A description of 352 blocks in the Guyton's 1972 model

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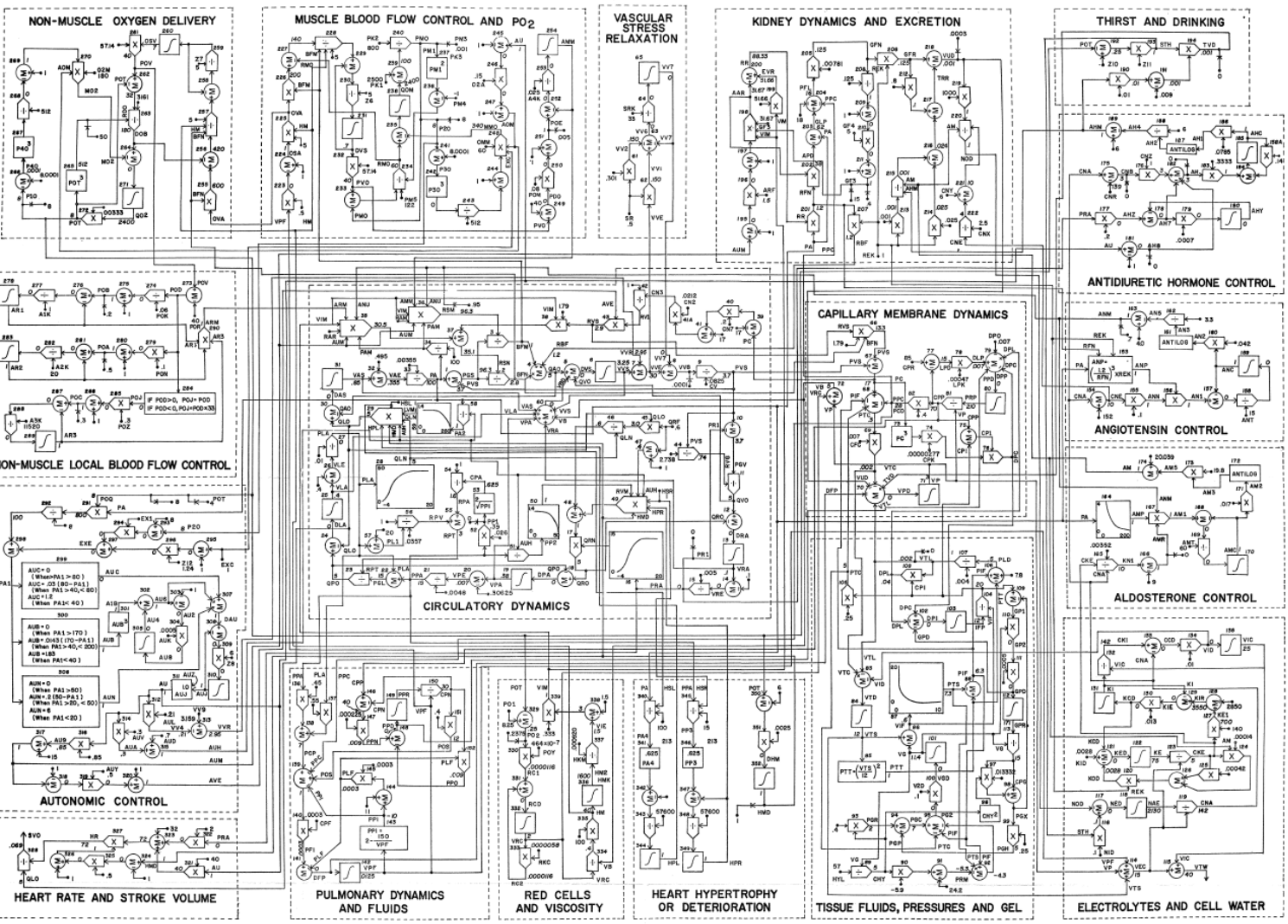
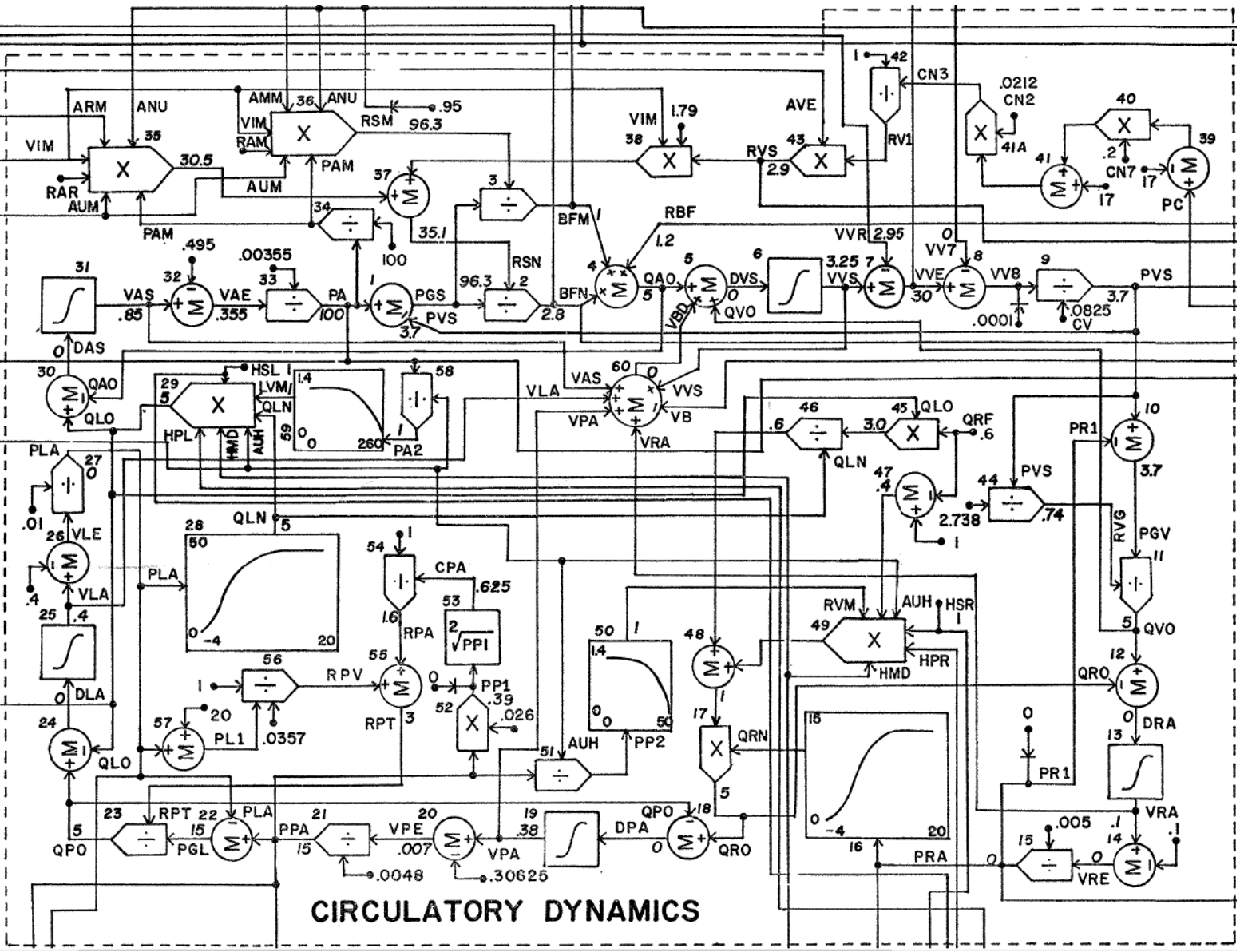


Original diagram from Guyton, Coleman, Granger: Circulation: overall regulation, Annual review of physiology, vol. 34, pp. 13-46, 1972, DOI 10.1146/annurev.ph.34.030172.000305. This iconic diagram was the part of Thomas Coleman dissertation.

In this text, we performed a comparison to the Fortran code in the NASA report by White (White 1973).

Thomas Coleman is great computer scientist and physiologist, who, instead of developing weapons, started work with Arthur Guyton, and he was design a lot of model of integrative physiology from this this old model to HumMod (www.hummod.org)



1 Circulatory dynamics

Diagram 1a. Circulatory dynamics in Guyton's diagram

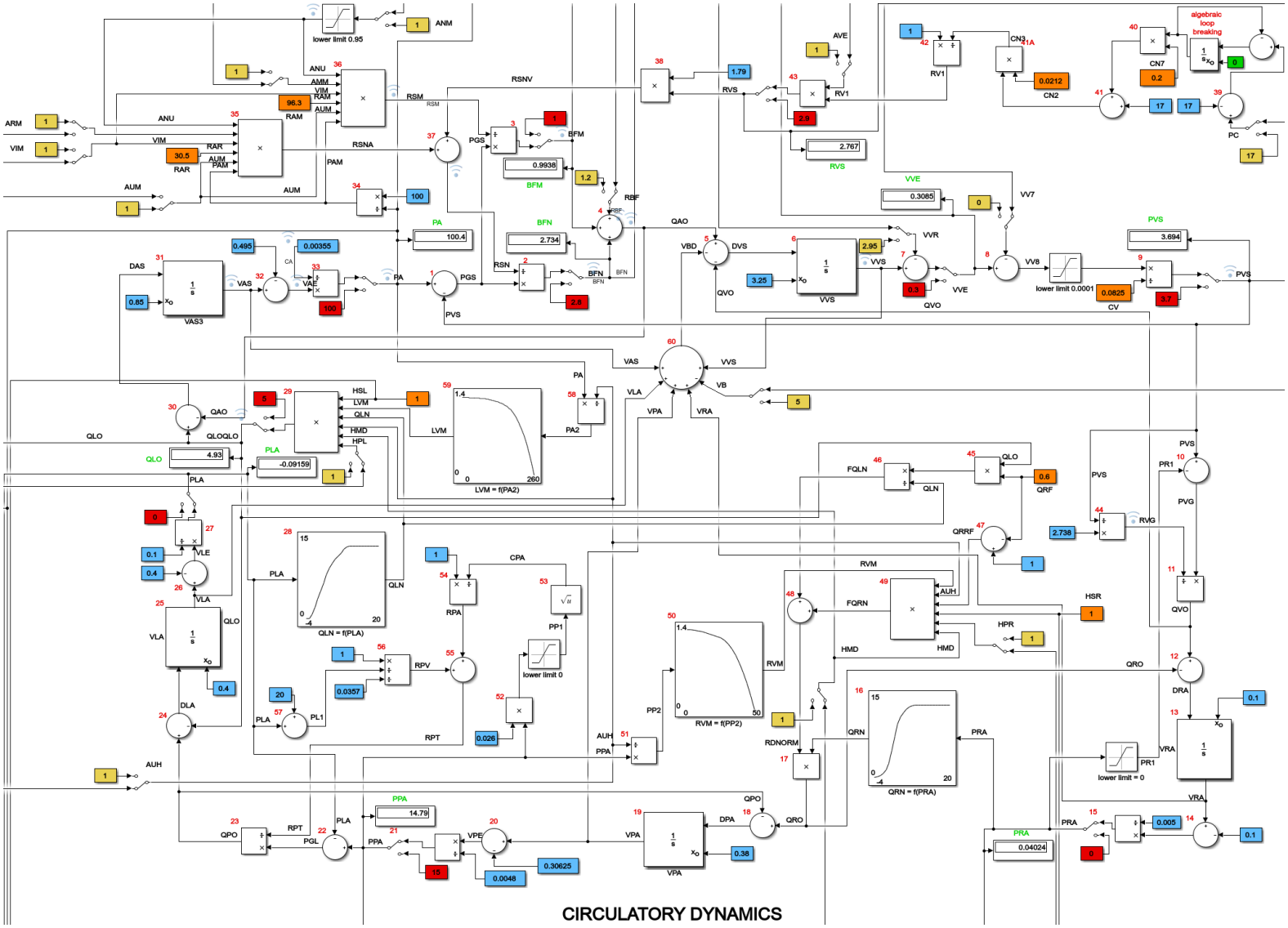


Diagram 1b. Circulatory dynamics in Simulink

Block 1: Arterial pressure (PA) [mmHg] minus pressure in the systemic veins and right veins (PVS) [mmHg] gives pressure gradient of the systemic circulation (PGS) [mmHg]:

$$PGS = PA - PVS$$

Block 2: Pressure gradient in the systemic circulation (PGS) [mmHg] divided by the resistance in the non-muscle, non-renal circulation (RSN) [mmHg min/l] gives blood flow in the non-muscle, non-renal circulation (BFN) [l/mi]:

$$BFN = PGS/RSN$$

Block 3: Pressure gradient in the systemic circulation (PGS) [mmHg] divided by resistance in the muscle circulation (RSM) [mmHg min/l] gives blood flow in the muscle circulation (BFM) [l/ming]:

$$BFN = PGS/BFM$$

Block 4: Addition of blood flow in the non-muscle, non-renal circulation (BFN) [l/min] plus muscle blood flow (BFM) [l/min] plus renal blood flow (RBF) [l/min] gives blood flow from aorta through the systemic circulation (QAO) [l/min]:

$$QAO = BFN + BFM + RBF$$

Block 5: Blood flow through the systemic circulation (QAO) [l/min] minus blood flow out of the systemic veins into the atria (QVO) [l/min] minus outflow of fluid volume from the circulation through the capillary walls (VBD) [l/min] (VBD is calculated in block 60) gives rate of change of volume in the systemic veins (DVS) [l/min] (note error in Guyton's diagram: QVO and VBD is subtracted instead of added as shown in diagram):

$$DVS = QAO - QVO - VBD$$

Block 6: Integration of rate of blood flow into the veins (DVS) [l/min] gives volume of blood in the veins of the systemic circulation (VVS) [l]:

$$dVVS/dt = DVS$$

Block 7 and Block 8: Venous volume (VVS) [l] is the sum of stressed venous volume (VV8) [l] and unstressed venous volume VVUS [l]: VVS=VVUS+VV8.
Unstressed venous volume (VVUS) is the volume of blood at zero pressure. Venous pressure rises when venous stressed volume increases (pressure = stressed volume/venous compliance - see block 9). Unstressed volume depends on venous tone - when venous tone increased, unstressed volume decreased and therefore stressed volume increased, and venous pressure increased. When venous tone decreased (e.g. in stress relaxation), unstressed volume increased and therefore stressed volume decreased and venous pressure dropped. Unstressed venous volume (VVUS) depends of basic stressed volume (VVR) [l] and the additional volume VV7 [l] that increases stressed during the reflex relaxation of large vein: VVUS=VR+VV7.
Stressed relaxation factor is calculated in module "Vascular stress relaxation" (blocks 61-65) from the difference VVE [l] between venous blood volume (VVS) [l] and basic unstressed volume (VR) [l]. This difference is calculated in **block 7:**

$$VVE = VVS - VVR$$

However, in in a later version of the model, described in the NASA reports (White 1973; Archer 1974), the factor caused by angiotensin (ANU) [ratio to normal effect] is also taken into account, (ANY [l] - constant weight factor used to calculate angiotensin effect on venous volume -0.2 l:

$$ANY = -0.2$$
$$VVE = VVS - VVR - (ANU - 1.) * ANY$$

Venous stressed volume (VV8) [l] is calculated as a difference of venous volume (VVS [l] and unstressed volume (VVUS=VVR+VV7). Therefore VV8=VVS-VVUS=VVE-VV7.

Lower limit of venous stressed volume VV8 is 0.0001, VV8 is calculated in **block 8:**

$$VV8 = VVE - VV7$$
$$if\ (VV8 < 0.0001)\ then\ VV8 = 0.0001$$

Block 9: Venous stressed volume (VV8) [l] divided by compliance of the veins (CV) [mmHg/l] gives pressure in the veins (PVS) [mmHg]:

$$PVS = VV8/CV$$

Block 10: Pressure in the systemic veins (PVS) [mmHg] minus pressure in the right atrium (but not to be less than zero) (PR1) [mmHg] (because then big intrathoracic veins collapse) gives pressure gradient from the veins to the right atrium (PGV) [mmHg]:

$$PR1 = PRA$$
$$if\ (PR1 < 0)\ then\ PR1 = 0$$
$$PGV = PVS - PR1$$

Block 11: Pressure gradient from the veins to the right atrium (PGV) [mmHg] divided by large vein resistance (RVG) gives rate of blood flow into right atrium (QVO) [l/min]:

$$QVO = PVG/RVG$$

Block 12: Rate of blood flow into right atrium (QVO) [l/min] minus rate of blood flow out of right atrium (pumping by right heart) (QRO) [l/min] gives rate of change of blood volume in right atrium (DRA) [l/min]:

$$DRA = QVO - QRO$$

Block 13: Integration of rate of change of blood volume in right atrium (DRA) [l/min] gives volume of blood in right atrium (VRA) [l]:

$$dVRA/dt = DRA, VRA_{t=0} = 0.1$$

Block 14: Volume of blood in right atrium (VRA) [l] minus unstressed volume of right atrium (VRA0 = 0.1) [l] gives excess stressed volume of blood in the right atrium (VRE) [l] that causes stretching of the right atrium:

$$VRE = VRA - VRA0$$

Block 15: Excess volume of blood in right atrium (VRE) [l] divided by compliance of the right atrium (CRA=0.005) [mmHg/l] gives right atrial pressure (PRA) [mm\hg]:

$$PRA = VRE/CRA$$

Block 16: Curve relating right atrial pressure (PRA) [mmHg] to output of right atrium under normal operating conditions of right atrium (QRN) [l/min] (cubic spline interpolation x=[-6, -3, -1, 0, 2, 4, 8], y=[0, 0.75, 2.6, 5.0, 9.8, 12.1, 13.5])

$$QRN = function\ StarlingRNorm\ (PRA)$$

Block 17: Output of right atrium under normal conditions (QRN) times factor for degree of normality of the right ventricle (RDNORM) [relation to normal function] (output from block 48) to give true output of right ventricle (QRO) [l/min]:

$$QRO = QRN * RDNORM$$

Block 18: Output of right ventricle into pulmonary arteries (QRO) [l/min] minus rate of blood flow from the pulmonary arteries through the pulmonary system (QPO) [l/min] gives the inflow to pulmonary arteries volume (DPA) [l/min]:

$$DPA = QRO - QPO$$

Block 19: Integration of rate of change of volume in the pulmonary arteries (DPA) [l/min] gives the instantaneous volume in the pulmonary arteries (VPA) [l]:

$$dVPA/dt = DPA, VPA_{t=0} = 0.38$$

Block 20: Volume in the pulmonary arteries (VPA) [l] minus the unstressed volume of pulmonary arteries (VPA0=0.30625) [l] gives the excess stressed volume in the pulmonary arteries that causes stretch of the arteries (VPE) [l]:

$$VPE = VPA - VPA0$$

Block 21: Excess stressed volume in the pulmonary arteries (VPE) [l] divided by compliance of the pulmonary arteries (CPA=0.00485) [mmHg/l] gives the pulmonary arterial pressure (PPA) [mmHg]:

$$PPA = VPE/CPA$$

Block 22: Pulmonary arterial pressure (PPA) [mmHg] minus left atrial pressure (PLA) [mmHg] gives the pressure gradient through the lungs (PGL) [mmHg]:

$$PGL = PPA - PLA$$

Block 23: Pressure gradient through the lungs (PGL) [mmHg] divided by resistance of the pulmonary circuit (RPT) [mmHg min/l] gives rate of blood flow into the pulmonary veins and left atrium (QPO) [l/min]:

$$QPO = PGL/RPT$$

Block 24: Rate of blood flow into the pulmonary veins and left atrium (QPO) [l/min] minus rate of blood flow out of pulmonary veins and left atrium (pumped by left ventricle)(QLO) [l/min] gives rate of change of volume in the left atrium and pulmonary veins (DLA) [l/min]:

$$DLA = QPO - QLO$$

Block 25: Integration of rate of change of volume in left atrium and pulmonary veins (DLA) [l/min] gives instantaneous volume in left atrium and pulmonary veins (VLA) [l]:

$$dVLA/dt = DLA, VLA_{t=0} = 0.4$$

Block 26: Volume of blood in pulmonary veins and left atrium (VLA=0.4) [l] minus unstressed volume (VL0) [l] gives excess stressed volume (VLE) causing stretch of left atrium and pulmonary veins:

$$VLE = VLA - VLA0$$

Block 27: Excess volume in left atrium and pulmonary veins (VLE) [l] divided by compliance of left atrium and pulmonary veins (CLA=0.01) [mmHg/l] gives pressure in the left atrium (PLA) [mmHg]:

$$PLA = VLE/CLA$$

Block 28: Function curve giving normal output of the left ventricle (QLN) [l/min] for each given value of pulmonary left atrial pressure (PLA) [mmHg] (note that upper point of scale on ordinate should read 15 instead of 50) (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]):

$$QLN = function\ StarlingLNorm(PLA)$$

Block 29: Calculation of actual output of left ventricle (QLO) [l/min] based on the following factors: Output of left ventricle under normal conditions (QLN) [l/min], effect of arterial pressure loading factor on left ventricle - “afterload effect” (LVM) [ratio to normal effect] (calculated in block 59), basic strength of left ventricle (HSL) [ratio to normal effect] - input parameter of the model, degree of autonomic stimulation of left ventricle (AUH) [ratio to normal effect] (output from block 315), degree of deterioration of left ventricle caused by low coronary blood flow (HMD) [ratio to normal] (output from block 352), and degree of hypertrophy on the left ventricle (HPL) [ratio to normal] (output from block 344):

$$QLO = QLN * LVM * HSL * AUH * HMD * HPL$$

Block 30: Actual rate of output of left ventricle (QLO) [l/min] minus rate of blood flow from systemic arteries through the systemic circulation (QAO) [l/min] gives rate of change of blood volume in systemic arteries (DAS) [l/min]:

$$DAS = QLO - QAO$$

Block 31: Integration of rate of change of volume in systemic arteries (DAS) [l/min] gives actual volume in systemic arteries (VAS) [l]:

$$dVAS/dt = DAS, VAS_{t=0} = 0.85$$

Block 32: Volume in systemic arteries (VAS) [l] minus constant (unstressed arterial volume - VAS0'=0.495) [l] gives excess stressed volume in systemic arteries (VAE) [l] that causes stretch of the arterial walls.

$$VAE = VAS - VAS0$$

Block 33: Excess volume in the systemic arteries (VAE) [l] divided by compliance of the systemic arteries (CAS=0.00355) [mmHg/l] gives arterial pressure (PA) [mmHg]:

$$PA = VAE/CAS$$

Block 34: Factor of 100 mmHg divided by arterial pressure (PA) [mmHg] gives arterial pressure multiplier factor for alteration of peripheral resistance caused by stretching of arteries resulting from arterial pressure (PAM) [ratio to normal pressure]:

$$PAM = 100/PA$$

Block 35: Calculation of resistance to blood flow in non-renal, non-muscle portion of the systemic circulation from the aorta to the mid-point of the capillaries RSNA [mmHg min/l] utilizing the following factors: basic resistance (RAR) [30.52 mmHg min/l] (instead of 30.5 value in original diagram), arterial pressure multiplier factor caused by arterial stretch (PAM) [ratio to normal], autonomic stimulation (AUM) [ratio to normal effect] (from block 317), viscosity of the blood (VIM) [ratio to normal blood viscosity] (from block 339), autoregulation multiplier (ARM) [ratio to normal effect] (from block 290), and vasoconstrictor factor caused by angiotensin (ANU) [ratio to normal effect] (calculated from ANM but not to fall below a value of .95, on the further versions of the model is mentioned lower limit as 0.8, ANM is output from block 163):.

$$RAR = 30.52$$
$$if\ ANU > 0.8\ then\ \ ANU = ANM, else\ ANU = 0.95$$
$$RSNA = RAR * PAM * AUM * VIM * ARM * ANU$$

Block 36: Similar to Block 35 and using essentially same factors but calculation of resistance through muscle circulation of body (RSM) [mmHg min/l]. Basic resistance to muscle circuit RAM [mmHg min/l] is multiplying by arterial pressure multiplier factor caused by arterial stretch (PAM) [ratio to normal], autonomic stimulation (AUM) [ratio to normal effect] (from block 317), viscosity of the blood (VIM) [ratio to normal blood viscosity] (from block 339), AMM, is the autoregulation multiplier for the muscle vascular circuit (AMM) [ratio to normal effect] (from block 254), and vasoconstrictor factor caused by angiotensin (ANU) [ratio to normal effect]:

$$RAM = 96.3$$
$$RSM = RAM * PAM * AUM * VIM * AMM * ANU$$

Block 37: Addition of resistance from the aorta to midpoint of the capillaries (RSNA) [mmHg min/l] to resistance from midpoint of the capillaries to veins (RSNV) [mmHg min/l] to give resistance of the non-muscle, non-renal portion of the systemic circulation (RSN) [mmHg min/l].

$$RSN = RSNA + RSNV$$

Block 38: Calculation of resistance in the non-renal, non-muscle circuit from midpoint of capillaries to veins by multiplying the basic resistance of the total venous system between the same two points (RVS) [mmHg min/l] times a constant factor 1.79. In original Guyton's scheme was also multiplied by relative viscosity of the blood (VIM) [ratio to normal blood viscosity]:

$$RSNV = 1.79 * RVS * VIM$$

But this multiplication leads to too strong dependency on hematocrit changes due erythropoietin feedback to pO_2 in non-muscle tissues (POT) (see RED CELLS AND VISCOSITY subsystem). The alternative meaning of blocks 38 is based on the implementation of the Guyton's model in Fortran used by NASA (Archer 1974; White 1973):

$$RSNV = 1.79 * RVS$$

Blocks 39 through 43: Curve fitting process to give effect of changing capillary pressure (PC) [mmHg] and finally effect of autonomic stimulation (AVE) [ratio to normal effect] (output form block 320) on venous resistance (RVS) [mmHg min/l], using constant CN7 =0.2 [dimensionless sensitivity constant], CN2=0.0212.
Unlike the original scheme, in the model version used by NASA (White 1973; Archer 1974), the effect of angiotensin (ANU) [ratio to normal effect of angiotensin] and viscosity of the blood (VIM) [ratio to normal blood viscosity] are taken into account (ANZ - dimensionless sensitivity constant):

$$CN7 = 0.2$$
$$CN2 = 0.212$$
$$ANZ = 0.4$$
$$\frac{dPCI}{dt} = (PC - 17) - PCI, PCI_{t=0} = 0.0$$

$$CN3 = (PCI * CN7 + 17) * CN2$$
$$RV1 = 1/CN3$$
$$RVS = AVE * RV1 * VIM * ((ANU - 1) * ANZ + 1)$$

Block 44: Calculation of resistance between veins and right atrium (RVG) [mmHg min/l] as determined by the level of systemic vein venous pressure (PVS) [mmHg] by dividing constant 2.738 [$mmHg^2$ min/l]. This equation is especially concerned with the reduction of venous resistance when venous pressure (PVS) increases the diameter of the veins.:

$$RVG = 2.738/PVS$$

Blocks 45 and 46: Calculation of fraction of right ventricular output caused by left ventricle pumping determined by ratio of actual left ventricular output (QLO) divided by output for a normal left ventricle (QLN) times QRF (explained below):

$$QRF = 0.6$$
$$FQLN = QLO/QLN * QRF$$

Block 47: Calculation of fraction of right ventricular output caused by right ventricular pumping (QRRF). Factor QRF (=0.6) determines the ratio of effect of left ventricular pumping to right ventricular pumping in determining the output of the right ventricle (because QRF=é.6, QRRF=0.4):

$$QRRF = (1 - QRF)$$

Block 48: Addition of actual fractional effects of left ventricular pumping [FQLN] and right ventricular pumping [FQRF] to determine the degree of normal pumping by right ventricle RDNORM [ratio to normal effect] calculation:

$$RDNORM = FQLN + FQRF$$

Block 49: Calculation of actual right ventricular fractional effect on right ventricular output (FQRF) [ratio to normal] utilizing basic factor (QRRF) [fraction of right ventricular output caused by right ventricular pumping = 0.4] from Block 47, effect of pulmonary arterial pressure load on right ventricular pumping ("afterload" influence) (RVM) [ratio to normal], calculated in block 50, effect of autonomic stimulation (AUH) [ratio to normal] (output from block 315), effect of basic strength of the heart (HSR) [ratio to normal] - input parameter of the model, effect of hypertrophy of right ventricle (HPR) [ratio to normal] (output from block 349), effect of deterioration of right ventricle caused by poor coronary nutritional supply (HMD) [ratio to normal] (output from block 352):

$$FQRF = QRRF * RVM * AUH * HSR * HPR * HMD$$

Block 50: Effect of pulmonary arterial pressure times autonomic effect (PP2) [mmHg] (from block 51) to load right ventricle and decrease pumping effectiveness of right ventricle (afterload effect) (RVM) [ratio to normal effect] - cubic spline interpolation x=[-0, 20, 24, 30, 38, 45], y=[1.06, 0.97, 0.93, 0.8, 0.46, 0]:

$$RVM = function\ rightHeartLoading(PP2)$$

Block 51: Calculation of effect of autonomic stimulation (AUH) [ratio to normal] (output from block 315) in affecting the degree of loading of the right ventricle caused by pulmonary arterial pressure (PPA) [mmHg]. Result is arterial pressure corrected to autonomic effect [PP2) [mmHg], that is input to right heart loading function (see bock 50) that influenced pumping effectiveness of right ventricle:

$$PP2 = PPA/AUH$$

Block 52 through Block 54: Curve fitting process to calculate resistance in pulmonary arteries to the midpoint of the pulmonary capillaries (RPA) [mmHg min/l] from pulmonary arterial pressure (PPA) [mmHg]:

$$PP1 = 0.026 * PPA$$
$$if(PP1 < 0.)\ then\ PP1 = 0$$
$$CPA = \sqrt{PP1}$$
$$RPA = 1/CPA$$

Block 55: Calculation of total pulmonary resistance (RPT) [mmHg min/l] by adding pulmonary arterial resistance to midpoint of capillaries (RPA) [mmHg min/l] plus pulmonary venous resis-tance from midpoint to capillaries to left atrium (RPV) [mmHg min/l] :

$$RPTRPA + RPV$$

Blocks 56 and 57: Curve fitting process based primarily on waterfall effect, to calculate resistance of pulmonary veins (RPV) [mmHg min/l], change in resistance depending primarily on level of left atrial pressure (PLA) [mmHg]:

$$PL1 = PLA + 20$$
$$RPV = 1/(PL1 * 0.0357)$$

Block 58: Effect of autonomic stimulation (AUH) [ratio to normal] (output from block 315) on loading effect of systemic arterial pressure (PA) [mmHg] on the pumping effectiveness of left

ventricle. Result is arterial pressure corrected to autonomic effect [PA2) [mmHg], that is input to left heart loading function (see bock 59) that influenced pumping effectiveness ofleft ventricle:

$$PA2 = PA/AUH$$

Block 59: Function curve showing effect of systemic arterial pressure in loading left ventricle and determining its pumping effectiveness (LVM) - cubic spline interpolation x=[0,60, 125, 160, 200, 240], y=[1.04, 1.025, 0.97, 0.88, 0.59, 0]:

$$LVM = function\ leftHeartLoading(PA2)$$

Block 60: Addition of volumes of blood in all portions of the systemic circulation (VAS, VVS, VRA, VPA, VLA) [l] and subtraction of blood volume (VB) [l] as calculated in Block 72 to give the net difference between blood volume and volume calculated in all the capacitive reservoirs of the systemic circula-tion; output of this block (VBD) [l/min] represents the rate of fluid outflowing from the circulation through capillary walls (VBD is used in block 5 to calculation of rate of change of volume in the systemic veins). This allows updating of blood volume when volumes pass through the capillary walls, when volume is gained by the process of drinking, or lost through the kidneys, and so forth:

$$VBD = d(VAS + VVS + VRA + VPA + VLA - VB)/dt$$

In NASA Fortran implementation: the derivation is missing here:
VBD=VP+VRC-VVS-VAS-VLA-VPA-VRA
dVP/dt = VPD
VPD=VPD+(TVD-VTC+VTL-VUD-DFP-VPD)/Z1
dVRC/dt = RCD
Z1 = 1.0

Maybe the logic is same, though the implementation different.

2 Vascular stress relaxation

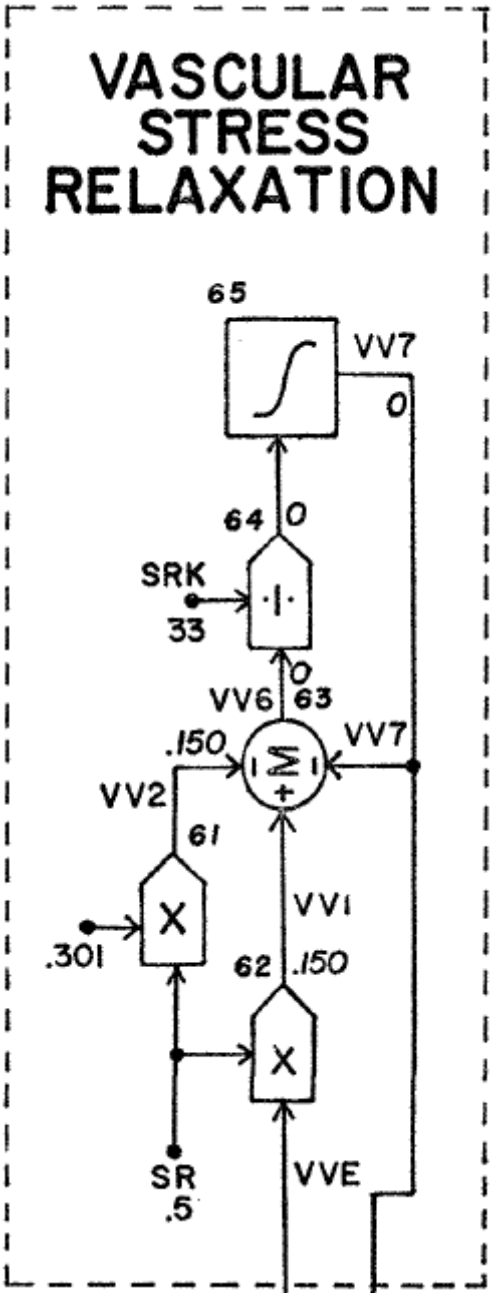


Diagram 2a. Vascular stress relaxation in Guyton's diagram

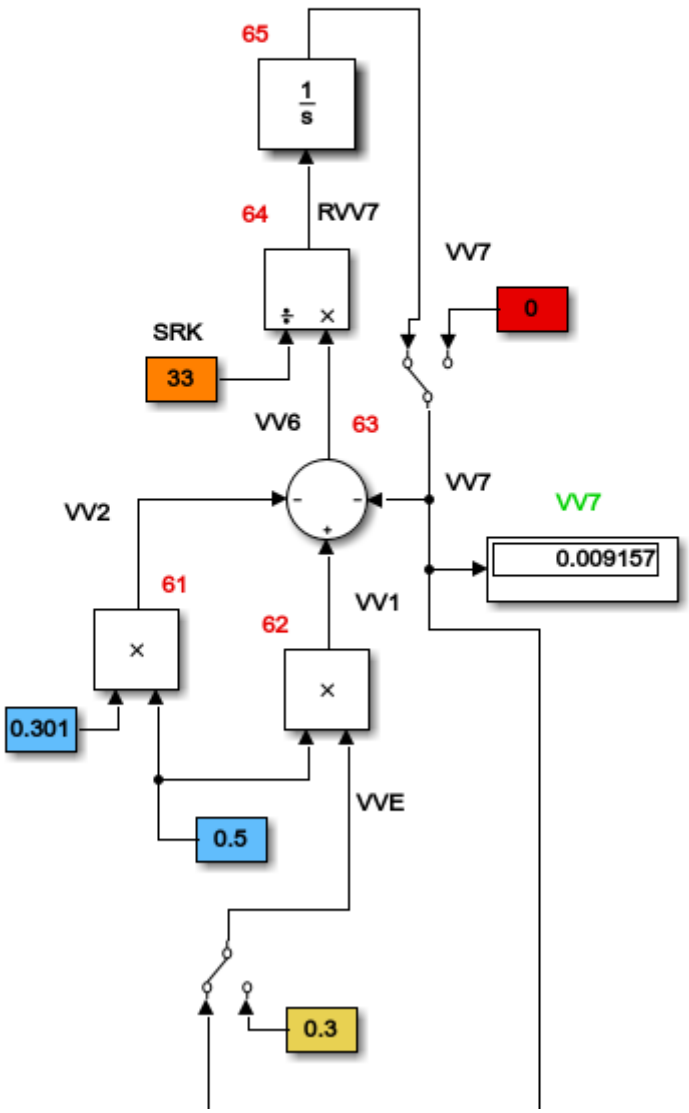


Diagram 2b. Vascular stress relaxation in Simulink

Blocks 61 through 65 calculate stress relaxation of the systemic veins. The amount of stress relaxation in these veins is set to be somewhat higher than the normal stress relaxation of the venous system to make up for the fact that similar stress relaxation factors are not calculated for other parts of the circulation.

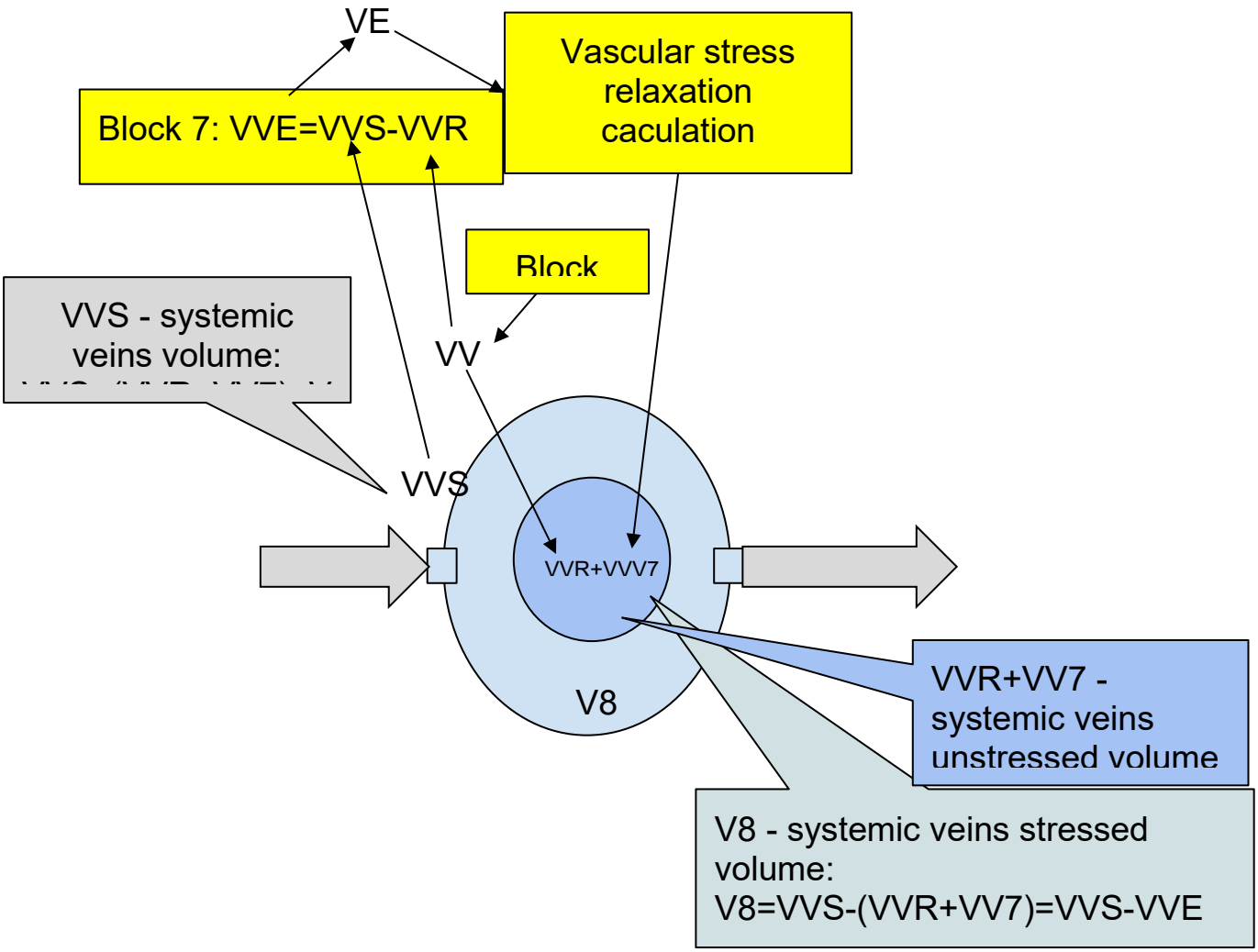


Figure 2.1 Vascular stress relaxation calculated the reflexive changes of systemic vein stressed volume depended on basic systemic stressed volume (VR) and total systemic veins volume (VVS).

Block 61: calculates the reference value (VV2) [l] above or below which stress relaxation occurs. Factor SR [unitless coefficient] represents the intensity of stress relaxation, which is an adjustable value [constant 0,301 is in l]:

$$SR = 0.5$$
$$VV2 = SR * 0.301$$

Block 62: calculates the factor VV [l] which is the portion of the stressed systemic venous volume (VVE) [l] (calculated in block 7) that is causing stress relaxation. Factor SR represents the intensity of stress relaxation, which is an adjustable value:

$$VV1 = SR * VVE$$

Block 63: sums excess volume (VV1) [l], reference volume (VV2) [l], and stress relaxation volume (VV7) [l] to determine whether or not the output of this block (VV6) has reached a steady-state of zero:

$$VV6 = VV1 - VV2 - VV7$$

Block 64: calculates the rate of progression of stress relaxation RVV7 [l/min]. Factor SRK = 33. [min] sets the time constant for this rate:

$$RVV7 = VV6 * SRK$$

Block 65: integrates the rate of progression of the stress relaxation to give the actual degree of stress relaxation (VV7) which is subtracted from the excess venous volume (VVE) in Block 8 to give the excess venous volume that causes elastic stretch of the veins (VV8):

$$dVV7/dt = RVV7, VV7_{t=0} = 0$$

3 Capillary membrane dynamics

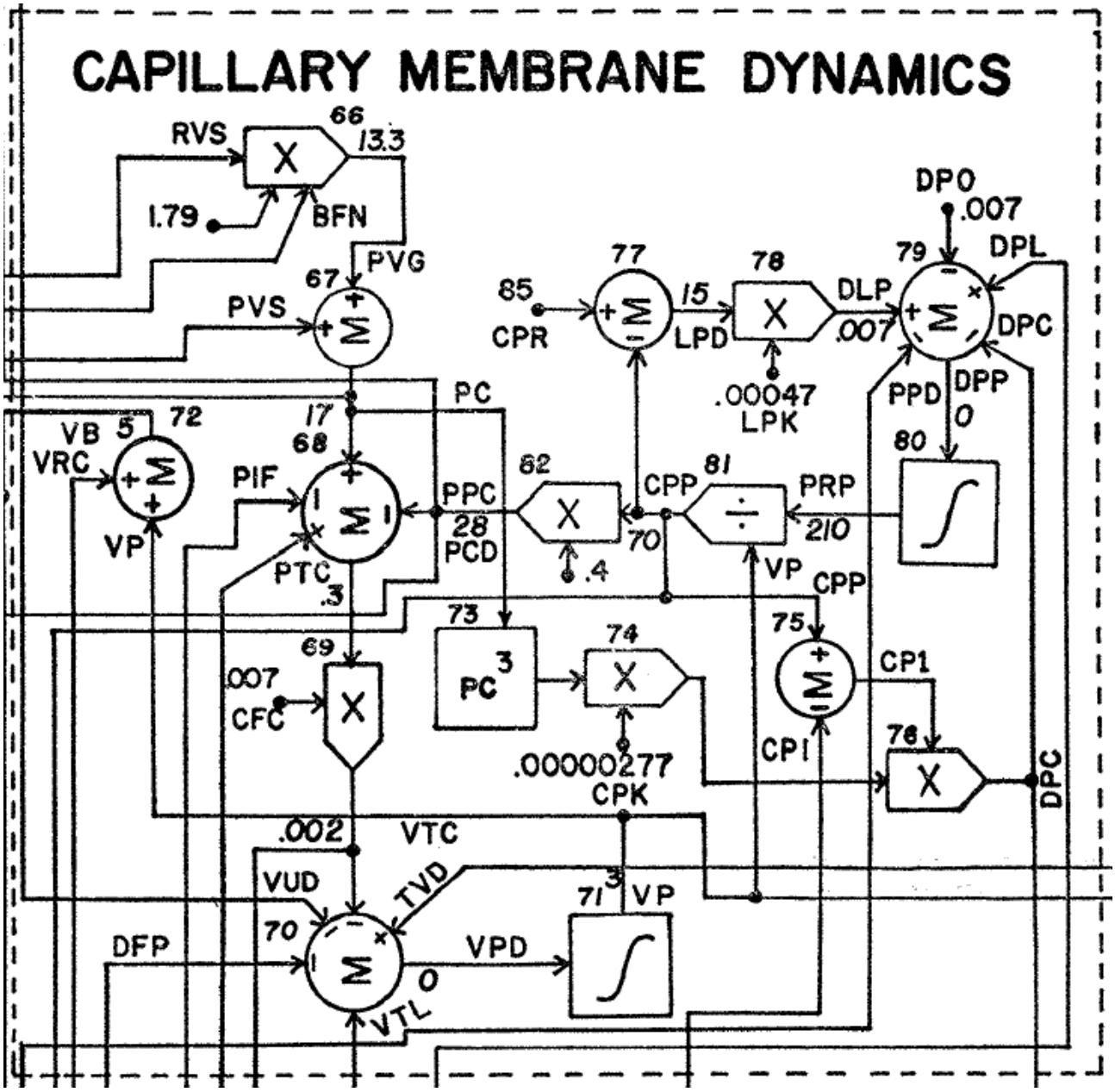


Diagram 3a. Capillary membrane dynamics in Guyton's diagram

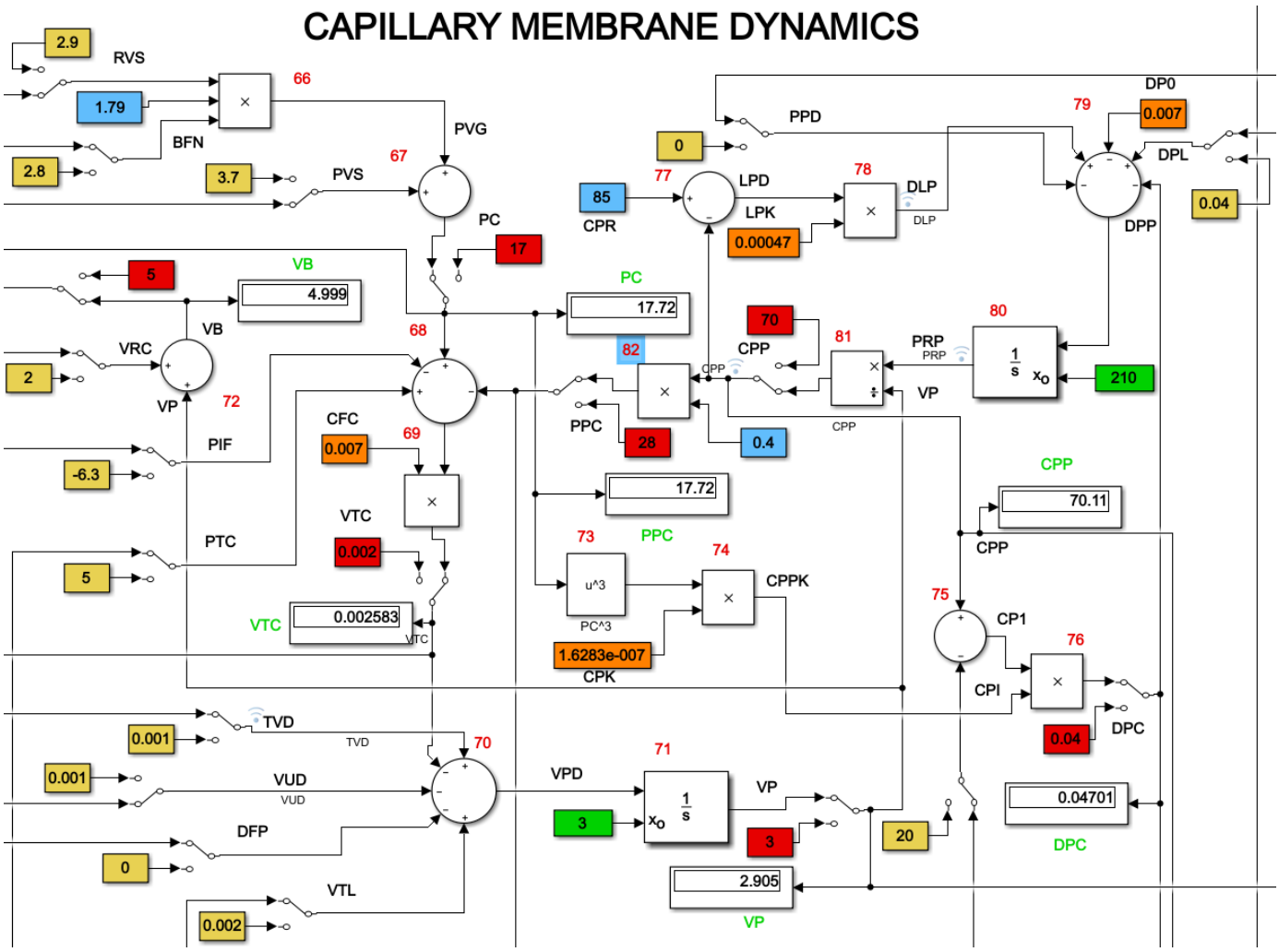


Diagram 2b. Capillary membrane dynamics in Simulink

Block 66: calculates pressure gradient from the midpoint of the capillaries to the veins (PVG) [mmHg] by multiplying resistance of the veins (RUS) [mmHg min/l] times the blood flow through the non-renal, non-muscular portions of the circulation (BFN) [l/min] and times a constant of 1.79 to account for blood flow through the other portions of the circulation:

$$PVG = RVS * 1.79 * BFN$$

Block 67: calculates capillary pressure (CP) [mmHg] by adding the pressure gradient from the capillaries to the veins (PVG) [mmHg] to the pressure that is in the veins (PVS) [mmHg]:

$$PC = PVG + PVS$$

Block 68: calculates the net pressure difference across the capillary membrane (PCD) [mmHg] to cause movement of fluid molecules through the capillary pores by adding capil-lary pressure (CP) plus tissue colloid osmotic pressure (PTC) [mmHg] and subtracting interstitial fluid pressure (PIF) [mmHg]and plasma colloid osmotic pressure (PPC) [mmHg]:

$$PCD = PC + PTC - PPC - PIF$$

Block 69: calculates rate of fluid movement through the capillary membrane (VTC) [l/min] by multiplying pressure gradient across the capillary membrane (PCD) [mmHg] times the capillary filtration coefficient (CFC) [l/min/mmHg]:

$$CFC = 0.007$$
$$VTC = CFC * PCD$$

Block 70: calculates rate of change of plasma volume (VPD) [l/min] by subtracting rate of movement of fluid through the capillaries (VTC) [l/min], subtracting urinary output (VUD) [l/min], subtracting rate of fluid loss from the plasma through the pulmonary capillary membranes into the pulmonary spaces (DFP) [l/min], and adding fluid intake by drinking (TVD) [l/min], and adding fluid return to the circulation by way of the lymphatics (VTL) [l/min]. Output of Block 70 is the rate of change of plasma volume (VPD) [l/min]. (Note that VTL is added, which is not shown in the diagram.):

$$VPD = TVD + VTL - VTC - VUD - DFP$$

Block 71: integrates rate of change of the plasma volume (VPD) [l/min] to give actual plasma volume (VP) [l] at a given time:

$$dVP/dt = VPD, VP_{t=0} = 3$$

Block 72: calculates blood volume (VB) [l] by adding plasma volume (VP) [l] plus red cell volume (VRC) [l]:

$$VB = VP + VRC$$

Block 73 and 74: calculate permeability of the capillaries to proteins (CPPK) [l/min], considering that this permeability increases with the cube of the capillary pressure (PC), (stretched pore phenomenon) and that its degree is set by constant CPK [l/mmHg^3/min]. Note - the value of the

coefficient CPK=0.00000277 shown in diagram is inconsistent with the other normal steady state values shown in the diagram (PC=17, CPP = 70, CPI = 20, DPL = 0.04). After correction, the value is of this coefficient CPK is 0.00000016283:

$$CPK = 1.6283 * 10^{-7}$$
$$CPPK = PC^3 * CPK$$

Block 75: calculates concentration between protein in plasma (CPP) [g/l] and protein in interstitial fluid (CPI) [g/l] to give the difference (CP1) [g/l]:

$$CP1 = CPP - CPI$$

Block 76: calculates the rate of protein movement through the capillary membrane (DPC) [g/min]:

$$DPC = CPPK * CPI$$

Block 77: calculates the difference (LPD) [g/l] between reference factor (CPR) [g/l] and concentration of plasma proteins (CPP) [g/l], this difference helping to determine the rate at which the liver will produce plasma proteins:

$$CPR = 85$$
$$LPD = CPR - CPP$$

Block 78: Multiplication of the above difference (LPD) [g/l] times adjustable constant (LPK) [l/min] to determine the actual rate at which the liver produces plasma proteins (DLP) [g/min]:

$$LPK = 0.00047$$
$$DLP = LPK * LPD$$

Block 79: Calculates rate of change of plasma proteins in plasma (DPP) [g/min] by summing the following factors: rate of formation of plasma proteins by liver (DLP) [g/min], rate of destruction or loss of plasma proteins in the body (DPO) [g/min], rate of return of proteins to the plasma by the lymphatics (DPL) [g/min], subtraction of rate of loss of proteins through the capillary membrane (DPC) [g/min], and subtraction of rate of loss of plasma proteins through pulmonary capillaries (PPD) [g/min]:

$$DPO = 0.007$$
$$DPP = DLP - DPO + DPL - DPC - PPD$$

Block 80: integrates above rate of change of proteins in the plasma (DPP) [g/min]to give the actual quantity of plasma proteins in the plasma (PRP) [g]:

$$dPRP/dt = DPP, PRP_{t=0} = 210$$

Block 81: divides above quantity (PRP) [g] by plasma volume (VP) [l] to give concentration of proteins in plasma (CPP) [g/l]:

$$CPP = PRP/VP$$

Block 82: calculates plasma colloid osmotic pressure (PPC) [mmHg] by multiplying concentration of plasma proteins (CPP) [g/l] times a constant 0.4 [mmHg l/g]:

$$PPC = 0.4 * CPP$$

4 Tissue fluids, pressures and gel

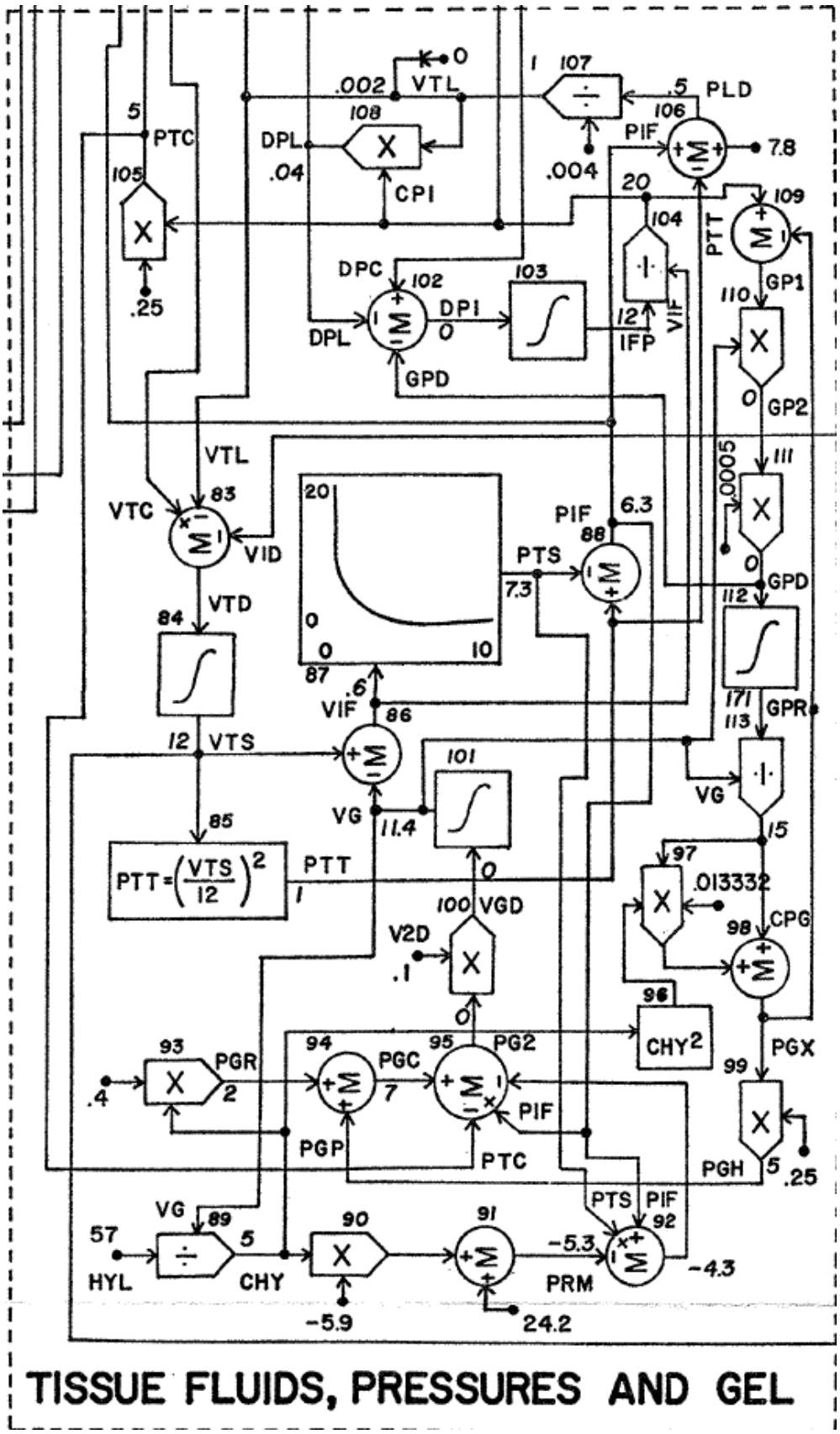


Diagram 4a. Tissue fluids, pressure and gel in Guyton's diagram

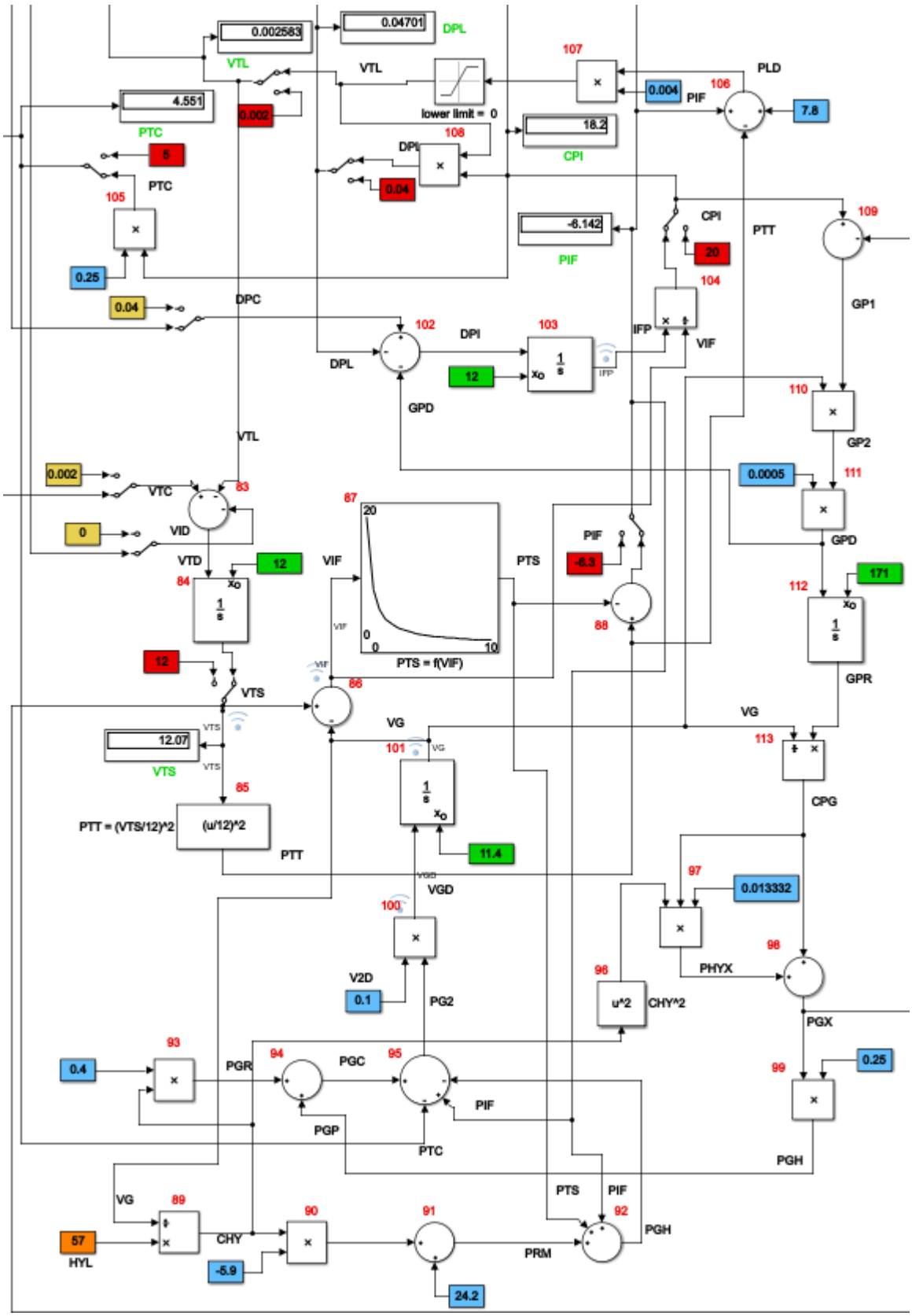


Diagram 4b. Tissue fluids, pressure and gel in Simulink

Block 83: calculates rate of change of fluid in interstitial fluid compartment (VTD) [l/min] by adding rate of movement of fluid into interstitial spaces from capillaries (VTC) [l/min], subtracting rate of loss of fluid from the interstitial fluid compartments by way of lymph flow (VTL) [l/min], and subtracting rate of movement of fluid from interstitial fluid compartment into cells (VID) [l/min]:

$$VTD = VTC - VTL - VID$$

Block 84: Integration of rate of change of fluid volume (VTD) [l/min] in interstitial fluid compartment to give total fluid (VTS) [l] in interstitial compartment:

$$dVTS/dt = VTD,\ VTS\ _{t=0} = 12$$

Block 85: Calculation of total tissue pressure (PTT) [mmHg] from total volume of fluid in the interstitial compartment (VTS) [l]:

$$PTT = (VTS/12.0)^2$$

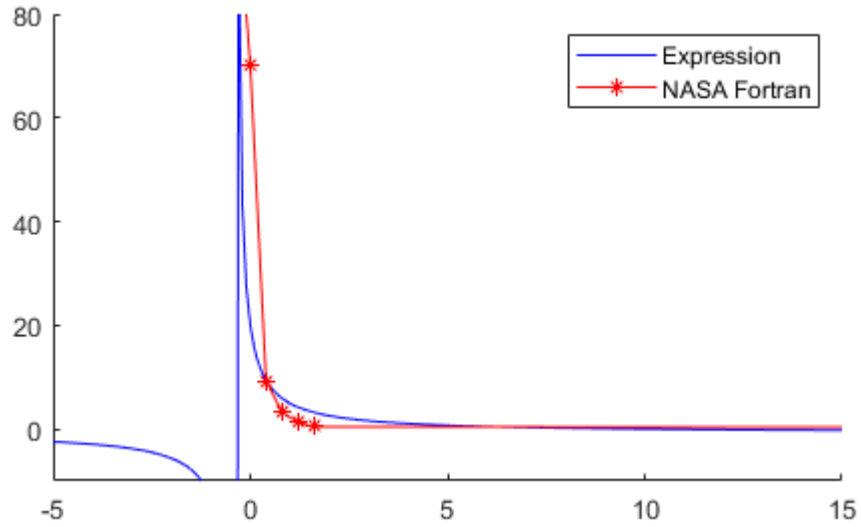
Block 86: Calculation of free fluid in the interstitial spaces (VIF) [l] by subtracting volume of gel fluid (VG) [l] from total interstitial fluid volume (VTS) [l]:

$$VIF = VTS - VG$$

Block 87: Relationship of solid tissue pressure (PTS) [mmHg] to volume of free interstitial fluid (VIF) [l]:

$$PTS = 7.617 * (1 - 0.1 * VIF)/(VIF + 0.3809)$$

NASA fortran uses different relationship, expressed by the FUN6:



Block 88: Calculation of pressure of free interstitial fluid (PIF) [mmHg] by adding total tissue pressure (PTT) [mmHg] and subtracting solid tissue pressure (PTS) [mmHg]. (Note that normal quantitative value of PIF is -6.3, not 6.3 as shown on diagram, notice: -5.98890 in NASA Fortran implementation):

$$PIF = PTT - PTS$$

Block 89: Calculation of concentration of hyaluronic acid in gel of interstitial spaces (CHY) [g/l] by dividing quantity of hyaluronic acid (HYL) [g] by volume of gel (VG) [l]:

$$CHY = HYL/VG$$

Blocks 90 and 91: Calculation of elastic suction of the hyaluronic acid in the tissues caused by elastic recoil of the gel (PRM):

$$PRM = 24.2 - 5.9 * CHY$$

Block 92: Calculation of net mechanical forces (PGH) [mmHg] attempting to cause movement of fluid into gel (if negative) and out of gel (if positive) by summing elastic recoil suction of gel (PRM) [mmHg], solid tissue pressure (PTS) [mmHg] and interstitial fluid pressure (PIF) [mmHg] (note that sign in circle for PRM should be + instead of -):

$$PGH = PIF + PTS + PRM$$

Block 93: Calculation of colloid osmotic pressure of the gel reticulum (PGR) [mmHg] caused by Donnan equilibrium.

$$PGR = 0.4 * CHY$$

Block 94: Calculation of total colloid osmotic pressure of the fluid inside the gel (PGC) [mmHg] by adding that caused by the reticulum itself (PGR) [mmHg] to that caused by the protein in the gel (PGP) [mmHg].

$$PGC = PGP + PGR$$

Block 95: Calculation of net pressure difference at the surface of the gel (PG2) [mmHg] to cause fluid movement into gel by summing the following pressures: adding total colloid osmotic fluid in the gel (PGC) [mmHg], adding pressure of the interstitial fluids (PIF) [mmHg], and subtracting colloid osmotic pressure of the free fluid of the interstitial spaces (PTC) [mmHg], and subtracting the net mechanical uction of the gel (PGH) [mmHg] calculated from Block 92:

$$PG2 = PIF + PGC - PTC - PGH$$

Blocks 96 and 97: calculate the effect of concentration of hyaluronic acid (CHY) [g/l] in gel to exacerbate the colloid osmotic pressure effect of protein in the gel (PHYX) which is the output of Block 97:

$$PHYX = CHY^2 * 0.01332 * CPG$$

Block 98: Calculation of an activity factor for protein (PGX) in inter-stitial fluid gel by summing the effect of concentration of the protein in the gel (CPG) [g/l] and the exacerbation of the activity caused by hyaluronic acid (PHYX) which is the output of Block 97:

$$PGX = PHYX + CPG$$

Block 99: Calculation of colloid osmotic pressure of the protein in the gel (PGP) [mmHg] calculated by multiplying the activity of the protein in the gel times a constant:

$$PGP = PGX * 0.25$$

Block 100: Calculation of rate of movement of fluid between gel and free interstitial fluid of the interstitial spaces by multiplying net pressure difference at the gel surface (PG2) [mmHg] times the resistance factor V2D [l/min/mmHg](0.02) to give the net rate of movement (VGD) [l/min]:

$$VGD = V2D * PG2$$

Block 101: Integration of net movement of fluid through the gel surface (VGD) [l/min] to give the instantaneous gel volume (VG) [l]:

$$dVG/dt = VGD,\ VG_{t=0} = 11.4$$

Block 102: Calculation of rate of change of protein in free fluid of inter-stitial spaces (DPI) [g/min] by adding rate of movement of protein into interstitial spaces through the capillary membranes (DPC) [g/min], subtracting rate of return of protein to the plasma by way of the lymph (DPL) [g/min], and subtracting rate of movement of protein from free interstitial fluid into interstitial gel fluid (GPD) [g/min]:

$$DPI = DPC - DPL - GDP$$

NOTICE: NASA Fortran version: DPI does not contain GDP, it is subtracked in dIFP/dt equation

Block 103: Integration of rate of increase of protein in free fluid (DPI) [g/min] to give instantaneous quantity of protein in the free fluid of the interstitial spaces (IFP) [g]:

$$dIFP/dt = DPI, IFP_{t=0} = 12$$

Block 104: Calculation of concentration of protein in free interstitial fluid (CPI) [g/l]by dividing quantity of protein (IFP) [g] by volume of free fluid (VIF) [l]:

$$CPI = IFP/VIF$$

Block 105: Calculation of colloid osmotic pressure of free interstitial fluid (PTC) [mmHg] by multiplying concentration of protein (CPI) [g/l] times a constant factor (this constant factor is set at a lower value than that for calculation of colloid osmotic pressure in plasma because of the non-linear relationship between protein concentration and colloid osmotic pressure):

$$PTC = 0.25 * CPI$$

Block 106: Calculation of the driving pressure for moving fluid into the lymphatics (PLD) [mmHg] by adding free interstitial fluid pressure (PIF) [mmHg], subtracting total tissue pressure (PTT) [mmHg], and adding a constant factor (the constant factor is a factor for lymphatic pumping; the total tissue pressure is considered to oppose lymph flow because of compression of the lymphatics, and the interstitial fluid pressure is considered to promote lymph flow):

$$PLD = PIF - PTT + 7.8$$

Block 107: Calculation of rate of lymph flow (VTL) [l/min] (but not to fall below zero as determined by the rectifier in the circuit at this point), determined by driving pressure for lymphatic flow (PLD) [mmHg] divided by resistance to lymph flow (0.004 mmHg min/l) which is set as a constant:

$$if\ PLD < 0\ then\ VTL = 0\ else\ VLT = PLD/0.004$$

Block 108: Calculation of rate of return of protein from interstitial spaces to the plasma (DPL) [g/min] by multiplying rate of lymph flow (VTL) [l/min] times con-centration of protein in free interstitial fluid (CPI) [g/min]:

$$DPL = CPI * VTL$$

Block 109: Calculation of protein difference between interstitial fluid (CPI) [g/l] and gel protein activity (PGX) to give protein activity factor for movement of protein into gel (GP1):

$$GP1 = CPI - PGX$$

Block 110: Calculation of corrected protein activity difference between free fluid and gel (GP2) corrected on the basis of volume of gel (VG) [l]:

$$GP2 = GP1 * VG$$

Block 111: Calculation of rate of protein movement into gel (GPD) [g/min] by multiplying activity difference between free fluid and gel (GP2) times a constant:

$$GPD = 0.0005 * GP2$$

Block 112: Integration of rate of movement of protein into gel (GPD) [g/min] to give quantity of protein in gel (GPR) [g]:

$$dGPR/dt = GPD, GPR_{t=0} = 171$$

Block 113: Division of quantity of protein in gel (GPR) [g] by volume of gel (VG) [l] to give concentration of protein in gel (CPG) [g/l]:

$$CPG = GPR/VG$$

5 Electrolytes and cell water

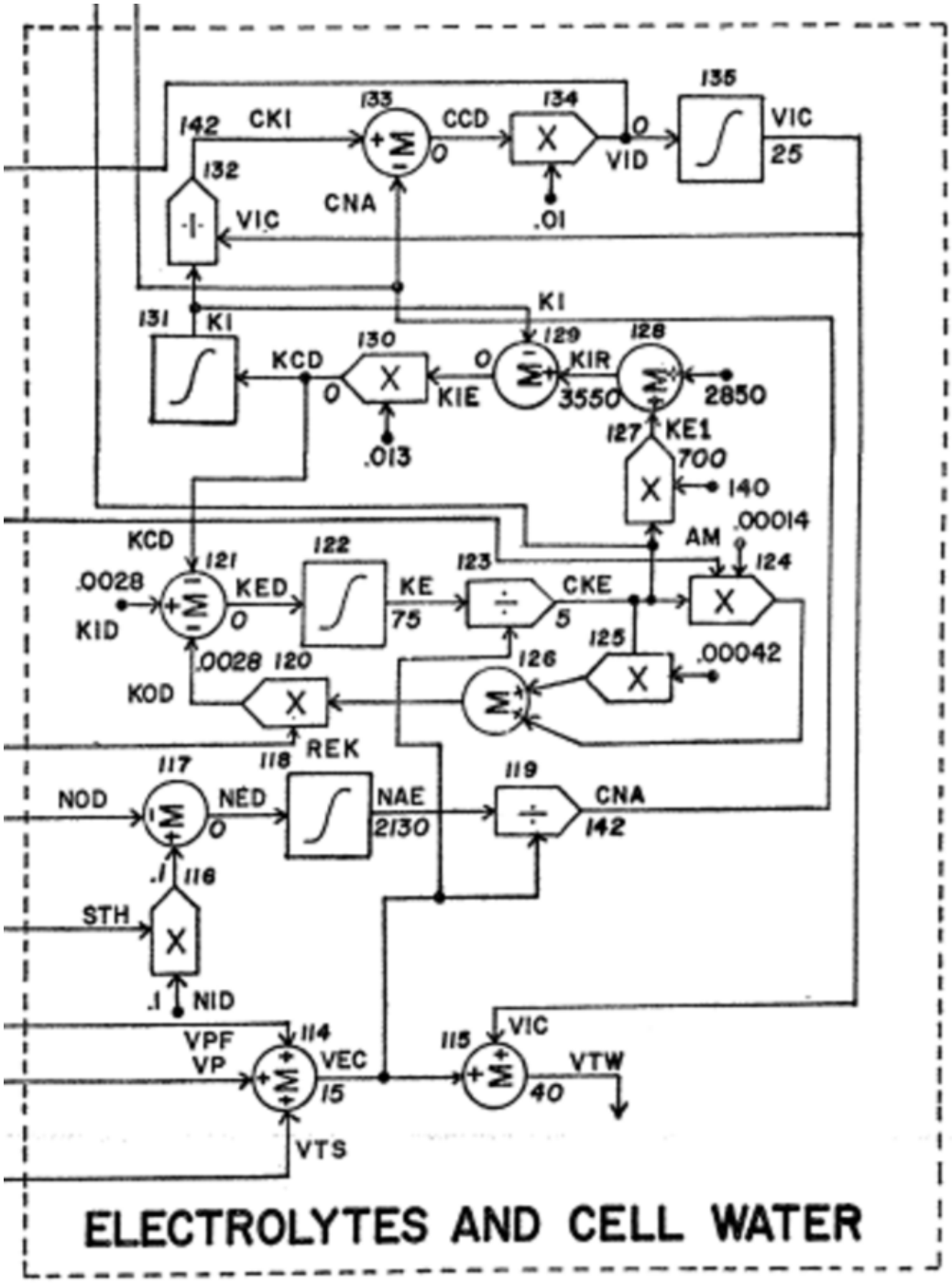


Diagram 5a Electrolytes and cell water in Guyton's diagram

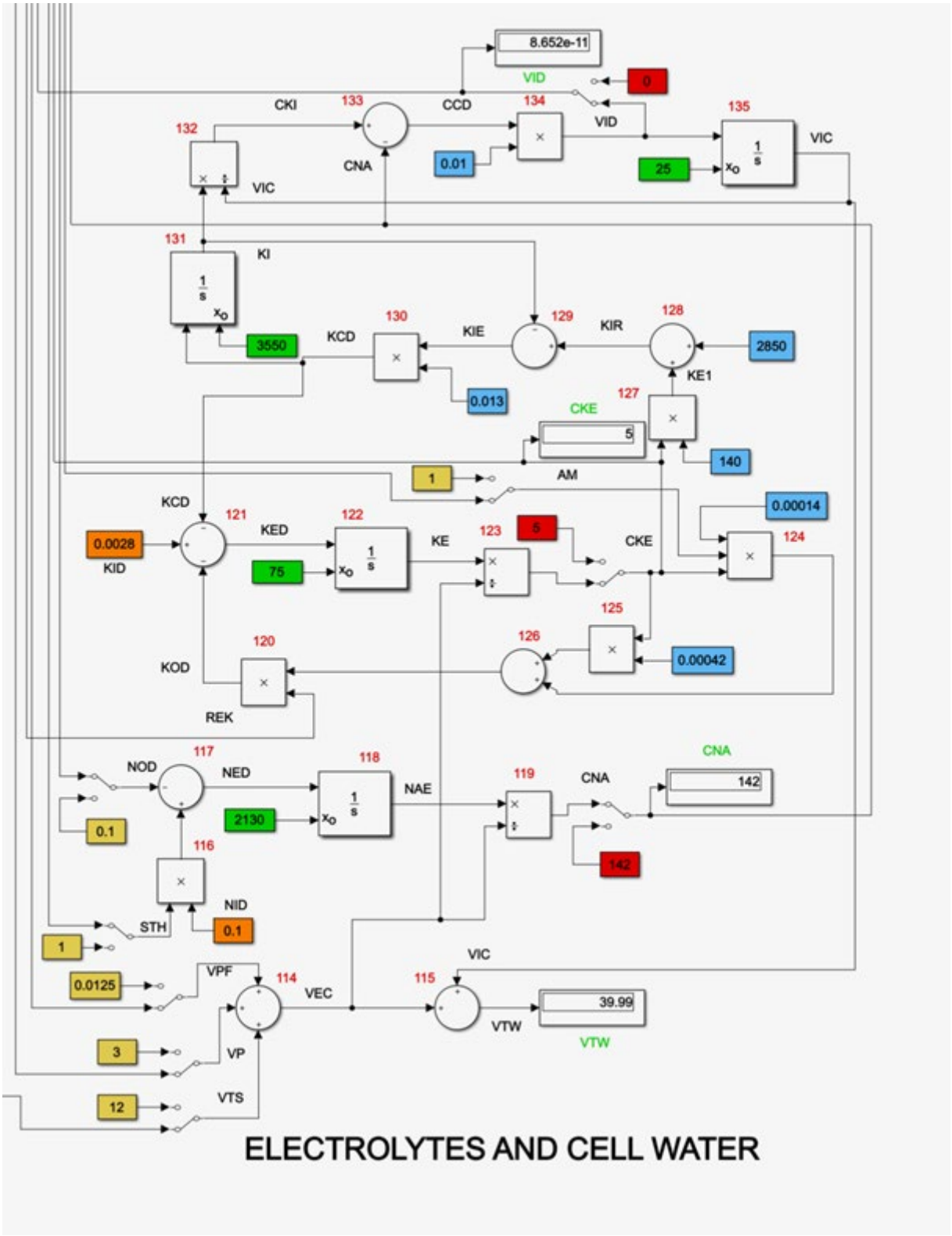


Diagram 5b Electrolytes and cell water in Simulink

Block 114: Volume of extracellular fluid (VEC) expressed in litres is the sum of interstitial fluid volume (VTS), plasma volume (VP) and pulmonary free fluid volume (VPF):

$$VEC = VTS + VP + VPF \quad \text{(EL1)}$$

Block 115: Total body water volume (VTW) is the sum of intracellular (VIC) and extracellular fluid (VEC):

$$\boldsymbol{VTW = VIC + VEC}$$

Block 116: Rate of input of sodium intake in organism (NAINT) expressed in mmol/min is the basal rate of sodium intake - NID (by gastrointestinal tract in mmol/min - as input of the model) times factor of appetite for salt intake and thirst (expressed as ratio to normal, normal value is 1) - STH - this factor is calculated in the "Thirst and drinking blocks" and are increased in hypoxia in non-muscle tissues (STH limited from 1 to 8):

$$NAINT = NID * STH$$

Block 117: The change rate in the amount of sodium ions in the extracellular fluid (NED), expressed in mmol / min, is equal to the difference between rate of sodium intake NAINT and rate of sodium excretion (NOD):

$$NED = NAINT - NOD$$

Block 118: By integrating the rate of this change (NED), we obtain sodium storage (in mmol) in extracellular fluid (NAE), initial value of NAE is 2130 mmol :

$$NAE = \int_0^t NED\ dt, \qquad NAE_{t=0} = 2130$$

or in differential equation form: $dNAE/dt = NED, NAE_{t=0} = 2130$

Block 119: Concentrations of sodium ions (expressed in mmol/l) in the extracellular fluid (as well as in plasma - it is assumed that the concentration of Na^+ in systemic and pulmonary interstitium and in the plasma are equal) - (CNA), we obtain from sodium storage in extracellular fluid (NAE) divided by volume of extracellular fluid (VEC):

$$CAN = NAE/VEC$$

Block 120: Renal loss of potassium (KOD), expressed in mmol/min, is calculated from excretion of potassium from intact kidney (KOD_N) times percent of normal renal function (REK, expressed as ratio to normal). Excretion of potassium from normal kidney (KOD_N) is the output from block 126:

$$KOD = KOD_N * REK$$

Block 121: The rate of change of extracellular potassium ions (KED), expressed in mmol / min, is equal to the potassium ion intake rate (KID) - Guyton shows normal values of 0.0028 mmol/min, minus the potassium transfer rate from extracellular to intracellular fluid (KCD) minus the rate of urinary potassium excretion (KOD):

$$NED = KID - KCD - KOD$$

Block 122: By integrating rate change of extracellular potassium, we obtain total K^+ potassium storage in the extracellular fluid (KE), expressed in mmol (initial value is 75 mmol):

$$KE = \int_0^t KED\ dt, KE_{t=0} = 75$$

or in differential equation form: $\frac{dKE}{dt} = KED, KE_{t=0} = 75$

Block 123: Dividing the extracellular potassium content (KE) by extracellular volume (VEC) we obtain concentration of potassium in extracellular fluid (CKE) (expressed in mmol/l):

$$CKE = KE/VEC$$

Block 124: Calculation of aldosterone controlled portion of potassium excretion rate (KOD_{ALD}) by multiplying concentration of potassium in extracellular fluids (CKE) times aldosterone multiplier factor (AM), expressed as ratio to normal effect, and times a constant factor (KOD_{ALD} is expressed in mmol/min):

$$KOD_{ALD} = CKE * AM * 0.00014$$

Block 125: Calculation of non-aldosterone controlled portion of potassium excretion rate in mmol/nin (KOD_{NOALD}) by multiplying concentration of potassium in extracellular fluid (CKE) times a constant factor :

$$KOD_{NOALD} = CKE * 0.00042$$

Block 126: Addition of aldosterone dependent potassium excretion (KOD_{ALD}) plus non--aldosterone dependent excretion of potassium (KOD_{NONALD}) to give total excretion of potassium for the normal kidney (KOD_N) in mmol/min:

$$\boldsymbol{KOD_N = KOD_{ALD} + KOD_{NOALD}}$$

Block 127: Multiplication of concentration of potassium in extracellular fluid (CKE) times a constant factor to give the quantity of potassium inside the intracellular fluid (expressed in mmol) that is dependent upon extracellular potassium concentration (KE1):

$$KE1 = CKE * 140$$

Block 128: Addition of potassium in intracellular fluid that is dependent upon extracellular potassium concentration (KE1) plus constant value for potassium in cells that is not dependent upon extracellular potassium concentration to give the total expected quantity of potassium in the intracellular fluid (expressed in mmol) under equilibrium conditions (KIR):

$$KIR = KE1 + 2850$$

Block 129: Difference between expected equilibrium level of potassium content (in mmol) in the intracellular fluid (KIR) and actual level of potassium in intracellular fluid (KI) (in mmol) to give potassium gradient that causes potassium movement into the cells (KIE):

$$KIE = KIR - KI$$

Block 130: Calculation of rate of movement of potassium through cell membranes (KCD), expressed in mmol/min, by multiplying difference between expected and actual (KIE) potassium contents in intracellular fluid times a constant for potassium diffusion:

$$KCD = KIE * 0.013$$

Block 131: Integration of rate of movement of potassium into the intracellular fluid (KCD) in mmol/min to give actual quantity of potassium in the intracellular fluids (KI) in mmol. Initial value is 3550 mmol:

$$KI = \int_0^t KCD\ dt, KI_{t=0} = 3550$$

or in differential equation form: $\frac{dKI}{dt} = KCD, KI_{t=0} = 25$

Block 132: Division of actual quantity of potassium in intracellular fluids (KI) in mmol by volume of intracellular fluid (VIC) in liters to give concentration of potassium in intracellular fluids (CKI) in mmol/l:

$$CKI = KI/VIC$$

Block 133: Addition of concentration of potassium inside the intracellular fluids (CKI as an indication of osmolarity inside the cells, and subtraction of concentration of sodium in the extracellular fluids (CNA) as an indication of the osmolarity of the fluids in the extracellular fluids, to give a factor related to the difference between the osmolarities of the two fluids (CCD).

$$CCD = CKI - CNA$$

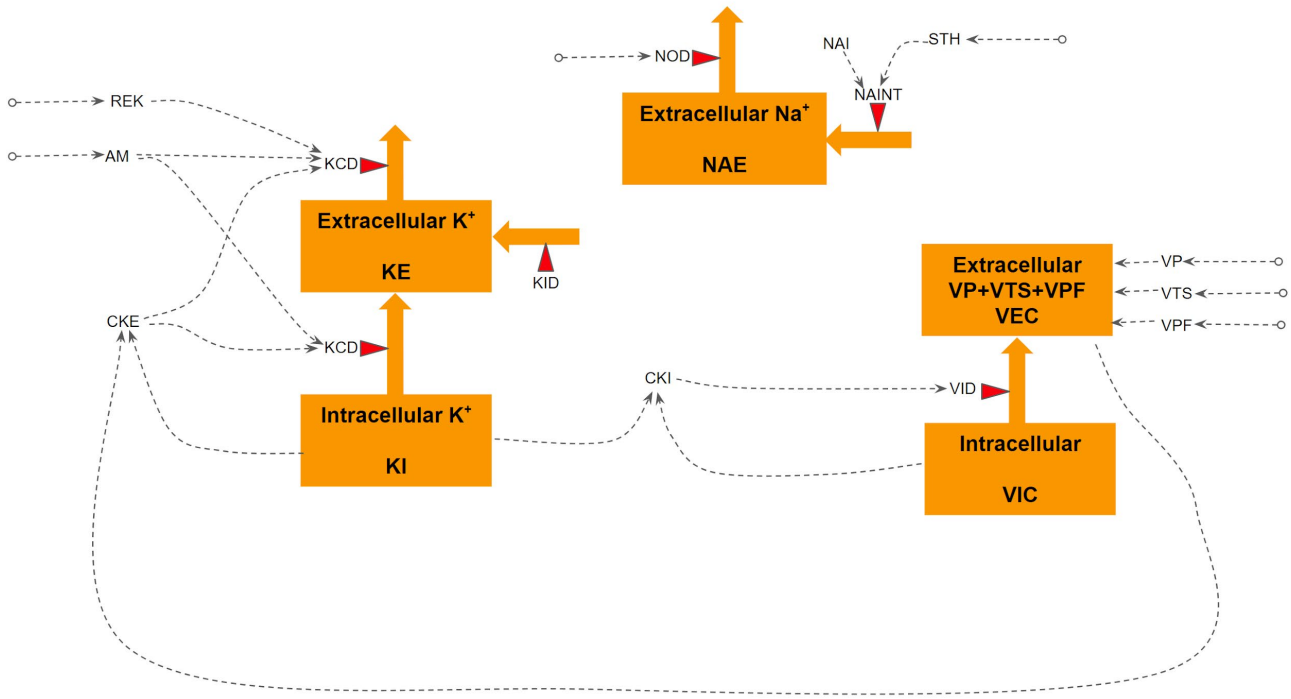
Block 134: Multiplication of osmolarity factor difference between intra-cellular fluids (CCD) times a constant to give the rate of movement of water into cells from the extracellular fluid space (VID) expressed in l/min:

$$VID = CCD * 0.01$$

Block 135: Integration of rate of movement of water into the cells (VID) to give actual volume of water in cells (VIC). Initial volume is 25 l:

$$\boldsymbol{VIC = \int_0^t VID\ dt, VIC_{t=0} = 25}$$

or in differential equation form: $\frac{dVIC}{dt} = VID, VIC_{t=0} = 25$



Physiological scheme of electrolytes and cell water. KE - potassium storage in the extracellular fluid, KI - potassium storage in the intracellular fluid, NAE - sodium storage in the extracellular fluid, VEC - volume of extracellular fluid, VIC - volume of intracellular fluid, PV - plasma volume, VPF - pulmonary free fluid volume, VTS - interstitial fluid volume, REK degree of normality of the kidneys [ratio to normal function], AM - aldosterone multiplier factor ratio to normal function], CKE - extracellular potassium concentration, CKI - intracellular potassium concentration, KCD - renal excretion rate of potassium, KID - potassium ion intake rate, KCD - flow of potassium from cells to extracellular fluid, NOD - renal excretion rate of sodium, NAIT - sodium ion intake rate, NID - basal rate of sodium intake by gastrointestinal tract, STH - factor of appetite for salt intake and thirst [expressed as ratio to normal, normal value is 1]

6 Angiotensin control

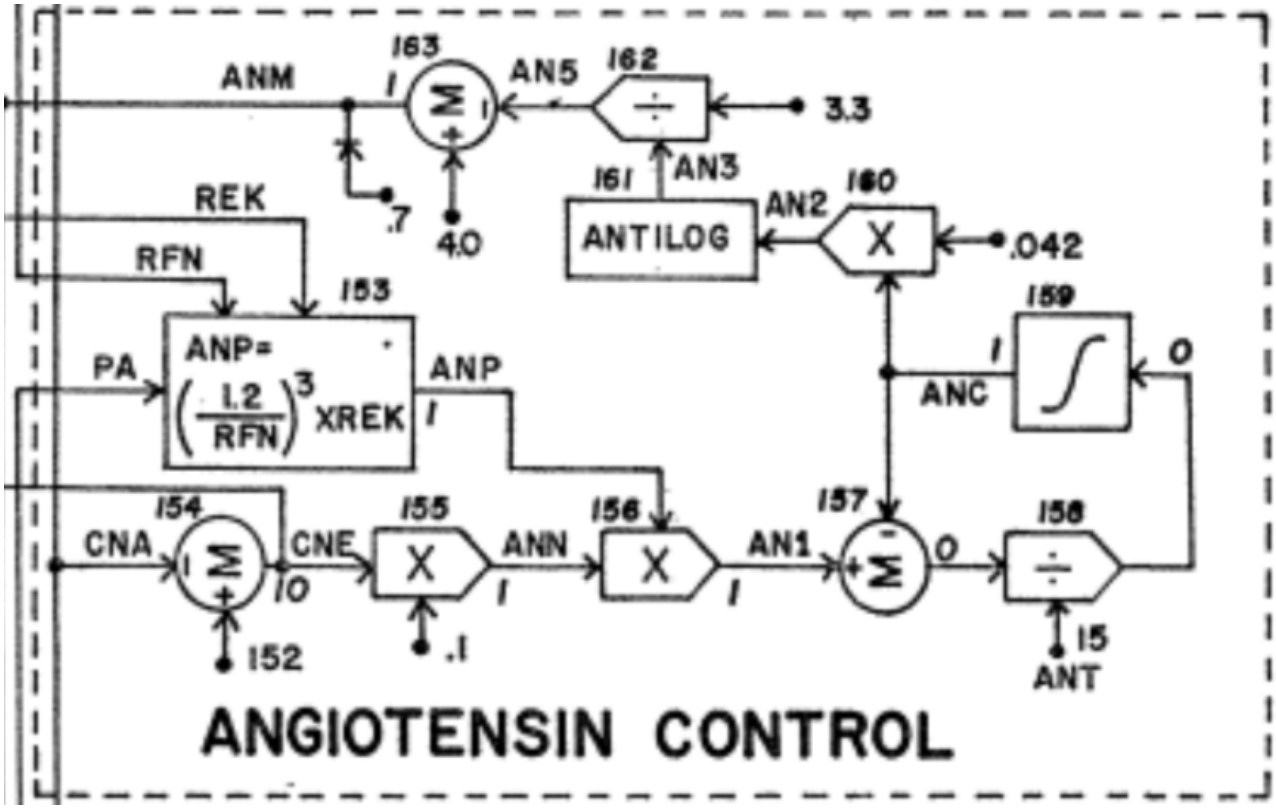
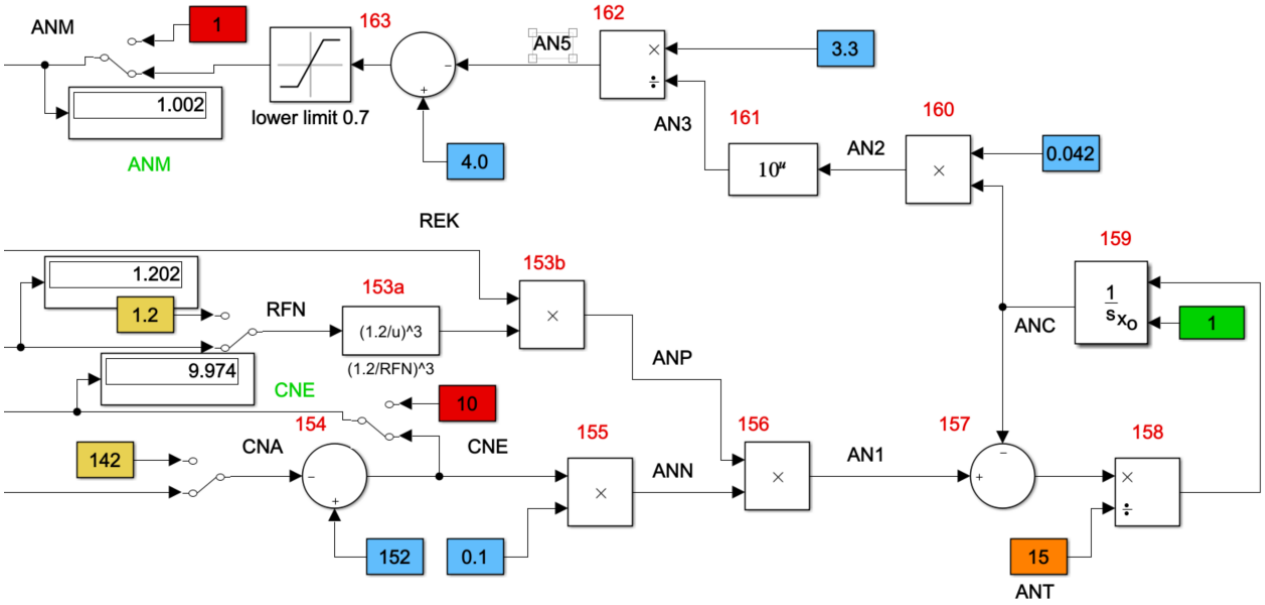


Diagram 6a Angiotensin control in Guyton's diagram



ANGIOTENSIN CONTROL

Diagram 6b Angiotensin control in Simulink

Block 153: Determination of effect of blood flow through normal kidneys (RFN) [in l/min] times the degree of normality of the kidneys (REK) [as a factor ratio to normal] in causing output of renin and subsequent formation of angiotensin (ANP) [ANP is ratio to normal factor]. (Note that input PA in original Guyton's diagram is in error):

$$ANP = (1.2/RFN)^3 * REK$$

However, in NASA implementation (White 1973; Archer 1974) effect of renal blood flow on angiotensin formation (i.e. ANP [ratio to normal factor]) is calculated differently.
At first is calculated the effect of glomerular filtration and sodium concentration on renin formation (GFN [l/min]) with consequent effect on angiotensin formation ANR [ratio to normal factor], corrected to renal functionality using the degree of normality of the kidneys - input parameter REK [as a factor ratio to normal] :

$$AGK = 0.2$$
$$ANR = ((17.75 - GFN * CNA) * AGK + 1.) * REK$$

Then was calculated the partial effect of renin on angiotensin formation ANW [ratio to normal], (ANV =0.0003 min) a integration controller loop (minimal value of ANW is 0.0):

$$ANV = 0.0003$$
$$dANW/dt = ((ANR - 1.) * 10. - ANW) * ANV, ANW_{t=0} = 0.0$$
$$if\ ANW < 0\ then\ ANW = 0$$

Finally, the effect of blood flow on angiotensin formation (ANP [ratio to normal]) is calculated:

$$ANP = ANR + ANW$$

Block 154: Subtraction of concentration of sodium in extracellular fluids (CNA) [mmol/l] from a constant value to give sodium concentration factor for control of angiotensin secretion (CNE) [mmol/l] (CNE is also used in block 222 in Kidney dynamics and excretion module):

$$CNE = 152 - CNA$$

Block 155: Sodium concentration factor for control of angiotensin (CNE) [mmol/l] times a constant scaling factor to give proportionate effect of sodium in the control of secretion of angiotensin (ANN) [ratio to normal factor]:

$$ANN = CNE * 0.1$$

Block 156: Addition of renal blood flow factor (ANP) [ratio to normal factor] and plasma sodium concentration factor (ANN) [ratio to normal factor] in causing angiotensin control to give total factor for angiotensin control (AN1) [ratio to normal factor] (because ANP and ANN are the ratio to normal factors, summation of theirs effect must be calculated as multiplication of these factors):

AN1 = ANN * ANP

Note: Instead blocks 155 and 156 in NASA implementation (White 1973; Archer 1974) is only upper and lower limit of ANP:

$$if\ AN1 > 100\ then\ AN1 = 100$$
$$else\ if\ ANP < 0.01\ then\ AN1 = 0.01$$
$$else\ AN1 = ANP$$

Blocks 157, 158 and 159: These blocks are a circuit to give a time delay in the buildup of the concentration of angiotensin in the circulation. Factor ANT determines the time constant of this time delay [min], and concentration of angiotensin in the fluids is ANC [angiotensin concentration expressed as ratio to normal], initial settings of ANC value is 1:

$$ANT = 15$$
$$ANC = \int_0^t (AN1 - ANC)/ANT\ dt, ANC_{t=0} = 1$$

or in differential equation form: $\frac{dANC}{dt} = (AN1 - ANC)/ANT, ANC_{t=0} = 1$

Blocks 160, 161, 162 and 163: These blocks are a curve fitting mechanism to convert concentration of angiotensin (ANC) [expressed as ratio to normal concentration] to the degree of effect of angiotensin, called the angiotensin multiplier (ANM) [factor - ratio to normal], which is proportional to the antilog of the angiotensin concentration and has limits between two constant values, and which has a lower limit set by the rectifier on the output of Block 163:

Block 160:

$$AN2 = ANC * 0.42$$

Note: in NASA implementation (White 1973; Archer 1974):

$$AN2 = ANC * -0.0967$$

Block 161:

$$AN3 = 10^{AN2}$$

Note: in NASA implementation (White 1973; Archer 1974) exponential function is used:

$$AN3 = e^{AN2}$$

Block 162:

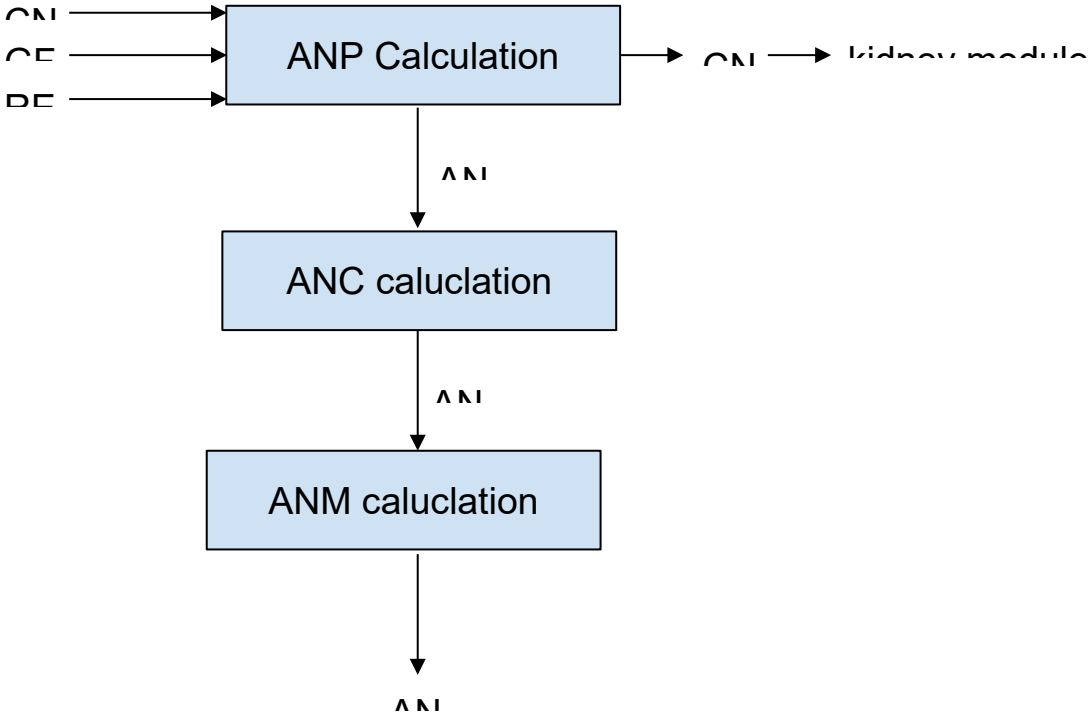
$$AN5 = 3.3/AN3$$

Note: in NASA implementation (White 1973; Archer 1974) instead of division there is multiplication:

$$AN5 = 3.3 * AN3$$

Block 163:

$$ANM0 = (4.0 - AN5)$$
$$if\ (ANM0 > 0.7)\ then\ ANM = ANM0\ else\ ANM = 0.7$$



Physiological scheme of angiotensin effect: degree of normality of the kidneys (REK) [as a factor ratio to normal], GFN - glomerular filtration rate in normal kidney [l/min], CNA - concentration of sodium in extracellular fluid [mmol/l], CNE - sodium concentration factor for control of angiotensin secretion [mmol/l] (CNE is also used in block 222 in Kidney dynamics and excretion module), ANP - effect of blood flow through normal kidneys and the degree of normality of the kidneys in causing output of renin and subsequent formation of angiotensin, ANC - concentration of angiotensin [ratio to normal factor], ANM - the degree of effect of angiotensin [factor - ratio to normal] (non linear, logarithmically depends to concentration of angiotensin).

7 Aldosterone control

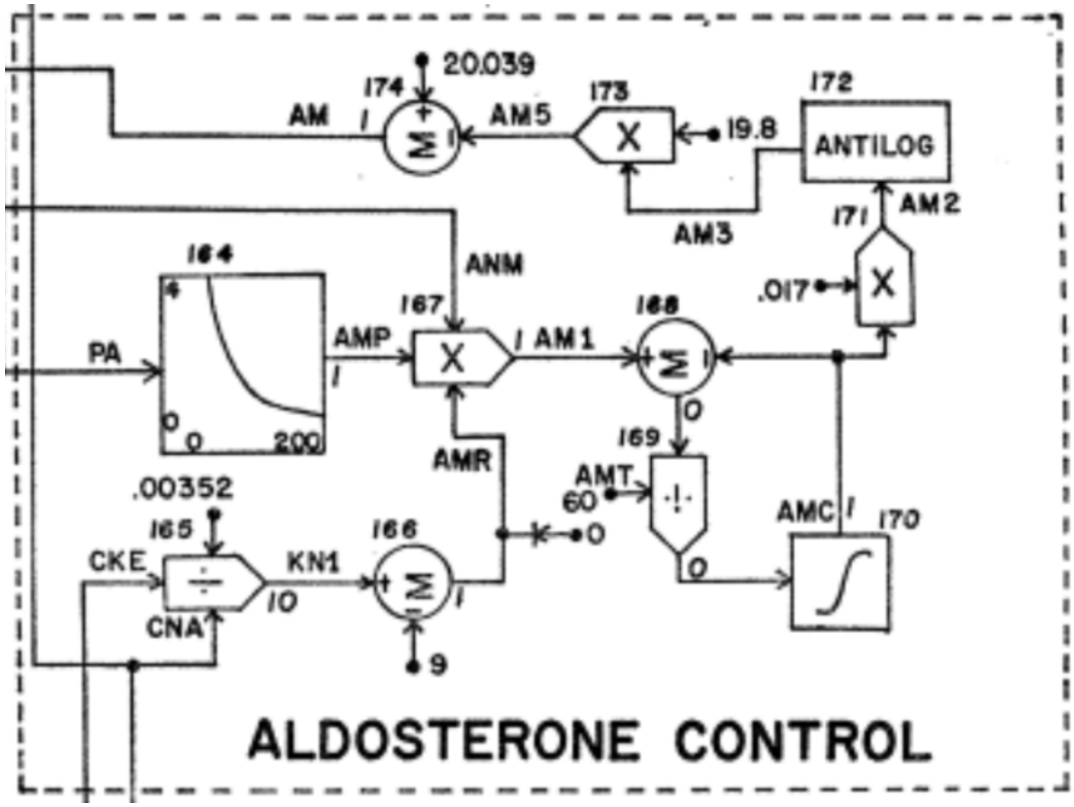


Diagram 7a Aldosterone control in Guyton's diagram

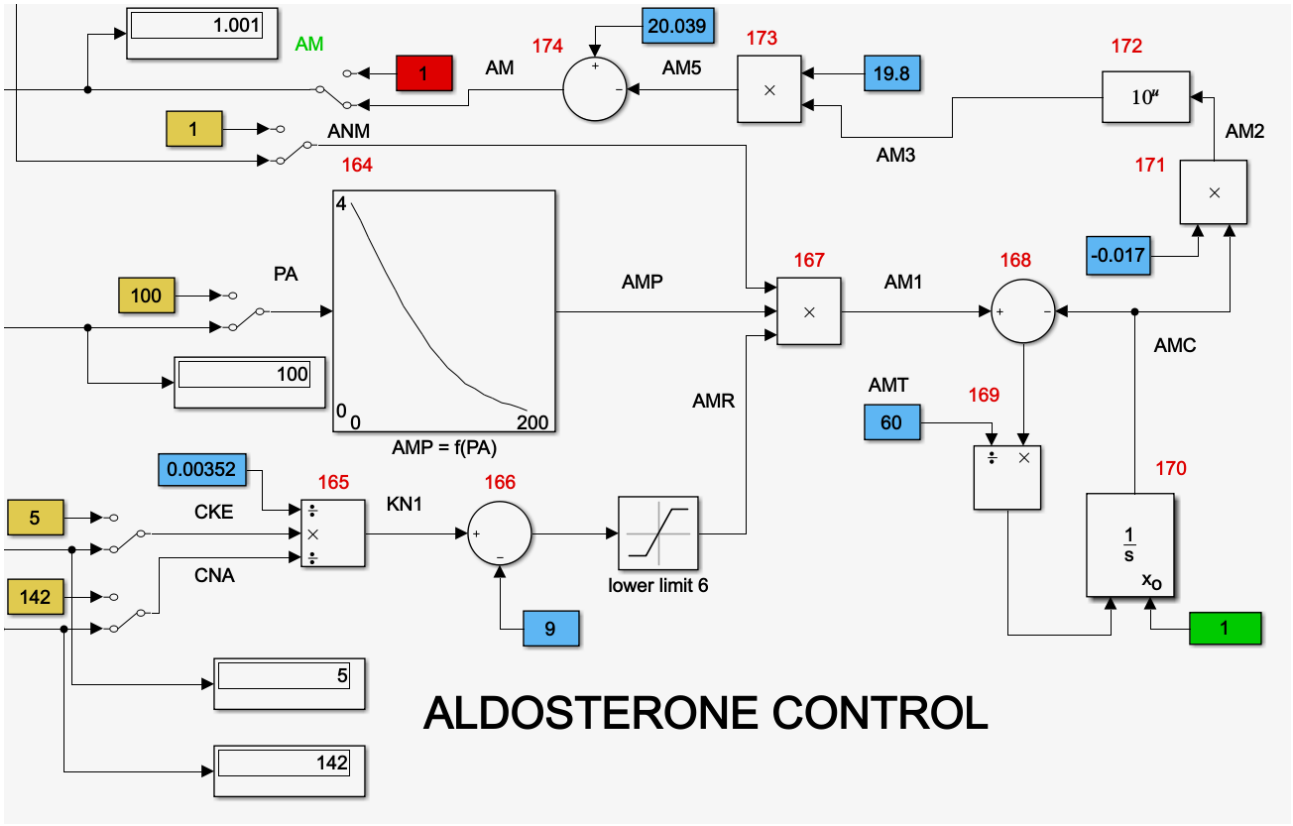
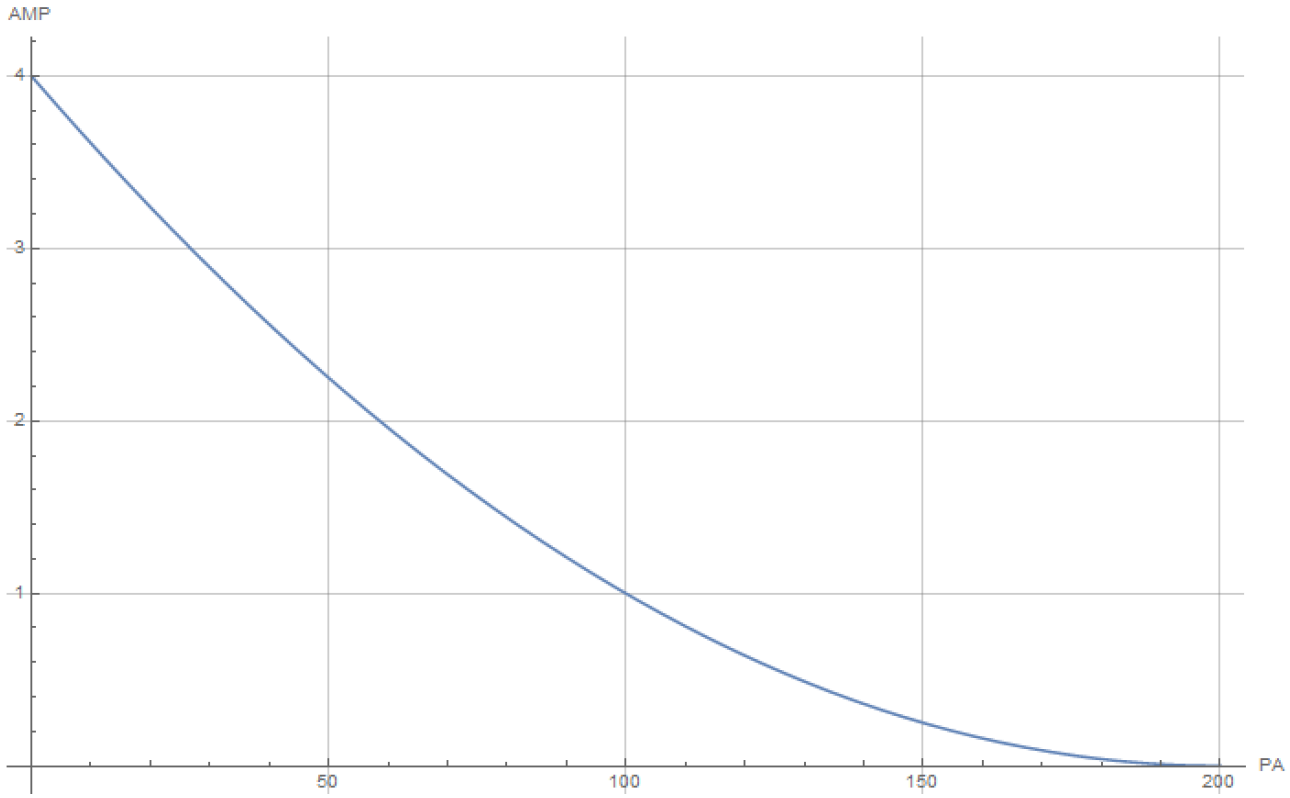


Diagram 7b Aldosterone control in Simulink

Block 164: Function curve to determine partial effect of arterial pressure (PA [mmHg] on aldosterone secretion (AMP) [effect of arterial pressure on rate of aldosterone secretion - ratio to normal] (calculated by spline interpolation):

$$AMP = Interpolation\,(PA), PA = [0, 100, 200], AMP = [4,1,0]$$



Graph of function AMP = Interpolation(PA)

Blocks 165 and 166: Determination of ratio (KN1) [ratio to normal effect] of extracellular fluid potassium concentration (CKE) [mmol/l] to sodium concentration (CNA) [mmol/l] along with curve fitting technique in Block 166 (plus a rectifier in the output of Block 166 to prevent the factor from going below zero) to give the partial effect of this ratio on the control of aldosterone secretion (AMR) [effect of sodium to potassium ratio on aldosterone secretion rate - ratio to normal]:

$$KN1 = CKE/CNA/0.00352$$
$$KN10 = KN1 - 9 if\ (KN1 - 9) > 6\ then\ AMR = KN1 - 9\ else\ AMR = 6$$

Block 167: Calculation of total control effect on aldosterone secretion (AM1) [ratio to normal effect] by multiplying partial effect of potassium to sodium ratio (AMR) [ratio to normal effect], pressure effect (AMP) [ratio to normal effect], and stimulatory effect of angiotensin (ANM) [angiotensin multiplier effect on vascular resistance - ratio to normal]:

$$AM1 = AMR * AMP * AMN$$

Blocks 168, 169 and 170: Delay circuit to specify rate of buildup of aldosterone in interstitial fluids to approach the level set by the aldosterone control (AM1). The time constant for this delay circuit is determined by AMT and the concentration of aldosterone (expressed as ratio of concentration to normal value) is AMC:

$$AMT = 60$$

$$AMC = \int_0^t (AM1 - AMC)/AMT \, dt, AMC_{t=0} = 1$$

or in differential equation form: $\frac{dAMC}{dt} = (AM1 - AMC)/AMT, AMC_{t=0} = 1$

Block 171, 172, 173 and 174: These blocks are curve fitting techniques to translate aldosterone concentration (AMC) into degree of effect of aldosterone expressed as aldosterone multiplier (AM), which is an antilog function of the concentration of aldosterone. (Note that effect of hormone depends on hormone concentration logarithmically):

$$AM2 = -0.017 * AMC$$

$$AM3 = 10^{AM2}$$

$$AM5 = 19{,}8 * AM3$$

$$AM = 20.039 - AM5$$

Notice: In NASA Fortran implementation: AM3 = EXP(-0.0391*AMC)

8 Antidiuretic hormone control

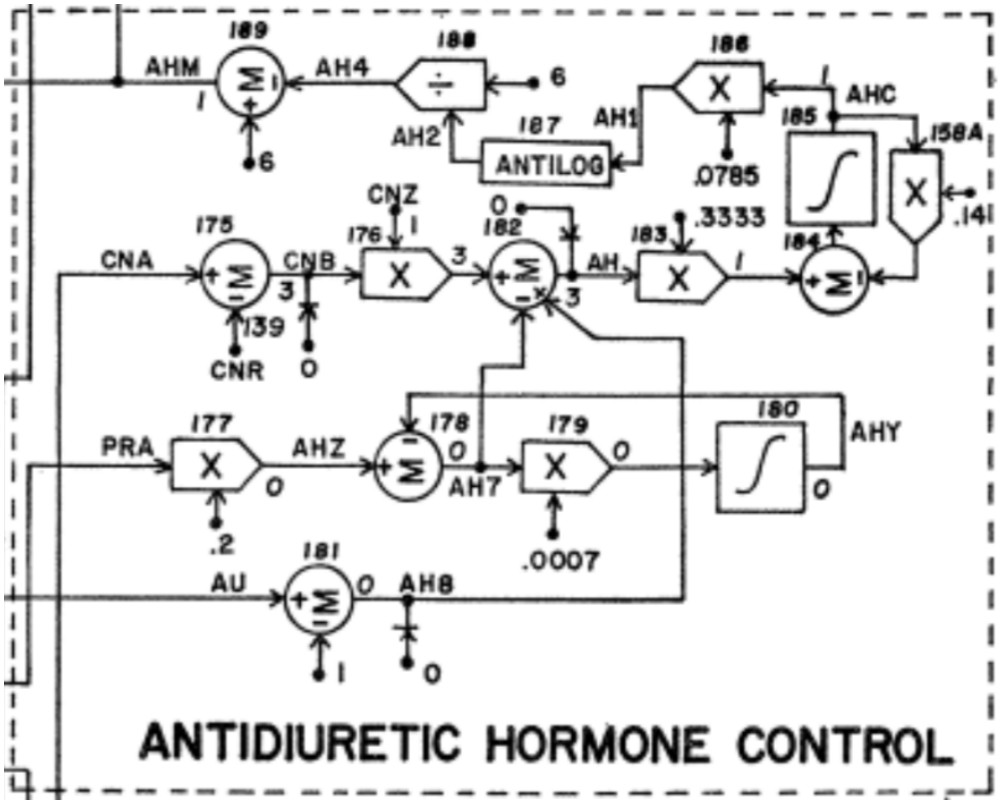
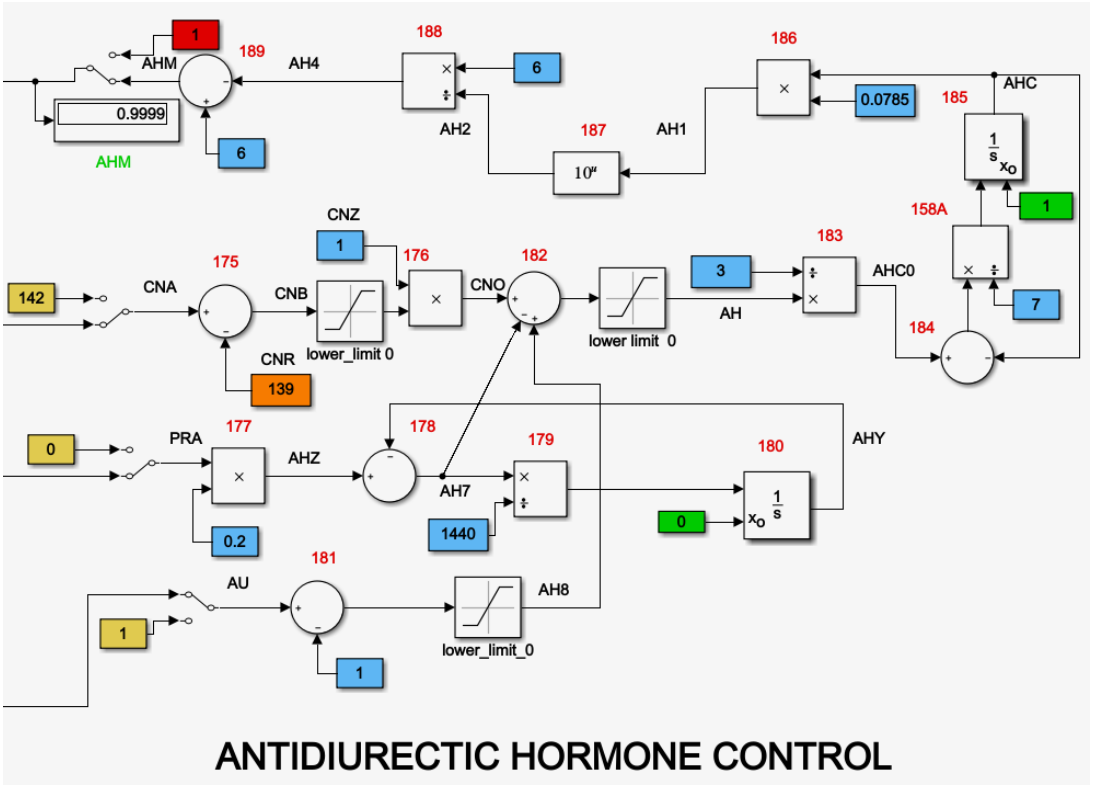


Diagram 8a Antidiuretic hormone control in Guyton's diagram



ANTIDIURECTIC HORMONE CONTROL

Diagram 8b Antidiuretic hormone control in Simulink

Block 175: Concentration of sodium in extracellular fluids as a measure of osmolarity of extracellular fluids (CNA) [mmol/l] minus reference value (CNR) [mmol/l] to determine the effect of extracellular fluid osmolality on antidiuretic hormone secretion (CNB) [ratio to normal], this factor prevented from going below zero by rectifier in output of Block 175:

$$if\ (CNA - 139) > 0\ then\ CNB\ =\ CNA - 139\ else\ CNB = 0$$

Block 176: Multiplication of osmolarity factor (CNB) [dimensionless weight factor] times a sensitivity constant (CNZ) to determine the proportional effect of osmolarity in control of antidiuretic secretion (CNO) [dimensionless weight factor]:

$$CNZ = 1$$
$$CNO\ =\ CNB * CNZ$$

Block 177: Stimulation of volumoreceptors in the right ventricle affects (reduces) the release of antidiuretic hormone. This volumoreceptor stretching is expressed by the variable AHZ [as dimensionless weight factor]. In this model is considered the linear relationship between right ventricular pressure (PRA) [mmHg] and the stretching of volumoreceptors characterised by value of variable AZH [dimensionless factor]

$$AHZ\ =\ PRA\ * 0.2$$

Blocks 178,179 and 180: Effect of stimulation of atrial volumoreceptors on ADH secretion (AH7) is calculated as a deviation of current stretching of volumoreceptors (AHZ) [dimensionless factor] and the value of resting stretching volumoreceptors (AHY) [dimensionless factor], which is a gradually adjusted in prolonged stimulation, with a time constant of 1 day (1440 min).

$$AH7 = AHZ - AY$$
$$\frac{dAHY}{dt} = AH7/1440, AHY_{t=0} = 0$$

(1440 min is time constant, 1/1440 is the same but more precise, than 0.0007 in Guyton's diagram)

Block 181: Autonomic multiplier (AU) - overall activity of autonomic system [ratio to normal] minus a constant to give the effect of autonomic stimulation on rate of antidiuretic hormone secretion (AH8) but this factor is prevented from going below zero by a rectifier in the circuit:

$$if\ AU - 1 > 0\ then\ AH8 = AU - 1\ else\ AH8 = 0$$

Block 182: Summation of the weight factors that cause antidiuretic hormone secretion (the sodium factor) calculated by Block 176, the right atrial pressure factor (AH7), and the autonomic factor (AH8). Output of Block 182 is the equilibrium control value of antidiuretic hormone secretion (AH), and this is prevented from going below zero by a rectifier at this point:

$$if\ CNO - AH7 + AH8 > 0\ then\ AH = CNO - AH7 + AH8\ else\ AH = 0$$

Block 183: Multiplication of equilibrium value of antidiuretic hormone (AH) [dimensionless factor] times a constant to give the normal antidiuretic secretion rate expressed as unity for normal level:

$AHC0\ =\ AH/3$ (it is the same, but more correct than in diagram: $AHC0 = AH * 0.3333$)

Blocks 184, 185 and 158A: These blocks represent a time delay circuit to calculate the rate of buildup of antidiuretic hormone concentration (AHC) [ratio to normal] in the body fluids when the secretion rate is changed to a new value. The constant in Block l58a determines the time constant of buildup (in Guyton's diagram is graphical typo, block 158A is connected incorrectly):

$AHC = \int_0^t \quad (AHC0 - AHC)/7\ dt, AHC_{t=0} = 1$

or in differential equation form: $\frac{dAHC}{dt} = (AHC0 - AHC)/7, AHC_{t=0} = 1$

(7 min is time constant, 1/7 is the same but more precise, than 0.14 in Guyton's diagram)

Block 186, 187, 188 and 189: These blocks represent a curve fitting system to convert antidiuretic hormone concentration' to degree of effect of antidiuretic hormone (AHM) [ratio to normal effect] (antidiuretic hormone multiplier) which is set at unity for normal activity. This value is an antilog function of antidiuretic hormone concentration (AHC) [ratio to normal concentration]. Note that effect of hormone depends on hormone concentration logarithmically:

$$AH1 = AHC * 0.0785$$
$$AH2 = 10^{AH1}$$
$$AHM = 6 - AH2 * 6 = 6 - 10^{AHC*0.785}$$

However in NASA implementation (Archer 1974; White 1973) effect of antidiuretic hormone from antidiuretic concentration is calculated differently:

$$AHM = 6.0 * (1 - e^{-0.1808*AHC})$$

9 Thirst and drinking

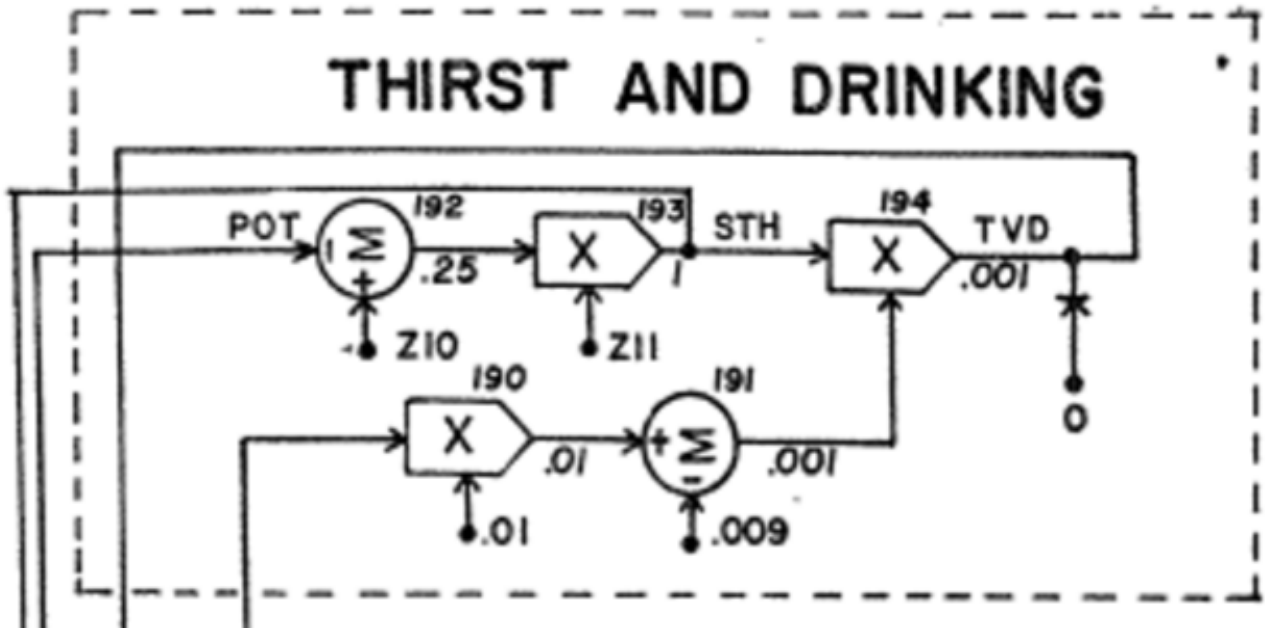


Diagram 9a Thirst and drinking in Guyton's diagram

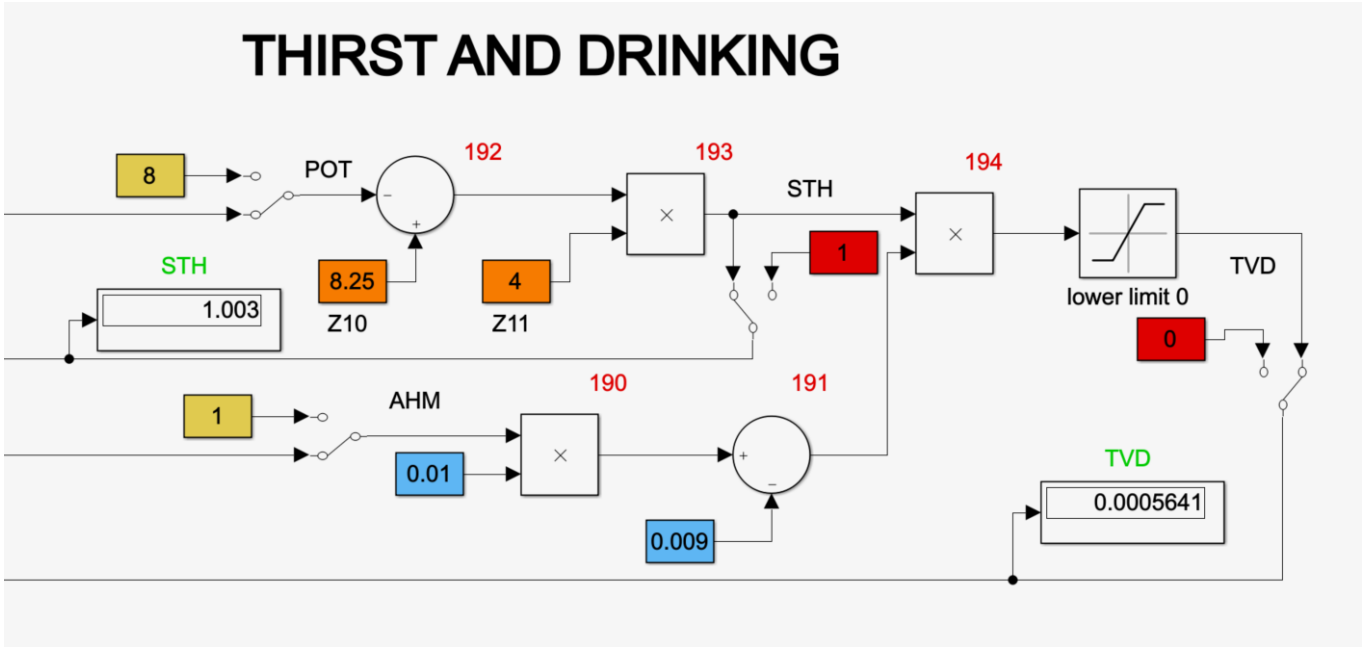


Diagram 9b Thirst and drinking in Simulink

Blocks 190 and 191: Curve fitting mechanism to convert antidiuretic hormone multiplier (AHM) to the drive that occurs simultaneously to elicit thirst (TVD_{AH}) expressed as water drinking rate l/min. (That is, it is considered that the same factors that drive antidiuretic hormone secretion playa similar role in causing thirst, the output of which is the output from Block 191).

$$TVD_{AH} = AHM * 0{,}01 - 0.009$$

Block 192 and 193: Curve fitting mechanism to determine effect of tissue perfusion (expressed in terms of tissue oxygenation (POT) in non muscle tissues, expressed in mmHg) on the mechanism of thirst and on appetite for salt intake (STH), expressed as a ratio to normal. (Note, value for Z10 is 8.25 and for Z11 is 4.0).

$$STH = (Z10 - POT) * Z11 = (8.25 - POT) * 4$$

Block 194: Multiplication of the thirst center drive (TVD_{AH} - output of 191) and the tissue perfusion factor for thirst stimulation (STH) to give the rate of intake of water in l/min (TVD). Factor TVD is prevented from going below zero by the rectifier in the output of Block 194.

$$TVD_0 = STH * TVD_{AH}$$
$$if\ (TVD_0 > 0)\ then\ TVD = TVD_0, else\ TVD = 0$$

10 Kidney dynamics and excretion

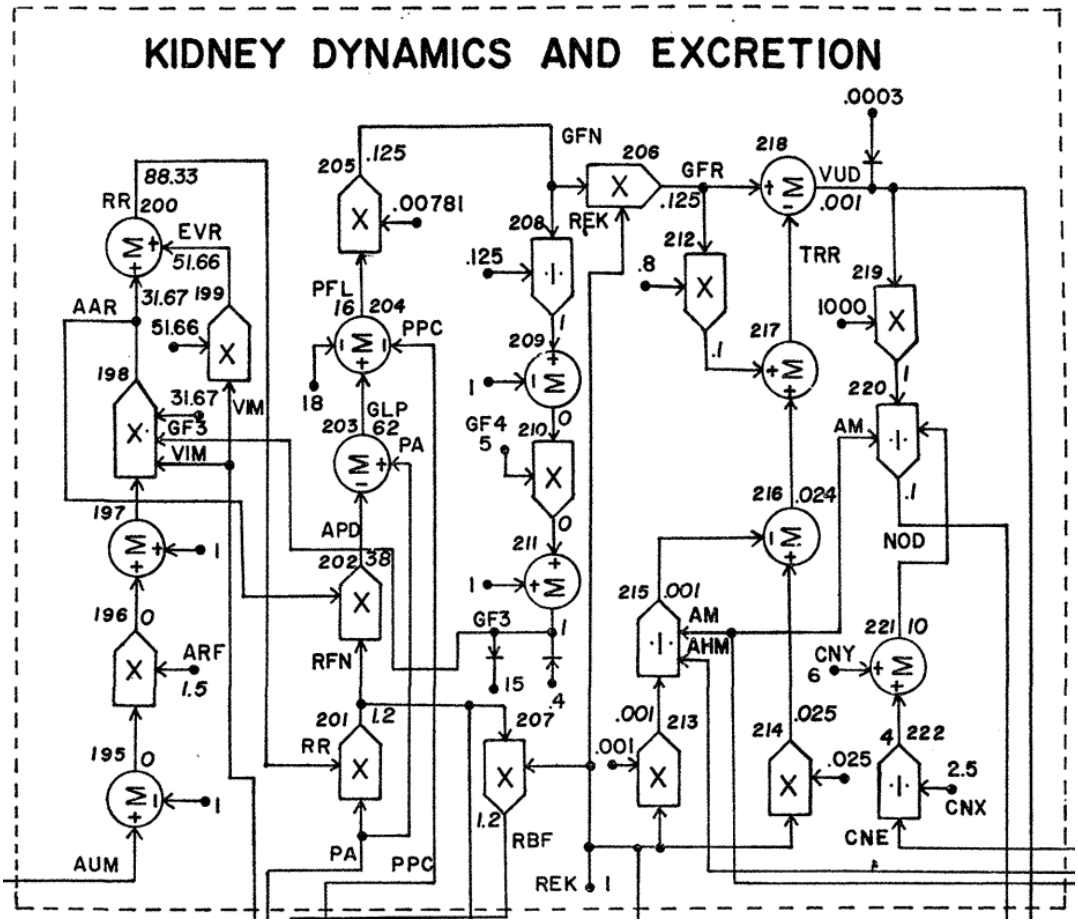


Diagram 10a Kidney dynamics and excretion in Guyton's diagram

KIDNEY DYNAMICS AND EXCRETION

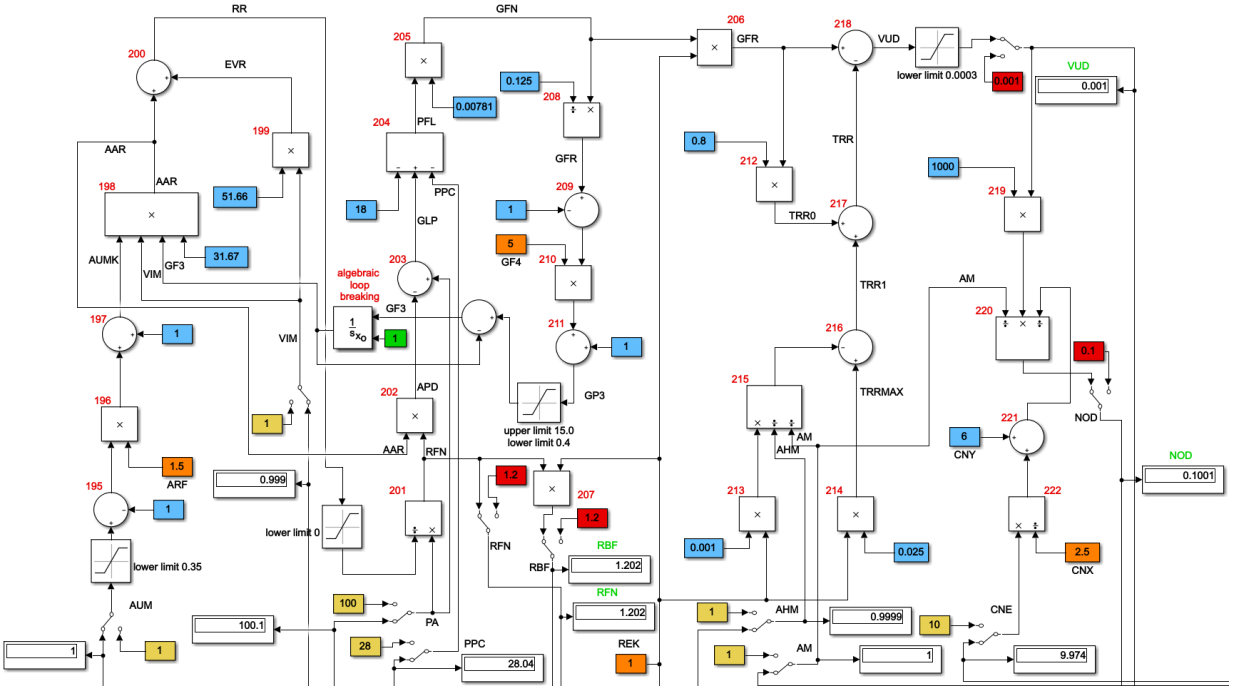


Diagram 10b Kidney dynamics and excretion in Simulink

Blocks 195, 196, and 197: Circuit for setting the sensitivity of autonomic drive and its effect on renal function. Input of this circuit is AUM (autonomic multiplier of sympathetic vasoconstrictor effect on arteries) [ratio to normal] and the factor for increasing or decreasing the effect of autonomics on the kidneys is ARF [unitless value]. A value of ARF of zero will set the sensitivity to zero, normal value is 1.5:

$$ARF = 1.5$$
$$AUMK = (AUM - 1) * ARF + 1$$

Block 198: Calculation of afferent arteriolar resistance (AAR) [mmHg min/l] by multiplying a constant value times autonomic drive from output (AUMK) of Block 197 times viscosity of the blood (VIM) [ratio to normal] and a resistance factor caused by feedback autoregulation from the macula densa (GF3) [ratio to normal]:

$$AAR = AUMK * VIM * GF3 * 31.67$$

Block 199: Calculation of efferent renal vascular resistance from the midpoint of the glomeruli to the renal veins (EVR) [mmHg min/l] by multiplying viscosity of the blood (VIM) [ratio to normal] times a constant:

$$EVR = 51.66 * VIM$$

Block 200: Addition of afferent arteriolar resistance (ARR) [mmHg min/l and efferent resistance (EVR) [mmHg/l/min] to give total renal resistance (RR) [mmHg min/l]:

$$RR = AAR + EVR$$

Block 201: Division of arterial pressure (PA) [mmHg] by renal resistance (RR) [mmHg min/l] to give blood flow through the kidneys (RFN) [l/min], assuming the kidneys to be entirely normal. (Note that in Block 201 the sign should be a division sign instead of a multiplication sign):

$$RFN = PA/RR$$

Block 202: Multiplication of normal renal blood flow (RFN) [l/min] times afferent arteriolar resistance (ARR) [mmHg min/l] to determine pressure drop in the afferent arterioles (APD) [mmHg]:

$$APD = AAR * RFN$$

Block 203: Subtraction of pressure drop in the afferent arterioles (APD) [mmHg] from arterial pressure (PA) [mmHg] to give glomerular pressure (GLP) [mmHg min/l]:

$$GLP = PPC - APD$$

Block 204: Calculation of glomerular filtration pressure (PFL) [mmHg] by adding glomerular pressure (GLP) [mmHg[and subtracting plasma colloid osmotic pressure (PPC) [mmHg] and also subtracting a constant value 18 mmHg to represent Bowman's capsule pressure:

$$PFL = GLP - PPC - 18$$

Block 205: Calculation of glomerular filtration if the kidneys are entirely normal (GFN) [l/min] by multiplying glomerular filtration pressure (PFL) [mmHg] times a constant to represent the glomerular filtration coefficient 0.00781 l/mmHg/min:

$$GFN = PFL * 0.00781$$

Block 206: Multiplication of glomerular filtration rate for normal kidneys (GFN) [l/min] times the degree of normality of the kidneys (REK) [ratio to normal function] to give actual glomerular filtration rate (GFR) [l/min]:

$$GFR = GFN * REK$$

Block 207: Multiplication of renal blood flow if the kidney is entirely normal (RFN) [l/min] times degree of normality of the kidneys (REK) [ratio to normal function] to give actual renal blood flow (RBF) [l/min]:

$$RBF = RFN * REK$$

Blocks 208, 209, 210 and 211: Blocks 208, 209, 210, and 211 represent calculation of feedback from glomerular filtration rate (GFN) [l/min] for control of degree of autoregulatory feedback at densa (GF3) to control afferent arteriolar resistance (ARR) [mmHg min/l] at Block 198. The degree of sensitivity of this feedback is controlled by factor GF4, which is the feedback gain of the autoregulatory loop. The limits (15>GP3>0.4) of the feedback controlled by the two rectifiers in the output of Block 211:

$$GFR4 = 5$$
$$GP3 = (GFR - 1) * GFR4 + 1$$
$$if\ GP3 > 15\ then\ GF3 = 15\ else\ if\ GP3 < 0.4\ then\ GF3 = 0.4\ else\ GF3 = GP3$$

Block 212: Calculation of the amount of glomerular filtrate that is reabsorbed irrespective of control by aldosterone and antidiuretic hormone (TRR0) [l/min]. (This is considered to be approximately 80 percent of the total GFR):

$$TRR0 = 0.8 * GFR$$

Block 214: Calculation of maximum amount of fluid capable of being reabsorbed by the tubules each minute and that is also entirely under the control of aldosterone and antidiuretic hormone. In normal kidney that amounts is 0.025 l/min, times this value by degree of normality of the kidneys (REK) [ratio to normal function] we give actual value (TRRMAX) [l/min]:

$$TRRMAX = 0.025 * REK$$

Blocks 213 and 215: Blocks calculate amount of fluid that is capable of being controlled by these two hormones but that is <u>not</u> reabsorbed by the tubules (NOREABS) [l/min]. Factors aldosterone multiplier (AM) [ratio to normal effect] and antidiuretic hormone multiplier (AHM) [ratio to normal effect] and degree of normality of the kidneys (REK) [ratio to normal function] are inputs to this circuit.

$$NOREABS = 0.001 * REK/(AHM * AM)$$

Block 216: Subtraction of amount of fluid not reabsorbed but that is capable of aldosterone and ADH control (NOREABS [l/min[) from the maximum amount that could have been controlled (TRRMAX [l/min] - output of Block 214) to give total amount of fluid reabsorbed from the tubules that was under the control of ADH and aldosterone (TRR1]l/min] - output of Block 216):

$$TRR1 = TRRMAX - NOREABS$$

Block 217: Calculation of total tubular reabsorption (TRR) [l/min] by adding reabsorption that was under the control of aldosterone and ADH (TRR1 [l/min] - output of Block 216) plus that amount of glomerular filtrate that was absorbed but was not under the control of these two hormones (TRR0 [l/min] - output of Block 212):

$$TRR = TRR1 + TRR0$$

Block 218: Subtraction of total tubular reabsorption (TRR) [l/min] from glomerular filtration rate (GFR) [l/min] to give rate of urinary output (VUD) [l/min] (the rectifier circuit in the output of Block 218 prevents urinary output from falling below an obligatory level of output - 0.0003 l/min):

$$if\ (GFR - TRR) > 0.0003\ then\ VUD = GFR - TRR\ else\ VUD = 0.0003$$

Blocks 219 and 220: Blocks calculate rate of sodium loss in urine (NOD)]mmol/min] assuming a normal concentration of sodium in the urine of 100 mmol/liter and assuming that there are three factors that affect this output, the volume of urine formed each minute (VUD) [l/min] the aldosterone multiplier effect (AM) [ratio to normal effect] and the "third factor" (THF [ratio to normal effect] output of Block 221):

$$NOD = VUD * 1000/(AM * THF)$$

Blocks 221 and 222: Determination of "third factor" effect on urinary loss of sodium, calculated from factor related to change in concentration of sodium in the extracellular fluids (CNE) [mmol/l] and two constant factors (CNX) and (CNY):

$$CNX = 2.5$$
$$CNY = 6$$
$$THF = CNE/CNX + CNY$$

Implementary notes: In Simulink in GF3 signal connection the additional block was included for algebraic loop breaking.

11 Muscle blood flow control and PO2

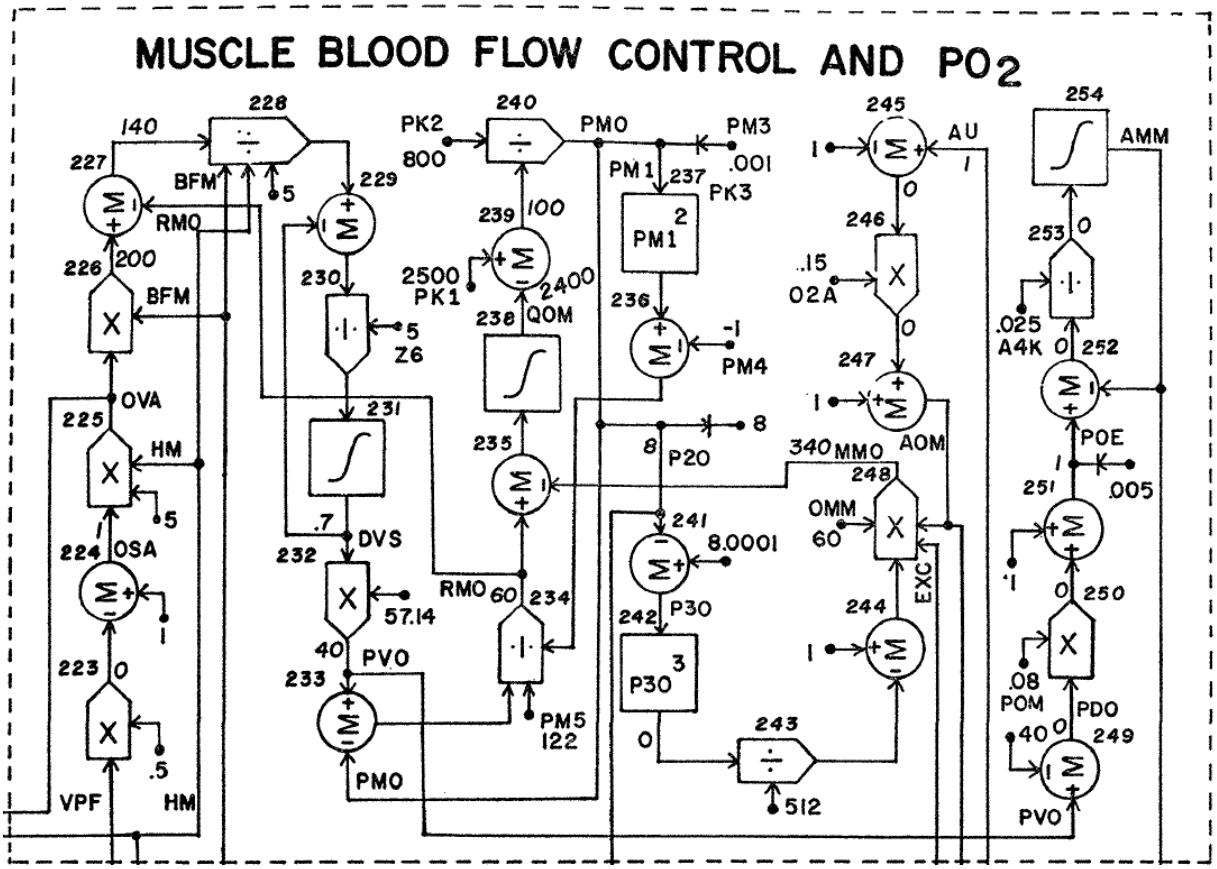


Diagram 11a Muscle blood flow control and PO2 in Guyton's diagram

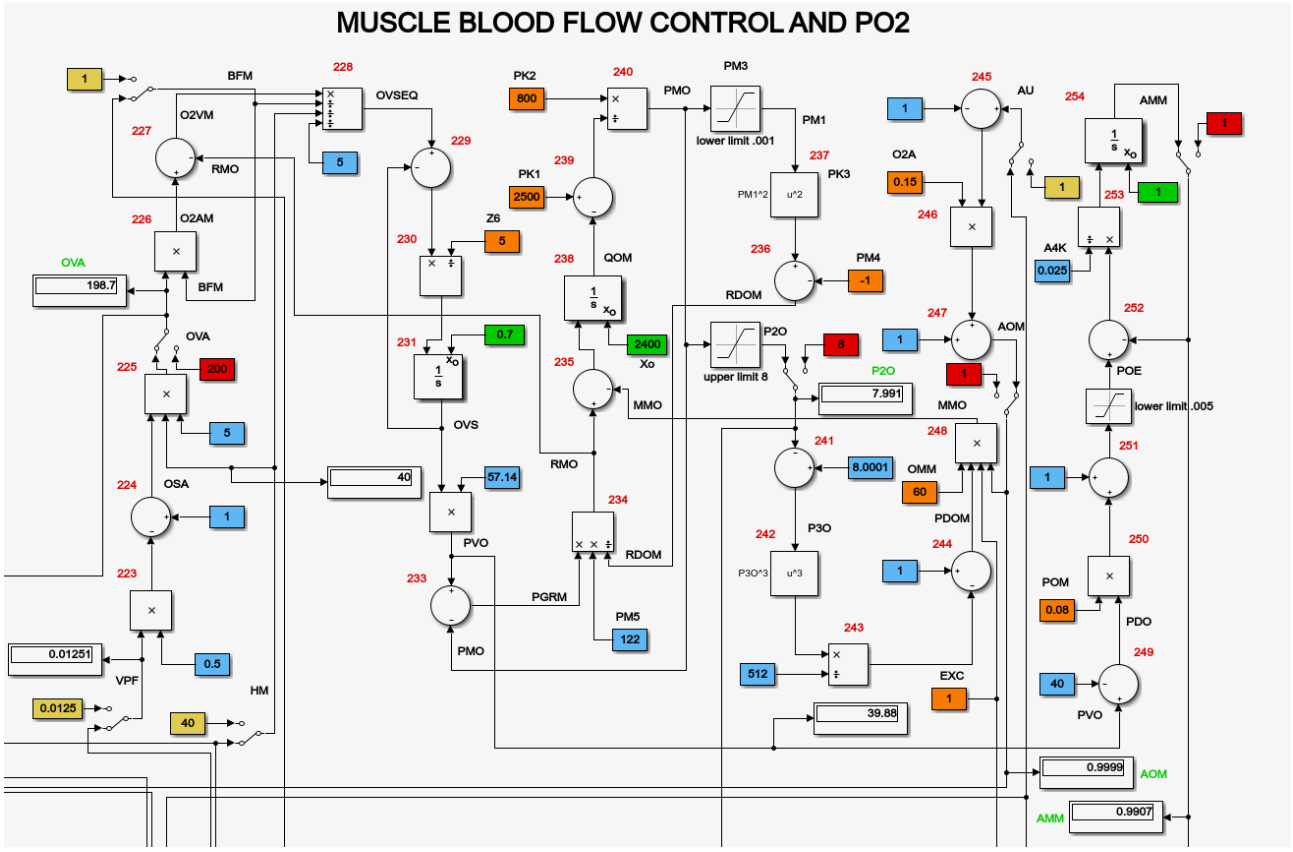


Diagram 11b Muscle blood flow control and PO2 in Guyton's diagram

Block 223: Calculation of fraction desaturation of arterial blood by multiplying quantity of free fluid in lungs (VPF) [l] times a constant factor:

$$ALO = VPF * 0.5$$

Block 224: Calculation of aortic arterial oxygen saturation (OSA) [as a fraction] by subtracting amount of desaturation from Block 223 from a maximum saturation of 1:

$$OSA = 1 - ALO$$

Block 225: Calculation of volume of oxygen per liter of aortic arterial blood (OVA) [ml O2/liter of blood] from hematocrit (HM) [%] and arterial oxygen saturation (OSA) [fraction]. This calculation is based on oxygen binding capacity of human haemoglobin. One gram of hemoglobin can bound 1.34 ml O2. Therefore oxygen concentration bound to hemoglobin HbO2 [ml/l]:

$$HbO2 = 1.34 * Hb * OSA$$

Concentration of hemoglobin (Hb) [g/l] can be calculate from hematocrit (HM) [%] and mean corpuscular hemoglobin concentration MCHC [g/l]:

$$Hb = MCHC * HM/100$$

Therefore:

$$HbO2 = (1.34 * MCHC/100) * HM * OSA$$

If we consider normal value of MCHC = 340 g/l:

$$HbO2 = (1.34 * 340/100) * HM * OSA = 4.556 * HM * OSA$$

Volume of oxygen per liter of aortic arterial blood (OVA) is the sum of oxygen bound to hemoglobin (HbO2) plus dissolved oxygen. If we neglect dissolved oxygen:

$$OVA = HbO2 = (1.34 * 340/100) * HM * OSA = 4.556 * HM * OSA$$

In model is taken instead of 4.556 the value of 5 [ml O2/l blood] (the concentration of dissolved oxygen is neglected):

$$OVA = 5 * HM * OSA$$

Block 226: Calculation of rate of delivery of oxygen to muscle cells (O2AM) [ml O2/min] by multiplying volume of oxygen per liter (OVA) [ml O2/l blood] times muscle blood flow (BFM) [l/min]:

$$O2AM = OVA * BFM$$

Block 227: Calculation of rate of delivery of oxygen to the veins (O2VM) [ml O2/min] by sub-tracting rate of oxygen utilization by the tissues (RMO) [ml O2/min] from a rate of delivery of oxygen by the arteries (O2AM [ml O2/min] - output of Block 226):

$$O2VM = O2A - RMO$$

Block 228: Calculation of venous oxygen saturation after equilibrium (O2VSEQ [fraction]). First we must calculate volume of oxygen per liter of venous blood (OVM) [ml O2/liter of blood] by dividing of muscle blood flow (BFM) [l/min]:

$$OVM = O2VM/BFM$$

Because blood oxygen concentration O2VV depends on hematocrit and saturation (analogically to Block 225):

$$OVM = 5 * HM * OVSEQ$$

we can calculate oxygen saturation:

$$OVSEQ = O2VV/HM/5$$

Summarizing: the venous oxygen saturation after equilibrium (O2VSEQ [fraction]) has been established by multiplying rate of oxygen delivery to the veins (O2VM [ml 02/min] - output of Block 227) and dividing by muscle blood flow (BFM) [l/min], dividing by hematocrit (HM) [%], and dividing by a constant:

$$OVSEQ = O2VM/BFM/HM/5$$

Blocks 229, 230, and 231: represent a delay circuit to determine the time interval required for venous oxygen saturation to rise to the equilibrium value. This circuit prevents oscillations in the case of severe saturation changes. The output of Block 231 (DVS) [fraction] is the actual venous oxygen saturation. The constant, Z6 controls the time constant [min] for this delay circuit:

$$Z6 = 5$$
$$dDVS/dt = (OVSEQ - DVS)/Z6, DVS_{t=0} = 0.7$$

Block 232: calculates venous oxygen pressure (PVO) [mmHg] by multiplying venous oxygen saturation (DVS) [fraction] times a constant (that represents the slope of linearized oxygen saturation curve):

$$PVO = DVS * 57.14$$

Block 233: calculates pressure difference (PGRM) [mmHg] between oxygen in the muscle capillaries and oxygen in the muscle cells (PMO) [mmHg], assuming that the oxygen in the capillaries is equal to the oxygen in the venous blood (PVO) [mmHg]:

$$PGRM = PVO - PMO$$

Block 234: Calculation of rate of delivery of oxygen from the capillaries to the muscle cells (RMO) [ml O2/min]. The delivery of oxygen to the muscle cells is directly proportional to the partial pressure gradient (PGRM) [mmHg] and the diffusion area of the capillaries and inversely proportional to resistance to oxygen flow between capillaries and muscle cell. Difusion area depends of number of opened capillaries. Constant part of difusion area is represented by PM5 constant and variable part of difusion area (depending on capillarity) is included in resistance factor

RDOM [ml O2/(mmHg min)]. Oxygen delivery from capillaries to muscle cells is calculated by multiplying pressure difference between capillaries and muscle cells (PGRM) [mmHg] (output of Block 233) times constant (PM5) [dimensionless] and divided by a resistance factor determined by the number of capillaries that are open at any given time (RDOM) [ml O2/(mmHg min)] - output of Block 236:

$$RMO = PGRM * PMS/RDOM = (PVO - PMO) * PMS/RDOM$$

Blocks 235 and 238: Calculation of total quantity of oxygen stored in muscle cells (QOM) [ml O2]. (Note that QOM represents oxygen stored in all of its energy forms, including dissolved oxygen, oxygen bound with myoglobin, and oxygen equivalents of energy compounds such as ATP and creatine phosphate). Block 235 calculate the rate of change of oxygen in muscle cells as a difference between rate of oxygen delivery from the capillaries (RMO) [mlO2/min] and rate of oxygen utilization by cells (MMO) [mlO2/min]. Integrating of this rate of change we can obtain the oxygen stored in cells:

$$dQOM/dt = RMO - MMO$$

Blocks 239 and 240: Curve fitting process to calculate pressure of oxygen in muscle cells (PMO) [mmHg] from quantity of oxygen in cells (QOM) [ml O2]:

$$PMO = (QOM - PK1)/PK2$$

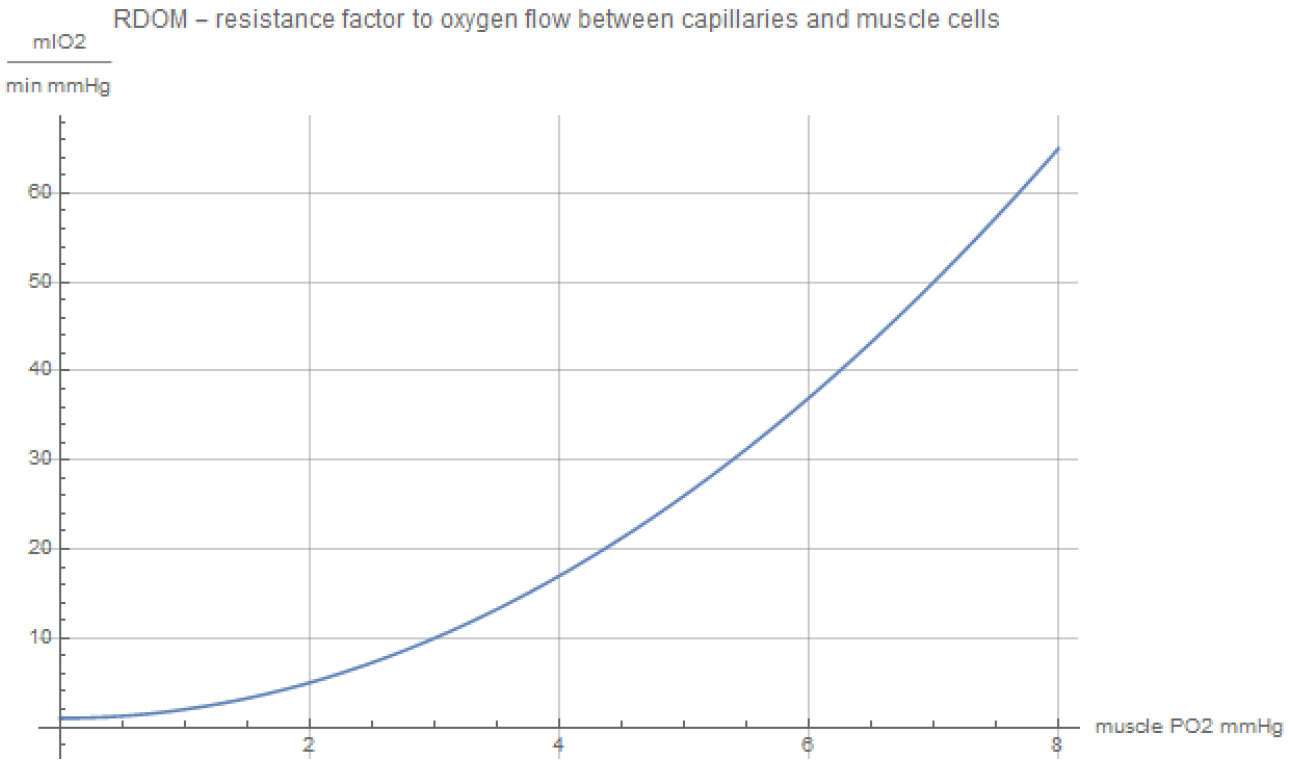
Blocks 236 and 237: Calculation of resistance factor to oxygen flow between capillaries and muscle cell (RDOM) [ml O2/(mmHg min)]. Curve fitting process to calculate capillarity of the muscle and to calculate the mean distance from capillaries to cells and the resistance to oxygen diffusion caused by this mean distance, which is one of the factors that determine the rate of delivery of oxygen from the capillaries to the muscle cells.
Note also that pressure of oxygen cannot fall below a very small minimum of 0.001 mm Hg:

$$PM1 = PMO\ if\ PMO < 0.001\ then\ PM1 = 0.001$$

$$PK3 = PM1^2$$

$PM4 = -1$

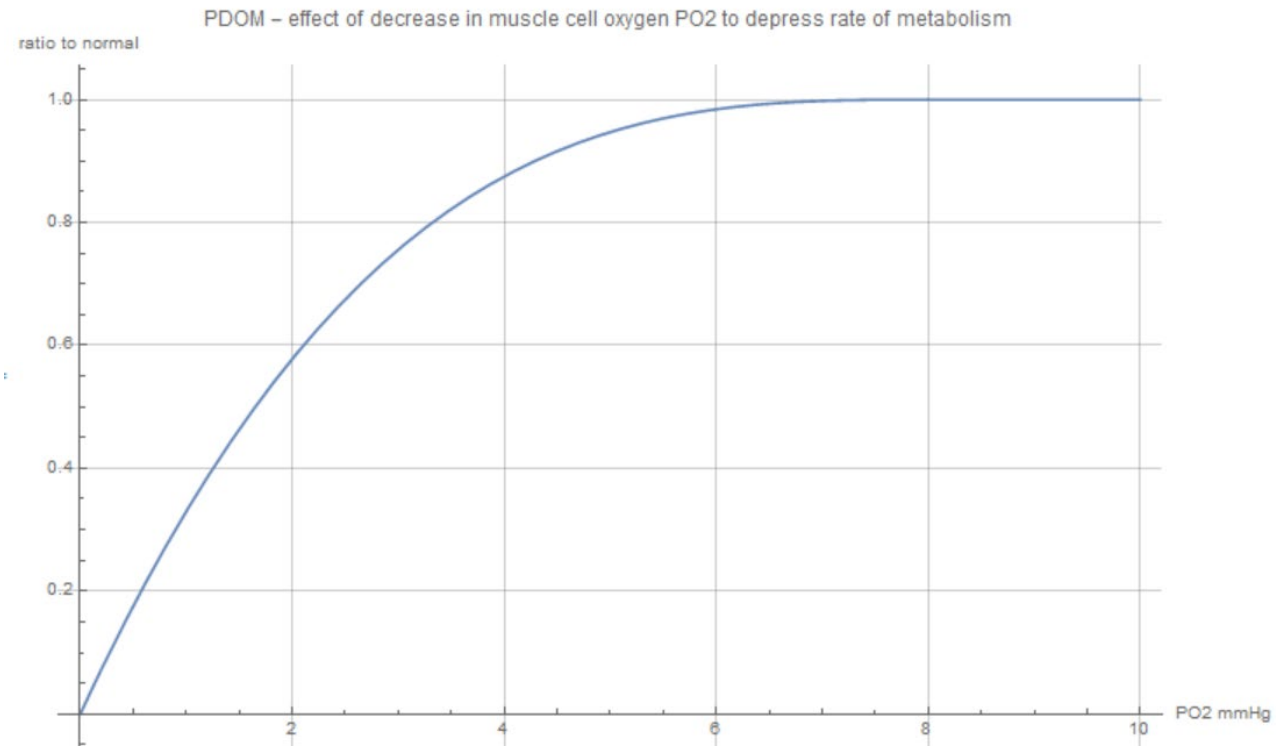
$$RDOM = PK3 - PM4$$



Reducing PO2 in muscle cells increases capillarity in muscle tissues and therefore decreases resistance factor to oxygen flow between capillaries and muscle cell: dependence RDOM to PO_2 in muscle cells

Blocks 241, 242, 243, and 244: Calculation of effect of decrease in muscle oxygen PO_2 to depress rate of metabolism in the cell (PDOM) [ratio to normal]. This is a curve fitting process that assumes that the oxygen must fall nearly to approach zero before very significant decrease in rate of metabolism occurs. Indicator of muscle hypoxia (P2O) [mmHg] expresses muscle PO2 if value of PO2 falls below 8, otherwise is equal 8.0:

$$P20 = PMO\ if\ PMO > 8\ then\ P20 = 8$$
$$PDOM = 1 - (8.0001 - P2O)^3/512$$



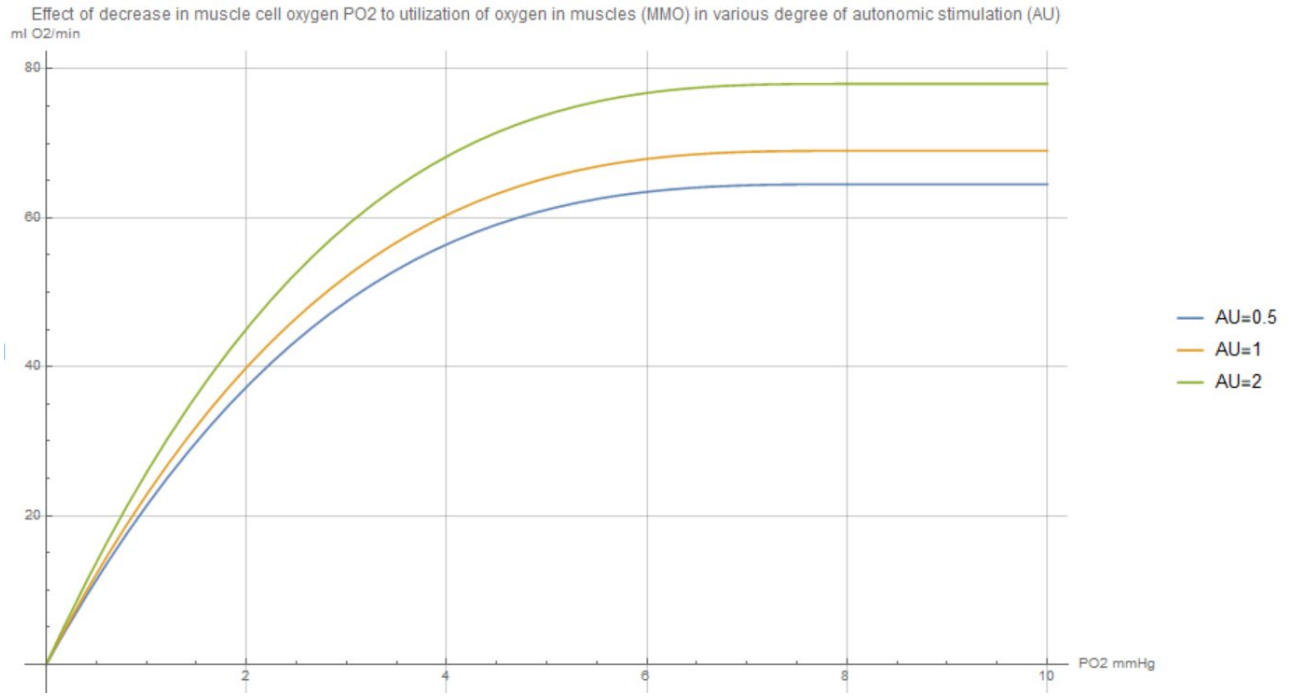
Decrease of resistance Dependence PDOM to PO_2 in muscle cells

Blocks 245, 246, and 247: Calculation of the effects of the degree of autonomic stimulation (AU) [ratio to normal] on rate of metabolism expressed as an autonomic multiplier effect on metabolism (AOM) [ratio to normal effect]. This value is normally expressed as unity. The sensitivity of the effect of autonomic stimulation on metabolism is determined by the constant of Block 246, O2A [dimensionless]:

$$O2A = 0.15$$
$$AOM = O2A * (1 - AU) + 1$$

Block 248: Calculation of rate of utilization of oxygen by the cells (MMO) [ml O2/min] by multiplying autonomic effect on oxygen utilization (AOM) [ratio to normal effect], effect of exercise on rate of oxygen utilization (EXC) [ratio to activity at rest], effect of decrease in oxygen concentration in muscle cells on muscle cellular oxygen utilization (PDOM) [dimensionless] - output of Block 244, and basal level of oxygen utilization by muscle cells (OMM) [ml O2/min]. (Note that normal value of MMO is 60 rather than 340 given in diagram.)

$$OMM = 60$$
$$MMO = OMM * PDOM * EXC * AOM$$



Dependence MMO to PO_2 in muscle cells in various degree of autonomic stimulation (AU)

Blocks 249 through 254 calculate factor for control of muscle blood flow resistance by changes in PO_2 in muscle tissue. Outflowing capillary blood is in equilibrium with the muscle interstitial tissue. Therefore PO_2 in muscle tissue is equal to venous PO_2 (PVO) [mmHg]. Blocks calculated the dependence of muscle vasoconstriction to PVO. This effect is expressed through multiplier AMM [ratio to resting state], that expressed muscle vascular constriction caused by local tissue control. Value of AMM is used to calculation of muscle resistance in CIRCULATORY DYNAMICS module.

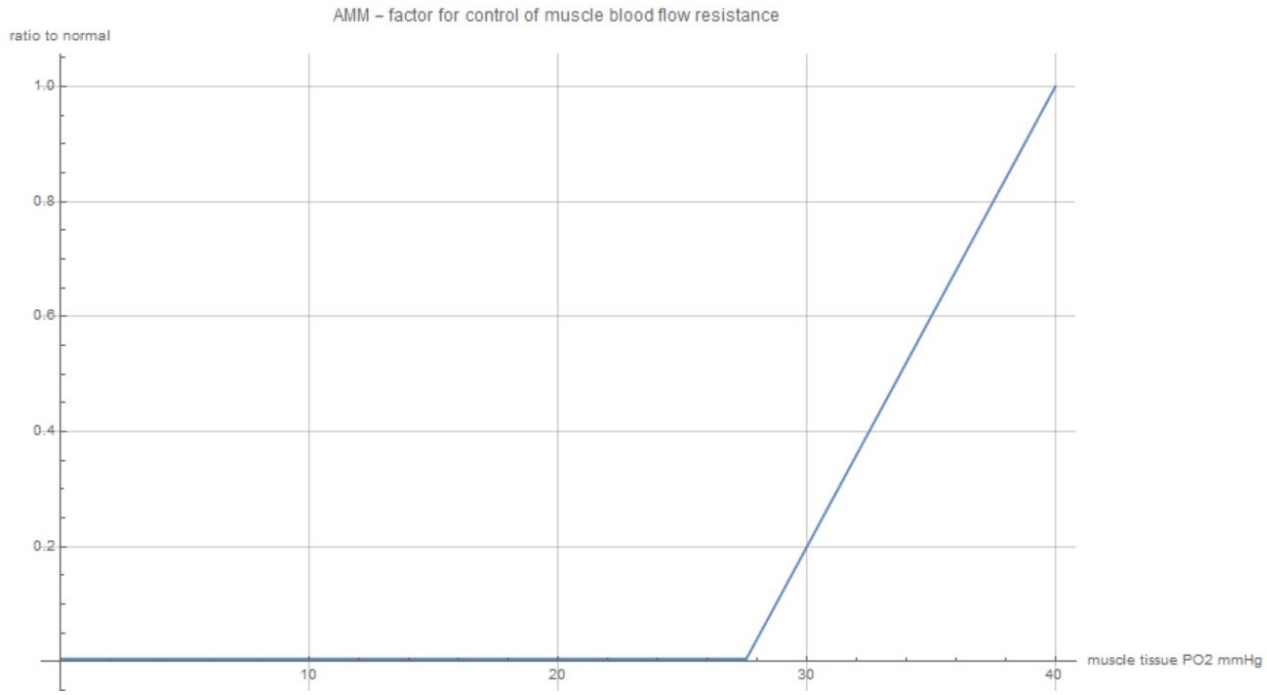
Block 249 calculates difference between capillary PO_2, assuming this to be equal to venous PO_2, (PVO) [mmHg] and the constant value of 40 to give a control value.
Block 250 is a sensitivity control for the oxygen feedback control loop. It calculates sensitivity of muscle flow resistance resistance to muscle venous PO_2 - (POE) [ratio to normal]. Constant POM [$mmHg^{-1}$] controls the degree of sensitivity.
Block 251 converts the control output of Block 250 to a unity output at normal muscle venous PO_2 of 40.
The output of Block 251 is prevented from falling below a low minimum value by the rectifier:

$$POM = 0.08$$
$$POE = 1 + (PVO - 40) * POM$$
$$if\ POE < 0.005\ then\ POE = 0.005$$

Blocks 252, 253, and 254 are a time delay circuit to determine the rapidity with which this mechanism comes to equilibrium. The time constant of this circuit is determined by constant A4K. Its output, AMM, is the autoregulation multiplier for the muscle vascular circuit, and it is one of the factors that determines resistance to blood flow through the muscles (RSM) in Block 36:

$$A4K = 0.025$$
$$dAMM/dt = (POE - AMM) * A4K, AMM_{t=0} = 1$$

A4K = 1



Dependency of steady state values of AMM to PO_2 in muscle tissue (minimal value of AMM is 0.025). Reducing PO2 in muscle tissue tissues decreases AMM and therefore decreases resistance to blood flow through the muscles.

12 Non-muscle oxygen delivery

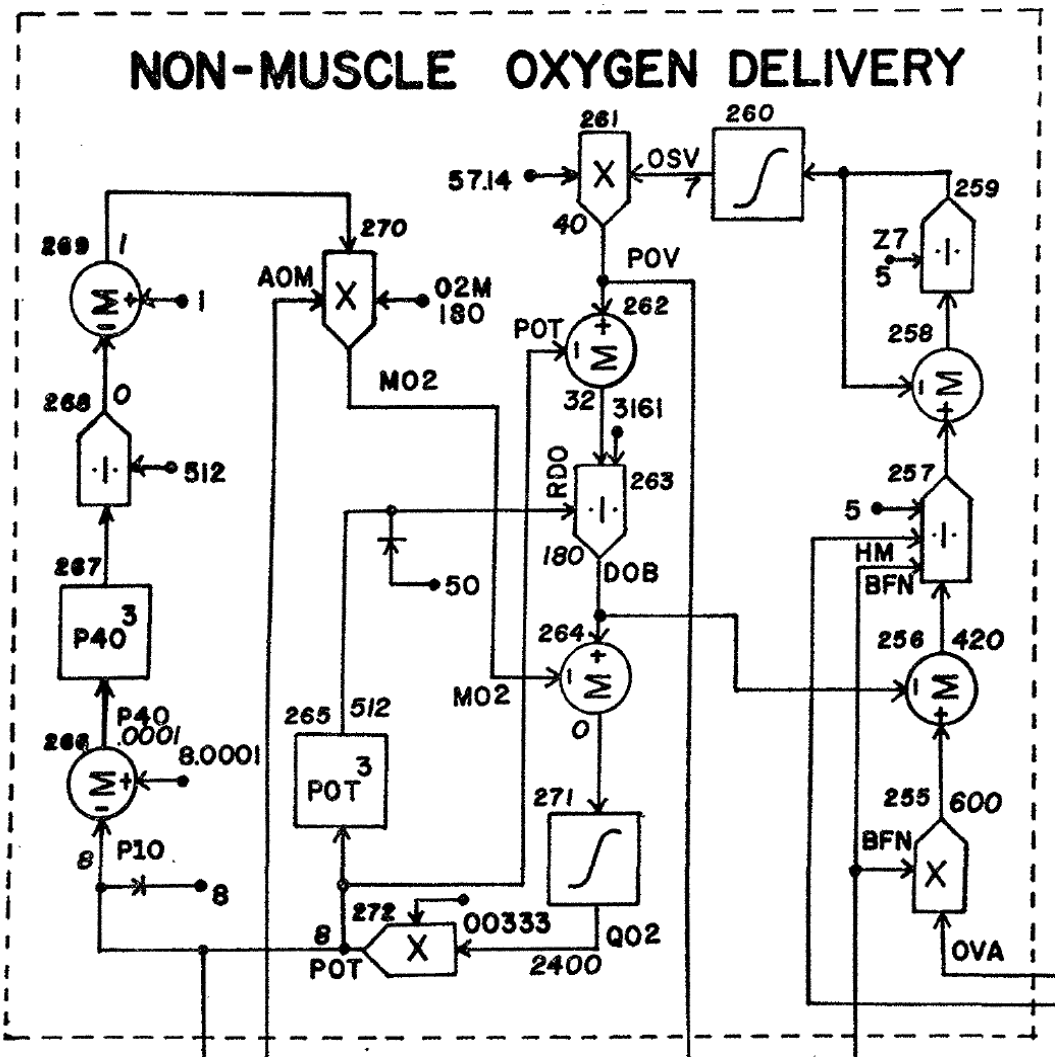


Diagram 12a Non-muscle oxygen delivery in Guyton's diagram

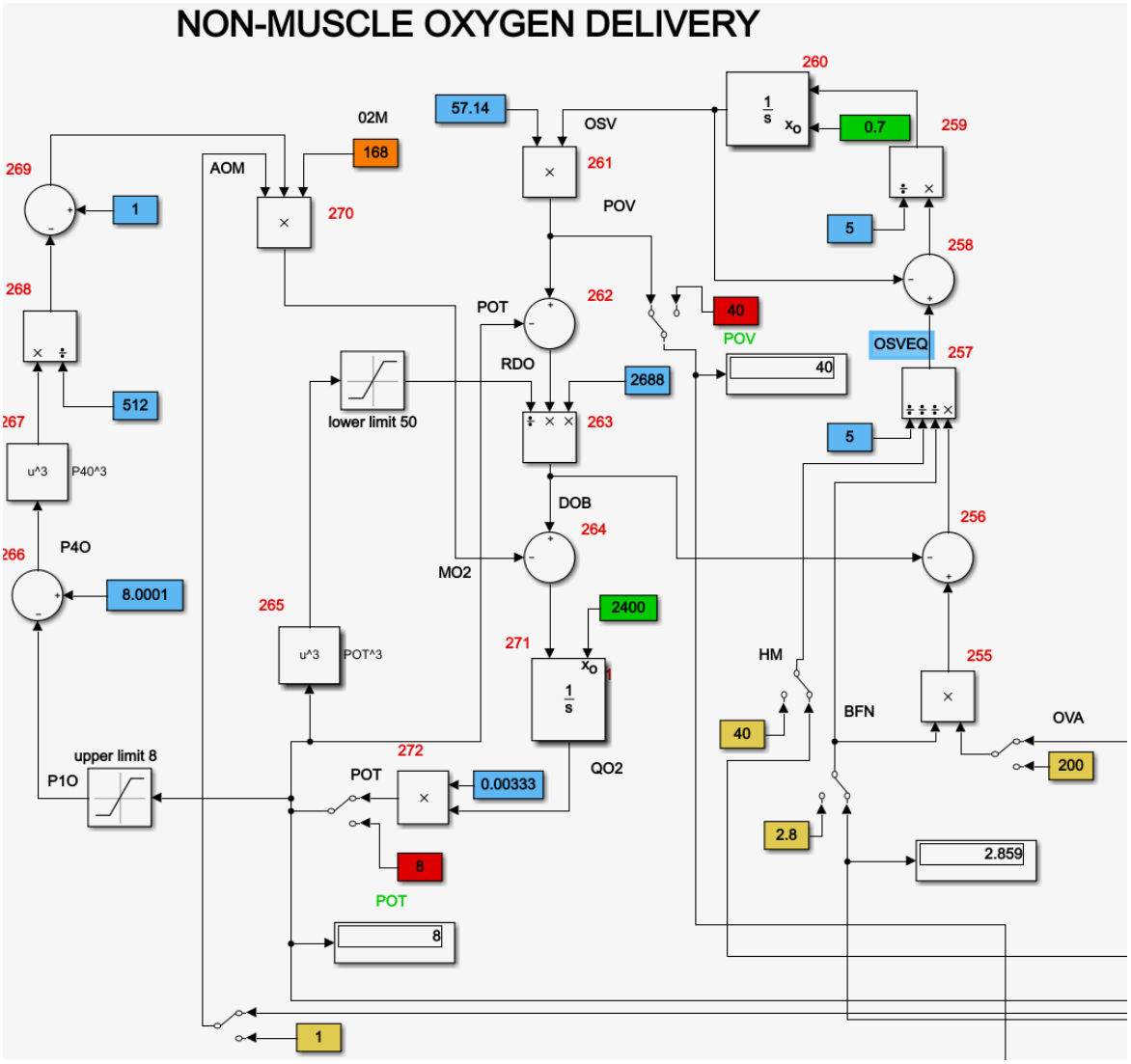


Diagram 121b Non-muscle oxygen delivery in Simulink

Block 255: Multiplication of volume of oxygen in each liter of arterial blood (OVA) [ml O2/l blood] times blood flow to the non-muscle tissues (BFN) [l/min] to give rate of transport of oxygen by arteries to these tissues (O2ART) [mlO2/min]:

$$O2ART = OVA * BFN$$

Block 256: Calculation of rate of delivery of oxygen to veins of these tissues (O2VEN) [mlO2/min] by subtracting rate of oxygen utilization by the tissues (DOB) [ml O2/min] from rate of delivery of oxygen by arteries (O2ART [ml O2/min] - output of Block 255):

$$O2VEN = O2ART - DOB$$

Block 257: Calculation of equilibrium venous oxygen saturation (OSVEQ) [fraction] based on rate of delivery of oxygen to the veins (O2VEN [mlO2/min] - output of Block 256) divided by blood flow to the tissues (BFN) [l/min] divided by hematocrit (HM) [%] and divided by a constant.
(how to calculate the oxygen saturation from oxygen delivery, hematocrit and constant see explanation in the block 224):

$$OSVEQ = O2VEN/BFN/HM/5$$

Block 258, 259, and 260: are a delay circuit to calculate the rate at which the actual venous oxygen saturation (OSV) [fraction] will come to equilibrium with the calculated equilibrium value (output of Block 257). The time constant of this circuit is determined by constant Z7 [min] in Block 259.
(Note, that in diagram the block 258 is incorrectly connected to the output of block 259 instead to the output of block 260!):

$$Z7 = 5$$
$$dOSV/dt = (OSVEQ - OSV)/Z7, OSV_{t=0} = 7$$

Block 261: Calculation of venous oxygen PO_2 (POV) [mmHg] from venous oxygen saturation (OSV) [fraction] times a constant (that represents the slope of linearized oxygen saturation curve):

$$POV = OSV * 57.14$$

Block 262: Calculation of pressure difference (PGRN) [mmHg] between oxygen in the end of tissue capillaries assumed to be equal to PO_2 in veins (POV) [mmHg] minus pressure of oxygen in the tissue cells (POT) [mmHg]:

$$PGRN = POV - POT$$

Block 263: Calculation of rate of delivery of oxygen from capillaries to tissue cells (DOB) [ml O2/min] by multiplying pressure difference from capillaries to cells (PGRN [mmHg] - output of Block 262) times a constant and dividing resistance for diffusion of oxygen (RDO) [ml O2/(mmHg min)] which is determined by the number of capillaries that are open
(Note that constant value is 2688 instead of 3161 as is shown in a chart!):

$$DOB = 2688 * PGRN/RDO$$

Block 264: Calculation of rate of accumulation of oxygen in tissue cells by subtracting rate of utilization of oxygen in cells (MO2) [ml O2/min] from rate of delivery of oxygen to cells (DOB) [ml O2/min]:

$$DO2N = DOB - MO2$$

Block 271: Integration of rate of accumulation of oxygen in cells (DO2N [mlO2/min] - output of Block 264) to determine actual quantity of oxygen accumulated in cells at any given instant (QO2) [ml O2]. (Note that QO2 represents oxygen accumulated in any of its energy forms such as dissolved oxygen, oxygen bound with substances in the cells, and the energy equivalent in the form of ATP and creatinine phosphate.):

$$dQO2/dt = DO2N, QO2_{t=0} = 2400$$

Block 272: Calculation of tissue cell PO_2 (POT) [mmHg] by multiplying quantity of oxygen accumulated in the cells by a constant:

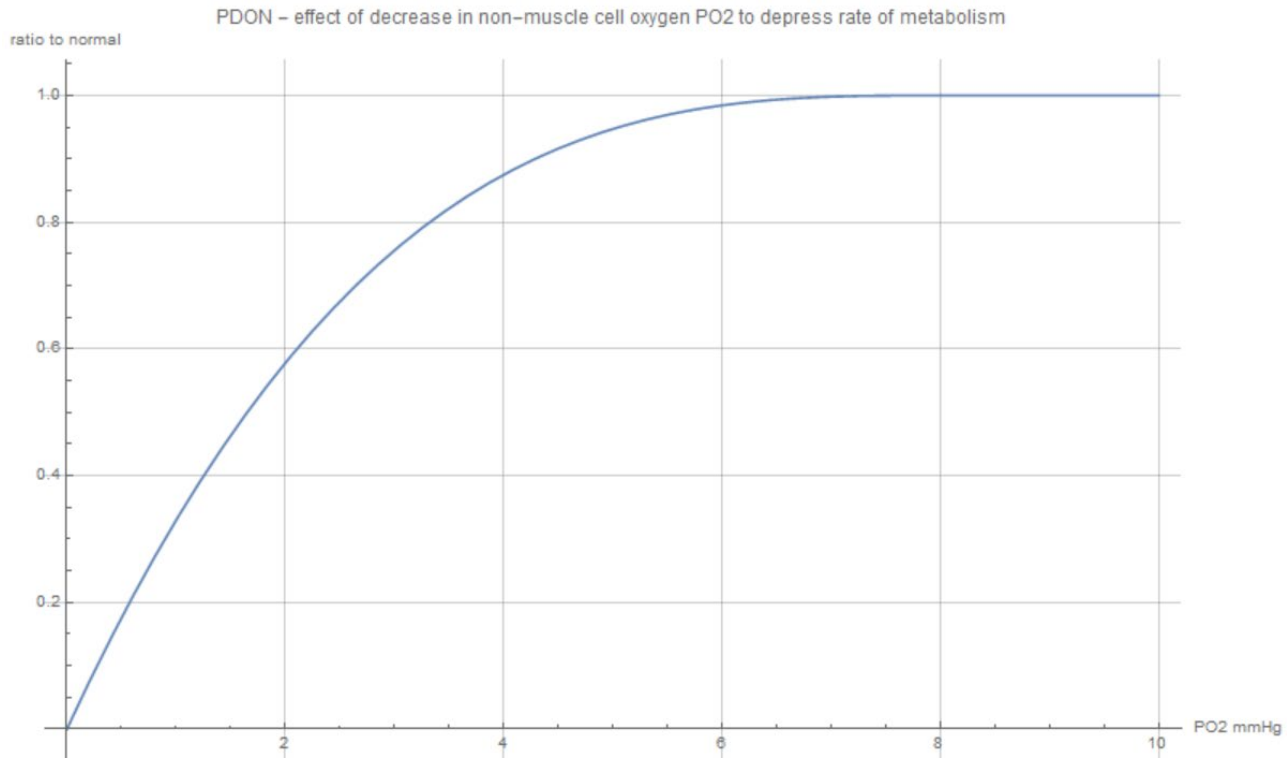
$$POT = QO2 * 0.003333$$

Block 265: Calculation of resistance of diffusion of oxygen from capillaries to cells (RDO) [ml O2/(mmHg min)], assuming that far greater numbers of capillaries open up and the resistance decreases as the tissue PO_2 (POT) [mmHg] falls below normal.

$$RDO = POT^3$$
$$if\ RDO < 50\ then\ RDO = 50$$

Blocks 266 through 269: calculate the effect of the reduction of cell PO_2 (PDON) [ratio to normal] to cause depression of cell metabolism. This circuit assumes that the oxygen PO_2 must fall near to zero before significant amount of depression occurs.

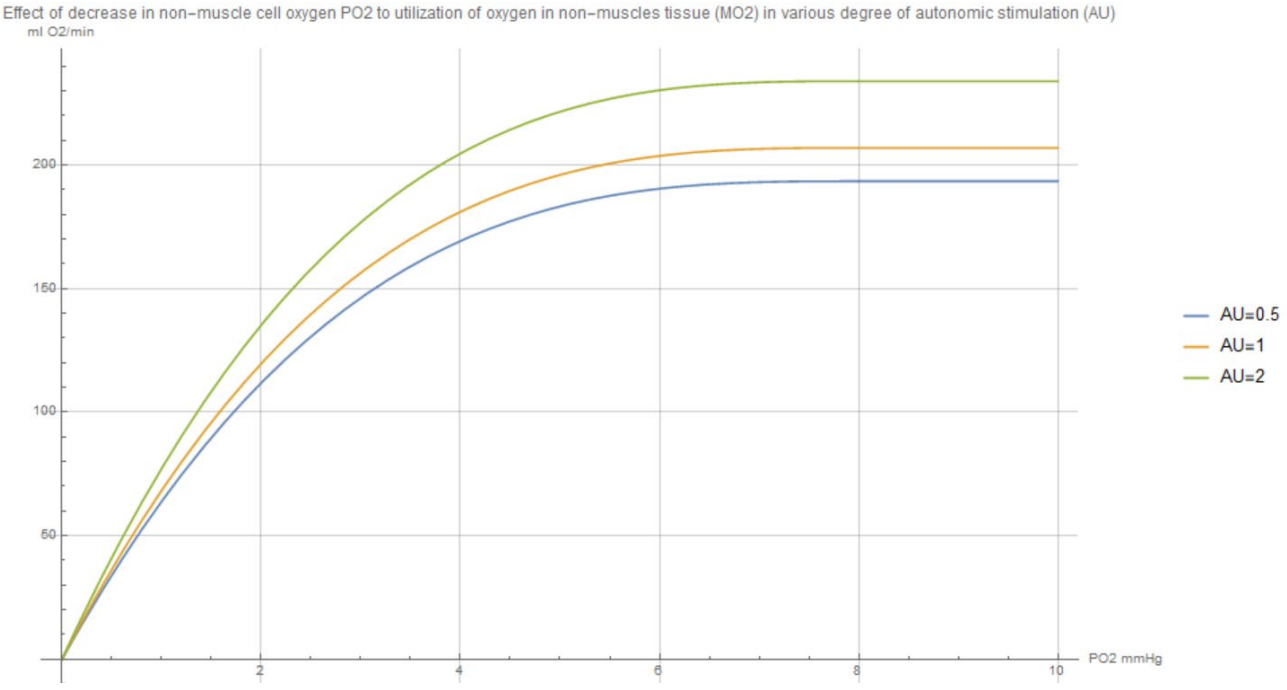
$$if\ POT > 8\ \ then\ P1O = 8\ else\ P1O = POT$$
$$PDON = 1 - (8.0001 - P1O)^3/512$$



Dependence PDOn to PO_2 in non-muscle cells

Block 270: calculates rate of oxygen utilization by cells (MO2) [ml O2/min] by multiplying basal level of oxygen utilization (O2M) [ml O2/min] times autonomic stimulatory effect (AOM) [ratio to normal] - calculated in block 247 and times the tissue PO_2 effect on oxygen utilization (PDON [ratio to normal] - output of Block 269).

$$O2M = 180$$
$$MO2 = O2M * AOM * PDON$$



Dependence MO2 to PO_2 in non-muscle cells in various degree of autonomic stimulation (AU)

13 Non-muscle local blood flow control

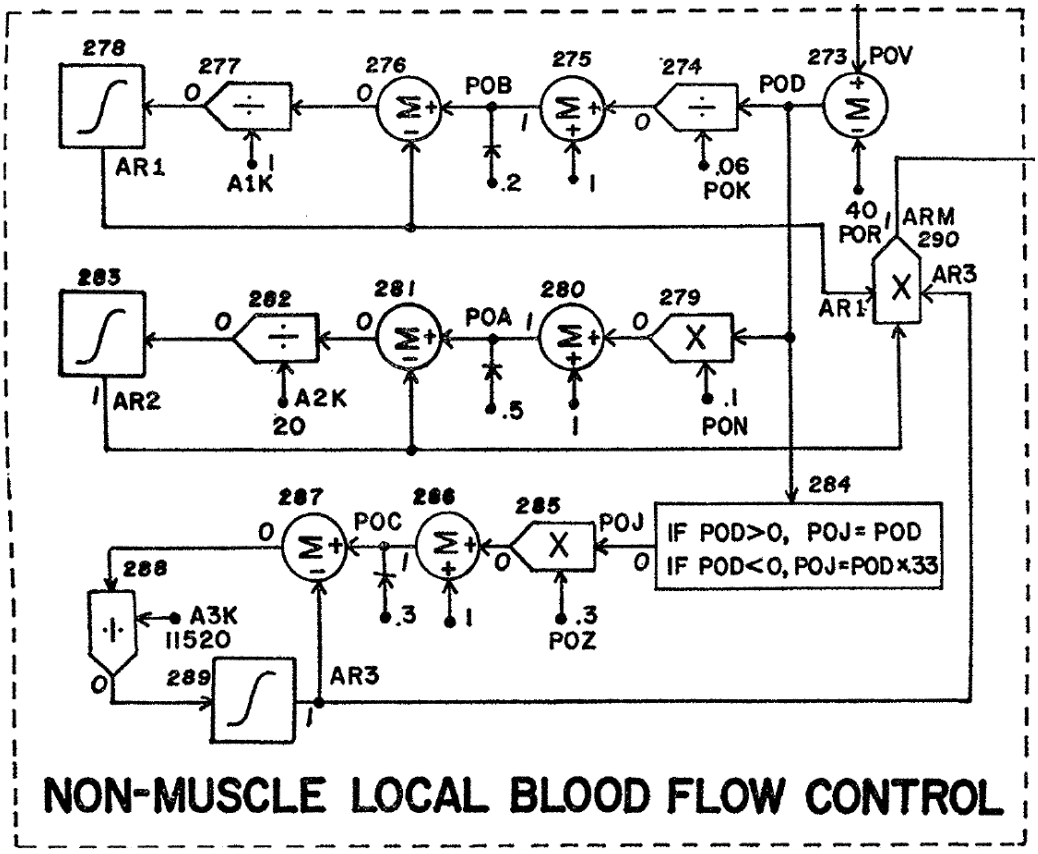


Diagram 13a Non-muscle local blood flow control in Guyton's diagram

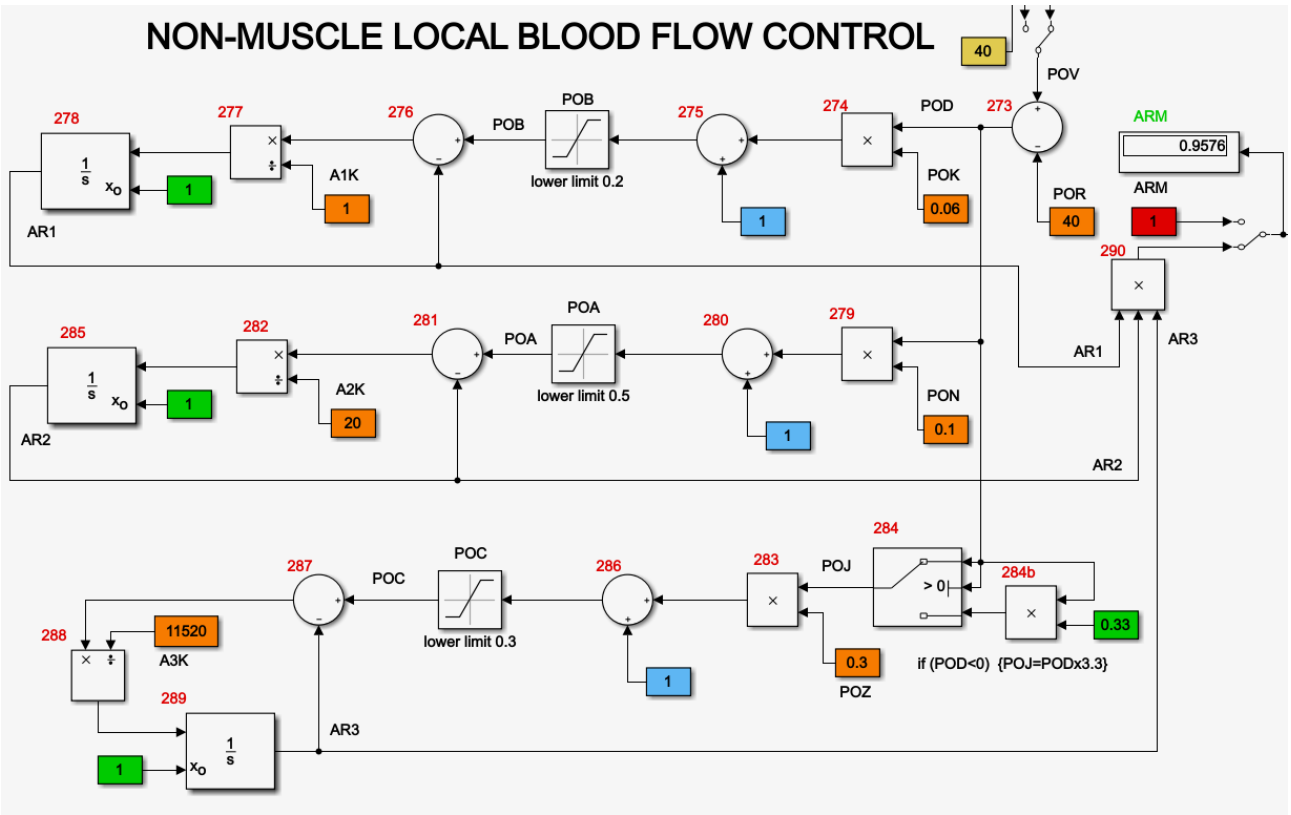


Diagram 13b Non-muscle local blood flow control in Simulink

Block 273: subtracts reference value (POR = 40.0 mmHb) from capillary PO_2 in non-muscle tissues, assuming this to equal to venous PO_2 (POV) [mmHg] to give pressure difference that acts as control factor for autoregulation of non-muscle blood flow (POD) [mmHg]:

$$POR = 40.0$$
$$POD = POV - POR$$

Blocks 274 and 275: Sensitivity control circuit for setting the gain of rapid autoregulation. Gain is set by factor POK=0.06 [$mmHg^{-1}$]. Output of Block 275 (POB) [factor, relation to normal value] is set not to fall below a given value by the rectifier circuit. (Note that division sign in Figure block 274 should be multiplication sign!):

$$POK = 0.06$$
$$POB = 1 + POD * POK$$
$$if\ POB < 0.2\ then\ POB = 0.2$$

Blocks 277, and 278: Time delay circuit for buildup of rapid auto-regulation. Time constant is determined by factor A1K [min] (A1K=1min). Output from Block 278, ARl [ratio to normal effect], represents rapid autoregulation multiplier factor:

$$A1K = 1$$
$$dAR1/dt = (POB - AR1)/A1K, AR1_{t=0} = 1$$

Blocks 279 through 283: are precisely the same as Blocks 274 through 278 except for different constants. Factor PON [$mmHg^{-1}$] controls gain of this intermediate time autoregulation. The value of PON in original Guyton's diagram is 0.1 $mmHg^{-1}$, but in NASA implementation PON = 0.3 $mmHg^{-1}$ (Archer 1974; White 1973). Factor A2K [min] sets the time constant for the intermediate time autoregulation (A2K=20 min). Output from Block 283, AR2 [ratio to normal effect], represents the autoregulation multiplier factor for intermediate time autoregulation:

$$PON = 0.1$$
$$POA = 1 + POD * PON$$
$$if\ POA < 0.5\ then\ POA = 0.5$$
$$A2K = 20$$
$$dAR2/dt = (POA - AR2)/A2K, AR2_{t=0} = 1$$

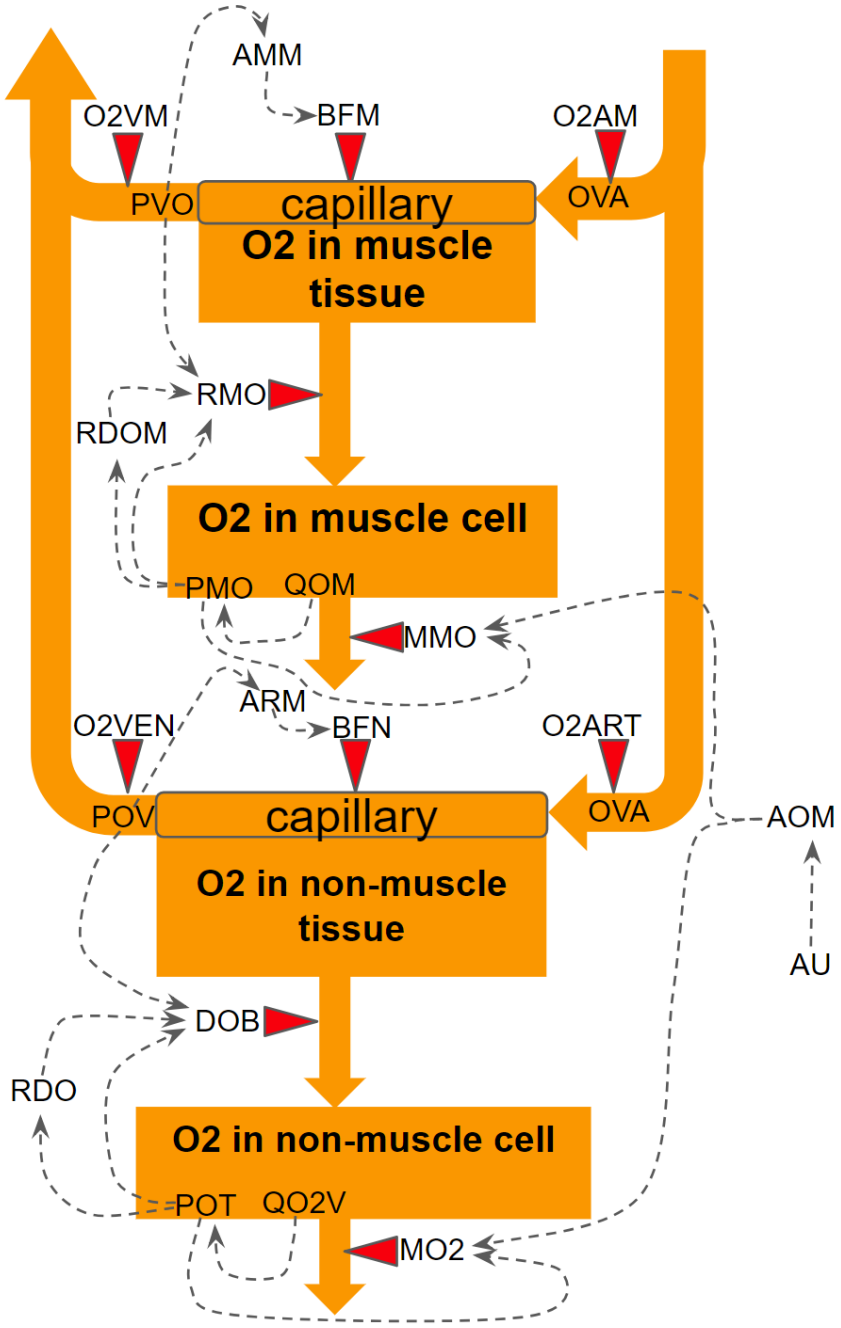
Blocks 284 through 289: calculate long time constant autoregulation multiplier factor (AR3) [ratio to normal effect]. Feedback gain for this is set by factor POZ [$mmHg^{-1}$] in Block 285. Time constant is set by factor A3K [min] (A3K = 8 days) in Block 288. Block 284 changes gain of circuit by a factor of three-fold when autoregulation control factor (POD) [mmHg] changes from a positive factor (capillary PO_2 is greater than reference factor POR [mmHg]) to a negative value, in which case POD is less than zero:

$$if\ POD > 0\ then\ POJ = POD\ else\ POJ = POD * 0.33$$
$$if\ POD > 0\ then\ POJ = POD\ else\ POJ = POD * 0.33$$
$$POZ = 0.3$$
$$POC = 1 + POJ * POZ$$

$$if\ POC < 0.3\ then\ POC = 0.3$$
$$A3K = 11520$$
$$dAR3/dt = (POC - AR3)/A3K, AR3_{t=0} = 1$$

Block 290: Multiplication of the three autoregulation factors, short-time (time constant 1 min) (ARl) [ratio to normal effect], intermediate-time (time constant 20 min) (AR2) [ratio to normal effect], and long-time (time constant 8 days) (AR3) [ratio to normal effect], to give total autoregulation factor (ARM) [ratio to normal effect], which multiplies the basic resistance for blood flow through the non-renal and non-muscle sector of the circulation in Block 35 (in “Circulatory dynamics” section):

$$ARM = AR1 * AR2 * AR3$$



Physiological scheme of muscle and non-muscle blood flow and oxygen delivery. *Calculated quantities: Oxygen pressure in muscle (PVO) and non-muscle tissues (POV) - there are equilibrated with outflowing venous blood, oxygen pressure in muscle (PMO) and in non muscle (POT) cells. Actual quantity of oxygen accumulated in muscle (QOM) and in non-muscle (QO2) cells. Oxygen delivery to muscle (O2AM) and to non-muscle (O2ART) tissues, rate of delivery of oxygen to the veins from muscle (O2VM) and from non-muscle (O2VEN) tissues. Rate of delivery of oxygen from the capillaries to the muscle (RMO) and to the non-muscle (DOB) cells. Rate of utilization of oxygen by the muscle (MMO) and by the non-muscle (MO2) cells. Blood flow to the muscle (BFM) and to the non-muscle (BFN) tissues. Autoregulation factors for muscle (AMM) and for non-muscle (ARM) tissues, that determines the resistance and therefore blood flow in muscle and in non-muscle tissues. Resistance factor to oxygen flow between capillaries and muscle cell (RDOM) and between capillaries and non-muscle cells (RDO). Overall activity of autonomic system (AU), autonomic stimulatory effect (AOM) to oxygen utilisation.*

14 Autonomic control

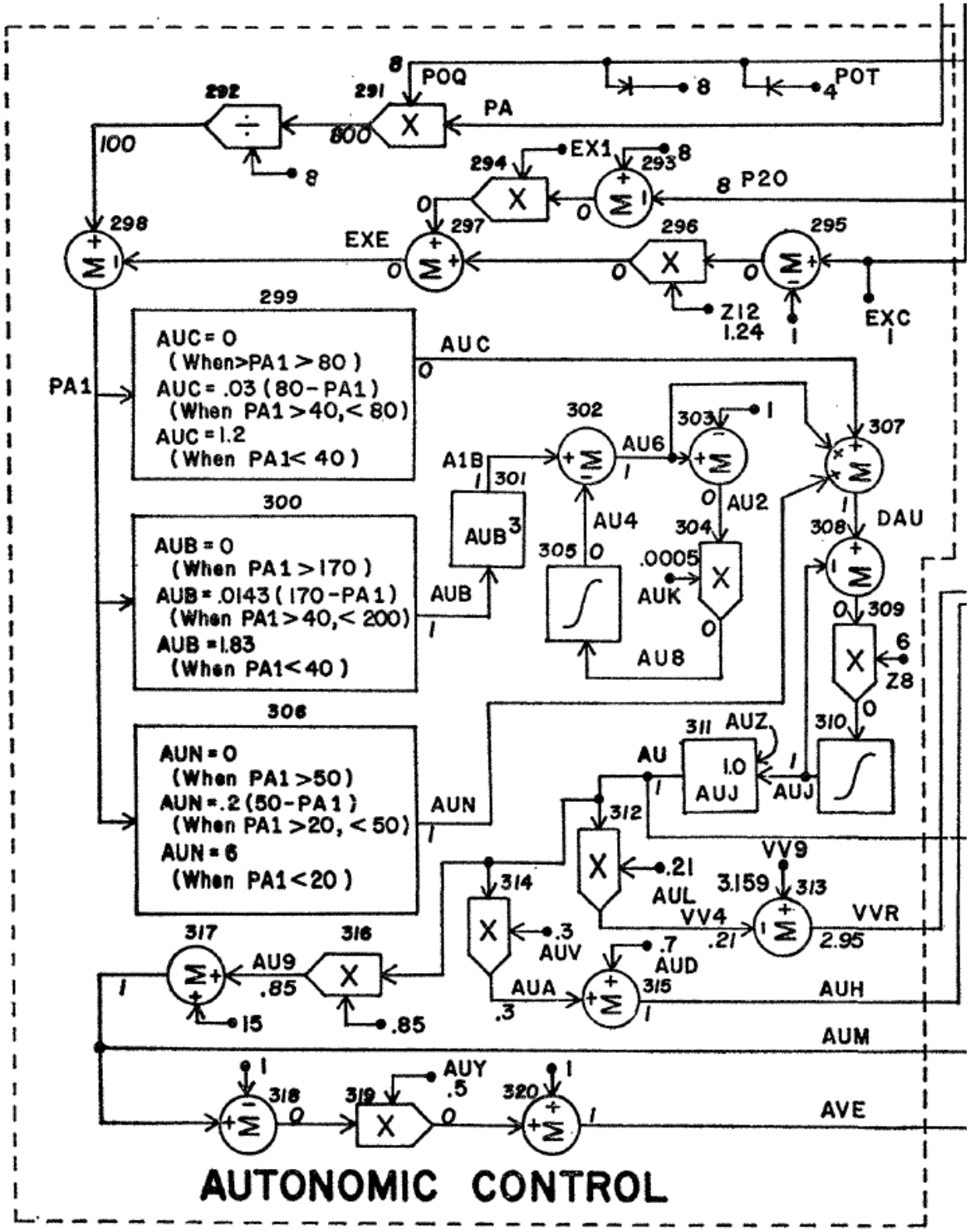
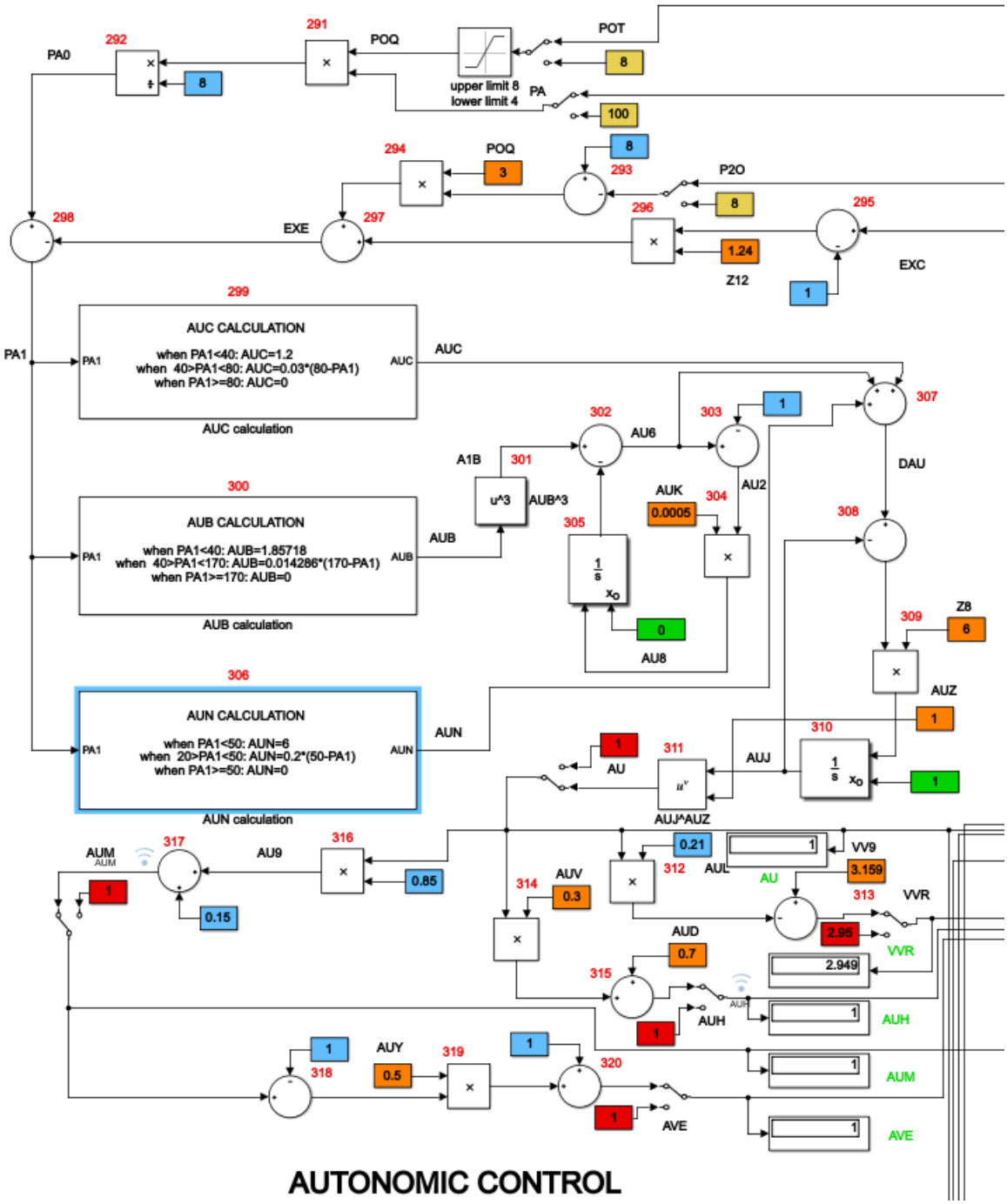


Diagram 14a Autonomic control in Guyton's diagram



AUTONOMIC CONTROL

Diagram 14b Autonomic control in Simulink

Blocks 291 and 292: calculate the factor PA0 [mmHg] that expresses effects of arterial pressure (PA) [mmHg] and non-muscle tissue PO_2 (POQ) [mmHg] limited between values of 4 and 8 mmHg, for determining the factor that drives the autonomic responses, assuming that the tissue PO_2 biases the setting of the effect of pressure on the central nervous system autonomic feedbacks. The PO_2 effect acts through direct effect of PO_2 on vasomotor center , through associated effects of CO_2 that go along with PO_2 changes, through possible cardiac receptors and other peripheral receptors that may be related to tissue blood flow and tissue PO_2:

$$if\ POT > 8\ then\ POQ = 8\ else\ if\ POT < 4\ then\ POQ = 4\ else\ POQ = POT$$
$$PA0 = POQ/8$$

Blocks 293 through 297: calculate effects of degree of exercise (EXC) [dimension factor - ratio to rest] and muscle PO_2 (P2O) [mmHg] to bias the setting of the autonomic drives in the central nervous system by multiplying EXC-1 by factor Z12=1.24 mmHg. The bias is expressed as factor EXE [mmHg] that is normally zero but that increases with degree of exercise or decrease in muscle PO_2 (P2O). The effect of muscle PO_2 (P2O) is presumably mediated through such factors as release of lactic acid and perhaps pH, CO_2, PO_2 changes in blood carried from muscles to chemoreceptive areas (EX1=3 mmHg is the constant concerned with effect of muscle cell PO2 on autonomic stimulation during exercise) :

$$EX1 = 3$$
$$Z12 = 1.24$$
$$EXE = EX1 * (8 - P2O) + Z12 * (EXC - 1)$$

Block 298: Summation of exercise and tissue oxygenation factors to cause biasing of the factor for control of autonomic outputs, The output of this block (PA1) [mmHg] rises or falls with changes in the above factors and, therefore, drives the autonomic system upward or downward:

$$PA1 = (PA0 - EXE)$$

Block 299: Calculation of the effect of chemoreceptors on autonomic stimulation AUC [dimensionless factor, ratio to difference to normal (normal is set to 1, normal difference is 0)]. Effect of drive factor on the vasomotor center (PA1) [mmHg] of the vasomotor center of the autonomic system caused by pressure effects operating indirectly through chemoreceptors (AUC) The function is expressed algebraically with two break points in the curve, at 80 and at 40. The autonomic output is expressed in terms of positive sympathetic drive and negative parasympathetic drive:

$$if\ PA1 < 40\ then\ AUC = 1.2\ else\ if\ PA < 80\ then\ AUC = 0.03 * (80 * PA1)\ else\ AUC = 0$$

Block 300: Calculation of the effect of baroreceptors on autoregulation AUB [dimensionless factor, ratio to normal effect]. Similar function as that of Block 299, but this time representing pressure effect operating through baroreceptors to stimulate the autonomic system, with break points at 170 and at 40. Output (AUB) represents positive sympathetic drive and negative parasympathetic drive:

$$if\ PA1 < 40\ then\ AUB = 1.85718\ else\ if\ PA1 < 170\ then\ AUB = 0.014286 * (170 - PA1)\ else\ AUB = 0$$

Block 301: Adjustment of sensitivity of baroreceptor drive, output of which is expressed as A1B [dimensionless factor, ratio to normal]:

$$A1B = AUB^3$$

Blocks 302 through 305: Adaptation of baroreceptor system. Time constant for adaptation is determined by constant AUK = 0.0005 min in Block 304. Output from this system is AU6 [dimensionless factor, ratio to normal], a value that always reapproaches the value of 1 with time because of adaptation of the baroreceptors:

$$AU6 = A1B - AU0$$
$$AU2 = AU6 - 1$$
$$AUK = 0.0005$$
$$dAU0/dt = AU2 * AUK, AU0_{t=0} = 0$$

Block 306: Calculation of the effect of chemoreceptors on autonomic stimulation AUN [dimensionless factor, ratio to difference to normal (normal is set to 1, normal difference is 0)] Similar autonomic drive to that in Blocks 299 and 300, but this time for central nervous ischemic response, with output designated as AUN. This too is expressed as positive sympathetic drive and negative parasympathetic drive. The break points in Block 306 are 50 and 20. (Normal output level of AUN is 0.):

$$if\ PA1 >= 50\ then\ AUN = 0\ else\ if\ AUN > 20\ then\ AUN = 0.2 * (50 - PA1)\ else\ AUN = 6$$

Block 307: Summation of autonomic stimulation from chemoreceptors (AUC) [dimensionless factor, ratio to difference to normal], baroreceptors (AU6) [dimensionless factor, ratio to difference to normal effect], and CNS ischemic response (AUN) [dimensionless factor, ratio to difference to normal], to give the summated autonomic drive of DAU [ratio to normal effect]. DAU represents the final equilibrium summated effect that will be approached once the full effect has been realized.

$$DAU = AUC + AU6 + AUN$$

Blocks 308 through 310: represent time delay circuit for full realization of autonomic drive. Output of Block 310 (AUJ) [ratio to normal effect] approaches the final equilibrium (DAU), and the time constant is determined by factor Z8 = 8 min:

$$Z8 = 8$$
$$dAUJ/dt = (DAU - AUJ) * Z8, AUJ_{t=0} = 1$$

Block 311: Exponential computation for changing sensitivity of autonomic drive to circulation. Output of this block (AU) represents positive sympathetic drive and negative parasympathetic drive [ratio to normal effect]. That is, this factor represents tendency to increase overall functional activity of the heart and to increase vascular constriction throughout the body:

$$AUZ = 1$$
$$AU = AUJ^{AUZ}$$

Blocks 312 through 320 represent circuits to set the degree of drive of the autonomic nervous system on different parts of the circulation.

Blocks 312 and 313: set the sensitivity for control of unstressed systemic venous vascular volume (VVR) [l] as determined by sympathetic stimulation of the systemic veins in Block 7.
In original Guyton's diagram VVR depends directly on AU, but in NASA implementation (Archer 1974; White 1973) VVR depends on AU indirectly, and this dependency can be modified by sensitivity coefficient AUQ.

$$AUQ = 1.0$$
$$VV9 = 3.159$$
$$AUL = 0.21$$
$$AUO = AU - 1$$
$$AUP = AUO * AUQ - 1$$
$$VVR = VV9 - AU * AUL$$

Blocks 314 and 315: determine autonomic sensitivity drive to the heart (AUH) [ratio to normal effect]:

$$AUH = AU * 0.3 + 0.7$$

In original Guyton's diagram AUH depends directly on AU, but in NASA implementation (Archer 1974; White 1973) AUH depends on AU indirectly using deviation of normal value (AUO=AU-1, see block 312A) and sensitivity coefficient AUV :

$$AUV = 0.3$$
$$AUH = AUO * AUV + 1$$

Block 315a:
In NASA implementation (Archer 1974; White 1973) is used variable AUR expressing the autonomic stimulation for heart rate [ratio to normal effect] (see block 321):

$$AUS = 1$$
$$AUR = AUO * AUS + 1$$

Blocks 316 and 317: determine sensitivity of the autonomic drive to control arteriolar resistance in the muscles and non-muscle portions of the circulation, and also to control the degree of stimulation of the afferent arterioles of the kidneys (AUM) [ratio to normal effect]:

$$AUM = AU * 0.85 + 0.15$$

In original Guyton's diagram AUM depends directly on AU, but in NASA implementation (Archer 1974; White 1973) AUM depends on AU indirectly using variable AUP=(AU-1)*AUQ+1 (see blocks 312A and 312B):

$$AUM = 0.15 + 0.85 * AUP$$

Blocks 318 through 320: set sensitivity of autonomic drive (AVE) [ratio to normal effect] to control venous resistance in the non-muscle, non-renal blood flow circuit:

AVE=0.5*(AUM-1)+1

15 Heart rate and stroke volume

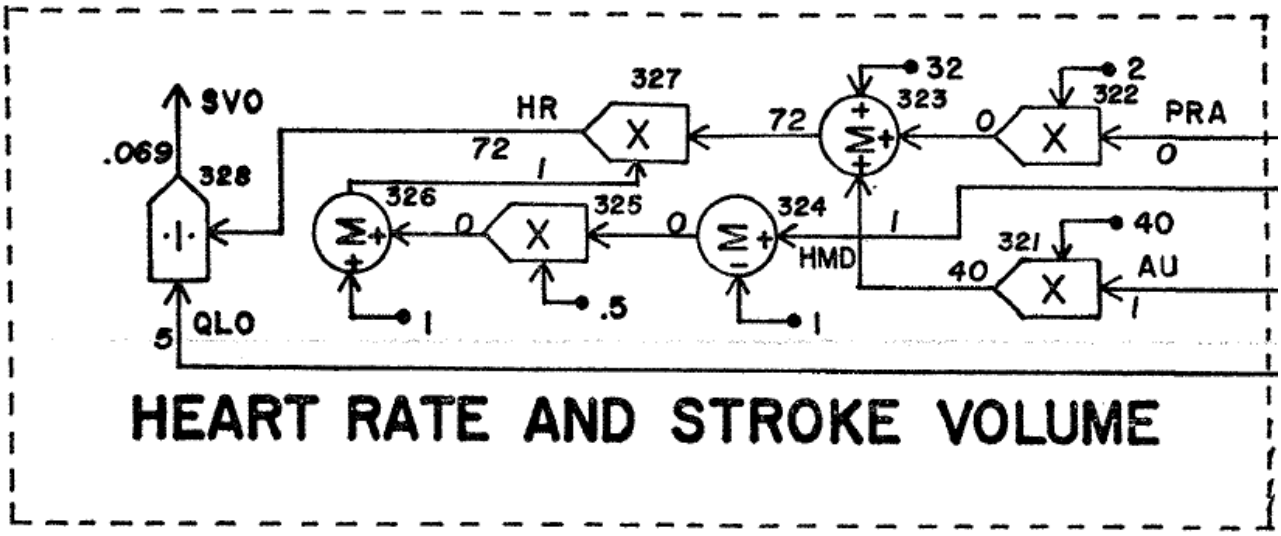
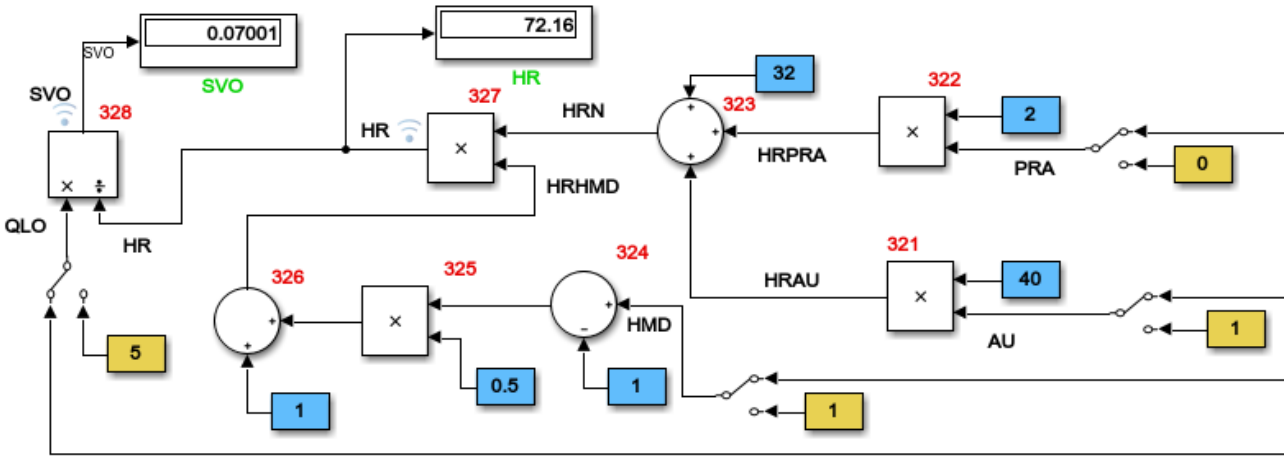


Diagram 15a Heart rate and stroke volume in Guyton's diagram



HEART RATE AND STROKE VOLUME

Diagram 15a Heart rate and stroke volume in Simulink

Block 321: Computation of HRAU [strokes/min] - portion of heart rate determined by autonomic drive (AU) [ratio to normal effect]:

$$HRAU = AU * 40$$

However in NASA implementation (Archer 1974; White 1973) instead of overall activity of autonomic system characterised by AU is used variable AUR expressing the autonomic stimulation for heart rate [ratio to normal effect]:

$$HRAU = AUR * 40$$

Block 322: Effect of right atrial pressure (PRA) [mmHg] to cause reflex effect on heart rate HRPRA [mmHg]:

$$HRPRA = PRA * 2$$

Block 323: Summation of basic heart rate factor (a constant 32 steokes/min), reflex effect from right atrial pressure - HRPRA [strokes/min] (output of Block 322), and autonomic drive effect - HRAU [strokes/min] (output of Block 321) to give the actual heart rate of the normal heart HRN [strokes/min]:

$$HRN = 32 + HRPRA + HRAU$$

Blocks 324 through 326: Calculation of effect of cardiac deterioration on heart rate HRMD [ratio to normal]. Input (HMD) [ratio to normal] represents degree of normality of heart. Sensitivity of this effect is determined by constant multiplier (0.5) in Block 325:

$$HRHMD = (HMD - 1) * 0.5 + 1$$

Block 327: Calculation of actual heart rate [strokes/min] by multiplying heart rate of normal heart HRN [strokes/min] times the effect of the deterioration factor on heart rate [HRMD [ratio to normal]:

$$HR = HRN * HRHMD$$

Block 328: Calculation of stroke volume output by dividing cardiac output (QLO) [l/min] by heart rate (HR) [strokes/min] to give stroke volume output (SVO) [l/stroke]:

$$SVO = QLO/HR$$

16 Red cells and viscosity

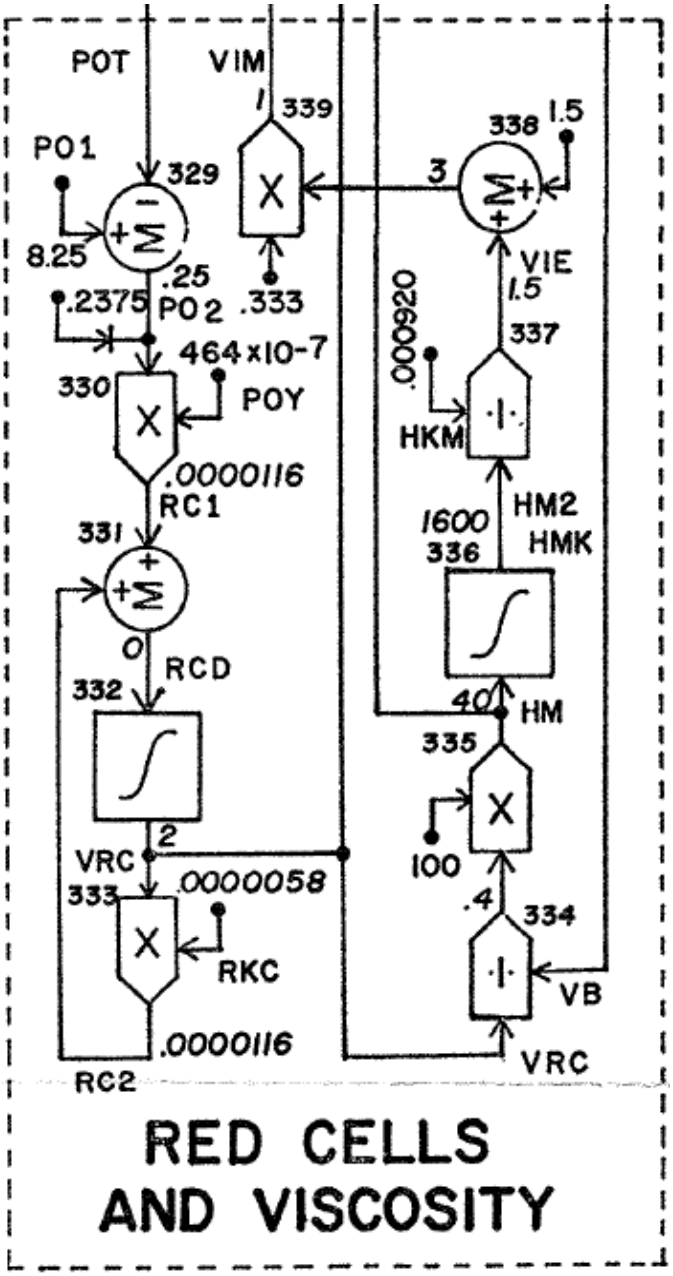
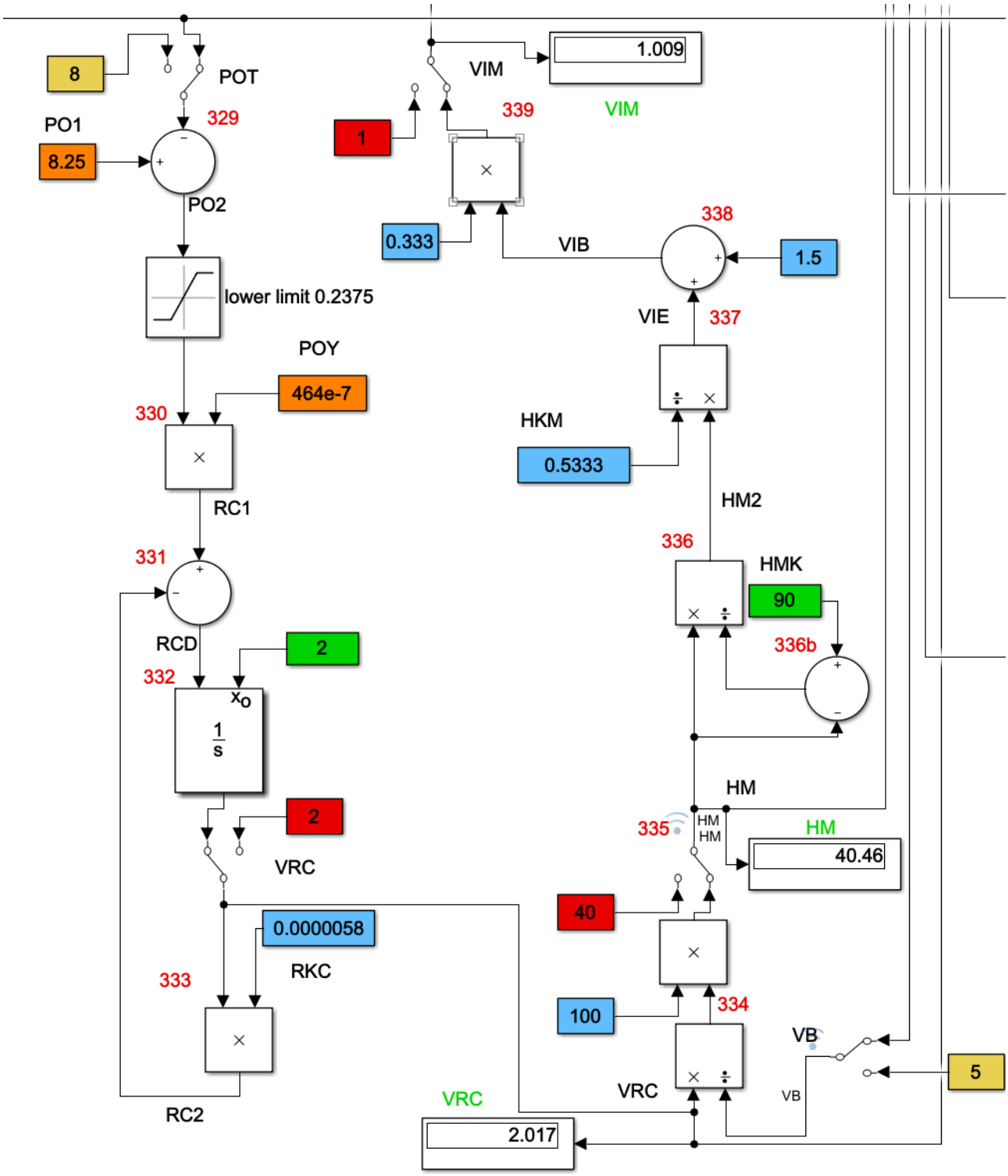


Diagram 16a Red cells and viscosity in Guyton's diagram



RED CELLS AND VISCOSITY

Diagram 16b Red cells and viscosity in Simulink

Block 329 and Block 330: Calculation of effect of non-muscle tissue PO_2 (POT) [mmHg] as a drive in causing formation of red blood cells. The drive is considered to be zero when POT equals the constant factor PO1=8.25 [mmHg] and to increase as the tissue PO_2 falls below this value. A minimum drive factor is determined by the rectifier circuit on the output of Block 329. Sensitivity of the circuit is determined by factor POY=464E-7 [min/(l*mmHg]. Output of Block 330 represents rate of red cell production (RC1) [l/min]:

$$PO1 = 8.25$$
$$PO2 = POT - PO1$$
$$POY = 0.0000464$$
$$if\ PO2 > 0.2375\ then\ RC1 = POY * PO2\ else\ RC1 = POY * 0.2375$$

Block 331: adds rate of the volume of red cell production (RC1) [l/min] and subtracts rate of the volume of red cell destruction (RC2) [l/min] to give net rate of change of red volume in circulation (RCD) [l/min] (note that in Guyton's diagram the subtraction in this block is incorrectly labeled as an addition):

$$RCD = RC1 - RC2$$

Block 332: integrates rate of red cell volume change (RCD) [l/min] to give volume of red cells in the circulation (VRC) [l]:

$$dVRC/dt = RCD, VRC_{t=0} = 2$$

Block 333: multiplies volume of red cells in circulation (VRC) [l] times constant (RKC) [min^{-1}] to determine rate of red cell destruction (RC2) [l/min]:

$$VKC = 0.0000058$$
$$RC2 = VKC * VRC$$

Blocks 334 and 335: calculate hematocrit (HM) [%] by dividing volume of red cells (VRC) [l] by blood volume (VB) [l] and multiplying by 100:

$$HM = 100 * VRC/VB$$

Blocks 336 and 237: calculates the portion of blood viscosity caused by red blood cells (VIE) [unitless relation number] caused by hematocrit. In Guyton's diagram these blocks are incorrectly depicted. Block 336 incorrectly labeled in the Guyton's diagram as an integration, Originally,block 336 might have meant a second power, as indicated by the values displayed on the diagram: squares the hematocrit to give HMK. The portion of blood viscosity (VIE) was calculated in block 337 by multiplying HMK times a constant. (note that the division sign in Guyton's diagram here is in error):

$$HMK = HM^2$$
$$VIE = HMK * 0.000920$$

The alternative meaning of blocks 336 and 337 is based on the implementation of the Guyton's model in Fortran used by NASA (Archer 1974; White 1973). The same structure of mathematical

relationships of blood viscosity calculation (VIE) was also used in the further modification of Guyton's Model in 1986. Therefore in Simulink implementation of Guyton's model we used these equations (Kofranek and Rusz 2010; Kofránek et al. 2007):

$$HMK = 90$$
$$HKM = 0.5333$$
$$VIE = HM/(HMK - HM)/HKM$$

Block 338: calculates total relative viscosity of the blood (assuming viscosity of water to equal one) - VIB [realtion to viscosity of water] by adding viscosity caused by red cells (VIE) to a constant factor representing viscosity of plasma:

$$VIB = VIE + 1.5$$

Block 339: calculates viscosity multiplier (VIM) [blood viscosity, ratio to normal blood] by multiplying relative viscosity times a constant. This factor is the viscosity multiplier factor that determines relative changes in vascular resistance with changes in viscosity from normal (normal relative viscosity is 3, therefore VIB is divided by 3 or multiplied by 0.3333 as in Guyton's diagram).

$$VIM = VIB * 0.3333$$

17 Heart hypertrophy and deterioration

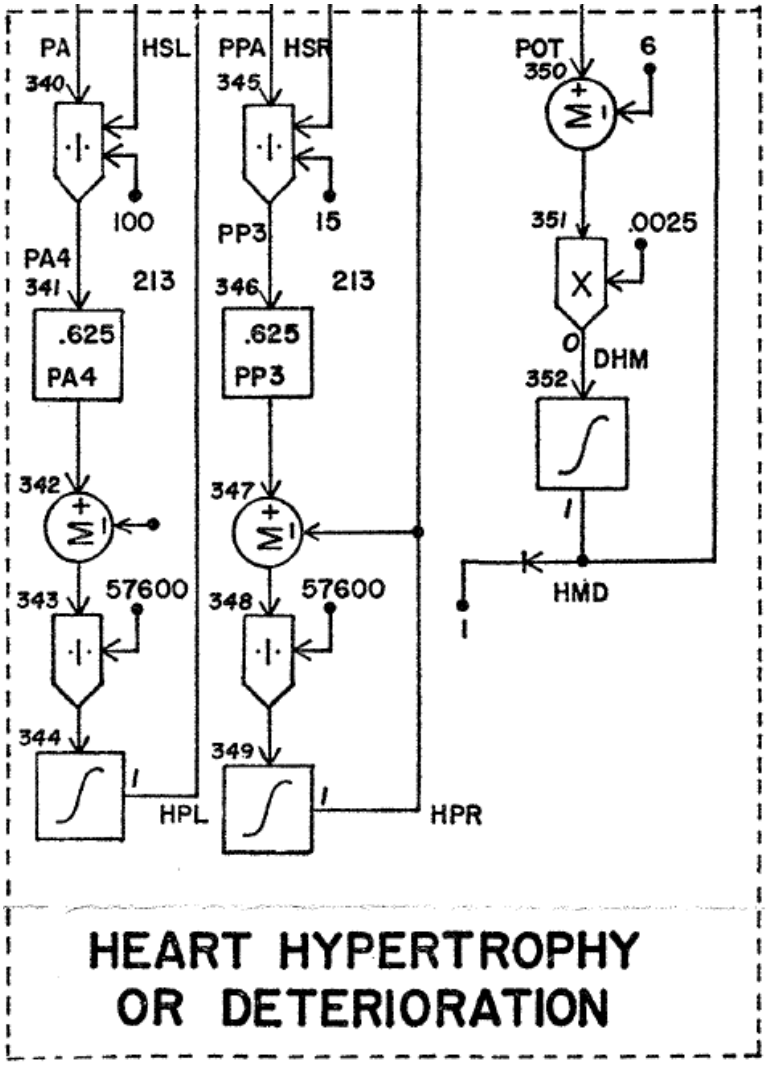


Diagram 17a Heart hypertrophy and deterioration in Guyton's diagram

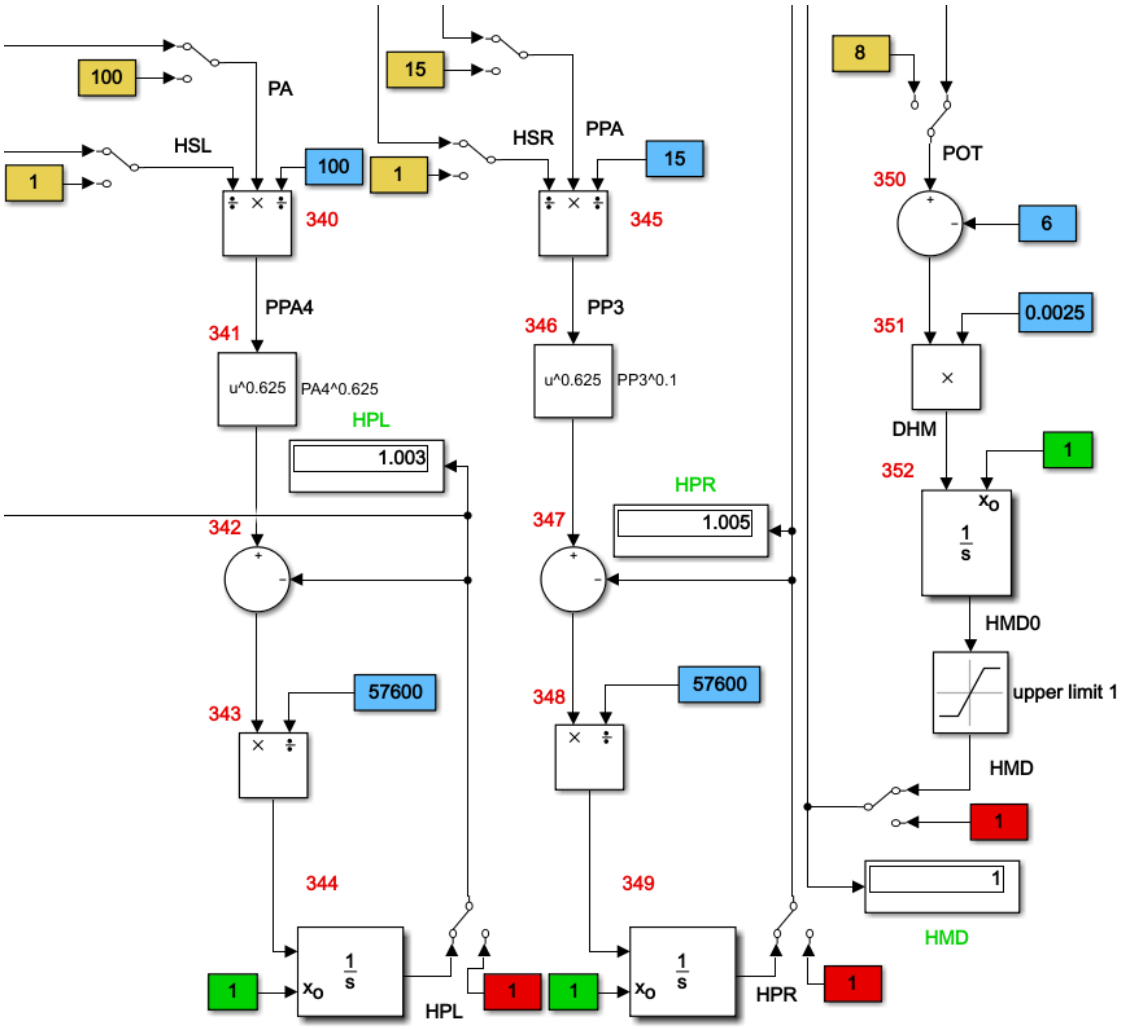


Diagram 17b Heart hypertrophy and deterioration in Simulink

Block 340: Arterial pressure (AP) [mmHg] divided by constant (100 mmHg - normal value of PA) and divided by strength of left ventricle (HSL) [relation to normal strength] to determine a drive factor for causing hypertrophy of left ventricle (PA4) [dimensionless]:

$$PPA4 = PA/100/HSL$$

Block 341: Calculation of equilibrium value of hypertrophy (HPLE) [realtive to normal effect] using exponential factor for determining sensitivity of left ventricular hypertrophy drive:

$$HPLE = PPA4^{0,625}$$

Blocks 342 through 344: represent a time delay circuit to determine approach of hypertrophy effect of the left ventricle (HPL) [relation to normal effect] to the equilibrium value of hypertrophy (output of Block 341). (Note that the subtraction factor of Block 342 should be connected to the line representing variable HPL). The time constant of this delay circuit is determined by the constant 576800 min feeding into Block 343.

$$dHPL/dt = (HPLE - HPL)/576800, HPL_{t=0} = 1$$

Block 345: Multiplication of pulmonary arterial pressure (PPA) [mmHg] and division by right heart strength (HSR) [relation to normal strength] and by a constant (13 mmHg - normal value of PA) to give a hypertrophy drive factor for right ventricle (PP3) [dimensionless factor]:

PP3=PPA/13/HSR

Block 346: Exponential sensitivity factor to adjust the degree of the hypertrophy drive factor HPRE [relation to normal effect]. The output of Block 346 represents the final degree of hypertrophy that will be achieved in response to the right heart hypertrophy drive (PP3):

$$HPRE = PP3^{0,625}$$

Blocks 347 through 349: Time delay for development of hypertrophy, with output of this circuit (HPR) equaling the actual degree of right heart hypertrophy and approaching as an equilibrium value the output of Block 346. Time delay is determined by the constant feeding Block 348.

$$dHPR/dt = (HPRE - HPR)/576800, HPR_{t=0} = 1$$

Blocks 350 through 352: represent deterioration of the heart caused by decreased tissue PO_2 (POT) [mmHg], assuming that the coronary circulation shares in this decreased tissue PO_2. Blocks 350 and 351 represent curve fitting process to indicate that rate of deterioration of the heart increases progressively as tissue PO_2 falls below 6 mm Hg. Constant feeding Block 351 determines rate of deterioration. Output of Block 351 (DHM) represents actual rate of deterioration. Block 352 integrates rate of deterioration (DHM) to give a multiplier factor to multiply strength of the two ventricles (HMD) depending upon the degree of deterior-ation. HMD is the cardiac depressant effect of hypoxia [relation to normal function]. This factor can never rise above one because of rectifier in output of Block 352, but the deterioration factor can fall to any degree below one and thereby decreases strength of the two ventricles.

$$dHMD0/dt = (POT - 6) * 0{,}0025,\ HMD0_{t=0} = 1$$

$if\ HMD0 > 1\ HMD = 1\ else\ HMD = HMD0$