration\_out\_s3 = Na\_pt\_out\_s3/water\_out\_s3;

glucose\_concentration\_out\_s1 = glucose\_pt\_out\_s1/water\_out\_s1;

glucose\_concentration\_out\_s2 = glucose\_pt\_out\_s2/water\_out\_s2;

glucose\_concentration\_out\_s3 = glucose\_pt\_out\_s3/water\_out\_s3;

urea\_concentration\_out\_s1 = urea\_out\_s1/water\_out\_s1;

urea\_concentration\_out\_s2 = urea\_out\_s2/water\_out\_s2;

urea\_concentration\_out\_s3 = urea\_out\_s3/water\_out\_s3;

osmolality\_out\_s1 = osmoles\_out\_s1/water\_out\_s1;

osmolality\_out\_s2 = osmoles\_out\_s2/water\_out\_s2;

osmolality\_out\_s3 = osmoles\_out\_s3/water\_out\_s3;

PT\_Na\_outflow = Na\_pt\_out\_s3\*number\_of\_functional\_tubules;

#Tubular sodium reabsorption per unit SA as the driver of tubular hypertrophy

PT\_Na\_reab\_perUnitSA = (SN\_filtered\_Na\_load\*e\_pt\_sodreab/(3.14\*Dc\_pt\*(L\_pt\_s1+L\_pt\_s2+L\_pt\_s3)));

normalized\_PT\_reabsorption\_density = PT\_Na\_reab\_perUnitSA/PT\_Na\_reab\_perUnitSA\_0;

PT\_Na\_reabs\_effect\_increasing\_tubular\_length = 0;#(maximal\_tubule\_length\_increase - tubular\_length\_increase) \* max(normalized\_PT\_reabsorption\_density - 1,0) / (T\_PT\_Na\_reabs\_PT\_length/C\_renal\_CV\_timescale);

PT\_Na\_reabs\_effect\_increasing\_tubular\_diameter = 0;#(maximal\_tubule\_diameter\_increase - tubular\_diameter\_increase) \* max(normalized\_PT\_reabsorption\_density - 1,0) / (T\_PT\_Na\_reabs\_PT\_diameter/C\_renal\_CV\_timescale);

### 2.10.6 Loop of Henle

##### 2.10.6.1 Descending Loop of Henle

water\_in\_DescLoH = water\_out\_s3; # L/min

Na\_in\_DescLoH = Na\_pt\_out\_s3;

urea\_in\_DescLoH = urea\_out\_s3;

glucose\_in\_DescLoH = glucose\_pt\_out\_s3;

osmoles\_in\_DescLoH = osmoles\_out\_s3;

Na\_concentration\_in\_DescLoH = Na\_concentration\_out\_s3;

Urea\_concentration\_in\_DescLoH = urea\_concentration\_out\_s3;

glucose\_concentration\_in\_DescLoH = glucose\_concentration\_out\_s3;

osmolality\_in\_DescLoH = osmoles\_out\_s3/water\_out\_s3;

#No solute reabsorption in descending limb

Na\_out\_DescLoH = Na\_in\_DescLoH;

urea\_out\_DescLoH = urea\_in\_DescLoH;

glucose\_out\_DescLoH = glucose\_in\_DescLoH;

osmoles\_out\_DescLoH = osmoles\_in\_DescLoH;

#For LoH, baseline osmoles reabsorbed per unit length is calculated from nominal fractional sodium reabsorption (see baseline parameters file)

#The rate of reabsorption per unit length may be flow-dependent, and may be modulated by tubular pressure-natriuresis

# If LoH\_flow\_dependence = 0, then no flow dependence.

deltaLoH\_NaFlow = min(max\_deltaLoH\_reabs,LoH\_flow\_dependence\*(Na\_out\_DescLoH-nom\_Na\_in\_AscLoH));

AscLoH\_Reab\_Rate =(2\*nominal\_loh\_na\_reabsorption\*(nom\_Na\_in\_AscLoH+deltaLoH\_NaFlow)\*loop\_diuretic\_effect)/L\_lh\_des; #osmoles reabsorbed per unit length per minute. factor of 2 because osmoles = 2

effective\_AscLoH\_Reab\_Rate =AscLoH\_Reab\_Rate\*pressure\_natriuresis\_LoH\_effect; #osmoles reabsorbed per unit length per minute. factor of 2 because osmoles = 2\*Na

#Min function necesssary to ensure that the LoH does not reabsorb more Na than is delivered to it

osmolality\_out\_DescLoH = osmolality\_in\_DescLoH\*np.exp(min(effective\_AscLoH\_Reab\_Rate\*L\_lh\_des,2\*Na\_in\_DescLoH)/(water\_in\_DescLoH\*osmolality\_in\_DescLoH));

water\_out\_DescLoH = water\_in\_DescLoH\*osmolality\_in\_DescLoH/osmolality\_out\_DescLoH;

Na\_concentration\_out\_DescLoH = Na\_out\_DescLoH/water\_out\_DescLoH;

glucose\_concentration\_out\_DescLoH = glucose\_out\_DescLoH/water\_out\_DescLoH;

urea\_concentration\_out\_DescLoH = urea\_out\_DescLoH/water\_out\_DescLoH;

##### 2.10.6.2 Ascending Loop of Henle

Na\_in\_AscLoH = Na\_out\_DescLoH;

urea\_in\_AscLoH\_before\_secretion = urea\_out\_DescLoH;

glucose\_in\_AscLoH = glucose\_out\_DescLoH;

osmoles\_in\_AscLoH\_before\_secretion = osmoles\_out\_DescLoH;

water\_in\_AscLoH = water\_out\_DescLoH;

#Urea Secretion --> Assume all urea reabsorbed and secreted only at tip of loop

urea\_in\_AscLoH = urea\_in\_AscLoH\_before\_secretion + reabsorbed\_urea\_cd\_delayed;

urea\_concentration\_in\_AscLoH = urea\_in\_AscLoH/water\_out\_DescLoH;

osmoles\_in\_AscLoH = osmoles\_in\_AscLoH\_before\_secretion + reabsorbed\_urea\_cd\_delayed;

osmolality\_in\_AscLoH = osmoles\_in\_AscLoH/water\_in\_AscLoH;

#Osmolality descreased due to sodium reabsorption along ascending loop

#min funNa\_in\_AscLoHction necessary so that LoH doesn't reabsorb more sodium than is delivered to it

osmolality\_out\_AscLoH = osmolality\_in\_AscLoH - min(L\_lh\_des\*effective\_AscLoH\_Reab\_Rate, 2\*Na\_in\_DescLoH)\*(np.exp(min(L\_lh\_des\*effective\_AscLoH\_Reab\_Rate, 2\*Na\_in\_DescLoH)/(water\_in\_DescLoH\*osmolality\_in\_DescLoH))/water\_in\_DescLoH);

osmoles\_reabsorbed\_AscLoH = (osmolality\_in\_AscLoH - osmolality\_out\_AscLoH)\*water\_in\_AscLoH;

Na\_reabsorbed\_AscLoH = osmoles\_reabsorbed\_AscLoH/2;

Na\_out\_AscLoH = max(0,Na\_in\_AscLoH - Na\_reabsorbed\_AscLoH);

#Water, glucose, and urea are not reabsorbed along the ascending limb

urea\_out\_AscLoH = urea\_in\_AscLoH; #urea secretion accounted for above

glucose\_out\_AscLoH = glucose\_in\_AscLoH;

water\_out\_AscLoH = water\_in\_AscLoH;

osmoles\_out\_AscLoH = osmolality\_out\_AscLoH\*water\_out\_AscLoH;

Na\_concentration\_out\_AscLoH = Na\_out\_AscLoH/water\_out\_AscLoH;

glucose\_concentration\_out\_AscLoH = glucose\_out\_AscLoH/water\_out\_AscLoH;

urea\_concentration\_out\_AscLoH = urea\_out\_AscLoH/water\_out\_AscLoH;

LoH\_reabs\_fraction = 1-Na\_out\_AscLoH/Na\_in\_AscLoH;

SN\_macula\_densa\_Na\_flow = Na\_out\_AscLoH;

MD\_Na\_concentration = Na\_concentration\_out\_AscLoH;

TGF0\_tubulo\_glomerular\_feedback = 1 - S\_tubulo\_glomerular\_feedback/2;

tubulo\_glomerular\_feedback\_signal = (TGF0\_tubulo\_glomerular\_feedback + S\_tubulo\_glomerular\_feedback / (1 + np.exp((MD\_Na\_concentration\_setpoint - MD\_Na\_concentration)/ F\_md\_scale\_tubulo\_glomerular\_feedback)));

### 2.10.7 Distal Convoluted Tubule

water\_in\_DCT = water\_out\_AscLoH;

Na\_in\_DCT = Na\_out\_AscLoH;

urea\_in\_DCT = urea\_out\_AscLoH;

glucose\_in\_DCT = glucose\_out\_AscLoH;

osmoles\_in\_DCT = osmoles\_out\_AscLoH;

Na\_concentration\_in\_DCT = Na\_concentration\_out\_AscLoH;

urea\_concentration\_in\_DCT = urea\_concentration\_out\_AscLoH;

glucose\_concentration\_in\_DCT = glucose\_concentration\_out\_AscLoH;

osmolality\_in\_DCT = osmolality\_out\_AscLoH;

#Assume only sodium reabsorbed along DCT, no water, glucose, or urea reabsorption

urea\_out\_DCT = urea\_in\_DCT;

glucose\_out\_DCT = glucose\_in\_DCT;

water\_out\_DCT = water\_in\_DCT;

urea\_concentration\_out\_DCT = urea\_out\_DCT/water\_out\_DCT;

glucose\_concentration\_out\_DCT = glucose\_out\_DCT/water\_out\_DCT;

#Assume sodium reabsorption at a constant fraction of delivery

R\_dct = -np.log(1-e\_dct\_sodreab)/L\_dct;

Na\_out\_DCT = Na\_in\_DCT\*np.exp(-R\_dct\*L\_dct);

Na\_concentration\_out\_DCT = Na\_out\_DCT/water\_out\_DCT;

osmolality\_out\_DCT = 2\*Na\_concentration\_out\_DCT + glucose\_concentration\_out\_DescLoH + urea\_concentration\_in\_AscLoH;

osmoles\_out\_DCT = osmolality\_out\_DCT\*water\_out\_DCT;

# # print("Na\_in\_DCT",Na\_in\_DCT)

DCT\_Na\_reabs\_fraction = 1-Na\_out\_DCT/Na\_in\_DCT;

### 2.10.8 Collecting Duct

water\_in\_CD = water\_out\_DCT;

Na\_in\_CD = Na\_out\_DCT;

urea\_in\_CD = urea\_out\_DCT;

glucose\_in\_CD = glucose\_out\_DCT;

osmoles\_in\_CD = osmoles\_out\_DCT;

#Use this to turn off osmotic diuresis effect

#osmoles\_in\_CD = osmoles\_out\_DCT - glucose\_in\_CD;

osmolality\_in\_CD = osmoles\_in\_CD/water\_in\_CD;

Na\_concentration\_in\_CD = Na\_concentration\_out\_DCT;

urea\_concentration\_in\_CD = urea\_concentration\_out\_DCT;

glucose\_concentration\_in\_CD = glucose\_concentration\_out\_DCT;

osmotic\_diuresis\_effect\_cd = 1-min(1,RUGE \*glucose\_diuresis\_effect\_cd);

####Assume sodium reabsorbed, then water follows

#### Then urea reabsorbed at end

#### Then additional water reabsorbed following urea reabsorption

#Assume sodium reabsorbed at fractional rate eta

e\_cd\_sodreab\_adj = e\_cd\_sodreab\*osmotic\_natriuresis\_effect\_cd;

R\_cd = -np.log(1-e\_cd\_sodreab\_adj)/L\_cd;

Na\_reabsorbed\_CD = min(Na\_in\_CD\*(1-np.exp(-R\_cd\*L\_cd)),CD\_Na\_reabs\_threshold);

Na\_out\_CD = Na\_in\_CD-Na\_reabsorbed\_CD;

CD\_Na\_reabs\_fraction = 1-Na\_out\_CD/Na\_in\_CD;

ADH\_water\_permeability\_old = min(0.99999,max(0,nom\_ADH\_water\_permeability\*normalized\_vasopressin\_concentration));

ADH\_water\_permeability = normalized\_vasopressin\_concentration/(0.15+normalized\_vasopressin\_concentration);

#Water reabsorption follows gradient but is regulated by ADH

osmoles\_out\_CD = osmoles\_in\_CD-2\*(Na\_in\_CD - Na\_out\_CD);

osmolality\_out\_CD\_before\_osmotic\_reabsorption = osmoles\_out\_CD/water\_in\_CD;

water\_reabsorbed\_CD = ADH\_water\_permeability\*osmotic\_diuresis\_effect\_cd\*water\_in\_CD\*(1-osmolality\_out\_CD\_before\_osmotic\_reabsorption/osmolality\_out\_DescLoH);

water\_out\_CD = water\_in\_CD-water\_reabsorbed\_CD;

osmolality\_out\_CD\_after\_osmotic\_reabsorption = osmoles\_out\_CD/water\_out\_CD;

glucose\_concentration\_after\_urea\_reabsorption = glucose\_in\_CD/water\_out\_CD;

urine\_flow\_rate = water\_out\_CD\*number\_of\_functional\_tubules;

daily\_urine\_flow = (urine\_flow\_rate \* 60 \* 24);

Na\_excretion\_via\_urine = Na\_out\_CD\*number\_of\_functional\_tubules;

Na\_balance = Na\_intake\_rate - Na\_excretion\_via\_urine;

water\_balance = daily\_water\_intake - daily\_urine\_flow;

FENA = Na\_excretion\_via\_urine/filtered\_Na\_load;

PT\_fractional\_glucose\_reabs = (SN\_filtered\_glucose\_load - glucose\_pt\_out\_s3)/SN\_filtered\_glucose\_load;

PT\_fractional\_Na\_reabs = (SN\_filtered\_Na\_load - Na\_pt\_out\_s3)/SN\_filtered\_Na\_load;

PT\_fractional\_urea\_reabs = ( SN\_filtered\_urea\_load - urea\_out\_s3)/SN\_filtered\_urea\_load;

PT\_fractional\_water\_reabs = ((SNGFR\_nL\_min / 1000 / 1000000) - water\_out\_s3)/(SNGFR\_nL\_min / 1000 / 1000000);

LoH\_fractional\_Na\_reabs = (Na\_in\_DescLoH - Na\_out\_AscLoH)/Na\_in\_DescLoH;

LoH\_fractional\_urea\_reabs = (urea\_in\_DescLoH-urea\_out\_AscLoH)/urea\_in\_DescLoH;

LoH\_fractional\_water\_reabs = (water\_in\_DescLoH - water\_out\_AscLoH)/water\_in\_DescLoH;

DCT\_fractional\_Na\_reabs = (Na\_in\_DCT - Na\_out\_DCT)/Na\_in\_DCT;

CD\_fractional\_Na\_reabs = (Na\_in\_CD - Na\_out\_CD)/Na\_in\_CD;

CD\_OM\_fractional\_water\_reabs = (water\_in\_CD - water\_out\_CD)/water\_in\_CD;

### 2.10.9 Renal Interstitial Hydrostatic pressure

######RIHP can be approximated from Starling's equation for the peritubular capillaries

### Flow out of the capillary = Kf\_peritubular\*(Peritubular pressure - RIHP - oncotic pressure difference)

### Assume that any fluid reabsorbed reenters the capillary.

### Therefore, RIHP = Peritubular Pressure - (oncotic pressure in peritubular capillary - interstitial oncotic pressure) + tubular reabsorption/KF

#Peritubular pressure is assumed to equal postglomerular pressure

#Oncotic pressure at the entrance to the peritubular circulation equals oncotic pressure at the exit of the glomerular

Oncotic\_pressure\_peritubular\_in = Oncotic\_pressure\_out;

plasma\_protein\_concentration\_peritubular\_out = (SNRBF\_nl\_min)\*plasma\_protein\_concentration/(SNRBF\_nl\_min-urine\_flow\_rate\*1e6\*1000/number\_of\_functional\_glomeruli);

Oncotic\_pressure\_peritubular\_out = 1.629\*plasma\_protein\_concentration\_peritubular\_out+0.2935\*(plasma\_protein\_concentration\_peritubular\_out\*\*2);

oncotic\_pressure\_peritubular\_avg = (Oncotic\_pressure\_peritubular\_in+Oncotic\_pressure\_peritubular\_out)/2;

#The amount of fluid reabsorbed is the difference between the amount filtered and the amount excreted

tubular\_reabsorption = GFR\_ml\_min/1000 - urine\_flow\_rate;

#Renal Interstitial Hydrostatic Pressure

RIHP = postglomerular\_pressure - (oncotic\_pressure\_peritubular\_avg - interstitial\_oncotic\_pressure) + tubular\_reabsorption/nom\_peritubular\_cap\_Kf;

### 2.10.10 Tubular Pressure

##### 2.10.10.1 Pressure convert

#####See written documentation for derivation of the equations below

#flow rates expressed in m3/min, rather than L/min

mmHg\_Nperm2\_conv = 133.32;

Pc\_pt\_s1 = Pc\_pt\_s1\_mmHg\*mmHg\_Nperm2\_conv;

Pc\_pt\_s2 = Pc\_pt\_s2\_mmHg\*mmHg\_Nperm2\_conv;

Pc\_pt\_s3 = Pc\_pt\_s3\_mmHg\*mmHg\_Nperm2\_conv;

Pc\_lh\_des = Pc\_lh\_des\_mmHg\*mmHg\_Nperm2\_conv;

Pc\_lh\_asc = Pc\_lh\_asc\_mmHg\*mmHg\_Nperm2\_conv;

Pc\_dt = Pc\_dt\_mmHg\*mmHg\_Nperm2\_conv;

Pc\_cd = Pc\_cd\_mmHg\*mmHg\_Nperm2\_conv;

P\_interstitial = 4.9\*mmHg\_Nperm2\_conv;

pi=3.14;

##### 2.10.10.2 CD

B1 = (4\*tubular\_compliance+1)\*128\*gamma/pi;

mean\_cd\_water\_flow = (water\_in\_CD-water\_out\_CD)/2;

B2\_cd = (Pc\_cd\*\*(4\*tubular\_compliance))/(Dc\_cd\*\*4);

P\_in\_cd = (0\*\*(4\*tubular\_compliance+1)+B1\*B2\_cd\*(mean\_cd\_water\_flow/1e3)\*L\_cd)\*\*(1/(4\*tubular\_compliance+1));

P\_in\_cd\_mmHg = (P\_in\_cd+P\_interstitial)/mmHg\_Nperm2\_conv;

##### 2.10.10.3 DCT

B2\_dt = (Pc\_dt\*\*(4\*tubular\_compliance))/(Dc\_dt\*\*4);

P\_in\_dt = (P\_in\_cd\*\*(4\*tubular\_compliance+1)+B1\*B2\_dt\*(water\_in\_DCT/1e3)\*L\_dct)\*\*(1/(4\*tubular\_compliance+1));

P\_in\_dt\_mmHg = (P\_in\_dt+P\_interstitial)/mmHg\_Nperm2\_conv;

##### 2.10.10.4 Asc LoH

B2\_lh\_asc = (Pc\_lh\_asc\*\*(4\*tubular\_compliance))/(Dc\_lh\*\*4);

P\_in\_lh\_asc = (P\_in\_dt\*\*(4\*tubular\_compliance+1)+B1\*B2\_lh\_asc\*(water\_in\_AscLoH/1e3)\*L\_lh\_asc)\*\*(1/(4\*tubular\_compliance+1));

P\_in\_lh\_asc\_mmHg = (P\_in\_lh\_asc+P\_interstitial)/mmHg\_Nperm2\_conv;

##### 2.10.10.5 Desc LoH

A\_lh\_des = effective\_AscLoH\_Reab\_Rate/(water\_in\_DescLoH\*osmolality\_in\_DescLoH);

B2\_lh\_des = (Pc\_lh\_des\*\*(4\*tubular\_compliance))\*(water\_in\_DescLoH/1e3)/((Dc\_lh\*\*4)\*A\_lh\_des);

P\_in\_lh\_des = (P\_in\_lh\_asc\*\*(4\*tubular\_compliance+1)+B1\*B2\_lh\_des\*(1-np.exp(-A\_lh\_des\*L\_lh\_des)))\*\*(1/(4\*tubular\_compliance+1));

P\_in\_lh\_des\_mmHg = (P\_in\_lh\_des+P\_interstitial)/mmHg\_Nperm2\_conv;

##### 2.10.10.6 PT

#Treat urea as if reabsorbed linearly along whole length of PT

Rurea = (SN\_filtered\_urea\_load - urea\_out\_s3)/(L\_pt\_s1+L\_pt\_s2+L\_pt\_s3);

urea\_in\_s2 = SN\_filtered\_urea\_load - Rurea\*L\_pt\_s1;

urea\_in\_s3 = SN\_filtered\_urea\_load - Rurea\*(L\_pt\_s1+L\_pt\_s2);

A\_na = Na\_reabs\_per\_unit\_length;

flow\_integral\_s3 = 2\*(Na\_pt\_out\_s2/A\_na)\*(1-np.exp(-A\_na\*L\_pt\_s3)) - (3/2)\*glucose\_pt\_out\_s2\*L\_pt\_s3\*\*2 + urea\_in\_s3\*L\_pt\_s3 - (1/2)\*Rurea\*(L\_pt\_s3\*\*2);

flow\_integral\_s2 = 2\*(Na\_pt\_out\_s1/A\_na)\*(1-np.exp(-A\_na\*L\_pt\_s2)) - (1/2)\*glucose\_pt\_out\_s1\*L\_pt\_s2\*\*2 + urea\_in\_s2\*L\_pt\_s2 - (1/2)\*Rurea\*(L\_pt\_s2\*\*2);

flow\_integral\_s1 = 2\*(SN\_filtered\_Na\_load/A\_na)\*(1-np.exp(-A\_na\*L\_pt\_s1)) - (1/2)\*SN\_filtered\_glucose\_load\*L\_pt\_s1\*\*2 + SN\_filtered\_urea\_load\*L\_pt\_s1 - (1/2)\*Rurea\*(L\_pt\_s1\*\*2);

#S3 segment

B2\_pt\_s3 = (Pc\_pt\_s3\*\*(4\*tubular\_compliance))/(Dc\_pt\*\*4);

B3\_pt\_s3 = (water\_out\_s2/1e3)/osmoles\_out\_s2;

P\_in\_pt\_s3= (P\_in\_lh\_des\*\*(4\*tubular\_compliance+1)+B1\*B2\_pt\_s3\*B3\_pt\_s3\*flow\_integral\_s3)\*\*(1/(4\*tubular\_compliance+1));

P\_in\_pt\_s3\_mmHg = (P\_in\_pt\_s3+P\_interstitial)/mmHg\_Nperm2\_conv;

B2\_pt\_s2 = (Pc\_pt\_s3\*\*(4\*tubular\_compliance))/(Dc\_pt\*\*4);

B3\_pt\_s2 = (water\_out\_s1/1e3)/osmoles\_out\_s1;

P\_in\_pt\_s2= (P\_in\_pt\_s3\*\*(4\*tubular\_compliance+1)+B1\*B2\_pt\_s2\*B3\_pt\_s2\*flow\_integral\_s2)\*\*(1/(4\*tubular\_compliance+1));

P\_in\_pt\_s2\_mmHg = (P\_in\_pt\_s2+P\_interstitial)/mmHg\_Nperm2\_conv;

B2\_pt\_s1 = (Pc\_pt\_s1\*\*(4\*tubular\_compliance))/(Dc\_pt\*\*4);

B3\_pt\_s1 = (SNGFR\_nL\_min / 1e12)/(2\*SN\_filtered\_Na\_load+SN\_filtered\_glucose\_load+ SN\_filtered\_urea\_load);

P\_in\_pt\_s1= (P\_in\_pt\_s2\*\*(4\*tubular\_compliance+1)+B1\*B2\_pt\_s1\*B3\_pt\_s1\*flow\_integral\_s1)\*\*(1/(4\*tubular\_compliance+1));

P\_in\_pt\_s1\_mmHg = (P\_in\_pt\_s1+P\_interstitial)/mmHg\_Nperm2\_conv;

### 2.10.11 Aldosterone and Renin Secretion

##### 2.10.11.1 Aldosterone is secreted in response to AT1-bound AngII and changes in potassium or sodium concentration

AT1\_aldo\_int = 1 - AT1\_aldo\_slope\*nominal\_equilibrium\_AT1\_bound\_AngII;

AngII\_effect\_on\_aldo = AT1\_aldo\_int + AT1\_aldo\_slope\*AT1\_bound\_AngII;

N\_als = (K\_Na\_ratio\_effect\_on\_aldo \* AngII\_effect\_on\_aldo );

##### 2.10.11.2 Renin is secreted in response to decreases in AT1-bound AngII, decreases in MD sodium flow, or increases in RSNA

#RSNA effect on renin secretion

rsna\_renin\_intercept = 1-rsna\_renin\_slope;

rsna\_effect\_on\_renin\_secretion = rsna\_renin\_slope \* renal\_sympathetic\_nerve\_activity + rsna\_renin\_intercept;

#Macula Densa Sodium flow effect on renin secretion

#This relationship is known to be non-linear, and md\_renin\_tau can be calibrated based on data on changes in renin as a functoin of sodium intake

# using mpnp.exp instead of np.exp

md\_effect\_on\_renin\_secretion = md\_renin\_A\*np.exp(-md\_renin\_tau\*(SN\_macula\_densa\_Na\_flow\_delayed\*baseline\_nephrons - nom\_LoH\_Na\_outflow));

#AT1-bound AngII feedback on renin secretion

AT1\_bound\_AngII\_effect\_on\_PRA = (10\*\*(AT1\_PRC\_slope \* np.log10(AT1\_bound\_AngII / nominal\_equilibrium\_AT1\_bound\_AngII) + AT1\_PRC\_yint));

#Aldo effect on renin secretion

aldo\_renin\_intercept = 1-aldo\_renin\_slope;

aldo\_effect\_on\_renin\_secretion = aldo\_renin\_intercept + aldo\_renin\_slope\*Aldo\_MR\_normalised\_effect;

#Plasma renin activity

plasma\_renin\_activity = concentration\_to\_renin\_activity\_conversion\_plasma\* plasma\_renin\_concentration\*(1-pct\_target\_inhibition\_DRI);

#Renin secretion

renin\_secretion\_rate = (np.log(2)/renin\_half\_life)\*nominal\_equilibrium\_PRC\*AT1\_bound\_AngII\_effect\_on\_PRA\*md\_effect\_on\_renin\_secretion\*HCTZ\_effect\_on\_renin\_secretion\*aldo\_effect\_on\_renin\_secretion\*(rsna\_effect\_on\_renin\_secretion\*(1-BB\_renin\_secretion\_effect\*BB\_signal));

#RAAS degradation rates

renin\_degradation\_rate = np.log(2)/renin\_half\_life;

AngI\_degradation\_rate = np.log(2)/AngI\_half\_life;

AngII\_degradation\_rate = np.log(2)/AngII\_half\_life;

AT1\_bound\_AngII\_degradation\_rate = np.log(2)/AT1\_bound\_AngII\_half\_life;

AT2\_bound\_AngII\_degradation\_rate = np.log(2)/AT2\_bound\_AngII\_half\_life;

#RAAS rate constants

ACE\_activity = nominal\_ACE\_activity\*(1 - pct\_target\_inhibition\_ACEi);

chymase\_activity = nominal\_chymase\_activity;

AT1\_receptor\_binding\_rate = nominal\_AT1\_receptor\_binding\_rate\*(1-pct\_target\_inhibition\_ARB\*ARB\_signal);

AT2\_receptor\_binding\_rate = nominal\_AT2\_receptor\_binding\_rate;

# 3. ODE

d\_venous\_volume\_dt = venous\_flow - tricuspid\_valve\_flow\_rate + C\_renal\_CV\_timescale\*(venous\_volume\_target - venous\_volume);

d\_LV\_volume\_dt = mitral\_valve\_flow\_rate - aortic\_valve\_flow\_rate;

d\_arterial\_volume\_dt = (aortic\_valve\_flow\_rate) - (systemic\_blood\_flow);

d\_peripheral\_circulation\_volume\_dt = systemic\_blood\_flow - venous\_flow;

d\_RV\_volume\_dt = (tricuspid\_valve\_flow\_rate) - (pulmonary\_valve\_flow\_rate);

d\_pulmonary\_arterial\_volume\_dt = pulmonary\_valve\_flow\_rate - pulmonary\_arterial\_blood\_flow;

d\_pulmonary\_venous\_volume\_dt = pulmonary\_arterial\_blood\_flow - mitral\_valve\_flow\_rate;

d\_aortic\_blood\_flow\_delayed\_dt = C\_cycle2 \* (aortic\_blood\_flow - aortic\_blood\_flow\_delayed);

d\_pulmonary\_blood\_flow\_delayed\_dt = C\_cycle2 \* (pulmonary\_blood\_flow - pulmonary\_blood\_flow\_delayed);

d\_change\_in\_myocyte\_length\_dt = kL\_HYPERTROPHY \* (LV\_EDS / LV\_passive\_stress\_along\_fiber\_threshhold - 1);

d\_change\_in\_myocyte\_diameter\_dt = kD\_HYPERTROPHY \* (LV\_active\_stress\_peak / LV\_active\_stress\_threshhold - 1);

d\_LV\_active\_stress\_peak\_dt = C\_cycle3 \*(LV\_active\_stress\_peak\_old - LV\_active\_stress\_peak);

d\_sim\_time\_dt =1;

d\_LV\_sarcomere\_length\_delayed\_dt = C\_cycle\* (LV\_sarcomere\_length - LV\_sarcomere\_length\_delayed);

d\_RV\_sarcomere\_length\_delayed\_dt = C\_cycle\* (RV\_sarcomere\_length - RV\_sarcomere\_length\_delayed);

d\_LV\_EDV\_dt = C\_cycle2 \* (LV\_EDV\_old - LV\_EDV);

d\_LV\_EDP\_dt = C\_cycle2 \*(LV\_EDP\_old - LV\_EDP);

d\_LV\_EDS\_dt = C\_cycle2 \*(LV\_EDS\_old - LV\_EDS);

d\_arterial\_pressure\_delayed\_dt = C\_cycle2 \* (arterial\_pressure - arterial\_pressure\_delayed);

d\_arterial\_pressure\_bigger\_delay\_dt = C\_cycle2 \* (arterial\_pressure\_delayed - arterial\_pressure\_bigger\_delay);

d\_systolic\_pressure\_dt = C\_cycle2 \* (systolic\_pressure\_old - systolic\_pressure);

d\_diastolic\_pressure\_dt = C\_cycle2 \* (diastolic\_pressure\_old - diastolic\_pressure);

d\_venous\_pressure\_delayed\_dt = C\_cycle2 \* (venous\_pressure - venous\_pressure\_delayed);

d\_venous\_pressure\_bigger\_delay\_dt = C\_cycle2 \* (venous\_pressure\_delayed - venous\_pressure\_bigger\_delay);

d\_systolic\_venous\_pressure\_dt = C\_cycle2 \* (systolic\_venous\_pressure\_old - systolic\_venous\_pressure);

d\_diastolic\_venous\_pressure\_dt = C\_cycle2 \* (diastolic\_venous\_pressure\_old - diastolic\_venous\_pressure);

d\_CO\_dt = C\_co\*(aortic\_valve\_flow\_rate\*60/L\_m3 - CO);

d\_CO\_delayed\_dt = C\_co\_delay\*(CO - CO\_delayed);

#RAAS Pathway

d\_AngI\_dt = plasma\_renin\_activity - (AngI) \* (chymase\_activity + ACE\_activity) - (AngI) \* AngI\_degradation\_rate;

d\_AngII\_dt = AngI \* (chymase\_activity + ACE\_activity) - AngII \* AngII\_degradation\_rate - AngII\*AT1\_receptor\_binding\_rate - AngII\* (AT2\_receptor\_binding\_rate);

d\_AT1\_bound\_AngII\_dt = AngII \* (AT1\_receptor\_binding\_rate) - AT1\_bound\_AngII\_degradation\_rate\*AT1\_bound\_AngII;

d\_AT2\_bound\_AngII\_dt = AngII \* (AT2\_receptor\_binding\_rate) - AT2\_bound\_AngII\_degradation\_rate\*AT2\_bound\_AngII;

d\_plasma\_renin\_concentration\_dt = renin\_secretion\_rate - plasma\_renin\_concentration \* renin\_degradation\_rate;

#Change in Interstitial fluid volume over time is determined by the different between water intake and urine outflow

d\_blood\_volume\_L\_dt = C\_renal\_CV\_timescale \*(water\_intake- urine\_flow\_rate + Q\_water\*(Na\_concentration - IF\_Na\_concentration));

d\_interstitial\_fluid\_volume\_dt = C\_renal\_CV\_timescale \*Q\_water\*(IF\_Na\_concentration - Na\_concentration);

#Change in total body sodium over time is determined by the different between sodium intake and excretion

d\_sodium\_amount\_dt = C\_renal\_CV\_timescale \* (Na\_intake\_rate - Na\_excretion\_via\_urine + Q\_Na\*(IF\_Na\_concentration - Na\_concentration));

d\_IF\_sodium\_amount\_dt = C\_renal\_CV\_timescale \*(Q\_Na\*(Na\_concentration - IF\_Na\_concentration) - sodium\_storate\_rate);

d\_stored\_sodium\_dt = C\_renal\_CV\_timescale \*sodium\_storate\_rate;

#These equations serve only to delay the input variable by one timestep. This allows the previous value of the input variable to be used in an equation that appears

#in the code before the input variable was defined

d\_tubulo\_glomerular\_feedback\_effect\_dt = C\_renal\_CV\_timescale\*(tubulo\_glomerular\_feedback\_signal-tubulo\_glomerular\_feedback\_effect);

d\_normalized\_aldosterone\_level\_dt = C\_renal\_CV\_timescale\*C\_aldo\_secretion \* (N\_als-normalized\_aldosterone\_level);

d\_preafferent\_pressure\_autoreg\_signal\_dt = C\_renal\_CV\_timescale\*100\*(preafferent\_pressure\_autoreg\_function - preafferent\_pressure\_autoreg\_signal);

d\_glomerular\_pressure\_autoreg\_signal\_dt = 0;#C\_glomerular\_pressure\_autoreg\_signal\*(glomerular\_pressure\_autoreg\_function - glomerular\_pressure\_autoreg\_signal);

#Error signals for PI controllers of cardiac output and sodium concentration

d\_CO\_error\_dt = C\_renal\_CV\_timescale\*C\_co\_error\*(CO\_delayed-CO\_nom);

d\_Na\_concentration\_error\_dt = C\_renal\_CV\_timescale\*C\_Na\_error\*(Na\_concentration - ref\_Na\_concentration);

#This equation allows a delay between the secretion of vasopression and its effect on water intake and tubular water reabsorption

d\_normalized\_vasopressin\_concentration\_delayed\_dt = C\_renal\_CV\_timescale\*C\_vasopressin\_delay\*(normalized\_vasopressin\_concentration - normalized\_vasopressin\_concentration\_delayed);

#TGF resetting. If C\_tgf\_reset = 0, no TGF resetting occurs. If it is greater than zero, the setpoint will change over time and will eventually

#come to equal the ambient MD sodium flow rate.

d\_F0\_TGF\_dt = C\_renal\_CV\_timescale\* C\_tgf\_reset\*(SN\_macula\_densa\_Na\_flow\*baseline\_nephrons - F0\_TGF);

#As above, these equations allow a variable to be used in equations that appear in the code before the variable was first defined.

d\_P\_bowmans\_dt = C\_renal\_CV\_timescale\*100\*(P\_in\_pt\_s1\_mmHg - P\_bowmans);

d\_oncotic\_pressure\_difference\_dt = C\_renal\_CV\_timescale\*100\*(oncotic\_pressure\_avg - oncotic\_pressure\_difference);

d\_renal\_blood\_flow\_L\_min\_delayed\_dt = C\_renal\_CV\_timescale\*C\_rbf\*(renal\_blood\_flow\_L\_min - renal\_blood\_flow\_L\_min\_delayed);

d\_SN\_macula\_densa\_Na\_flow\_delayed\_dt = C\_renal\_CV\_timescale\*C\_md\_flow\*( SN\_macula\_densa\_Na\_flow - SN\_macula\_densa\_Na\_flow\_delayed);

d\_rsna\_delayed\_dt = C\_renal\_CV\_timescale\*C\_rsna\*(renal\_sympathetic\_nerve\_activity - rsna\_delayed);

###Disease effects (turned off by default)

#Glomerular hypertrophy

d\_disease\_effects\_increasing\_Kf\_dt = GP\_effect\_increasing\_Kf;

#Loss of CD pressure natriuresis response over time

d\_disease\_effects\_decreasing\_CD\_PN\_dt = CD\_PN\_loss\_rate;

#Tubular hypertrophy

d\_tubular\_length\_increase\_dt = PT\_Na\_reabs\_effect\_increasing\_tubular\_length;

d\_tubular\_diameter\_increase\_dt = PT\_Na\_reabs\_effect\_increasing\_tubular\_diameter;

d\_water\_out\_s1\_delayed\_dt = C\_renal\_CV\_timescale\* C\_pt\_water\*(water\_out\_s1 - water\_out\_s1\_delayed);

d\_water\_out\_s2\_delayed\_dt = C\_renal\_CV\_timescale\*C\_pt\_water\*(water\_out\_s2 - water\_out\_s2\_delayed);

d\_water\_out\_s3\_delayed\_dt = C\_renal\_CV\_timescale\*C\_pt\_water\*(water\_out\_s3 - water\_out\_s3\_delayed);

d\_reabsorbed\_urea\_cd\_delayed\_dt = 0;#C\_pt\_water\*(reabsorbed\_urea\_cd - reabsorbed\_urea\_cd\_delayed);

#Urinary glucose excretion

d\_UGE\_dt = C\_renal\_CV\_timescale\*\*RUGE; #mg/hr #solo

#Serum Creatinine

d\_serum\_creatinine\_dt = C\_renal\_CV\_timescale\*(creatinine\_synthesis\_rate - creatinine\_clearance\_rate);

d\_cumNaExcretion\_dt = C\_renal\_CV\_timescale\*Na\_excretion\_via\_urine; #solo

d\_cumWaterExcretion\_dt = C\_renal\_CV\_timescale\*\*urine\_flow\_rate; #solo

d\_cumCreatinineExcretion\_dt = C\_renal\_CV\_timescale\*creatinine\_clearance\_rate; #solo

d\_RTg\_compensation\_dt = C\_renal\_CV\_timescale\*excess\_glucose\_increasing\_RTg;

d\_SGLT2\_inhibition\_delayed\_dt = C\_renal\_CV\_timescale\*C\_sglt2\_delay\*(SGLT2\_inhibition - SGLT2\_inhibition\_delayed);

d\_RUGE\_delayed\_dt = C\_renal\_CV\_timescale\*C\_ruge\*(RUGE - RUGE\_delayed);

d\_postglomerular\_pressure\_delayed\_dt = C\_renal\_CV\_timescale\*C\_postglomerular\_pressure\*(postglomerular\_pressure - postglomerular\_pressure\_delayed); #necessary to prevent large oscillations

d\_postglomerular\_pressure\_error\_dt = C\_renal\_CV\_timescale\*(postglomerular\_pressure - RIHP0);

d\_mitral\_valve\_leak\_dt = mitral\_valve\_leak\_rate; #solo