Electronic appendix to the article:
Jiří Kofránek, Jan Rusz, Stanislav Matoušek: **Guyton's Diagram Brought to Life - from Graphic Chart to Simulation Model for Teaching Physiology.** In: *Proceedings of Technical Computing Prague 2007. 15th Annual Conference, (*P. Byron Ed.), January 2007, ISBN 978-80-7080-658- 6
Proceedings article is available at: *http://dsp.vscht.cz/konference_matlab/MATLAB07/prispevky/kofranek_rusz/kofranek_rusz.pdf*

Basic structure of the mathematical model of human physiological functions

(modification of the A.C.Guyton model in the form of simulation chips)

Detailed description of the simulation model equations and

debugged model schematics in Simulink

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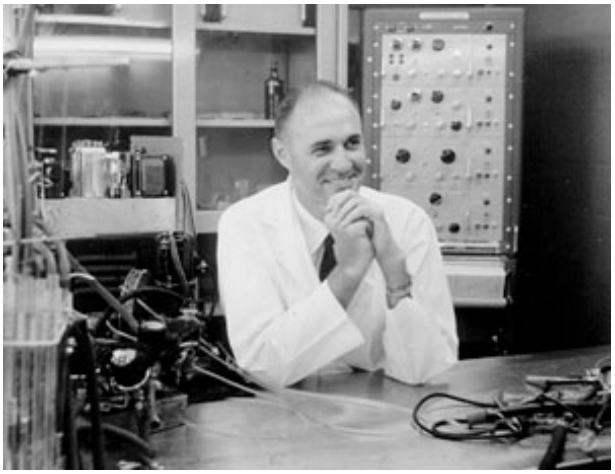
Arthur C. Guyton, together with T.G. Coleman and H.J. Grander, published a seminal paper in the Annual Reviews of Physiology in 1972: Circulation: overall regulation, in which he described an extensive model of the physiological regulation of the circulatory system and its neuroendocrine regulation, including its connections to other subsystems of the organism - the kidneys, volume regulation and electrolyte balance. The description of the equations was only in the form of a basic (but still fully illustrative) figure; the comments and justifications for the formulations of these relationships were very brief. The model was the first large-scale model of the interconnected physiological functions of an organism and started the field that is sometimes described today as integrative physiology. Later, A. Guyton's group expanded the model further and even provided interested readers with Fortran listings of the model's programs (most recently in 1986).

In the nineties, thanks to the development of computer technology and the subsequent possibility of practical applications of physiological models, their structure often becomes technological know-how and, for example, the company Biological Simulators Inc. (owned by T. Coleman - one of A. Guyton's close collaborators) offers an educational simulator, but only in a compiled form, without a description of the equations and relationships behind the simulator.

The following text describes in detail the modified Guyton model, the physiological meanings of the individual relationships and the implementation of the model in the form of simulation chips in the Matlab/ Simulink environment.



A. C. Guyton (1919-2003) - one of the founders of the systems approach to physiological regulation.

The following page contains the diagram from Guyton's publication: Arthur C. Guyton, Thomas C. Coleman, Harris J. Granger: **Circulation: Overall Regulation.** Annual Review of Physiology, Vol. 34:13-44 (Volume publication date March 1972), available at https://doi.org/10.1146/annurev.ph.34.030172.000305

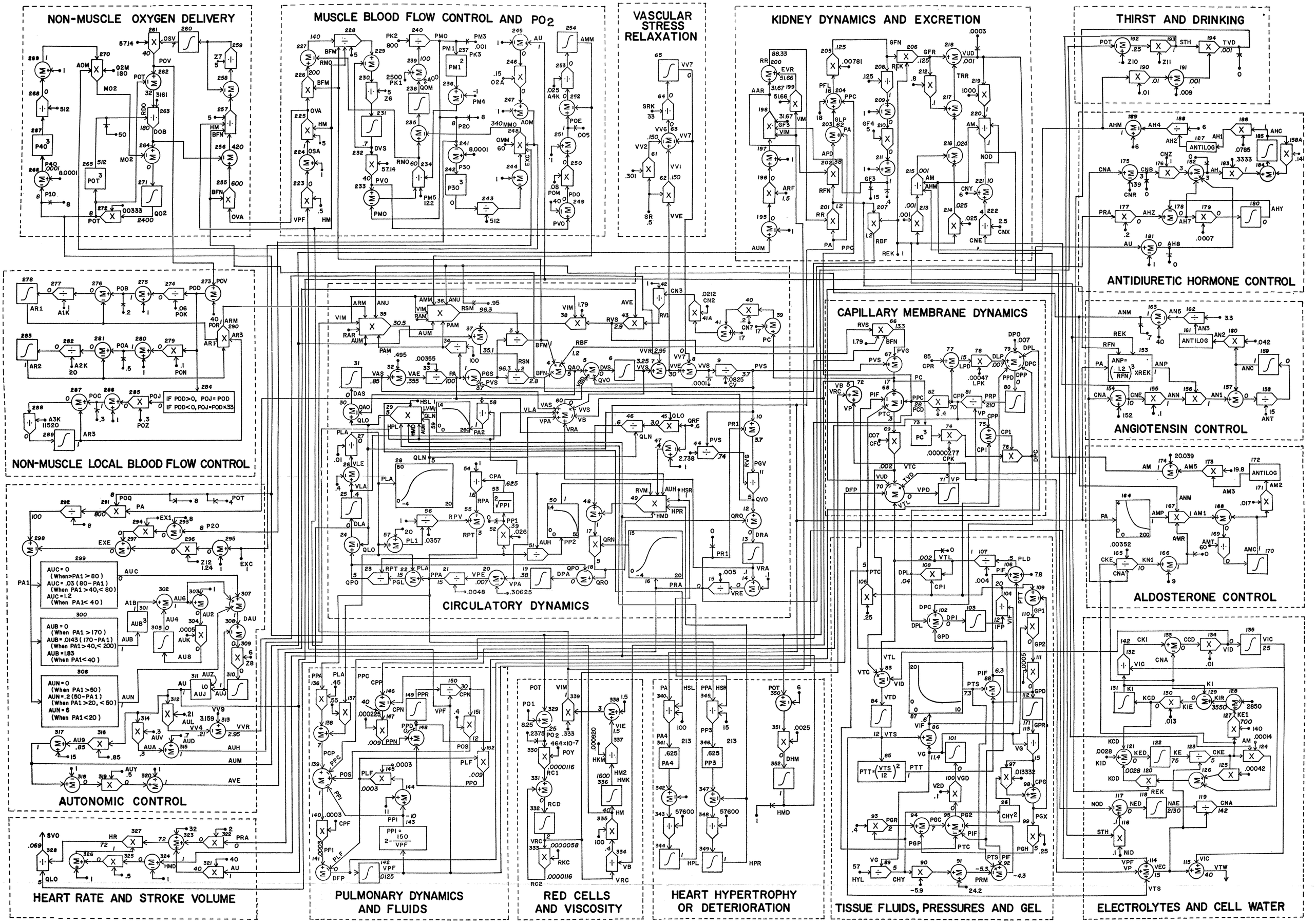
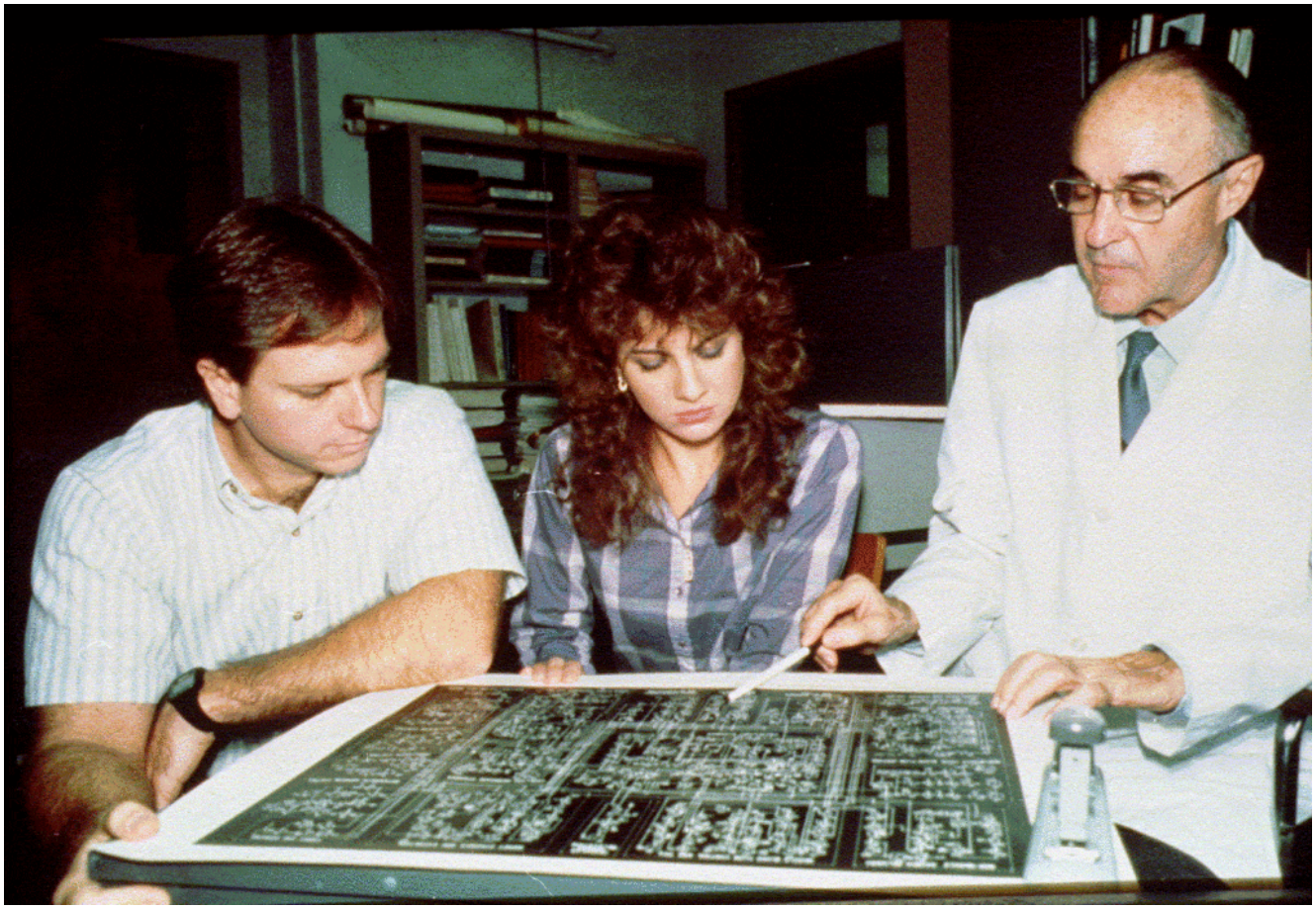


FIGURE 1. Systems analysis diagram for regulation of the circulation. Units are the following: volume in liters; mass in grams; time in minutes; chemical units in milliequivalents; pressure in millimeters of mercury; control factors in arbitrary units but in most instances expressed as the ratio to normal— for instance, a value of 1 represents normal. Normal values are given on the lines that represent the respective variables.

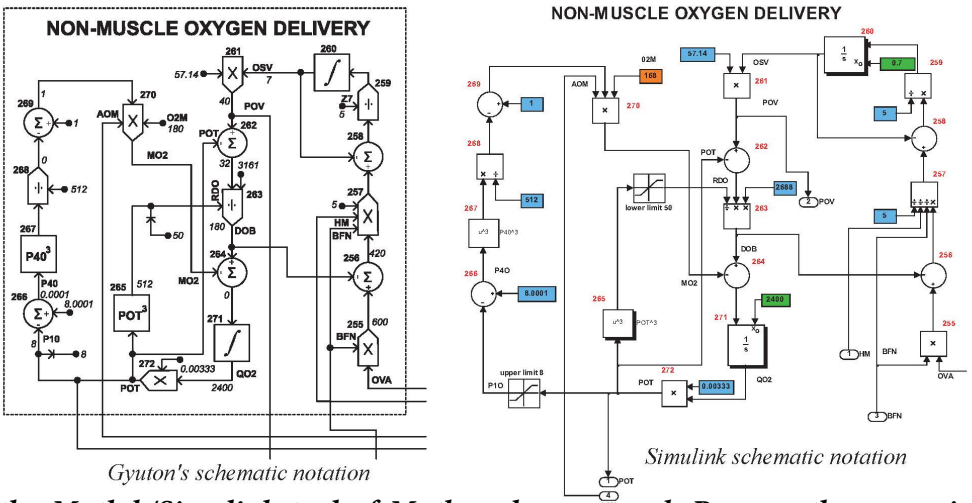
The following is a list of the important dependent and independent variables in the analysis (additional variables are present for purposes of calculation but generally have no physiological significance):

AAR—afferent arteriolar resistance
AHM—antidiuretic hormone multiplier, ratio of normal effect
AM—aldosterone multiplier, ratio of normal effect
AMC—aldosterone concentration
AMM—muscle vascular constriction caused by local tissue control, ratio to resting state
AMP—effect of arterial pressure on rate of aldosterone secretion
AMR—effect of sodium to potassium ratio on aldosterone secretion rate
AMT—time constant of aldosterone accumulation and destruction
ANC—angiotensin concentration
ANM—angiotensin multiplier effect on vascular resistance, ratio to normal
ANN—effect of sodium concentration on rate of angiotensin formation
ANP—effect of renal blood flow on angiotensin formation
ANT—time constant of angiotensin accumulation and destruction
ANU—nonrenal effect of angiotensin
AOM—autonomic effect on tissue oxygen utilization
APD—afferent arteriolar pressure drop
ARF—intensity of sympathetic effects on renal function
ARM—vasoconstrictor effect of all types of autoregulation
AR1—vasoconstrictor effect of rapid autoregulation
AR2—vasoconstrictor effects of intermediate autoregulation
AR3—vasoconstrictor effect of long-term autoregulation
AU—overall activity of autonomic system, ratio to normal
AUB—effect of baroreceptors on autoregulation
AUC—effect of chemoreceptors on autonomic stimulation
AUH—autonomic stimulation of heart, ratio to normal
AUK—time constant of baroreceptor adaptation
AUL—sensitivity of sympathetic control of vascular capacitance
AUM—sympathetic vasoconstrictor effect on arteries
AUN—effect of CNS ischemic reflex on autoregulation
AUV—sensitivity control of autonomics on heart function
AUY—sensitivity of sympathetic control of veins
AUZ—overall sensitivity of autonomic control
AVE—sympathetic vasoconstrictor effect on veins
A1K—time constant of rapid autoregulation
A2K—time constant of intermediate autoregulation
A3K—time constant of long-term autoregulation
A4K—time constant for muscle local vascular response to metabolic activity
BFM—muscle blood flow
BFN—blood flow in non-muscle, non-renal tissues
CA—capacitance of systemic arteries
CCD—concentration gradient across cell membrane
CHY—concentration of hyaluronic acid in tissue fluids
CKE—extracellular potassium concentration
CKI—intracellular potassium concentration
CNA—extracellular sodium concentration
CNE—sodium concentration abnormality causing third factor effect
CPG—concentration of protein in tissue gel
CPI—concentration of protein in free interstitial fluid
CPN—concentration of protein in pulmonary fluids
CPP—plasma protein concentration
CV—venous capacitance
DAS—rate of volume increase of systemic arteries
DFP—rate of increase in pulmonary free fluid
DHM—rate of cardiac deterioration caused by hypoxia
DLA—rate of volume increase in pulmonary veins and left atrium
DLP—rate of formation of plasma protein by liver
DOB—rate of oxygen delivery to non-muscle cells
DPA—rate of increase in pulmonary volume
DPC—rate of loss of plasma proteins through systemic capillaries
DPI—rate of change of protein in free interstitial fluid
DPL—rate of systemic lymphatic return of protein
DPO—rate of loss of plasma protein
DRA—rate of increase in right atrial volume
DVS—rate of increase in venous vascular volume
EVR—postglomerular resistance
EXC—exercise activity, ratio to activity at rest
EXE—exercise effect on autonomic stimulation
GFN—glomerular filtration rate of undamaged kidney
GFR—glomerular filtration rate
GLP—glomerular pressure
GPD—rate of increase of protein in gel
GPR—total protein in gel
HM—hematocrit
HMD—cardiac depressant effect of hypoxia
HPL—hypertrophy effect on left ventricle
HPR—hypertrophy effect on heart, ratio to normal
HR—heart rate
HSL—basic left ventricular strength
HSR—basic strength of right ventricle
HYL—quantity of hyaluronic acid in tissues
IFP—interstitial fluid protein
KCD—rate of change of potassium concentration
KE—total extracellular fluid potassium
KED—rate of change of extracellular fluid concentration
KI—total intracellular potassium concentration
KID—rate of potassium intake
KOD—rate of renal loss of potassium
LVM—effect of aortic pressure on left ventricular output
MMO—rate of oxygen utilization by muscle cells
MO2—rate of oxygen utilization by non-muscle cells
NAE—total extracellular sodium
NED—rate of change of sodium in intracellular fluids
NID—rate of sodium intake
NOD—rate of renal excretion of sodium
OMM—muscle oxygen utilization at rest
OSA—aortic oxygen saturation
OSV—non-muscle venous oxygen saturation
OVA—oxygen volume in aortic blood
OVS—muscle venous oxygen saturation
O2M—basic oxygen utilization in non-muscle body tissues
PA—aortic pressure
PAM—effect of arterial pressure in distending arteries, ratio to normal
PC—capillary pressure
PCD—net pressure gradient across capillary membrane
PCP—pulmonary capillary pressure
PDO—difference between muscle venous oxygen Po_2 and normal venous oxygen Po_2
PFI—rate of transfer of fluid across pulmonary capillaries
PFL—renal filtration pressure
PGC—colloid osmotic pressure of tissue gel
PGH—absorbency effect of gel caused by recoil of gel reticulum
PGL—pressure gradient in lungs
PGP—colloid osmotic pressure of tissue gel caused by entrapped protein
PGR—colloid osmotic pressure of interstitial gel caused by Donnan equilibrium
PIF—interstitial fluid pressure
PLA—left atrial pressure
PLD—pressure gradient to cause lymphatic flow
PLF—pulmonary lymphatic flow
PMO—muscle cell Po_2
POD—non-muscle venous Po_2 minus normal value
POK—sensitivity of rapid system of autoregulation
PON—sensitivity of intermediate autoregulation
POS—pulmonary interstitial fluid colloid osmotic pressure
POT—non-muscle cell Po_2
POV—non-muscle venous Po_2
POY—sensitivity of red cell production
PO2—sensitivity of long-term autoregulation
PO2—oxygen deficit factor causing red cell production
PPA—pulmonary arterial pressure
PPC—plasma colloid osmotic pressure
PPD—rate of change of protein in pulmonary fluids
PPI—pulmonary interstitial fluid pressure
PPN—rate of pulmonary capillary protein loss
PPO—pulmonary lymph protein flow
PPR—total protein in pulmonary fluids
PRA—right atrial pressure
PRM—pressure caused by compression of interstitial fluid gel reticulum
PRP—total plasma protein
PTC—interstitial fluid colloid osmotic pressure
PTS—solid tissue pressure
PTT—total tissue pressure
PGV—pressure from veins to right atrium
PVG—venous pressure gradient
PVO—muscle venous Po_2
PVS—average venous pressure
QAO—blood flow in the systemic arterial system
QLN—basic left ventricular output
QLO—output of left ventricle
QOM—total volume of oxygen in muscle cells
QO2—non-muscle total cellular oxygen
QPO—rate of blood flow into pulmonary veins and left atrium
QRF—feedback effect of left ventricular function on right ventricular function
QRN—basic right ventricular output
QRO—actual right ventricular output
QVO—rate of blood flow from veins into right atrium
RAM—basic vascular resistance of muscles
RAR—basic resistance of non-muscular and non-renal arteries
RBF—renal blood flow
RCI—red cell production rate
RC2—red cell destruction rate
RCD—rate of change of red cell mass
REK—percent of normal renal function
RFN—renal blood flow if kidney is not damaged
RKC—rate factor for red cell destruction
RMO—rate of oxygen transport to muscle cells
RPA—pulmonary arterial resistance
RPT—pulmonary vascular resistance
RPV—pulmonary venous resistance
RR—renal resistance
RSM—vascular resistance in muscles
RSN—vascular resistance in non-muscle, non-renal tissues
RVG—resistance from veins to right atrium
RVM—depressing effect on right ventricle of pulmonary arterial pressure
RVS—venous resistance
SR—intensity factor for stress relaxation
SRK—time constant for stress relaxation
STH—effect of tissue hypoxia on salt and water intake
SVO—stroke volume output
TRR—tubular reabsorption rate
TVD—rate of drinking
VAS—volume in systemic arteries
VB—blood volume
VEC—extracellular fluid volume
VG—volume of interstitial fluid gel
VGD—rate of change of tissue gel volumes
VIB—blood viscosity, ratio to that of water
VIC—cell volume
VID—rate of fluid transfer between interstitial fluid and cells
VIE—portion of blood viscosity caused by red blood cells
VIF—volume of free interstitial fluid
VIM—blood viscosity (ratio to normal blood)
VLA—volume in left atrium
VP—plasma volume
VPA—volume in pulmonary arteries
VPD—rate of change of plasma volume
VPF—pulmonary free fluid volume
VRA—right atrial volume
VRC—volume of red blood cells
VTC—rate of fluid transfer across systemic capillary membranes
VTD—rate of volume change in total interstitial fluid
VTL—rate of systemic lymph flow
VTS—total interstitial fluid volume
VTW—total body water
VUD—rate of urinary output
VV7—increased vascular volume caused by stress relaxation
VVR—diminished vascular volume caused by sympathetic stimulation
VVS—venous vascular volume
Zs—time constant of autonomic response

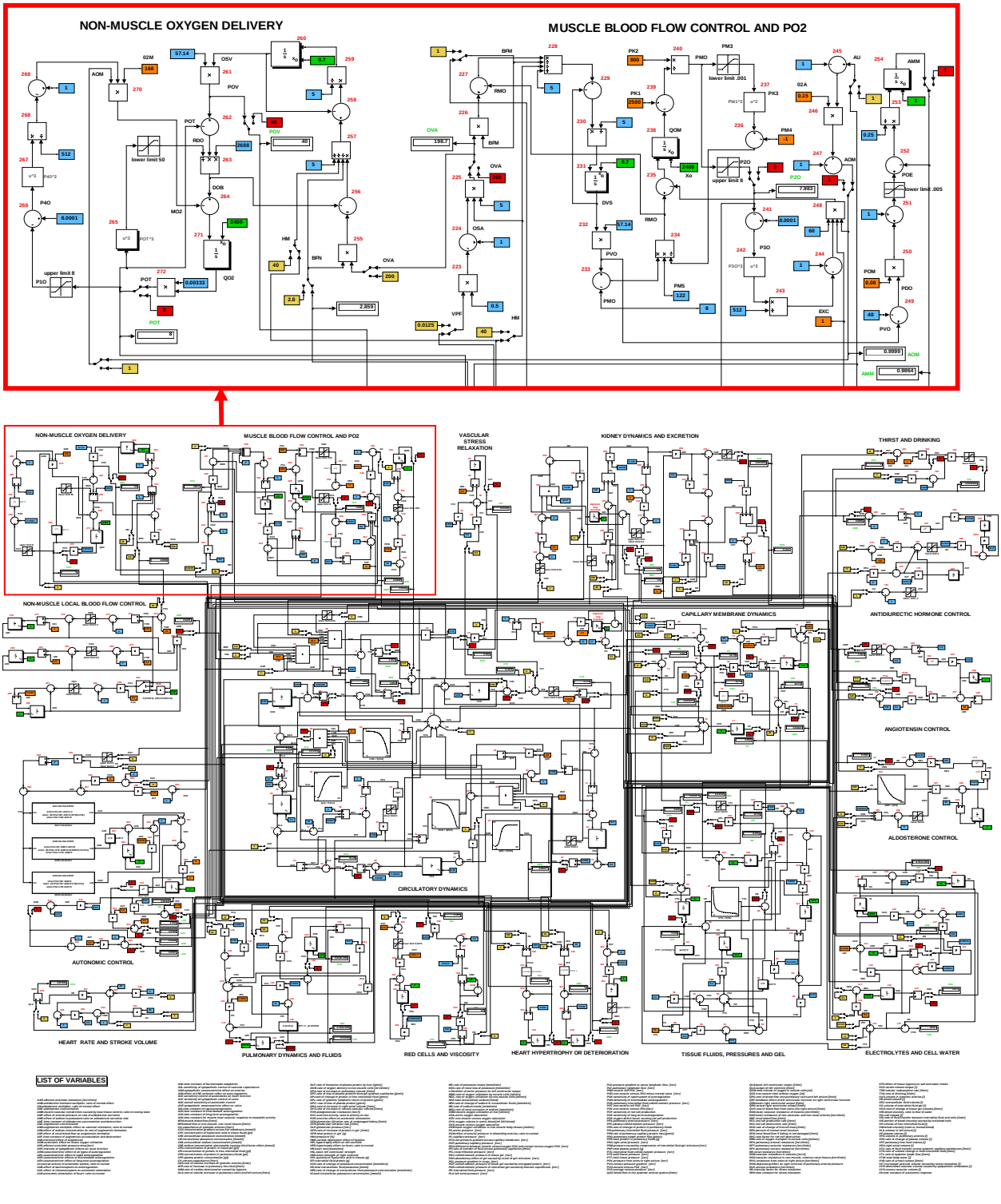
Guyton's scheme from the publication "Circulation: Overall Regulation" has been reprinted many times in many publications. However, the authors who reprinted this image did not always understand what this scheme expresses. The description of this scheme in the original article in the Annual Review of Physiology from 1972 was comprehensive but very brief. The scheme was only a formalized illustration of regulatory physiological relationships, not a program. The actual model was implemented in the Fortran language. In addition, there were some errors in the diagram (one could say - graphic typos), which could be easily detected with knowledge of physiology and understanding of the model.



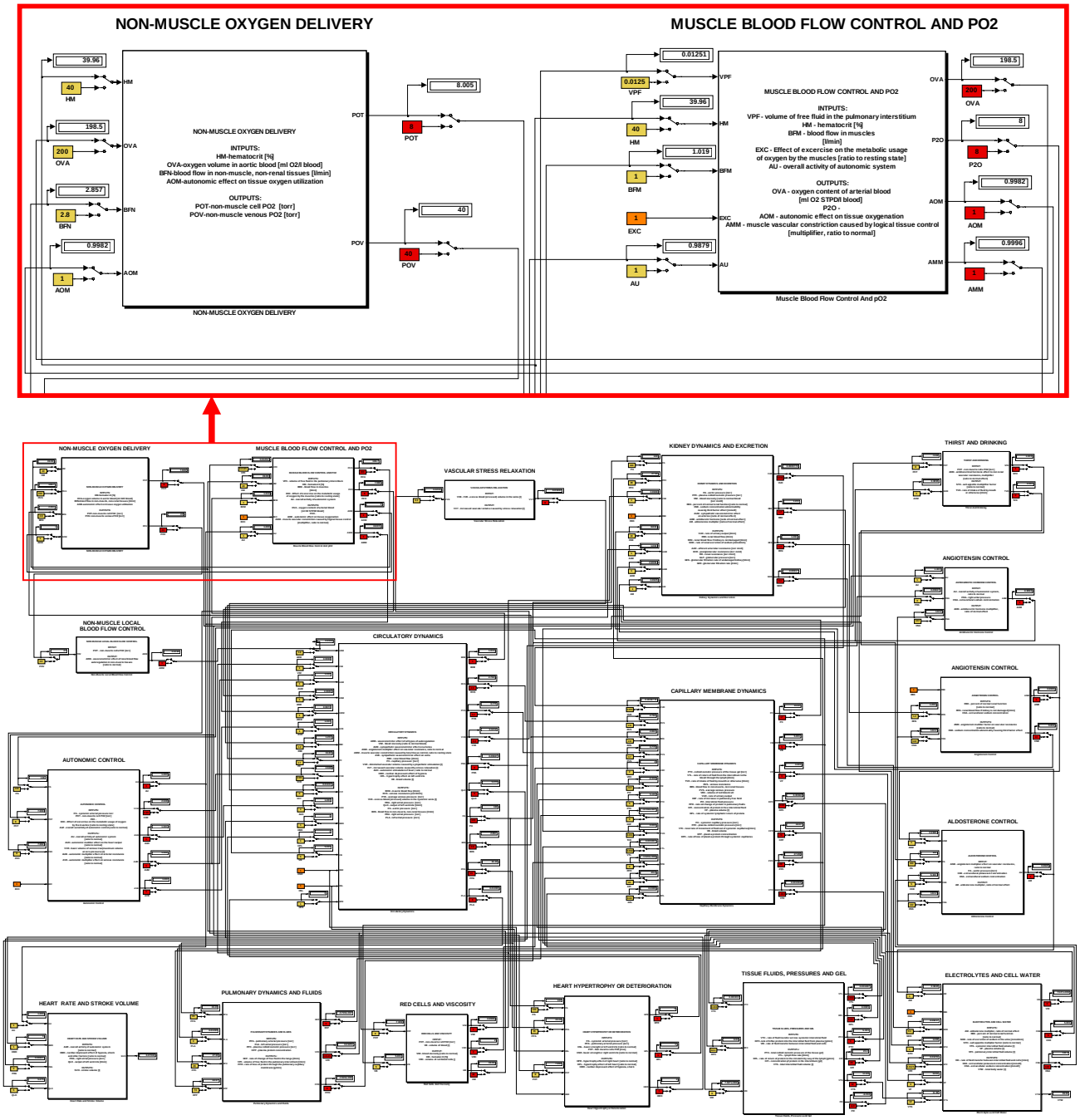
Guyton used a graphical diagram of the model and the outputs of a running computer model implemented in Fortran in teaching physiology and pathophysiology.



In the 1990s, the Matlab/Simulink tool of Mathworks appeared. Because the numerical blocks that Guyton et al. used in the schematic diagram were similar to those used by Simulink, we implemented Guyton's model in Simulink so that the Simulink schematic was identical to that in Guyton's diagram.

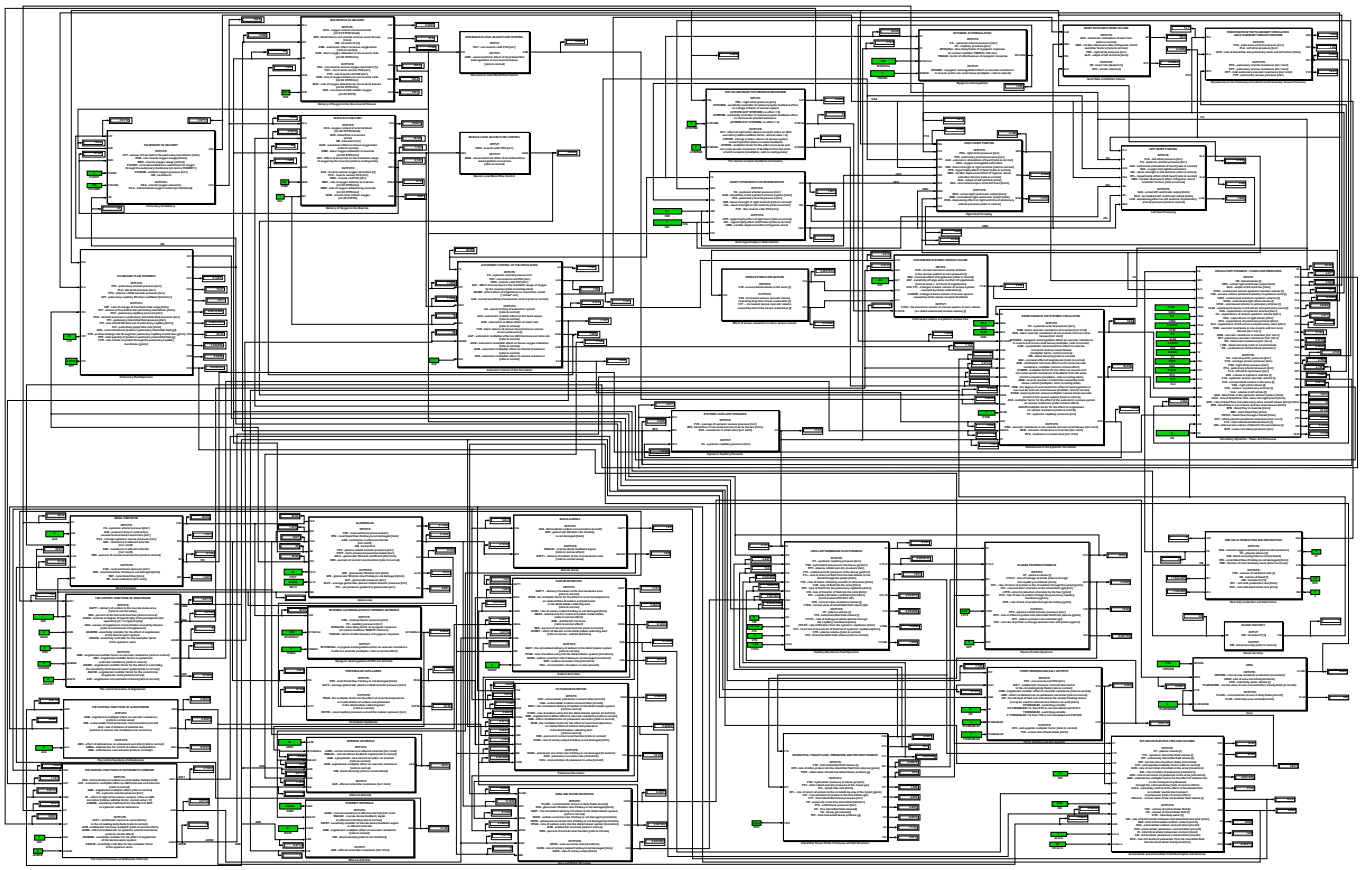


The structure of the Guyton scheme implemented in Simulink is the same as the original diagrammatic scheme of the Guyton model. In contrast to the graphic image, the Simulink diagram is "live" - we can monitor the course of all variables in the model on the running model.
The image representing the diagram of the model is in vector graphics. In the electronic version of this file, you can enlarge the image arbitrarily and look at all the details of the model diagram.



The flat relationship diagram is a bit confusing for users. If we use the possibilities of using Simulink's subsystems, we can make the Simulink diagram much more straightforward. We will divide the entire model into interconnected components. We will hide our calculation blocks inside the Simulink subsystems; we will only show inputs and outputs on the outside.
In the subsystem mask, we describe what the individual inputs and outputs mean. The components then function as a kind of "simulation chips." For the physiologist, they are significantly more understandable than the computer's network, hidden from him inside the "simulation chips." However, the physiologist can test the behavior of individual components in Simulink - and monitor the reaction of the outputs to the progress of the specified inputs. We connect the individual "simulation chips" into a model, which resembles an electrical diagram of connected electronic chips. Instead of electric current, information flows in the wires connecting the pins of the "simulation chips."
If we compare this diagram with the diagram in the previous figure, we can see that the model expressed by "simulation chips" is much more readable for the user at first glance.
In the electronic version of this page, you can enlarge the image and see all the details of the model diagram.

Guyton's 1972 model was initially concerned with the regulation of circulation. However, the circulatory system is related to other subsystems of the organism, in particular to the regulation of volume, osmolarity, transfer of blood gases, essential ions (sodium and arsenic), albumin metabolism, and the movement of ions and water between cells, interstitium, and blood, hemopoiesis, kidneys are involved in its regulation, lungs, and neural and hormonal control influences. Therefore, Guyton's model had to include all these influences. He thus opened the stage of integrative physiology modeling.



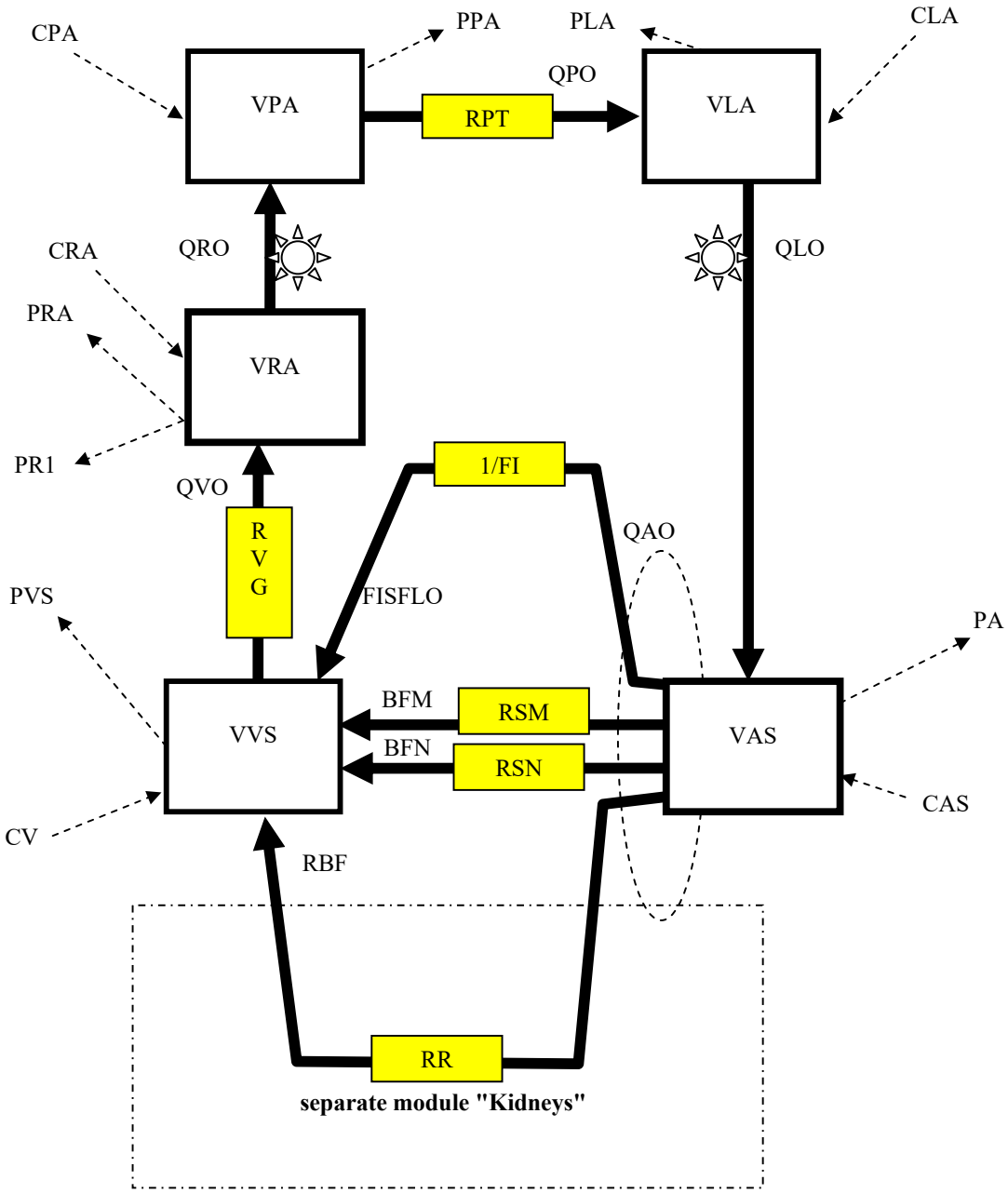
Guyton's team further developed the 1972 model. Here is the basic diagram of Gyuton's complex model of human physiological functions from 1986. The model was implemented in Fortran; we converted it to Simulink using the aforementioned "simulation chips" - it consists of 40 interconnected blocks. Compared to the previous image, we can see how the structure of the model has changed in 1986. The image in the electronic version contains sufficient details. When viewing the electronic version of this text on a computer, it is possible to use the magnifying tool (Magnifier) and look at all the model details in the viewer.pdf file (e.g., Adobe Reader).

All the individual blocks and equations of the model are discussed in the following pges.

HAEMODYNAMICS MODULE

Basic loop of fillings, flows and pressures in the different parts of the bloodstream

The bloodstream is divided into five volume compartments - aorta and great arteries (VAS), systemic veins (VVS), right atrium (VRA), pulmonary arteries (VPA), pulmonary veins and left atrium (VLA).



When the blood volume (VB) changes from outside the vasculature - this change (VBD), calculated at each time step as the difference between the current blood volume value (coming as an external input to the module) and the sum of the blood volumes in all five parts of the bloodstream:

$$VBD=VB-VAS-VVS-VRA-VPA-VLA \quad \text{(HD 01)}$$

shall be distributed among VAS,VVS,VRA,VPA and VLA in the following proportions:

$$DVBD\_VAS= 0.261*VBD \quad \text{(HD 02)}$$
$$DVBD\_VVS=0. 3986*VBD \quad \text{(HD 03)}$$
$$DVBD\_VRA=0.0574*VBD \quad \text{(HD 04)}$$
$$DVBD\_VPA=0.155*VBD \quad \text{(HD 05)}$$
$$DVBD\_VLA=0.128*VBD \quad \text{(HD 06)}$$

The volume in the aorta and large arteries (VAS) depends on the difference (DAS) between the blood inflow from the left heart - QLO [l/min] and the blood outflow from the aorta and large arteries - QAO [l/min] and the rate of change of blood volume from the outside of the vascular system distributed to the arterial part of the bloodstream (DVBD_VAS):

$$DAS=QLO-QAO \quad \text{(HD 07)}$$

$$VAS = \int (DAS + DVBD\_VAS)\, dt \quad \text{(HD 08)}$$

The volume of blood filling the aorta and large arteries (VAE) is the difference between the total volume of blood in the arteries (VAS) and the volume filling the aorta and large arteries at zero pressure (VAS0)

$$VAE=VAS-VAS0 \quad \text{(HD 09)}$$

Mean arterial pressure is then proportional to the volume stressing the aorta and inversely proportional to the compliance of the arterial systemic circulation:

$$PA=VAE/CAS \quad \text{(HD 10)}$$

The arterio-venous pressure gradient in the systemic circulation (PGS) is the difference between the pressure in the aorta (PA) and the mean pressure in the large systemic veins (PVS):

$$PGS=PA-PVS \quad \text{(HD 11)}$$

Blood flow through the non-muscular part of the bloodstream excluding the kidneys (BFN) is calculated from the pressure gradient in the systemic circulation between the aorta and the pressure in the great veins and the resistance of the non-muscular part of the bloodstream (not involving the kidneys) - RSN:

$$BFN=PGS/RSN \quad \text{(HD 12)}$$

Blood flow through muscle (BFM) is equal to the arterio-venous pressure gradient in the systemic circulation and the blood flow resistance in muscle (RSM):

$$BFM=PGS/RSM \quad \text{(HD13)}$$

Total renal resistance (RR) is calculated in the "kidney" module and is an input parameter in the hemodynamics module. Renal blood flow (RBF) is calculated from the gradient in between arterial and systemic venous pressure (PGS) and renal resistance (RR).

$$RBF=PGS/RR \quad \text{(HD 14)}$$

The rate of arterial blood flow is equal to the blood flow through the muscle (BFM), the blood flow through the kidney (RBF), the blood flow through the remaining non-muscular part of the bloodstream not involving the kidney (BFN), and possibly the blood flow through the artificially created arteriovenous shunts (FISFLO):

$$QAO=BFM+BFN+RBF+FISFLO \quad \text{(HD 15)}$$

The flow through an artificial arteriovenous shunt is directly proportional to the pressure gradient between the artery (PA) and the right atrium (PRA), and the conductivity of the shunt (FIS).

$$FISFLO=(PA-PRA)*FIS \quad \text{(HD 16)}$$

Volume in the systemic veins - VVS depends on the difference (DVS) between blood inflow to the systemic veins (QAO) and blood outflow to the right atrium (QVO) and the rate of change of blood volume from the outside of the vascular system distributed to the venous part of the bloodstream (DVBD_VVS):

$$DVS=QAO-QVO \quad \text{(HD 17)}$$

$$VVS = \int (DVS + DVBD\_VVS)\, dt \quad \text{(HD 18)}$$

The volume of blood filling the venous systemic circulation VVE is calculated as the difference between the current value of the blood volume in the large veins (VVS) and the value of the maximum blood volume in the venous systemic circulation at zero pressure, i.e. the volume at which the veins fill but the pressure does not rise (VVS0):

$$VVE=VVS-VVS0 \quad \text{(HD 19)}$$

The value of the maximal venous filling that does not change pressure (VVS0) is the sum of several volumes - the residual volume, independent of the action of other factors (VVR), the volume changing due to tensile relaxation of the musculature of the veins caused by pressure in the venous wall (VV6 and VV7), the additional volume produced by reflex feedback relaxation by tension receptors from the atria (ATRRVFB - when the atria dilate, the great veins dilate), and the increase in volume due to angiotensin - (VV_ANU), where ANU is the non-renal effect of angiotensin, expressed as a relative value to normal angiotensin levels, and ANY is the sensitivity of the great veins to angiotensin[1] :

$$VV\_ANU=(ANU-1)*ANY \quad \text{(HD20)}$$

$$VVS0=VVR+VV\_ANU+VV7+VV6+ATRVFB \quad \text{(HD 21)}$$

The mean pressure in the venous system (PVS) is proportional to the volume straining the venous vasculature (VVE) and inversely proportional to the compliance of the venous systemic circulation (CV):

$$PVS=VVE/CV \quad \text{(HD 22)}$$

The pressure gradient for blood flow from the venous system to the right atrium (PGV) is equal to the difference between the mean pressure in the systemic venous system (PVS) and the outflow pressure in the great veins in the chest (PR1):

$$PGV=PVS-PR1 \quad \text{(HD 23)}$$

The resistance of blood flow through the venous system (RVG) is equal to a constant value dependent on the viscosity of blood (VIM) divided by the mean venous pressure (PVS):

$$RVG=2.738*VIM/PVS \quad \text{(HD 24)}$$

The velocity of blood flow from the venous system to the right heart (QVO) is equal to the pressure gradient in the venous system (PGV) divided by the resistance of blood flow through the venous system (RVG):

$$QVO=PGV/RVG \quad \text{(HD 25)}$$

[1] These dependencies are realized in the block "Unstressed venous volume"

The right atrial blood volume - VRA depends on the difference (DRA) between the blood inflow from the great veins into the right atrium (QVO) and the blood outflow (QVO) and the rate of change of the blood volume from the outside of the vascular system distributed to the part of the bloodstream in the right atrium (DVBD_VRA):

$$DRA=QVO-QRO \quad \text{(HD 26)}$$

$$VRA = \int (DRA + DVBD\_VRA)\, dt \quad \text{(HD 27)}$$

The right atrial blood volume (VRE) is calculated as the difference of the instantaneous actual value of the right atrial blood volume (VRA) minus the constant value of the right atrial blood volume under conditions of a constant value representing the residual right atrial blood volume at zero pressure (VRA0=0.1 litres):

$$VRE=VRA-VRA0 \quad \text{(HD 28)}$$

Right atrial pressure (PRA) is equal to the volume of blood straining the right atrium (VRE) divided by a constant representing the compliance of the right atrium (CRA=0.005 torr/l):

$$PRA=VRA/CRA \quad \text{(HD 29)}$$

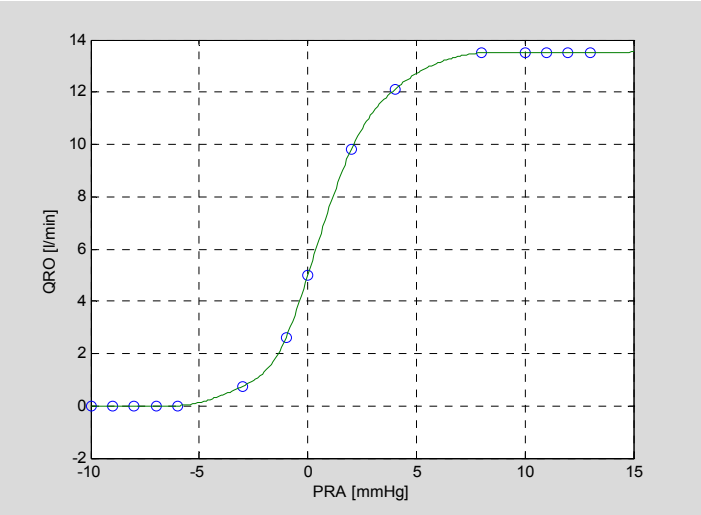
The calculation of the pressure in the great saphenous veins in the chest (PR1) is used in the calculation of the outflow of blood from the venous system (see equations HD 23-25). This pressure is equal to the right atrial pressure (PRA). However, if the right atrial pressure is negative, the great veins in the chest collapse and therefore the pressure in them does not fall below a certain minimum value (PR1LL):

$$if\ PRA>PR1LL,\ then\ PR1=PRA \quad \text{(HD 30a)}$$
$$else\ \ PR1=PRLL \quad \text{(HD 30b)}$$

The dependence between right heart outflow tract (QRN) on right atrial pressure (PRA) in the normalized healthy heart (Starling curve) is approximated by interleaving the nodal points of the following table[2] :

$$QRN = function\ StarlingRNorm(PRA) \quad \text{(HD 31)}$$

PRA	QRN
<-6	0
-6	0
-3	0.75
-1	2.6
0	5.0
2	9.8
4	12.1
8	13.5
>8	13.5



[2] In the future it will be better to define the Starling curve as the dependence of StrokeWork on preload /eliminating the influence of afterload/.

Calculation of right heart blood outflow (QRO) based on pump efficiency factor (HPEF) and healthy heart normalized outflow (QRN):

$$QRO=QRN*HPEF \quad \text{(HD 32)}$$

The volume of blood in the pulmonary arterial circulation - VPA depends on the difference (DPA) between the inflow of blood from the right heart (QRO) and the outflow of blood from the pulmonary arterial circulation to the pulmonary venous circulation (QPO) and the rate of change of the volume of blood from the outside of the vascular system distributed to the part of the pulmonary blood circulation (DVBD_VPA):

$$DPA=QRO-QPO \quad \text{(HD 33)}$$

$$VPA = \int (DPA + DVBD\_VPA)\, dt \quad \text{(HD 34)}$$

The volume of blood straining the pulmonary arterial blood flow (VPE) is calculated as the difference of the instantaneous current value of the pulmonary arterial blood flow volume (VPA) minus the value of the residual pulmonary arterial blood flow volume that completely fills the flow but does not yet increase the pressure from zero (VPA0 = 0.30625 litres):

$$VPE=VPA-VPA0 \quad \text{(HD 35)}$$

The pulmonary artery pressure (PPA) is equal to the volume of blood stretching the arterial pulmonary circulation (VPE) divided by a constant representing the compliance of the pulmonary arteries (CPA=0.0048 l/torr):

$$PPA=VPE/CPA \quad \text{(HD 36)}$$

We calculate the pressure gradient between mean pulmonary artery pressure (MAP) and pulmonary vein pressure (PVP) as the difference between pulmonary artery pressure (PAP) and left atrial pressure (PLA):

$$PGL=PPA-PLA \quad \text{(HD 37)}$$

Blood flow from the pulmonary arterial to the pulmonary venous circulation (QPO) is proportional to the pressure gradient between the arterial and pulmonary venous circulation (PGL) and inversely proportional to the resistance in the pulmonary circulation (RPT):

$$QPO=PGL/RPT \quad \text{(HD 38)}$$

The volume of blood in the left atrium (and in the pulmonary veins) - VLA depends on the difference (DLA) between blood inflow from the pulmonary arterial circulation (QPO) and blood outflow from the left atrium into the left ventricular systemic arterial circulation (QLO). To this must be added the rate of change of blood volume from the outside of the vascular system distributed to the pulmonary bloodstream portion (DVBD_VPA):

$$DLA=QPO-QLO \quad \text{(HD 39)}$$

$$VLA = \int (DLA + DVBD\_VLA)\, \mathrm{dt} \quad \text{(HD 40)}$$

The volume of blood that expands and stretches the left atrium (and pulmonary veins) - VLE is calculated as the difference between the total volume of blood in the left atrium and pulmonary veins (VLA) and the residual volume of blood in the pulmonary veins and left atrium (VLA0 =0.4 l) , which completely fills this part of the bloodstream but does not yet increase the pressure:

$$VLE=VLA-VLA0 \quad \text{(HD 41)}$$

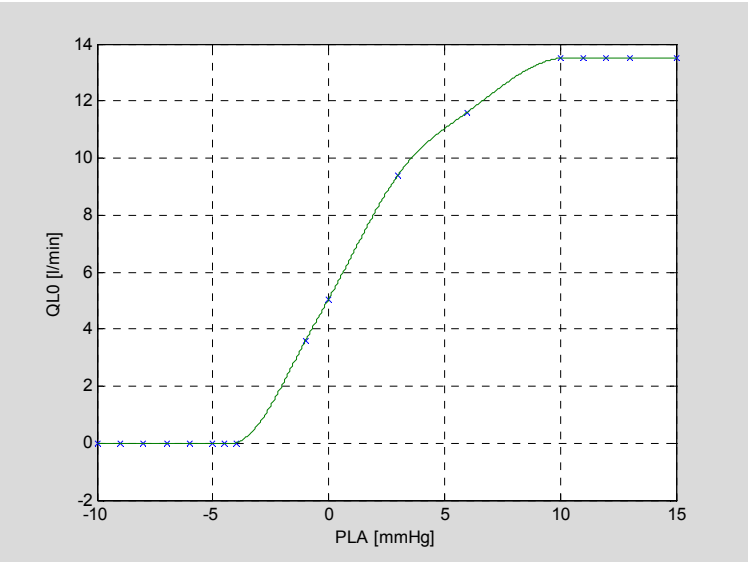
Left atrial pressure (PLA) is equal to the instantaneous value of the volume stressing the pulmonary veins and left atrium (VLE) divided by the compliance of the left atrium and pulmonary veins (CLA=0.01 l/torr):

$$PLA=VLE/CLA \qquad \text{(HD 42)}$$

The dependence between right heart blood outflow (QLN) on left atrial filling pressure (PLA) in a normalised healthy heart (Starling curve) is approximated by interleaving the nodal points of the following table:

$$QLN = function\ StarlingLNorm(PLA) \qquad \text{(HD 43)}$$

PLA	QLN
<-4.5	0
-4	0.01
-1	3.6
3	9.4
6	11.6
10	13.5
>10	13.5



Left ventricular outflow (QLO) is influenced by a number of factors that multiply the blood flow from the left ventricle of a normal healthy heart (QLN). These include - cardiac pressure load (LVM), a factor altering efficiency with abnormal change in left ventricular stiffness (HSL), a factor increasing stiffness due to left ventricular hypertrophy (HPL), a factor decreasing myocardial stiffness with low blood flow (HMD), and a factor altering stiffness due to increase or decrease in autonomic pacing (AUH):

$$QLO=LVM*QLN*AUH*HSL*HMD*HPL \qquad \text{(HD 44)}$$

Resistance calculations in the systemic circulation

The principle of calculating resistances is to include the effect of various circumstances on the change in the basal value of the resistance. These effects are expressed as multiplicative factors by which the basal resistance value is multiplied (or divided)3 .

The peripheral resistance system is considered in the model in three aggregates: muscle, kidney and other soft tissues. Peripheral resistance and the corresponding blood flow in the kidney will be described later in a separate kidney module. In the haemodynamics module, resistances in the bloodstream of muscles (RSM) and resistances in other 'non-muscular' and 'non-renal' tissues (RSN) are calculated.

3 It is appropriate to focus on testing the possibility of using fuzzy algebra to record the multiplication of multipliers in the future.

If the pressure in the vasculature increases, and if we do not consider other mechanisms, then the increase in pressure leads to dilation (distension) of the vessel and thus reduces vascular resistance. The effect of the arterial pressure (PA) value on the change in resistance due to arterial distension is expressed as a proportional multiplicative factor (PAM), by which the basal resistance value is divided. The normal value of this factor is 1. The effect of arterial pressure on this factor is exponential - it is calculated from the ratio of the current value of mean arterial pressure (PA) to the normal value (PA_norm = 100 torr) via an exponential factor (PAEX=1.41):

$$PAM=(PA/PA\_norm)^{PAEX} = (0.01*PA)^{1.41} \quad \text{(HD 45)}$$

Calculation of a common cumulative multiplicative factor (R1) affecting both systemic arterial resistance in muscle and resistance in the bloodstream in soft tissues (not including kidneys). The following factors are used as input factors (expressed as a ratio to the norm): the level of autonomic sympathetic stimulation (AUM), the influence of viscosity (VIM), the (non-renal) influence of angiotensin (ANU), the influence of antithyroid hormone (AHMR) on resistance (hence vasopressin is synonymous with ADH). Another factor is the feedback effect of atrial stretch receptors (ATRRFB), which leads to vasodilatation, and therefore the multiplicative factor in the denominator as well as the distensibility factor expressing the direct effect of arterial pressure on the dilatation of the vessel (PAM):

$$R1=AUM*VIM*ANU*AHMR/PAM/ATRRFB \quad \text{(HD 46)}$$

The calculation of resistance in the systemic muscular circulation (RSM) is calculated as the influence of multiplicative factors on the basal resistance value (RAM). These factors include the cumulative multiplicative factor (R1) from the HD 46 equation, as well as a multiplicative factor expressing the local autoregulatory influence of the musculature (AMM), and finally a factor expressing myogenic autoregulation (MYOGRS), increasing resistance when tension in the arteriolar circulation increases.

$$RSM=R1*AMM*MYOGRS*RAM \quad \text{(HD 47)}$$

Systemic resistance in "non-muscular" and "non-renal" soft tissues (RSN) consists of an arterial (more precisely, arteriolar) component of resistance in the vasculature (RSNA) and a venous (or venular) component of resistance (RSNV).

$$RSN=RSNA+RSNV \quad \text{(HD 48)}$$

Resistance in the arteriolar portion of the soft tissue vasculature (RSNA) ("non-muscular" and "non-renal") is calculated by modifying the basal resistance value (RAR) in these tissues with the cumulative multiplicative factor (R1) from equation HD 46 and the autoregulatory effect of microcirculation in these tissues (ARM):

$$RSNA=R1*ARM*RAR \quad \text{(HD 49)}$$

To calculate the venous part of the resistance in the "non-renal" and "non-muscular "soft tissues, we must first know its basal value (RV1), which takes into account the tension setting of the vascular wall of the venous part of the circulation and depends, among other things, on two factors - the pressure at the beginning of the venous system, i.e. the capillary pressure (PC) and the basal systemic venous multiplier (RVSM) - normally equal to 1.0. Note that the capillary pressure (PC) value is calculated somewhat iteratively , because to determine the PC value we need to know, among other things, the RVS value, which depends on RV1 but which depends on the PC value (see equation HD 54). The damping feedback factor in equation HD 50a-b prevents oscillations in the system:

$$DCN3=(((PC-17.0)*CN7+17.0)*CN2-CN3)*0.1 \quad \text{(HD 50a)}$$

$$CN3 = \int DCN3\ dt \quad \text{(HD 50b)}$$

$$RV1=RVSM/CN3 \quad \text{(HD 51)}$$

The calculation of the actual value of venous resistance (RVS) depends on modification of the basal value of venous resistance (RV1) by modifying multipliers reflecting the influence of the autonomic nervous system (AVE), the effect of angiotensin on venous tone (ANUVN) and the influence of blood viscosity (VIM) on venous resistance:

$$RVS=AVE*VIM*ANUVN*RV1 \quad \text{(HD 52)}$$

The venous part of the resistance in "non-renal" and "non-muscular" soft tissues is calculated using the current venous resistance value (RVS) multiplied by a proportion factor of 1.794 (this calculates the portion of the total venous resistance that is attributable to "non-renal" and "non-muscular" tissues - the minute flow is approximately 1.79 times the flow through "non-renal" and "non-muscular" tissues), and at the same time we apply here the possibility of myogenic autoregulation by a factor (MYOGRGS) - as also in the arterial part of the resistance (RSNA), where the MYOGRS variable was "hidden" in the R1 variable:

$$RSNV=RVS*1.79*MYOGRS \quad \text{(HD 53)}$$

Calculation of the average capillary pressure in tissues (PC). The capillary pressure is proportional to the resistance of blood flow through small veins (RVS) and blood flow in soft "non-renal and non-muscular" tissues (BFN) multiplied by a factor of 1.79 correcting the flow of "non-renal and non-muscular" tissues to the total flow including the flow through muscle and kidney plus the pressure in large veins (PVS):

$$PC=RVS*1.79*BFN+PVS \quad \text{(HD 54)}$$

The total systemic peripheral resistance (as an output parameter from the hemodynamic module) is calculated from the gradient of arterial (PA) and right atrial (PRA) pressure and the arterial blood flow:

$$RTP = (PA-PRA)/QAO \quad \text{(HD 55)}$$

Calculation of resistances in the pulmonary circulation

Total resistance in the lungs (RPT) is calculated as the sum of the arteriolar and venous components of resistance.

The calculation of resistance to flow through the pulmonary arterioles of the RPA is based on the value of pulmonary arterial pressure (we assume autoregulation of resistance to pulmonary arterial pressure). This dependence is nonlinear. Equation 56b bounds the intermediate outcome values. Equation 57 calculates the exponential dependence of pulmonary arteriolar conductance, and equation 58 calculates resistance as the inverse of conductance:

$$PP1=0.026*PPA \quad \text{(HD 56a)}$$

$$\text{if } PP1<0.00001, \text{ then } PP1=0.00001 \quad \text{(HD 56b)}$$

$$CPA=PP1^{0.5} \quad \text{(HD 57)}$$

$$RPA=1.0/CPA \quad \text{(HD 58)}$$

The calculation of venous pulmonary resistance is related to the value of left atrial pressure (PLA) - higher pressure leads to distension of the pulmonary veins and a decrease in their resistance:

4 This part will need to be revised - the coefficient of 1.79 will not be constant during blood redistributions in shock states, etc.

PL1=PLA+20.0 (HD 59)
RPV=1.0/PL1/0.0357 (HD 60)

Total pulmonary resistance is the sum of arteriolar and venous resistance:

RPT=RPV+RPA (HD 61)

We can still calculate the pulmonary vein pressure (PVP). From the outflow from the pulmonary arteries to the pulmonary vein and left artery compartment (QPO) and the pulmonary vein resistance (RPV), we calculate the corresponding pressure gradient and subtract this value from the pulmonary artery pressure (PPA):

PVP=PPA-QPO/RPV (HD 62)

Calculation of the pumping performance of the left heart

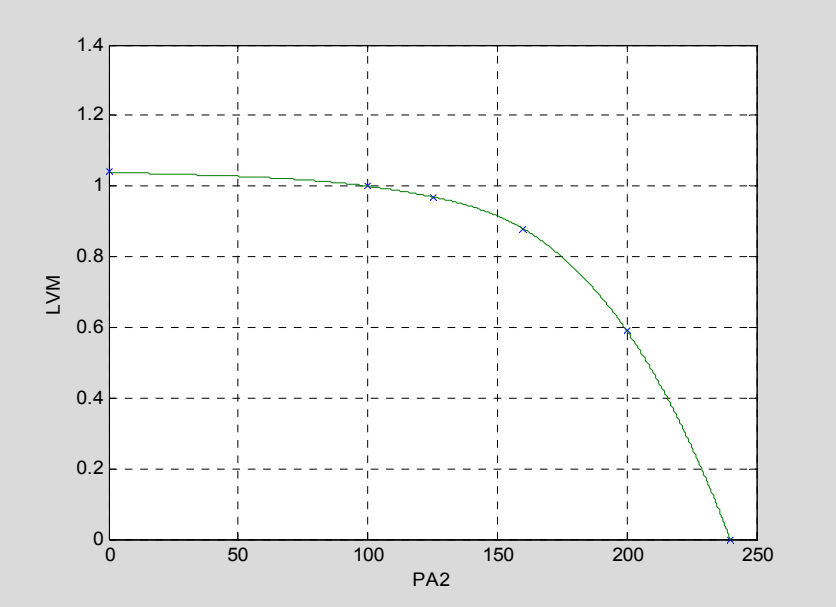
Calculation of the PA2 multiplication factor in relation to three factors affecting left heart pump performance. The first is the stimulation of the left heart by the autonomic nervous system (AUH), the influence of myocardial function by arterial blood oxygen saturation (OSA), and the influence of ventricular pumping function by pressure load dependent on the value of arterial systemic pressure (AP):

*PA2=PA/(AUH*OSA)* (HD 63)

The function curve calculates the dependence of the cumulative parameter characterizing the effect of left heart pressure (LVM) on the coefficient of PA2 (the LVM coefficient is subsequently used in equation HD 44). The empirical function is approximated by interleaving the nodal points of the following table:

LVM=function leftHeartLoading(PA2) (HD 64)

PA2	LVM
<0	1.04
0	1.04
70	1.025
125	0.97
160	0.98
200	0.59
240	0
>240	0



Calculation of the pumping performance of the right heart

The multiplicative factor (PP2) cumulatively expresses the ability of the right heart to work against the increased load represented by increased pulmonary artery pressure (PPA). This ability is influenced by the activity of sympathetic stimulation.

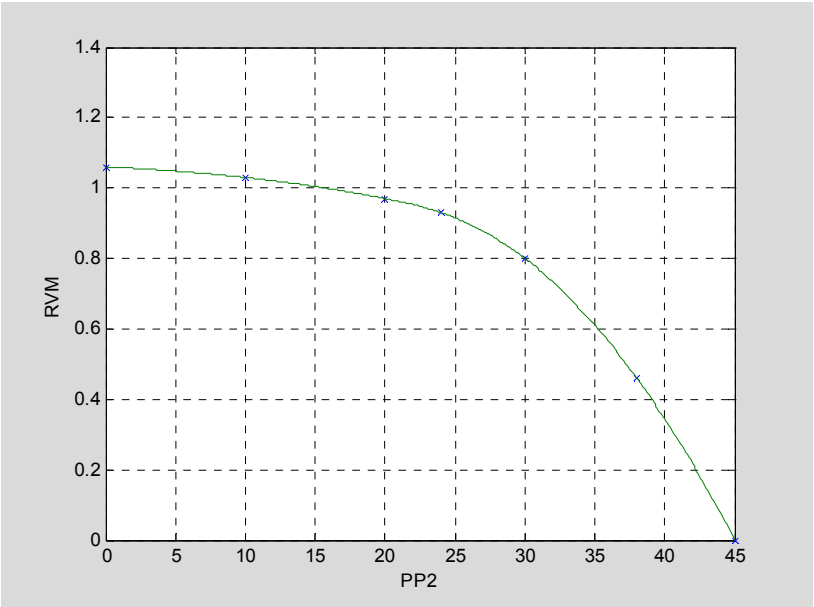
(AUH) and the availability of oxygen in the coronary vessels - therefore, another factor is the arterial oxygen saturation of haemoglobin:

*PP2=PPA/(AUH*OSA)* (HD 65)

The functional curve calculates the dependence of the cumulative parameter characterizing the influence of the pressure load on the right heart (RVM) on the PP2 coefficient (the RVM coefficient is subsequently used in the following equation HD 66).
The empirical function is approximated by interleaving the nodal points of the following table:

RVM=function rightHeartLoading(PP2) (HD 66)

PA2	RVM
<0	1.06
0	1.06
10	1.03
20	0.97
24	0.93
30	0.8
38	0.46
45	0
>45	0



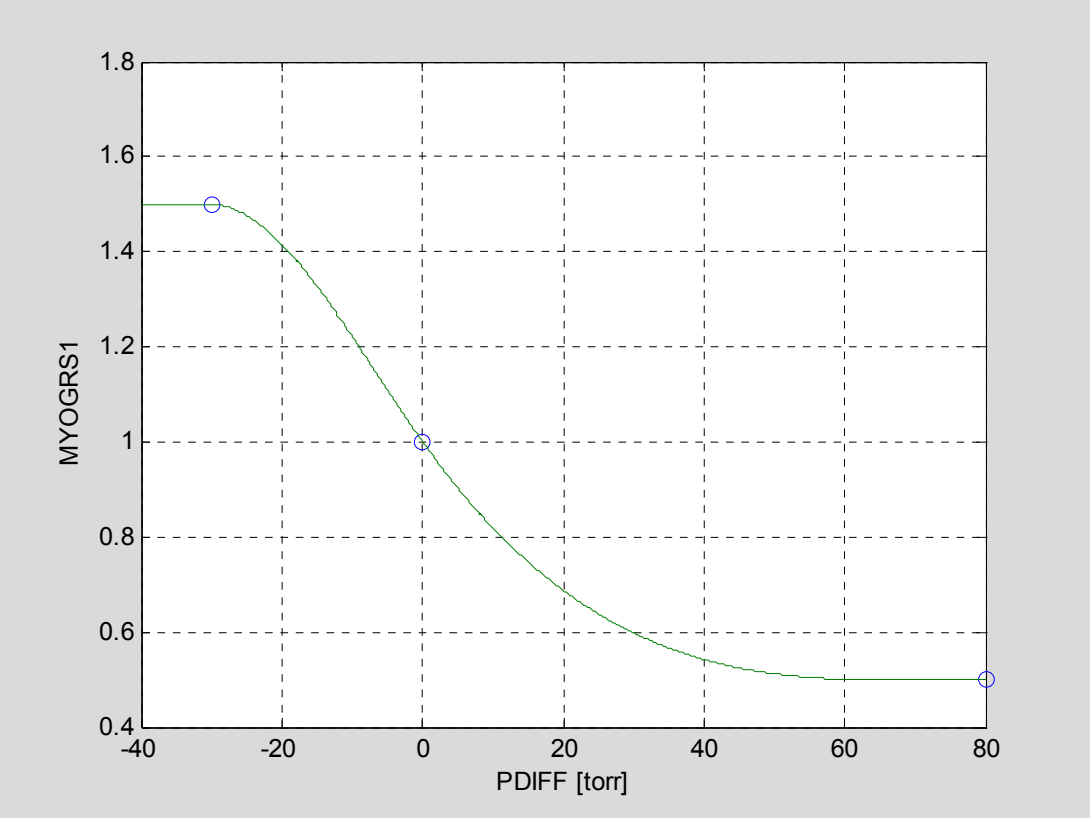
Calculate the cumulative pump efficiency factor (HPEF) by which to multiply the normalized right heart blood flow in equation (HD 31). This coefficient is influenced (roughly 60%) by the contractile activity of the left heart - therefore the left heart influence weighting factor (QRF=0.6) is multiplied by the ratio of the left ventricular instantaneous cardiac output (QLO) to the normalized value (QLN) - normalized with respect to the filling pressure in the left atrium - see equation (HD 43). The next part cumulatively calculates the effect of factors on the right ventricle - the effect of right ventricular pressure load, expressed by the factor (RVM) - from the previous equation, the effect of autonomic pacing on right ventricular inotropy (AUH), the effect of right heart inotropy, expressed by the ratio to normal (HSR), the effect of possible myocardial damage during shock and other factors, expressed by the factor (HMD), and the inotropic effect of right heart hypertrophy (HPR):

*HPEF=(1.-QRF)*RVM*AUH*HSR*HMD*HPR+QRF*QLO/QLN* (HD 67)

Calculation of the effect of myogenic stimulation

Myogenic stimulation consists in increasing the resistance of the arterioles of the peripheral tissues of the large circulation at an increase in pressure. Myogenic stimulation is dependent on arterial pressure (PA) and capillary pressure (PC). The rate of myogenic response is influenced by the time constant MYOGTAU (normally 240 min)). The magnitude of the intrinsic response is approximated by a spline function interleaving the experimental data of conductivity change (inverse of resistance) proposed by Coleman. The multiplicative factor TENSGN determines the amplification of the myogenic response (normally TENSGN=1).

PDIFF	MYOGRS1	SLOPE
-30	1.5	0
0	1	-0.02
80	0.5	0



$$PDIFF=(PA+PC)-PADAPT \quad \text{(HD 68)}$$

$$DPADAPT=PDIFF/MYOGTAU \quad \text{(HD 69)}$$

$$PADAPT=\int (DPADAPT)\, dt \quad \text{(HD 70)}$$

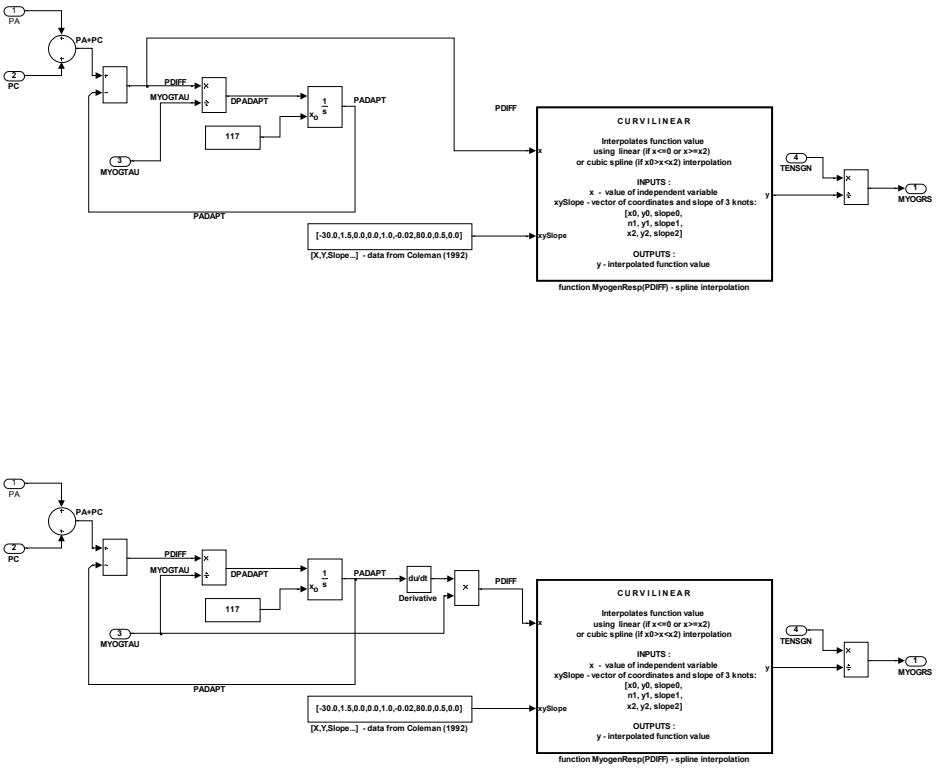
$$MYOGRS1=function\ myogenResp(PDIFF) \quad \text{(HD 71)}$$

$$MYOGRS=TENSGN/MYOGRS1 \quad \text{(HD 72)}$$

Implementation note:

When implementing the complex model in the Simulink environment, to avoid algebraic looping, we include the function myogenResp(PDIFF) (Eq. HD71) after the integrator calculating PADPT (in Eq. 70). Therefore, to get back the value of PDIFF we derive the value of PADAPT and multiply the result by the constant MYOGTAU:

*MYOGRS1=function myogenResp(PDIFF)=function myogenResp((dPADAPT/dt)*MYOGTAU)*



Original and modified implementation of myogenic control to remove the algebraic loop

Introduction of damping for numerical stability in model implementation

In order to improve the numerical stability of the simulation when the flow volumes of the model are changed, it is advisable to introduce damping factors for the filling of the right and left atria when implementing the model. Therefore, in each integration step, just before calculating the changes in the blood volumes of the pulmonary arteries and left atrium including the pulmonary veins (see equations HD 33-34, HD 39-40), we correct the currently calculated value of the blood outflow from the pulmonary arteries to the pulmonary veins and left atrium (QPO) with respect to the instantaneous value of the blood outflow from the left atrium (QLO):

$$QPO=(QPO-QLO)*0.25+QLO \qquad \text{(HD 73)}$$

Similarly, just before calculating the blood volume in the systemic veins and in the right atrium (see equations HD7-8 and HD17-18), we correct the currently calculated value of the blood outflow from the systemic veins to the right atrium (QVO) with respect to the current value of the blood outflow from the right atrium (QRO):

$$QVO=(QVO-QRO)*0.25+QRO \qquad \text{(HD 74)}$$

Heart rate and systolic volume

The input to the module is the multiplication coefficient of the effect of autonomic stimulation on heart rate (AUR), the direct effect of right atrial pressure (PRA) on the increase in heart rate - a rise in pressure by 5 torr leads to an increase in frequency by 10 beats, the multiplier (HMD) expressing the effect of heart damage - the depressing effect of hypoxia, shock and other factors on the heart (in an intact heart HMD=1, in damaged heart HMD>1):

$$HR=(32.+40.*AUR+PRA*2.)*((HMD-1.)*.5+1.) \quad \text{(HD 74)}$$

Systolic volume is calculated from the blood flow from the left heart (QLO) divided by the heart rate (HR):

$$SVO=QLO/HR \quad \text{(HD 75)}$$

Effect of tensile relaxation of large veins on residual venous volume (VVS0)

With an increase in the filling of the venous system due to relaxation of the musculature of the large veins, the residual volume (filling the venous system at zero pressure) increases. Two mechanisms of tensile relaxation of the great veins are considered in the model, which differ in the speed of the reflex response.

Calculation of the long time response to venous volume envelope (VVE) depends on the time constant (SRK2=10,000) and the response sensitivity coefficient (SR2=8), (note in the original Guyton model of 72 the SR2=5, in 86 Guyton gives a value of SR2=8):

$$DVV6=((VVE-.3)*SR2-VV6)/SRK2 \quad \text{(HD 76)}$$

$$VV6=\int (DVV6)\,dt \quad \text{(HD 77)}$$

The calculation of the shorter time response to venous filling (VVE) is similar - it depends on the time constant (SRK=60) and the response sensitivity coefficient (SR=1):

$$DVV7=(VVE-.3)*SR-VV7)/SRK \quad \text{(HD 78)}$$

$$VV7=\int (DVV7)\,dt \quad \text{(HD 79)}$$

Feedback effect of volumoreceptors in the right atrium

Stimulation of volumoreceptors in the right atrium affects (inhibits) the output of antidiuretic hormone - this contribution of atrial receptor stimulation to ADH secretion is expressed by the variable AH7. Atrial volumoreceptor stimulation also affects reflex relaxation of the musculature of the great veins, which is reflected by an increase in residual venous volume (ATRVFB - see equation HD 21) and a decrease in resistance in the nonmuscular and muscular parts of the circulation (ATRRFB - affects the R1 coefficient see equation HD 46).

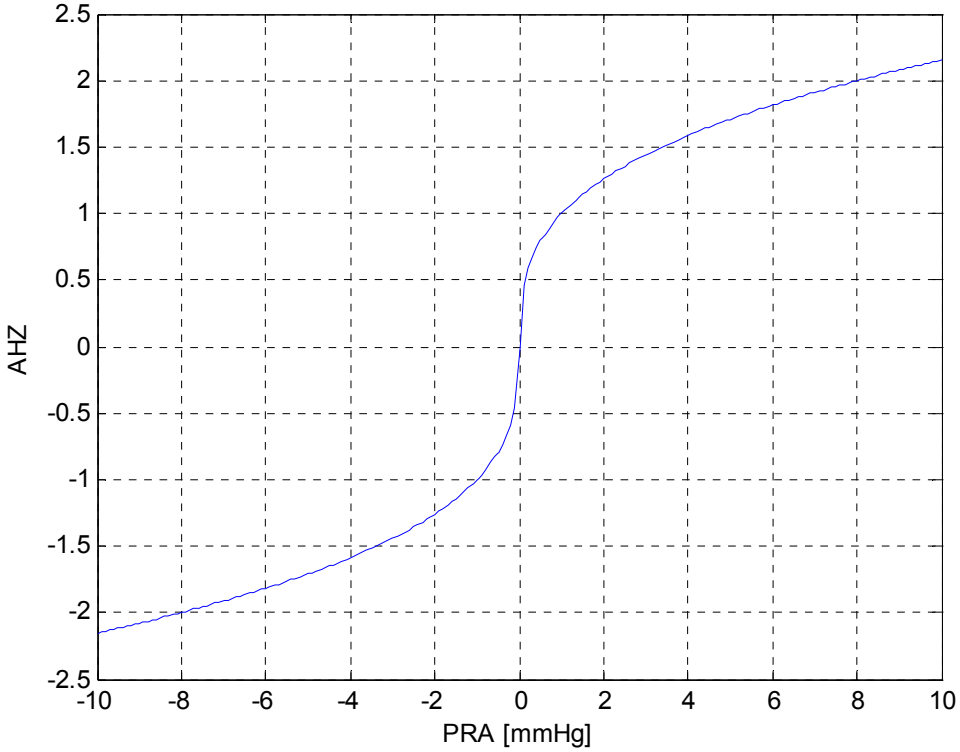
First, the nonlinear dependence of the AHZ intermediate factor on right atrial pressure (PRA) is calculated using a functional polynomial approximation, considering the sensitivity coefficient (AH9=1.0):

$$AH10=0.333 \quad \text{(HD 80a)}$$

$$AHZ2=(abs(PRA))\text{^}AH10 \quad \text{(HD 80b)}$$

$$\text{if } PRA<0, \text{ then } AHZ2=-AHZ2 \quad \text{(HD 80c)}$$

*AHZ=AH9*AHZ2* (HD 81)



The output value of the effect of atrial volumoreceptor stimulation (AH7) is calculated as the deviation of the intermediate value of AHZ from the currently set value of resting volumoreceptor stretch (AHY). The "resting activity" setting of the volumoreceptors (AHY) gradually adapts to the prolonged stretch - in the model this is expressed by the integration term. The rate of adaptation depends on the time constant of volumoreceptor adaptation (AH11=1000):

DAHY=(AHZ-AHY)/AH11 (HD 82)

$AHY=\int (DAHY)\, dt$ (HD 83)

AH7=(AHZ-AHY) (HD 84)

Note: In the original classical Guyton model from 1972, the value of AHZ was calculated as linearly dependent on PRA (AHZ=0.2*PRA) and the value of the time constant AH11 was 10000/7.

The effect of volumoreceptors in the right atrium on the change in the residual volume of the systemic venous circulation (ATRVFB - see equation HD 21) is calculated from the value of the effect of volumoreceptor irritation (AH7) as a function of the sensitivity coefficient (ATRVFBM). The value of the sensitivity coefficient is reported by Guyton in 86 as zero in normal subjects - i.e., in practice, this effect does not normally apply. For reasons of damping the oscillations in the system, we still introduce a damping integration term when calculating the ATRVFB value.

*ATRVFB0=ATRVFBM*AH7* (HD 85a)

$$DATRVFB=(ATRVFB0-ATRVFB)*0.1 \quad \text{(HD 85b)}$$

$$ATRVFB=\int (DATRVFB)\,dt \quad \text{(HD 85c)}$$

Similarly, the application of the influence of atrial volumoreceptors on the reflex change in the resistance of the systemic vasculature of the non-muscular tissues (ATRRFB - see equation HD 46) depends on the sensitivity coefficient (ATRRFBM)- but its value is also reported by Guyton in 86 as zero in normal subjects - so practically this influence does not normally apply. The value of the multiplication coefficient ATRRFB in the equation HD 46 is in the denominator and must not be negative, therefore we still introduce a check for underestimation of the value 0.1 (kdz, see equation HD 46 due to the reflex must not decrease the resistance more than ten times) :

$$ATRRFB=ATRRFBM*AH7+1.0 \quad \text{(HD 86a)}$$
$$if\ ATRRFB<0.1\ then\ ATRRFBM=0.1 \quad \text{(HD 86b)}$$

Application of cardiac hypertrophy and cardiac damage by tissue hypoxia

The inotropic effect of right heart hypertrophy (HPR), expressed as a relative ratio to the norm (which is applied in equation HD 67) depends mainly on the long-term effect of pulmonary artery pressure (PPA), or its ratio to the norm, on the basal inotropy of the right heart, expressed as a ratio to the norm (HSR) - the greater the basal inotropy, the less the tendency to hypertrophy (HSR is an input parameter of the model). Another factor that applies here is the cardiac output per minute (QAO), more precisely, its ratio to the norm. Multiplying these realistic factors we get:

$$PP3=(PPA/15)*(QAO/5)/HSR=PPA*QAO/HSR/75 \quad \text{(HD 87)}$$

The target degree of hypertrophy (HPR1) is then determined by the sensitivity exponent (Z13=0.625):

$$HPR1=PP3\text{^}Z13 \quad \text{(HD 88)}$$

Hypertrophy develops slowly, the time constant here is 57 600 min:

$$DHPR=(HPR1-HPR)/57600 \quad \text{(HD 89)}$$

$$HPR=\int (DHPR)\,dt \quad \text{(HD 90)}$$

Similarly, the inotropic effect of left heart hypertrophy (HPL), expressed as a relative ratio to the norm (which is applied in equation HD 44), depends mainly on the long-term effect of systemic arterial pressure (PA), or its ratio to the norm, on the basal inotropy of the left heart, expressed as a ratio to the norm (HSL) - the greater the basal inotropy, the less the tendency to hypertrophy (HSL is the input parameter of the model).
Another factor that applies here is the minute heart rate (QAO), more precisely, its ratio to the norm. By multiplying these realistic factors we get:

$$PA4=(PA/100)*(QAO/5)/HSL=PA*QAO/HSL/500 \quad \text{(HD 91)}$$

The target degree of hypertrophy (HPL1) is then determined by the sensitivity exponent (Z13=0.625):

$$HPL1=PA4\text{^}Z13 \quad \text{(HD 92)}$$

Hypertrophy develops slowly, the time constant here is 57 600 min:

DHPL=(HPL1-HPL)/57600 (HD 93)

$HPL=\int (DHPL)\, dt$ (HD 94)

ČMyocardial pumping function can be affected by hypoxia - the depressing effect of tissue hypoxia on cardiac pumping function is expressed by the multiplicative factor HMD (see equations HD 44, HD 67, HD 74), its value is normally 1, in hypoxia it can be less than 1. If the oxygen tension in the non-muscular tissues (POT) falls below 5 torr, the value of HMD will decrease - the integration term in equation HD 96 is bounded above by one (and below by zero):

*DHM=(POT-5.0)*0.0025* (HD 95)

$$HMD = \int_0^1 (DHM)dt$$ (HD 96a)

if HMD>1, thn HMD=1 (HD 96b)
if HMD<0, then HMD=0 (HD 96c)

Calculation of the mean circulatory filling pressure and the initial values of the volumes of individual parts of the bloodstream

First, we calculate the total residual volume expanding vessels but not yet increasing pressure (total unstressed volume) (VT0) as the sum of the residual blood volumes in the pulmonary veins and left atrium (VLA0), in the pulmonary arterial circulation (including the right ventricle) (VPA0), in the right atrium (VRA0) in the venous systemic circulation (VVS0) and in the systemic arterial circulation (including the left ventricle) (VAS0):

VT0=VLA0+VPA0+VRA0+VVS0+VAS0 (HD 97)

From the total blood volume (VB) we then calculate the total volume of blood stretching the blood vessels (VE0):

VE0=VB-VT0 (HF 98)

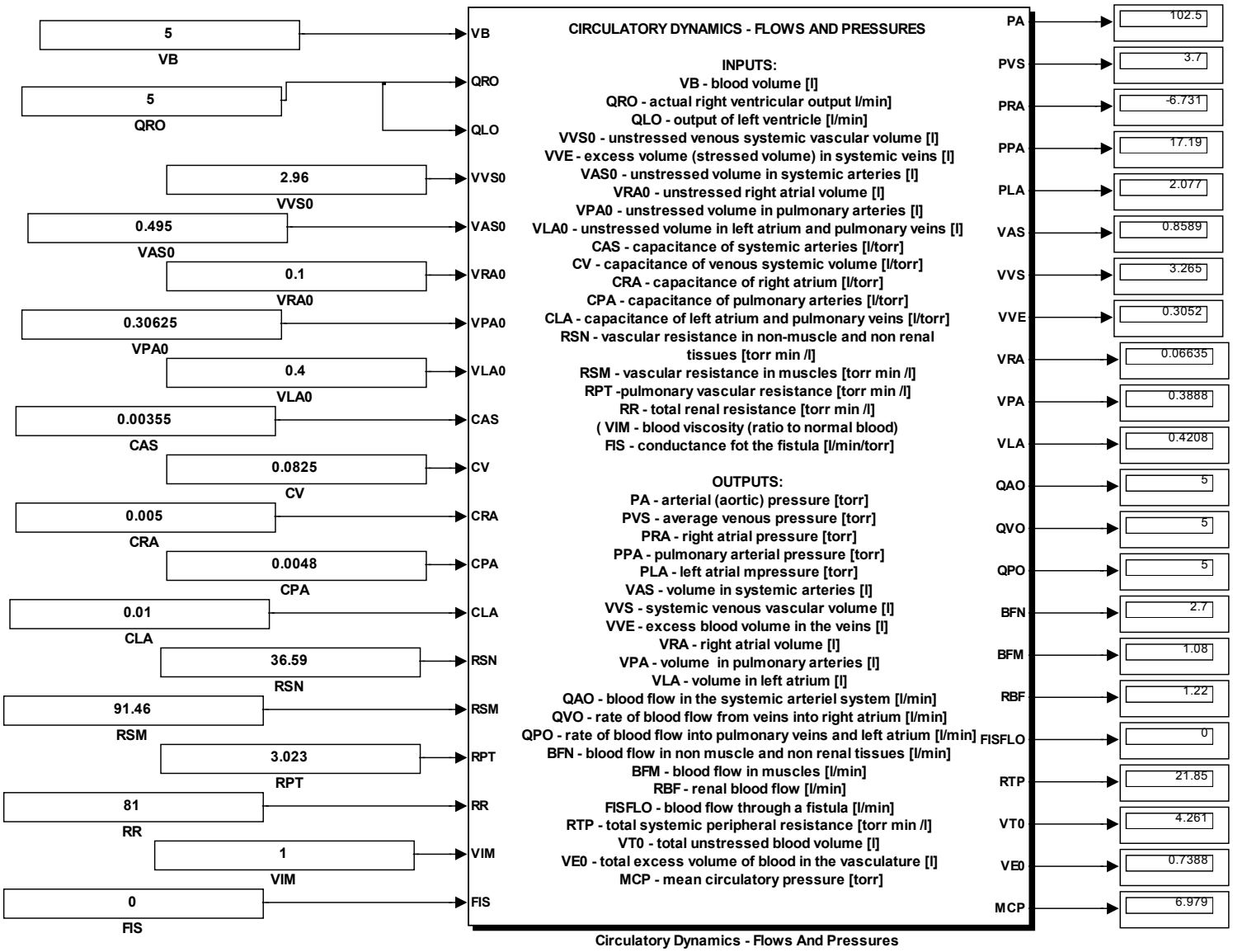
From the total volume of the dilating vessel and the compliance of the left atrium and pulmonary veins (CLA), the compliance of the pulmonary arteries (CPA), the compliance of the right atrium (CRA), the compliance of the venous systemic circulation (CV) and the compliance of the systemic ascending circulation (CAS), we can calculate the mean circulatory pressure, which is established in the bloodstream during circulatory arrest (this equation is the result of solving the system of equations (HD 98) and (HD 99) and the equations MCP=VEi/Ci, where VEi and Ci are the respective filling volumes of the different parts of the bloodstream dilating vessels and the respective compliance):

MCP=VE0/(CLA+CPA+CRA+CV+CAS) (HD 99)

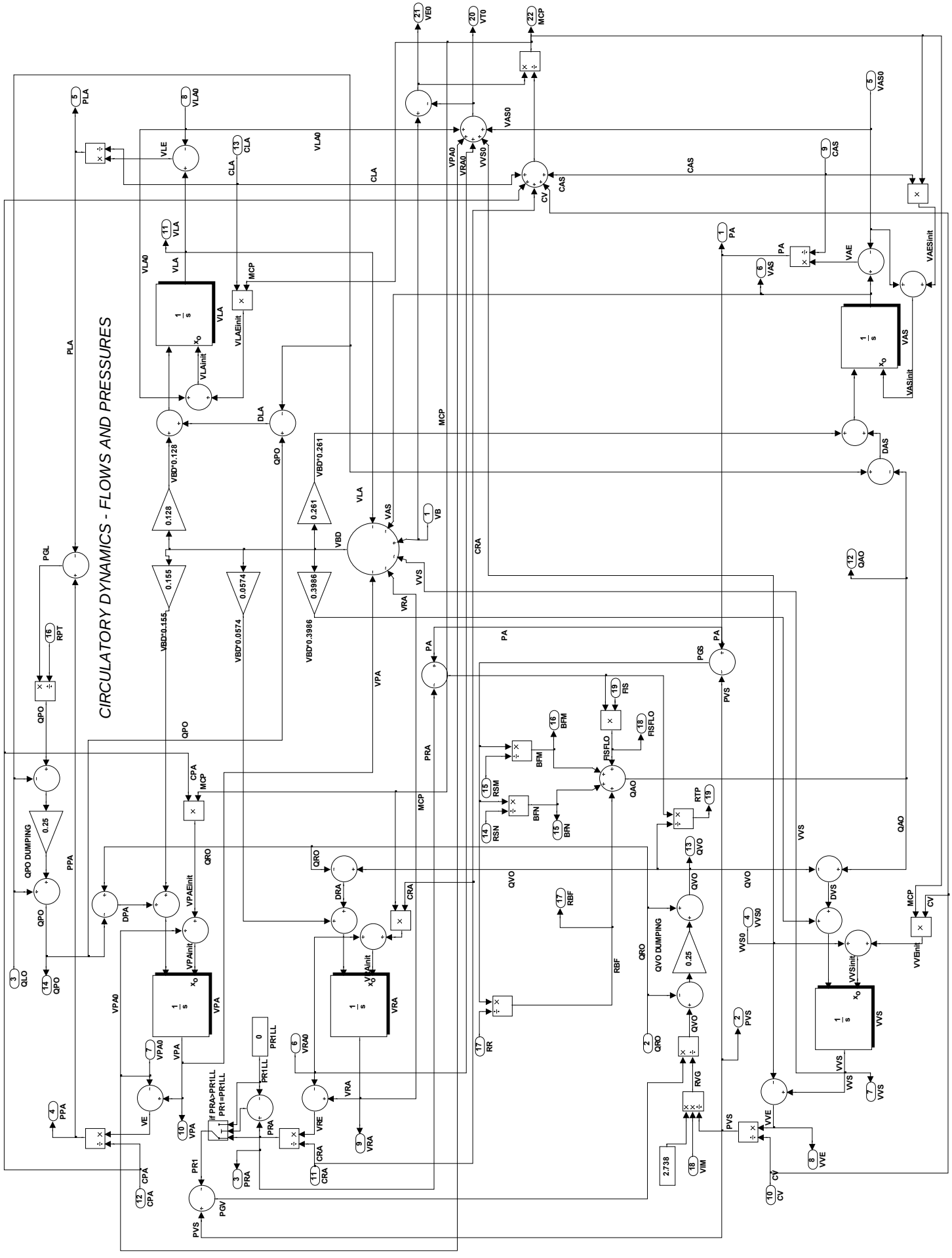
Finally, we calculate the blood volumes in the different parts of the bloodstream after circulatory arrest, when the mean circulatory filling pressure is established throughout the bloodstream and the blood is distributed to the different parts of the bloodstream according to their respective compliance. Calculate the initial blood volume in the arterial systemic circulation, including the left ventricle (VASinite), in the venous systemic circulation (VVSinite), in the right atrium (VRAinite), in the pulmonary arteries, including the right ventricle (VPAinite), and in the left atrium and pulmonary veins (VLAinite). We use these values as initial values in the integration terms in the equations (HD 08, HD 18, HD 27, HD 34, HD 40)[5] :

[5] This setting of initial values is based on zero minute flow conditions, where all pressures in the vasculature are equal to the mean circulating filling pressure of the MCP. A second alternative, setting to normative

VASinit=VAS0+MCP*CAS (HD 100)
VVSinit=VVS0+MCP*CV (HD 101)
VRAinit=VRA0+MCP*CRA (HD 102)
VPAinit=VPA0+MCP*CPA (HD 103)
VLAinit=VLA0+MCP*CLA (HD 104)



Circulatory Dynamics - Flows And Pressures


CIRCULATORY DYNAMICS - FLOWS AND PRESSURES
21 VED
20 VT0
22 MCP
5 PLA
8 VLA0
13 CLA
VLE
VLA0
CLA
VAS0
VPA0
VRA0
VVS0
5 VAS0
9 CAS
CAS
CV
1 PA
PA
6 VAS
VAE
VAEinit
11 VLA
VLA
MCP
VLAEinit
VLAinit
VAS
VASinit
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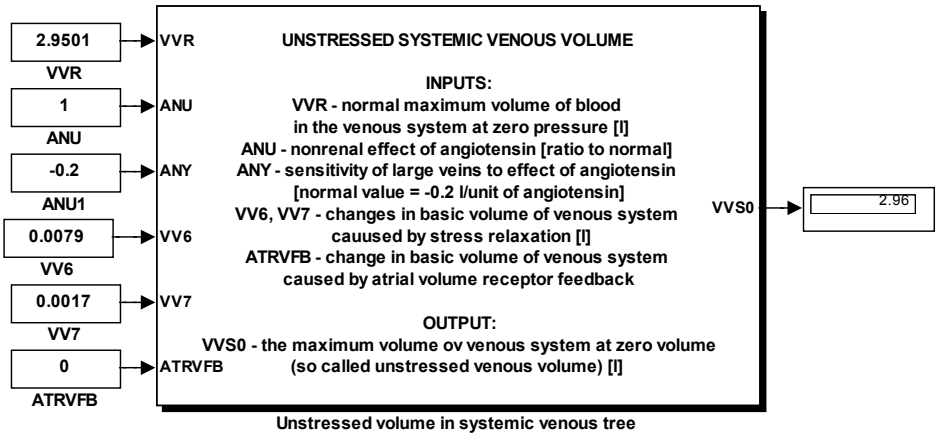
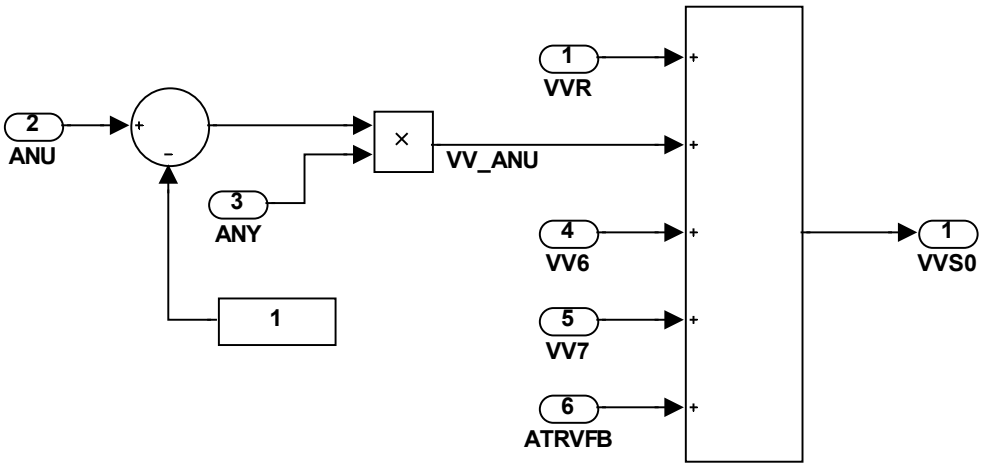
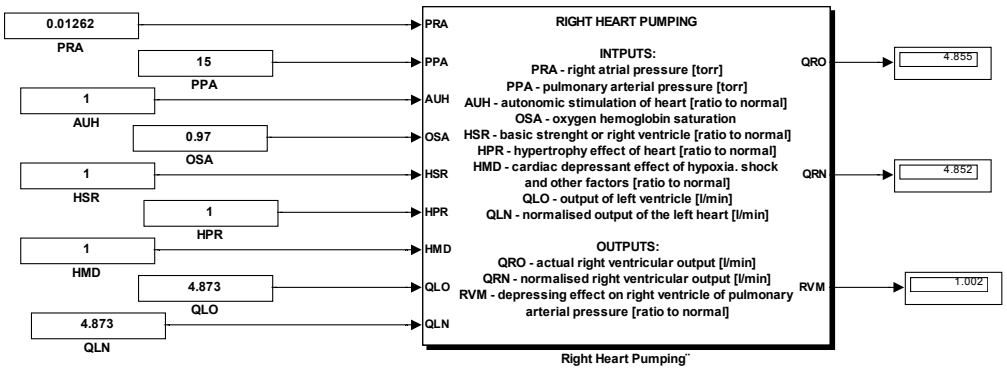
16 RPT
PA
PGS
PVS
19 FIS
16 BFM
18 FISFLO
BFM
FISFLO
QAO
15 RSM
BFN
14 RSN
15 BFN
RTP
19
13 QVO
QVO
VVS
QAO
QPO DUMPING
0.25
PPA
QPO
3 QLO
14 QPO
CPA
MCP
QRO
DRA
CRA
DPA
VPAEinit
VPAinit
VRAinit
17 RBF
RBF
QRO
QVO DUMPING
0.25
DVS
4 VVS0
VVS0
VVSinit
VVEinit
MCP
CV
VPA0
VPA
VRA
7 VPA0
0
PR1LL
6 VRA0
if PRA>PR1LL
PR1=PR1LL
17 RR
2 QRO
2 PVS
VVS
7 VVS
4 PPA
VE
10 VPA
PRA
VRE
9 VRA
RVG
VVE
8 VVE
PR1
3 PRA
CRA
11 CRA
2738
18 VIM
PGV
PVS
12 CPA
CPA
10 CV
CV

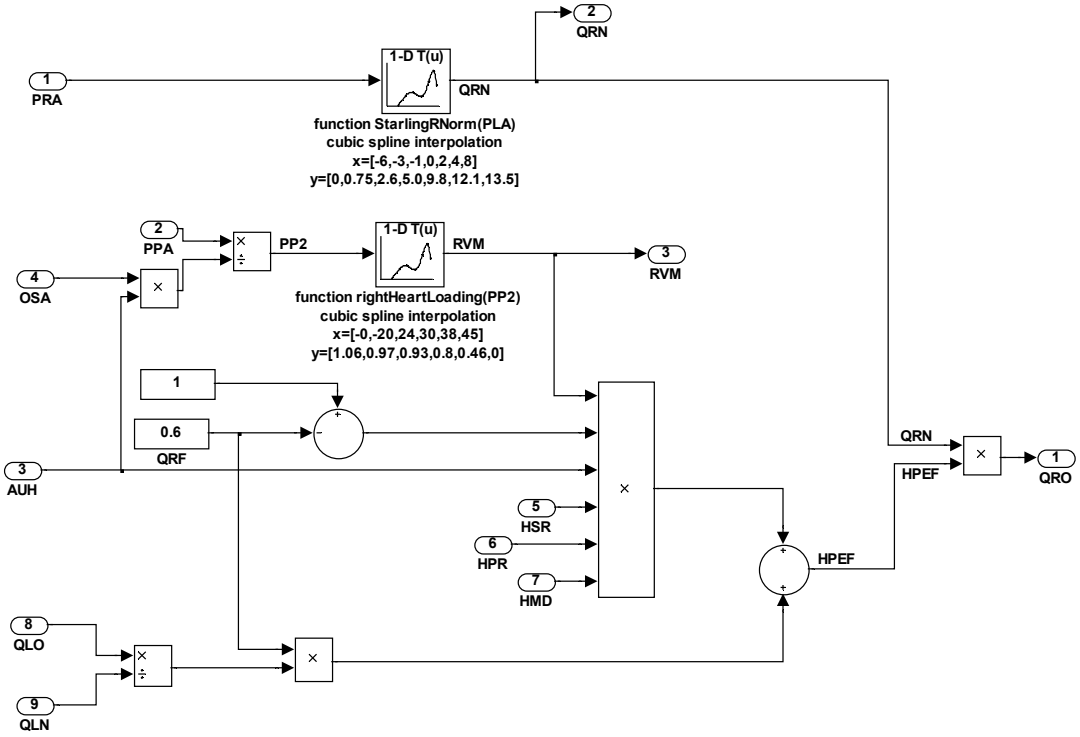


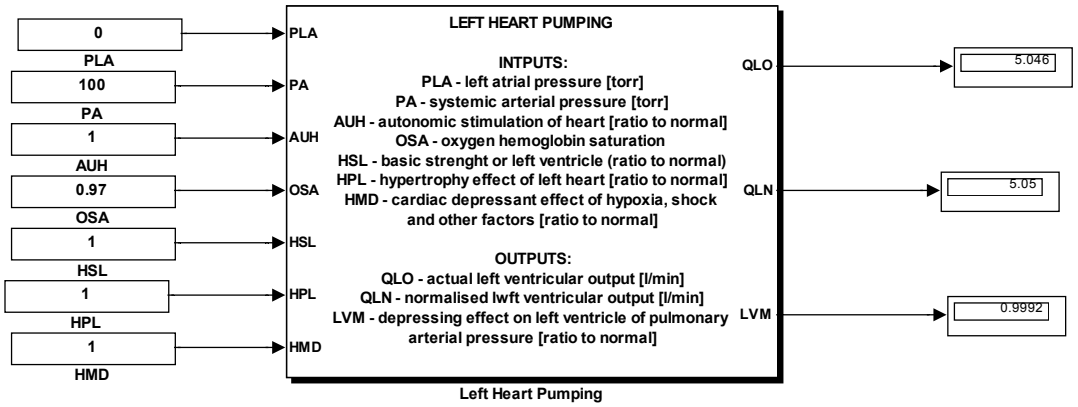
UNSTRESSED VOLUME IN SYSTEMIC VENOUS TREE

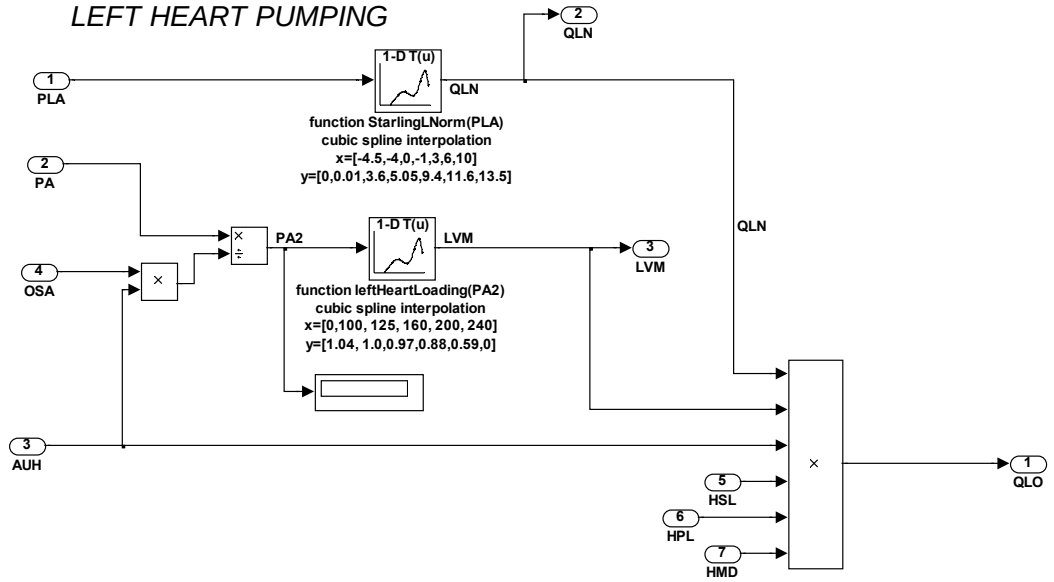


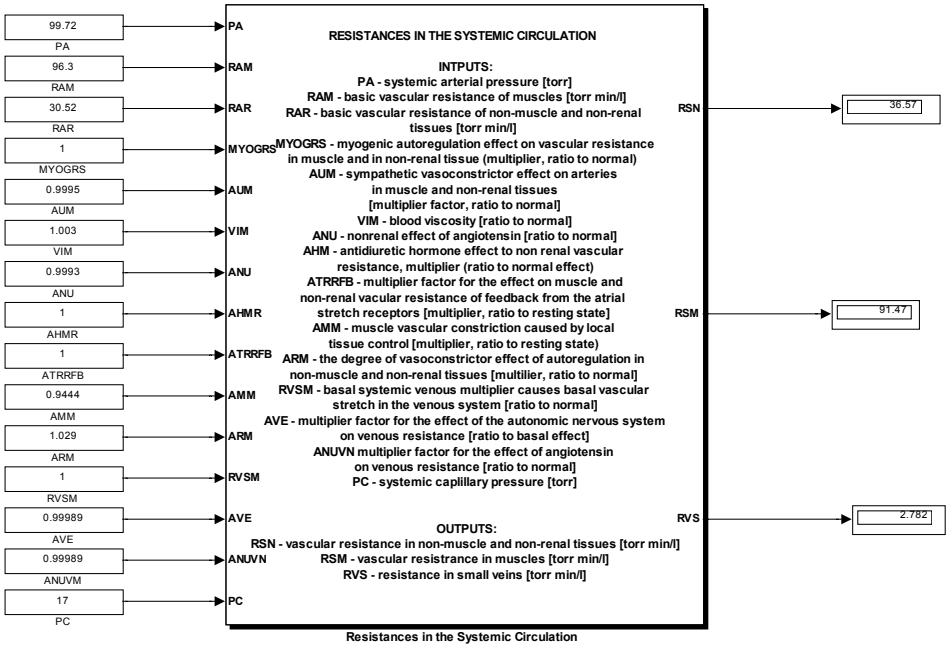


RIGHT HEART PUMPING

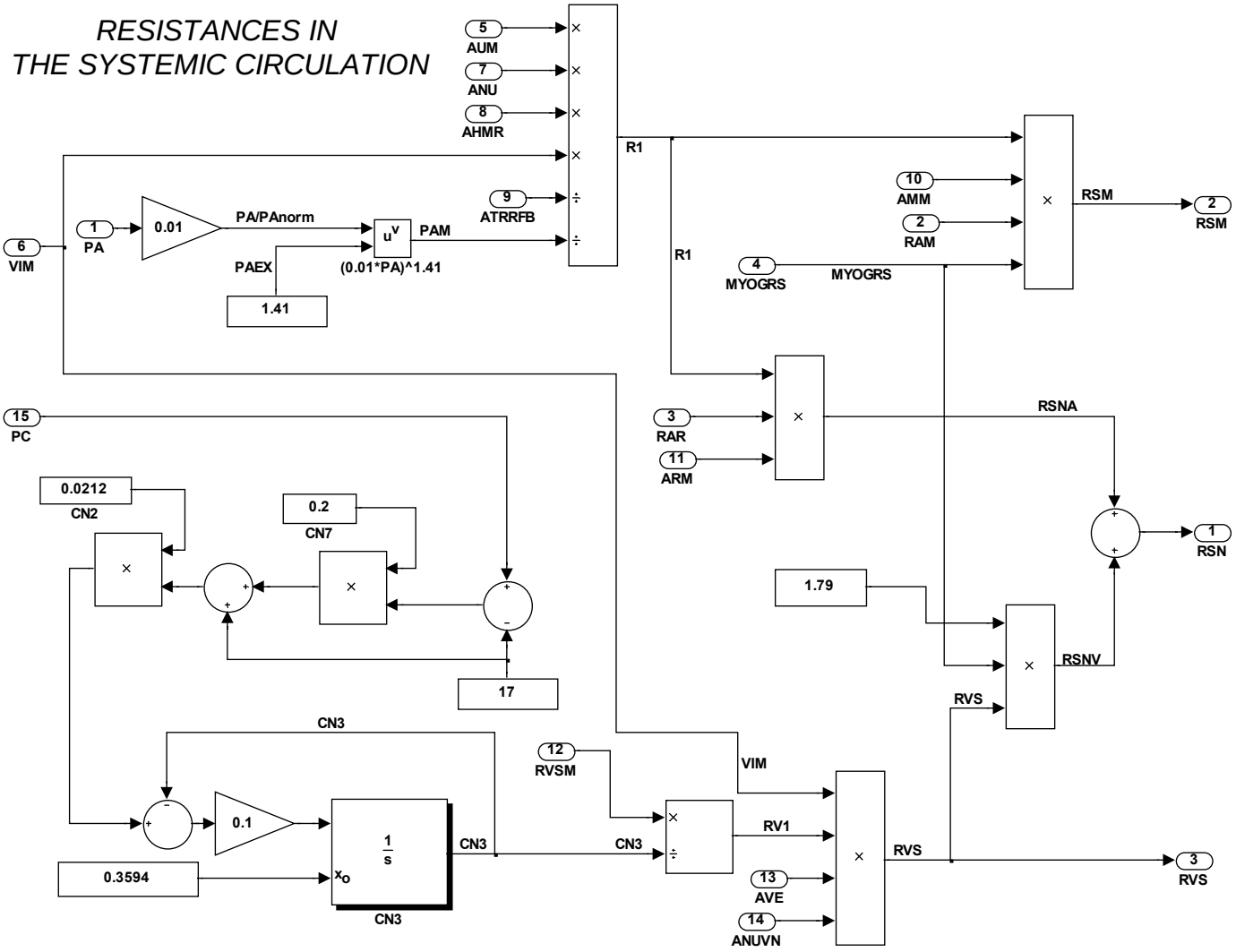


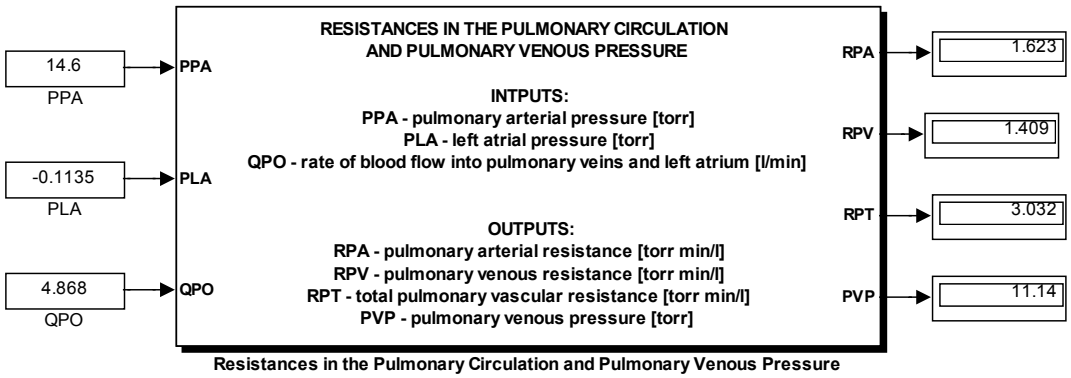

0
PLA
100
PA
1
AUH
0.97
OSA
1
HSL
1
HPL
1
HMD
LEFT HEART PUMPING
INTPUTS:
PLA - left atrial pressure [torr]
PA - systemic arterial pressure [torr]
AUH - autonomic stimulation of heart [ratio to normal]
OSA - oxygen hemoglobin saturation
HSL - basic strenght or left ventricle (ratio to normal)
HPL - hypertrophy effect of left heart [ratio to normal]
HMD - cardiac depressant effect of hypoxia, shock and other factors [ratio to normal]
OUTPUTS:
QLO - actual left ventricular output [l/min]
QLN - normalised lwft ventricular output [l/min]
LVM - depressing effect on left ventricle of pulmonary arterial pressure [ratio to normal]
QLO
QLN
LVM
5.046
5.05
0.9992
Left Heart Pumping


LEFT HEART PUMPING
1
PLA
1-D T(u)
QLN
2
QLN
function StarlingLNorm(PLA)
cubic spline interpolation
x=[-4.5,-4,0,-1,3,6,10]
y=[0,0.01,3.6,5.05,9.4,11.6,13.5]
2
PA
PA2
1-D T(u)
LVM
3
LVM
4
OSA
function leftHeartLoading(PA2)
cubic spline interpolation
x=[0,100, 125, 160, 200, 240]
y=[1.04, 1.0,0.97,0.88,0.59,0]
QLN
3
AUH
5
HSL
6
HPL
7
HMD
1
QLO



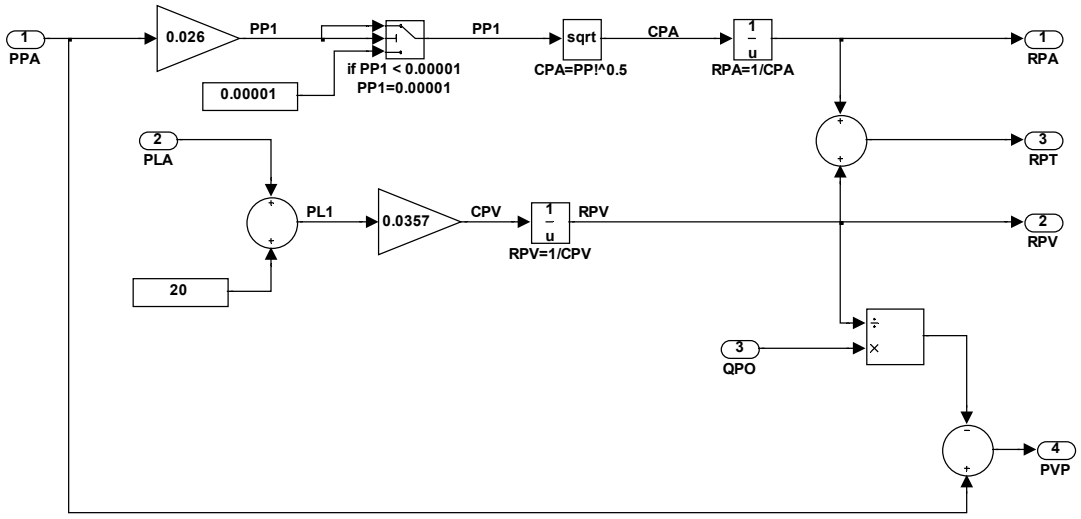
Resistances in the Systemic Circulation

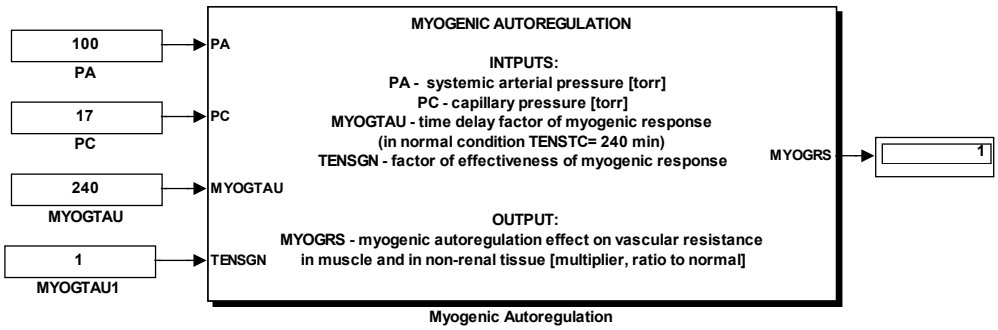


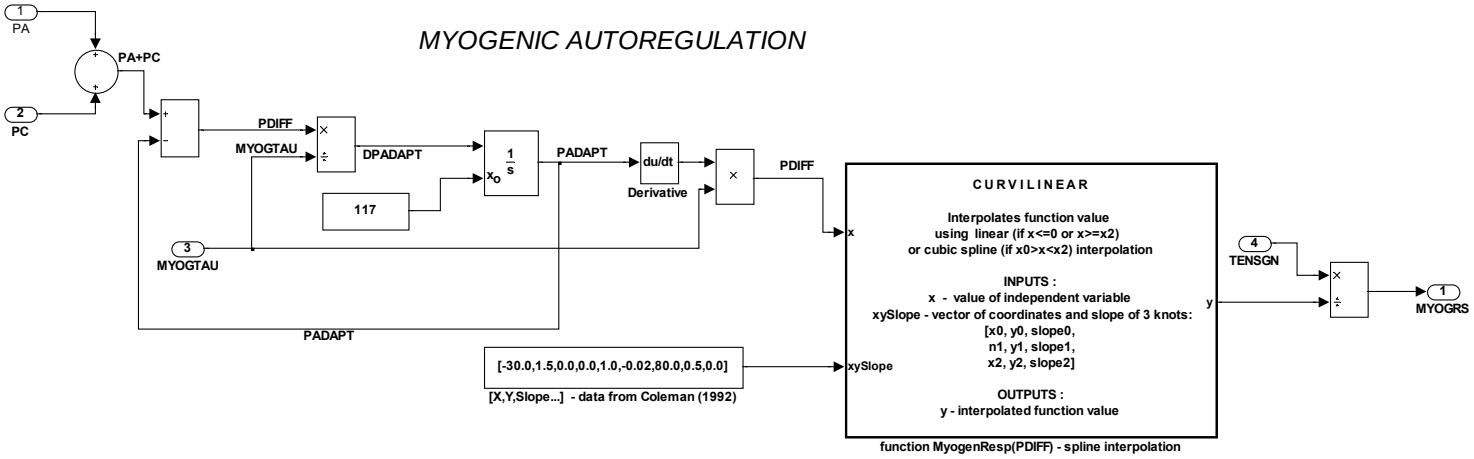


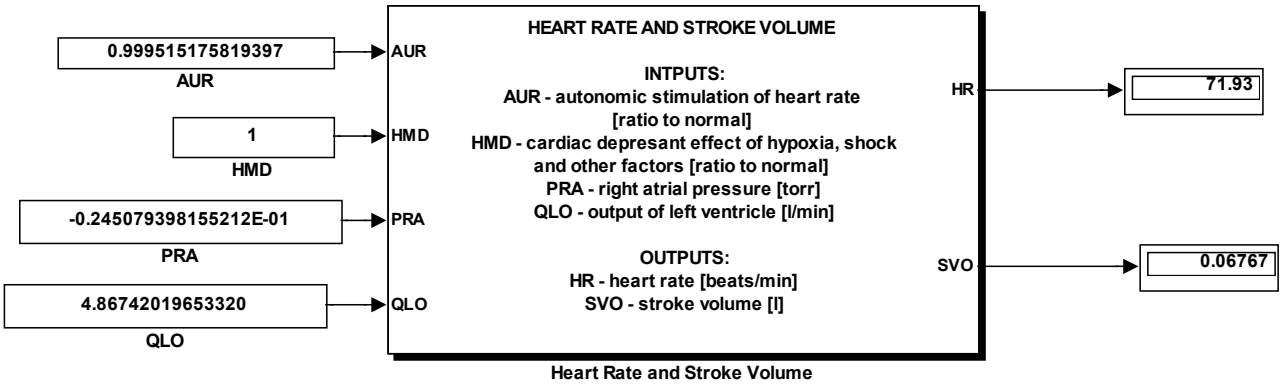
Resistances in the Pulmonary Circulation and Pulmonary Venous Pressure

RESISTANCES IN THE PULMONARY CIRCULATION AND PULMONARY VENOUS PRESSURE

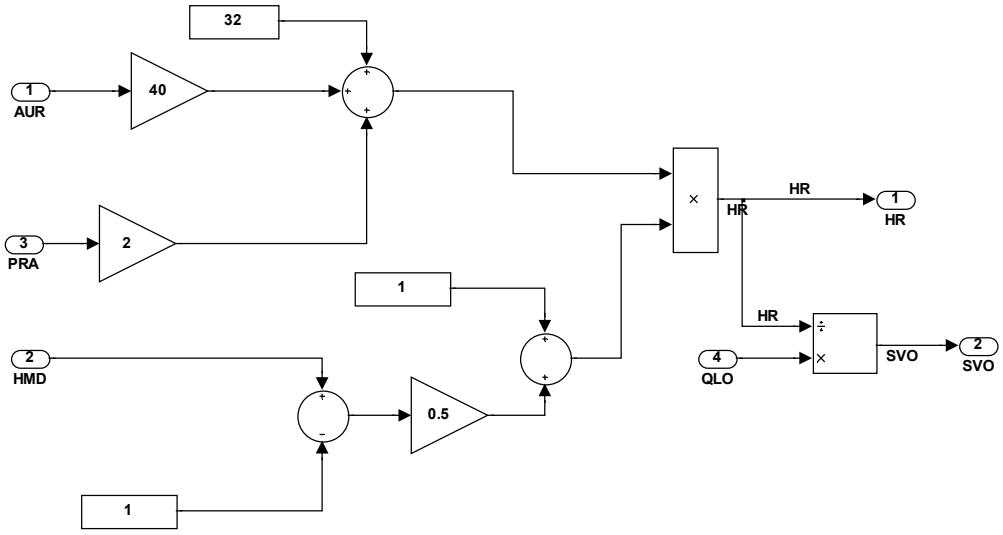


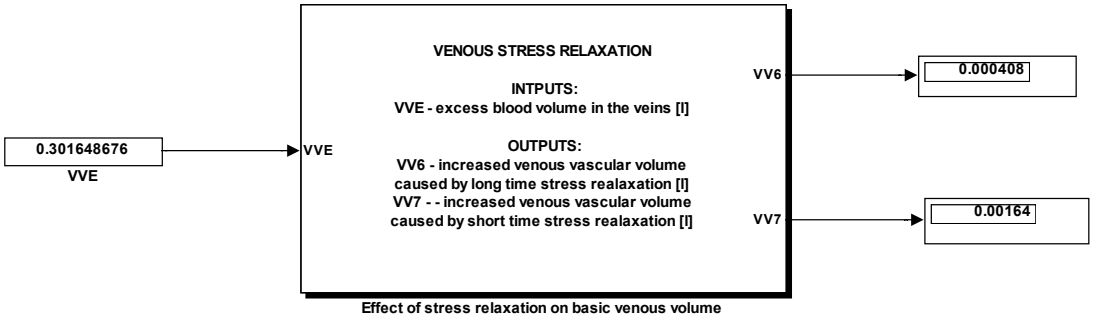

MYOGENIC AUTOREGULATION
100
PA
PA
17
PC
PC
240
MYOGTAU
MYOGTAU
1
TENSGN
MYOGTAU1
INTPUTS:
PA - systemic arterial pressure [torr]
PC - capillary pressure [torr]
MYOGTAU - time delay factor of myogenic response
(in normal condition TENSTC= 240 min)
TENSGN - factor of effectiveness of myogenic response
OUTPUT:
MYOGRS - myogenic autoregulation effect on vascular resistance
in muscle and in non-renal tissue [multiplier, ratio to normal]
MYOGRS
1
Myogenic Autoregulation


MYOGENIC AUTOREGULATION
1
PA
2
PC
PA+PC
PDIFF
MYOGTAU
DPADAPT
117
1/s
PADAPT
du/dt
Derivative
PDIFF
3
MYOGTAU
PADAPT
[-30.0,1.5,0.0,0.0,1.0,-0.02,80.0,0.5,0.0]
[X,Y,Slope...] - data from Coleman (1992)
CURVILINEAR
Interpolates function value
using linear (if x<=0 or x>=x2)
or cubic spline (if x0>x<x2) interpolation
INPUTS :
x - value of independent variable
xySlope - vector of coordinates and slope of 3 knots:
[x0, y0, slope0,
n1, y1, slope1,
x2, y2, slope2]
OUTPUTS :
y - interpolated function value
x
xySlope
y
function MyogenResp(PDIFF) - spline interpolation
4
TENSGN
1
MYOGRS

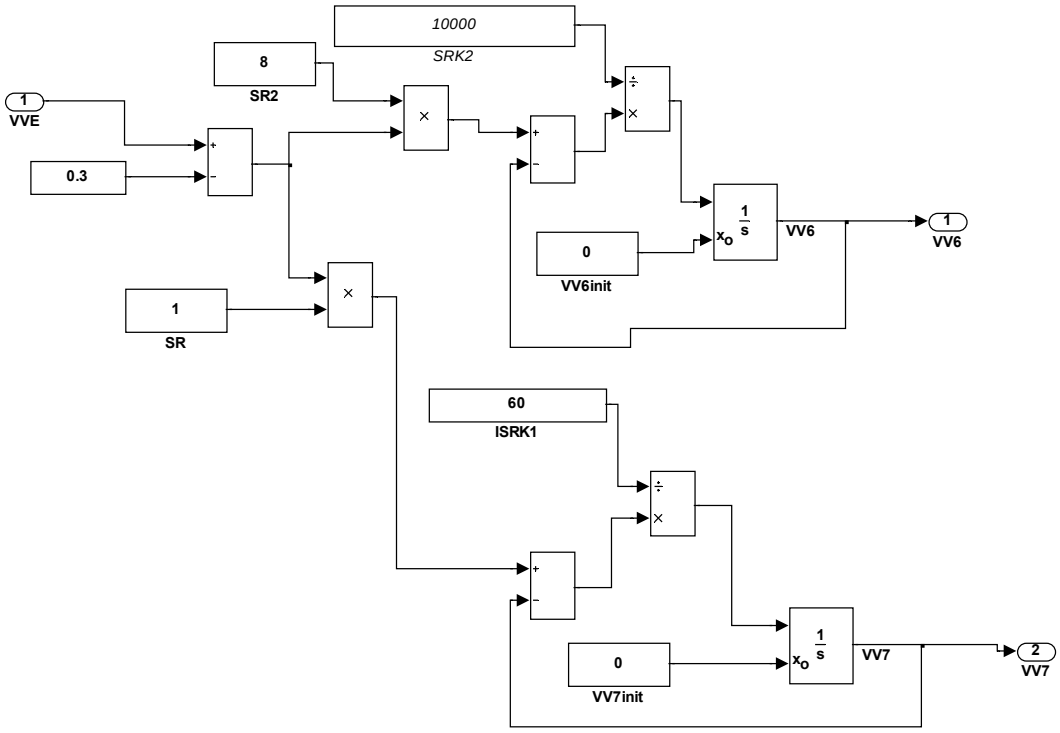


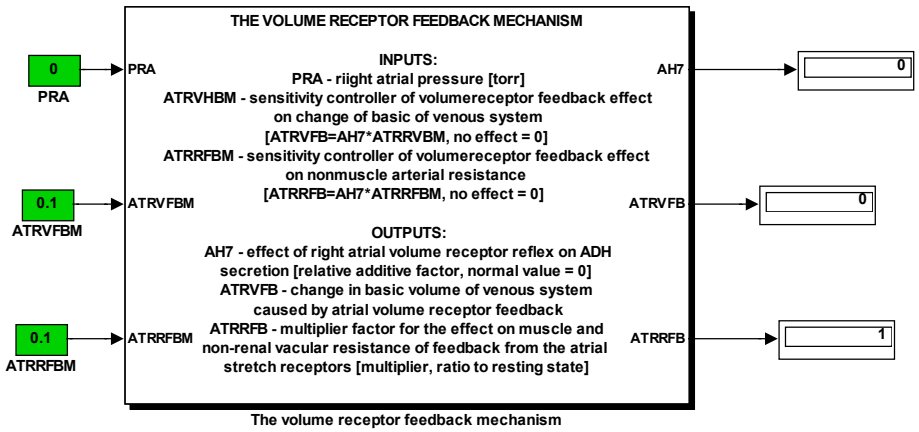
HEART RATE AND STROKE VOLUME





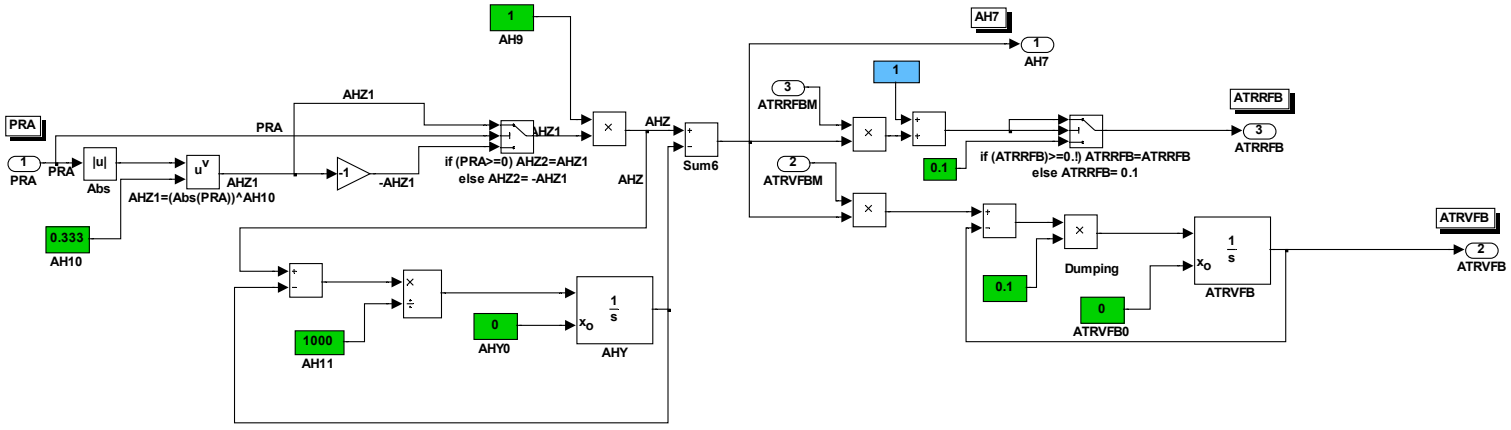
EFFECT OF STRESS RELAXATION ON BASIC VENOUS VOLUME

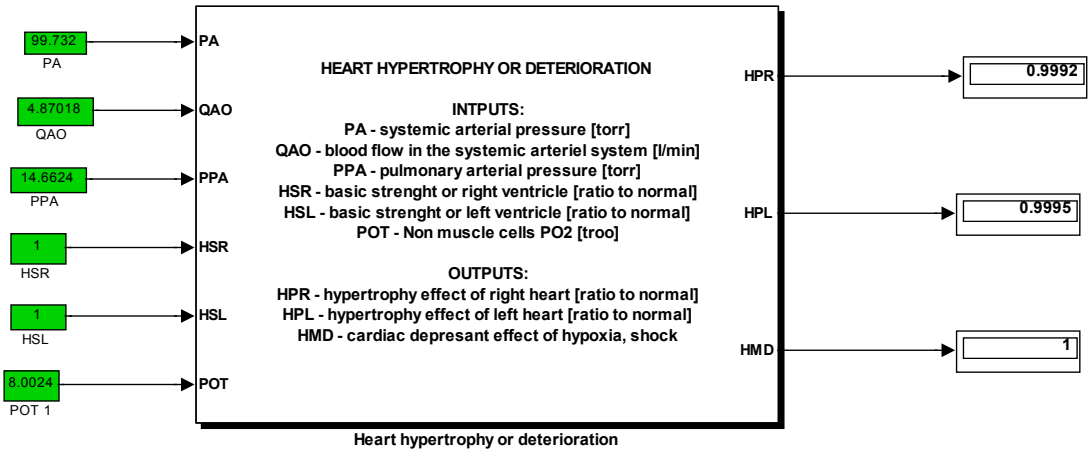




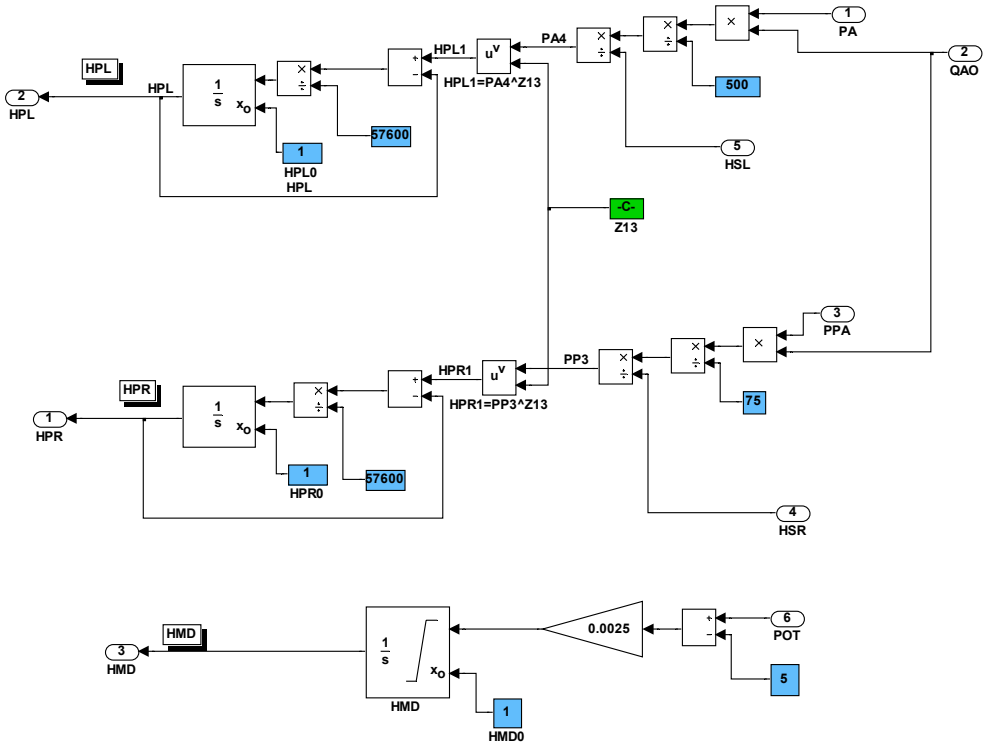
The volume receptor feedback mechanism

THE VOLUME RECEPTOR FEEDBACK MECHANISM





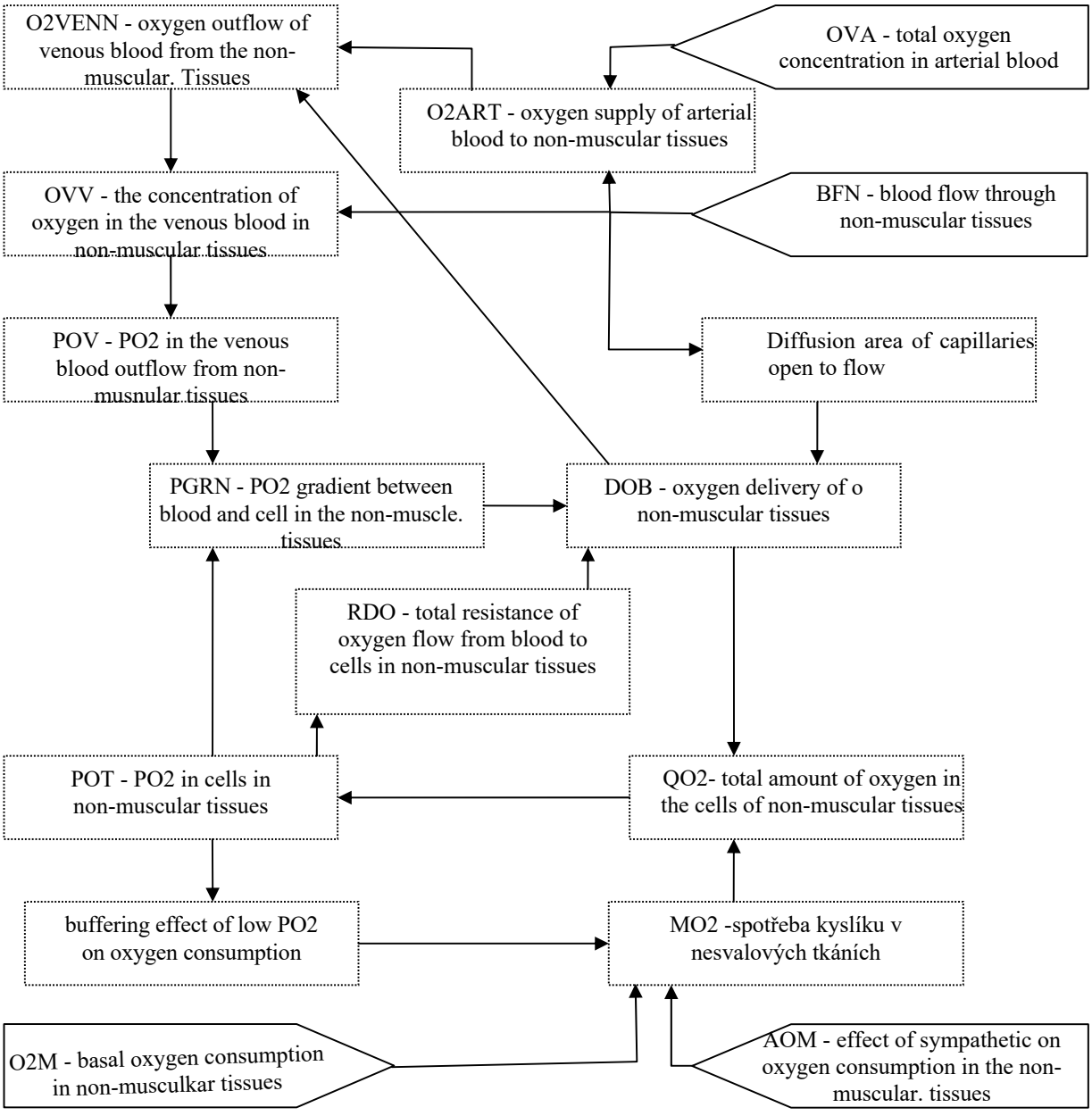
HEART HYPERTROPHY OR DETERIORATION



SUPPLY OF OXYGEN TO THE TISSUES

Tissues are divided into muscle and non-muscle tissues and the oxygen delivery to each of them is calculated separately. Oxygen delivery is calculated from total arterial blood oxygen concentrations, flow rates and oxygen consumption which can be inhibited by low tissue oxygen tension.

Oxygen delivery to non-muscular tissues



Arterial blood oxygen flux is calculated from the blood flow through non-muscular tissue (BFN) from the total arterial blood oxygen concentration (OVA):

$$O2ART=BFN*OVA \quad \text{(OD 01)}$$

The oxygen flux outflowing from non-muscular tissues is calculated from the oxygen flux flowing in arterial blood (O2ART) minus the rate of oxygen delivered to the tissues (DOB):

$$O2VENN=O2ART-DOB \quad \text{(OD 02)}$$

From the flow of oxygen in the venous blood and from the blood flow we can determine the concentration of oxygen in the venous blood flowing out of the non-muscular tissues:

$$OVV=O2VENN/BFN \quad \text{(OD 03)}$$

Dividing this concentration by the haematocrit (HK, expressed as a percentage) gives the oxygen concentration per litre of erythrocytes, and by dividing by the oxygen capacity of the blood, we can approximate the oxygen saturation of haemoglobin (as a percentage) in the venous blood flowing away from the non-muscular tissues of OSV1 - in this calculation Guyton neglected dissolved oxygen:

$$OSV1=O2VENN/BFN/HM/5 \quad \text{(OD 04)}$$

To prevent oscillations during abrupt saturation changes, damping is introduced using integration and damping coefficient (Z7) -value of this coefficient Z7=5:

$$DOSV=(OSV1-OSV)/Z7 \quad \text{(OD 05)}$$

$$OSV=\int (\ DOSV)\ dt \quad \text{(OD 06)}$$

The calculation of the partial pressure of oxygen in the outflowing venous blood (POV) is calculated according to the linearized slope of the initial part of the hemoglobin saturation curve:

$$POV=OSV*57.14 \quad \text{(OD 07)}$$

The partial pressure gradient of oxygen between venous (or outflowing capillary) blood and tissues (PGRN) is taken in the model as the difference between the oxygen tension in venous blood (POV) and the oxygen tension in cells (POT):

$$PGRN=POV-POT \quad \text{(OD 09)}$$

Oxygen delivery to tissues (DOB) is directly proportional to the partial pressure gradient of oxygen (PGRN) and the diffusion area of capillaries - the latter is proportional to blood flow (BFN). The coefficient (PN5=960) expresses the influence of the diffusion area of the capillaries, the density of the capillary network, etc... Oxygen delivery is inversely proportional to the resistance of oxygen flow between capillaries and cells (the diffusion pathway is hidden in this resistance):

$$DOB=PGRN*BFN*PN5/RDO \quad \text{(OD 10)}$$

The rate of change of the amount of oxygen in the tissues is equal to the difference between the oxygen influx from the blood (DOB) and its metabolic consumption (MO2):

$$DO2N=DO2-MO2 \quad \text{(OD 11)}$$

The total amount of oxygen (QO2) in non-muscle tissue cells will then

$$QO2 = \int DO2N\ dt \quad \text{(OD 12)}$$

The partial pressure of oxygen in non-muscular tissues (POT) is calculated from the total amount of dissolved oxygen in the tissues:

$$POT=QO2*0.00333 \quad \text{(OD 13)}$$

Calculation of the resistance of oxygen flow from capillaries to cells (RDO) - the resistance includes the diffusion pathway. Resistance is roughly cubically dependent on tissue pO2, because the calculation takes into account the increase in capillary density at low values of oxygen tension (POT), when more capillaries are opened, therefore the diffusion pathway is reduced and therefore the value of resistance to oxygen flow. The sensitivity is determined by the exponent (EP=3) and the threshold value (RDOmin=50):

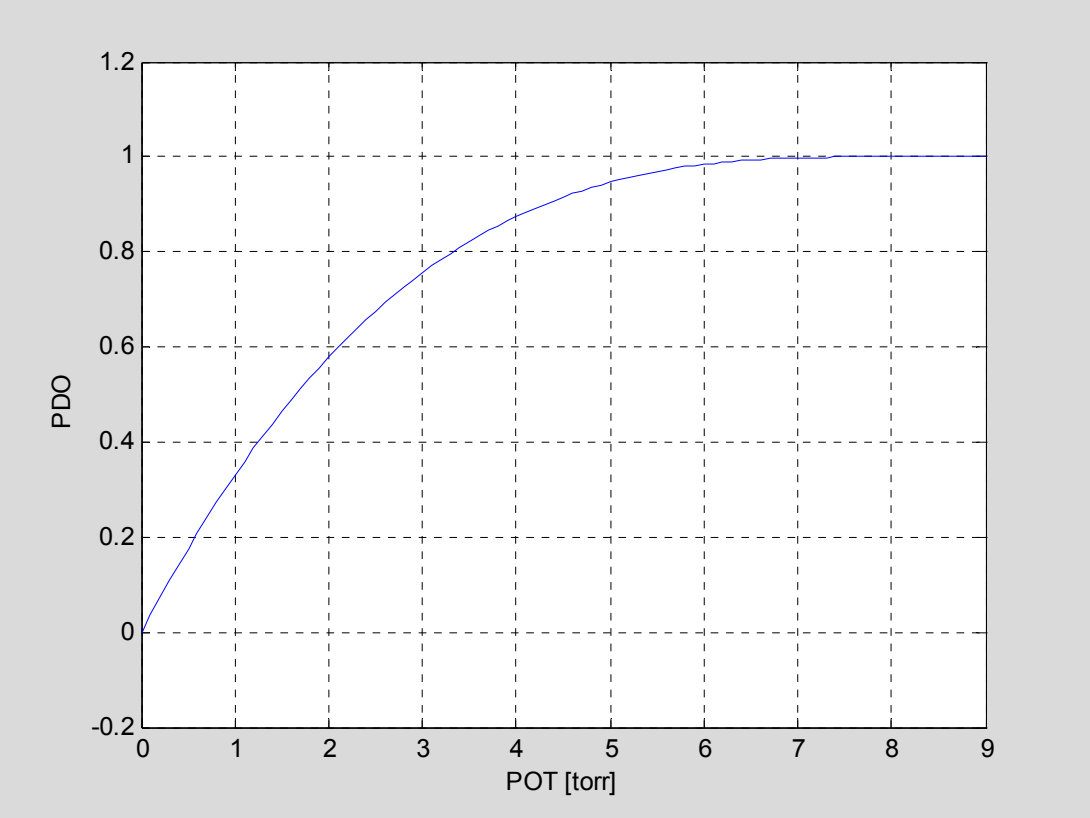
$$RDO=POT^{EP} \quad \text{(OD 14a)}$$
$$\text{if } RDO<RDOMIN, \text{ then } RDO=RDOmin \quad \text{(OD 14b)}$$

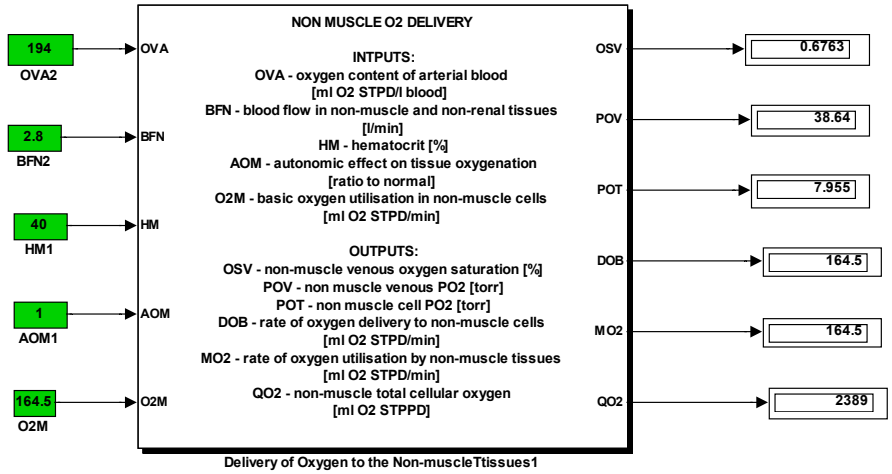
Oxygen consumption in non-muscle tissues (MO2) is influenced by sympathetic stimulation and can be inhibited by low tissue oxygen tension. Therefore, when calculating the oxygen consumption in non-muscle tissues (MO2), the multiplicative factor expressing this dependence (AOM) together with the multiplicative factor excluding the dampening effect of low oxygen tensions on oxygen consumption (PDO) multiplies the basal oxygen consumption in non-muscle tissues (O2M):

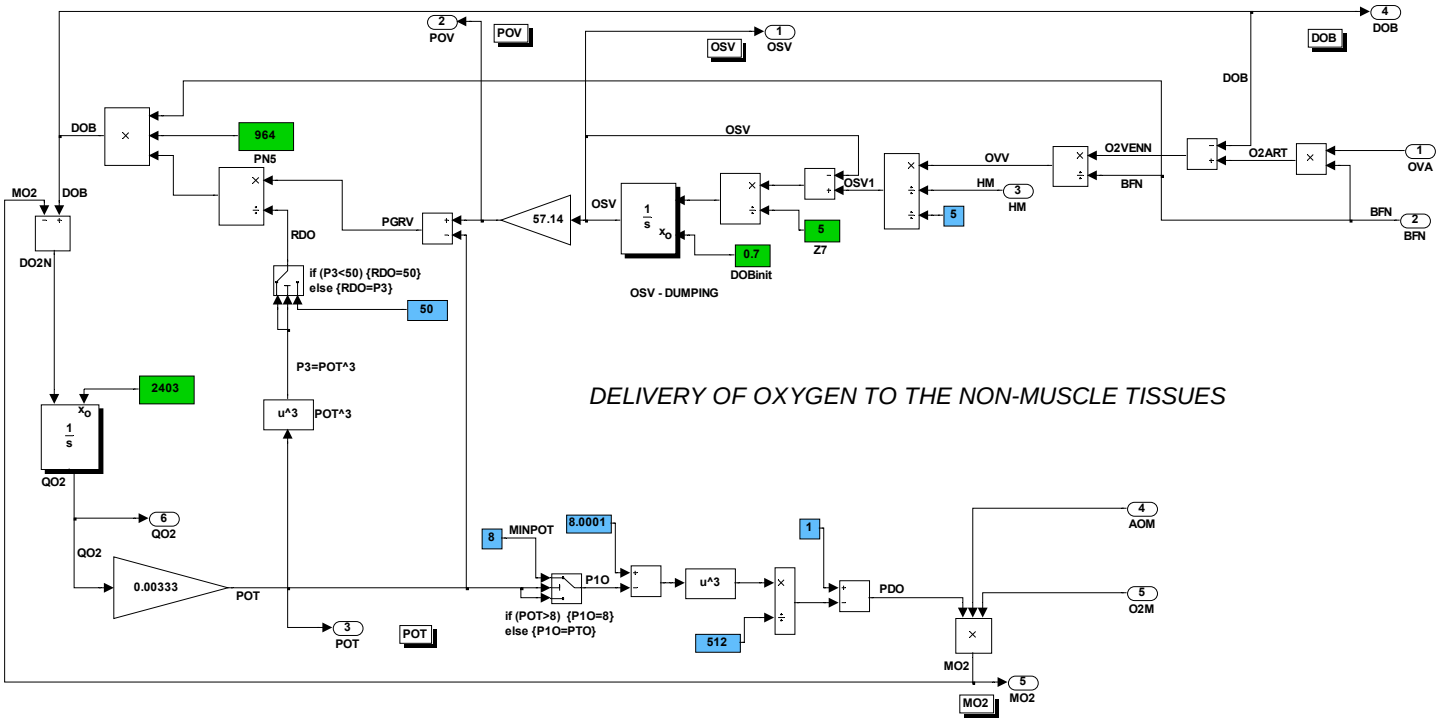
$$MO2=AOM*PDO*O2M \quad \text{(OD15)}$$

Oxygen consumption in non-muscle tissues decreases if the oxygen tension in the tissue drops below a certain threshold value (8 torr is considered in the model). The multiplicative factor (PDO), which expresses the effect of low tissue oxygen tension (POT) on oxygen consumption, is equal to one at oxygen tensions above 8 torr and gradually decreases to zero as oxygen tensions decrease:

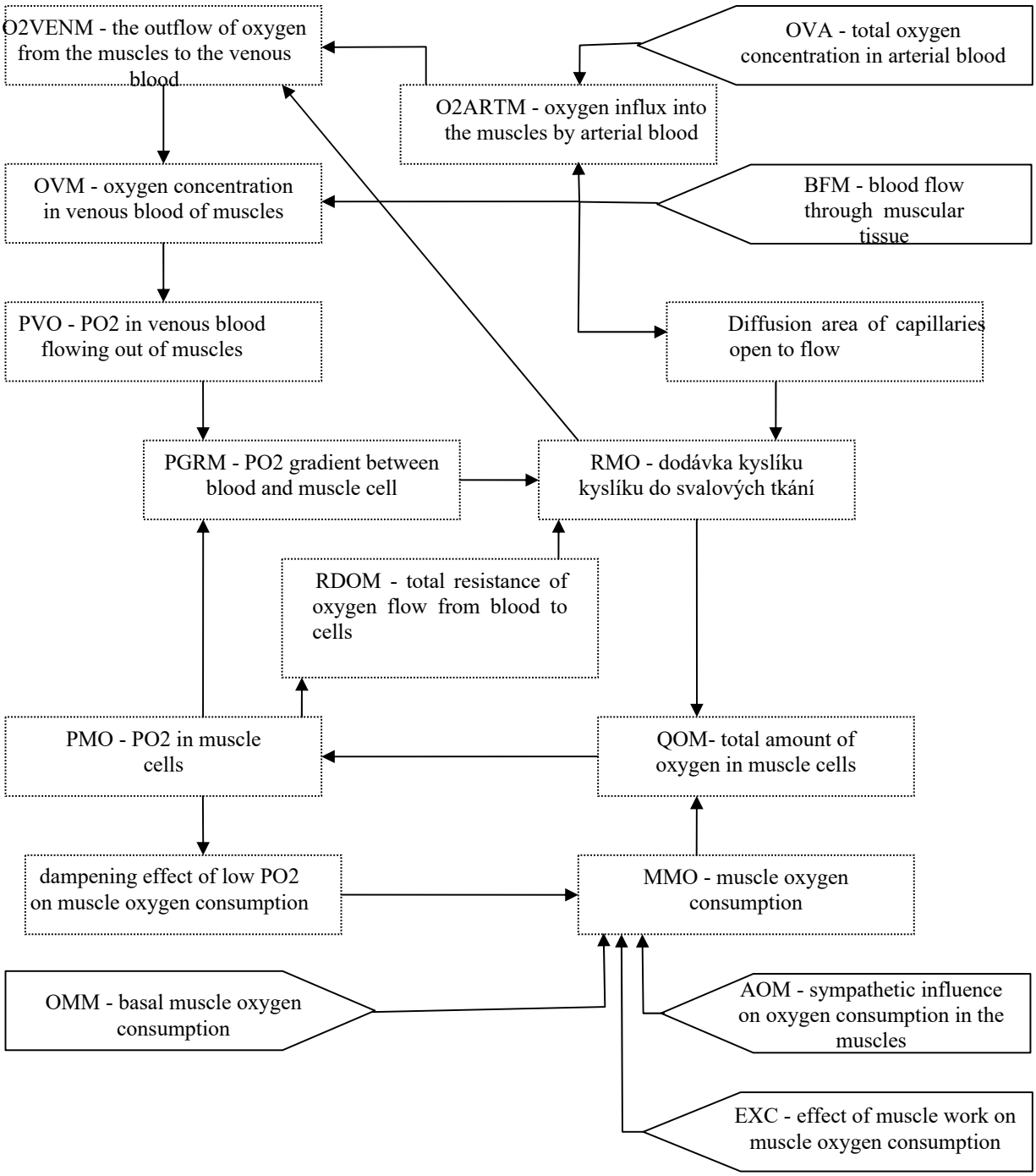
$$\text{if } (POT>8.0) \text{ then } P1O=8.0 \text{ else } P1O=POT \quad \text{(OD 16a)}$$
$$PDO=1.-(8.0001-P1O)^3/512.0 \quad \text{(OD 16b)}$$




NON MUSCLE O2 DELIVERY
194
OVA2
OVA
2.8
BFN2
BFN
40
HM1
HM
1
AOM1
AOM
164.5
O2M
O2M
INTPUTS:
OVA - oxygen content of arterial blood
[ml O2 STPD/l blood]
BFN - blood flow in non-muscle and non-renal tissues
[l/min]
HM - hematocrit [%]
AOM - autonomic effect on tissue oxygenation
[ratio to normal]
O2M - basic oxygen utilisation in non-muscle cells
[ml O2 STPD/min]
OUTPUTS:
OSV - non-muscle venous oxygen saturation [%]
POV - non muscle venous PO2 [torr]
POT - non muscle cell PO2 [torr]
DOB - rate of oxygen delivery to non-muscle cells
[ml O2 STPD/min]
MO2 - rate of oxygen utilisation by non-muscle tissues
[ml O2 STPD/min]
QO2 - non-muscle total cellular oxygen
[ml O2 STPPD]
OSV
0.6763
POV
38.64
POT
7.955
DOB
164.5
MO2
164.5
QO2
2389
Delivery of Oxygen to the Non-muscleTtissues1


2
POV
POV
1
OSV
OSV
4
DOB
DOB
DOB
964
PN5
DOB
MO2
DO2N
RDO
PGRV
57.14
OSV
OSV
OSV1
OVV
HM
3
HM
5
O2VENN
BFN
O2ART
1
OVA
BFN
2
BFN
5
Z7
0.7
DOBinit
OSV - DUMPING
if (P3<50) {RDO=50}
else {RDO=P3}
50
P3=POT^3
2403
QO2
u^3
POT^3
DELIVERY OF OXYGEN TO THE NON-MUSCLE TISSUES
6
QO2
QO2
0.00333
POT
3
POT
POT
8
MINPOT
8.0001
P1O
if (POT>8) {P1O=8}
else {P1O=PTO}
u^3
512
1
PDO
4
AOM
5
O2M
MO2
5
MO2
MO2

Oxygen supply to the muscles



The arterial blood oxygen flux to muscle (O2ARTM) is calculated from the blood flow through muscle tissue (BFM) from the total arterial blood oxygen concentration (OVA):

$$O2ARTM=BFM*OVA \quad \text{(OD 17)}$$

The oxygen flow out of muscle tissue (O2VENNM) is calculated from the oxygen flow in arterial blood (O2ARTM) minus the rate of oxygen delivery to muscle (RMO):

$$O2VENM=O2ARTM-RMO \quad \text{(OD 18)}$$

From the flow of oxygen in the venous blood and from the blood flow we can determine the concentration of oxygen in the venous blood flowing out of the muscles:

$$OVM=O2VENM/BFM \quad \text{(OD 19)}$$

Dividing this concentration by the hematocrit (HK, expressed as a percentage) gives the concentration of oxygen per liter of erythrocytes, and by dividing by the oxygen capacity of the blood, we can approximate the oxygen saturation of hemoglobin (as a percentage) in the venous blood flowing out from the OVS1 muscles - in this calculation Guyton neglected dissolved oxygen:

$$OVS1=O2VENM/BFM/HM/5 \quad \text{(OD 20)}$$

To prevent oscillations during abrupt saturation changes, damping is introduced using integration and damping coefficient (Z6) -value of this coefficient Z6=5:

$$DOVS=(OVS1-OVS)/Z6 \quad \text{(OD 21)}$$

$$OSV=\int DOVS\,dt \quad \text{(OD 22)}$$

The calculation of the partial pressure of oxygen in the outflowing venous blood (PVO) is calculated according to the linearized slope of the initial part of the hemoglobin saturation curve:

$$PVO=OVS*57.14 \quad \text{(OD 23)}$$

The partial pressure gradient of oxygen between venous (or outflowing capillary) blood and muscle tissue (PGRM) is taken in the model as the difference between the oxygen tension in venous blood (PVO) and the oxygen tension in muscle cells (PMO):

$$PGRM=PVO-PMO \quad \text{(OD 24)}$$

The oxygen delivery to the muscles (RMO) is directly proportional to the partial pressure gradient of oxygen (PGRM) and the diffusion area of the capillaries - the latter is proportional to the blood flow (BFM). The coefficient (PM5=125) expresses the influence of the diffusion area of the capillaries, the density of the capillary network, etc. Oxygen delivery is inversely proportional to the resistance to oxygen flow between capillaries and muscle cells (RDOM) - this resistance hides the diffusion pathway, the resistance is lower than in non-muscle tissue:

$$RMO=PGRM*BFM*PM5/RDOM \quad \text{(OD 25)}$$

The rate of change of the amount of oxygen in the muscles is equal to the difference between the blood oxygen influx (RMO) and the metabolic oxygen consumption (MMO):

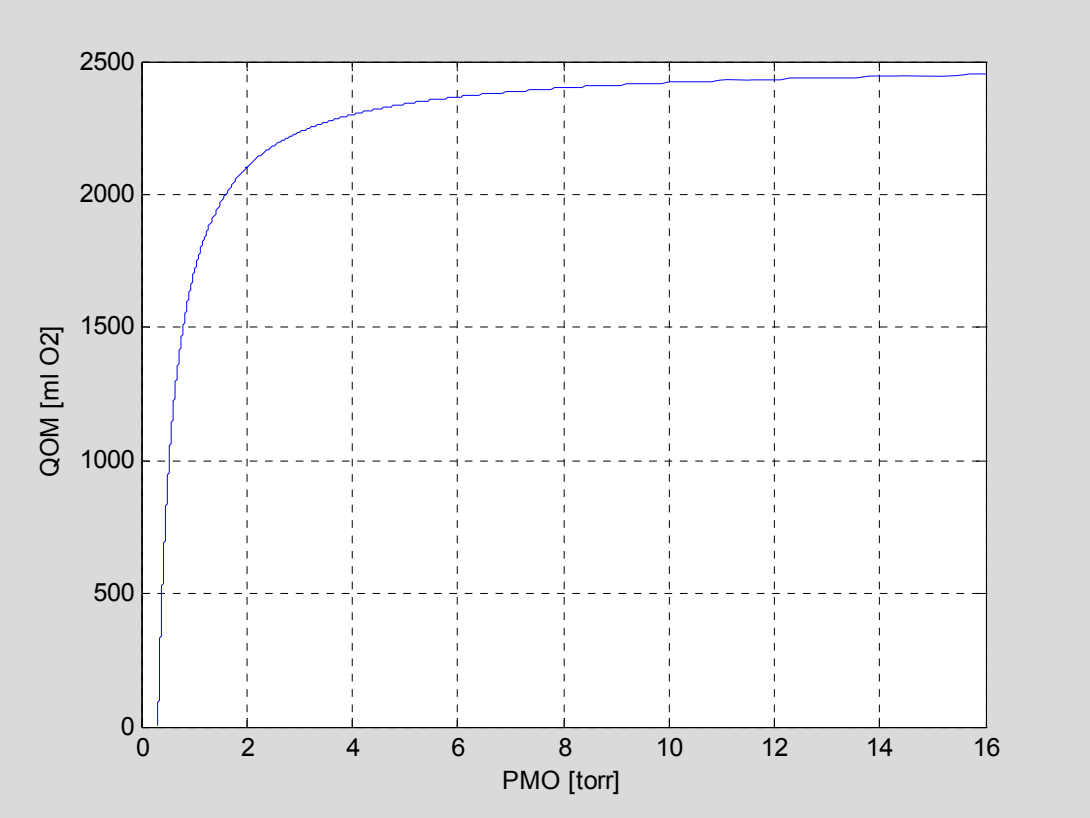
$$DQOM=RMO-MMO \quad \text{(OD 26)}$$

The total amount of oxygen (QOM) in the muscle cells will then be:

$$QOM=\int DQOM\,dt \qquad \text{(OD 27)}$$

The partial pressure of oxygen in the muscle cells (PMO) is calculated from the total amount of oxygen in the muscles (QOM). The calculation must take into account the binding of oxygen to myoglobin. The binding curve is approximated by an expression with coefficients (PK1=2500u and (PK2=800):

$$PMO=PK2/(PK1-QOM) \qquad \text{(OD 28)}$$

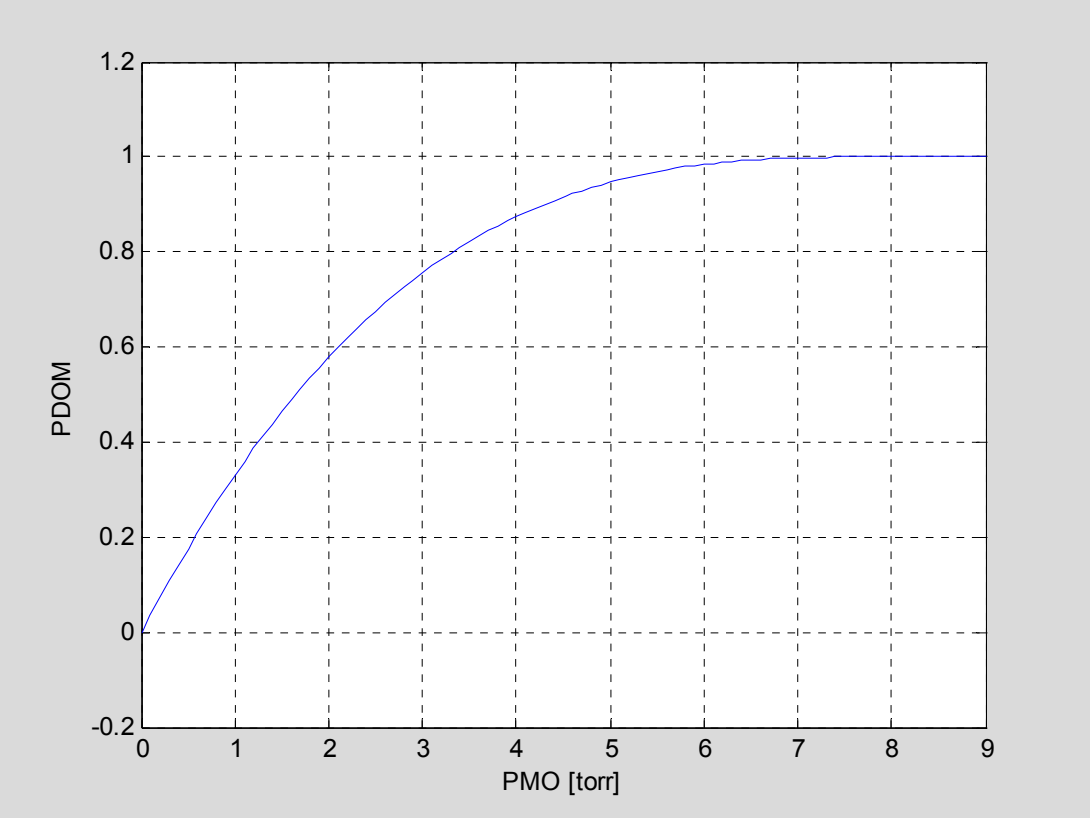


Calculation of resistance to oxygen flow from capillaries to muscle cells (RDOM) - resistance includes the diffusion pathway. Resistance is roughly quadratically dependent on tissue pO2 because the calculation takes into account the increase in capillary density at low values of oxygen tension (PMO), when more capillaries open, therefore the diffusion pathway is reduced and therefore the value of resistance to oxygen flow. The sensitivity is determined by the exponent (PK3=2), the bounding coefficient (PM4=-1) and the cutoff value (PM3=0.001):

$$\text{if } PMO<PM3, \text{ then } PM1=PM3 \text{ else } PM1=PMO \qquad \text{(OD 29a)}$$
$$RDOM=PM1^{PK4}- PM4 \qquad \text{(OD 29b)}$$

Muscle oxygen consumption (MMO) is influenced by sympathetic stimulation and may increase with exercise. Therefore, when calculating oxygen consumption, we multiply basal muscle oxygen consumption (OMM) by a multiplicative factor expressing the influence of sympathetic activity (AOM) , a factor expressing the influence of muscle work on the increase in basal resting oxygen consumption (EXC). When the PO2 in the muscles drops below the threshold value of 8 torr, the oxygen consumption is attenuated, so we further multiply the expression by a multiplicative factor expressing the dampening effect of low oxygen tensions on oxygen consumption (PDOM):

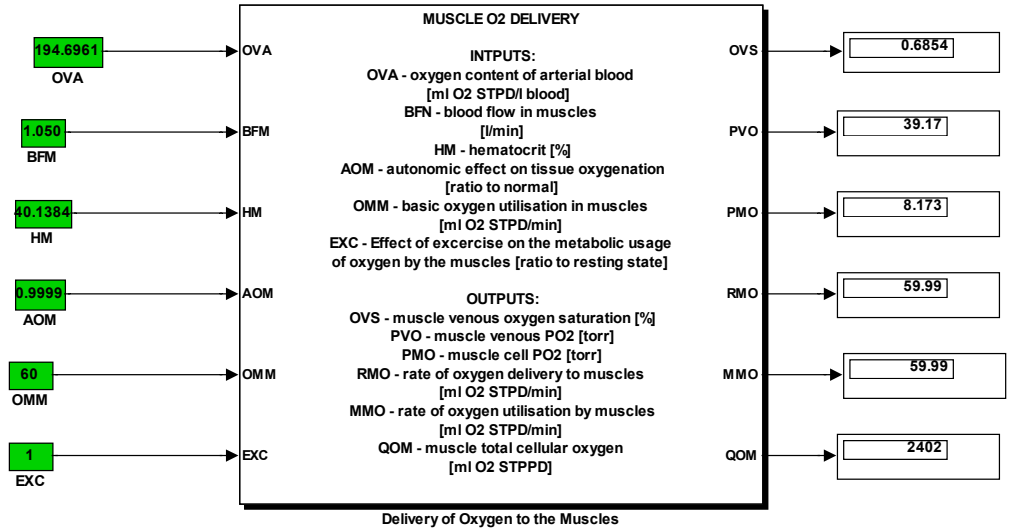
$$MMO=AOM*EXC*PDOM*OMM \quad \text{(OD 30)}$$



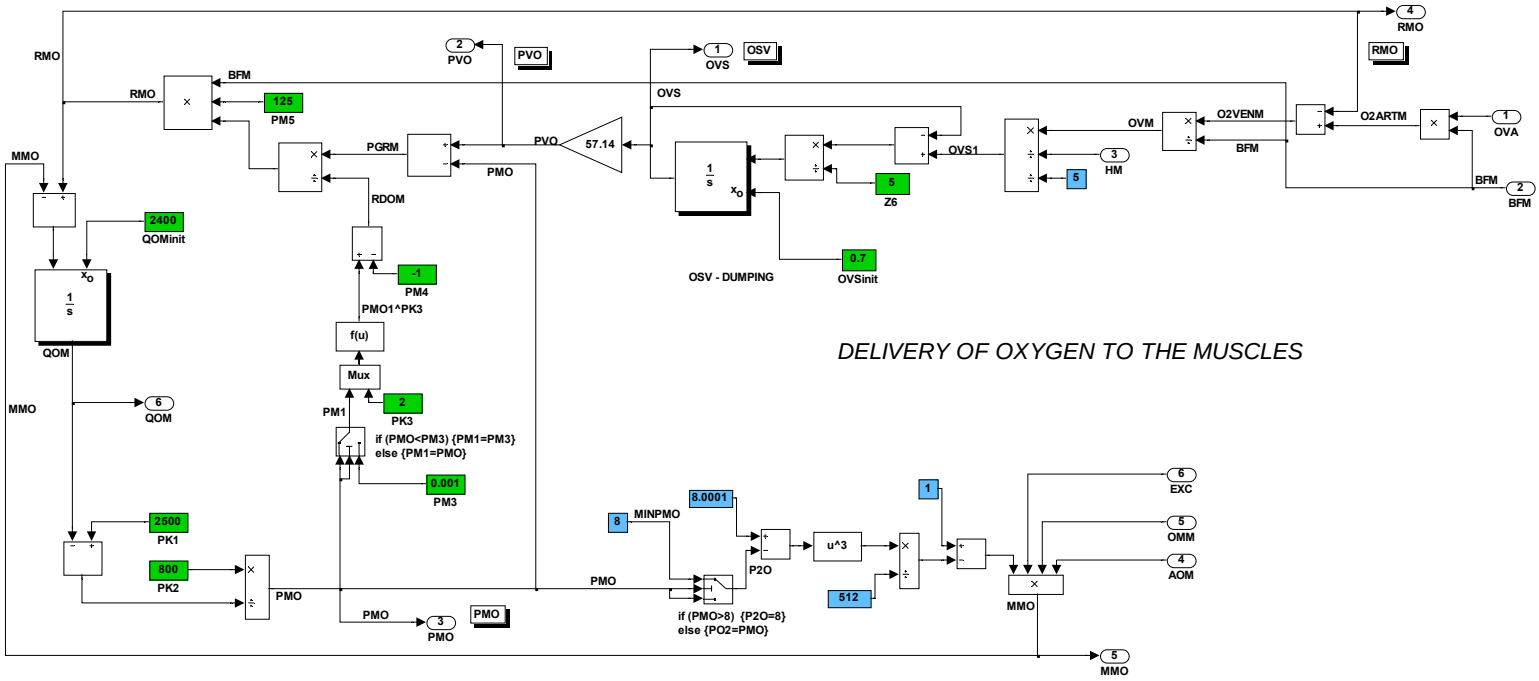
Oxygen consumption in the muscle decreases if the oxygen tension in the tissue falls below a threshold of 8 torr. This "critical" value of tension (P2O) then affects oxygen consumption. If it is above 8 torr, then oxygen consumption is controlled only by the metabolic demands of the cells and is unaffected by PO2 tension; if it falls below this value, oxygen consumption in the muscle is reduced. This dependence is approximated by a cubic polynomial. The result is a multiplicative factor (PDOM) expressing the dampening effect of low tissue oxygen tension (PMO) on oxygen consumption. At oxygen tensions above 8 torr, this factor is equal to one, gradually decreasing to zero as oxygen tensions decrease (the damping effect is approximated by the same dependence as in non-muscle tissue):

$$if\ (PMO>8.0)\ then\ P2O=8.0\ else\ P2O=PMO \quad \text{(OD 31a)}$$

$$PDOM=1.-(8.0001-P2O)^3/512.0 \quad \text{(OD 31b)}$$



Delivery of Oxygen to the Muscles



DELIVERY OF OXYGEN TO THE MUSCLES

AUTOREGULATION OF LOCAL BLOOD FLOW

In terms of autoregulatory flow control, the circulatory system is divided into three separate parts: the kidneys (which are included in a separate module), autoregulation of blood flow through other non-muscular (and non-renal) tissues, and autoregulation of blood flow in muscle tissue.

Autoregulation of local blood flow in non-muscular tissue

The controller itself is made up of three integration components with different control speeds: fast, medium and slow. All three depend on the oxygen level in the tissues. The first two components correspond to rapid metabolic changes, the first is almost instantaneous, the second occurs within twenty minutes to an hour. The third slow component represents the structural changes occurring after a week or more and is the result of vasoconstriction or vasodilation occurring in the vasculature as a result of two short-term metabolic responses.

In Guyton's original 1972 model, the regulatory deviation was calculated from the oxygen tension in the venous blood of the non-muscular tissues (POV). In later modifications, Guyton calculated the regulatory deviation from the tissue oxygen tension (POT). Therefore, in this model, the regulatory deviation of the local control of blood flow in non-muscular tissue for all three regulators is calculated from the difference between the instantaneous value of oxygen tension in non-muscular tissue cells (POT) and its proper value (POR=8 torr):

$$POD=POT-POR \quad \text{(AR 01)}$$

The sensitivity of the fast control component is controlled by a variable (POK), normally POK=0.1. The output of the integrating damping component, influenced by the coefficient (Z=5), is the variable POB:

$$DPOB=(POK*POD+1-POB)/Z \quad \text{(AR 02)}$$

$$POB=\int DPOB\,dt \quad \text{(AR 03)}$$

The output of the POB is bounded at the bottom by a value of 0.4 (which means that this component of the controller responds to a drop in POT<2 torr in the same way as if POT=2 torr) and is then input to an integrating delay component with a time constant (A1K) whose value is 1 min. The output is the fast control component AR1 (due to the POB boundary, its smallest possible value is 0.4):

$$if\ (POB<0.4)\ then\ POB=0.4 \quad \text{(AR 04)}$$

$$DAR1=(POB-AR1)/A1K \quad \text{(AR 05)}$$

$$AR1=\int DAR1\,dt \quad \text{(AR 06)}$$

The sensitivity of the medium control component is controlled by a variable (PON), normally PON=0.1, is damped by an integration term influenced, as in the previous case of the fast component, by a coefficient (Z=5). The output of the integration term is the variable POA.

$$DPOA=(PON*POD+1.-POA)/Z \quad \text{(AR 07)}$$

$$POA=\int DPOA\,dt \quad \text{(AR 08)}$$

The POA output is bottom bounded by 0.5 (which means that this component of the controller no longer changes its response intensity if the POT drops below 3 torr, i.e. at POT<3 torr it responds as if POT=3 torr. This also means that the AR2 control component has the smallest possible value of 0.5). After the limits have been checked, the POT is input to an integrating delay component with a time constant (A2K=20 min). The output is the mean control component AR2:

$$if\ (POA<0.5)\ then\ POA=0.5 \quad \text{(AR 09)}$$

$$DAR2=(POA-AR2)/A2K \quad \text{(AR 10)}$$

$$AR2=\int DAR2\ dt \quad \text{(AR 11)}$$

The sensitivity of the slow control component is controlled by a variable (POC), normally POC=16. The output of the POC is bounded at the bottom by a value of 0.3. This means that if the POT drops to a value lower than 7.9562, then the POC will no longer drop below 0.3 (and consequently the slow control component of AR3 has the smallest possible value of 0.3). After controlling the limits, the POC variable is the input to the integration delay component with a time constant (A3K=10,000 min, i.e. approximately 7 days). The output is the long-term control component AR3:

$$POC=POZ*POD+1.0 \quad \text{(AR 12)}$$

$$if\ (POC<0.3)\ then\ POC=0.3 \quad \text{(AR 13)}$$

$$DAR3=(POC-AR3)/A3K \quad \text{(AR 14)}$$

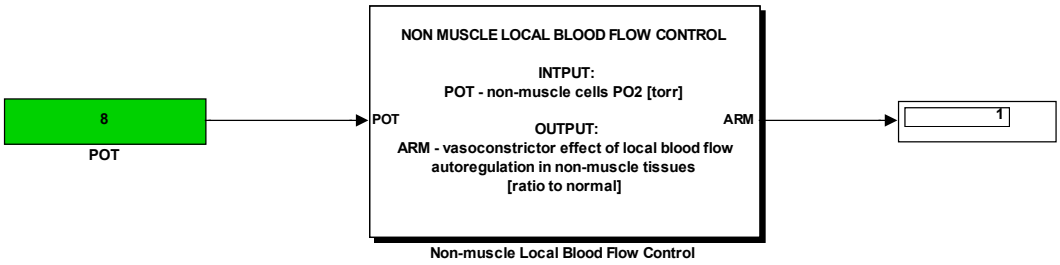
$$AR3=\int DAR3\ dt \quad \text{(AR 15)}$$

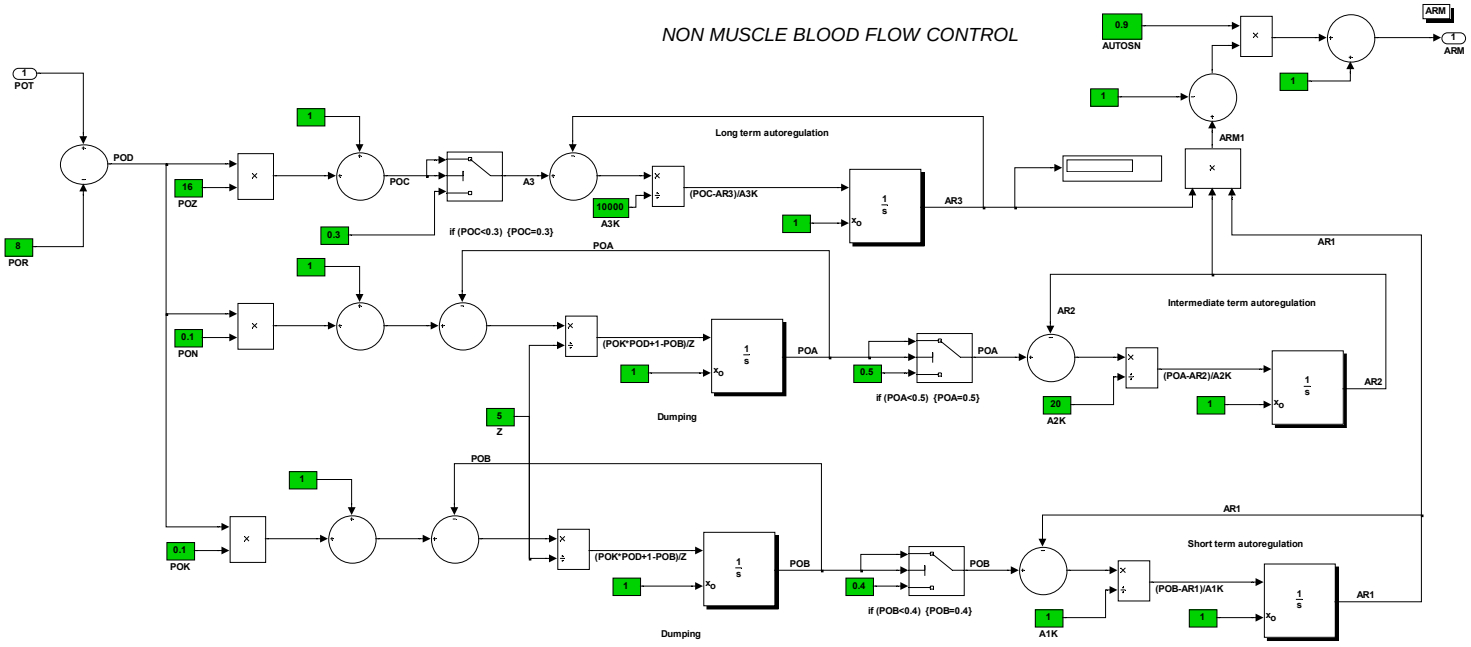
The cumulative effect of all three regulatory components, i.e. fast s(AR1), medium (AR2) and slow (AR3) is calculated as their product - the result is the variable ARM1:

$$ARM1=AR1*AR2*AR3 \quad \text{(AR 16)}$$

From the cumulative effect of all three regulatory components (ARM1), the cumulative regulatory response of the vasculature to tissue oxygen tension in non-muscular soft tissues (ARM) is finally calculated. The resulting response is cumulatively affected by the sensitivity, characterized by the AUTOSN coefficient (its value is equal to 0.9 under normal circumstances):

$$ARM=(ARM1-1)*AUTOSN+1 \quad \text{(AR 17)}$$


NON MUSCLE LOCAL BLOOD FLOW CONTROL
INTPUT:
POT - non-muscle cells PO2 [torr]
OUTPUT:
ARM - vasoconstrictor effect of local blood flow autoregulation in non-muscle tissues [ratio to normal]
POT
ARM
8
POT
1
Non-muscle Local Blood Flow Control


NON MUSCLE BLOOD FLOW CONTROL
POT
POD
POR
POZ
POC
A3
A3K
Long term autoregulation
(POC-AR3)/A3K
AR3
if (POC<0.3) {POC=0.3}
POA
PON
POK
(POK*POD+1-POB)/Z
Dumping
if (POA<0.5) {POA=0.5}
AR2
A2K
Intermediate term autoregulation
(POA-AR2)/A2K
Z
POB
if (POB<0.4) {POB=0.4}
AR1
A1K
Short term autoregulation
(POB-AR1)/A1K
AUTOSN
ARM1
ARM

Autoregulation of local blood flow in muscle tissue

In contrast to regulation in non-muscle tissue, the local blood flow regulator in muscle is composed of only two integrative components with different rates of regulation: a fast-response component that allows immediate adaptation of blood flow to the metabolic demands of the muscle and a slow, long-term component representing structural adaptive changes occurring on the order of a week after exposure to the eliciting stimulus. Guyton, in his original 1972 classical model, considered only the fast regulatory component.

In addition, in Guyton's original 1972 model, the regulatory deviation was calculated from the oxygen tension in the venous blood flowing out of the muscles (PVO). In later modifications, Guyton calculated the regulatory deviation from the oxygen tension in the muscle cells (POM) and added a long-term component to the controller. The regulatory deviation of the local control of blood flow in muscle tissue for both controllers is calculated from the difference between the instantaneous value of the muscle cell oxygen tension (POM) and its proper value (PORM=8 torr):

$$PDO=PMO-PORM \quad \text{(AR 18)}$$

The sensitivity of the fast control component is controlled by a variable (POM), normally POM=0.2. The control output pressure entering the controller is stored in the POE variable:

$$POE=POM*PDO+1.0 \quad \text{(AR 19)}$$

The POE output is bounded at the bottom by a value of 0.005 (which means that this component of the controller responds to a POM<3.025 torr drop in the same way as if POM=3.025 torr) and then is input to an integrating delay component with a time constant (A4K) of 10 min (in 72 Guyton considered an extremely fast adaptation with a time constant of 0.025 min). The output is the fast control component AMM1 (due to the POM bounding, its smallest possible value is 0.005):

$$if\ (POE<0.005)\ then\ POE=0.005 \quad \text{(AR 20)}$$

$$DAMM1=(POE-AMM1)/A4K \quad \text{(AR 21)}$$

$$AMM1=\int DAMM1\ dt \quad \text{(AR 22)}$$

The input to the slow component (POF) is calculated from the control deviation and the sensitivity coefficient (POM2=16).).

$$POF=POM2*PDO+1.0 \quad \text{(AR 23)}$$

The variable POF is the input to the integration delay component with a time constant (A4K2=10 000 min, i.e. approximately 7 days). The output is the long-term control component of AMM2. The POF variable is bounded from below by a value of 0.3. This means that if the PMO drops to a value lower than 7.9562, then the POF will no longer drop below 0.3 (and consequently the slow regulation component AR3 has the smallest possible value of 0.3). If no lower bound were introduced, the AMM2 variable could take on negative values as the PMO falls below 7.9375.

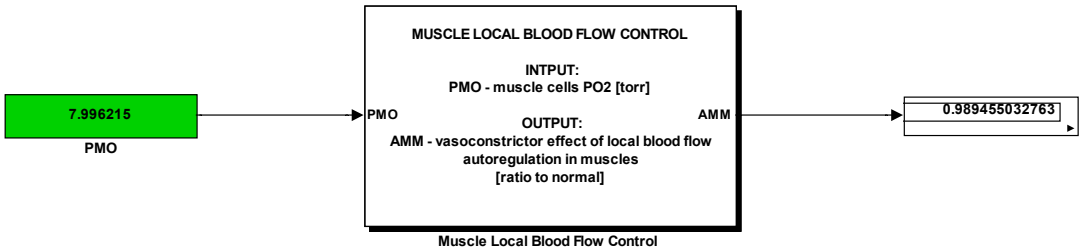
$$if\ \ (POF<0.3)\ \ then\ \ POF=0.3 \quad \text{(AR 24)}$$

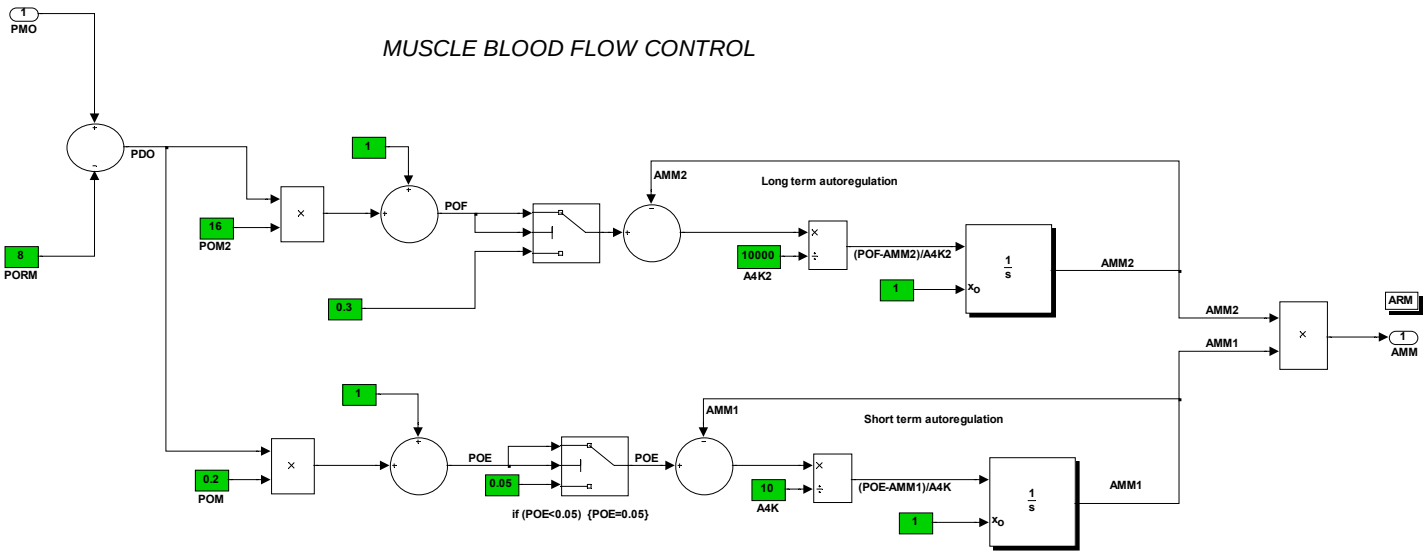
$$DAMM2=(POF-AMM2)/A4K2 \quad \text{(AR 25)}$$

$$AMM2=\int DAMM2\ dt \quad \text{(AR 26)}$$

The influence of the two regulatory components, i.e. fast (AMM1), slow (AMM2) not the overall regulatory response is calculated as their product - the result is the aggregate regulatory response of the vasculature to tissue oxygen tension in non-muscle soft tissues (AMM).

$$AMM=AMM1*AMM2 \quad \text{(AR 27)}$$


MUSCLE LOCAL BLOOD FLOW CONTROL
INTPUT:
PMO - muscle cells PO2 [torr]
OUTPUT:
AMM - vasoconstrictor effect of local blood flow autoregulation in muscles [ratio to normal]
PMO
AMM
7.996215
PMO
0.989455032763
Muscle Local Blood Flow Control


MUSCLE BLOOD FLOW CONTROL
1
PMO
PDO
8
PORM
16
POM2
1
POF
0.3
AMM2
Long term autoregulation
10000
A4K2
(POF-AMM2)/A4K2
1
AMM2
AMM2
AMM1
ARM
1
AMM
1
AMM1
Short term autoregulation
0.2
POM
POE
0.05
if (POE<0.05) {POE=0.05}
POE
10
A4K
(POE-AMM1)/A4K
1
AMM1

AUTONOMOUS CIRCULATION CONTROL

Influence of PO2 on the degree of activation of the autonomic system: the input is the oxygen tension in non-muscle tissues (POT). The input is bounded from above and below (8 and 4 torr):

if (POT<4) {POQ=4} else {POQ=POT} (AU 01)

if (POT>8) then {POQ=8) (AU 02)

Calculation of the factor which is the main determinant of autonomic control pressure (PA1), calculated in equation (AU 07) from the arterial systemic pressure value and the corrected oxygen tension in non-muscular tissue (POQ):

*PAPQ=PA*POQ/8.0* (AU 03)

Calculation of the correction factor (EXE1) expressing the effect of muscle oxygen tension (PMO) on circulation: the autonomic system is affected by muscle oxygen tension only when the oxygen tension in muscle cells falls below the critical value of 8 torr, then it also reduces oxygen consumption (see module Oxygen delivery to tissues, equation OD 31a). Therefore, first calculate the corrected oxygen tension in muscle cells that may affect the metabolic and autonomic system (P2O) and calculate the influencing factor from the magnitude of the decrease below the critical value of 8 torr. The sensitivity coefficient (EX1=3) represents the sensitivity of the autonomic system to a deficit in muscle oxygen tension. Note that equation AU 04a is identical to equation OD 31a, so Guyton has directly P2O as the input variable to the module here, but we prefer to choose the current muscle cell oxygen tension (PMO) as the input value due to the emphasis on modularity, and recalculate the P2O value here:

if (PMO>8.0) then P2O=8.0 elseP2O=PMO (AU 04a)
*EXE1=(8-P20)*EX1* (AU 04b)

Calculation of the correction factor EXE2 expressing the effect of physical load on the autonomic system. The input here is a coefficient (EXC) expressing the intensity of muscle load expressed as a proportion of basal muscle oxygen consumption during exercise relative to the resting state. The sensitivity coefficient (Z12=0.5) here expresses the strength of the effect of exercise on the autonomic system - Guyton in the original 1972 model gave a normal value of this coefficient of 1.24, later in 1986 he reduced its value to 0.5:

*EXE2=(EXC-1)*Z12* (AU 05)

Summarizing the effect of affecting the autonomic circulatory control system by decreased PO2 tension in muscle cells (EXE1) and increased exercise (EXE2):

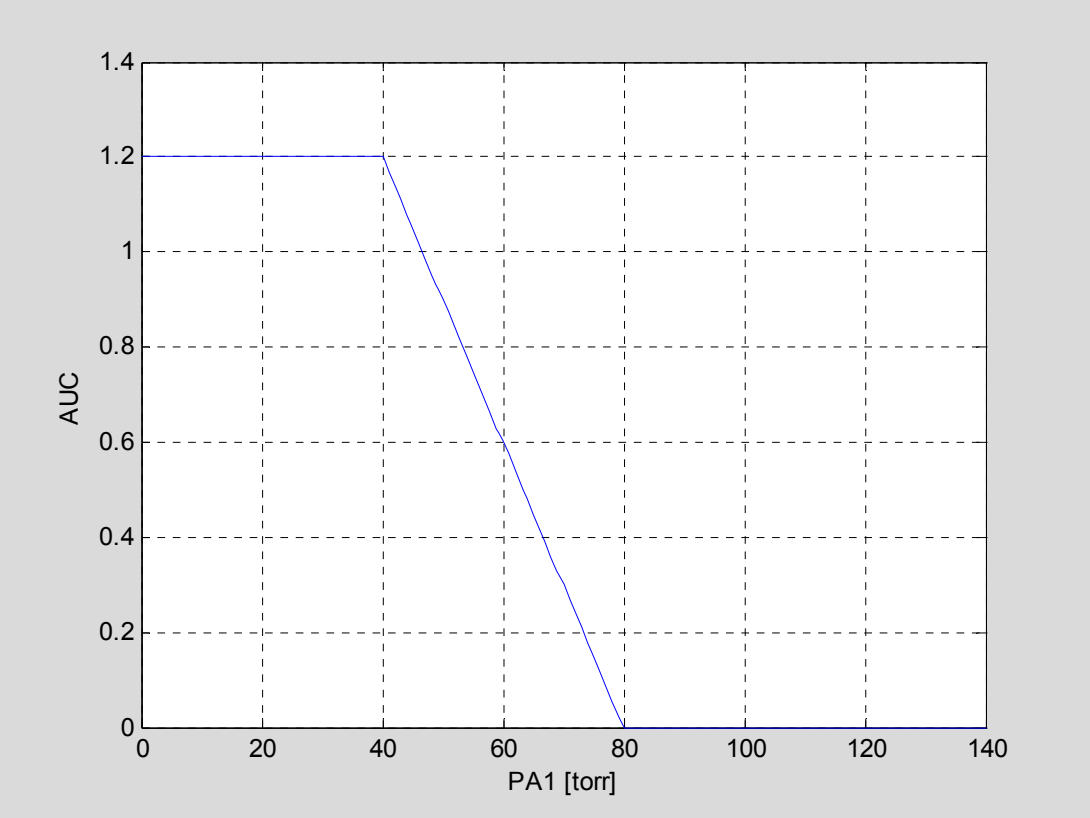
EXE=EXE1+EXE2 (AU 06)

Calculation of autonomic control pressure by factors expressing the influence of arterial systemic pressure and oxygen tension in non-muscle tissues (PAPQ), a factor expressing the influence of the increase in basal oxygen consumption and exercise (EXE), and a factor expressing the direct influence of angiotensin on the vasomotor center (ANUBR):

PA1=PAPQ+EXE-ANUBR (AU 07)

Influence of peripheral chemoreceptors on the vasomotor centre: the controlling influence of peripheral chemoreceptors on the vasomotor centre (AUC) is calculated from the autonomic control pressure (PA1). If the PA1 value is greater than 80 torr (as it is under normal circumstances), then the AUC is zero. Linearly increases from zero to 1.2 as PA1 drops from 80 to 40 torr. When PA1 drops below 40 torr, it remains constant at 1.2:

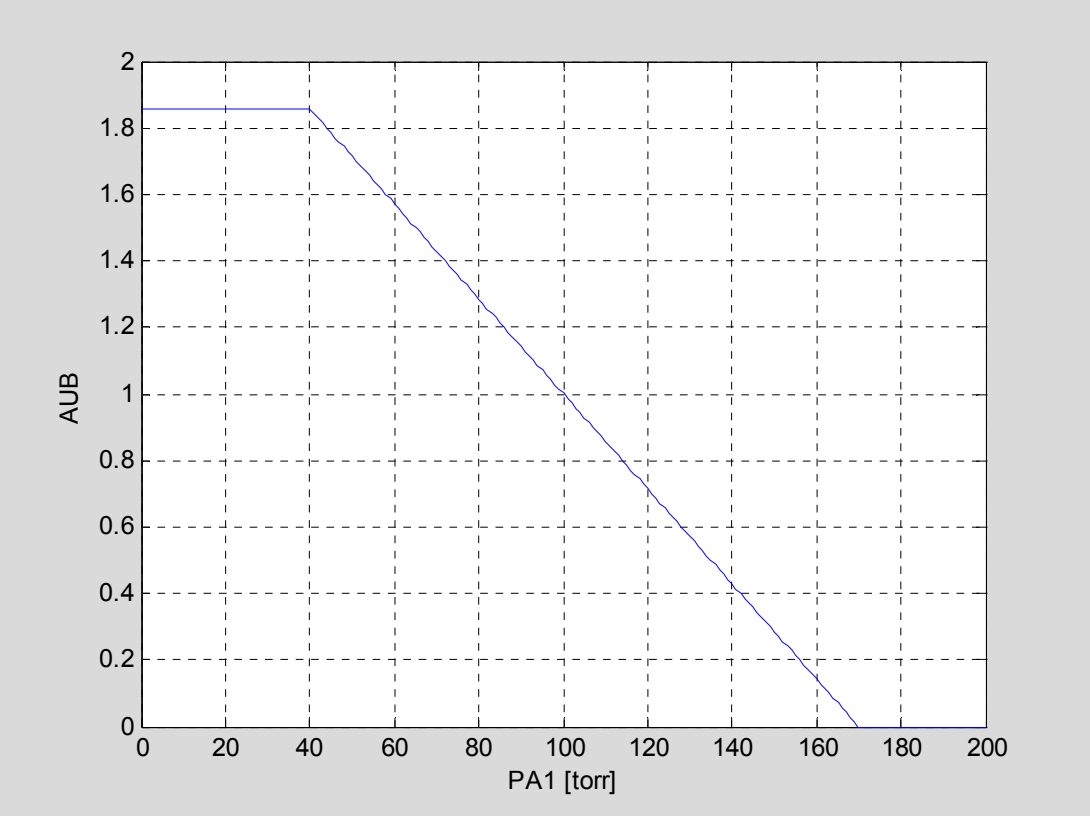
if (PA1>80), then AUC=0 (AU 08a)
if (40<=PA1<=80), then AUC=0.03(80-PA1)* (AU 08b)
if (PA1<40), then AUC=1.2 (AU 08c)



Dependence of AUC values on PA1 calculated according to equation AU 08

The influence of baroreceptors on the vasomotor centre: the controlling influence of baroreceptors on the vasomotor centre (AUB) is calculated from the autonomic control pressure (PA1). If the PA1 is greater than 170 torr, then the AUC is zero. When PA1 decreases from 170 to 40 torr, it increases linearly to its maximum value (1.85718) and remains at this maximum value when PA1 decreases further below 40 torr (at normal PA1=40, AUB=0):

if (PA1>170), then AUB=0 (AU 09a)
if (170<=PA1<=40), then AUB=0.014286(170-PA1)* (AU 09b)
if (PA1<40), then AUB=1.85718 (AU 09c)

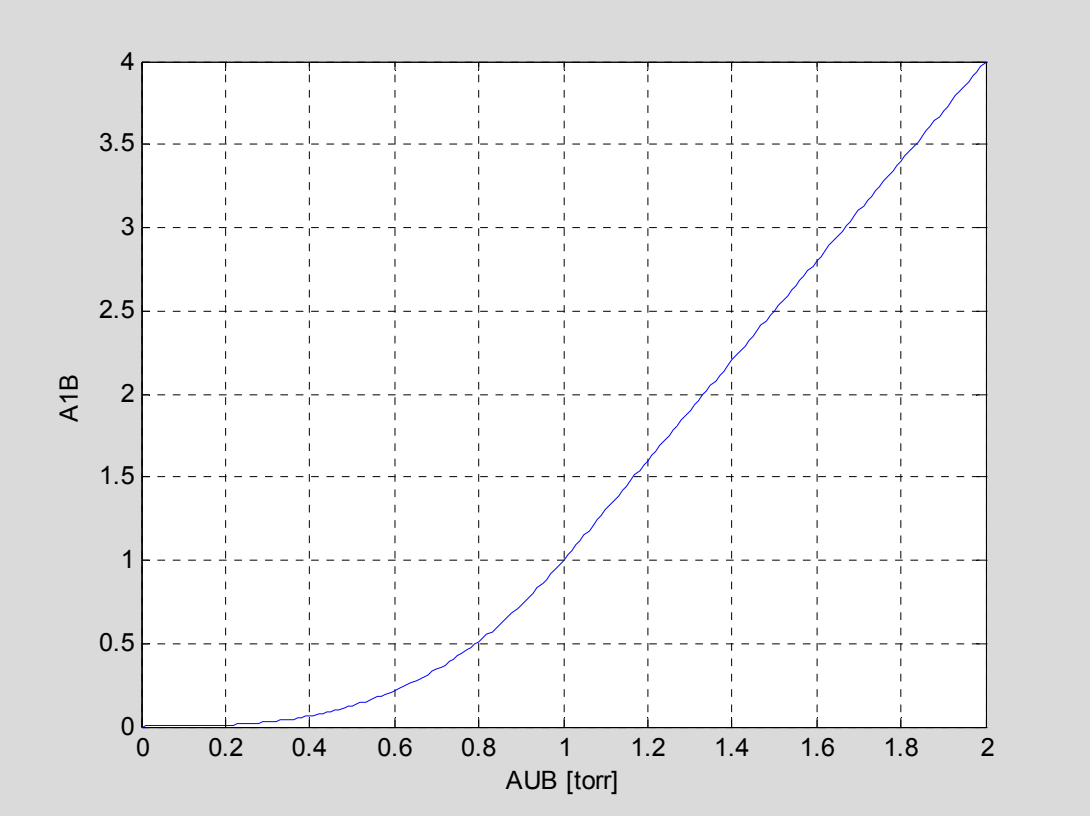


Dependence of AUB values on PA1 calculated according to equation AU 09

This linear dependence is further modified in a non-linear way, from the AUB value the resulting A1B value is calculated, expressing the controlling influence of the baroreceptors on the vasomotor centre also with respect to the baroreception sensitivity, represented by the coefficient (AUX), normal value AUX=3:

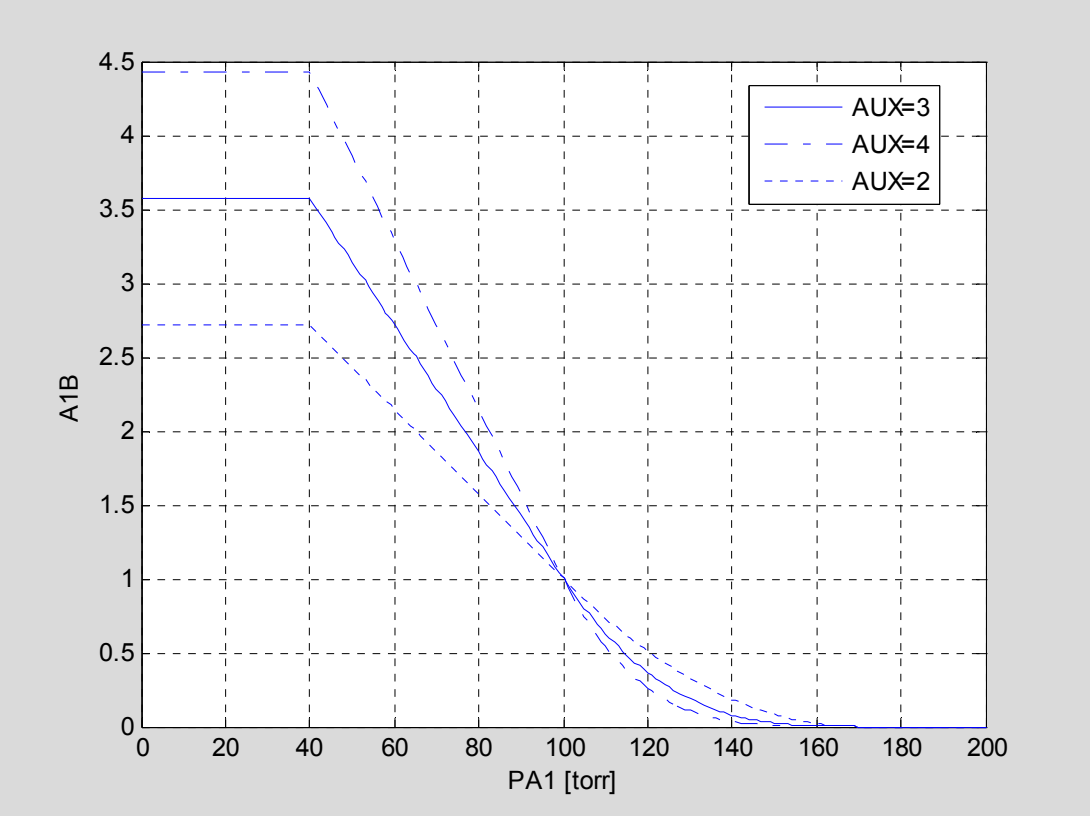
$$\text{if } (AUB<1), \text{ then } A1B=AUB^{AUX} \quad \text{(AU 10a)}$$

$$\text{if } (AUB>=1), \text{ then } A1B=(AUB-1)*AUX+1 \quad \text{(AU 10b)}$$



Dependence of A1B values on AUB calculated according to the equation AU 10

The dependence of baroreceptor control influence (A1B) on autonomic control pressure (PA1) is then non-linear in the lower part of the curve (at PA1>100 and subsequent A1B<1). The slope of the curve depends on the baroreceptor sensitivity, expressed by the AUX coefficient (normally AUX=3).



Dependence of A1B values on PA1 at different AUX values (calculated according to AU 09 and AU 10)

The last part of the calculation involves the adaptation of the baroreceptors to the changed pressure. The resulting baroreceptor control effect considering adaptation (AU6) is calculated as the difference between the current A1B value and the historically accumulated deviation from the norm (AU4) calculated in the integration term. The rate of adaptation depends on the coefficient (AUK) whose value here represents the inverse of the time constant AUK=0.005=1/(2000 min). After the adaptation has stabilized, the value of AU6 is equal to 1:

$$AU6=A1B-AU4 \quad \text{(AU 11)}$$

$$DAU4=AUK*(AU6-1) \quad \text{(AU 12)}$$

$$AU4=\int DAU4\ dt \quad \text{(AU 13)}$$

In terms of numerical calculations, it is necessary to set the initial value AU4 in the initial time step. This initial value (AU4init) is zero:

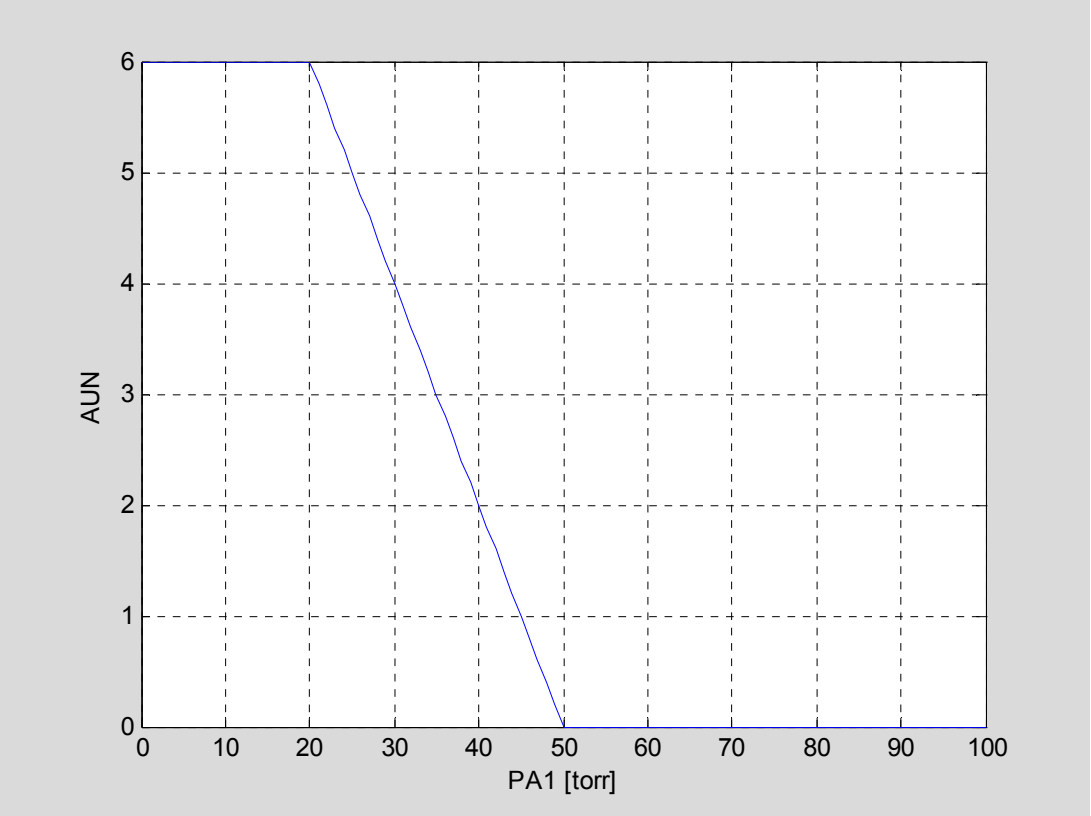
$$AU4init=0 \quad \text{(AU 14)}$$

Direct effect of cerebral ischemia on the vasomotor center: the controlling effect of ischemia of the intrinsic vasomotor center (AUN) is calculated from the autonomic control pressure (PA1). If the PA1 value is greater than 50 torr (as it is under normal circumstances), then the AUN value is zero. It increases linearly from zero to 6 as PA1 decreases from 50 to 20 torr. When PA1 falls below 20 torr, it remains constant at 6:

$$\text{if } (PA1>50), \text{ then } AUN=0 \quad \text{(AU 15a)}$$

$$\text{if } (20<=PA1<=50), \text{ then } AUN=0.2*(50-PA1) \quad \text{(AU 15b)}$$

$$\text{if } (PA1<20), \text{ then } AUB=6 \quad \text{(AU 15c)}$$



Dependence of AUN values on PA1

The calculation of the controlling influence of the vasomotor center (DAU) is realized as the sum of all three controlling influences that affect this center - the influence of inputs from peripheral chemoreceptors (AUC), from baroreceptors (AU6) and the direct influence of ischemia in the central nervous system on the vasomotor center (AUN):

$$DAU=AUC+AU6+AUN \qquad \text{(AU 16)}$$

Under normal circumstances (with PA1=100 torr and normal oxygenation of muscle and non-muscle tissue) the value of AU6=1, the other two inputs in the previous equation are zero (AUC=0, AUN=0), therefore DAU is equal to one. When the input parameters are changed, the autonomic center responds and the DAU values change as a result. To prevent Guyton oscillations, two damping terms are inserted here. The first damping term (see Eqs. AU 17-18) appeared in the 1986 version of the model and has damping coefficients (Y=1 and Z=5) , the second damping term (Eqs. AU 19-20) was already in the original 1972 model (damping coefficient value Z8=1). Here the value of the AUJ integration term is bounded from below by 10-6 . The initial values of the integrators AUJ1 and AUJ2 are set to an initial value of 1 in the initial time step.

$$DAUJ1=(DAU-AUJ1)/Y/Z \qquad \text{(AU 17)}$$

$$AUJ1=\int DAUJ\,dt \qquad \text{(AU 18)}$$

$$DAUJ=(AUJ-DAU1)*6.0/Z8 \qquad \text{(AU 17)}$$

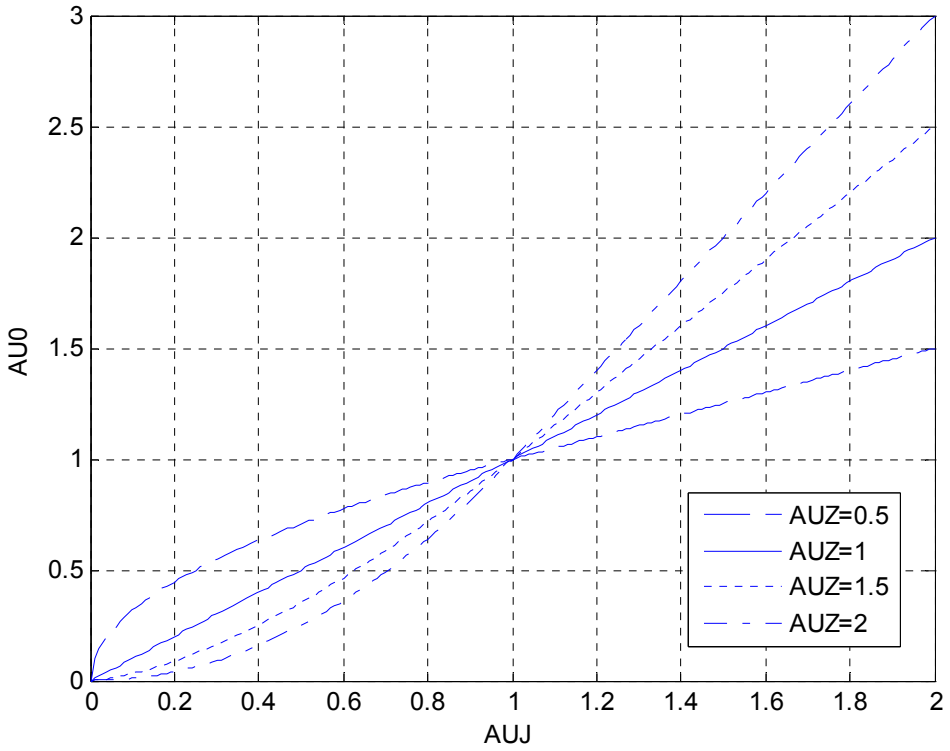
$$AUJ=\int DAUJ\,dt \qquad \text{(AU 18a)}$$

$$if\ (AUJ<0)\ then\ AUJ=0.000001 \qquad \text{(AU 18b)}$$

Conversion of the controlling influence of the vasomotor centre after application of damping effects limiting oscillations in the system (AUJ) into a multiplicative coefficient expressing the general influence of sympathetic autonomic nervous system (AU) activity on the circulation (expressed as a ratio relative to the norm). The sensitivity of the influence of vasomotor centre activity (AUJ) on the resulting value of autonomic system activity (AU0) is determined by the sensitivity coefficient (AUZ). The normal value of the sensitivity coefficient: AUZ=1. Its influence is different if the value of the AUJ is greater or less than one:

$$if\ (AUJ>=1),\ then\ AU0=(AUJ-1)*AUZ+1 \quad \text{(AU 19a)}$$

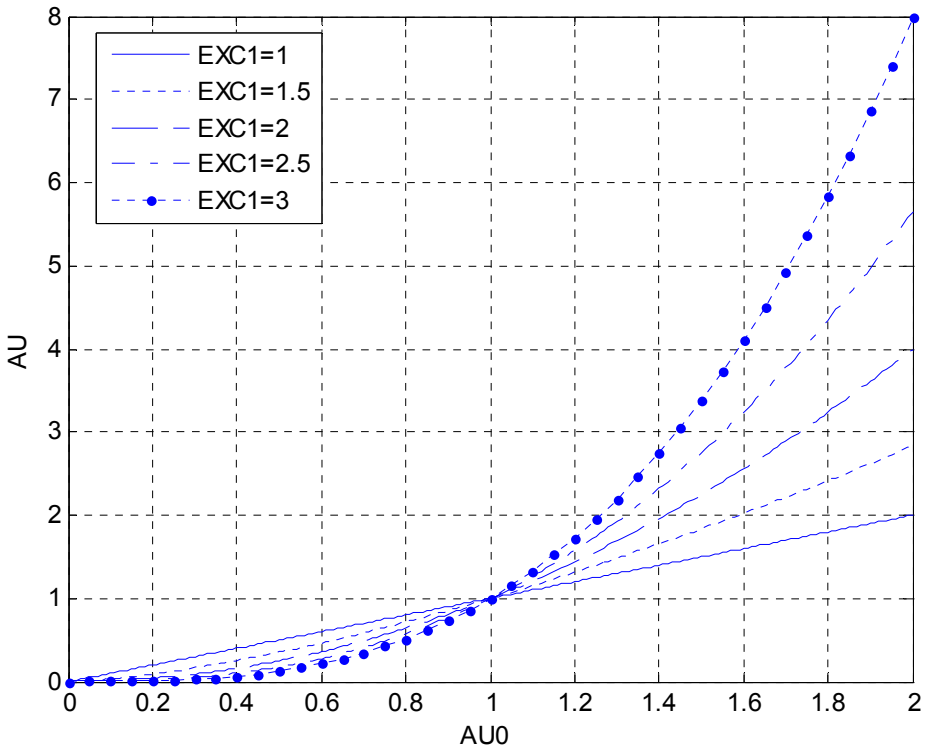
$$if\ (AUJ<1),\ then\ AU0=AUJ^{AUZ} \quad \text{(AU 19b)}$$



Dependence of AU0 values on AUJ at different AUZ values

The activity of the autonomic system is also influenced by physical activity. The level of physical activity (EXC) is an external input to the system. This input parameter expresses the current level of physical activity as a ratio of basal muscle oxygen consumption to resting oxygen consumption. Through the exponent EXC1=0.35, this input modifies the activity of the autonomic system (AU0). The result is the total activity of the autonomic system (AU), according to which the multiplicative coefficients expressing the specific influence of the autonomic nervous system on the individual subsystems of the organism are then calculated. Note: In his original 1972 model, Guyton used the AU value to influence heart rate, muscle oxygen consumption and the effect on ADH production; in this model, specialized multipliers are used for this purpose, but the AU value is the basis for their calculation:

$$AU=AU0*EXC^{EXC1} \quad \text{(AU 20)}$$



AU values calculated according to the AU 20 equation at different values of EXC1

As a basis for the calculation of the relevant multipliers, expressing the influence of the autonomic nervous system on other subsystems of the organism, we calculate the deviation (AUO) of the total activity of the autonomic nervous system (AU) from the norm:

$$AUO=AU-1.0 \quad \text{(AU 21)}$$

Calculation of the multiplier, expressing the influence of the autonomic nervous system on the inotropy of the heart (AUH), this coefficient affects the systolic volume of the left and right ventricles. The corresponding sensitivity coefficient (AUV=0.3) expresses the strength by which a deviation from normal sympathetic tone (expressed by the value of the AUO variable) will affect the change in the value of the multiplier affecting left and right ventricular minute output:

$$AUH=AUO*AUV+1 \quad \text{(AU 22)}$$

Calculation of the multiplier expressing the effect of the autonomic nervous system on heart rate (AUR). The corresponding sensitivity coefficient (AUS=1) expresses the strength with which a deviation from normal sympathetic tone (expressed by the value of the AUO variable) will affect the change in the value of the heart rate multiplier:

$$AUR=AUO*AUS+1.0 \quad \text{(AU 23)}$$

Calculation of a multiplier expressing the influence of the autonomic nervous system on the excretion of ADH and on the control of certain circulatory functions (AUP). The corresponding sensitivity coefficient (AUQ=1) expresses the strength with which a deviation from normal sympathetic tone (expressed by the value of the variable AUO) will affect the change in the value of multiplier affecting ADH excretion and some other circulatory functions (the value of the AUP multiplier depends on the value of the other multipliers (AOM, VVR, AUM and AVE) calculated below:

$$AUP=AUO*AUQ+1.0 \quad \text{(AU 24)}$$

Calculation of a multiplier expressing the effect of the autonomic nervous system on muscle and non-muscle oxygen consumption (AOM). The corresponding sensitivity coefficient (O2A=0.15) expresses the strength with which a deviation from normal sympathetic tone (expressed by AUP -1) will change the value of the AOM multiplier:

$$AOM=(AUP-1.0)*O2A+1.0 \quad \text{(AU 25)}$$

Calculation of the effect of the autonomic system on the residual blood volume in the venous systemic vasculature that does not stretch the vessels (maximum volume at zero pressure). Increasing sympathetic activity will decrease this residual volume (VVR). The reduction in this volume due to vascular venous wall tension influenced by sympathetic nervous system tone (VVRDM) is subtracted from the baseline volume, which is determined by the anatomical characteristics of each individual (VV9=3.16). This reduction depends on the deviation from the basal sympathetic tone (AUO) and the sensitivity coefficient (AUL=0.21) . Thus, an increase in sympathetic tone is reflected by an increase in VVRDM and a decrease in VVR:

$$VVRDM=0.21+AUO*AUL \quad \text{(AU 26)}$$

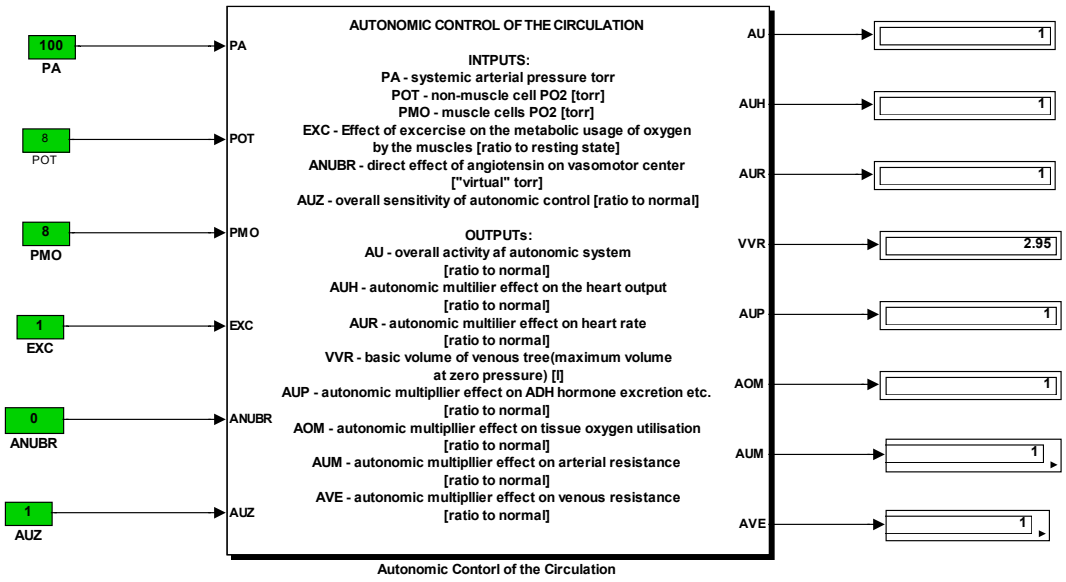
$$VVR=VV9-VVRDM \quad \text{(AU 27)}$$

Calculation of a multiplier expressing the influence of the autonomic nervous system on arterial vasoconstriction and the subsequent increase in resistance in the arterial (and arteriolar) circulation (AUM):

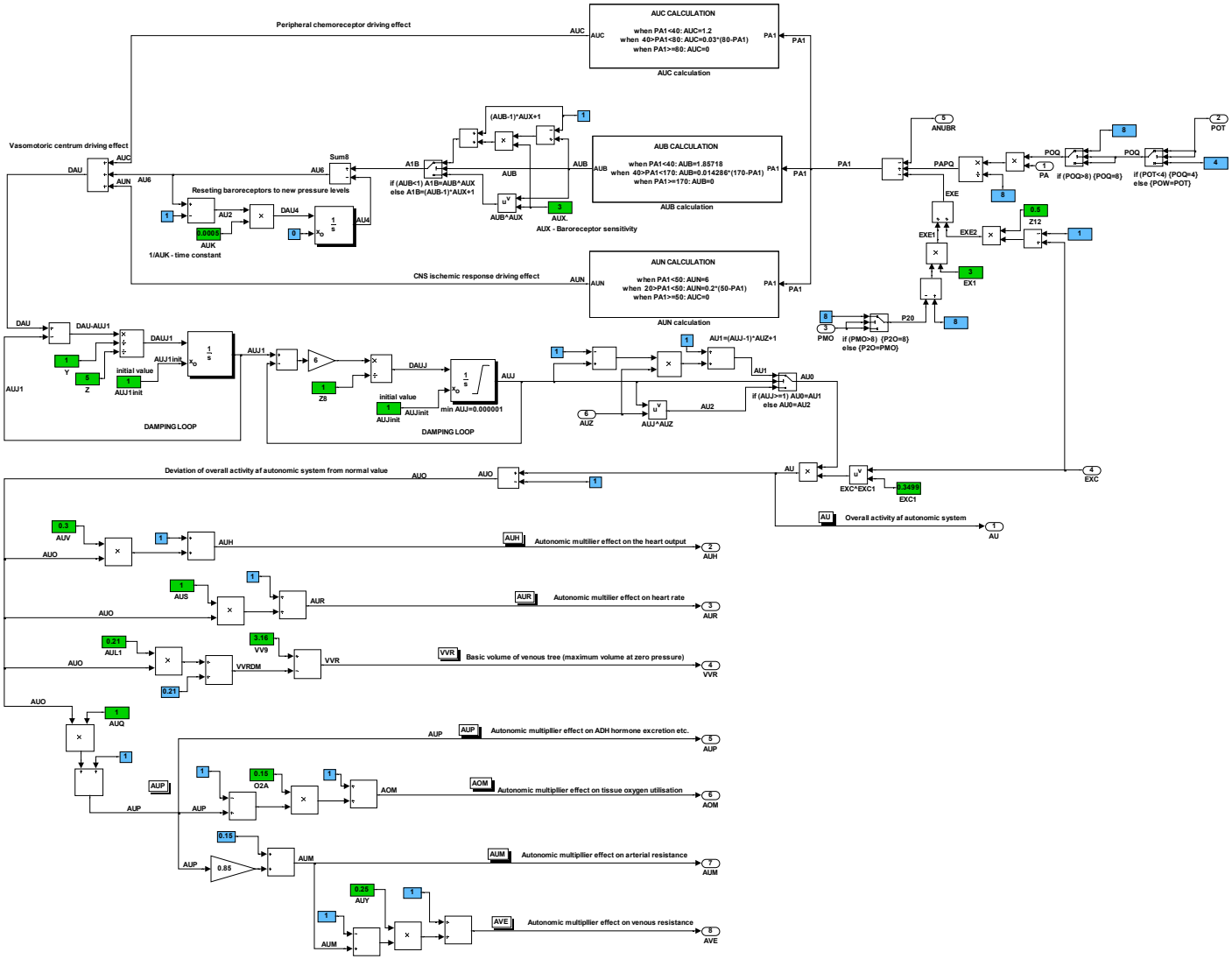
$$AUM=0.85*AUP+0.15 \quad \text{(AU 28)}$$

Calculating the multiplier expressing the influence of the autonomic nervous system on venous vasoconstriction and the subsequent increase in resistance in the venous circulation (AVE), the sensitivity coefficient (AUY=0.25) expresses the sensitivity of venous vasoconstrictor stimulation to changes in autonomic stimulation of the arterial circulation:

$$AVE=(AUM-1.0)*AUY+1.0 \quad \text{(AU 29)}$$



AUTONOMIC CONTROL OF THE CIRCULATION



ERYTHROCYTES AND BLOOD VISCOSITY

Regulation of erythrocyte formation and death

The total volume of erythrocytes in the body (VRC) is given by the integration of the difference (RCD) between the rate of their formation (RC1) and the rate of their disappearance (RC2):

$$RCD=RC1-RC2 \quad \text{(RC 01)}$$

$$VRC=\int RCD\ dt \quad \text{(RC 02)}$$

The lifetime of erythrocytes is on average 120 days. However, this model does not yet consider the lifetime of erythrocytes. The erythrocyte death rate (RC2) in the original classical model according to Guyton 1972 is calculated in direct proportion to the total volume of erythrocytes. The coefficient of proportionality (RKC) has a value of 0.0000058. Guyton in added another parameter, blood viscosity, as a relative value to the norm (VIM=1), the higher the blood viscosity, the faster the erythrocytes disappear:

$$RKC=58*10^{-7} \quad \text{(RC 03a)}$$

$$RC2=RKC*VIM*VRC \quad \text{(RC 03b)}$$

The rate of erythrocyte production, i.e. erythropoiesis (RC1), depends on the production of erythropoietin. Erythropoietin is formed predominantly in the kidneys. The regulatory stimulus is the partial pressure of oxygen in the renal tissues - this depends on the concentration of oxygen in arterial blood and blood flow through the kidneys (i.e., oxygen influx to the kidneys) and its consumption by the kidneys. Since renal oxygen consumption decreases as blood flow decreases, then the main regulator will be the total arterial blood oxygen concentration.

In Guyton's original model, the rate of erythrocyte production was dependent on the partial pressure of oxygen in the non-muscle tissue (POT) - the normal value is 8 torr, the difference (DPOT) from a constant value (POT1=8.25 torr) is calculated. The lower the partial pressure of oxygen, the higher the DPOT value. The DPOT value is bounded from below and above, and the rate of erythrocyte production is proportional to the DPOT value, the coefficient of proportionality representing the sensitivity POY=469*10-7 .

$$DPOT=POT-POT1 \quad \text{(RC 04)}$$

$$if\ DPOT<0.2375\ then\ DPO=0.2375 \quad \text{(RC 05)}$$

$$RC1=DPOT*POY \quad \text{(RC 06)}$$

In the 1986 model, Guyton made the rate of erythrocyte production proportional to the deviation of the arterial blood erythrocyte saturation (OSA) from normal (0.97) and inversely proportional to the renal erythrocyte flow, i.e., renal blood flow (RFN) and hematocrit (HM), expressed here as a percentage. Another multiplicative factor is the proportion of normal functioning kidney (REK=1) to model renal failure. The coefficient of proportionality is 0.0005568. The resulting erythrocyte production rate is bounded from below and above:

$$RC1=0.0005568*(1+0.9*(0.97-OSA))*REK/(RFN*HM) \quad \text{(RC 07)}$$

$$if\ RC1<0.000004\ then\ RC1=0.000004 \quad \text{(RC 08)}$$

$$if\ RC1>0.00014\ then\ RC1=0.00014 \quad \text{(RC 09)}$$

The total volume of erythrocytes in the body (VRC) is determined by the difference between the rate of formation (RC1) and extinction (RC2) erythrocytes:

$$RCD=RC1-RC2 \quad \text{(RC 10)}$$

$$VRC=\int RCD\ dt \quad \text{(RC 11)}$$

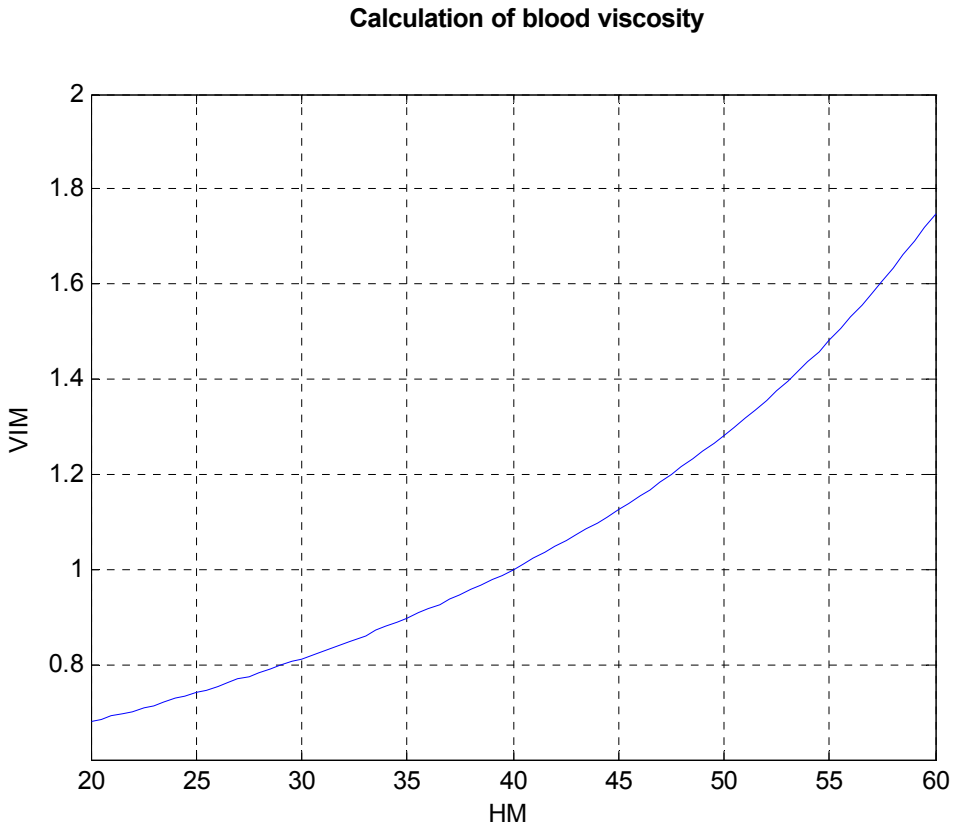
From the total erythrocyte volume (VRC) and plasma volume (VP), calculate the total blood volume (VB) and hematocrit expressed as a ratio from 0-1 (HM1) or as a percentage (HM):

$$VB=VP+VRC \quad \text{(RC 12)}$$

$$HM1=VRC/VB \quad \text{(RC 13)}$$

$$HM=HM1*100 \quad \text{(RC 14)}$$

This module of erythropoiesis and erythrocyte death kinetics does not account for the delay in erythropoietin action or erythrocyte lifespan. In the future, this part of the model will have to be substantially revised in this sense.



Dependence of viscosity (VIM) on hematocrit (HM)

From the hematocrit (HM), expressed as a percentage, the value of blood viscosity attributable to erythrocytes (expressed as a ratio of viscosity to water) is calculated using the coefficients (HMK=90) and (HKM=0.53333) in the empirical equation:

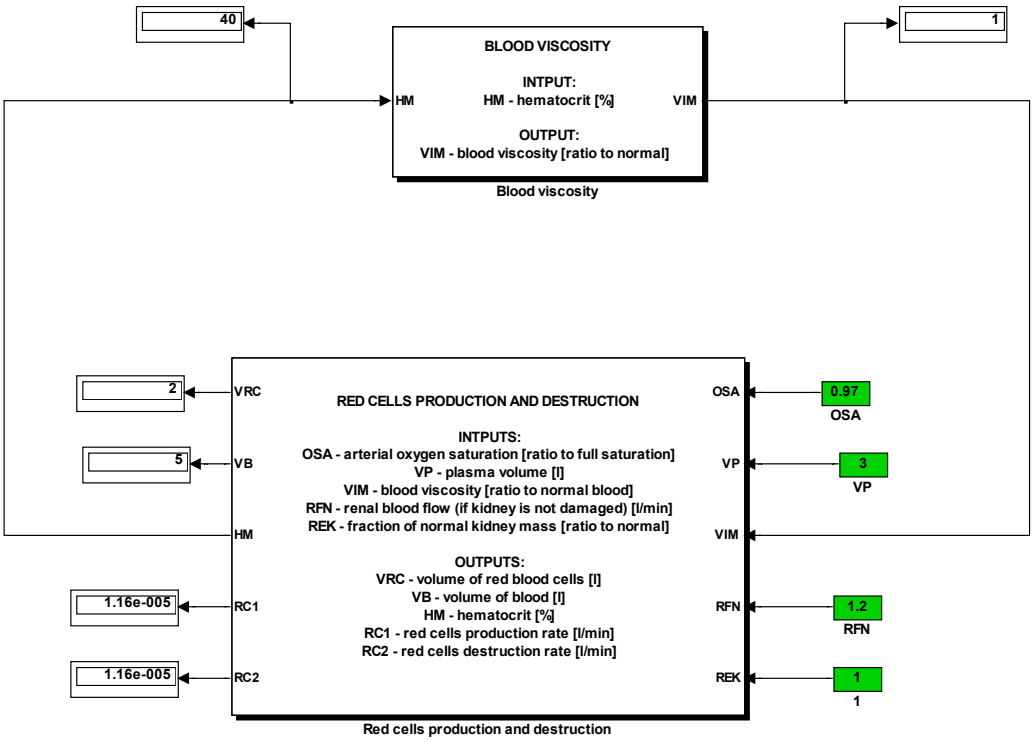
$$VIE=HM/((HMK-HM)*HKM) \quad \text{(RC 15)}$$

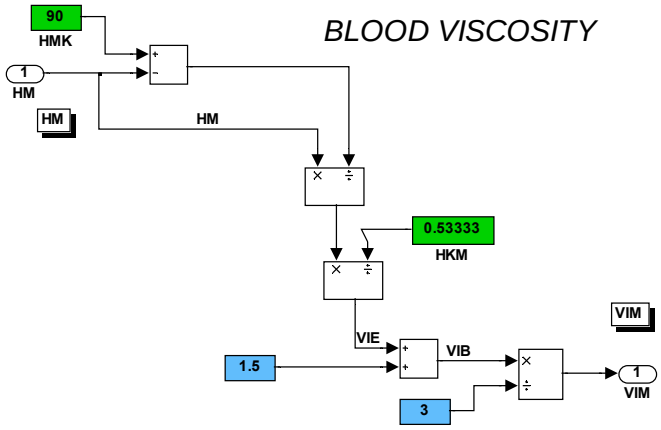
From the viscosity of erythrocytes (VIE) and a constant representing the viscosity of plasma, the viscosity of blood (VIB) is calculated as a number proportional to the viscosity of water.

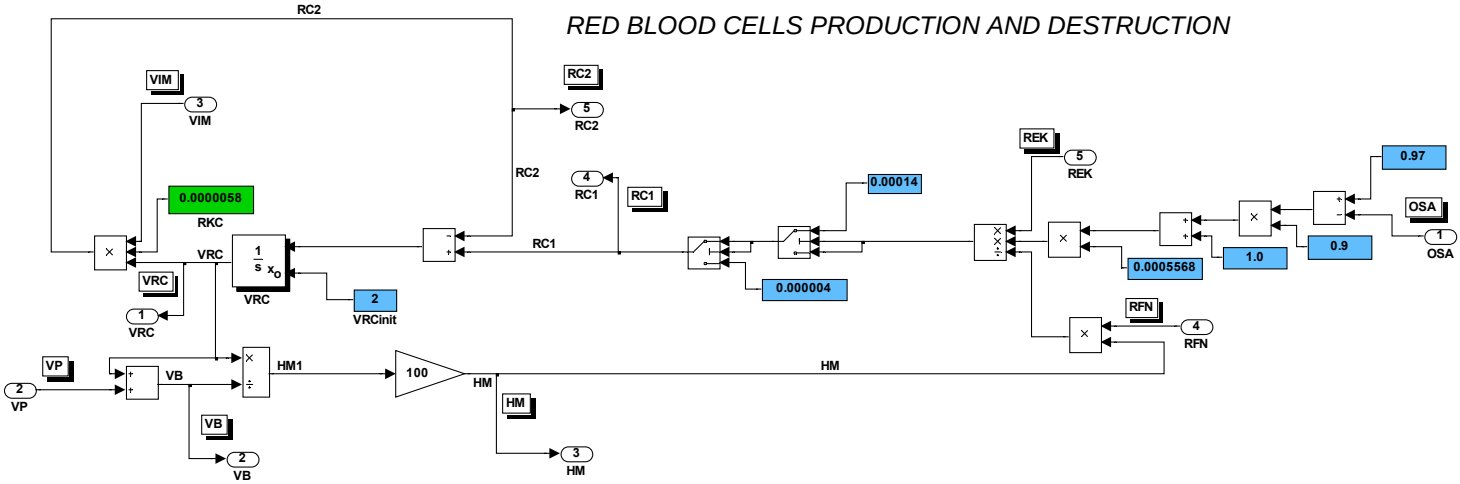
$$VIB=VIE+1.5 \quad \text{(RC 16)}$$

Finally, the normalized blood viscosity (VIM) is calculated as the ratio of the blood viscosity (VIB) to the normal viscosity value:

$$VIM=VIB/3.0 \quad \text{(RC 17)}$$


40
BLOOD VISCOSITY
INTPUT:
HM
HM - hematocrit [%]
VIM
OUTPUT:
VIM - blood viscosity [ratio to normal]
Blood viscosity
1
2
VRC
5
VB
HM
1.16e-005
RC1
1.16e-005
RC2
RED CELLS PRODUCTION AND DESTRUCTION
INTPUTS:
OSA - arterial oxygen saturation [ratio to full saturation]
VP - plasma volume [l]
VIM - blood viscosity [ratio to normal blood]
RFN - renal blood flow (if kidney is not damaged) [l/min]
REK - fraction of normal kidney mass [ratio to normal]
OUTPUTS:
VRC - volume of red blood cells [l]
VB - volume of blood [l]
HM - hematocrit [%]
RC1 - red cells production rate [l/min]
RC2 - red cells destruction rate [l/min]
OSA
0.97
OSA
VP
3
VP
VIM
RFN
1.2
RFN
REK
1
1
Red cells production and destruction


BLOOD VISCOSITY
90
HMK
1
HM
HM
HM
0.53333
HKM
VIE
VIB
VIM
1.5
3
1
VIM


RED BLOOD CELLS PRODUCTION AND DESTRUCTION
RC2
VIM
3
VIM
RC2
5
RC2
RC2
4
RC1
RC1
0.0000058
RKC
RC1
0.00014
0.000004
REK
5
REK
0.97
OSA
1
OSA
0.9
1.0
0.0005568
VRC
VRC
VRC
1
VRC
2
VRCinit
RFN
4
RFN
VP
2
VP
VB
HM1
100
HM
HM
HM
VB
2
VB
3
HM

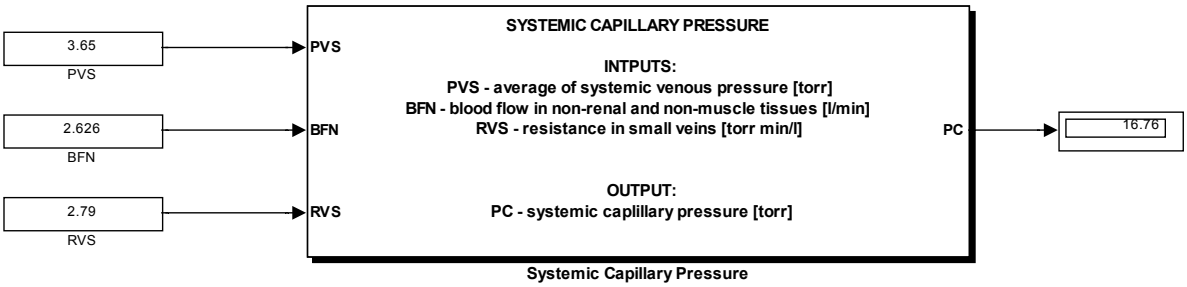
DYNAMICS OF CAPILLARIES, INTERSTITIAL FLUID, PLASMA AND TISSUE PROTEINS

Calculation of mean capillary pressure

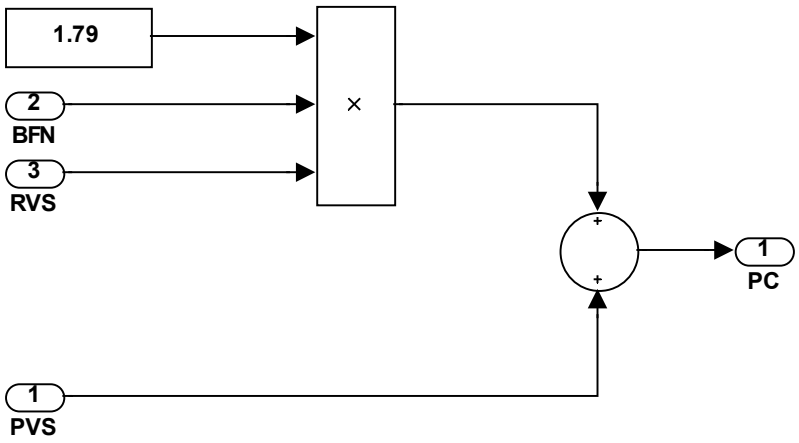
The blood flow through the small veins of the soft non-renal (and non-muscular) tissues (BFN) multiplied by a factor of 1.79 increases this flow by the normal flow through the kidneys and muscle tissue, multiplied by the resistance of small veins (RSV) gives a pressure gradient between the pressure in the great veins (PVS) and the mean capillary pressure (PC) equal to the blood flow through the small veins multiplied by the resistance of small veins (RVS):

$$PC\text{-}PVS=RVS*1.79*BFN \qquad \text{(CP 01)}$$

The calculation of the mean capillary pressure is based on this relationship, which is calculated in equation (HD 54) in the chapter devoted to the calculation of resistances in the systemic circulation.



SYSTEMIC CAPILLARY PRESSURE



Starling equilibrium on the capillary

The pressure gradient between the capillary and the interstitial fluid (PCGR) is equal to the difference between the pressures that drive fluid from the capillary into the interstitium and the back pressures that suck fluid from the tissues di the capillary - i.e. the difference between the mean capillary pressure (PC) and tissue gel colloid-osmotic pressure (PTC), counter-pressures that draw fluid from the capillaries, and the plasma colloid-osmotic pressure (PPC) and tissue gel hydraulic counter-pressure (PGH) that draw fluid into the capillaries:

$$PCGR=PC-PPC-PGH+PTC \quad \text{(CP 02)}$$

The capillary filtration rate (CFILTR) is proportional to the pressure gradient between the capillary and the interstitium (PCGR); the coefficient of proportionality here is the capillary filtration coefficient (CFC), which includes the capillary wall resistance and the total capillary surface area:

$$CFILTR=PCGR*CFC \quad \text{(CP 03)}$$

The total rate of fluid transfer from the capillaries to the interstitial space from the systemic capillaries (VTC) is equal to the capillary filtration rate (CFILTR) plus the fluid flow through the "leaky capillaries" (VTCPL):

$$VTC=CFILTR+VTCPL \quad \text{(CP 04)}$$

The leakage of plasma from capillaries into the tissue interstitium through the pores in the capillary emmbrane depends on the pressure gradient (PRCD), which is equal to the difference between the mean capillary pressure (PC) and the critical capillary pressure, above which the capillary pores open (PCR=15). If the mean capillary pressure is lower than the critical capillary pressure, no plasma leakage occurs (and the corresponding PRCD pressure gradient is zero):

$$PCR=15.0 \quad \text{(CP 05a)}$$
$$PRCD=PC-PCR \quad \text{(CP 05b)}$$
$$\text{if } (PRCD<0.0) \quad \text{(CP 05c)}$$
$$\text{then} PRCD=0.0$$

The rate of plasma flow through the capillary pores (DCP) depends on the pressure gradient calculated above (PRCD) according to an empirical relation, where the constants CPK denote the conductivity and the constant PCE (normally equal to 1) expresses the possible nonlinearity of this relation:

$$CPK=0.000253 \quad \text{(CP 06a)}$$
$$PCE=1.0 \quad \text{(CP 06b)}$$
$$VTCPL=(PRCD*CPK)^{PCE} \quad \text{(CP 06c)}$$

The rate of change in plasma volume (VPD) is equal to the difference between the total lymph to plasma flow (VTL), the rate of water inflow from the GIT or elsewhere in the body (TVD), and fluid outflow from systemic capillaries to the systemic interstitium (VTC), fluid outflow from pulmonary capillaries to the pulmonary interstitium (DFP), and diuresis (VUD):

$$VPD=VTL+TVD-VUD-VTC-DFP \quad \text{(CP 07)}$$

We then subtract the total plasma volume (VP) by integrating the rate of change of this volume (VPD):

$$VP=\int VPD\, dt \quad \text{(CP 08)}$$

The relative interstitial volume (VPREL) relative to the norm (VPN) for a given individual will be:

$$VPREL=VP/VPN \quad \text{(CP 09)}$$

The rate of change in the volume of interstitial fluid in the systemic interstitial space (VTD) is equal to the total rate of fluid transfer from systemic capillaries to the interstitium (VTC) minus the outflow of fluid from the interstitium to the blood via the lymph (VTL) minus the transfer of water from the interstitium to the cells (VID):

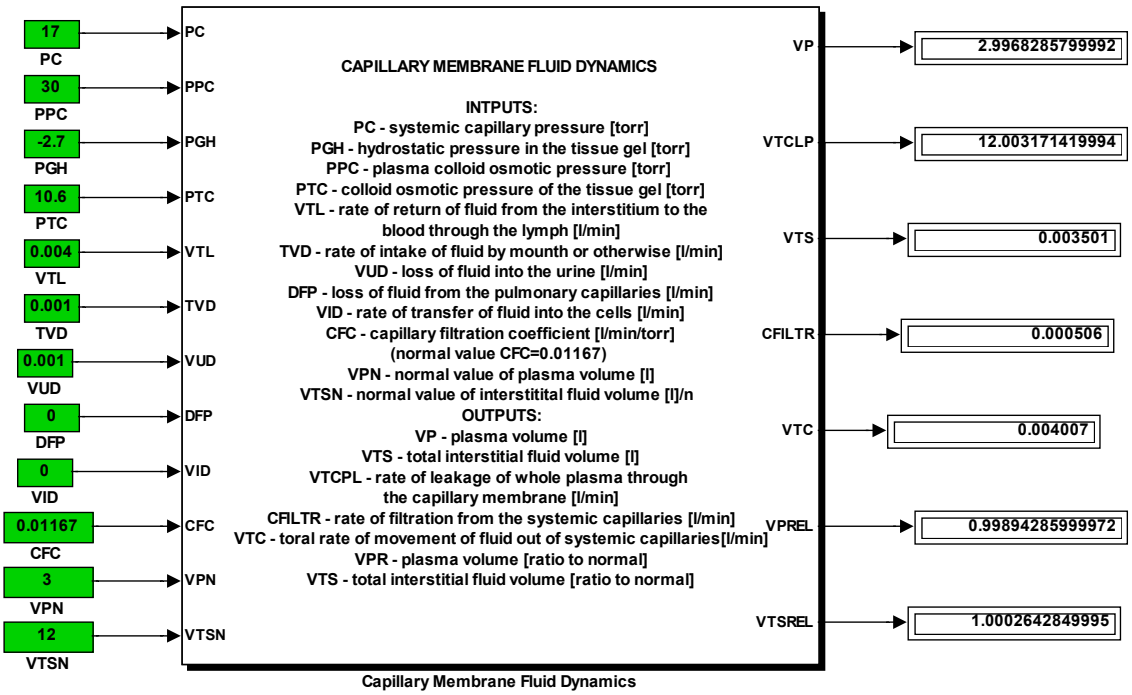
$$VTD=VTC-VTL-VID \quad \text{(CP 10)}$$

We then subtract the total volume of the systemic interstitial space (VTS) by integrating the rate of change of this volume (VTD):

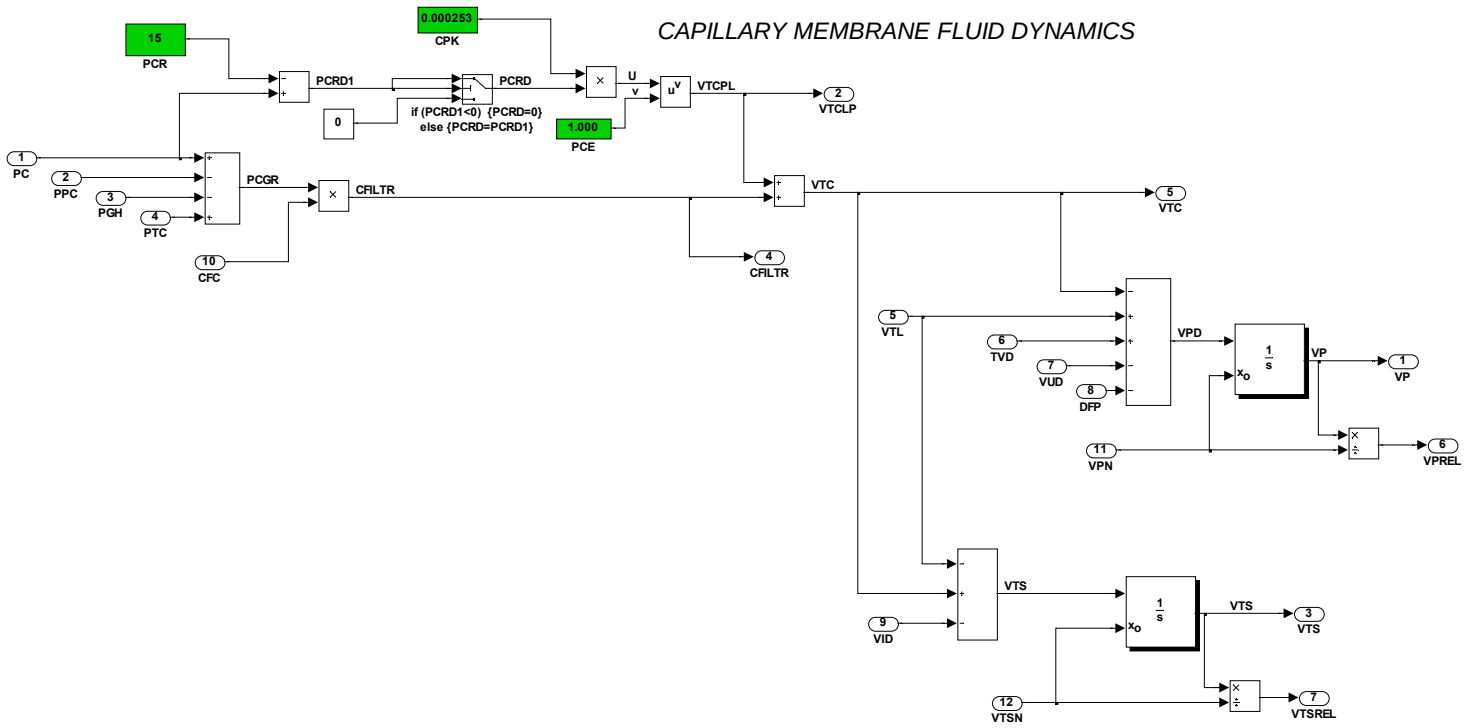
$$VTS=\int VTD\,dt \quad \text{(CP 11)}$$

The relative volume of systemic interstitial space (VTSREL) is calculated relative to the norm for an individual of a given body constitution:

$$VTSREL=VTS/VTSN \quad \text{(CP 12)}$$



Capillary Membrane Fluid Dynamics



Plasma protein dynamics

Plasma protein concentration (CPP) depends on the amount of plasma protein (PRP) and plasma volume

$$CPP=PRP/VP \quad \text{(VP):} \qquad \text{(CP 13)}$$

Plasma protein colloid osmotic pressure (PPC) depends nonlinearly on plasma protein concentration (CPP):

$$PPC=0.28*CPP+.0019*CPP^{2.0} \qquad \text{(CP 14)}$$

Plasma to interstitial protein flux (DPC) consists of protein flux due to plasma permeation through capillary pores (PLPRL) dependent on plasma permeation rate (VTCPL) and plasma protein concentration (CPP) and protein flux across the capillary membrane (PLPRDF) dependent on the concentration gradient of protein levels between plasma (CPP) and interstitial fluid (CPI):

$$PLPRL=VTCPL*CPP \qquad \text{(CP 15)}$$
$$PLPRDF=(CPP-CPI)*0.00104 \qquad \text{(CP 16)}$$
$$DPC=PLPRL+PLPRDF \qquad \text{(CP 17)}$$

Plasma to interstitial protein flux (DPC) consists of protein flux due to plasma permeation through capillary pores (PLPRL) dependent on plasma permeation rate (VTCPL) and plasma protein concentration (CPP) and protein flux across the capillary membrane (PLPRDF) dependent on the concentration gradient of protein levels between plasma (CPP) and interstitial fluid (CPI):

$$CPR=40 \qquad \text{(CP 18a)}$$
$$CPPD=CPP-CPR \qquad \text{(CP 18b)}$$
$$if\ (CPPD<0.0)\ then\ CPPD=0.0 \qquad \text{(CP 18c)}$$

The calculation of the liver plasma protein destruction rate (LPPRDS) versus the above factor (CPPD) is performed using an empirical equation in which (LPK) and (LPDE) are empirically determined coefficients based on comparison with measured data:

$$LPK=0.2728*10^{-13} \qquad \text{(CP 19a)}$$
$$LPDE=8.0 \qquad \text{(CP 19b)}$$
$$LPPRDS=LPK*CPPD^{LPDE} \qquad \text{(CP 19c)}$$

The total net plasma-liver protein exchange rate - (DPL), i.e. the rate of synthesis minus the rate of destruction of plasma proteins in the liver, depends on the difference between the rate of plasma protein synthesis (LPPR=0.03), which is given as a constant input, and the rate of plasma protein destruction (LPPRDS), calculated in equation CP 19:

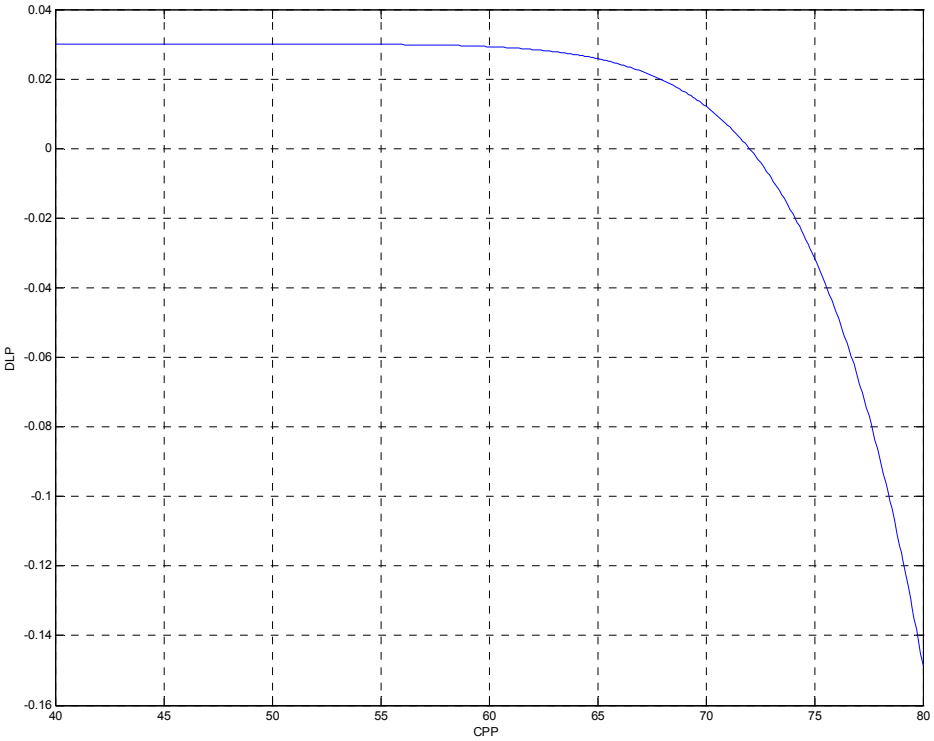
$$LPPR=0.03 \qquad \text{(CP 20a)}$$
$$DLP=LPPR-LPPRDS \qquad \text{(CP 20b)}$$

The rate of change in plasma protein quantity (DPP) is equal to the rate of protein synthesis in the liver (DLP) and the rate of protein return to plasma via lymph flow (DPL) minus the rate of protein transfer from systemic capillaries to the interstitium (DPC) minus the rate of protein flow from pulmonary capillaries (PPD) minus the rate of protein loss from plasma under pathological circumstances (DPR) - i.e., loss through the kidneys or during burns.

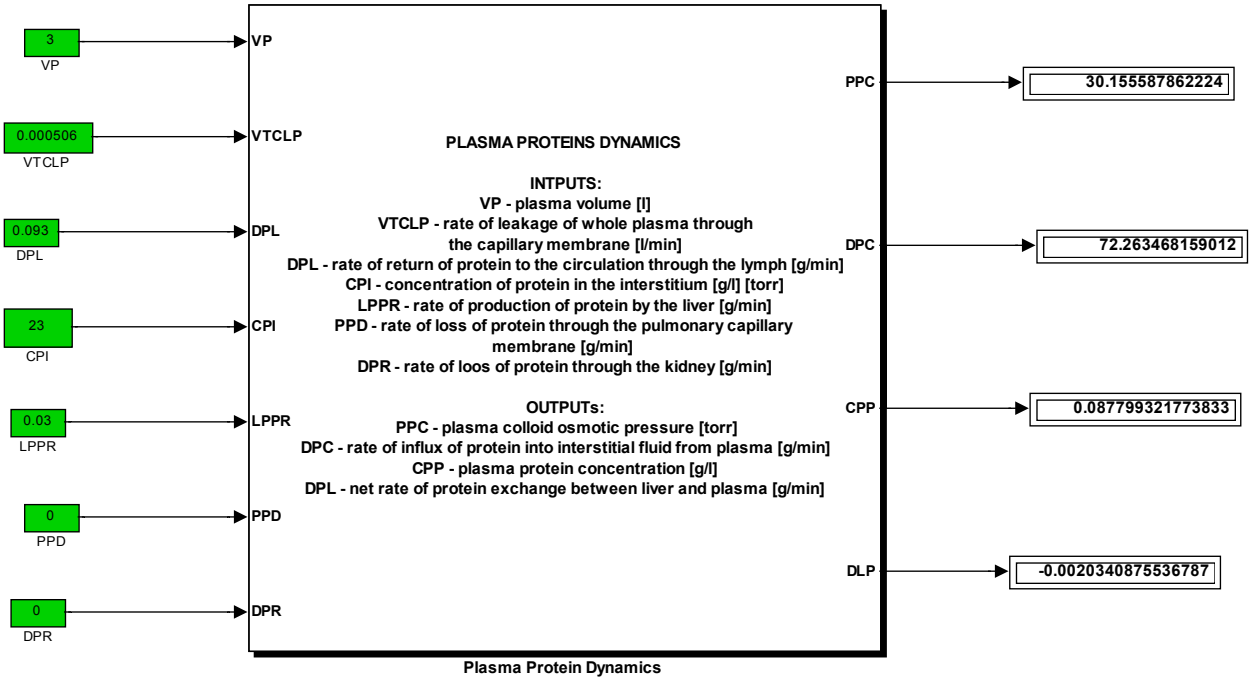
$$DPP=DLP+DPL-DPC-PPD-DPR \qquad \text{(CP 21)}$$

The total amount of plasma protein (PRP) is then subtracted by integrating the rate of change of this amount (DPP):

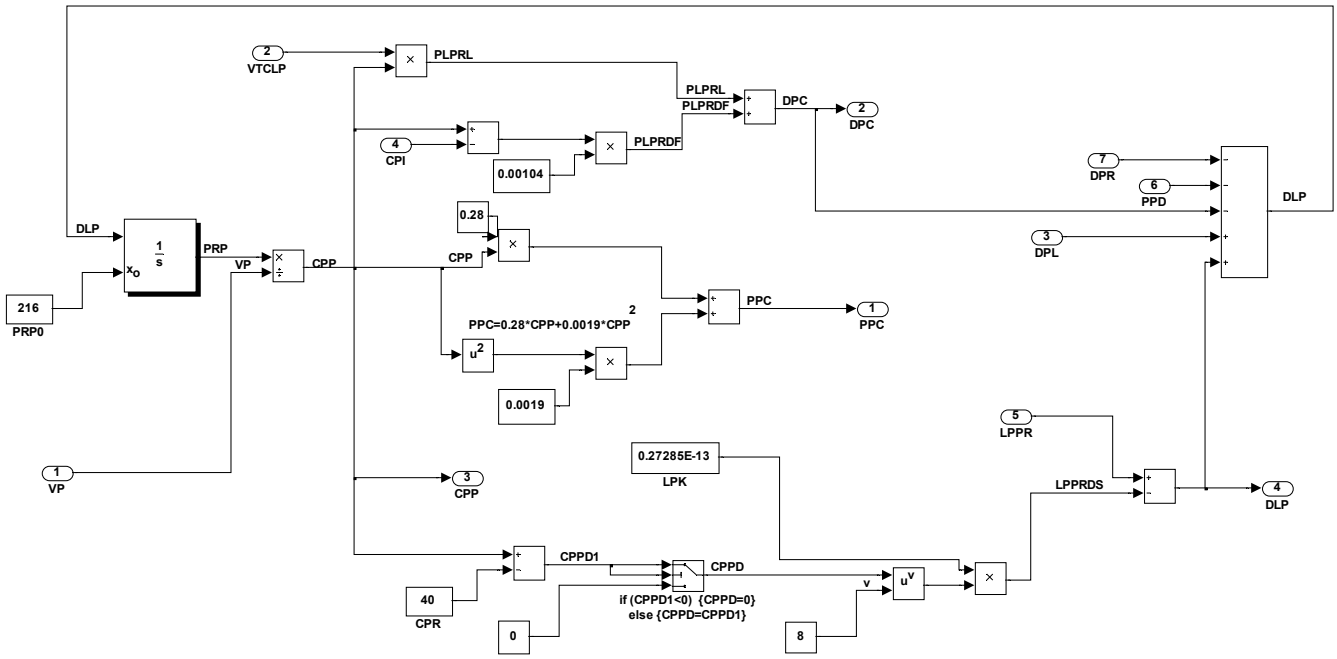
$$PRP = \int DPP\ dt \qquad \text{(CP 22)}$$



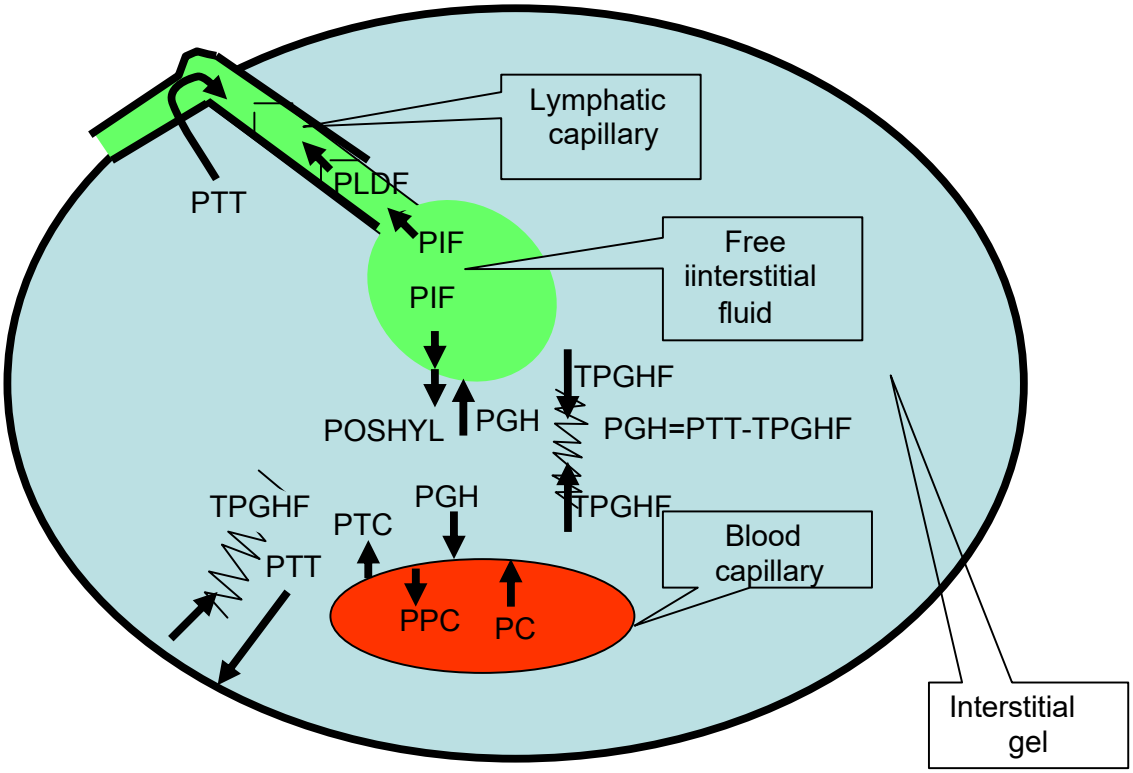
Non-linear dependence of the total rate of protein formation/destruction in the liver (DLP) on its plasma concentration (CPP)



PLASMA PROTEIN DYNAMICS



Dynamics of interstitial fluid, interstitial tissue gel and interstitial proteins

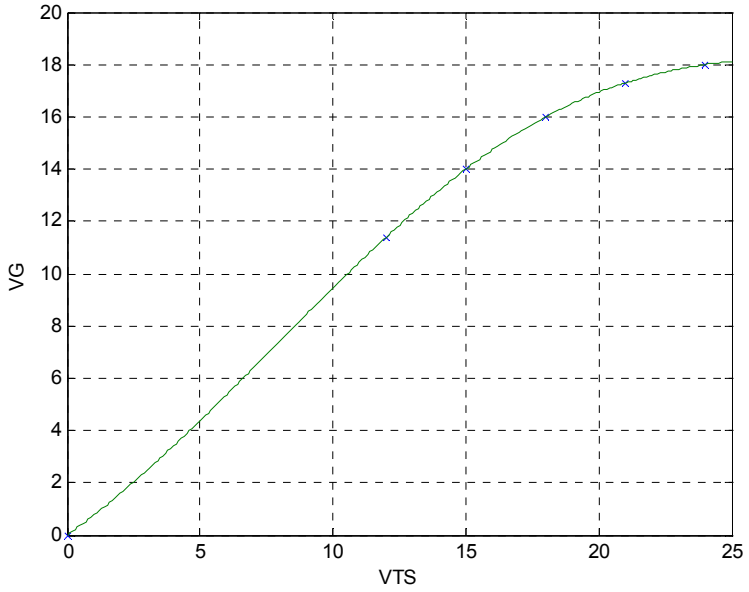


Relationships between model variables on blood and lymphatic capillaries, in interstitial fluid, in interstitial gel (explanation in text).

Water in the interstitial fluid is found bound in the gel and free. The ratio of the volume of fluid in the gel to the free fluid changes as the total volume of the interstitium changes. As the total interstitial fluid volume increases, the gel volume increases nonlinearly and more free fluid volume is realistically added. We calculate the gel volume (VG) as a function of the total interstitial fluid volume (VTS) according to an empirical relationship approximating the experimental data results using splines:

VG= function interstitislGelVolume(VTS) (CP 23)

VTS	VG
0	0
12.0	11.4
15.0	14.0
18.0	16.0
21.0	17.3
24.0	18.0



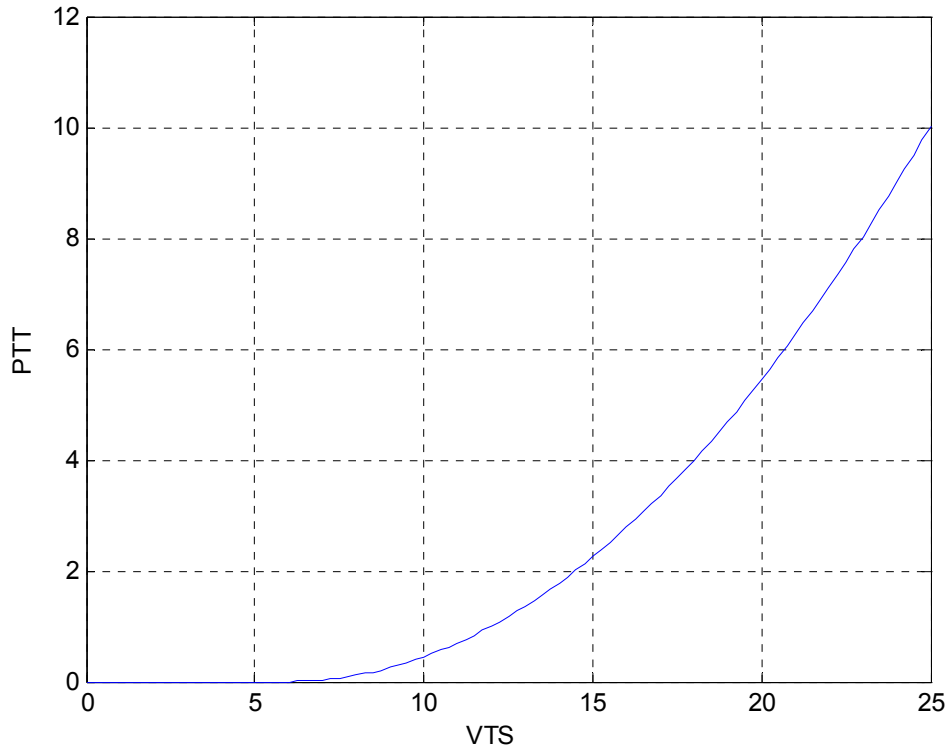
Dependence of tissue gel volume (VG) on total interstitial volume (VTS)

The volume of free fluid in the interstitium (VIF) is calculated as the difference between the total (systemic) interstitial volume (VTS) and the volume of the tissue gel (VG)::

$$VIF=VTS-VG \quad \text{(CP 24)}$$

The total pressure in the PTT systemic interstitial tissues depends nonlinearly on the total interstitial volume according to the empirical equation:

$$VTSF=6.0 \quad \text{(CP 25a)}$$
$$\text{if } VTS<VTSF \text{ then } PTT=0 \quad \text{(CP 25b)}$$
$$\text{else } PTT=((VTS-VTSF)/VTSF)^2 \quad \text{(CP 25c)}$$



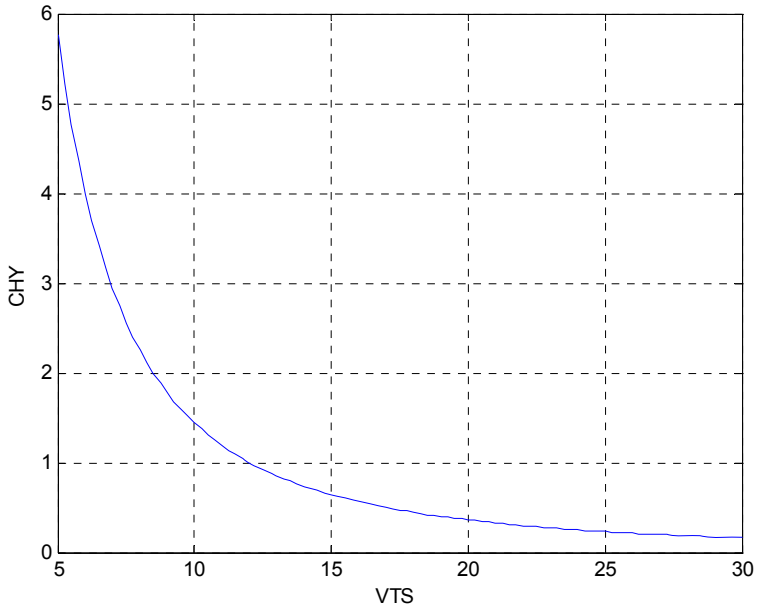
Dependence of total systemic interstitial pressure (PTT) on total interstitial volume (VTS)

The total pressure in the interstitial tissues (PTT) is higher than the hydraulic pressure inside the tissue gel (PPGH).The gel, for example, acts as a tissue counterpressure during the hydraulic equilibrium of the fluid at the capillary. The cause of the pressure reduction is the hyalluronic acid abundantly present in the tissue gel. Hyaluronic acid acts as a stretched spring that reduces the overall pressure in the tissue gel (PGHF=3.7). The hydraulic pressure of the tissue gel (PGH) is therefore calculated from the total interstitial pressure (PTT) component minus the "spring" pressure (TPGHF), which is dependent on the concentration of hyaluronic acid (CHY):

$$TPGHF=CHY*3.7 \quad \text{(CP 26)}$$
$$PGH=PTT-TPGHF \quad \text{(CP 27)}$$

The concentration of hyaluronic acid in the interstitium (CHY) depends nonlinearly on the total amount of hyaluronic acid in the interstitium (HYL) and the total volume of the interstitium (the coefficient CMPTSS=2 characterizes the degree of this nonlinearity):

$$CMPTSS=2 \quad \text{(CP 28a)}$$
$$CHY=(HYL/VTS/5.0)^{CMPTSS} \quad \text{(CP 28b)}$$



Non-linear dependence of interstitial fluid hyaluronic acid concentration (CHY) on total interstitial volume (VTS)

The colloid osmotic pressure in the tissue gel caused by hyaluronic acid (POSHYL) depends on the concentration of hyaluronic acid:

$$POSHYL=CHY*2.0 \quad \text{(CP 29)}$$

The proteins present in the tissue gel are equilibrated between the free fluid in the interstitium and the fluid in the tissue gel (they are "sucked" from the free fluid into the gel). Although the concentration of proteins inside the tissue gel is lower than in the free interstitial fluid, their osmotic activity (potentiated by hyaluronic acid) is higher. Therefore, when calculating the pressure interface between the free interstitial fluid and the fluid in the tissue gel, we assume a colloidal osmotic equilibration between the free fluid and the gel in terms of proteins. Therefore, we neglect proteins in terms of their influence on osmolarity, and we calculate the colloid osmotic pressure of hyaluronic acid (POSGYL) as the only osmotically active factor affecting the hydraulic pressures at the interface between the free fluid and the tissue gel. Thus, the pressure in the free interstitial fluid (PIF) is equal to the hydraulic pressure of the interstitial tissue gel minus the suction colloid osmotic pressure of the hyaluronic acid in the tissue gel (POSHYL):

$$PIF=PGH-POSHYL \quad \text{(CP 30)}$$

The interstitial pressure of the solid tissues (PTS) is equal to the total tissue pressure (PTT) minus the pressure in the free interstitial fluid (PIF))

$$PTS=PTT-PIF \quad \text{(CP 31)}$$

From the intersitial space, the fluid (and dissolved substances including proteins) is drained by the lymph. Lymphatic vessels have valves and therefore lymph cannot flow out of them. The higher the pressure of the free interstitial fluid, the higher the pressure gradient between the inflowing interstitial fluid and the lymphatic vessel. However, when lymph drains from the tissues, the back pressure of the interstitium, which compresses the lymphatic vessels, must be overcome. The pressure gradient that causes lymph to flow from the lymphatic interstitial fluid into the lymphatic vessels (PLD) is therefore calculated as the difference of the sum of constant (PLDF=5.9) and the pressure in the free interstitial fluid (PIF) minus the total tissue pressure (PTT). The resulting pressure is bounded above by the maximum possible value of 7.0 torr:

$$PLDF=5.9 \quad \text{(CP 32a)}$$
$$PLD=PIF+PLDF-PTT \quad \text{(CP 32b)}$$
$$if\ (PLD>7.0)\ then\ PLD=7.0 \quad \text{(CP 32c)}$$

Total lymph flow (VTL) is equal to the pressure gradient for lymph flow (PLD) multiplied by a constant representing the conductivity of the lymphatic vessels. The calculated lymph flow is bounded at the bottom by 0 (lymph does not flow from the lymphatic vessels into the tissues):

$$VTL=PLD*0.02 \quad \text{(CP 33a)}$$
$$if\ (VTL<0.0)\ then\ VTL=0.0 \quad \text{(CP 33b)}$$

The interstitium contains proteins that are equilibrated in both the free interstitial fluid and the tissue gel. For simplicity, we do not distinguish here between the protein concentrations in the gel and in the free interstitial fluid, and we assume a single protein concentration for the entire interstitium. We therefore simply calculate the protein concentration in the interstitium (CPI) from the total protein in the tissue interstitium (TSP) and the total volume of the systemic interstitium (VTS):

$$CPI=TSP/VTS \quad \text{(CP 34)}$$

The colloid-osmotic pressure in the interstitial free fluid (PTCPR) is calculated from the protein concentration in the interstitium (CPI) using the same empirical equation we used to calculate the colloid-osmotic pressure of proteins in plasma (see equation CP 14):

$$PTCPR=0.28*CPI+0.0019*CPI^{2.0} \quad \text{(CP35)}$$

If at the gel-free fluid interface in the interstitium we could neglect the osmotic influence of tissue proteins, then at the blood capillary-tissue gel interface this is no longer the case and we have to take proteins into account when calculating the total colloid osmotic pressure of the interstitial gel. The osmotic influence of proteins and hyaluronic acid on the total colloid-osmotic pressure of the tissue gel are mutually potentiating, therefore the influence of osmotic pressure of hyaluronic acid and osmotic pressure of plasma proteins is not calculated as a sum but as a product. The total osmotic pressure of the interstitial tissue gel (PTC) is then equal to the osmotic pressure of the hyaluronic acid in the tissue gel (POSHYL) multiplied by the colloid osmotic pressure due to the plasma proteins in the interstitial free fluid (PTCR) that are in equilibrium with the proteins in the tissue gel. The constant of proportionality here is (GCOPF=0.7):

$$GCOPF=0.7 \quad \text{(CP 36a)}$$

$$PTC=POSHYL*PTCPR*GCOPF \quad \text{(CP 37b)}$$

The proteins enter the tissue interstitium from the plasma (see equations CP 15-17), and from the tissue interstitium they are taken back into the circulation by the lymph. The rate of return of plasma proteins to the plasma via the lymph (DPL) is proportional to the concentration of proteins in the systemic interstitium (CPI) and the rate of lymph flow from the interstitium to the plasma (VTL):

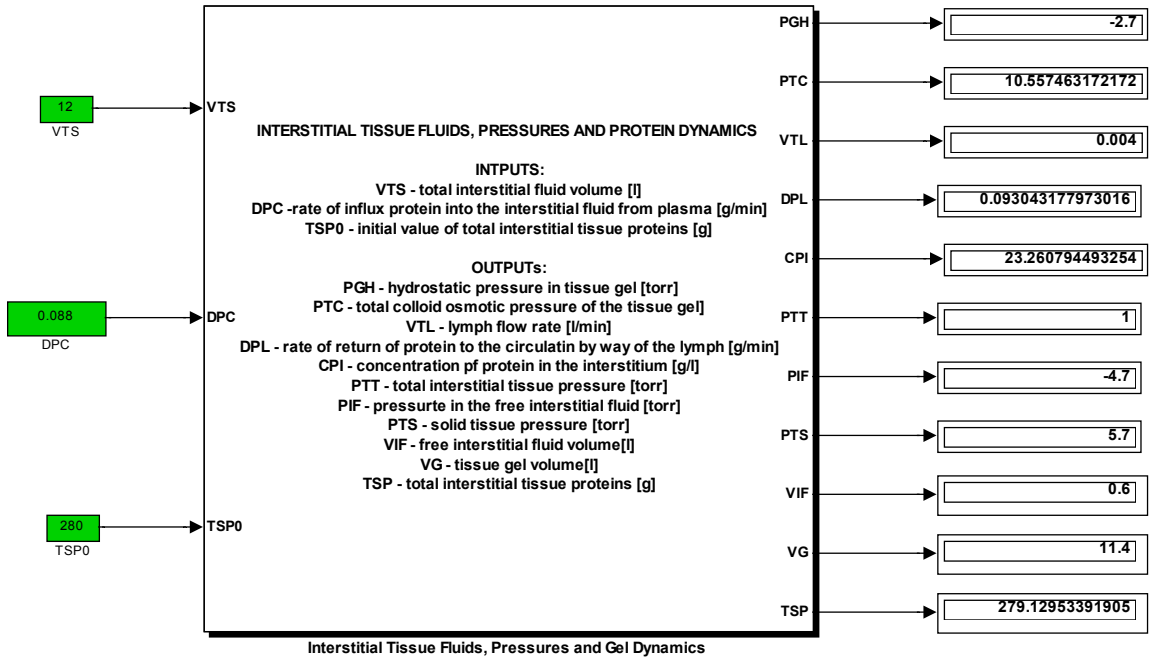
$$DPL=CPI*VTL \quad \text{(CP 38)}$$

The balance of proteins in the interstitium depends on the difference between the rate of influx of proteins from the plasma (DPC), calculated in the CP equation 17, and the rate of their removal from the interstitium by the lymph (DPL). Therefore, the rate of change of the total amount of proteins in the systemic interstitium (DPI) is equal to:

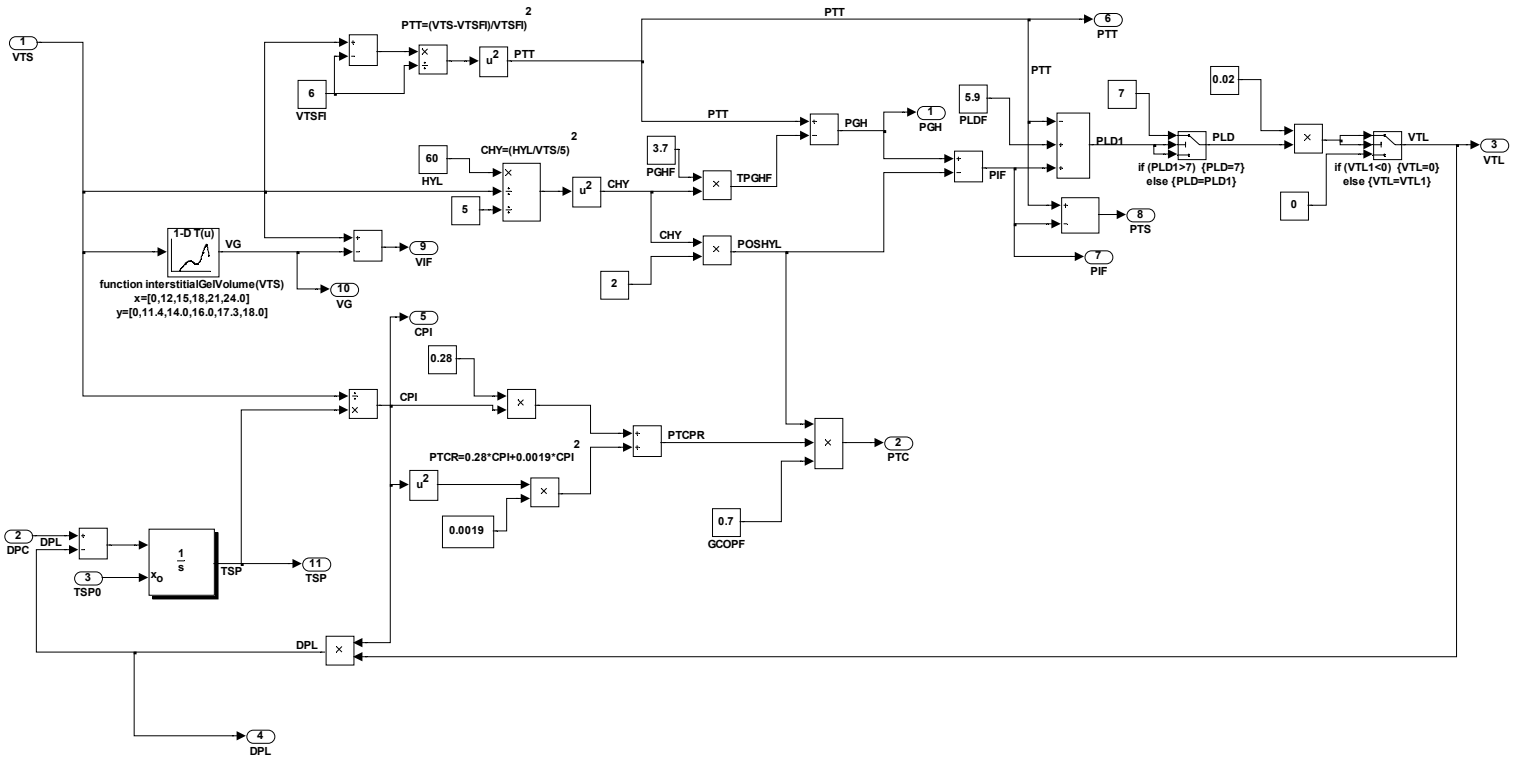
$$DPI=DPC-DPL \quad \text{(CP 39)}$$

The total amount of proteins in the tissue interstitium (TSP) is then subtracted by integrating the rate of change of this amount (DPI):

$$TSP=\int DPI\ dt \quad \text{(CP 40)}$$



INTERSTITIAL TISSUE FLUIDS, PRESSURES AND PROTEIN DYNAMICS



FLUID AND GAS DYNAMICS IN THE LUNGS

Fluid and protein dynamics in the lungs

This is a very simplified analysis of pulmonary fluid dynamics. The gel component of the pulmonary fluid is neglected, so the pulmonary fluid (VPP) is approximated as a freely mobile fluid. Similarly, the pressure-volume curves of the pulmonary interstitium are highly simplified, as is the lymph flow in the lungs.

Pulmonary capillary pressure (PPA) is calculated as the sum of 45% pulmonary arterial pressure (PPA) and 55% left pulmonary atrial pressure (PLA):

$$PCP=0.45*PPA+0.55*PLA \quad \text{(PD 01)}$$

The pressure gradient across the pulmonary capillary (PGRPCM), acting in the direction of fluid filtration into the pulmonary interstitium, is calculated from the pulmonary capillary pressure (PCP) and the colloid osmotic pressure of the pulmonary interstitial fluid (POS), and the counter-pressures, the pulmonary interstitial fluid pressure (PPI) and the colloid osmotic pressure of the plasma proteins (PPC), sucking fluid into the capillary:

$$PGRPCM=PCP-PPI+POS-PPC \quad \text{(PD 02)}$$

From the pressure gradient across the pulmonary capillaries (PGRPCM) and the capillary filtration factor (CPF), the filtration rate of fluid into the lung interstitium (PFI) is calculated:

$$PFI=PGRPCM*CPF \quad \text{(PD 03)}$$

The rate of change of pulmonary interstitial fluid volume (DPF) is equal to the difference between the rate of filtration from the pulmonary capillaries (PFI) and the rate of return of fluid from the lungs to the lymphatic circulation (PLF):

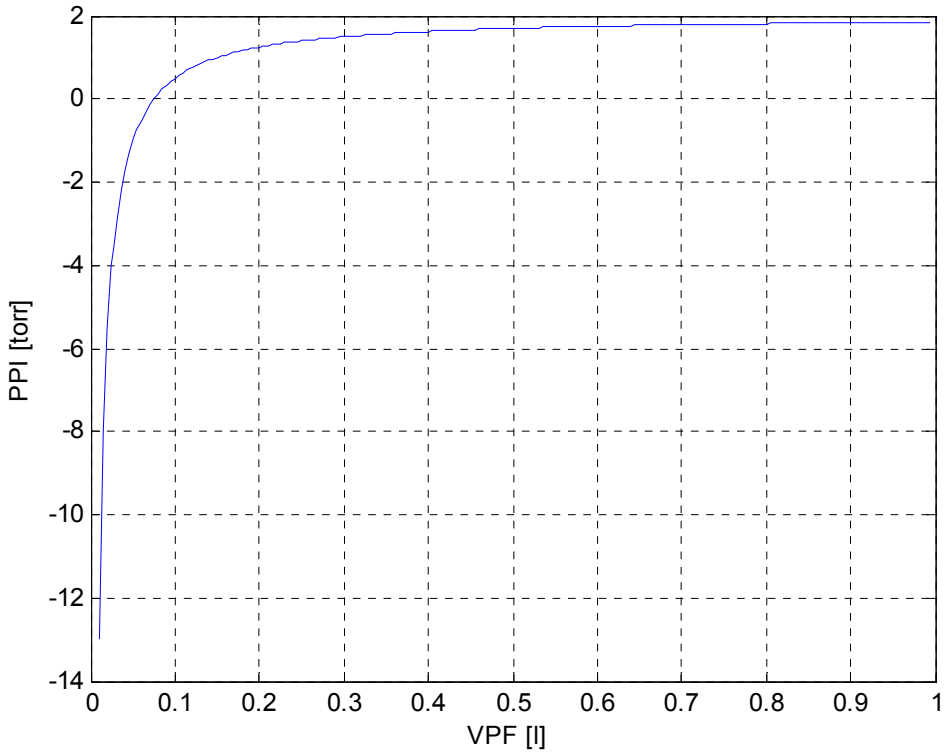
$$DFP=PFI-PLF \quad \text{(PD 04)}$$

By integrating the rate of change of pulmonary interstitial fluid volume (DFP), we obtain the volume of free fluid in the pulmonary interstitium (VPF):

$$VPF=\int DFP\,dt \quad \text{(PD 06)}$$

Based on the empirical relationship corresponding to the experimentally measured dependence, we calculate the hydraulic pressure of the fluid in the pulmonary interstitium (PPI) from the volume of the pulmonary interstitium (VPF):

$$PPI=2.0-0.150/VPF \quad \text{(PD 07)}$$



Dependence of pulmonary interstitial hydraulic pressure (PPP) on total pulmonary interstitial volume (VPF)

Lung lymph flow rate (PLF) depends on pulmonary interstitial fluid pressure (PPI) according to an empirically established relationship corresponding to measured dependencies:

$$PLF=(PPI+11.0)*0.0003 \quad \text{(PD 08)}$$

From the lymph flow (PLF) and the concentration of proteins in the pulmonary interstitium (CPN) we can calculate the rate of return of proteins from the pulmonary interstitium to the circulation via the lymph (PPO):

$$PPO=PLF*CPN \quad \text{(PD 09)}$$

From the difference in plasma (CPP) and pulmonary interstitium (CPN) protein concentrations, we calculate the rate of protein leakage from plasma to pulmonary interstitium (PPN):

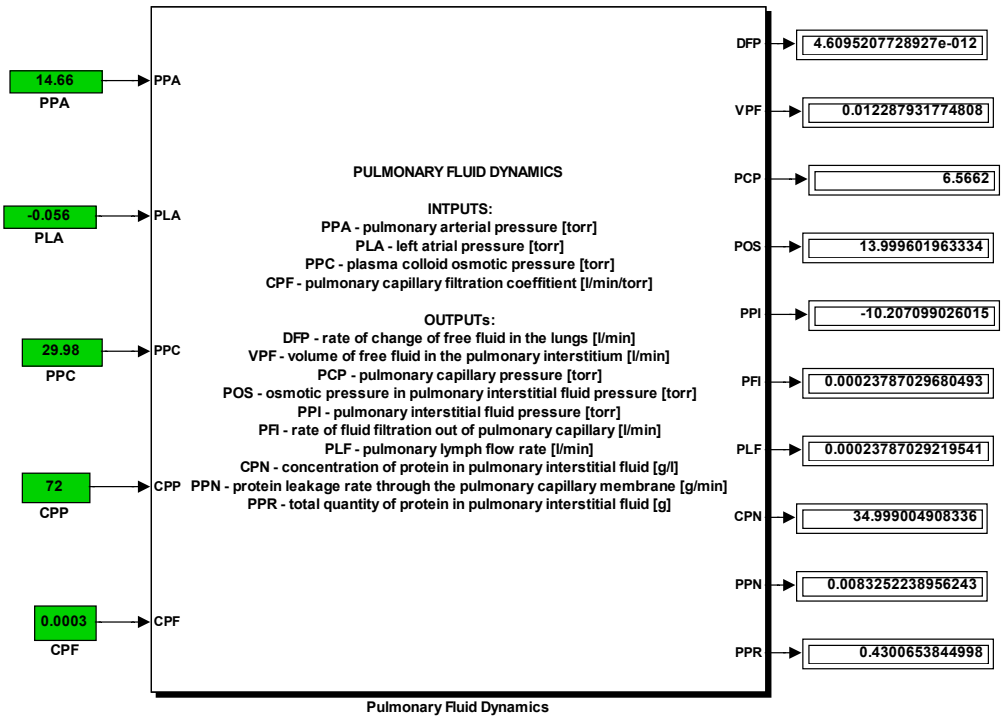
$$PPN=(CPP-CPN)*.000225 \quad \text{(PD 10)}$$

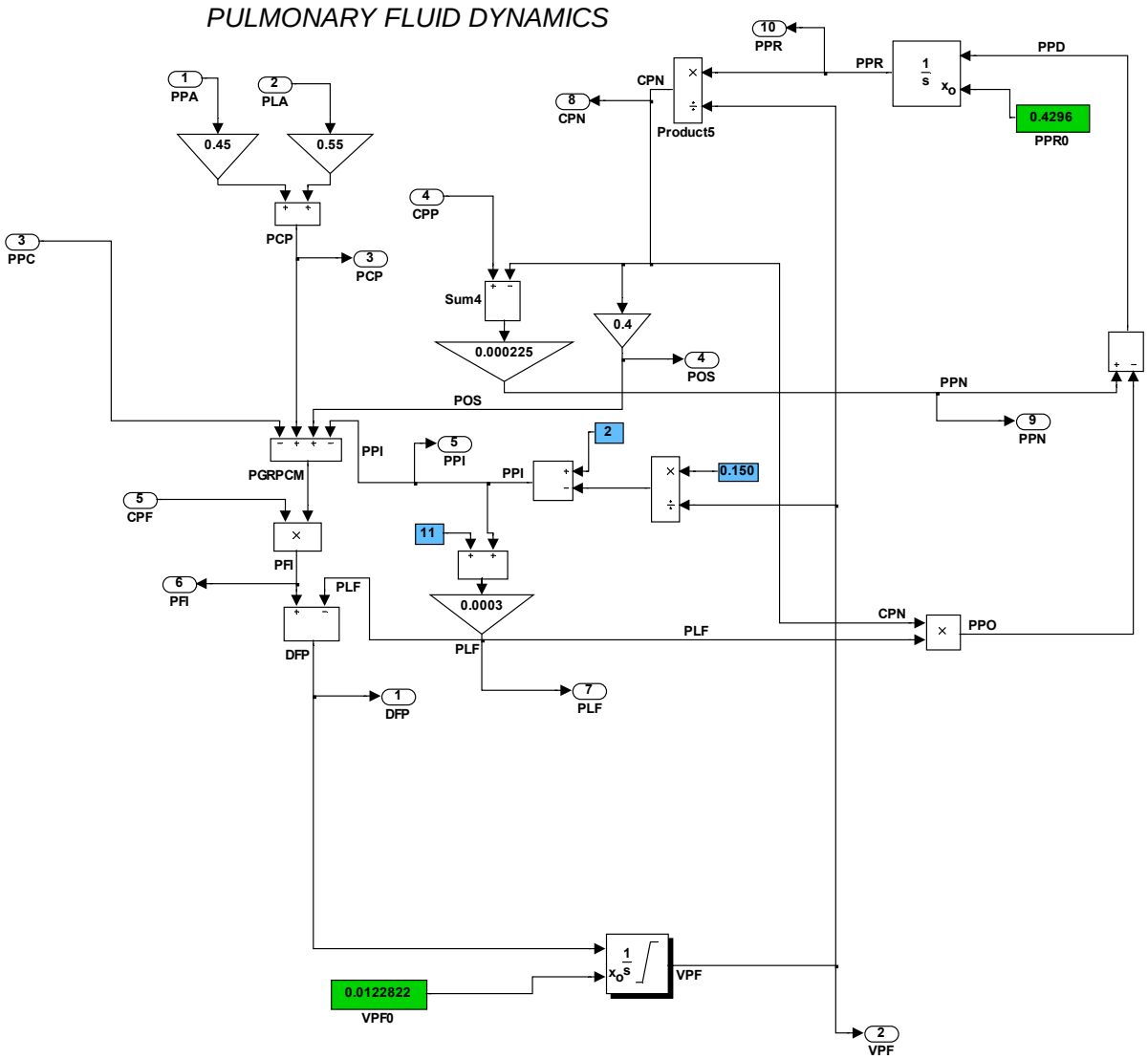
The rate of change of protein content in the lung interstitium (PPD) is equal to the difference between the rate of protein influx into the interstitium by leakage from pulmonary capillaries (PPN) and the rate of removal from the interstitium by lymph (PPO):

$$PPD=PPN-PPO \quad \text{(PD 11)}$$

By integrating the rate of this change (PPD), we subtract the total amount of protein in the pulmonary interstitium (PPR):

$$PPR=\int PPD\,dt \quad \text{(PD 12)}$$


14.66
PPA
PPA
-0.056
PLA
PLA
29.98
PPC
PPC
72
CPP
CPP
0.0003
CPF
CPF
PULMONARY FLUID DYNAMICS
INTPUTS:
PPA - pulmonary arterial pressure [torr]
PLA - left atrial pressure [torr]
PPC - plasma colloid osmotic pressure [torr]
CPF - pulmonary capillary filtration coeffitient [l/min/torr]
OUTPUTs:
DFP - rate of change of free fluid in the lungs [l/min]
VPF - volume of free fluid in the pulmonary interstitium [l/min]
PCP - pulmonary capillary pressure [torr]
POS - osmotic pressure in pulmonary interstitial fluid pressure [torr]
PPI - pulmonary interstitial fluid pressure [torr]
PFI - rate of fluid filtration out of pulmonary capillary [l/min]
PLF - pulmonary lymph flow rate [l/min]
CPN - concentration of protein in pulmonary interstitial fluid [g/l]
PPN - protein leakage rate through the pulmonary capillary membrane [g/min]
PPR - total quantity of protein in pulmonary interstitial fluid [g]
DFP
4.6095207728927e-012
VPF
0.012287931774808
PCP
6.5662
POS
13.999601963334
PPI
-10.207099026015
PFI
0.00023787029680493
PLF
0.00023787029219541
CPN
34.999004908336
PPN
0.0083252238956243
PPR
0.4300653844998
Pulmonary Fluid Dynamics


PULMONARY FLUID DYNAMICS
1
PPA
2
PLA
0.45
0.55
PCP
3
PCP
3
PPC
4
CPP
Sum4
0.000225
0.4
4
POS
POS
PGRPCM
PPI
5
PPI
PPI
2
0.150
5
CPF
PFI
11
0.0003
6
PFI
PLF
DFP
PLF
1
DFP
7
PLF
10
PPR
PPR
CPN
8
CPN
Product5
1
s
x0
PPD
0.4296
PPR0
PPN
9
PPN
CPN
PPO
0.0122822
VPF0
VPF
2
VPF

Oxygen transport in the lungs

Total oxygen consumption (O2UTIL) is calculated as the sum of oxygen consumption in non-muscle tissues (DOB) and muscles (RMO)::

O2UTIL=DOB+RMO (PD13)

Calculation of arterial blood oxygen saturation (OSA) from partial pressure of oxygen in inspired air (PO2AMB=150 torr), total metabolic oxygen demand (O2UTIL), normalized diffusion coefficient for oxygen across the aleveolocapillary membrane (PO2DEF=1), and free fluid in the pulmonary interstitium (VPF), which can impair oxygen transport in pulmonary edema:

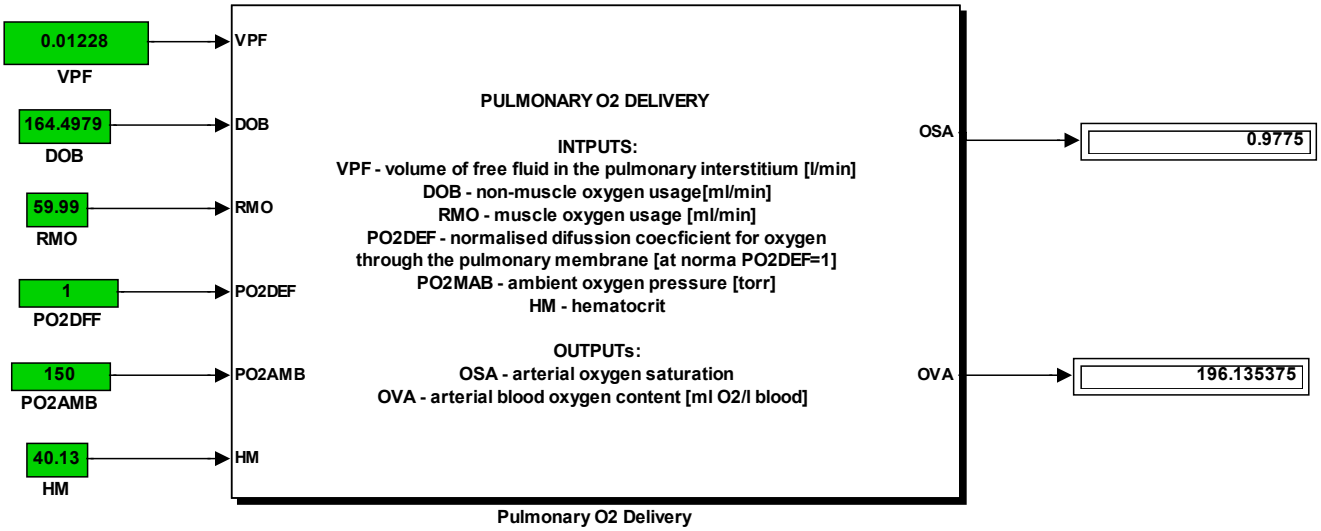
OSA=(PO2AMB-(O2UTIL.0266667/PO2DFF))/100.0* (PD 14)

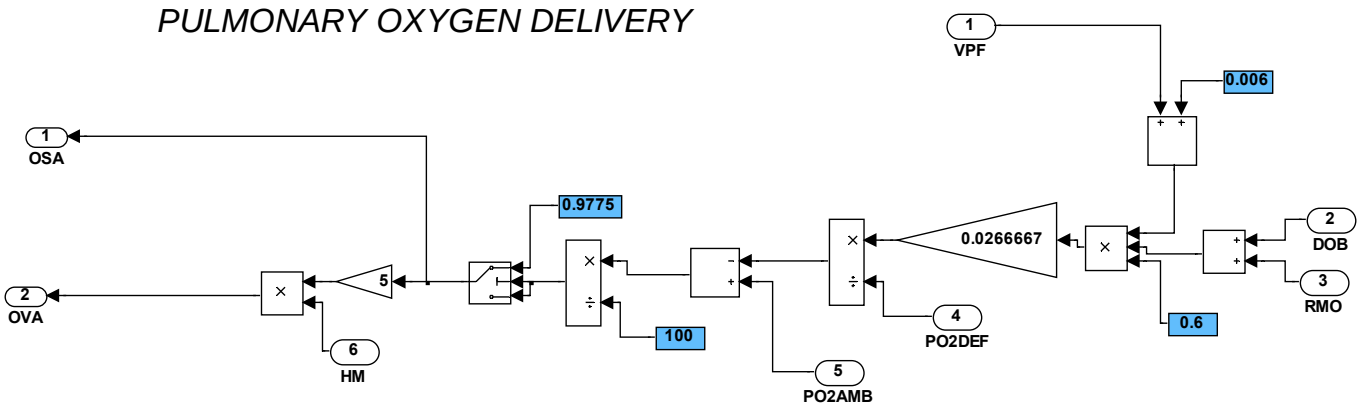
if (OSA>0.9775) then OSA=0.9775 (PD 15)

*OSA=OSA-VPF*0.6* (PD 16)

The total arterial blood oxygen concentration (OVA) is obtained by multiplying the oxygen saturation of hemoglobin (OSA), hematocrit (HM) and a constant (characterizing the oxygen capacity of the blood):

*OVA=OSA*HM*5.0* (PD 17)


0.01228
VPF
VPF
164.4979
DOB
DOB
59.99
RMO
RMO
1
PO2DFF
PO2DEF
150
PO2AMB
PO2AMB
40.13
HM
HM
PULMONARY O2 DELIVERY
INTPUTS:
VPF - volume of free fluid in the pulmonary interstitium [l/min]
DOB - non-muscle oxygen usage[ml/min]
RMO - muscle oxygen usage [ml/min]
PO2DEF - normalised difussion coecficient for oxygen
through the pulmonary membrane [at norma PO2DEF=1]
PO2MAB - ambient oxygen pressure [torr]
HM - hematocrit
OUTPUTs:
OSA - arterial oxygen saturation
OVA - arterial blood oxygen content [ml O2/l blood]
OSA
0.9775
OVA
196.135375
Pulmonary O2 Delivery


PULMONARY OXYGEN DELIVERY
1
VPF
0.006
1
OSA
0.9775
0.0266667
2
DOB
3
RMO
2
OVA
5
6
HM
100
4
PO2DEF
5
PO2AMB
0.6

DYNAMICS OF ELECTROLYTES AND WATER IN EXTRACELLULAR AND INTRACELLULAR FLUID

Water, sodium and potassium in ICT and ECT

The volume of extracellular fluid (VEC), expressed in litres, is the sum of the volumes of (systemic) interstitial fluid VTS, pulmonary interstitial fluid (VPF) and plasma (VP):

$$VEC=VTS+VPF+VP \quad \text{(EL 01)}$$

The rate of sodium ion Na+ uptake into the body (NAINT), expressed in mmol/min, is equal to the normal sodium uptake rate (NID) (Guyton gives a value=0.1 mmol/min) multiplied by the salt taste factor (STH), which is normally equal to 1:

$$NAINT=NID*STH \quad \text{(EL 02)}$$

The change in the amount of sodium ion stores in the extracellular fluid (NED), expressed in mmol/min, is equal to the difference between the rate of sodium ion uptake into the body (NAINT) and the rate of sodium ion loss through urine (NOD):

$$NED=NAINT-NOD \quad \text{(EL 03)}$$

By integrating the rate of this change (NED), we remove the sodium ion stores (in mmol) in the extracellular fluid (NAE):

$$NAE=\int NED\,dt \quad \text{(EL 04)}$$

The concentration of sodium ions in the extracellular fluid (and in plasma - we assume that the Na+ concentrations in the systemic and pulmonary interstitium and in plasma are balanced) - (CNA) is obtained after dividing the sodium ion stores (NAE) in the extracellular fluid by the volume of extracellular fluid (VEC):

$$CNA=NAE/VEC \quad \text{(EL 05)}$$

The rate of change of potassium ion stores in the extracellular fluid (KED), expressed in mmol/min, is equal to the rate of potassium ion uptake (KID) - Guyton gives normal values of 0.6 mmol/min, minus the rate of potassium ion transfer from the extracellular to the intracellular fluid (KCD), minus the rate of potassium ion excretion into the urine (KOD):

$$KED=KID-KCD-KOD \quad \text{(EL 06)}$$

Integration of these changes yields the total potassium ion K+ stores in the extracellular fluid (EF), expressed in mmol:

$$KE=\int KED\,dt \quad \text{(EL 07)}$$

The concentration of potassium ions (in mmol/l) in the extracellular fluid (and in plasma - we assume that the concentrations of K+ in the systemic and pulmonary interstitium and in plasma are equilibrated) - (CKE) is obtained after dividing the potassium ion stores (KE) in the extracellular fluid by the volume of extracellular fluid (VEC)::

$$CKE=KE/VEC \quad \text{(EL 08)}$$

The distribution of potassium between the cell and the extracellular fluid depends, among other things, on the level of aldosterone. An increase in aldosterone level increases the activity of the Na /K++ pump and leads to a partial transfer of potassium ions from the extracellular to the intracellular fluid. Aldosterone affects only a part of the potassium ions in the cell, the larger part depends on metabolic processes inside the cell (and is bound e.g. to some intracellular polymers such as glycogen). Therefore, in the model, when calculating the target level of intracellular potassium stores (KIR), two parts of the stores are distinguished, one is taken as constant (KE2=2850 mmol) in the model, influenced by metabolic processes, and the other (KE1) is a variable that depends on the concentration of extracellular potassium and on the concentration of aldosterone.

We first calculate the value of the fraction of intracellular potassium stores dependent on extracellular potassium concentration and aldosterone level (KE1). The normal value of this part of the intracellular potassium stores (KE1N) is normally 140 times greater than the concentration of extracellular potassium:

$$KE1N=RKIE*CKE \quad \text{(EL 00)}$$

The multiplication factor RKIE (under normal circumstances RKIE=140) is expressed through the appropriate intracellular fluid volume (VICnorm=25), thus giving an expression that allows us to account for potassium transfer even in individuals with different constitutions and weights (and different appropriate intracellular fluid volume values):

$$RKIE = 5.6*VICnorm \quad \text{(EL 10)}$$

If the level of aldosterone increases, the potassium content in the cells increases. The value of the fraction of intracellular potassium stores that depends on the concentration of extracellular potassium and the aldosterone level (KE1) is calculated from the appropriate value of these stores corresponding to the instantaneous extracellular potassium level (KE1N) and the multiplicative coefficient expressing the effect of aldosterone (AMK), the sensitivity coefficient expressing the sensitivity of the effect of aldosterone to the change in intracellular stores (ACLK):

$$KE1=((AMK-1.)*ALCLK+1.0)*KE1N \quad \text{(EL 11)}$$

The second, more quantitatively significant part of the potassium stock, dependent on metabolic processes (KE2), is a constant in the model. We derive its value from the appropriate value of total cellular potassium stores (KInorm), which we calculate from the appropriate value of intracellular fluid volume (VICnorm) multiplied by the nourmal value of intracellular potassium concentration (142 mmol/l):

$$KInorm=142*VICnorm \quad \text{(EL 12)}$$

We calculate the value of the metabolic process-dependent part of the potassium reserve (KE2) by subtracting the mormal value of the second part of the potassium reserve influenced by aldosterone and the level of extracellular potassium from the value of the proper potassium reserve (KInorm) - therefore the multiplication factor (RKIE) is multiplied by the normal value of the extracellular potassium concentration, i.e. 5:

$$KE2=KInorm- RKIE*5 \quad \text{(EL 13)}$$

The sum of the values of aldosterone-dependent potassium stores and extracellular fluid potassium levels (KE1) and the potassium stores dependent only on cellular metabolic processes (KE2) is the target value for the amount of potassium stores in cells:

$$KIR=KE1+KE2 \quad \text{(EL 14)}$$

The rate of potassium flux from extracellular fluid into cells (KCD) is proportional to the difference (KIE) between the target value of cellular potassium stores (KIR) and the instantaneous value of cellular potassium stores (KI). To prevent oscillations, we do not calculate the potassium flux rate KCD from the difference between the instantaneous and target potassium stock value (KIE) directly, but use a damping term here:

$$KIE=KIR-KI \quad \text{(EL 15)}$$

$$KCZ=KIE*0.013 \quad \text{(EL 16)}$$

$$DKCZ=(KCZ-KCD)/5.0 \quad \text{(EL 17)}$$

$$KCD=\int DKCZ\ dt \quad \text{(EL 18)}$$

By integrating the potassium flux rate into the cells (KCD), we then obtain the value of the potassium stores in the cells:

$$KI=\int KCD\ dt \quad \text{(EL 19)}$$

Intracellular potassium concentrations (CKI) are calculated from the volume of intracellular fluid (VIC) and total cellular potassium stores (CI):

$$CKI=KI/VIC \quad \text{(EL 20)}$$

The difference in electrolyte concentrations between the cell and the extracellular fluid (CCD) is calculated as the difference between the concentration of potassium ions in the cells (CKI) and the concentration of sodium ions in the extracellular fluid (CNA). It is assumed that the concentration of other electrolytes on both sides of the membrane is approximately the same and that the osmotic water demand depends on the difference between the concentrations of intracellular potassium and extracellular sodium:

$$CCD=CKI-CNA \quad \text{(EL 21)}$$

The rate of osmotic water transfer between the extracellular fluid and the cell (VID) is proportional to the difference in electrolyte concentrations in the cell and in the extracellular fluid (CCD). To prevent oscillations in the calculation of VID, we introduce a damping term:

$$VIZ=0.01*CCD \quad \text{(EL 22)}$$

$$DVID=(VIZ-VID)/5.0 \quad \text{(EL 23)}$$

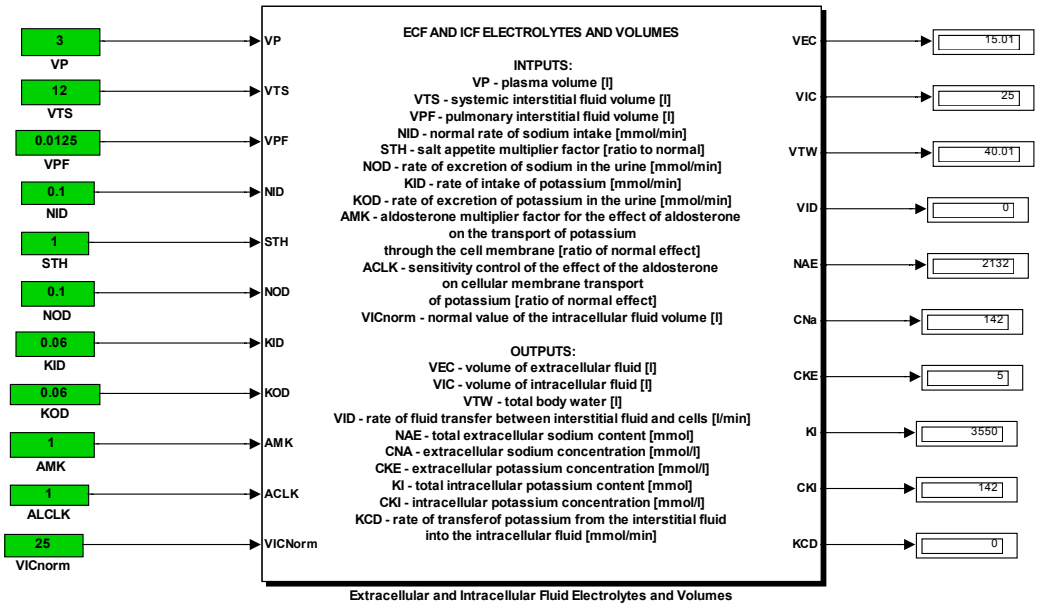
$$VID=\int DVID\ dt \quad \text{(EL 24)}$$

By integrating the rate of water transfer from extracellular fluid to cells (VID), we obtain the total volume of intracellular fluid (VIC):

$$VIC=\int VID\ dt \quad \text{(EL 25)}$$

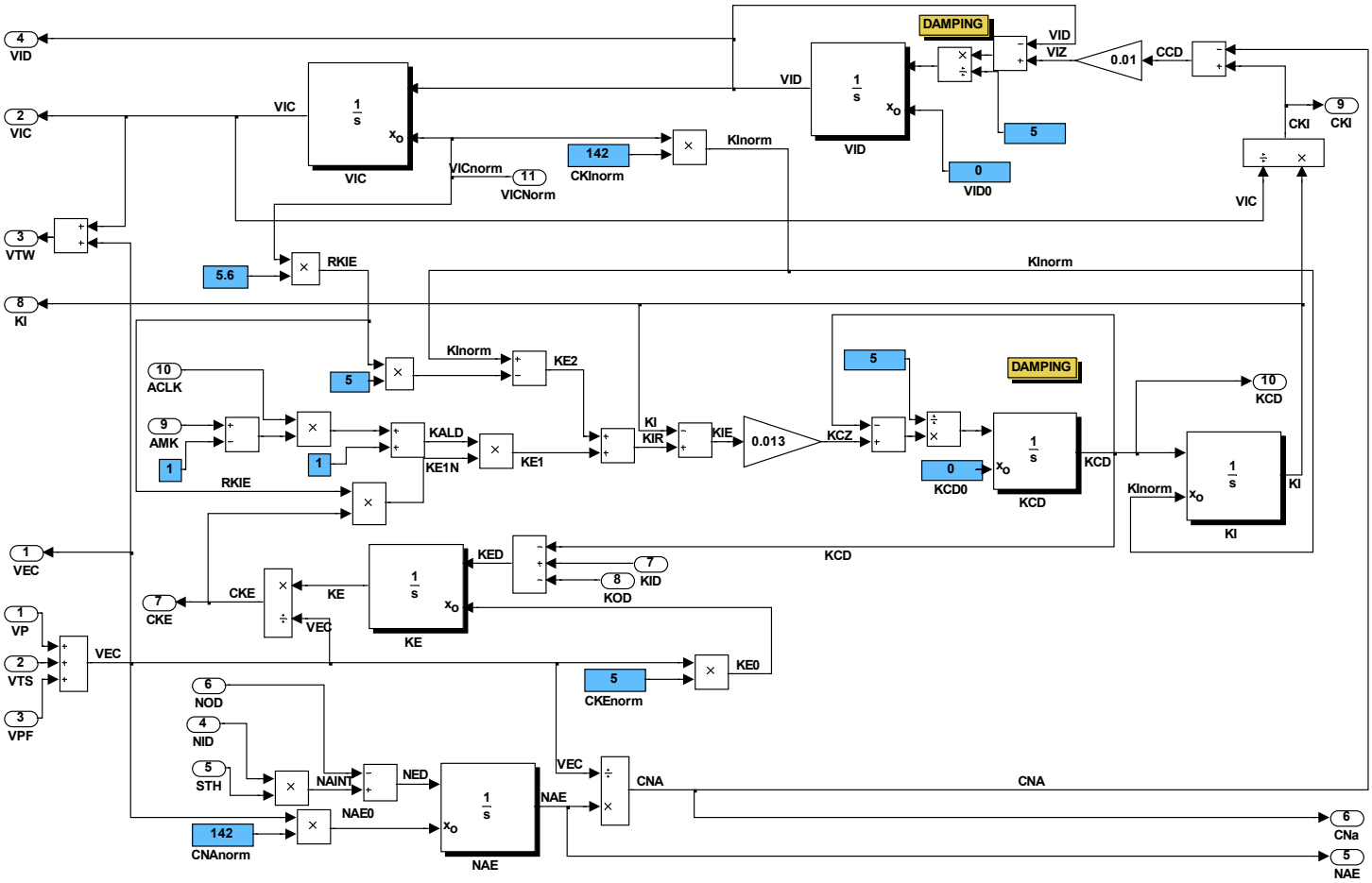
Total body water volume (VTW) is the sum of intracellular (VIC) and extracellular fluid (VEC):

$$VTW=VIC+VEC \quad \text{(EL 26)}$$



Extracellular and Intracellular Fluid Electrolytes and Volumes

ECF AND ICF ELECTROLYTES AND VOLUMES



Urea in ECT and ICT

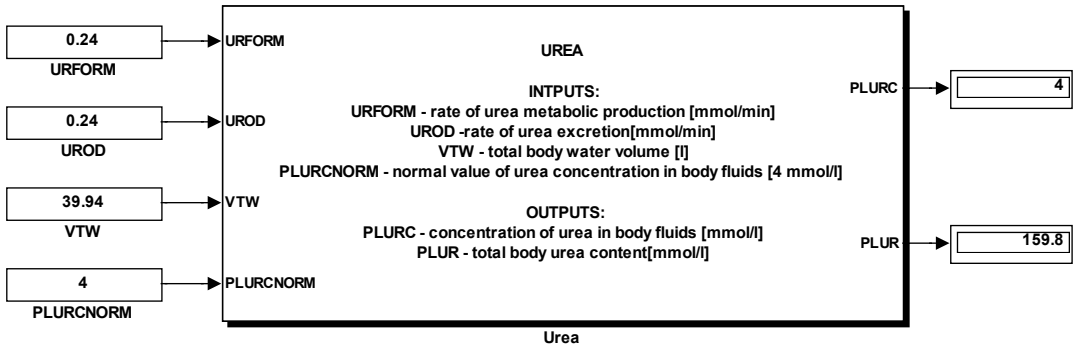
The total amount of urea in the body (PLUR) is determined by the difference between the rate of metabolic urea production (URFORM - under normal circumstances URFORM=0.24 mmol/min) and the rate of its elimination in urine (UROD):

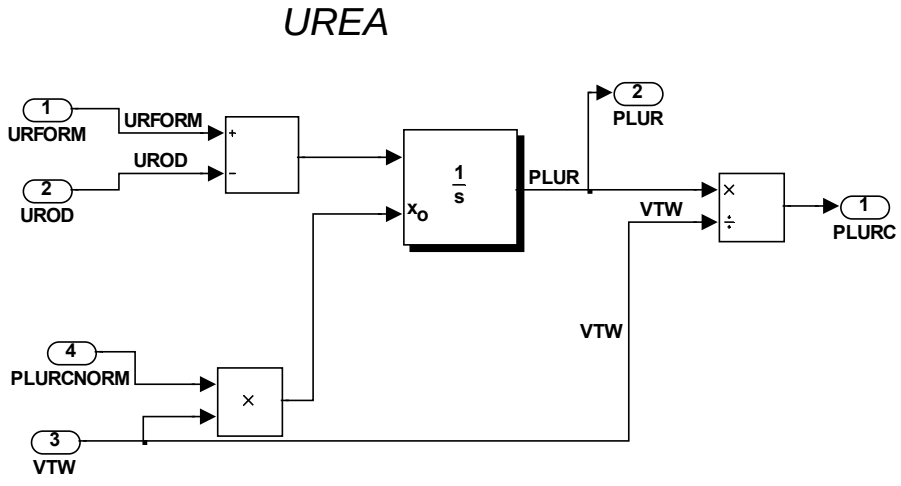
$$DPLUR=(URFORM-UROD) \quad \text{(UR 01)}$$

$$PLUR=\int DPLUR\,dt \quad \text{(UR 02)}$$

Urea easily passes through cell membranes - its concentration is practically the same in cells and in extracellular fluid. The urea concentration (PLURC) is calculated from the total amount of urea (PLUR) and the volume of total body water (WTV):

$$PLURC=PLUR/VTW \quad \text{(UR 03)}$$





KIDNEY FUNCTIONS

The renal model is based on a simplified analysis of renal function, including blood flow through the kidney, glomerular filtration rate and changes in filtrate composition during flow through the renal tubules. Only four substances are considered: water, sodium ions, potassium ions and urea. The model includes regulation by angiotensin, aldosterone and nerve stimuli. It is based on the 1986 Guyton and Coleman model and is more complex than the original classical Guyton model of 1976.

Perfusion of the kidneys

Perfusion pressure (PAR) - i.e. the pressure in the renal artery before it enters the kidney is calculated from the arterial systemic pressure from which the pressure gradient (GLB) caused by renal artery constriction is subtracted (normally the renal artery is not compressed and this gradient is zero). This block allows modelling of renal hypertension caused by vasoconstriction of the feeding artery (Goldblatt hypertension).[6]:

$$PAR=PA-GBL \qquad \text{(KD 01)}$$

Blood flow through (two) normal kidneys (RFN) is equal to the gradient between perfusion pressure (PAR) and systemic venous pressure (PVS) divided by total intrarenal resistance (RR):

$$RFN=(PAR-PVS)/IRR \qquad \text{(KD 02)}$$

The renal blood flow (RBF) is equal to the renal blood flow in healthy kidneys (RFN) multiplied by a factor (REK) representing the proportion of functional kidney tissue to normal (in healthy kidneys REK=1):

$$RBF=REK*RFN \qquad \text{(KD 03)}$$

[6] In the 1986 Fortran extract of Guyton's model, additional blocks are considered to model perfusion pressure (PAR) as a variable independent of systemic arterial pressure (PA) and thus allow simulation of cases where the altered perfusion pressure in the kidney becomes independent of arterial pressure over a long period of time and asymptotically approaches the normal value of 100 torr. Therefore, he introduced the input parameter RASP into the model, which, when non-zero, represents the value of the perfusion pressure:

$$if\ RASP>0\ then\ PAR=RASP$$

Další blok umožnil simulovat asymptotické přibližování změněné hodnoty perfúzního tlaku k normální hodnotě 100 torrů. Blok se zapínal dalším přepínačem:

$$if\ RASP1>0 then\ PAR=PARI$$

Another block allowed to simulate asymptotic approximation of the changed perfusion pressure value to the normal value of 100 torr. The block was activated by another switch:

$$DPAR=((100.0+(PA-100.0)*RCDFPC)-PARI)/RCDFDP$$

$$PARI=\int DPAR\,dt$$

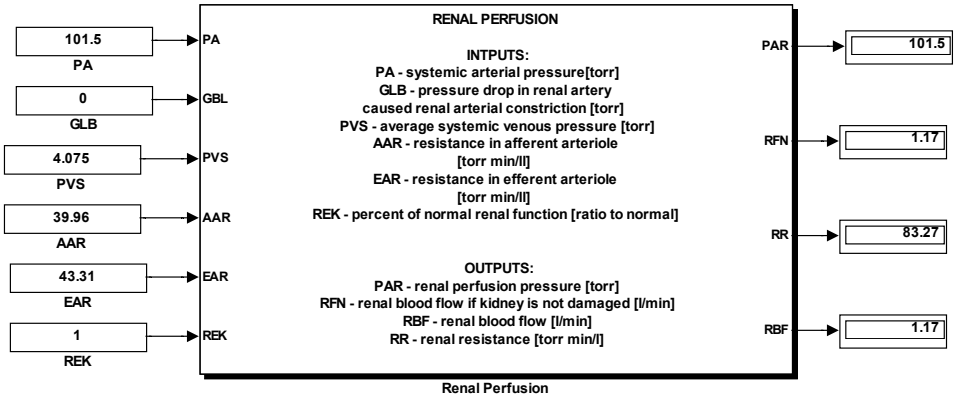
The value of perfusion pressure (PARI) was gradually approached from the value of ambient arterial pressure to the value dependent on the coefficient of RCDFPC (when RCDFPC=0, the resulting value approached 100 torr) at a rate dependent on the value of the coefficient of RCDFDP (Guyton used here the value of RCDFDP=2000):

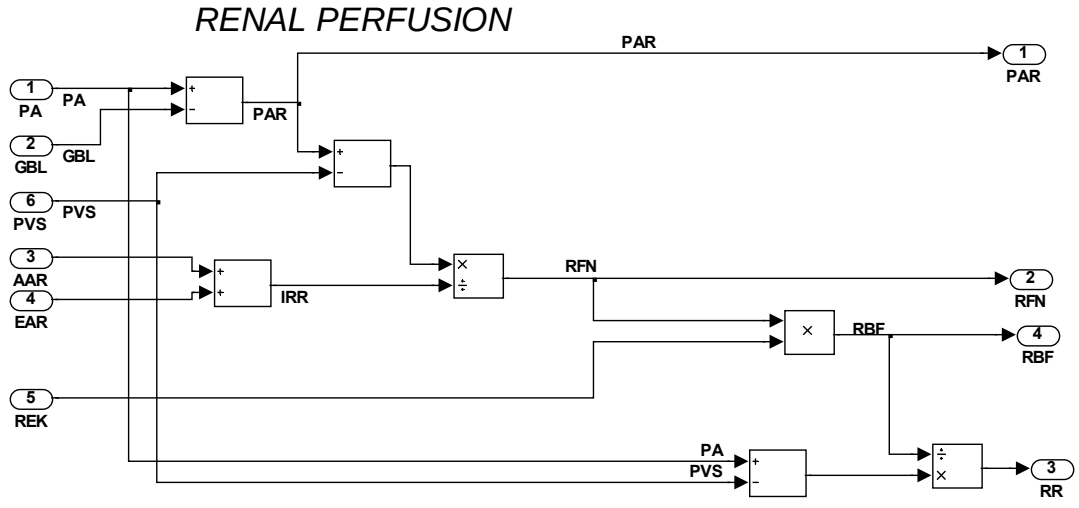
Total intrarenal resistance (IRR) is calculated in this model as the sum of afferent resistance (AAR) and efferent (EAR) arteriole. The resistance of the remaining part of the bed (vasa recta and renal veins) is neglected here - Coleman[7], in his kidney model, states their value to be around five torr min/l - and in his model, the resistance of the afferent arteriole is also lower by about this value. In this model, therefore, all vascular resistance in the kidney is concentrated in the afferent and efferent arterioles:

$$IRR=AAR+EAR \qquad \text{(KD 04)}$$

Total renal resistance (including possible obstruction in the renal artery and renal tissue restriction, characterized by the input parameter REK) is calculated from the total renal blood flow (RBF) and the gradient of systemic arterial pressure and systemic venous pressure (PVS):

$$RR=(PAS-PVS)/RBF \qquad \text{(KD 05)}$$





[7] Coleman, Thomas G; Hall, John E: A mathematical model of renal hemodynamics and excretory function. In Structuring Biological Systems: A Computer Modelling Approach. Sitharama Yengar, S (ed), CRC Boca Raton, FL, 1992, ISBN: 9780849379611

Afferent arteriole

The output of the block is the resistance of the afferent arteriole, on which glomerular filtration depends to a significant extent, Resistance is controlled by nervous influences, hormonal influences (angiotensin), as well as signals from the macula densa, which mediates tubuloglomerular feedback - an increase in glomerular filtration leads to increased filtration of sodium and chloride ions, and their subsequent increased concentration in the distal tubule inflow, where this increased concentration is detected by macula densa cells, resulting in a signal that leads to a feedback increase in resistance in the afferent arteriole and a subsequent decrease in glomerular filtration.

The afferent arteriolar resistance (AAR) is calculated from its normal value (AARK=40 torr) by multiplying multipliers expressing the influence of sympathetic nerve innervation (AUMK), the influence of angiotensin (ANMAR), the effect of tubuloglomerular feedback via the macula densa (RNAUG1), the effect of the myogenic response of the vessel to pressure (MYOGRSAA) and a multiplier expressing the relative viscosity of the blood (to normal) - (VIM).
The resulting value is bounded from below by the minimum resistance value AARL=18 torr min/l, corresponding to the maximum stretch of the afferent arteriole:

*AAR=AUMK*RNAUG1*ANMAR*MYOGRSAA*VIM*AARK* (KD 06)

if (AAR<AARLL) then AAR=AARLL (KD 07)

The effect of angiotensin on the resistance of the afferent arteriole is expressed by a factor (ANMAR), which is calculated from the effect of angiotensin on vascular resistance (ANM), expressed as the ratio of the effect of the instantaneous angiotensin level to the norm and the sensitivity coefficient of the effect of angiotensin on the resistance of the afferent arteriole (ANMAM=0.5).
The resulting ANMAR value is bounded from below by the lowest allowed value (ANMARL=0.86):

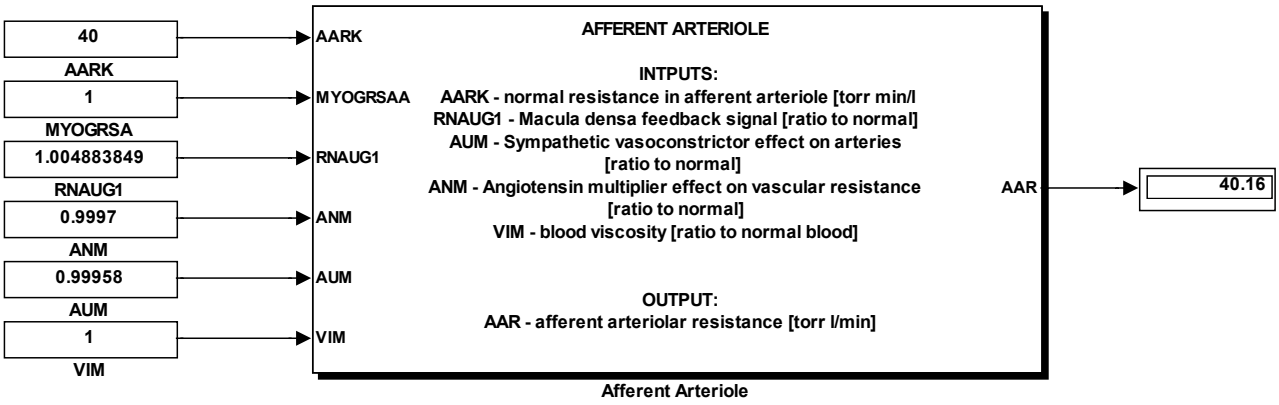
*ANMAR=(ANM-1.)*ANMAM+1.0* (KD 08)

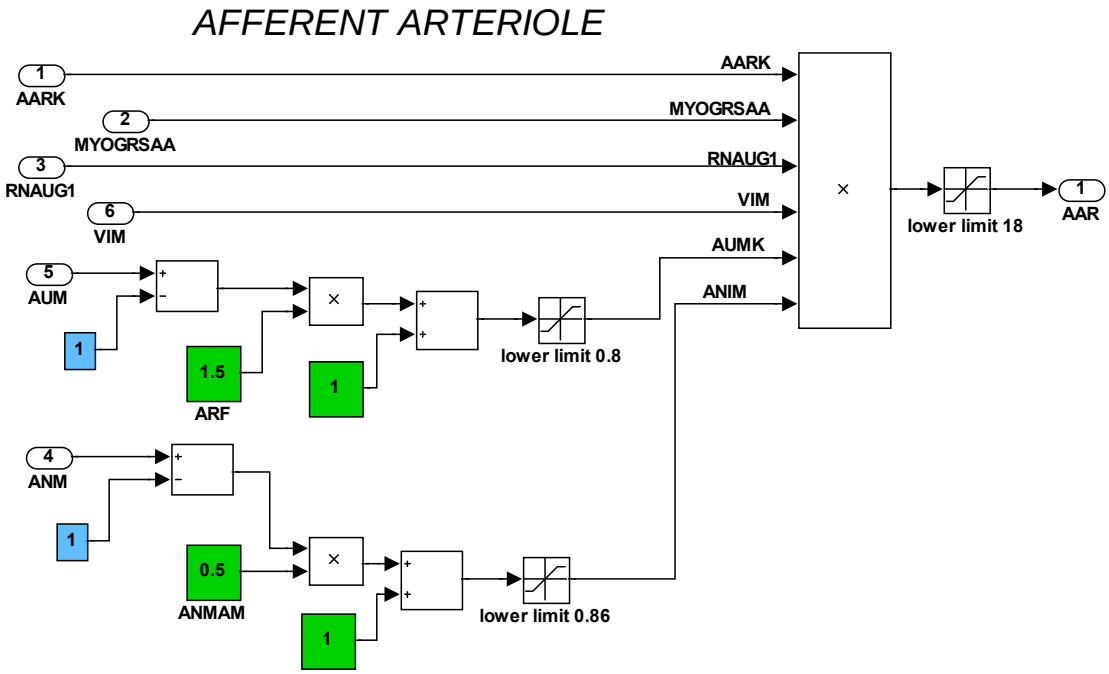
if (ANMAR<ANMARL) then ANMAR=ANMARL (KD 09)

The influence of sympathetic nerve innervation on the resistance of the afferent arteriole is expressed by the multiplicative factor (AUMK). Its value is calculated from the multiplicative factor (AUM), expressing the general influence of the sympathetic nerve on vascular resistance. Sympathetic tone fluctuations are amplified by an amplification factor (ARF=1.5)

*AUMK=(AUM-1.0)*ARF+1.0* (KD 10)

if (AUMK<0.8) then AUMK=0.8 (KD 11)


40
AARK
1
MYOGRSA
1.004883849
RNAUG1
0.9997
ANM
0.99958
AUM
1
VIM
AARK
MYOGRSAA
RNAUG1
ANM
AUM
VIM
AFFERENT ARTERIOLE
INTPUTS:
AARK - normal resistance in afferent arteriole [torr min/l
RNAUG1 - Macula densa feedback signal [ratio to normal]
AUM - Sympathetic vasoconstrictor effect on arteries [ratio to normal]
ANM - Angiotensin multiplier effect on vascular resistance [ratio to normal]
VIM - blood viscosity [ratio to normal blood]
OUTPUT:
AAR - afferent arteriolar resistance [torr l/min]
AAR
40.16
Afferent Arteriole


AFFERENT ARTERIOLE
1
AARK
2
MYOGRSAA
3
RNAUG1
6
VIM
5
AUM
1
1.5
ARF
1
4
ANM
1
0.5
ANMAM
1
AARK
MYOGRSAA
RNAUG1
VIM
AUMK
ANIM
lower limit 0.8
lower limit 0.86
lower limit 18
1
AAR

Efferent arteriole

The resistance of the efferent arteriole, together with the resistance of the afferent arteriole, is important for the regulation of glomerular capillary pressure and thus for the regulation of glomerular filtration. However, the afferent arteriole is of greater importance here. In contrast to the afferent arteriole, when calculating resistance in the efferent arteriole, the model does not consider the influence of sympathetic innervation as well as myogenic regulation (in Guyton's 1986 model, myogenic regulation is formally considered but with a mutliplier of 1; in the later Coleman model, available on the web at[8] , this regulation is omitted altogether).

The efferent arteriolar resistance (EAR) is calculated from its normal value (EARK=43.333 torr) by multiplying the multipliers expressing the effect of angiotensin (ANMER), the effect of tubuloglomerular feedback via macula densa (MDEF) and the effect of blood viscosity (VIM), expressed as a relative value to the norm. The resulting value of the resistance of the efferent arteriole is bounded from below by the minimum resistance value EARL=24 torr min/l, corresponding to the maximum stretch of the efferent arteriole:

:

$$EAR=43.333*ANMER*MDEF*VIM \quad \text{(KD 12)}$$

$$if\ (EAR<EARLL)\ then\ EAR=EARLL \quad \text{(KD 13)}$$

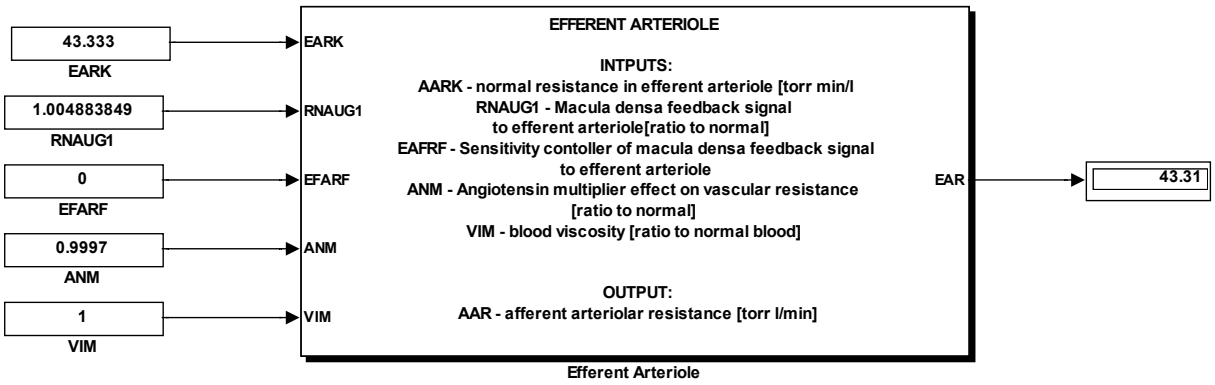
Angiotensin affects the resistance of the afferent and efferent arterioles. It affects the efferent arteriole more strongly. The angiotensin effect on resistance of the efferent arteriole (ANMER) multiplication factor is calculated from the angiotensin effect on vascular resistance (ANM), expressed as the ratio of the effect of the instantaneous angiotensin level to the norm and the sensitivity coefficient of the angiotensin effect on resistance of the efferent arteriole (ANMEM=1.5):

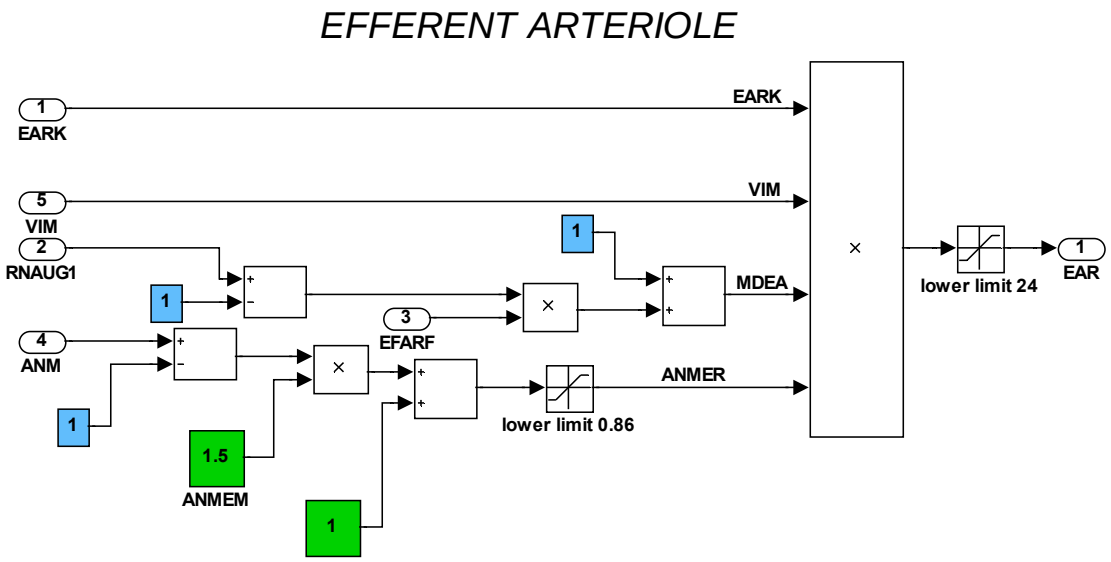
$$ANMER=(ANM-1.)*ANMEM+1.0 \quad \text{(KD 14)}$$

The multiplier expressing the effect of tubuloglomerular coupling on resistance of the efferent arteriole (MDEF) is calculated from the signal generated by the macula densa acting on both the efferent and the efferent arteriole (RNAUG1). However, the tubuloglomerular coupling on the efferent arteriole is mediated by angiotensin rather than directly - hence the deviation of the MDEF coefficient from one is less than that of RNAUG1 (which the macula densa exerts on the afferent arteriole). The ratio of the direct effect of macula densa on the efferent and afferent arteriole is determined by the sensitivity coefficient EFAFR (it should generally be less than 1, if its value were 1 then MDEF=RGNAUG1, i.e. as in the afferent arteriole). Guyton in the 1986 model considers a value of this coefficient of zero - then MDEF is a constant of 1.0 and macula densa then has no direct effect on the efferent arteriole:

$$MDEF=((RNAUG1-1.0)*EFAFR+1.0) \quad \text{(KD 15)}$$

[8] http://physiology.umc.edu/themodelingworkshop/Model%20Library/Kidney%20Model/Kidney%20Model.HTML


43.333
EARK
1.004883849
RNAUG1
0
EFARF
0.9997
ANM
1
VIM
EARK
RNAUG1
EFARF
ANM
VIM
EFFERENT ARTERIOLE
INTPUTS:
AARK - normal resistance in efferent arteriole [torr min/l
RNAUG1 - Macula densa feedback signal
to efferent arteriole[ratio to normal]
EAFRF - Sensitivity contoller of macula densa feedback signal
to efferent arteriole
ANM - Angiotensin multiplier effect on vascular resistance
[ratio to normal]
VIM - blood viscosity [ratio to normal blood]
OUTPUT:
AAR - afferent arteriolar resistance [torr l/min]
EAR
43.31
Efferent Arteriole


EFFERENT ARTERIOLE
1
EARK
5
VIM
2
RNAUG1
4
ANM
1
1
1
3
EFARF
1
1.5
ANMEM
1
EARK
VIM
MDEA
ANMER
lower limit 0.86
lower limit 24
1
EAR

Myogenic stimulation of the afferent arteriole

The myogenic regulation of the afferent arteriole is that a sudden increase in perfusion pressure, which would otherwise lead to an increase in flow, induces vasoconstriction and the subsequent increase in resistance (decrease in conductivity) of the arteriole restricts the increased flow. Conversely, a decrease in pressure (and subsequent decrease in flow) will dilate the vessel, decrease resistance, and increase flow. If the increase or decrease in pressure lasts for an extended period of time, the vessel will adapt to the increased or decreased pressure over time and will resist changes in this newly set pressure. The input is the renal perfusion pressure (PAR), the output is the MYOGRSAA multiplier, which in the KD 05 equation affects the resistance of the afferent arteriole. The set pressure is "remembered" in the integrating component (PADAPT). The rate of myogenic response is affected by the time constant MYOGTAU (normally 240 min). The magnitude of the intrinsic response is approximated by a spline function interleaving the experimental data of conductivity change (inverse of the resistance value) proposed by Coleman. The multiplicative factor TENSGN determines the amplification of the myogenic response (normally TENSGN=1)[9] .

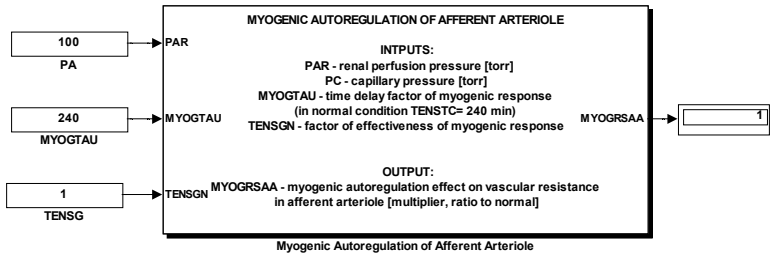
$$PDIFF=PAR-PADAPT \quad \text{(KD 16)}$$

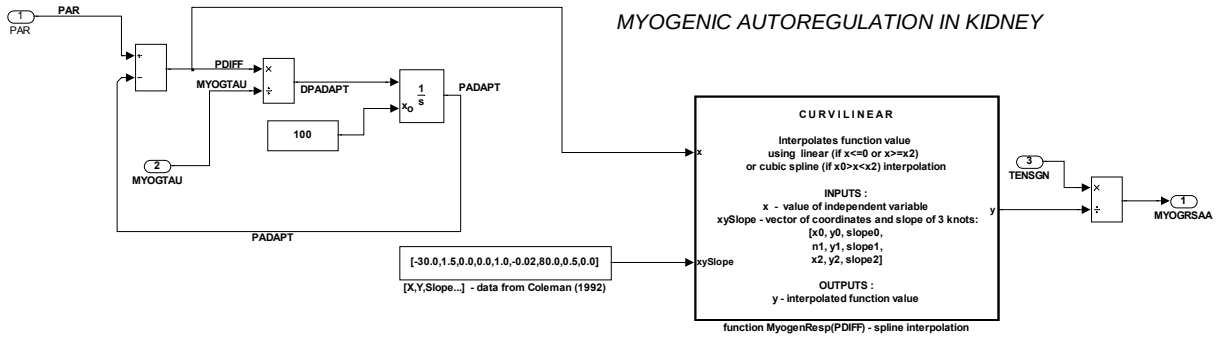
$$DPADAPT=PDIFF/MYOGTAU \quad \text{(KD 17)}$$

$$PADAPT=\int (DPADAPT)\, dt \quad \text{(KD 18)}$$

$$MYOGRS1=function\ myogenResp(PDIFF) \quad \text{(KD 19)}$$

$$MYOGRSAA=TENSGN/MYOGRS1 \quad \text{(KD 20)}$$





[9]The structure is the same as that of myogenic regulation for other non-renal tissues, except that instead of perfusion reanal pressure, the sum of arterial and capillary pressure is considered. In addition, the structure of the myogenic adaptation block is modified to avoid an algebraic loop through this block.

Glomerulus

The pressure gradient at the afferent arteriole (APD) is calculated from the total renal flow of healthy kidneys (RFN) and the resistance of the vas afferens (AAR). Thus, it is assumed that in kidneys whose function has been reduced (by loss of renal tissue) and flow restricted (when the constant REK<1), the resistance of the afferent arteriole will also increase in the same proportion, and the pressure gradient of the APD is independent of REK:

$$APD=AAR*RFN \quad \text{(KD 21)}$$

Glomerular pressure (GLP), i.e., glomerular capillary pressure, is equal to renal perfusion pressure (PAR) without the pressure gradient at the afferent arteriole:

$$GLP=PAR-APD \quad \text{(KD 22)}$$

Plasma flow to two kidneys (with 100% functioning renal tissue) - (RPNIN) is calculated from the blood flow through the intact kidneys (RFN), plasma volume (VP) and blood volume (VB), or hematocrit (HM)::

$$RPNIN=RFN*VP/VB= RFN*(1-HM) \quad \text{(KD 23)}$$

The plasma outflow (RPNOUT) will be less than the plasma inflow (RPNIN) by the filtered glomerular filtrate (GFN):

$$RPNOUT=RPNIN-GFN \quad \text{(KD 24)}$$

Plasma proteins do not pass through the glomerular membrane (in intact kidneys) and therefore become concentrated in the outflowing plasma - the ratio of the concentration of proteins in the outflowing plasma to the concentration of proteins in the inflowing plasma (EFAFPR) is equal to the ratio of the flow volume of plasma flowing into the glomerulus (PRNIN) to the flow volume of plasma flowing out of the glomerulus (PRNOUT):

$$EFAFPR=RPNIN/RPNOUT \quad \text{(KD25)}$$

To prevent oscillations, we introduce here a "watchdog" boundary condition, expressing that the volume of plasma flowing out of the glomerulus can never be greater than the volume of plasma flowing out of the glomerulus:

$$if\ (EFAFPR<1.0)\ then\ EFAFPR=1.0 \quad \text{(KD 26)}$$

The colloid osmotic pressure in the blood flowing into the glomerulus (PPC) and the ratio of the protein concentrations in the outflowing and inflowing blood to/from the glomerulus (EFAFPR) are the input values from which the average colloid osmotic pressure in the glomerular capillary is calculated. Colloid-osmotic pressure is nonlinearly (quadratically) dependent on plasma protein concentration (see equation CP 14). The average colloid-osmotic pressure (GLPC0) for a given PPC and EFAFPR Guyton calculates according to the empirical relationship:

$$GLPC0=0.98*EFAFPR^{1.35}*PPC \quad \text{(KD 27)}$$

To prevent oscillations (and also to eliminate the algebraic loop: glomerular filtration rate is the basis for the calculation of oncotic pressure in the glomerular capillary, which in turn affects glomerular filtration rate), a damping term with a time constant (GPPD=50) is introduced when calculating the mean colloid osmotic pressure (GLPC):

$$DGLPC=(GLPC0-GLPC)/GPPD \quad \text{(KD 28)}$$

$$GLPC=\int DGLPC\,dt \quad \text{(EL 29)}$$

The pressure gradient across the capillary glomerular membrane (PFL) is equal to the glomerular pressure (GLP) minus the suction-averaged colloid-osmotic pressure in the glomerular capillary (PFL) minus the backpressure in the proximal tubule (PXTP=8), which is considered a constant in this model:

$$PFL=GLP-GLPC-PXTP \quad \text{(KD 30)}$$

Glomerular filtration rate in intact kidneys (GFN0) is proportional to the filtration pressure gradient across the glomerular capillary membrane (PFL) multiplied by the glomerular filtration coefficient (GFLC=0.0208 l/min/torr):

$$GFN0=PFL*GFLC \quad \text{(KD 31)}$$

To prevent oscillations (and also to eliminate possible algebraic loops), a damping term with a time constant (GFNDMP=3) is inserted in the calculation of glomerular filtration rate (GFN):

$$DGFN=(GFN0-GFN)/GFNDMP \quad \text{(KD 32)}$$

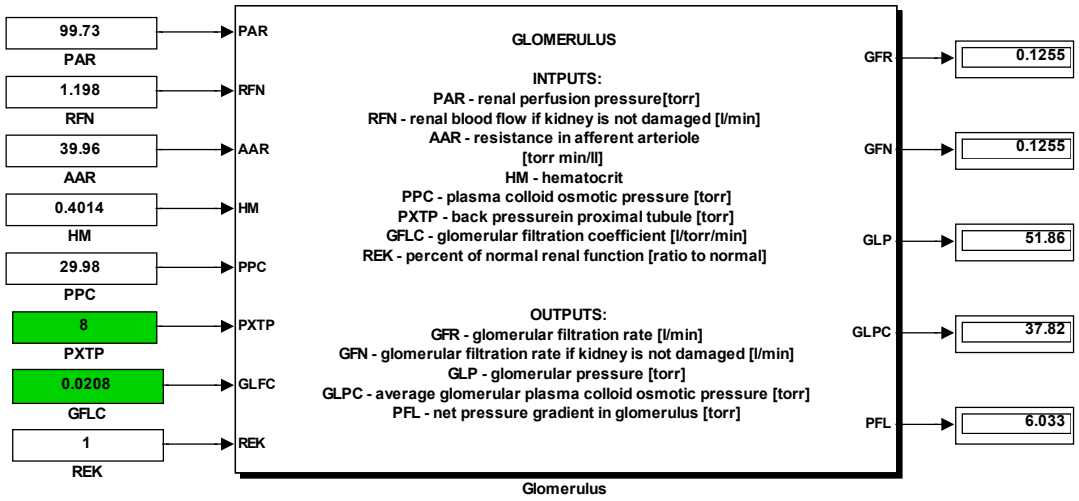
$$GFN=\int DGFN\,dt \quad \text{(KD 33)}$$

Finally, a boundary limiting condition is inserted to prevent the glomerular filtration rate (GFN) from falling below the lower limit (GFNL=0.001 l/min)

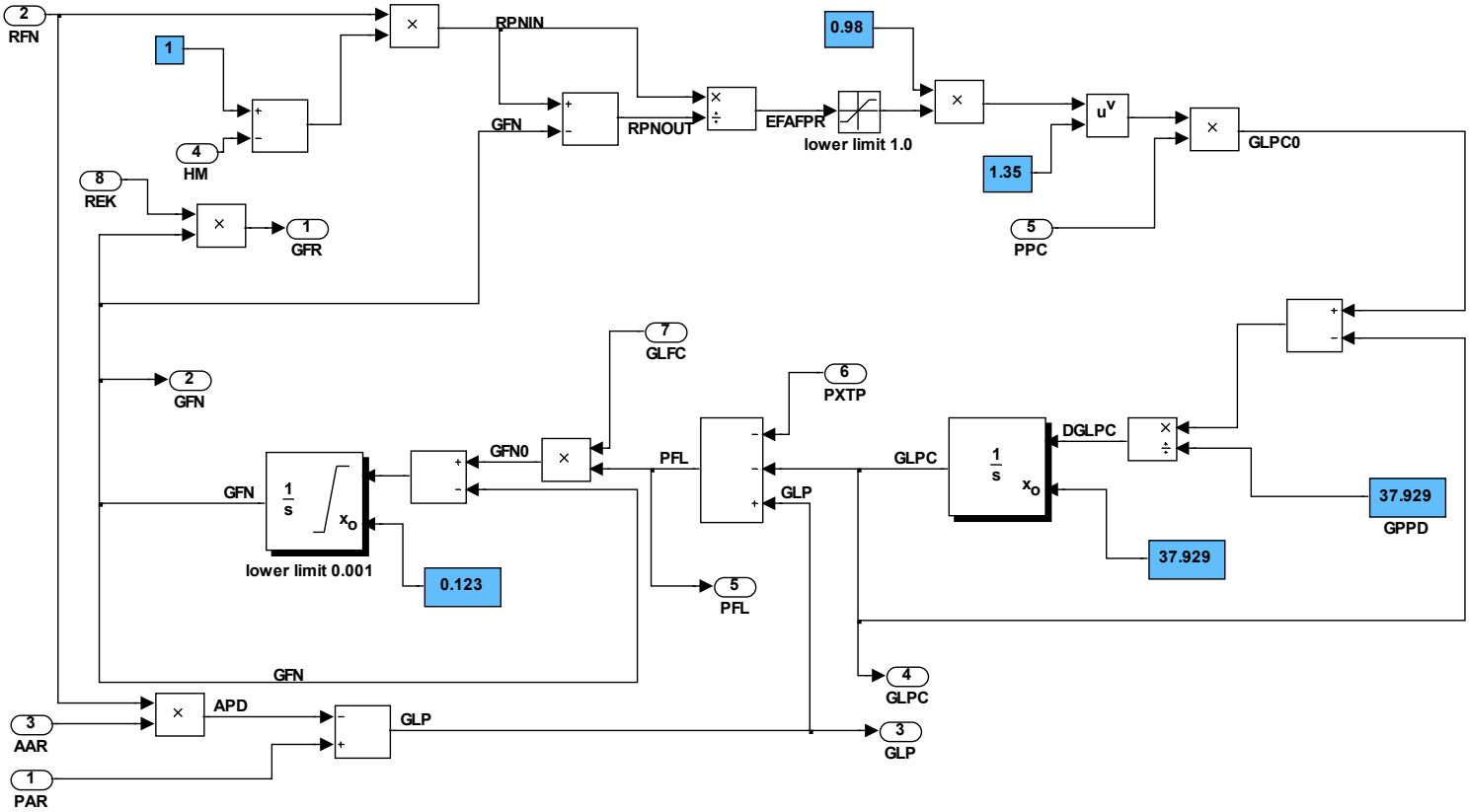
$$if\ (GFN<GFNLL)\ then\ GFN=GFNLL \quad \text{(KD 34)}$$

So far, we have calculated the glomerular filtration rate in kidneys that have not been damaged (GFN). If we multiply this glomerular filtration rate value by a coefficient expressing the proportion of functional kidney tissue to the normal (REK) - in healthy kidneys REK=1, we get the actual glomerular filtration rate (GFR):

$$GFR=GFN*REK \quad \text{(KD 35)}$$


99.73
PAR
1.198
RFN
39.96
AAR
0.4014
HM
29.98
PPC
8
PXTP
0.0208
GFLC
1
REK
PAR
RFN
AAR
HM
PPC
PXTP
GLFC
REK
GLOMERULUS
INTPUTS:
PAR - renal perfusion pressure[torr]
RFN - renal blood flow if kidney is not damaged [l/min]
AAR - resistance in afferent arteriole
[torr min/l]
HM - hematocrit
PPC - plasma colloid osmotic pressure [torr]
PXTP - back pressurein proximal tubule [torr]
GFLC - glomerular filtration coefficient [l/torr/min]
REK - percent of normal renal function [ratio to normal]
OUTPUTS:
GFR - glomerular filtration rate [l/min]
GFN - glomerular filtration rate if kidney is not damaged [l/min]
GLP - glomerular pressure [torr]
GLPC - average glomerular plasma colloid osmotic pressure [torr]
PFL - net pressure gradient in glomerulus [torr]
GFR
GFN
GLP
GLPC
PFL
0.1255
0.1255
51.86
37.82
6.033
Glomerulus

GLOMERULUS


2
RFN
1
4
HM
8
REK
1
GFR
RPNIN
GFN
RPNOUT
0.98
EFAFPR
lower limit 1.0
1.35
5
PPC
GLPC0
2
GFN
7
GLFC
6
PXTP
GFN0
PFL
GLP
GLPC
DGLPC
37.929
GPPD
37.929
GFN
lower limit 0.001
0.123
5
PFL
GFN
4
GLPC
3
AAR
APD
GLP
3
GLP
1
PAR

Macula densa

The magnitude of sodium flux from the beginning of the distal tubule to the macula densa cells is important for tubuloglomerular coupling. This magnitude of the flux depends on the amount of sodium filtered into the glomerulus and also on sodium resorption in the proximal tubule and in the Henle's villus.

Here, however, it is simplistically assumed that sodium influx into macula densa cells is dependent only on the filtered sodium ion (FNA), which is calculated from the plasma sodium concentration (CNA) and the glomerular filtration rate in the intact kidney (GFN):

$$FNA=GFN*CNA \quad \text{(KD 36)}$$

The input signal to the macula densa (NAPT), then, is proportional to the rate of sodium ion pumping into the macula densa cells, and is linearly dependent on sodium filtration (FNA) with a coefficient of proportionality (KNAPT=0.057). The magic number of 0.057 is based on the fact that the sodium influx signal into macula densa cells is normally one. With a normal glomerular filtration rate of 0.125 L/min and a blood sodium concentration of 140 mmol/L, the sodium filtration rate will be: FNA=17.5 mmol/min. In order to yield a signal value of one, the value of the constant must be 1/17.5=0.0571:

$$NAPT=FNA*0.057 \quad \text{(KD 37)}$$

This value is bounded by a constant value (NAPTLL=0.1):

$$if\ (NAPT<NAPTLL)\ then\ NAPT=NAPTLL \quad \text{(KD 38)}$$

The NAPT value is also bounded above (NAPTUL=3):

$$if\ (NAPT>NAPTUL)\ then\ NAPT=NAPTUL \quad \text{(KD 39)}$$

To dampen oscillations, a feedback loop with a damping constant (GF=0.1) is introduced,resulting in a normalized sodium supply value for macula densa cells (NAPT1) - its value is normally equal to one:

$$(NAPT-NAPT1)*GF2 \quad \text{(KD 40)}$$

$$NAPT1=\int DNAPT1\ dt \quad \text{(KD 41)}$$

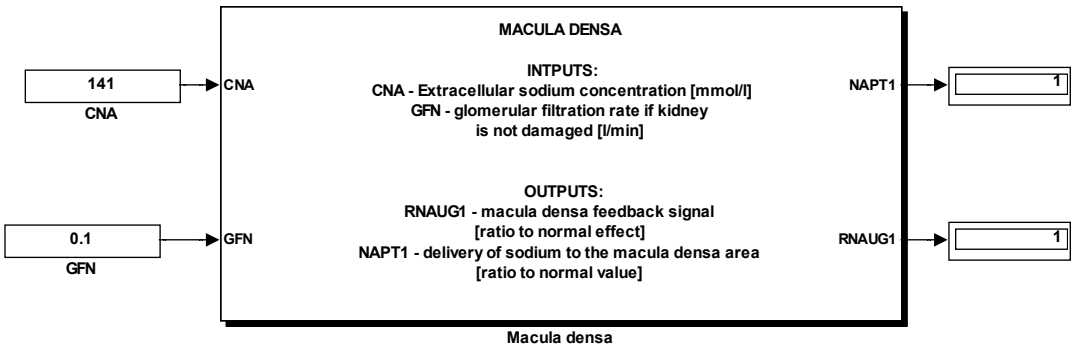
To calculate the intrinsic signal for the afferent arteriole, the deviation of the NAPT1 signal from unity is amplified by the coefficient RNAUGN=5.0, which represents the normal signal magnitude from the macula densa for the afferent arteriole. The resulting value (RNAUG1) is bounded from above (RNAUG1UL=10.0) and below (RNAUG1LL=0.3). The result is the multiplicative coefficient of RNAUG1 - as a signal from the macula densa for the adjacent afferent arteriole, which influences its resistance. The signal is determined possibly also by the efferent arteriole where its value is modified by a multiplication coefficient indicating the sensitivity to this signal (in Guyton's 1986 model the sensitivity to this signal on the efferent arteriole is set to zero, but in Coleman's model[10] , available on the Internet, the influence of macula densa on the efferent arteriole is accounted for, but the model has a somewhat different structure):

$$RNAUG1=(NAPT1-1)*RNAUGN \quad \text{(KD 42)}$$

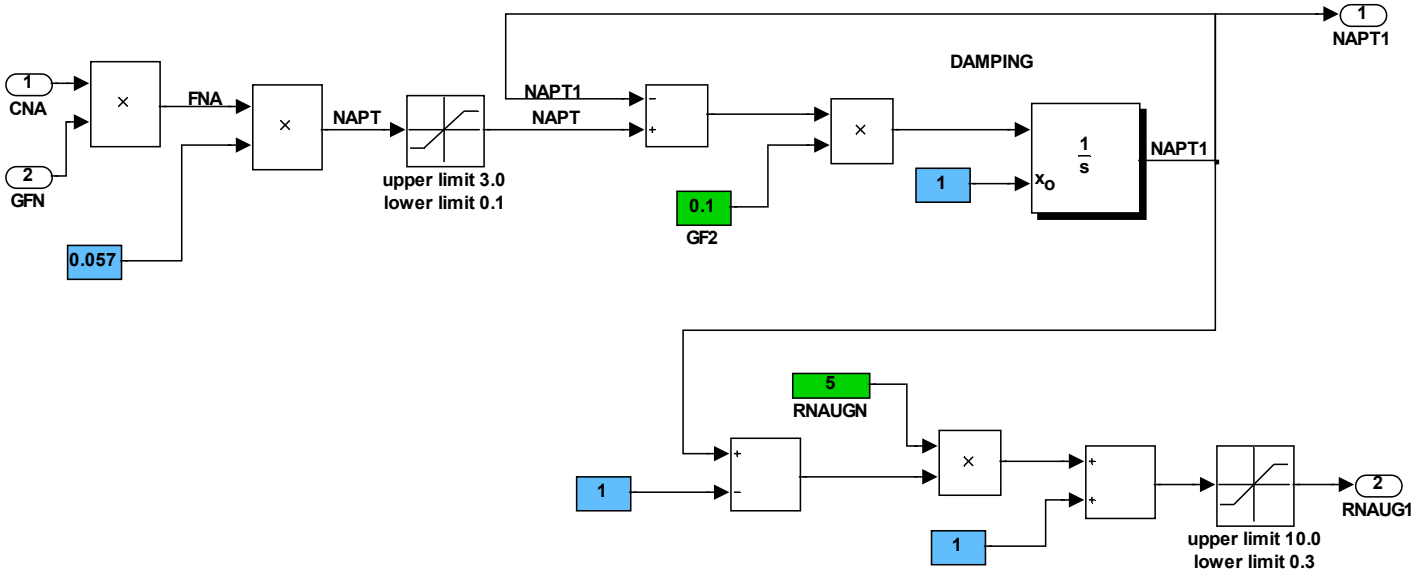
$$if\ (RNAUG1<RNAUG1LL)\ then\ RNAUG1=RNAUG1LL \quad \text{(KD 43)}$$

$$if\ (RNAUG1>RNAUG1UL)\ then\ RNAUG1=RNAUG1UL \quad \text{(KD 44)}$$

[10] http://physiology.umc.edu/themodelingworkshop/Model%20Library/Kidney%20Model/Kidney%20Model.HTML



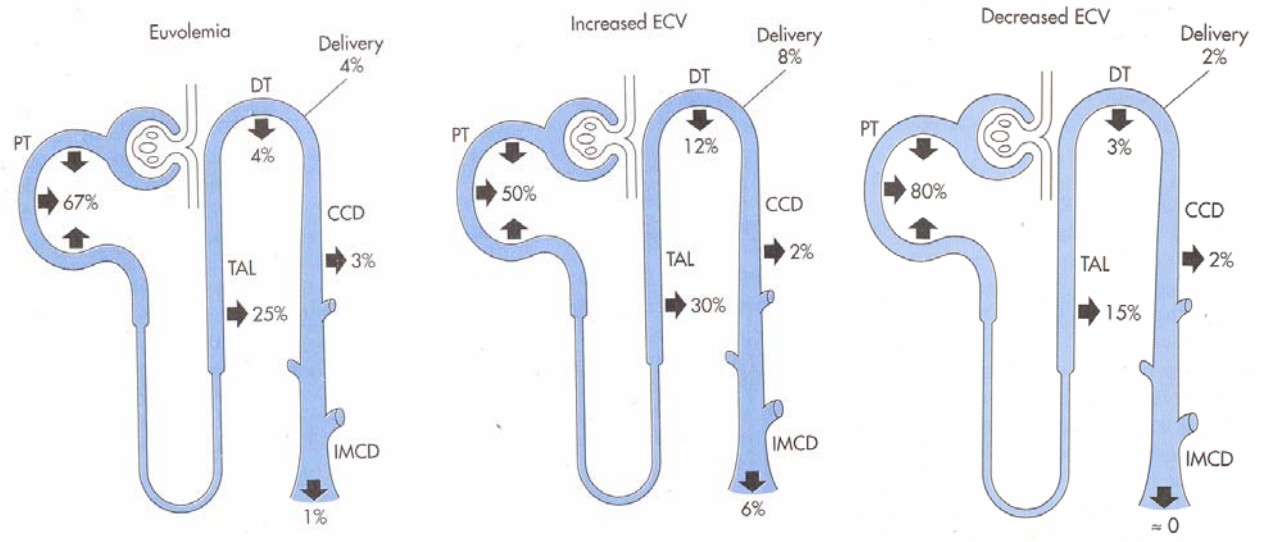
MACULA DENSA



Sodium excretion

According to textbook sources, under normal circumstances (with a normal volume of extraxellular fluid), most of the filtered sodium is absorbed in the proximal tubule (see table). Resorption in the proximal tubule is regulated and may decrease or increase depending on neurohumoral stimuli. The collecting tubules normally resorb ¾ of the delivered sodium (4% of the filtered sodium flows into them and 3% of the filtered sodium is absorbed). When sodium resorption in the proximal tubule increases in response to a decrease in ECT volume, less sodium flows into the collecting ducts (only 2% of the total filtered amount instead of 4%), but the relative sodium resorption in the collecting ducts increases (due to the action of aldosterone, almost all of the sodium flowing into the collecting ducts can be absorbed). Conversely, when the resorption in the proximal tubule decreases in response to an increase in ECT volume, the sodium influx into the collecting ducts increases but relatively less sodium is resorbed from them than under normal circumstances (due to a decrease in aldosterone levels) - perhaps only ¼ of the amount delivered instead of ¾.

Sodium absorption in individual parts of the nephron (% of filtered amount)			
	Standard	Responce to ECT volume increase	Responce to ECT volume reduction
From glomerular filtrate	100%	100%	100%
Proximal tubulus	-67%	-50%	-80%
Inflow to Henle's loop	33%	50%	20%
Henle's loop	-25%	-30%	-15%
Inflow to distsl tubule	8%	20%	5%
Distal tubule	-4%	-12%	-3%
Inflow to collecting duct	4%	8%	2%
Collecting duct	-3%	-2%	-2%
Urine output	1%	6%	0%



Renal excretion of sodium with normal extracellular fluid volume (euvolemia), with increased ECT volume and with decreased ECT volume. PT, proximal tubule; TAL, thick part of Henle's branch; DT, distal tubule; CCD, cortical collecting duct; IMCD, inner medullary collecting duct. Schematic picture from monograph B. Koepen. B. Stanton: Renal Physiology, Mosby, Second Edition, 1996, ISBN 0-8151-5202-7.

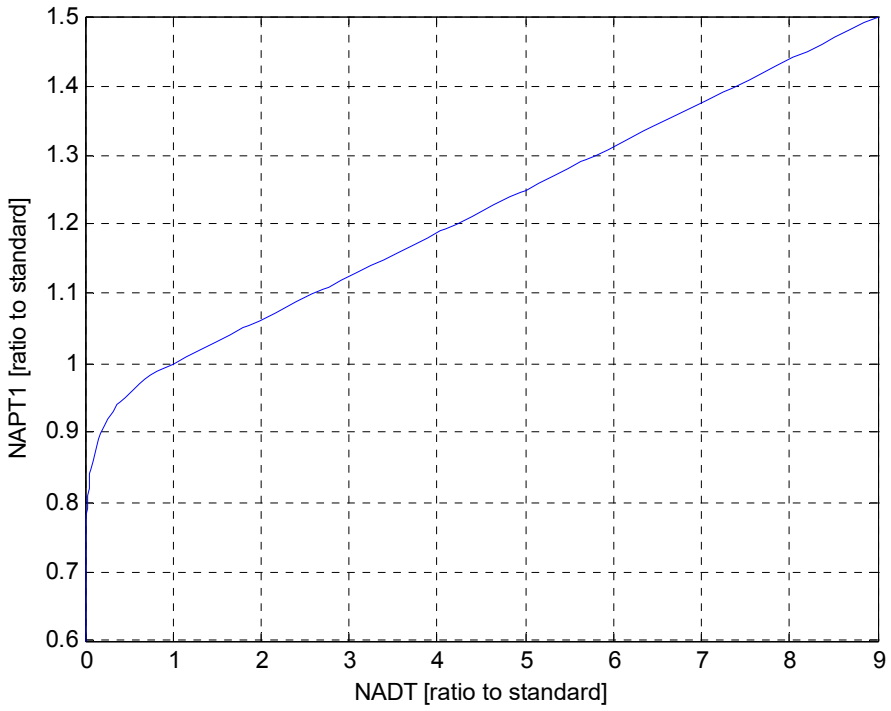
If we express the percentages of filtered sodium in numerical terms, then at a filtration rate of 17.5 mmol/min, 4.02 mmol/min flows at the inlet to the Henle's branch under normal circumstances, 8.75 mmol/min flows in hypervolaemia, 3.5 mmol/min flows in hypovolaemia, and 1 flows at the inlet to the distal tubule in euvolaemia.4 mmol/l, with an increase in volume there is an increase to 3.5 mmol/min, with a decrease in volume we observe a decrease to 0.875 mmol/min; the outflow into the collecting ducts is normally 0.7 mmol/min, with an increase in ECT volume there is an increase to double - 1.4 mmol/min, with a decrease in ECT there is a decrease to half 0.35 mmol/min, the outflow into the urine is normally
0.175 mmol/min, when ECT rises there is up to a sixfold increase of 1.05 mmol/min, when ECT volume decreases urinary sodium drops to almost zero.

In this model, the normalized sodium delivery (NADT) to the distal tubular system of the kidney is first calculated (the distal tubule and collecting ducts are taken as one unit in the model). This value is expressed as a ratio to the normal value. It is calculated based on the values of normalized sodium delivery to macula densa cells (NAPT1). The relationship is linear if the NAPT1 value is greater than the normal (i.e. greater than 1). The calculation is based on the normalized relationship between sodium delivery to the distal tubule (NADT) and sodium pumping from this flux to the macula densa (NAPT1). When sodium flux to the distal tubules increases above the norm, sodium pumping to the macula densa cells increases linearly. When the sodium supply to the distal tubules decreases, sodium pumping to the macula densa decreases nonlinearly (see figure). In the model, however, we do not calculate sodium delivery to the macula densa (NAPT1) from sodium delivery to the distal nephron (NADT) but the other way around; NADT is calculated from NAPT1. The relationship is determined by a sensitivity coefficient (NARSB1=16), reflecting the influence of renal tubular and vascular dynamics:

$$NADT=(NAPT1-1.0)*NARSB1+1.0 \quad \text{(KD 45)}$$

$$\text{if } NADT<1.0, \text{ then } NADT=NAPT1^{NARSB1} \quad \text{(KD 46)}$$

The relationship between NAPT1 and NADT is shown in the following graph:



Dependence of NAPT1 values on NATD calculated according to equations KD 44-45

The actual value of sodium ion delivery to the distal part of the nephron (DTNAI) is then calculated from the normalized value (NADT) and the corresponding constant[11] :

$$DTNAI=NADT/2.0 \quad \text{(KD 47)}$$

Urinary excretion of sodium ions in the intact kidney (NODN) is calculated as the difference between the delivery of sodium ions to the distal nephron (NADT) and the rate of absorption in the distal nephron (DTNARA):

$$NODN=DTNAI-DTNARA \quad \text{(KD 48)}$$

To avoid a situation where sodium excretion is negative, a lower limit for sodium excretion into the urine is set in the model as a precaution:

$$if\ (NODN<0.00000001)\ then\ NODN=0.00000001 \quad \text{(KD 49)}$$

The resulting renal sodium excretion rate (NOD) is obtained from the sodium excretion rate in intact kidneys (NODN) after multiplying by a coefficient (REK) that expresses the proportion of actually functioning kidneys to normal (to simulate kidney damage by loss of kidney tissue - normally REK=1):

$$NOD=REK*NODN \quad \text{(KD 50)}$$

The urinary sodium concentration (CNU) is calculated from the urinary sodium excretion rate in the intact kidneys (NODN) and the diuresis rate in the intact kidneys (VUDN) (if only part of the kidneys are working - REK<1, then the NODN and VUDN are reduced equally, the resulting urinary sodium concentration is unchanged). Since such concentration is considered in the model as one of the factors influencing the reabsorption in the distal nephron, then to prevent oscillations (and to eliminate the algebraic loop) an integration block is incorporated into the concentration calculation (initial value DTNAC=100 mmol/l, time constant NADMP=40):

$$CNU=NODN/VUDN \quad \text{(KD 51)}$$

$$DDTNAC=(DTNAC-CNU)/NADMP \quad \text{(KD 52)}$$

$$DTNAC=\int DDTNAC\,dt \quad \text{(KD 53)}$$

The damping integration term is also used in the calculation of sodium absorption in the distal part of the nephron (DTNARA), where the calculated value of reabsorption (DTNAR1) is damped by an integration term with a time constant (GFR3=0.1). The value of the integral is constrained from below by the minimum value of reuptake (DTNARL=0.999*10-6):

$$DDTNARA=(DTNARA-DTNAR1)/GFR3 \quad \text{(KD 54)}$$

$$DTNARA=\int_{DTNARL}^{\infty}(DDTNARA)dt \quad \text{(KD 55)}$$

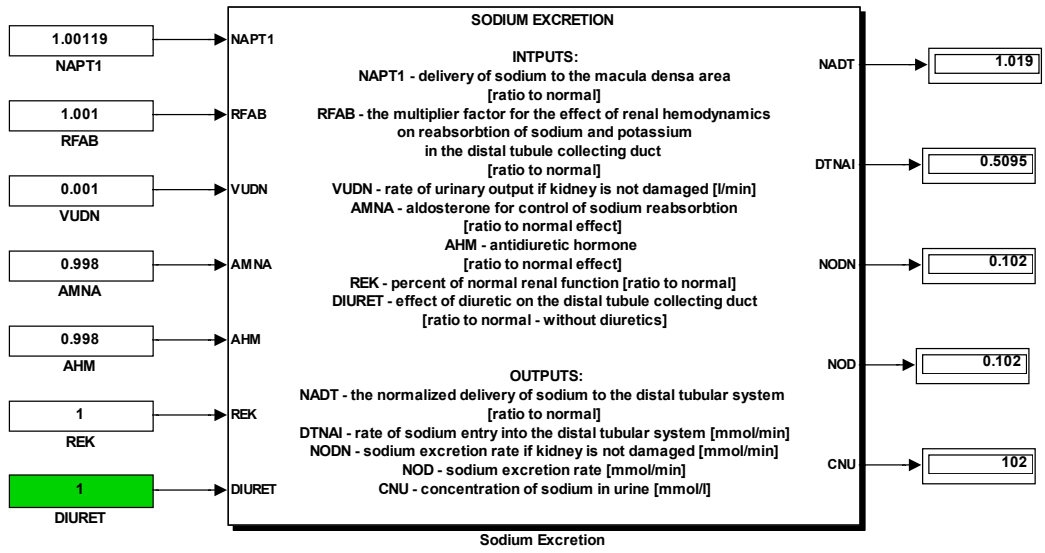
[11] Under normal values, according to this relationship, the delivery of sodium ions is 0.5 mmol/min - but this is less than other models and some physiological sources, according to which the delivery from the Henle's loop to the distal tubule is around 1.5-3.5 mmol/min. Rather, the delivery of sodium ions to the distal part of the nephron (DTNAI) represents the delivery of sodium to the collecting ducts. In fact, the calculated value of sodium absorption rate in the distal nephron under normal circumstances (DTNARA= 0.4 mmol/l) corresponds to this in the model. The collecting ducts normally absorb about 2-3% of the filtered amount, i.e. about 3.5-5 mmol/min.

The value of sodium absorption in the distal part of the nephron (DTNAR1) is calculated as the product of the normal value (DTNARN=0.4) and the multiplicative coefficient (MDTNAR) which cumulatively expresses the relevant regulatory influences (sodium ion concentration in the tubules, the influence of aldosterone, the mediated effect of water reabsorption by antidiuretic hormone, the influence of renal haemodynamics on sodium reabsorption and the possible influence of diuretics).

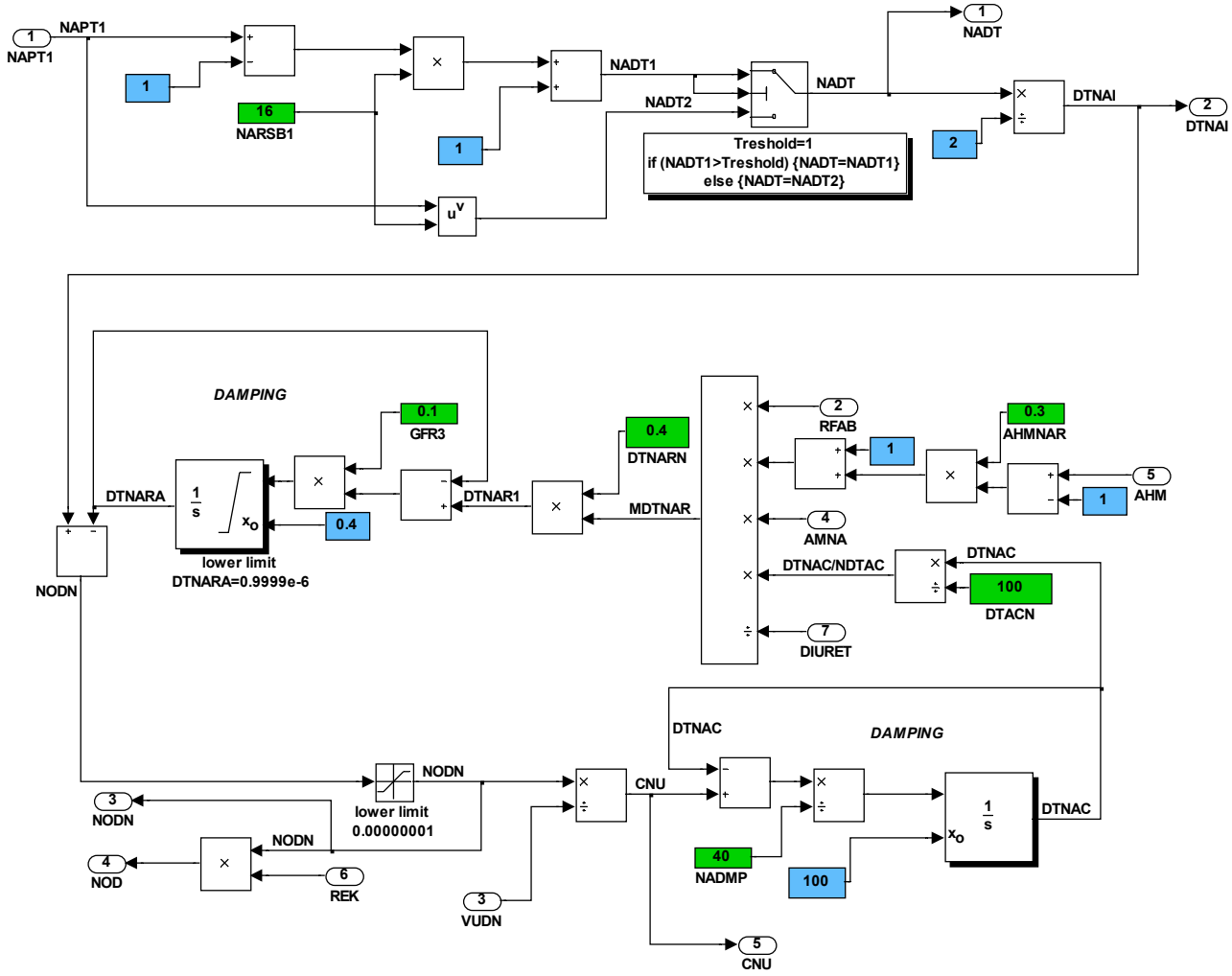
*DTNAR1=DTNARN*MDTNAR* (KD 56)

For the calculation of the MDTNAR multiplication factor, the dependence of the sodium reabsorption rate in the distal part of the nephron on the concentration of flowing sodium ions in the tubules is considered - therefore, the resulting sodium concentration at the end of the collecting ducts - i.e., the urinary sodium concentration (DTNAC) divided by its normal value (NDTAC=100 mmol/l) is used in the model for the multiplier. Another effect considered is the level of aldosterone, or its effect on sodium reabsorption, expressed as the ratio of the effect of aldosterone relative to normal (AMNA). Another influence is the antidiuretic hormone mediated effect (AHM), expressed as a ratio to the norm, which stimulates the absorption of water from the collecting ducts into the renal medulla, and dissolved sodium ions are partially removed with the absorbed water - the sensitivity here is determined by AHMNAR=0.3. Absorption is also influenced by the blood supply to the marrow - the normalised effect of the haemodynamic factor on sodium resorption is expressed here by the RFAB coefficient. Finally, the last factor considered is the influence of diuretics (characterized by the DIURET coefficient, which is normally one, since diuretics reduce reabsorption this coefficient is in the denominator):

*MDTNAR=DTNAC/DTACN*AMNA*((AHM-1)*AHMNAR+1)*RFAB/DIURET* (KD 57)



SODIUM EXCRETION



Potassium excretion

Healthy kidneys are able to excrete the amount of dietary potassium and reduce the loss of potassium in the urine when there is a deficiency. There is no significant regulation of potassium excretion in the proximal tubule and the loop of Henle under physiological circumstances. In contrast, the distal tubule and collecting ducts are capable of absorbing or excreting potassium (see table).

	Standard	Response to potassium restriction	Response to potassium intake
From glomerular filtrate	100%	100%	100%
Proximal tubule	-67%	-67%	-67%
Inflow to Henle's loop	33%	33%	33%
Henle's loop	-20%	-20%	-20%
Vtok do distálního tubulu	13%	13%	13%
Distal tubule	-3%	-3%	-3% až +37%
Inflow ro collecting duct	10%	10%	10-50%
Collecting duct	+5%	-9%	+5až+30%
Urine output	15%	1%	15-80 %

In the model, potassium is assumed to be absorbed proportionally as well as sodium in the proximal tubule and in Henle's loop. Therefore, the calculation of the distal tubular influx rate (DTKI) is calculated from the distal tubular sodium influx rate (DTNAI) and the ratio of potassium (CKE) and sodium (CNA) concentrations in the extracellular fluid.

$$DTKI=DTNAI*CKE/CNA \quad \text{(KD 58)}$$

The model first accounts for factors that influence potassium secretion into the distal nephron. These are the influence of sodium flux in the tubules, the influence of angiotensin, the influence of potassium concentration in the extracellular fluid and the influence of aldosterone.

The effect of sodium flux in the distal tubules on potassium secretion is expressed by the multiplicative factor NADTK, which is calculated from the normalized value of the distal tubular sodium flux (NADT) and the sensitivity constant (NADTKM=0.5). The result is bounded from below by a value of 0.1:

$$NADTK=(NADT-1.0)*NADTKM+1.0 \quad \text{(KD 59)}$$
$$if\ (NADTK<0.1)\ then\ NADTK=0.1 \quad \text{(KD 60)}$$

Potassium secretion is affected by the level of angiotensin. The calculation of the multiplicative factor expressing the effect of angiotensin on potassium excretion (ANMKE) is based on the level of angiotensin (AMN), expressed as a ratio to normal. The deviation of the AMN value from one is taken, multiplied by the sensitivity factor (ANMKEM=2) and the result added to one. The result is bounded at the bottom by the value (ANMKEL=0.3):

$$ANMKE=(ANM-1.0)*ANMKEM+1.0 \quad \text{(KD 61)}$$
$$if\ (ANMKE<ANMKEL)\ then\ ANMKE=ANMKEL \quad \text{(KD 62)}$$

The multiplier, expressing the influence of extracellular potassium concentration on potassium secretion in the distal nephron (MCKE), is calculated as the fourth power of the ratio of the extracellular potassium level (CKE) to the normal value (5 mmol/l) - the exponent (CKEEX=4):

$$MCKE=(CKE/5)^{CKEEX} \quad \text{(KD 63)}$$

The rate of potassium secretion into the distal tubular system of the nephron (DTKSC) is calculated by multiplying the basal value (0.06) by multipliers expressing the effect of the ECT potassium level (MCKE), the effect of aldosterone (AMK), the effect of sodium influx into the distal tubules (NADTK) and the effect of angiotensin (ANMKE) - the latter reduces secretion, which is why it is in the denominator:

$$DTKSC=0.06*AMK*MCKE*NADTK/ANMKE \quad \text{(KD 64)}$$

The potassium resorption in the distal nephron (RFABK) by hemodynamic factors depends on the multiplier expressing the influence of hemodynamics (RFAB) and the sensitivity coefficient (RFABKM=0.03).

$$RFABK=(RFAB-1.0)*RFABKM \quad \text{(KD 65)}$$

The potassium resorption in the distal part of the nephron (DTKA) depends linearly on the potassium concentration at the end of the collecting ducts - i.e. on the urinary potassium concentration (CKU) - an integration term for damping oscillations with time constant (KDMP=3) is inserted into the calculation:

$$DTKA1=CKU*0.000293 \quad \text{(KD 66)}$$

$$DDTKA=(DTKA1-DTKA)/KDMP+0.00000001 \quad \text{(KD 67)}$$

$$DTKA=\int DDTKA\,dt \quad \text{(KD 68)}$$

Potassium excretion in both intact kidneys (KODN) depends on the potassium flux to the distal part of the nephron (DTKI), potassium secretion to the distal nephron (DTKSC), from the sum of these fluxes is subtracted potassium resorption in the distal tubule and possibly additional resorption due to the hemodynamic factor (normally they are zero) RFABK. The result is zero bounded from below:

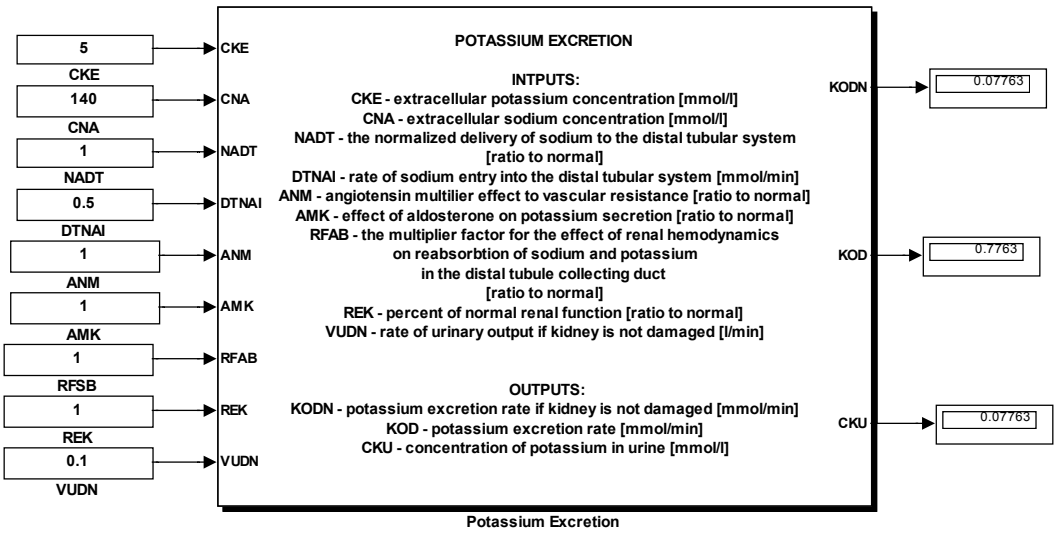
$$KODN=DTKI+DTKSC-DTKA-RFABK \quad \text{(KD 69)}$$
$$if\ (KODN<0)\ then\ KODN=0.0 \quad \text{(KD 70)}$$

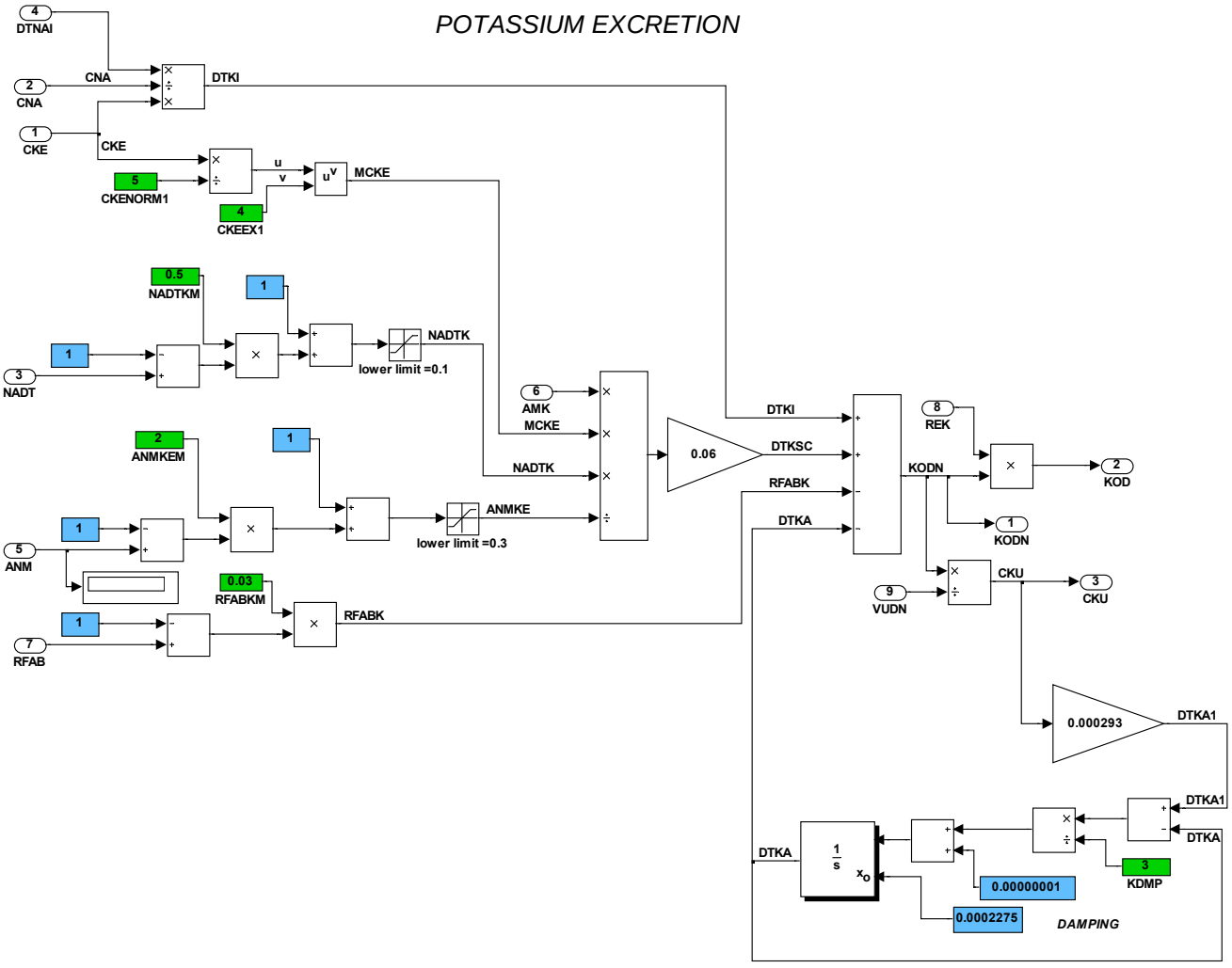
The resulting renal potassium excretion rate (KOD) is obtained from the sodium excretion rate in intact kidneys (KODN) after multiplying by a coefficient (REK), which expresses the proportion of actually functioning kidneys to normal (to simulate kidney damage by loss of kidney tissue - normally REK=1):

$$KOD=KODN*REK \quad \text{(KD 71)}$$

The urinary potassium concentration (CKU) is calculated from the urinary potassium excretion rate in the intact kidneys (KODN) and the diuresis rate in the intact kidneys (VUDN) (if only part of the kidneys is working - REK<1, then the NODN and VUDN are reduced equally, the resulting urinary sodium concentration is unchanged).

$$CKU=KODN/VUDN \quad \text{(KD 72)}$$


5
CKE
140
CNA
1
NADT
0.5
DTNAI
1
ANM
1
AMK
1
RFSB
1
REK
0.1
VUDN
CKE
CNA
NADT
DTNAI
ANM
AMK
RFAB
REK
VUDN
POTASSIUM EXCRETION
INTPUTS:
CKE - extracellular potassium concentration [mmol/l]
CNA - extracellular sodium concentration [mmol/l]
NADT - the normalized delivery of sodium to the distal tubular system [ratio to normal]
DTNAI - rate of sodium entry into the distal tubular system [mmol/min]
ANM - angiotensin multilier effect to vascular resistance [ratio to normal]
AMK - effect of aldosterone on potassium secretion [ratio to normal]
RFAB - the multiplier factor for the effect of renal hemodynamics on reabsorbtion of sodium and potassium in the distal tubule collecting duct [ratio to normal]
REK - percent of normal renal function [ratio to normal]
VUDN - rate of urinary output if kidney is not damaged [l/min]
OUTPUTS:
KODN - potassium excretion rate if kidney is not damaged [mmol/min]
KOD - potassium excretion rate [mmol/min]
CKU - concentration of potassium in urine [mmol/l]
KODN
0.07763
KOD
0.7763
CKU
0.07763
Potassium Excretion


POTASSIUM EXCRETION
4
DTNAI
2
CNA
CNA
DTKI
1
CKE
CKE
5
CKENORM1
u
v
u^v
MCKE
4
CKEEX1
0.5
NADTKM
1
1
3
NADT
NADTK
lower limit =0.1
6
AMK
MCKE
NADTK
2
ANMKEM
1
1
5
ANM
ANMKE
lower limit =0.3
0.03
RFABKM
1
7
RFAB
RFABK
0.06
DTKI
DTKSC
RFABK
DTKA
8
REK
KODN
2
KOD
1
KODN
CKU
3
CKU
9
VUDN
0.000293
DTKA1
DTKA1
DTKA
1/s
x0
3
KDMP
0.00000001
0.0002275
DAMPING

Excretion of urea and water

The kidneys excrete approximately 40% of the filtered urea (this percentage varies depending on the glomerular filtration rate) - the model uses the empirical dependence of urea excretion on the glomerular filtration rate of healthy kidneys (GFN) and the urea concentration (PLURC) in the ECT to calculate the rate of urea excretion by healthy kidneys (DTURI):

$$DTURI=PLURC*3.84*GFN^2 \quad \text{(KD 73)}$$

We calculate the actual rate of renal urea excretion from the rate of excretion by healthy kidneys (DTURI) by multiplying the coefficient (REK), expressing the proportion of functional kidney tissue to the normal (normally REK=1):

$$UROD=DTURI*REK \quad \text{(KD 74)}$$

The excretion rate of urea and electrolyte mimics (OSMPN) of intact kidneys is calculated from the excretion of urea by healthy kidneys (DTURI) and the excretion of sodium (KODN) and potassium (NODN):

$$OSMOPN=DTURI+2.0*(NODN+KODN) \quad \text{(KD 75)}$$

We calculate that the flow up to 0.56 mmosm/min is under the influence of ADH, what is above this limit - ADH has no influence on it. Therefore, we calculate the rate of excretion of excess milliosmolar flux above 0.56 mmosm/min (OSMOP1) from the total rate of milliosmolar excretion (OSMOPN). If the value of OSMOPN is less than 0.56 mosm/min, then of course the value of OSMOP1 flux is zero:

$$OSMOP1=OSMOPN-0.56 \quad \text{(KD 76)}$$
$$if\ (OSMOP1<0.0)\ then\ OSMOP1=0.0 \quad \text{(KD 77)}$$

To determine the osmotic flux that is influenced by the ADH level (OSMO0), we truncate the rate of excretion of total electrolytes and urea (OSMOPN) by an upper limit of 0.56::

$$OSMOPN0=OSMOPN \quad \text{(KD 78)}$$
$$if\ (OSMOPN>0.56)\ then\ OSMOPN0=0.56 \quad \text{(KD 79)}$$

We now have the excretion of osmotically active substances divided into two fluxes: the flux influenced by ADH (OSMOPN0) and an additional flux not influenced by ADH. For the calculation of diuresis, the model assumes that at normal ADH levels the urine concentration of osmotically active substances is 560 mmol/l. This amount may vary depending on the ADH level. We can then calculate what diuresis (VUDN0) corresponds to this concentration:

$$VUDN0=OSMOPN0/560.0/AHM \quad \text{(KD 80)}$$

Similarly, we calculate the volume of urine excretion corresponding to the excretion of the second part of the osmotic fluxes (OSMOP1), assuming that the target concentration of osmotically active substances in urine is 360 mmol/l:

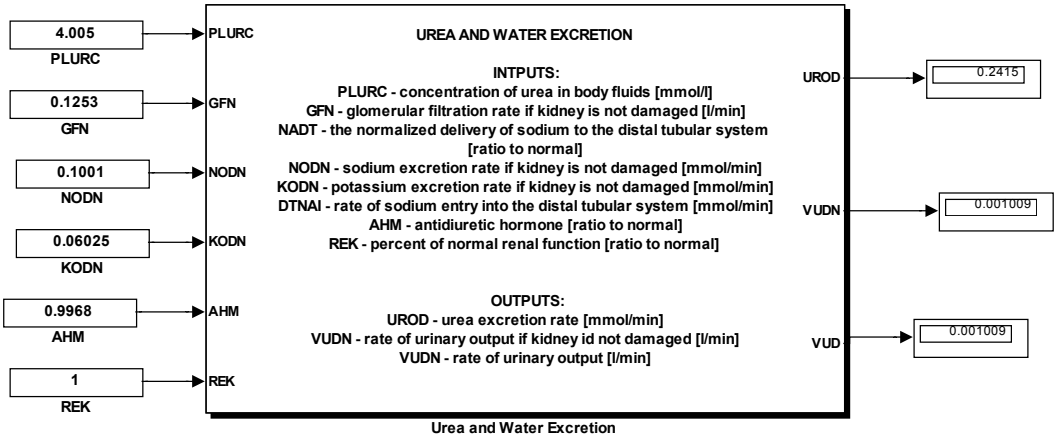
$$VUDN1=OSMOP1/360.0 \quad \text{(KD 81)}$$

The total diuresis in the intact kidney (VUDN) will then be the sum of these fluxes (VUDN0) and (VUDN1):

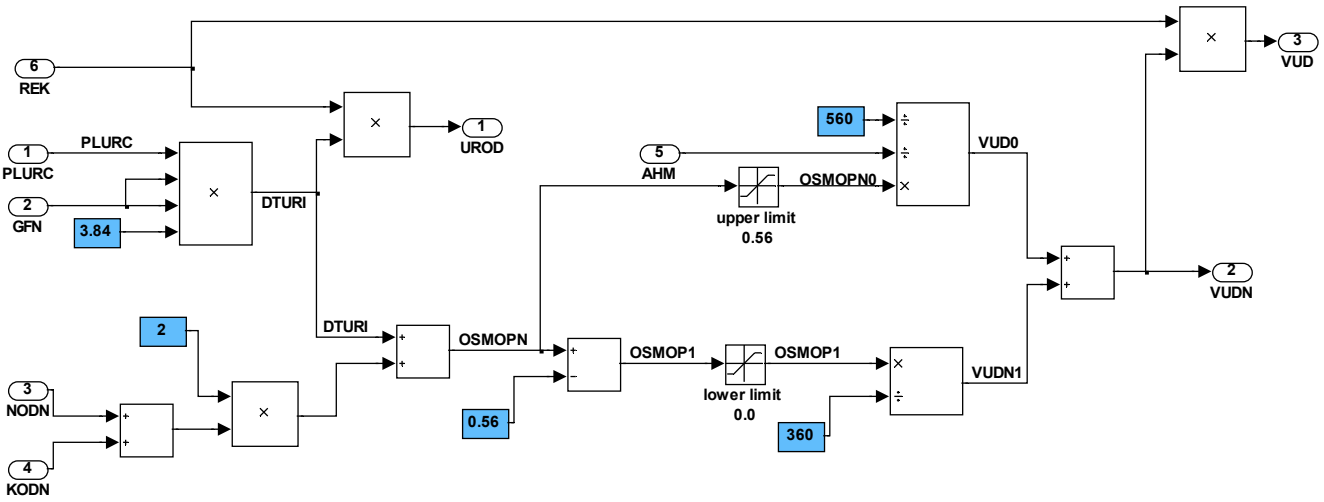
$$VUDN=VUDN0+VUDN1 \quad \text{(KD 82)}$$

We calculate the actual diuresis (VUD) from the diuresis of healthy kidneys (VUDN) by multiplying the coefficient (REK), expressing the proportion of functional kidney tissue to the normal (normally REK=1):

$$VUD=VUDN*REK \quad \text{(KD 83)}$$



WATER AND UREA EXCRETION



Peritubular capillaries

Resorbed substances from the tubules are drained into the peritubular capillaries. As blood flows into the capillaries, where, due to filtration in the glomeruli, the colloid-osmotic pressure has increased, so has the uptake of resorbed water and solutes from the renal interstitium. Hemodynamic conditions may thus influence resorption processes in the renal tubules. This module calculates the RFAB factor by which hemodynamics affects sodium and potassium absorption. The basis is again Starling equilibrium (this time on the peritubular) capillaries.

First, the renal peritubular capillary pressure (RCPRS) is calculated from the difference between the normal renal flow (1.2 l/min) and the actual flow, the difference is multiplied by a constant (RFABX=0.8) and again added to the value of 1.2 - the obtained capillary flow is multiplied by the resistance of the venous renal circulation (RVRS=19.1669):

$$RCPRS=((RFN-1.2)*RFABX+1.2)*RVRS \quad \text{(KD 84)}$$

The calculation of the renal tissue colloid-osmotic pressure (RTSPPC) is calculated from the average glomerular colloid-osmotic pressure (GLPC) multiplied by a factor (RTPPR=0.8999) that reduces this pressure due to fluid resorption into the peritubular capillaries minus a factor representing the difference in protein concentration between plasma and peritubular tissue (RTPPRS=15.19999). The calculation is bounded from below:

$$RTSPPC=GLPC*RTPPR-RTPPRS \quad \text{(KD 85)}$$
$$if\ (RTSPPC<1.0)\ then\ RTSPPC=1.0 \quad \text{(KD 86)}$$

The calculation of the gradient causing fluid resorption into the peritubular capillaries (RABSPR) is calculated from the suction oncotic pressure in the peritubular capillaries, which is taken as the mean glomerular glomerular capillary colloid osmotic pressure (GLPC) plus renal tissue back pressure (RTSPRS=6) minus peritubular capillary capillary pressure (RTSPRS) minus renal tissue suction colloid osmotic pressure (RTSPPC):

$$RABSPR=GLPC+RTSPRS-RCPRS-RTSPPC \quad \text{(KD 87)}$$

Now, the reabsorption factor (RFAB1) is calculated, characterizing reabsorption into the peritubular capillaries based on the pressure gradient between the renal tissue and the peritubular capillary and the peritubular capillary absorption coefficient (RABSC=0.5):

$$RFAB1=RABSPR*RABSC \quad \text{(KD 88)}$$

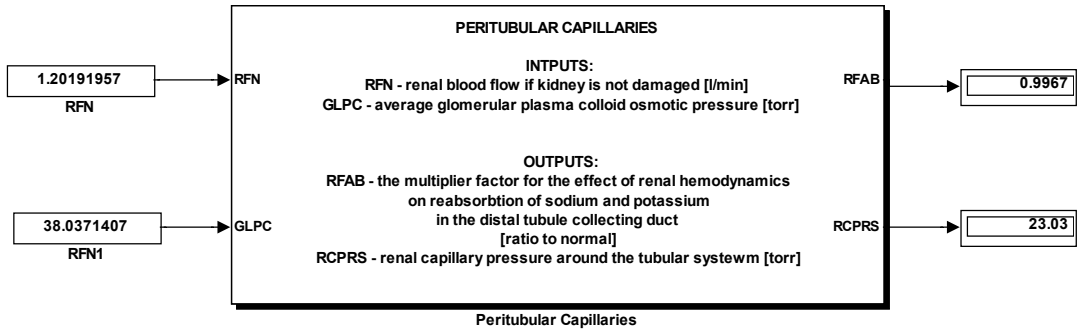
To prevent oscillations, we include an integrating damping term with time constant RFABD=1:

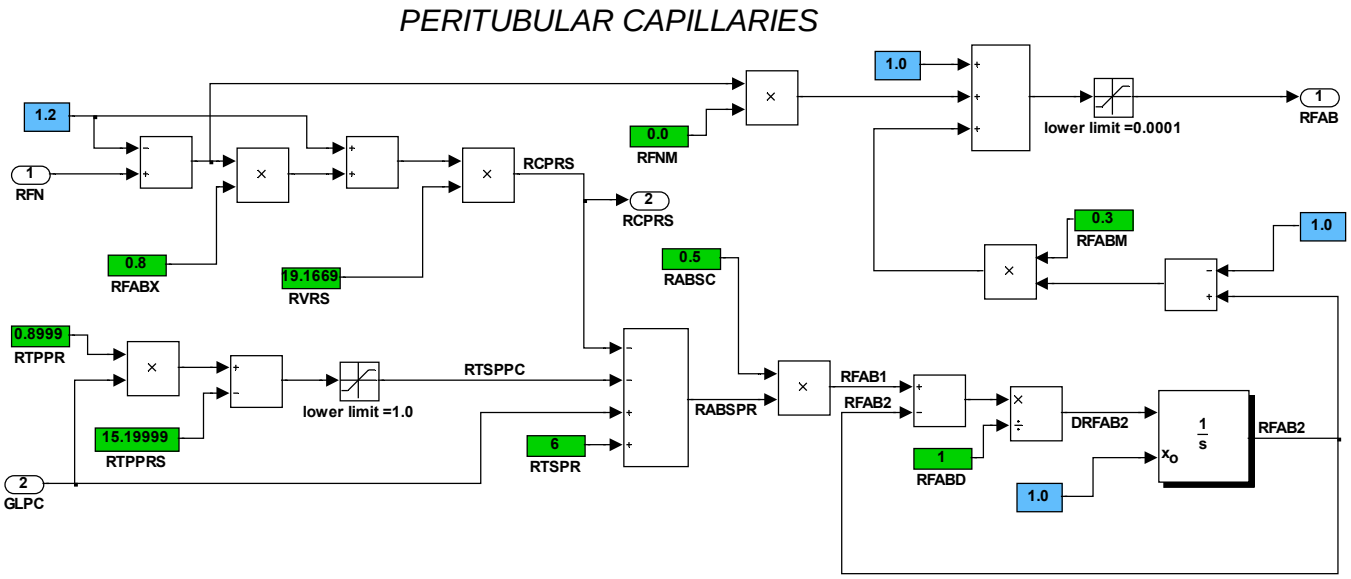
$$DRFAB2=(RFAB1-RFAB2)/RFABD \quad \text{(KD 89)}$$

$$RFAB2=\int DRFAB2\ dt \quad \text{(KD 90)}$$

Finally, we calculate the normalized RFAB multiplier, expressing the effect of renal hemodynamics on tubular sodium and potassium reabsorption. First, we subtract the resulting RFAB2 from the norm (which is 1.0) and multiply by a weighting factor (RFABM=0.3), characterizing the weighting of the influence of perturbations in plasma protein levels and changes in peritubular capillary pressure on changes in sodium and potassium reabsorption. The second part of the normalized multiplier is an expression of the influence of changes in renal blood flow on changes in sodium and potassium resorption (the weighting factor RFNM=0 is set to zero here, but this input value can be changed). Finally, we bound the resulting RFAB factor from below with a value of 0.0001.

$$RFAB=(RFAB2-1.0)*RFABM+(RFN-1.2)*RFNM+1.0 \quad \text{(KD 90)}$$
$$if\ (RFAB<0.0001)\ then\ RFAB=0.0001 \quad \text{(KD 91)}$$


PERITUBULAR CAPILLARIES
1.20191957
RFN
RFN
INTPUTS:
RFN - renal blood flow if kidney is not damaged [l/min]
GLPC - average glomerular plasma colloid osmotic pressure [torr]
RFAB
0.9967
OUTPUTS:
RFAB - the multiplier factor for the effect of renal hemodynamics
on reabsorbtion of sodium and potassium
in the distal tubule collecting duct
[ratio to normal]
RCPRS - renal capillary pressure around the tubular systewm [torr]
38.0371407
RFN1
GLPC
RCPRS
23.03
Peritubular Capillaries


PERITUBULAR CAPILLARIES
1.2
1
RFN
0.8
RFABX
19.1669
RVRS
RCPRS
2
RCPRS
0.0
RFNM
1.0
lower limit =0.0001
1
RFAB
0.3
RFABM
1.0
0.5
RABSC
0.8999
RTPPR
15.19999
RTPPRS
lower limit =1.0
RTSPPC
6
RTSPR
RABSPR
RFAB1
RFAB2
1
RFABD
DRFAB2
1
s
RFAB2
1.0
2
GLPC

THIRST, DRINKING AND CRAVING FOR SALTY

The taste for salty is expressed by the STH coefficient - the change in the rate of sodium intake depends on it (see the electrolyte module, equation EL 02). The normal value of this coefficient is 1. A rise in salt craving can occur, for example, in circulatory shock when adequate oxygen supply to the tissues is reduced. In the model, this is accounted for via the olive coefficient of STH through the oxygen tension in the non-muscle tissue cells (POT)

We calculate the effect of a decrease in PO2 in non-muscle tissue cells (POT) on the salty taste coefficient (STH), activation occurs when POT decreases from a value (Z10=8.25), through the enhancement coefficient (Z11=4). The resulting value is bounded from below (1) and above (8):

$$STH=(Z10-POT)*Z11 \quad \text{(TS 01)}$$
$$\text{if } (STH<1.0) \text{ then } STH=1.0 \quad \text{(TS 02)}$$
$$\text{if } (STH>8.0) \text{ then } STH=8.0 \quad \text{(TS 03)}$$

Next, we calculate the influence of thirst, which depends on the coefficient of "salty taste" (STH) and the influence of antidiuretic hormone (AHC1) - the result is the cumulative coefficient AHTH, expressing the rate of drinking, the result is bounded from below:

$$AHTH=((AHC1-1.0)*AHTHM+1.0)*STH*0.001 \quad \text{(TS 04)}$$
$$\text{if } (AHTH<0) \text{ then } AHTH=0.0 \quad \text{(TS 05)}$$

Another factor that influences (and potentiates) the sensation of thirst is the level of angiotensin (AMN). From the value expressed as the ratio of the level of angiotensin to the norm, we calculate the additional contribution of ANMTH (expressed as the rate of drinking):

$$ANMTH=(ANM-1.0)*ANMTM*0.001 \quad \text{(TS 06)}$$

Finally, we add the sum of the two contributions and get the value of the required water inflow rate (TVZ), the result is bounded at the bottom by zero:

$$TVZ=ANMTH+AHTH \quad \text{(TS 07)}$$
$$\text{if } (TVZ<0.0) \text{ then } TVZ=0.0 \quad \text{(TS 08)}$$

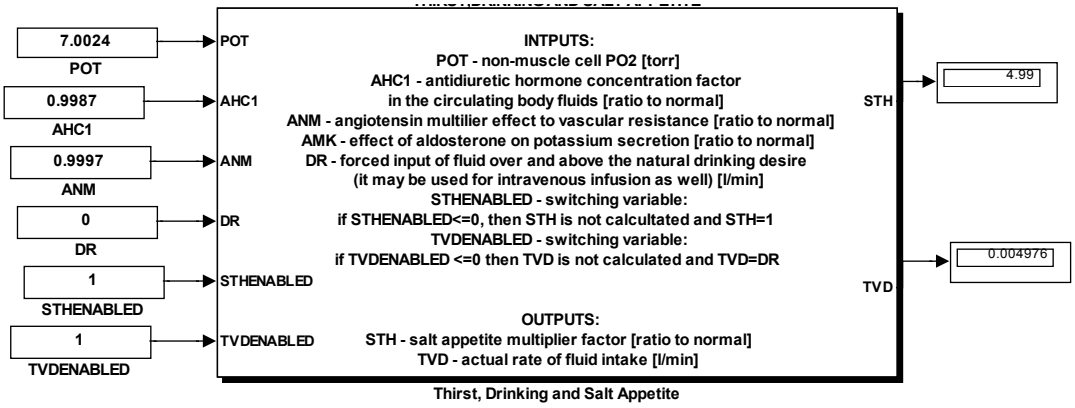
Finally, we insert an integrating damping term with time constant TVDDL=30 between the desired water supply rate (TVZ) and the actual water intake (vodx). In addition to the calculated value of the thirst-driven fluid intake, another input is directly the input value of the fluid intake rate DR - this value can be used to simulate e.g. infusions etc.

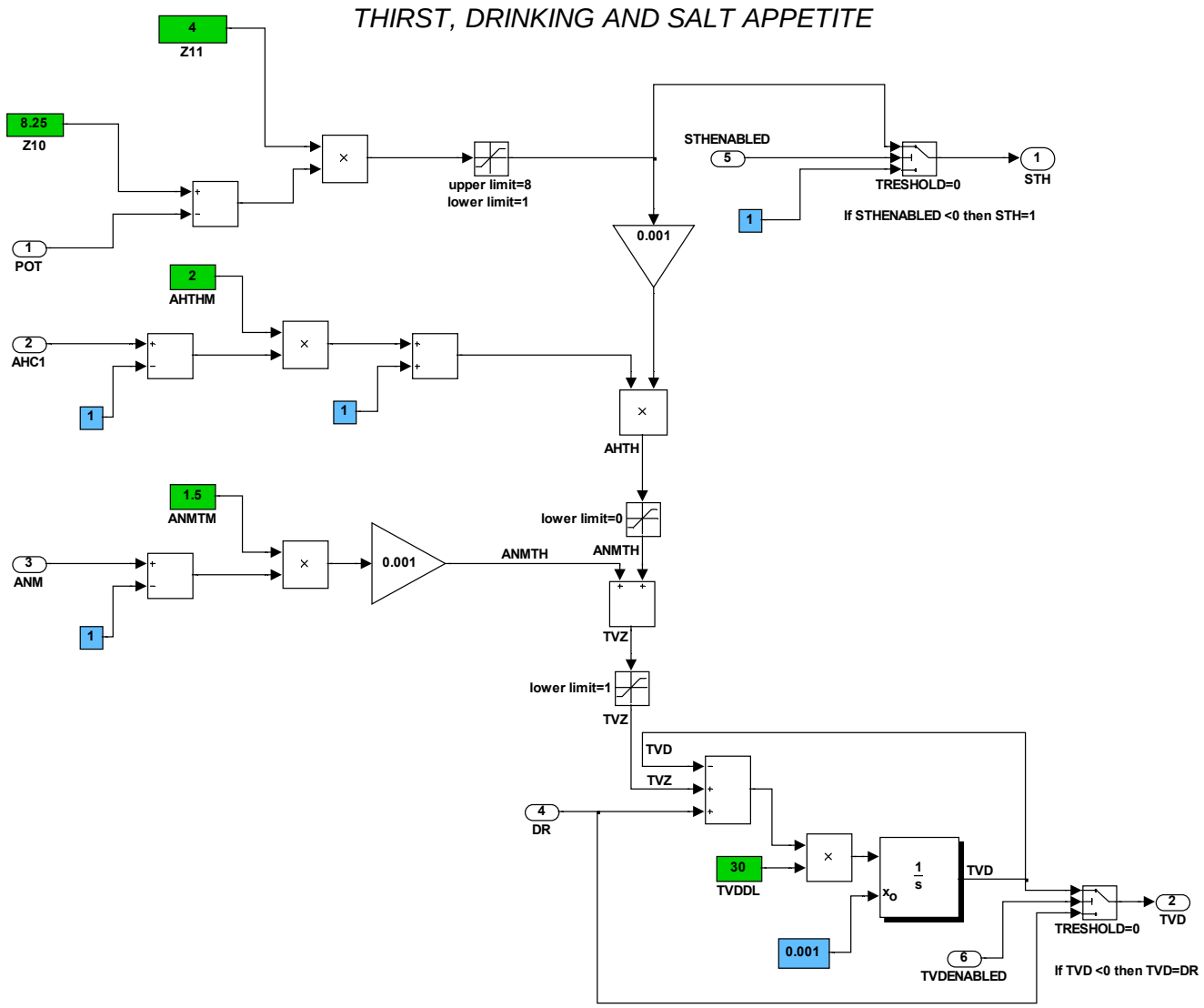
$$DTVD=(TVZ+DR-TVD)/TVDDL \quad \text{(TS 09)}$$

$$TVD=\int DTVD\,dt \quad \text{(TS 10)}$$

Finally, two control variables are considered in the module, if they are positive the calculation is performed according to the above equations, if they are zero or negative, then the value of STH (on which the rate of sodium intake depends) is one and the rate of sodium intake will be determined by the value of NID (see equation EL 02). If the value of the input control variable TVDENABLED is set to negative or zero, then the rate of fluid intake will be determined by the value of the variable DR:

$$\text{if } (STHENABLED <=0) \text{ then } STH=1 \quad \text{(TS 11)}$$
$$\text{if } (TVDENABLED<=0) \text{ pthen } TVD=DR \quad \text{(TS 12)}$$


7.0024
POT
POT
0.9987
AHC1
AHC1
0.9997
ANM
ANM
0
DR
DR
1
STHENABLED
STHENABLED
1
TVDENABLED
TVDENABLED
INTPUTS:
POT - non-muscle cell PO2 [torr]
AHC1 - antidiuretic hormone concentration factor
in the circulating body fluids [ratio to normal]
ANM - angiotensin multilier effect to vascular resistance [ratio to normal]
AMK - effect of aldosterone on potassium secretion [ratio to normal]
DR - forced input of fluid over and above the natural drinking desire
(it may be used for intravenous infusion as well) [l/min]
STHENABLED - switching variable:
if STHENABLED<=0, then STH is not calcultated and STH=1
TVDENABLED - switching variable:
if TVDENABLED <=0 then TVD is not calculated and TVD=DR
OUTPUTS:
STH - salt appetite multiplier factor [ratio to normal]
TVD - actual rate of fluid intake [l/min]
STH
4.99
TVD
0.004976
Thirst, Drinking and Salt Appetite


THIRST, DRINKING AND SALT APPETITE
4
Z11
8.25
Z10
1
POT
upper limit=8
lower limit=1
STHENABLED
5
TRESHOLD=0
1
STH
1
If STHENABLED <0 then STH=1
0.001
2
AHTHM
2
AHC1
1
1
AHTH
1.5
ANMTM
lower limit=0
3
ANM
1
0.001
ANMTH
ANMTH
TVZ
lower limit=1
TVZ
TVD
TVZ
4
DR
30
TVDDL
1
s
TVD
0.001
6
TVDENABLED
TRESHOLD=0
2
TVD
If TVD <0 then TVD=DR

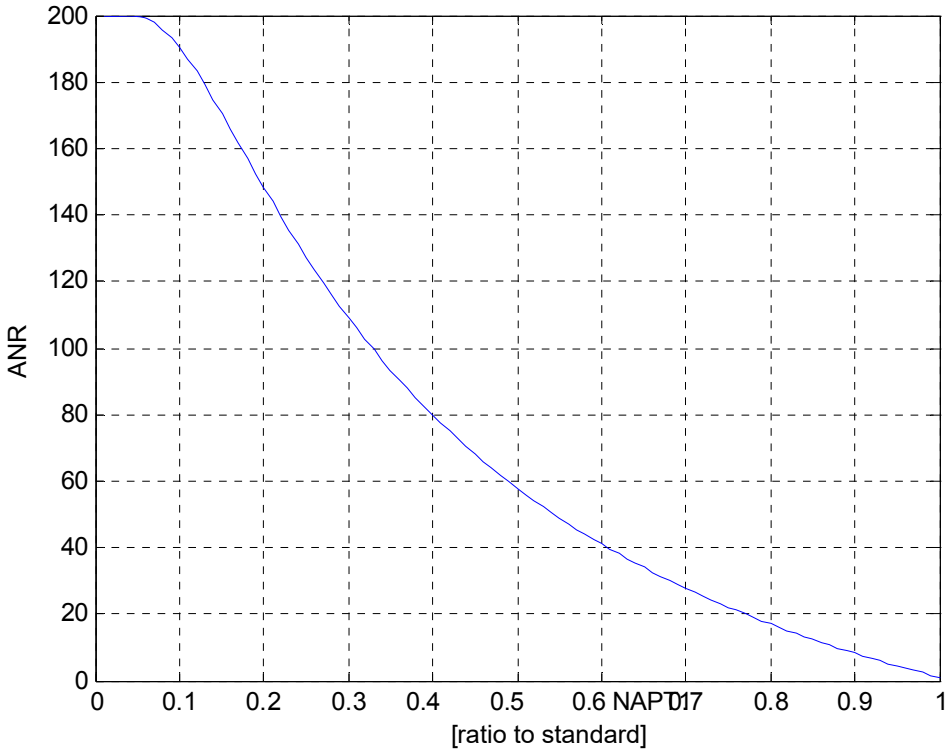
REGULATORY FUNCTION OF ANGIOTENSIN

The stimulus for angiotensin secretion is the sodium uptake from the macula densa - expressed by the normalized NAPT1 input value (see Macula Densa module). The first three equations calculate the dependence of basal angiotensin secretion on the NAPT1 value. The constants (ANRUL=200) and (SLOPE=0.4) affect the slope and maximum of the resulting curve of the dependence of the basal secretion rate (ANR) on sodium pumping from the tubule in the macula densa region (see graph):

$$NAPTR=1.0/NAPT1 \quad \text{(AN 01)}$$

$$\text{if } (NAPTR>100.0) \text{ than } NAPTR=100.0 \quad \text{(AN 02)}$$

$$ANR=ANRUL-(ANRUL-1.)/(1.+SLOPE1)^{(NAPTR-1.0)} \quad \text{(AN 03)}$$



Other equations account for the effect of hypertrophy of the juxtaglomerular apparatus in response to chronic irritation of macula densa cells. The degree of hypertrophy is controlled by the control variable ANXM (no hypertrophy at ANXM=0). The output variable ANX1 characterizes the additional secretion rate due to hypertrophy:

$$ANX=(ANR-1.)*ANXM \quad \text{(AN 03)}$$

$$DANX1=(ANX-ANX1)/ANV \quad \text{(AN 04)}$$

$$ANX1=\int DANX1\ dt \quad \text{(AN 05)}$$

The other equations calculate the total secretion of angiotensin from normal and hypertrophied cells of the juxtaglomerular apparatus (ANP). The total secretion rate (ANP) is modified by the REK multiplier which represents the proportion of functional renal tissue to normal (normal REK=1) and allows to simulate pathological conditions when the renal parenchyma is reduced.

$$ANP=(ANR+ANX1)*REK \quad \text{(AN 06)}$$
$$if\ (ANP<0.00001)\ then\ ANP=.00001 \quad \text{(AN 07)}$$

Further, on the basis of secretion rates, the gradual accumulation of angiotensin in the body and the corresponding changes in its level are calculated. The angiotensin level (ANCN) is calculated - as a ratio to the norm with the time constant ANT=50:

$$DANCN=(ANP-ANCN)/ANT \quad \text{(AN 08)}$$

$$ANCN=\int DANCN\,dt \quad \text{(AN 09)}$$

Angiotensin concentration (ANC) is calculated from self-produced (ANCN) and infused angiotensin (ANG):

$$ANC=ANCN+ANG \quad \text{(AN 10)}$$

When calculating the multiplicative factors corresponding to the effect of angiotensin on various functions (e.g. on vascular resistance), we must take into account that the effect is not directly proportional to the concentration. Therefore, when calculating the effect of angiotensin on vascular resistance (AMN), we calculate this multiplier according to a non-linear relationship from the angiotensin level (ANC). ANCE=0.699, ANMM=0.15 and ANMM1=0.85 are empirically determined parameters in this equation:

$$ANM=ANC^{ANCE}*ANMM+ANMM1 \quad \text{(AN 11)}$$

The multiplier corresponding to the effect of angiotensin on systemic arterial resistance (ANU) is calculated from the general multiplier expressing the effect of angiotensin on vascular resistance (ANM), ANUM=3 is an empirically determined coefficient:

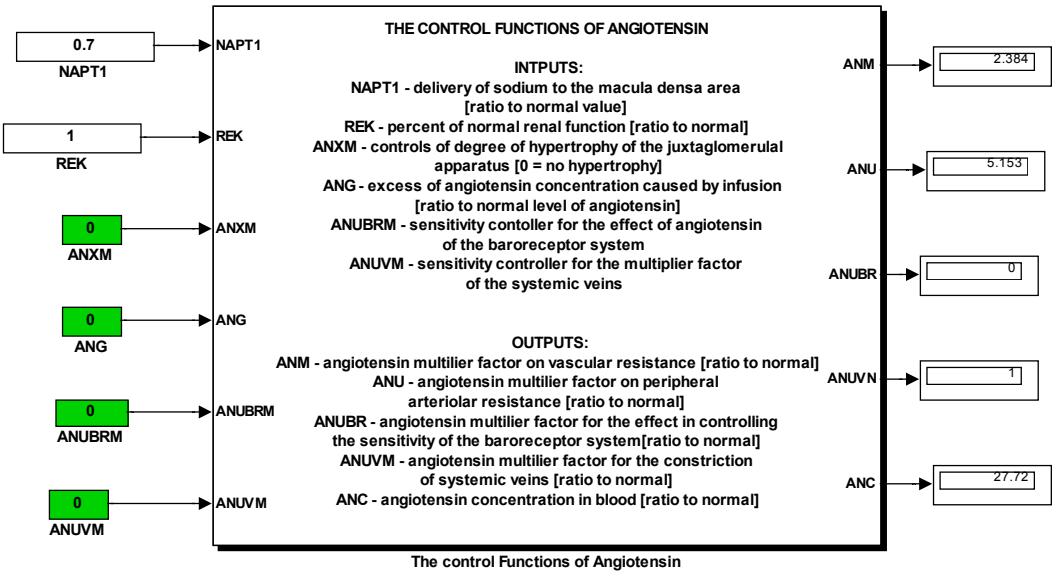
$$ANU=(ANM-1.)*ANUM+1 \quad \text{(AN 12)}$$
$$if\ (ANU<0.8)\ then\ ANU=0.8 \quad \text{(AN 13)}$$

The next equations calculate a multiplier expressing the effect on arteriolar systemic resistance (ANUVN) - the amplification factor ANUVM is the input (no effect is considered when ANUVM=0).

$$ANUVN=(ANU-1.)*ANUVM+1.0 \quad \text{(AN 14)}$$

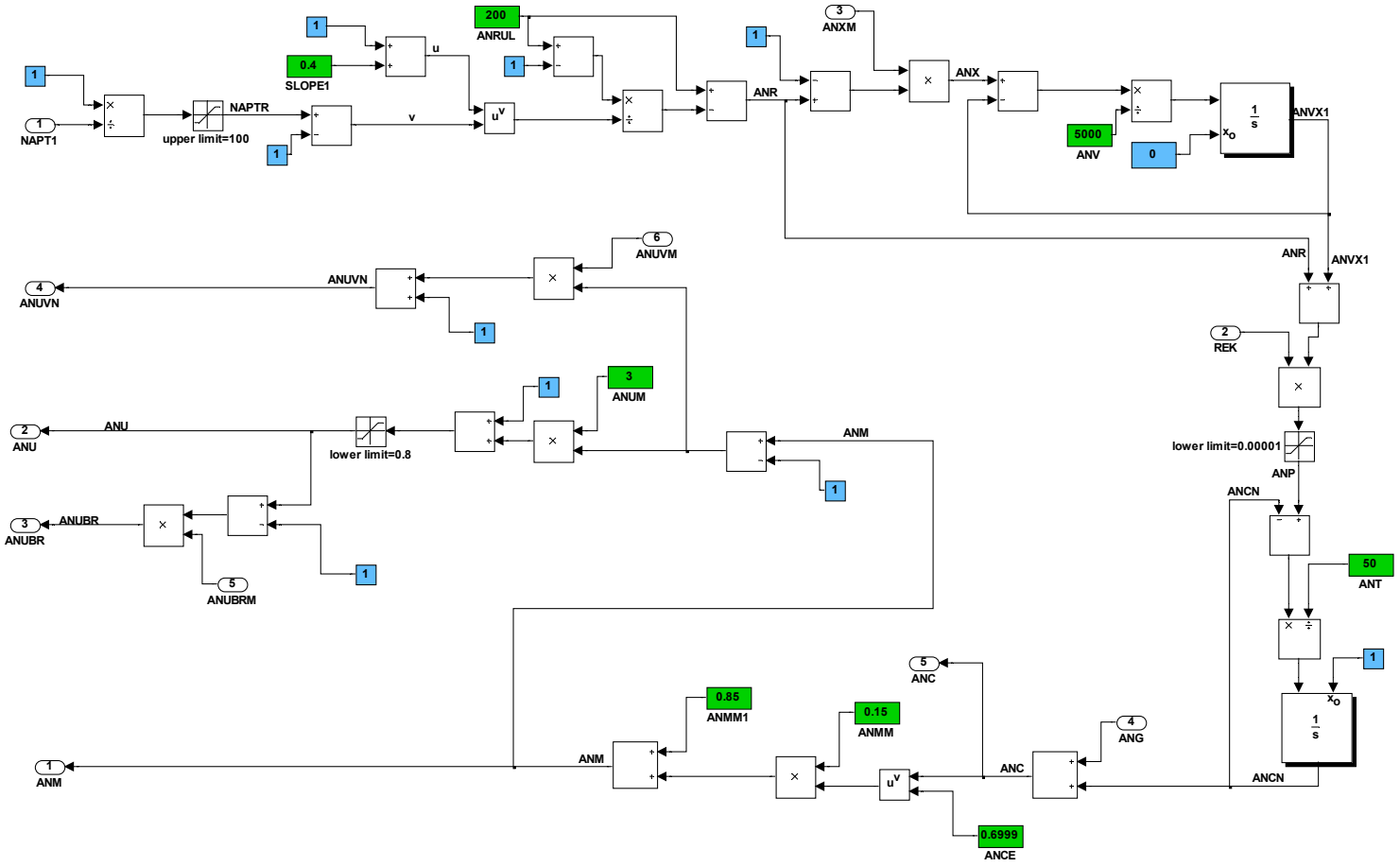
Calculation of the coefficient expressing the effect of angiotensin on baroreceptor sensitivity (ANUBR). The amplification coefficient ANUBRM is the input of the model:

$$ANUBR=(ANU-1.)*ANUBRM \quad \text{(AN 15)}$$



The control Functions of Angiotensin

THE CONTROL FUNCTIONS OF ANGIOTENSIN



REGULATORY FUNCTION OF ALDOSTERONE

The controlling signals for aldosterone secretion are angiotensin and extracellular potassium levels. Here, the general angiotensin multiplication term (ANM) and the concentration of potassium in the extracellular fluid (CKE) are taken as input. First, the effect of angiotensin is calculated - the sensitivity is controlled by the value in the control variable (ANMALM=3), the resulting value has a bounding box from below (-0.2). The potassium level is added to the result, and the sum is divided by the normal potassium level (5 mmol/l). The difference from one is then multiplied by the sensitivity coefficient (AKMNUL=12), and the result is the basis for calculating the aldosterone formation rate (AMR), expressed as a ratio to the normal::

$$ANMAL=(ANM-1.0)*ANMALM \quad \text{(AL 01)}$$
$$\text{if } (ANMAL<-0.2) \text{ then } ANMAL=-0.2 \quad \text{(AL 02)}$$

$$AMR=((CKE+ANMAL)/5.0-1.0)*AMKMUL+1.0 \quad \text{(AL 03)}$$
$$\text{if } (AMR<0.0) \text{ then } AMR=0.0 \quad \text{(AL 04)}$$

The aldosterone secretion rate (AMR) and possibly the aldosterone infusion rate (ALD) are then used to calculate the aldosterone concentration AMC, a time constant: AMT=60. The result is the aldosterone concentration (AMC) expressed as a ratio to the normal value:

$$DAMC=(AMR+ALD-AMC)/AMT \quad \text{(AL 05)}$$

$$AMC=\int DAMC\,dt \quad \text{(AL 06)}$$

Since the effect of aldosterone is not linearly dependent on its level, a general multiplier expressing the effect of aldosterone (AM) is first calculated from the aldosterone level (AMC), expressed realistically as a ratio to the norm. The coefficients of the empirical function are AMREX=0.3 and ALDMM=6.0:

$$AM1=AMC^{AMREX} \quad \text{(AL 07)}$$

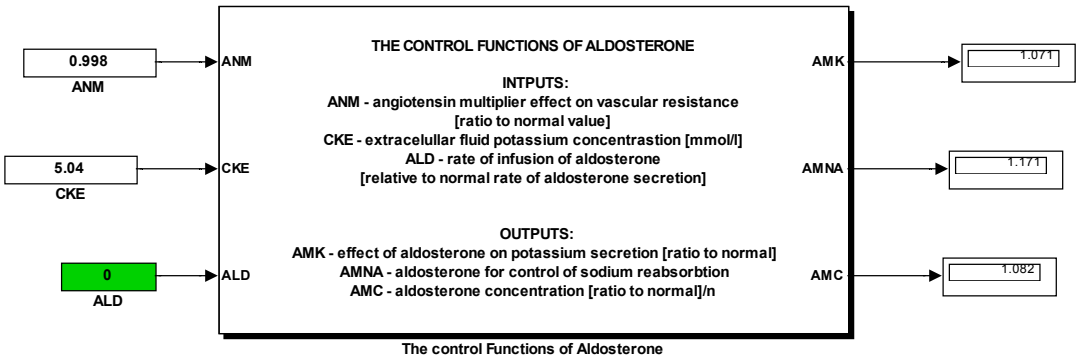
$$AM=(AM1-1.0)*ALDMM+1.0 \quad \text{(AL 08)}$$

From the general multiplier expressing the effect of aldosterone, the multiplier expressing the effect of aldosterone on the potassium transport across the cell membrane (AMK) is calculated. The sensitivity coefficient here is AMKM=0.5:

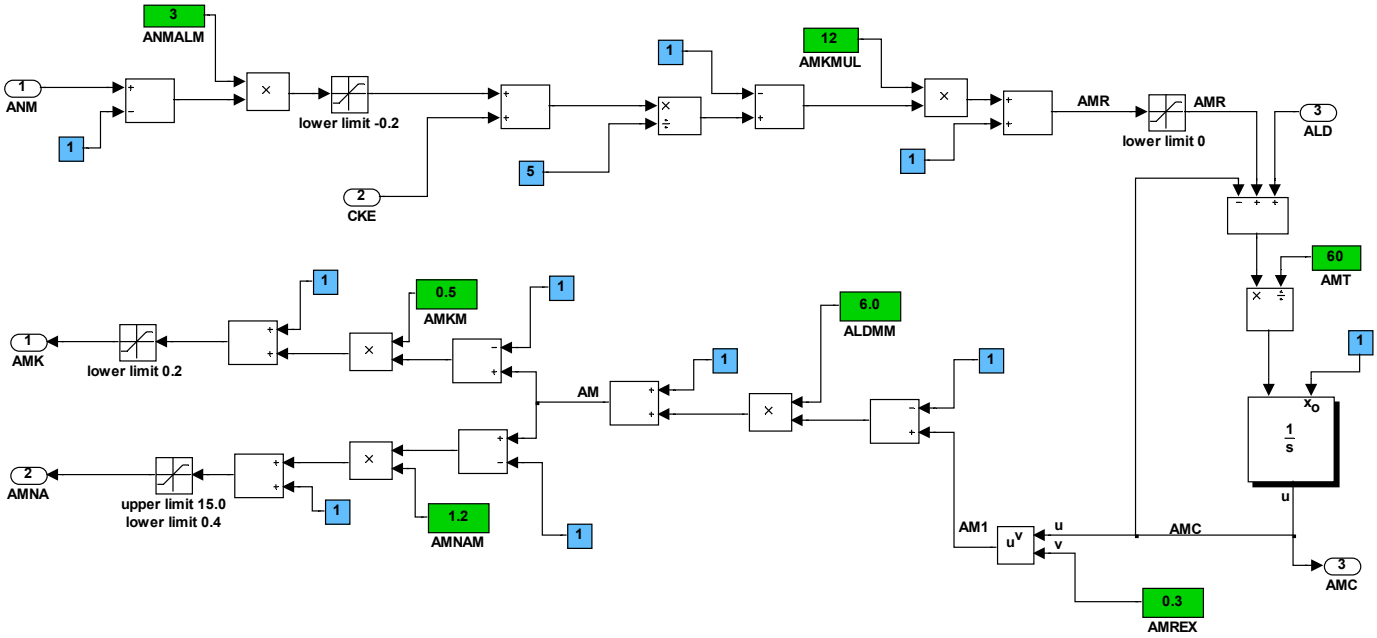
$$AMK=(AM-1.0)*AMKM+1.0 \quad \text{(AL 09)}$$
$$\text{if } (AMK<0.2) \text{ then } AMK=0.2 \quad \text{(AL 10)}$$

The second multiplier is a multiplier expressing the effect of aldosterone on sodium transport across the cell membrane (AMNA) in renal tubular cells. The sensitivity coefficient AMNAM=1.2 indicates that aldosterone generally has a greater effect on sodium trasport than on potassium trasport:

$$AMNA=(AM-1.0)*AMNAM+1.0 \quad \text{(AL 11)}$$
$$\text{if } (AMNA<0.4) \text{ then } AMNA=0.4 \quad \text{(AL 12)}$$
$$\text{if } (AMNA>15) \text{ then } AMNA=15 \quad \text{(AL 13)}$$



THE CONTROL FUNCTIONS OF ALDOSTERONE



REGULATORY FUNCTION OF ANTIDIURETIC HORMONE

First, the individual partial influences acting on antidiuretic hormone secretion are accumulated. The partial effect of autonomic stimulation (AUP) on antidiuretic hormone secretion (AH8) is easy to calculate - one is subtracted from the input real value:

$$AH8=AUP-1.0 \quad \text{(AD 01)}$$

The partial effect of extracellular sodium concentration (CNA) on antidiuretic hormone output (CNAH) is calculated by subtracting the constant (CNR=139) from the CNA value and multiplying the difference by the sensitivity coefficient (CNZ=1):

$$CNB=CNA-CNR \quad \text{(AD 02)}$$
$$CNAH=CNZ*CNB \quad \text{(AD 03)}$$

The partial effect of angiotensin (ANM) together with the effect of arterial pressure (PA) on ADH output (AH12) depends on the sensitivity coefficients (ANAPDM=12 and ANADHS=0.15):

$$AH12=((ANM-1.)*ANADPM+100.0-PA)*ANADHS \quad \text{(AD 04)}$$

All these partial effects, together with the effect of the contribution of atrial receptor stimulation on ADH secretion during volumoreception (expressed by the variable AH7), are summed and multiplied by a coefficient to normalize the resulting number to 1 under normal input values (CNA=142, PA=100, AUP=1, ANM=1, AH7=0):

$$AH=CNZ*CNB+AH8-AH7+AH12 \quad \text{(AD 05)}$$
$$\text{if } (AH<0.0) \text{ then } AH=0.0 \quad \text{(AH 06)}$$
$$AH1=AH*0.33333 \quad \text{(AH 07)}$$

AH1 represents the ADH secretion rate (normalized as a ratio to the norm) - on this basis, the ADH concentration expressed as a ratio to the norm (AHC1) is calculated by the integration term (time constant AHK=15):

$$DAHC1=(AH1-AHC1)/AHK \quad \text{(AH 08)}$$

$$AHC1=\int DAHC1\ dt \quad \text{(AH 09)}$$

The current ADH concentration (AHC) is calculated from AHC1 (but the exponent of AHMM is equal to 1) and added here to the initial ADH infusion:

$$AHC=AHC1^{AHMM}+ADH \quad \text{(AH 10)}$$

The effect of ADH, expressed as a multiplicative factor (AHM), is not directly proportional to concentration. Therefore, an empirical non-linear function is used to calculate this multiplier from the concentration (AHC):

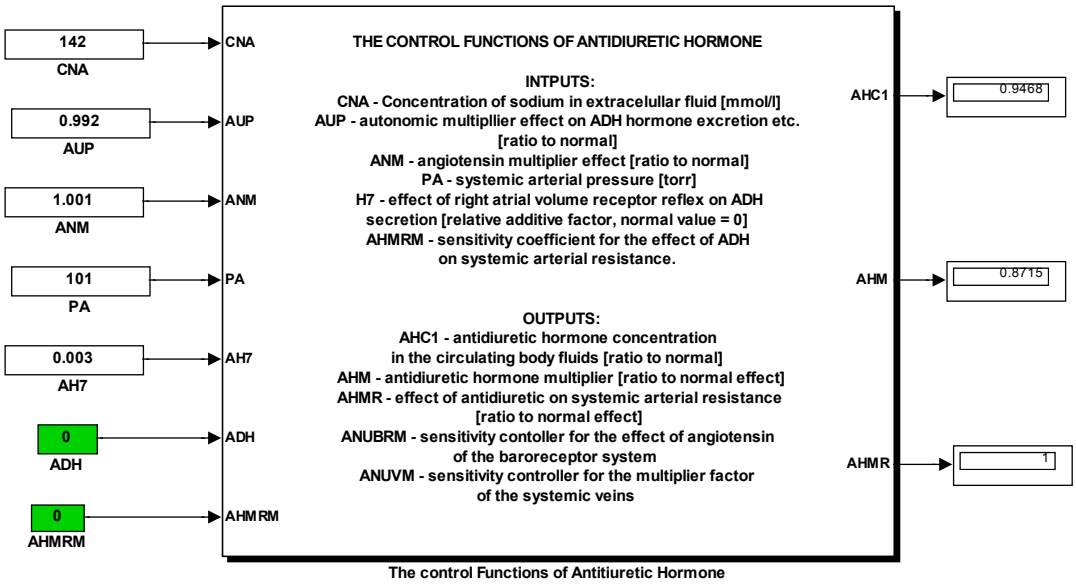
$$\text{if } (AHC>1.0) \quad \text{(AH 11)}$$
$$\text{then } AHM=(3.15-4.0*AHC)/(0.15-AHC)$$
$$\text{else } AHM=0.15+0.85*AHC^3$$

The result is bounded from below and above:

$$\text{if } (AHM<0.12) \text{ then } AHM=0.12 \quad \text{(AH 12)}$$
$$\text{if } (AHM>2.5) \text{ then } AHM=2.5 \quad \text{(AH 13)}$$

Finally, from (AHM) the multiplier of the effect of ADH on arterial resistance (AHMR) is calculated, AHMRM is the sensitivity coefficient (but Guyton gives the value of this coefficient as zero!)

$$AHMR=(AHM-1.)*AHMRM+1.0 \quad \text{(AH 14)}$$



The control Functions of Antitiuretic Hormone

THE CONTROL FUNCTIONS OF ANTIDIURETIC HORMONE