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A bond graph model of the cardiorespiratory system

Introduction

This document provides the technical details of the modelling framework used for regulation of the cardiorespiratory system in a number of ABI projects, including the MBIE 12 Labours project (heart-lung interaction), the Horizon Europe VITAL project (blood pressure regulation), SPARC/REVEAL (interpretation of cardiovascular responses to autonomic stimulation) and a new course being developed for teaching modelling techniques to pharmacology students at the University of Indiana. We describe how the FC map is being developed as a user-interface to multiscale modelling and its associated data. We also document the strategy for incorporating the bond graph (BG) modules used for protein-level interactions (available in graphical form on the FC map and in CellML models on PMR for solving with OpenCOR) into the Circulatory Autogen python-based software that can link CellML models with 1D and 3D Navier-Stokes flow solvers and with finite element cardiac electromechanics models.

We first describe the bond graph approach to physiological modelling and provide an overview of the components of the cardiorespiratory system relevant to regulation of blood pressure. We then discuss a number of simple biophysical mechanisms relevant to simple bond graph models that demonstrate the coupling between processes at the cell level and the whole-body level for control of sodium, water and glucose. This simple model uses a 2-compartment CVS (cardiovascular system) model with two epithelial ducts (gut and kidney) and three epithelial cell transport models. This is subsequently extended to a CVS model with about 50 vascular compartments, six tissue compartments (gut, kidney, lungs, liver, muscle and brain) and six corresponding cell-level transport models for sodium, water and glucose. To include feedback mechanisms, we then add models of respiratory mechanics and autonomic neural feedback. We show how the FC map is used both to display these models and to provide a user-interface to explore a model, to run simulations and to analyse model predictions.

1. The bond graph modelling framework

Bond graphs provide a useful way of formulating and visualising a thermodynamically valid biophysical model because they ensure that mass, charge and energy are each conserved, and they clearly distinguish the mechanisms for (i) transmission of power (the product of flux v and potential u), (ii) energy storage (mechanically in a spring, electrically in a capacitor or chemically in a solute dissolved in a solvent), (iii) energy dissipation to heat (a mechanical damper, an electrical resistance or a chemical reaction), and (iv) energy transfer between mechanical, electrical or biochemical domains. Most importantly they distinguish between the conservation laws of physics and the empirically measured constitutive parameters that characterise particular materials.

For example, a chemical species i is *stored* as a solute q_j^i (moles) in a solution at location j with a particular *solubility* that generates a chemical potential u_j^i (J.mol^{-1}). The diffusion of this solute through a dissipative medium from one location to another is a molar flux $v_j^i = \frac{dq_j^i}{dt}$ (mol.s^{-1}) that depends both on the difference in chemical potential between the two locations and on the *diffusivity* of that medium. The measured values for *solubility* and *diffusivity* are two distinct material constants, and both are quite separate from the equations representing mass and energy conservation.

We use the symbol q_j^i to denote the quantity in moles (mol) of a chemical species i at location j. Similarly, q_j^e represents electrical charge in Coulombs (C), and q_j^m represents distance in meters (m) or volume in m^3. Molar flux is denoted $v_j^i = \frac{dq_j^i}{dt}$ (mol.s^{-1}), where u_j^i (J.mol^{-1}) is the chemical potential generated by solute q_j^i, and $v_j^e = \frac{dq_j^e}{dt}$ (C.s^{-1}) is the electrical current associated with electrical potential u_j^e (J.C^{-1}). In mechanics $v_j^m = \frac{dq_j^m}{dt}$ is the velocity (m.s^{-1}) associated with a force u_j^m (J.m^{-1}), or fluid flow (m^3.s^{-1}) associated with pressure (J.m^{-3}), or angular velocity (rad.s^{-1}) associated with torque (J.rad^{-1}).

These units express the energy flux (J.s^{-1}) as the product of a potential in Joules per unit quantity (mol, C, m, m^3 or rad) that is driving the flow of that quantity in a way that is common to all physical systems. i.e. the product of potential u_j^i (J.mol^{-1}) and flux v_j^i (mol.s^{-1}), or potential u_j^e (J.C^{-1}) and flux v_j^e (C.s^{-1}), is always power (J.s^{-1}). Similarly, the product of mechanical potential (force, pressure, or torque) and mechanical flux (velocity, fluid flow, or angular velocity) is power. The product of heat flow, which is an entropy flux (entropy.s^{-1}), and thermal potential (J.entropy^{-1} or temperature in Kelvin K) is also power. It is therefore convenient to use the symbol q to represent any chemical, electrical, mechanical or heat quantity (with v and u being the flux and potential), with the superscript identifying the quantity and the subscript identifying the compartmental location.

Lines of power transmission called 'bonds' always have an associated flux v and potential u (see Figure 1). If these bonds meet, the sum of powers must be zero: $\sum u.v = 0$, to ensure power conservation. If they share a common potential u (called a '0:node'), power conservation $u\sum v = 0$ becomes just $\sum v = 0$ (for non-zero u), which is *mass conservation* if v is a molar flux or mechanical flow and *charge conservation* if v is an electrical flux. Alternatively, if they share a common flux v (called a '1:node'), power conservation $v\sum u = 0$ becomes just $\sum u = 0$ (for non-zero v), which is *energy conservation*. For chemical reactions these correspond to mass conservation and stoichiometric relations, respectively. For electrical circuits they correspond to Kirchhoff's current law and voltage law, respectively. For mechanical systems they correspond to kinematic consistency and force or torque balance, respectively.

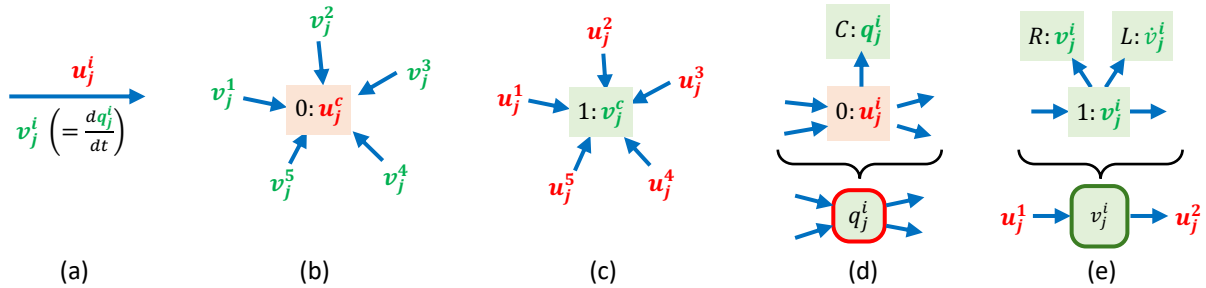


Figure 1. Key bond graph concepts: (a) a bond, which transmits energy, carries both a flow v_j^i and a potential u_j^i; (b) a 0:node is a bond junction where the potential is the same for all bonds and therefore the sum of flows is zero (conservation of mass or charge); (c) a 1:node is a bond junction where the flow is the same for all bonds and therefore the sum of potentials is zero (conservation of energy); (d) a 0:node is usually associated with capacitive energy storage (*C*) as well as flux balance and can be more succinctly expressed by the red-bordered box where the potential u_c^1 is given by an empirically defined capacitive storage relationship $u_j^i = f(q_j^i)$; (e) a 1:node is usually associated with energy dissipation (*R*) and inertia (*L*) as well as energy balance and can be more succinctly expressed by the green-bordered box where the energy balance includes the dependence on viscous loss $R(v_j^i)$ and inertia or inductance $L\dot{v}_j^i$: i.e., $u_j^1 = u_j^2 + R(v_j^i) + L\dot{v}_j^i$.

The bond graph diagram for a reaction can often be usefully simplified as shown in Figure 2.

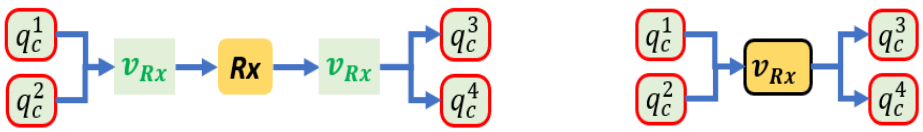


Figure 2. The bond graph diagram for the reaction shown in (a) can be represented by (b). Note the black border around the *Rx* reaction box.

2. Overview of blood pressure regulation

A major goal of the VITAL project is to model the regulation of blood pressure with all relevant physiological mechanisms. A schematic showing the mechanisms involved in the control of blood pressure is shown in Figure 3. We will explore aspects of this schematic in the following sections.

Average blood pressure is primarily determined by the volume of fluid in the circulatory system since excess fluid is accommodated by the elastic distension of the blood vessels, which requires a higher pressure. This circulatory blood volume is primarily dependent on the osmotic pressure generated by sodium ions, chloride ions and proteins (colloidal pressure). The osmotic pressure of sodium is used to absorb water from the GI tract and the salivary glands, and to reabsorb some of the water lost to the renal tubules in Bowman's capsule and to sweat glands (for temperature control). *Natriuresis*, the process of sodium excretion in the urine via the kidneys, is promoted by atrial and ventricular natriuretic peptides (ANP and BNP - in response to atrial and ventricular stretch), and by calcitonin (which regulates calcium and phosphate levels in the blood). Natriuresis is inhibited by aldosterone acting on the epithelial cells of the distal tubule where the final stage of sodium reabsorption is regulated (see below).

Central systemic arterial blood pressure is further controlled by three mechanisms: (i) *cardiac output*, which is dependent on heart rate, myocardial contractility and LV filling pressure (determined by both atrial pressure and the upstream impedance), (ii) *peripheral vascular resistance*, and (iii) *arterial blood volume fraction* (i.e. shifting blood from the veins to the arteries by contracting the venous circulatory volume). Note that normally the venous system holds about 70% of blood volume, but contraction of smooth muscle cells (SMCs) in the walls of the large veins in the abdomen can shift up to 10% of blood volume from the venous system to the arterial system and thereby raise arterial pressure. Physical exercise also affects venous return since muscle activity helps propel venous blood towards the heart.

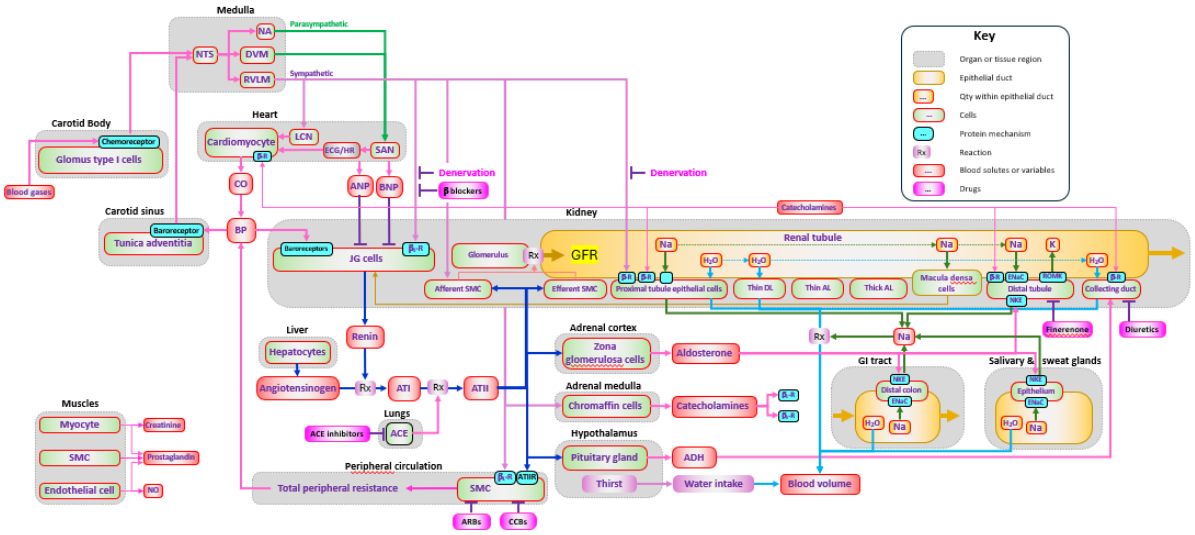


Figure 3. Schematic of the mechanisms used in the control of blood pressure.

The signalling pathways used for controlling sodium levels in the blood (and hence blood volume), cardiac output, peripheral vascular resistance and the fraction of blood in the arteries are the autonomic nervous system (sympathetic and parasympathetic activity) and the release of the circulating catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline).

Renin, released by the juxta-glomeruli cells of the kidney in response to baroreceptor and sympathetic stimulation, and tubular sodium levels (sensed by the macula densa cells), catalyses the conversion of angiotensinogen (released by hepatocytes in the liver) to AT-1 (angiotensin 1). AT-1 is converted to AT-2 by ACE (angiotensin converting enzyme) in the lung circulation.

AT-2 stimulates (i) SMC contraction in both the afferent and efferent arterioles before and after the glomerular capillaries, respectively, to control perfusion pressure in the glomeruli; (ii) the release of aldosterone from the zona glomerulosa cells of the adrenal cortex (thereby upregulating NKE expression in the epithelial cells of the distal tubules and the distal colon to increase sodium uptake into the blood); (iii) the release of epinephrine from the chromaffin cells of the adrenal medulla which acts on α_1- adrenoreceptors in endothelial cells to increase vascular tone; and (iv) the release of ADH (antidiuretic hormone) from the pituitary gland of the hypothalamus to increase the reabsorption of water from the collecting ducts in the kidney.

3. Water movement and the control of osmolality and ECF

The most significant aspect of blood pressure regulation is the control of the volume of water within the CVS, both in total volume and between the arterial and venous sides. The non-cellular liquid component of blood (plasma), making up about 55% of blood volume, contains water, proteins, salts, hormones, enzymes, vitamins, etc. The other 45%, called the haematocrit, is the percentage volume occupied by red blood cells (RBCs).

The uptake of water into the blood from the gut and the reuptake of water in the renal tubules (that then excrete excess water), is largely controlled by the difference in the concentration of sodium between blood and those compartments, since blood sodium (and to a lesser extent chloride ions) creates the osmotic pressure for fluid movement. Note that, in comparison with the 140mM sodium concentration on blood, potassium (4.5mM) and glucose (5-10mM) provide a much smaller contribution to the osmotic pressure.

Osmolality (solute per kg; cf. 'osmolarity' is per litre) is controlled by drinking water and renal excretion of solute-free water. Controlling water independently of Na^+ is essential for controlling osmolality. Receptors in the hypothalamus that detect changes in plasma osmolality send signals to brain thirst centres and initiated the release of ADH (antidiuretic hormone, also called vasopressin) from the pituitary gland.

65% of sodium is in the ECF (extracellular fluid), 10% in the intracellular fluid and 25% in bone (bound as Na^+ apatites). The concentration of Na^+ in plasma and interstitial fluid is 135-145mM. The kidneys excrete Na^+ in response to an increase in the circulating ECF (especially in thoracic blood vessels), not $[Na^+]$. E.g. the increase in thoracic blood volume when a person lies down or is immersed in warm water, increases Na^+ excretion.

4. Hydrostatic pressure and the elasticity of blood vessels

Hydrostatic pressure is the potential u_j^w (in units $J.m^{-3}$ or $kJ.L^{-1}$ or kPa) associated with the quantity of water q_j^w (L) in compartment j. Note that because water is an incompressible fluid, the potential u_j^w is not defined by an equation of state (e.g. dependency on density) but rather is determined by the boundary conditions at surfaces where the water is subjected to imposed forces (e.g. the compressive force of ventricular muscle). Systolic blood pressure is about 16 kPa.

Note that gravitational effects on hydrostatic pressure are significant: 1 kg is 1 $J.m^{-1}/m.s^{-2}$ = 1 $J.s^2.m^{-2}$ (mass=force/acceleration) and water has a density of

$$\rho = 1\ g.cm^{-3} = 1\ kg.L^{-1} = 1\ J.s^2.m^{-2}.L^{-1} \times 10^3\ L.m^{-3} = 10^3\ J.s^2.m^{-5}.$$

The pressure from the gravitational (mass) effect of a height difference of $h = 1$ m is therefore:

$$p = \rho g h = 10^3\ J.s^2.m^{-5} \times 9.81\ m.s^{-2} \times 1\ m \approx 10^4\ J.m^{-3} = 10\ kPa$$

i.e. when a person stands up, the pressure in their feet increases by about 10 kPa per meter. Therefore, for someone whose heart is 1.3 m above their feet, an additional 13 kPa pressure at the feet adds to the 16 kPa generated by the heart.

We need constitutive relations that define the storage of blood via the elasticity of compliant blood vessels. The constitutive relationship between the pressure and volume of blood in an elastic vessel is given by the following J-shaped 'pole-zero' relation (see Figure 4):

$$u_j^b = E_j . \frac{q_j^b - \bar{q}_j^b}{\left(\hat{q}_j^b - q_j^b\right)^2}$$

where

u_j^b is blood pressure

q_j^b is blood volume

$\bar{q}_j^b$ is unstressed volume

$\hat{q}_j^b$ is maximum volume

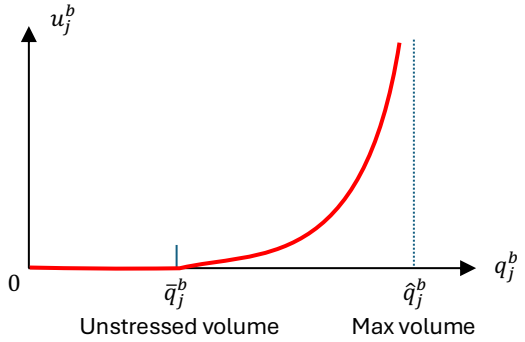


Figure 4. Pressure-volume relation for a blood vessel. The parameter E_j scales the pressure at a given volume.

The elasticity parameter E_j, which incorporates the effects of both vessel wall compliance and smooth muscle contraction, needs to be a function of both sympathetic neural activity to the peripheral vessels (q_j^{symp}) and to the level of the hormone AT2 circulating in the blood (q_j^{AT2}).

5. Sodium potential and osmotic pressure

The constitutive relationship between the chemical potential and molar quantity of sodium is given by

$$u_j^{Na^+} = RTln\left(\bar{q}_j^{Na^+}\right),$$

where $\bar{q}_j^{Na^+} = K_j^{Na^+} . q_j^{Na^+}$ is dimensionless and $K_j^{Na^+}$ is the thermodynamic constant for sodium.

Osmotic pressure in compartment j (for a dilute solution) is given by the van't Hoff equation:

$$u_j^{osmotic} = RTc_j^{Na^+},$$

which is analogous to the ideal gas law $p = \frac{n}{V}RT$. Most physiology textbooks assume that this 'osmotic pressure' is the chemical potential of the fluid (altered by the presence of the solute), but Manning and Kay, 2023, based on original work by Debye in 1923, point out that the impact on water flow through a membrane of a solute concentration difference across the membrane which is impermeable to that solute is a property of the *membrane* (and its '*reaction*'), and is not a property of the fluid on either side. It is the effect of the solute gradient within the membrane that provides an imbalance of molecular forces that impede the flow of water across the membrane. The flow of water across the membrane is given by

$$v_m^w = k_m^w \left\{u_1^w - u_2^w - RT\left(\frac{q_1^s}{q_1^w} - \frac{q_2^s}{q_2^w}\right)\right\} \quad (\text{L.s}^{-1})$$

where u_j^w (kPa) is the hydrostatic pressure (i.e. potential) of the water in compartment j containing q_j^w (L) of water and q_j^s (mol) of solute. k_m^w (L.s^{-1}.kPa^{-1}) is the hydraulic permeability of the membrane. Note that this is a constitutive law for the membrane reaction and that the power dissipation associated with this reaction is $(u_1^w - u_2^w).v_m^w$ (J.s^{-1}).

If sodium is the only solute at a concentration difference of 140 mM, zero flow is obtained when

$$\Delta u_j^w = RT.\Delta\left(\frac{q_j^{Na^+}}{q_j^w}\right) = RT.\Delta([Na^+]) = 25 \text{ kJ.mol}^{-1} \text{ x } 140 \text{ mol.m}^{-3} = 3500 \text{ kPa}.$$

This is 200 times greater that blood pressure and about 10 times the pressure sustainable by a bilipid membrane, therefore cells must maintain equal osmolarity across their membranes (the consequences of not doing so are seen in dysentery and severe clinical conditions such as cholera).

6. Intracellular pH

Intracellular pH has a major impact on many aspects of subcellular function and is therefore closely regulated. For most cells the pH is about 7 with blood being slightly more alkaline (pH>7) since the higher levels of bicarbonate in blood mop up the hydrogen ions in the carbonic anhydrase reaction. Here we assume an intracellular pH of 7, or $[H^+]_i$ =10^{-7} (mol.L^{-1} or M), or $[H^+]_i = 10^{-4}$ mM.

7. Energy considerations: Hydrolysis of ATP

We illustrate the application of bond graph modelling to a biochemical reaction by examining the hydrolysis of ATP, which supplies the energy to drive nearly all physiological processes.

The hydrolysis of ATP to ADP and P_i (inorganic phosphate) is represented as chemically and as a bond graph process in Figure 5.

$$ATP^{4-} + H_2O \underset{A^r}{\overset{A^f}{\rightleftarrows}} ADP^{3-} + HPO_4^{2-} + H^+$$

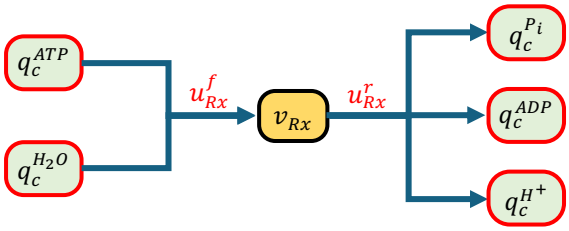


Figure 5. The bond graph representation of the ATP hydrolysis reaction.

The forward reaction potential is expressed in terms of the nondimensionalised quantity of ATP by

$$u_{Rx}^f = u_c^{ATP} + u_c^{H_2O} = RT.ln\left(\bar{q}_c^{ATP}.\bar{q}_c^{H_2O}\right) = RT.ln(\bar{q}_c^{ATP}),$$

where

$$\bar{q}_c^{ATP} = K_c^{ATP}.q_c^{ATP} = K_c^{ATP}.V.[ATP],\ \ \bar{q}_c^{H_2O} = K_c^{H_2O}.q_c^{H_2O} = 1$$

and K_c^{ATP} is the Boltzmann thermodynamic constant for ATP. [.] indicates a concentration and V is the compartment volume of containing q_c^{ATP} moles of ATP.

Similarly, the reverse reaction potential is

$$u_{Rx}^r = u_c^{ADP} + u_c^{P_i} + u_c^{H^+} = RTln(\bar{q}_c^{ADP}) + RTln\left(\bar{q}_c^{P_i}\right) + RTln\left(\bar{q}_c^{H^+}\right) = RT.ln\left(\bar{q}_c^{ADP}.\bar{q}_c^{P_i}.\bar{q}_c^{H^+}\right),$$

where

$$\bar{q}_c^{ADP} = K_c^{ADP}.q_c^{ADP} = K_c^{ADP}.V.[ADP],\ \ \bar{q}_c^{P_i} = K_c^{P_i}.q_c^{P_i} = K_c^{P_i}.V.[P_i],\ \bar{q}_c^{H^+} = K_c^{H^+}.q_c^{H^+} = K_c^{H^+}.V.[H^+]$$

The molar flux through the reaction is

$$v_{Rx} = \kappa_{Rx}\left(e^{u_{Rx}^f/RT} - e^{u_{Rx}^r/RT}\right) = A^f q_c^{ATP} - A^r q_c^{ADP}.q_c^{P_i}.q_c^{H^+} \quad \text{(mol.s}^{-1}\text{)},$$

where $A^f = \kappa_{Rx}.K_c^{ATP}$ and $A^r = \kappa_{Rx}.K_c^{ADP}.K_c^{P_i}.K_c^{H^+}$ are the forward and reverse 'affinities' for the reaction, but note that these are a combination of the kinetic reaction rate parameter κ_{Rx} and the thermodynamic (Boltzmann) parameters K_c^i.

The reaction is at equilibrium when the flux is zero:

$$v_{Rx} = 0 \text{ when } \frac{q_c^{ADP}.q_c^{P_i}}{q_c^{ATP}} = \frac{A^f}{A^r} = \frac{K_c^{ATP}}{K_c^{ADP}.K_c^{P_i}} = k^{equil} \text{ (mol)},$$

where k^{equil} is the equilibrium constant for the hydrolysis reaction.

The Gibbs free energy per mole of ATP available to drive the flow of ions against their concentration gradients is the difference in chemical potentials:

$$\Delta G^{ATP} = u_{Rx}^r - u_{Rx}^f = RT.ln\left(\frac{\bar{q}_c^{ADP}.\bar{q}_c^{P_i}.\bar{q}_c^{H^+}}{\bar{q}_c^{ATP}}\right) = RT.ln\left(\frac{[ADP].[P_i].[H^+]}{[ATP]}.\frac{K_c^{ADP}.K_c^{P_i}.K_c^{H^+}}{K_c^{ATP}.}.V\right) = RT.ln\left(\frac{[ADP].[P_i].[H^+]}{[ATP].k_{equil}^{ATP}}\right).$$

With RT = 2.5 kJ.mol^{-1}, concentrations of $[ATP]$= 4.4mM, $[ADP]$= 0.5mM, $[P_i]$ = 1mM, $[H^+]$ = 10^{-4}mM, and an equilibrium constant k_{equil}^{ATP} =1.4 10^5 mM,

$$\Delta G^{ATP} = 2.5ln\left(\frac{0.5}{6.16.10^5.}\right) = -35 \text{ kJ.mol}^{-1}.$$

Note that the ΔG^{Na} required to move 3 sodium ions from 10mM to 130mM in the NKE pump is

$$\Delta G^{Na} = 3RT.ln\left(\frac{\bar{q}_o^{Na^+}}{\bar{q}_i^{Na^+}}\right) = 3RT.ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right) = 3RT.ln\left(\frac{130}{10}\right) = 19 \text{ kJ.mol}^{-1}$$

Similarly, the ΔG^K required to move 2 potassium ions from 5mM to 120mM in the NKE pump is

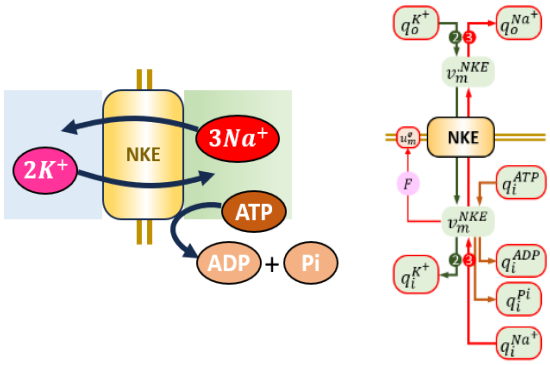
$$\Delta G^K = 2RT.ln\left(\frac{\bar{q}_i^{K^+}}{\bar{q}_o^{K^+}}\right) = 3RT.ln\left(\frac{[K^+]_i}{[K^+]_o}\right) = 3RT.ln\left(\frac{120}{5}\right) = 16 \text{ kJ.mol}^{-1}$$

ΔG^{ATP} = -54 kJ.mol^{-1} is therefore barely sufficient to operate the pump.

The presence of Mg^{2+} can increase ΔG^{ATP} to -54 kJ.mol^{-1} (i.e. about 21 x *RT*) which would generate 19 kJ.mol^{-1} of heat and give the NKE pump an efficiency of $\frac{35}{54}.100 = 65\%$

8. Sodium-potassium ATPase pump (NKE)

Figure 6 shows a chemical schematic and bond graph model of the NKE ATPase pump.



(a) (b)

Figure 6. The NKE ATPase pump. (a) NKE chemistry, (b) bond graph model,

Under Briggs-Haldane conditions, the NKE flux is given by

$$v_m^{NKE} = \frac{K_6\kappa_6 q_{tot}}{C-AD}\left\{\left(\frac{\bar{q}_i^{Na^+}}{\bar{q}_o^{Na^+}}\right)^3.\frac{\bar{q}_i^{ATP}}{\bar{q}_i^{ADP}.\bar{q}_i^{P_i}.\bar{q}_i^{H^+}} - \left(\frac{\bar{q}_i^{K^+}}{\bar{q}_o^{K^+}}\right)^2.e^{\frac{Fu_m^e}{RT}}\right\}, \quad (1)$$

where A, C and D are algebraic expressions involving all the ligand quantities along with the membrane potential and a number of additional parameters which, like K_6, κ_6 and q_{tot}, must be fitted to experimental data.

Substituting in terms of concentrations, this becomes

$$v_m^{NKE} = \frac{K_6\kappa_6 q_{tot}}{C-AD}\left\{\left(\frac{[Na^+]_i}{[Na^+]_o}\right)^3.\frac{[ATP].k_{equil}^{ATP}}{[ADP].[P_i].[H^+]} - \left(\frac{[K^+]_i}{[K^+]_o}\right)^2.e^{\frac{Fu_m^e}{RT}}\right\}, \quad (1)$$

where $k_{equil}^{ATP} = 1.4e5$mM (Pellufo & Hernández, 2023).

The NKE flux is zero at the reversal potential

$$u_m^e = \frac{RT}{F}ln\left[\left(\frac{[Na^+]_i}{[Na^+]_o}\right)^3.\left(\frac{[K^+]_o}{[K^+]_i}\right)^2.\frac{[ATP].k_{equil}^{ATP}}{[ADP].[P_i].[H^+]}\right]. \quad (2)$$

Typical values for epithelial cells are $[Na^+]_i$= 10mM, $[Na^+]_o$= 140mM, $[K^+]_i$= 140mM, $[K^+]_o$= 5mM, $[ATP]$ = 10mM, $[ADP]$ = 0.1mM, $[P_i]$ = 0.1mM, with $\frac{RT}{F} = \frac{2.5\ \mathrm{kJ/mol}}{10^5\ \mathrm{C/mol}}$ = 25mV. Substituting these values together with $k_{equil}^{ATP} = 1.4e5$ mM gives a reversal potential of

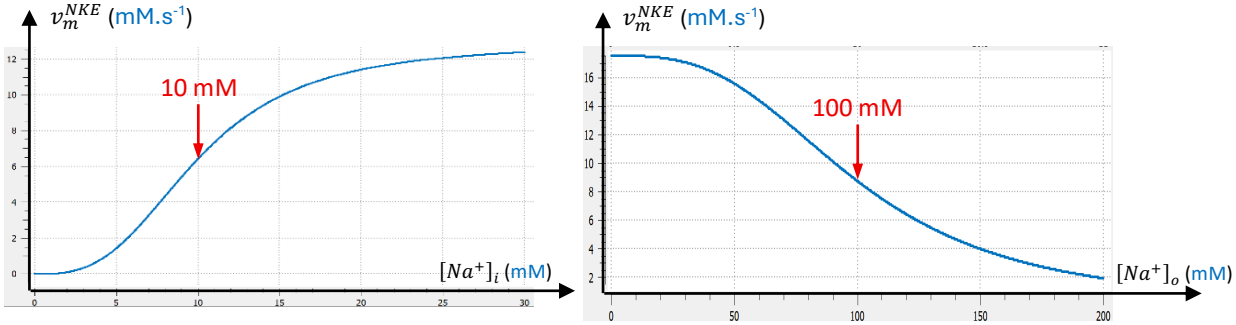
$$u_m^e = 25.ln\left[\left(\frac{10}{140}\right)^3.\left(\frac{5}{140}\right)^2.1.4e8\right] = 104 \text{ mV}.$$

i.e. potentials more positive than this result in the NKE flux being inward rather than outward.

For the current simple model we assume fixed concentrations of potassium inside and outside the cell, fixed concentrations of ATP, ADP and phosphate P_i inside the cell, a fixed membrane potential u_m^e, and a sigmoid expression for the dependence of NKE flux on the concentrations of sodium inside and outside the cell ($c_i^{Na^+}$, $c_o^{Na^+}$). The flux is then given by

$$v_m^{NKE} = k_m^{NKE}.\frac{([Na^+]_i)^3.([K^+]_o)^2.[ATP].k_{equil}^{ATP} - ([Na^+]_o)^3.([K^+]_i)^2.[ADP].[P_i].e^{Fu_m^e/RT}}{\left\{1+\left([Na^+]_i/k_i^{NKE}\right)^3\right\}.\left\{1+\left([Na^+]_o/k_0^{NKE}\right)^3\right\}}. \quad (3)$$

where all ligand concentrations in red are prescribed, and k_i^{NKE}, k_o^{NKE} and k_m^{NKE} are parameters used for fitting the v_m^{NKE} flux dependence on $[Na^+]_i$ and $[Na^+]_o$ and the overall level of NKE expression, respectively. For a given value of $[Na^+]_o$, the v_m^{NKE} flux depends sigmoidally on $[Na^+]_i$, as illustrated in Figure 7. And similarly for $[Na^+]_o$ when $[Na^+]_i$ is fixed.



(a) (b)

Figure 7. Dependence of NKE flux on (a) intracellular sodium concentration $[Na^+]_i$, and (b) extracellular sodium concentration $[Na^+]_o$, when all other ligands (*ATP*, *ADP*, P_i, K_i^+, K_o^+ and H_i^+) are held at their normal physiological values. The parameters k_i^{NKE}= 10mM and k_i^{NKE}= 100mM determine the mid-point (50% of maximum flux) for each curve. The parameter k_m^{NKE} is used to set the maximum flux.

9. Sodium-driven glucose transport (SGLT1)

The steady-state flux through the sodium-glucose cotransporter SGLT1 (encoded by the *SLC5A1* gene), under the Briggs-Haldane assumption (see Hunter, AI, Nickerson, 2025), is given by

$$v_m^{SGLT1} = q_{tot}\kappa_6 K_1\left\{\left(\frac{\bar{q}_o^{Na^+}}{\bar{q}_i^{Na^+}}\right)^2.\frac{\bar{q}_o^{Glc}}{\bar{q}_i^{Glc}} - e^{2Fu_m^e/RT}\right\}/B,$$

where B is a function of $\bar{q}_o^{Na^+}$, $\bar{q}_i^{Na^+}$, $\bar{q}_o^{Glc}$, $\bar{q}_i^{Glc}$ and the membrane potential u_m^e. In the first use of this model (section 10) we keep glucose and the membrane potential fixed at physiological values and use the following simplified version for sodium transport:

$$v_m^{SGLT1} = k_m^{SGLT1}.\frac{\left([Na^+]_o\right)^2.[Glc]_o - \left([Na^+]_i\right)^2.[Glc]_i.e^{2Fu_m^e/RT}}{\left\{1+\left([Na^+]_i/k_i^{SGLT1}\right)^2\right\}.\left\{1+\left([Na^+]_o/k_0^{SGLT1}\right)^2\right\}},$$

where the quantities in red are fixed and the parameters k_i^{SGLT1}, k_0^{SGLT1} and k_m^{SGLT1} are fitted to match the experimental flux dependence on internal and external sodium concentrations.

10. A simple model of blood volume control

Figure 8 shows a very simple model of the movement of water and sodium. The volume of water or blood, q_j^w or q_j^b (L), and the amount of sodium $q_j^{Na^+}$ (mol) is defined in each compartment j. There are three major compartments: (i) a circulation system including a specified left ventricular cardiac output v_{lv}^b (with arterial blood pressure u_{ac}^b determined by the arterial compliance) and a return circulation from the arterial circulation (flow v_{ac}^b) to the venous circulation via the capillary compartment (flow v_{cc}^b); (ii) a gastrointestinal compartment that takes in water (v_{in}^w) and sodium ($v_{in}^{Na^+}$) at the mouth and expels waste water (v_{out1}^w) and sodium ($v_{out1}^{Na^+}$); (iii) a kidney compartment that receives water flow (v_{gl}^w) and sodium flux ($v_{gl}^{Na^+}$) at the glomeruli and expels water (v_{out2}^w) and sodium ($v_{out2}^{Na^+}$) in the urine.

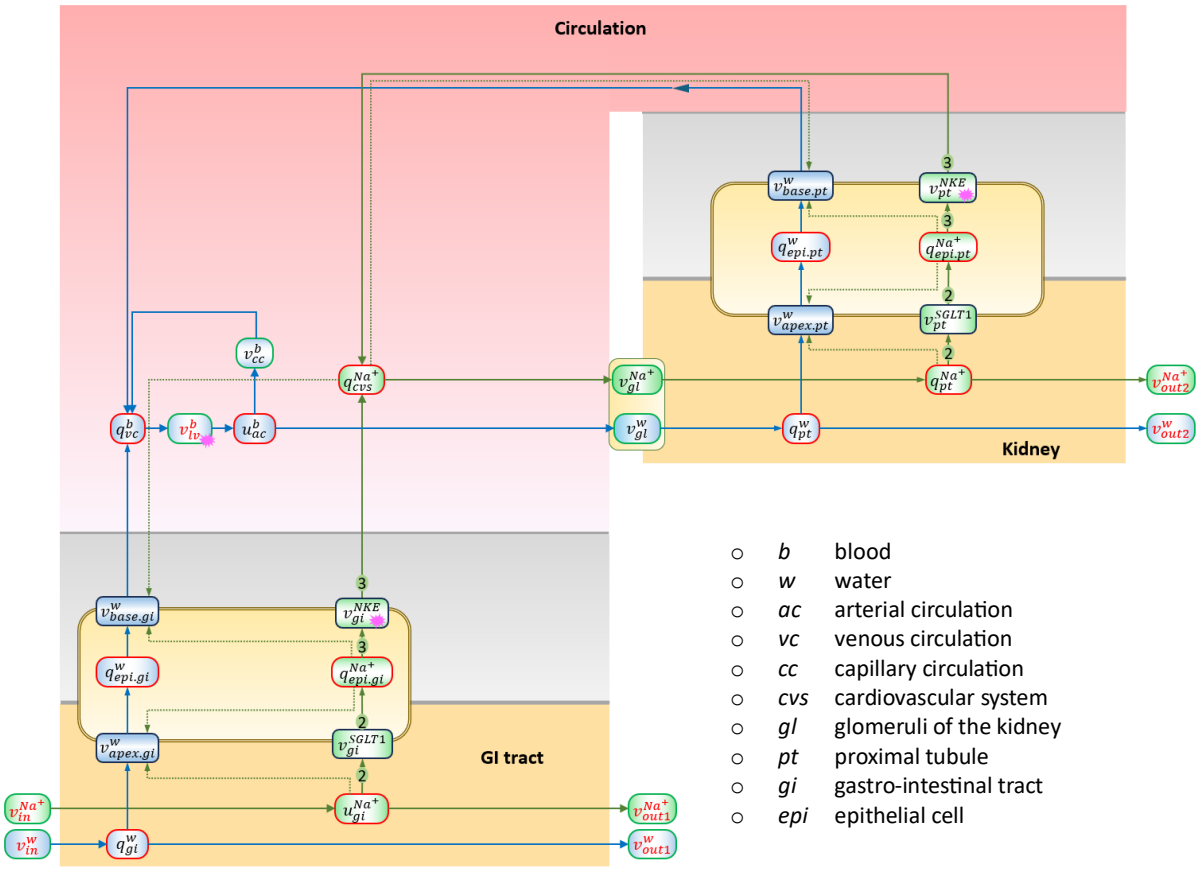


Figure 8. A simple model of the control of blood volume by sodium. The two epithelial compartments (GI tract and kidney tubule) communicate with the circulation system via epithelial cells containing the membrane transport mechanisms for water and sodium. The 0:nodes and 1:nodes provide the link to protein mechanisms in subcellular compartments. The variables shown in red are specified boundary conditions. The dotted lines indicate the influence of sodium concentration on the constitutive law for osmotic effects in the epithelial cell membranes.

The concentration of sodium in compartment j (with volume q_j^w) is given by

$$[Na^+]_j = q_j^{Na^+}/q_j^w \quad \text{(millimol.L}^{-1}\text{ or mM is equivalent to mol.m}^{-3}\text{)}$$

Sodium is pumped by NKE ATPase in the basolateral membrane against its concentration gradient from the epithelial cells to the circulation. This is the key energy consuming mechanism (see below) that maintains the large difference in sodium concentration difference across the cell membrane but thereby also the difference between the epithelial tracts and the blood. This epithelial cell sodium gradient allows water and sodium to be absorbed into the circulation (v_{gi}^w and $v_{gi}^{Na^+}$, respectively) from

the GI tract and reabsorbed (v_{pt}^{w} and $v_{pt}^{Na^+}$, respectively) into the venous circulation from the proximal tubule.

Note that three sodium ions are swapped for two potassium ions (not shown) for each ATP consumed. Sodium transport at the apical membrane of the epithelial cells is via the SGLT1 protein with two sodium ions transported for each glucose molecule (not shown). Note that the grey background regions in Figure 6 represent interstitial compartments that in this model have the same sodium concentration as blood and provide no barrier to water transport. In reality the exclusion of blood proteins from the interstitial space by endothelial cells and endothelial basement membrane means that there is a small osmotic pressure generated by the blood proteins, but we ignore that here.

(i) ***Cardiac output***

Cardiac output (L.s^{-1}), which is stroke volume (L.beat^{-1}) times heart rate (beats.s^{-1}), is a major determinant of the balance of blood volume between the venous and arterial compartments. The volume of plasma (water) q_{ac}^{w} (L) in the arterial circulation is the volume of blood q_{ac}^{b} (L) times the haematocrit (k_{ac}^{Hb}), or

$$q_{ac}^{b} = q_{ac}^{w}/k_{ac}^{Hb} \text{ (L)}.$$

A very simple characterisation of cardiac output (called "Starling's law") is

$$v_{lv}^{b} = k_{heart}^{b}.u_{vc}^{b},$$

in which cardiac output (the flow v_{lv}^{b}) is proportional to filling pressure u_{vc}^{b} and a parameter k_{heart}^{b} that depends on heart rate and the strength of myocyte contraction.

In our first model of blood volume control, cardiac output is set as an input variable.

(ii) ***Bond graph equations for mass and energy balance***

The 0:node mass balance equations for the model shown in Figure 8, with the variables specified as boundary conditions shown in red, are

Water storage (L.s^{-1})

$$\frac{dq_{gi}^{w}}{dt} = v_{in}^{w} - v_{apex.gi}^{w} - v_{out1}^{w}$$
$$\frac{dq_{epi.gi}^{w}}{dt} = v_{apex.gi}^{w} - v_{base.gi}^{w}$$
$$\frac{dq_{pt}^{w}}{dt} = v_{gl}^{w} - v_{apex.pt}^{w} - v_{out2}^{w}$$
$$\frac{dq_{epi.pt}^{w}}{dt} = v_{apex.pt}^{w} - v_{base.pt}^{w}$$
$$\frac{dq_{vc}^{b}}{dt} = \left(v_{base.gi}^{w} + v_{base.pt}^{w}\right)/k_{ac}^{Hb} + v_{cc}^{b} - v_{lv}^{b}$$
$$\frac{dq_{ac}^{b}}{dt} = v_{lv}^{b} - v_{cc}^{b} - v_{gl}^{w}/k_{ac}^{Hb}$$

Adding the 6 eqns for water gives the total change in volume of water q_{tot}^{w}:

$$\frac{dq_{tot}^{w}}{dt} = \frac{d}{dt}\left(q_{gi}^{w} + q_{epi.gi}^{w} + q_{pt}^{w} + q_{epi.pt}^{w} + k_{ac}^{Hb}.q_{vc}^{b} + k_{ac}^{Hb}.q_{ac}^{b}\right) = v_{in}^{w} - v_{out1}^{w} - v_{out2}^{w}$$

Sodium storage (mol.s^{-1})

$$\frac{dq_{gi}^{Na^+}}{dt} = v_{in}^{Na^+} - 2v_{gi}^{SGLT1} - v_{out1}^{Na^+}$$
$$\frac{dq_{epi.gi}^{Na^+}}{dt} = 2v_{gi}^{SGLT1} - 3v_{gi}^{NKE}$$
$$\frac{dq_{pt}^{Na^+}}{dt} = v_{gl}^{Na^+} - 2v_{pt}^{SGLT1} - v_{out2}^{Na^+}$$
$$\frac{dq_{epi.pt}^{Na^+}}{dt} = 2v_{pt}^{SGLT1} - 3v_{pt}^{NKE}$$

$$\frac{dq_{cvs}^{Na^+}}{dt} = 3v_{gi}^{NKE} + 3v_{pt}^{NKE} - v_{gl}^{Na^+}$$

Adding the 5 equations for sodium gives the total change in the amount of sodium

$$\frac{dq_{tot}^{Na^+}}{dt} = \frac{d}{dt}\left(q_{gi}^{Na^+} + q_{epi.gi}^{Na^+} + q_{pt}^{Na^+} + q_{epi.pt}^{Na^+} + q_{cvs}^{Na^+}\right) = v_{in}^{Na^+} - v_{out1}^{Na^+} - v_{out2}^{Na^+}$$

Sodium concentrations (mol.L^{-1})

$$[Na^+]_{gi} = q_{gi}^{Na^+}/q_{gi}^{w}; \qquad [Na^+]_{pt} = q_{pt}^{Na^+}/q_{pt}^{w};$$

$$[Na^+]_{epi.gi} = q_{epi.gi}^{Na^+}/q_{epi.gi}^{w}; \quad [Na^+]_{epi.pt} = q_{epi.pt}^{Na^+}/q_{epi.pt}^{w};$$

$$[Na^+]_{cvs} = q_{cvs}^{Na^+}/(q_{vc}^{b} + q_{vc}^{b});$$

The 1:node flux equations are

Water flux (L.s^{-1})

$$v_{apex.gi}^{w} = k_m^w.\left\{u_{gi}^{w} - u_{epi.gi}^{w} - RT\left([Na^+]_{gi} - [Na^+]_{epi.gi}\right)\right\}$$
$$v_{base.gi}^{w} = k_m^w.\left\{u_{epi.gi}^{w} - k_{ac}^{Hb}.u_{vc}^{b} - RT\left([Na^+]_{epi.gi} - [Na^+]_{cvs}\right)\right\}$$
$$v_{apex.pt}^{w} = k_m^w.\left\{u_{pt}^{w} - u_{epi.pt}^{w} - RT\left([Na^+]_{pt} - [Na^+]_{epi.pt}\right)\right\}$$
$$v_{base.pt}^{w} = k_m^w.\left\{u_{epi.pt}^{w} - k_{ac}^{Hb}.u_{vc}^{b} - RT\left([Na^+]_{epi.pt} - [Na^+]_{cvs}\right)\right\}$$
$$v_{cc}^{b} = k_{cc}^{b}.\left(u_{ac}^{b} - u_{vc}^{b}\right)$$
$$v_{gl}^{w} = k_{gl}^{w}.\left(u_{ac}^{b} - u_{pt}^{w}\right)$$

Sodium flux (mol.s^{-1})

$$v_{gi}^{SGLT1} = k_{gi}^{SGLT1}.\frac{\left([Na^+]_{gi}\right)^2.[Glc]_{gi} - \left([Na^+]_{epi.gi}\right)^2.[Glc]_{epi.gi}.e^{2Fu_m^e/RT}}{\left\{1+\left([Na^+]_{gi}/k_{gi}^{SGLT1}\right)^2\right\}.\left\{1+\left([Na^+]_{epi.gi}/k_{epi.gi}^{SGLT1}\right)^2\right\}}$$

$$v_{pt}^{SGLT1} = k_{pt}^{SGLT1}.\frac{\left([Na^+]_{pt}\right)^2.[Glc]_{pt} - \left([Na^+]_{epi.pt}\right)^2.[Glc]_{epi.pt}.e^{2Fu_m^e/RT}}{\left\{1+\left([Na^+]_{pt}/k_{pt}^{SGLT1}\right)^2\right\}.\left\{1+\left([Na^+]_{epi.pt}/k_{epi.pt}^{SGLT1}\right)^2\right\}}$$

$$v_{gi}^{NKE} = k_{gi}^{NKE}.\frac{\left([Na^+]_{epi.gi}\right)^3.\left([K^+]_{cvs}\right)^2.[ATP].k_{equil}^{ATP} - \left([Na^+]_{cvs}\right)^3.\left([K^+]_{epi.gi}\right)^2.[ADP].[P_i].e^{Fu_m^e/RT}}{\left\{1+\left([Na^+]_{epi.gi}/k_{epi.gi}^{NKE}\right)^3\right\}.\left\{1+\left([Na^+]_{cvs}/k_{cvs}^{NKE}\right)^3\right\}}$$

$$v_{pt}^{NKE} = k_{pt}^{NKE}.\frac{\left([Na^+]_{epi.pt}\right)^3.\left([K^+]_{cvs}\right)^2.[ATP].k_{equil}^{ATP} - \left([Na^+]_{cvs}\right)^3.\left([K^+]_{epi.pt}\right)^2.[ADP].[P_i].e^{Fu_m^e/RT}}{\left\{1+\left([Na^+]_{epi.pt}/k_{epi.pt}^{NKE}\right)^3\right\}.\left\{1+\left([Na^+]_{cvs}/k_{cvs}^{NKE}\right)^3\right\}}$$

$$v_{gl}^{Na^+} = k_{gl}^{Na^+}.\left([Na^+]_{cvs} - [Na^+]_{pt}\right)$$

Constitutive equations for compliant vessels

The hydrostatic pressures generated by the elastic stiffness of the compliant water containing vessels (GI tract and kidney tubule, epithelial cells, and arteries and veins) are based on the pole-zero law described above:

$$u_{gi}^{w} = E_{gi}.\frac{q_{gi}^{w} - \bar{q}_{gi}^{w}}{\left(\hat{q}_{gi}^{w} - q_{gi}^{w}\right)^2}\ \text{(kPa)}, \qquad u_{pt}^{w} = E_{pt}.\frac{q_{pt}^{w} - \bar{q}_{pt}^{w}}{\left(\bar{q}_{pt}^{w} - q_{pt}^{w}\right)^2}\ \text{(kPa)},$$

$$u_{epi.gi}^{w} = E_{epi.gi}.\frac{q_{epi.gi}^{w} - \bar{q}_{epi.gi}^{w}}{\left(\hat{q}_{epi.gi}^{w} - q_{epi.gi}^{w}\right)^2}\ \text{(kPa)}, \qquad u_{epi.pt}^{w} = E_{epi.pt}.\frac{q_{epi.pt}^{w} - \bar{q}_{epi.pt}^{w}}{\left(\hat{q}_{epi.pt}^{w} - q_{epi.pt}^{w}\right)^2}\ \text{(kPa)},$$

$$u_{vc}^{b} = E_{vc}.\frac{q_{vc}^{b} - \bar{q}_{vc}^{b}}{\left(\hat{q}_{vc}^{b} - q_{vc}^{b}\right)^2}\ \text{(kPa)}, \qquad u_{ac}^{b} = E_{ac}.\frac{q_{ac}^{b} - \bar{q}_{ac}^{b}}{\left(\hat{q}_{ac}^{b} - q_{ac}^{b}\right)^2}\ \text{(kPa)},$$

where E_{gi}, E_{pt}, $E_{epi.gi}$, $E_{epi.pt}$, E_{vc} & E_{vt} have units of joules (so that the pressures have units kPa).

Below here still needs updating

(iii) ***Parameterising the model***

Initial values for the volume of water and molar quantity of sodium are given in Table 1.

Parameter	Name	Value	Units	Note
$q_{ac}^{H_2O}$	Volume of water in the arteries	1	L	
$q_{vc}^{H_2O}$	Volume of water in the veins	2	L	
$q_{gi}^{H_2O}$	Volume of water in the GI tract	0.1	L	
$q_{pt}^{H_2O}$	Volume of water in the proximal tubule	0.01	L	
$q_{gi.epi}^{H_2O}$	Volume of water in the GI epithelial cells	0.1	L	
$q_{pt.epi}^{H_2O}$	Volume of water in the PT epithelial cells	0.1	L	
$q_{cvs}^{Na^+}$	Amount of sodium in the blood	0.42	mol	$c_{cvs}^{Na^+} = \frac{0.42}{3} = 140$ mM
$q_{gi}^{Na^+}$	Amount of sodium in the GI tract	0.01	mol	$c_{gi}^{Na^+} = \frac{0.01}{0.1} = 100$ mM
$q_{pt}^{Na^+}$	Amount of sodium in the proximal tubule	0.001	mol	$c_{pt}^{Na^+} = \frac{0.001}{0.01} = 100$ mM
$q_{gi.epi}^{Na^+}$	Amt of sodium in the GI epithelial cells	0.0012	mol	$c_{gi.epi}^{Na^+} = \frac{0.0012}{0.1} = 12$ mM
$q_{pt.epi}^{Na^+}$	Amt of sodium in the PT epithelial cells	0.0012	mol	$c_{pt.epi}^{Na^+} = \frac{0.0012}{0.1} = 12$ mM
$q_{cvs}^{K^+}$	Amount of potassium in the blood	0.015	mol	$c_{cvs}^{K^+} = \frac{0.015}{3} = 5$ mM
$q_{gi}^{K^+}$	Amt of potassium in the GI epithelial cells	0.0015	mol	$c_{gi}^{K^+} = \frac{0.0015}{0.1} = 15$ mM

Table 1. Initial values for the simple blood volume control model.

The recommended daily intake of water is 2.1 L for men and 2.6 L for men. With 8.64e4 s.day^{-1} and assuming an intake of 2.4 L.day^{-1}, $v_{in}^{H_2O}$ averages $\frac{2.4}{8.64}$ =28e-6 L.s^{-1}. The daily intake of sodium is about 2.3 g, which with a molecular mass of 23 g.mol^{-1} is 0.1 mol.day^{-1} or 1.16e-6 mol.s^{-1}.

Boundary conditions are given in Table 2.

Parameter	Name	Value	Units	Note
$v_{in}^{H_2O}$	Water flow from drinking	28e-6	L	2.4 L.day^{-1}
$v_{out1}^{H_2O}$	Water flow excreted in faeces	0	L	
$v_{out2}^{H_2O}$	Water flow excreted in urine	28e-6	L	2.4 L.day^{-1}
$v_{in}^{Na^+}$	Input sodium flux at the mouth	1.16e-6	mol.s^{-1}	0.1 mol.day^{-1}
$v_{out1}^{Na^+}$	Excreted sodium flux in faeces	0	mol.s^{-1}	
$v_{out2}^{Na^+}$	Excreted sodium flux in urine	1.16e-6	mol.s^{-1}	0.1 mol.day^{-1}

Table 2. Boundary conditions for the simple blood volume control model.

Parameter values are given in Table 3. The parameters shown in bold are adjustable in the FC interface.

Parameter	Name	Value	Units
$k_{gi}^{H_2O}$	Membrane permeability	1	L.s^{-1}.kPa^{-1}
$k_{gl}^{H_2O}$	Membrane permeability	1	L.s^{-1}.kPa^{-1}
$k_{pt}^{H_2O}$	Membrane permeability	0	L.s^{-1}.kPa^{-1}
$k_{cc}^{H_2O}$	Vascular conductance	1	L.s^{-1}.kPa^{-1}
$v_{lv}^{H_2O}$	**Cardiac output**	0	L.s^{-1}
E_{ac}	Vascular stiffness (arteries)	1	kPa.L
$\hat{q}_{ac}^{H_2O}$	Unstressed volume (arteries)	2	L
$\bar{q}_{ac}^{H_2O}$	Limiting volume (arteries)	3	L
E_{vc}	**Vascular stiffness** (veins)	1	kPa.L
$\hat{q}_{vc}^{H_2O}$	Unstressed volume (veins)	4	L
$\bar{q}_{vc}^{H_2O}$	Limiting volume (veins)	5	L
$k_{gi}^{Na^+}.K^{Na^+}$	Sodium transporter flux rate (GI tract)	1	s^{-1}
$k_{pt}^{Na^+}.K^{Na^+}$	**Sodium transporter flux rate** (proximal tubule)	1	s^{-1}
$k_{gl}^{Na^+}.K^{Na^+}$	Sodium transporter flux rate (glomerulus)	1	s^{-1}

Table 3. Parameter values for the simple blood volume control model.

(iv) ***Steady state solutions***

Assuming $v_{out1}^{H_2O} = 0$, $v_{out1}^{Na^+} = 0$, $v_{out2}^{H_2O} = v_{in}^{H_2O}$, and $v_{out2}^{Na^+} = v_{in}^{Na^+}$, and setting derivatives to zero,

$$\frac{dq_{gi}^{H_2O}}{dt} = v_{in}^{H_2O} - v_{gi}^{H_2O} = 0 \quad \text{or } v_{gi}^{H_2O} = v_{in}^{H_2O} \tag{1}$$

$$\frac{dq_{pt}^{H_2O}}{dt} = v_{gl}^{H_2O} - v_{pt}^{H_2O} - v_{in}^{H_2O} = 0 \quad \text{or } v_{gl}^{H_2O} = v_{pt}^{H_2O} + v_{in}^{H_2O} \tag{2}$$

$$\frac{dq_{vc}^{H_2O}}{dt} = v_{cc}^{H_2O} + v_{gi}^{H_2O} + v_{pt}^{H_2O} - v_{lv}^{H_2O} = 0 \quad \text{or } v_{cc}^{H_2O} + v_{gi}^{H_2O} + v_{pt}^{H_2O} = v_{lv}^{H_2O} \tag{3}$$

$$\frac{dq_{ac}^{H_2O}}{dt} = v_{lv}^{H_2O} - v_{cc}^{H_2O} - v_{gl}^{H_2O} = 0 \quad \text{or } v_{cc}^{H_2O} + v_{gl}^{H_2O} = v_{lv}^{H_2O} \tag{4}$$

$$\frac{dq_{gi}^{Na^+}}{dt} = v_{in}^{Na^+} - v_{gi}^{Na^+} = 0 \quad \text{or } v_{gi}^{Na^+} = v_{in}^{Na^+} \tag{5}$$

$$\frac{dq_{pt}^{Na^+}}{dt} = v_{gl}^{Na^+} - v_{pt}^{Na^+} - v_{in}^{Na^+} = 0 \quad \text{or } v_{gl}^{Na^+} = v_{pt}^{Na^+} + v_{in}^{Na^+} \tag{6}$$

$$\frac{dq_{vc}^{Na^+}}{dt} = v_{gi}^{Na^+} + v_{pt}^{Na^+} - v_{gl}^{Na^+} = 0 \quad \text{or } v_{gl}^{Na^+} = v_{pt}^{Na^+} + v_{gi}^{Na^+} \tag{7}$$

From (1), (2),

$$v_{gl}^{H_2O} - v_{pt}^{H_2O} = v_{gi}^{H_2O} = v_{in}^{H_2O}, \tag{8}$$

and from (3) & (4),

$$v_{cc}^{H_2O} = v_{lv}^{H_2O} - v_{in}^{H_2O}. \tag{9}$$

From (5), (6) & (7),

$$v_{gl}^{Na^+} - v_{pt}^{Na^+} = v_{gi}^{Na^+} = v_{in}^{Na^+}. \tag{10}$$

The steady state requires the difference in water flow $v_{gl}^{H_2O} - v_{pt}^{H_2O}$ to match the input flow $v_{in}^{H_2O}$, and the difference in sodium flux $v_{gl}^{Na^+} - v_{pt}^{Na^+}$ to match the input flux $v_{in}^{Na^+}$, but the actual values of $v_{gl}^{H_2O}$, $v_{pt}^{H_2O}$, $v_{gl}^{Na^+}$ & $v_{pt}^{Na^+}$ will be determined by solving the differential equations subject to specified initial conditions.

Solutions

In the following sections we analyse the solutions from the blood volume control model.

Solution 1

Set the initial values given in Table 1 and boundary conditions that are consistent with achieving a steady state solution. i.e.

$$v_{out1}^{H_2O} = 0,\ v_{out1}^{Na^+} = 0,\ v_{out2}^{H_2O} = v_{in}^{H_2O} = 0, \text{ and } v_{out2}^{Na^+} = v_{in}^{Na^+} = 0.$$

In this first example we set the cardiac output to $v_{lv}^{H_2O} = 0$.

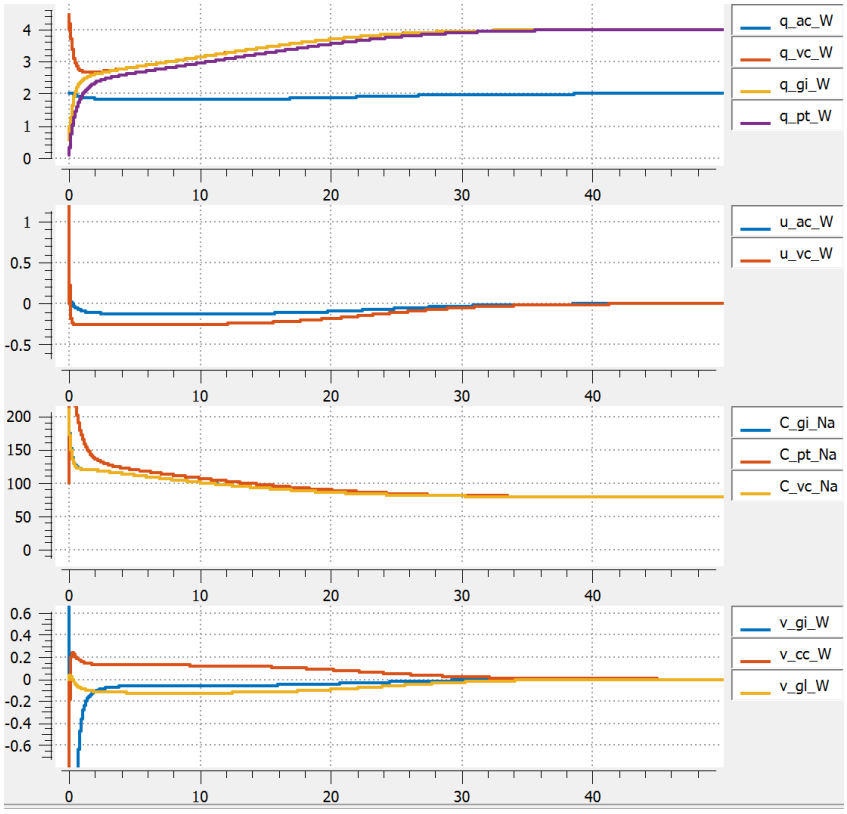


Figure 9.

The solution reaches steady state after about 40s with

$q_{ac}^{H_2O} = 2L$, and $q_{vc}^{H_2O} = q_{gi}^{H_2O} = q_{pt}^{H_2O} = 4L$

$C_{gi}^{Na^+} = C_{pt}^{Na^+} = C_{vc}^{Na^+} = 79.2mM$, consistent with $\frac{q_{gi}^{Na^+}}{q_{gi}^{H_2O}} = \frac{q_{pt}^{Na^+}}{q_{pt}^{H_2O}} = \frac{q_{vc}^{Na^+}}{q_{vc}^{H_2O}} = \frac{0.317}{4} = 0.0792\ mol.L^{-1}$

Changing the boundary sodium fluxes ($v_{out2}^{Na^+} = v_{in}^{Na^+}$ = 1.16e-6) gives the same steady state results.

Solution 2

As above with $v_{out2}^{Na^+} = v_{in}^{Na^+}$ = 1.16e-6 (mol.s^{-1}) and now with $v_{out2}^{H_2O} = v_{in}^{H_2O}$ = 28e-6 (L.s^{-1})

11. A model with respiration and metabolism

To extend the model to include a dependence on metabolic supply we add processes for the transport of glucose, oxygen and carbon dioxide, as shown in Figure 10.

Given the close association between the transport of sodium and water with the transport and consumption of glucose, we add (i) the SGLT1 cotransporter into the apical membrane and the GLUT2 transporter into the basolateral membrane of the epithelial cells, (ii) the consumption of intracellular glucose by oxidative metabolism to convert 36 moles of ADP and phosphate, plus 6 moles of O_2 and water, to 36 moles of ATP and 6 moles of CO_2,

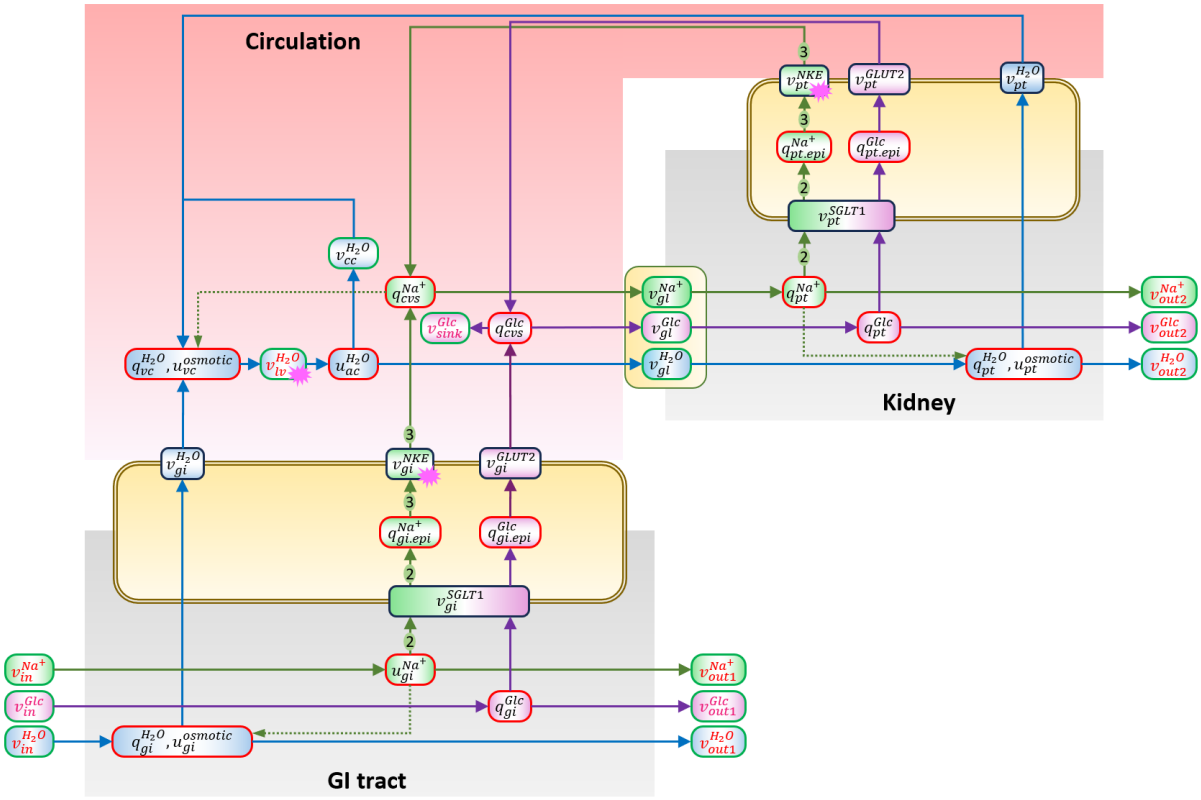


Figure 10.

The 0:node mass balance equations for the model are:

$$\frac{dq_{gi}^{H_2O}}{dt} = v_{in}^{H_2O} - v_{gi}^{H_2O} - v_{out1}^{H_2O}$$

$$\frac{dq_{pt}^{H_2O}}{dt} = v_{gl}^{H_2O} - v_{pt}^{H_2O} - v_{out2}^{H_2O}$$

$$\frac{dq_{vc}^{H_2O}}{dt} = v_{cc}^{H_2O} + v_{gi}^{H_2O} + v_{pt}^{H_2O} - v_{lv}^{H_2O}$$

$$\frac{dq_{ac}^{H_2O}}{dt} = v_{lv}^{H_2O} - v_{cc}^{H_2O} - v_{gl}^{H_2O}$$

$$\frac{dq_{gi}^{Na^+}}{dt} = v_{in}^{Na^+} - 2v_{gi}^{SGLT1} - v_{out1}^{Na^+}$$

$$\frac{dq_{gi.epi}^{Na^+}}{dt} = 2v_{gi}^{SGLT1} - 3v_{gi}^{NKE}$$

$$\frac{dq_{pt}^{Na^+}}{dt} = v_{gl}^{Na^+} - 2v_{pt}^{SGLT1} - v_{out2}^{Na^+}$$

$$\frac{dq_{pt.epi}^{Na^+}}{dt} = 2v_{pt}^{SGLT1} - 3v_{pt}^{NKE}$$

$$\frac{dq_{cvs}^{Na^+}}{dt} = 3v_{gi}^{NKE} + 3v_{pt}^{NKE} - v_{gl}^{Na^+}$$

$$\frac{dq_{gi}^{Glc}}{dt} = v_{in}^{Glc} - v_{gi}^{SGLT1} - v_{out1}^{Glc}$$

$$\frac{dq_{gi.epi}^{Glc}}{dt} = v_{gi}^{SGLT1} - v_{gi}^{GLUT2}$$

$$\frac{dq_{pt}^{Glc}}{dt} = v_{gl}^{Glc} - v_{pt}^{SGLT1} - v_{out2}^{Glc}$$

$$\frac{dq_{pt.epi}^{Glc}}{dt} = v_{pt}^{SGLT1} - v_{pt}^{GLUT2}$$

$$\frac{dq_{cvs}^{Glc}}{dt} = v_{gi}^{GLUT2} + v_{pt}^{GLUT2} - v_{gl}^{Glc} - v_{sink}^{Glc}$$

(the variables specified as boundary conditions are shown in red).

Note that adding the first 4 eqns gives

$$\frac{d}{dt}\left(q_{gi}^{H_2O}+q_{pt}^{H_2O}+q_{vc}^{H_2O}+q_{ac}^{H_2O}\right)=\frac{dq_{tot}^{H_2O}}{dt}=v_{in}^{H_2O}-v_{out1}^{H_2O}-v_{out2}^{H_2O}$$

Adding the next 5 equations gives

$$\frac{d}{dt}\left(q_{gi}^{Na^+}+q_{gi.epi}^{Na^+}+q_{pt}^{Na^+}+q_{pt.epi}^{Na^+}+q_{cvs}^{Na^+}\right)=v_{in}^{Na^+}-v_{out1}^{Na^+}-v_{out2}^{Na^+}$$

Adding the next 5 equations gives

$$\frac{d}{dt}\left(q_{gi}^{Glc}+q_{gi.epi}^{Glc}+q_{pt}^{Glc}+q_{pt.epi}^{Glc}+q_{cvs}^{Glc}\right)=v_{in}^{Glc}-v_{out1}^{Glc}-v_{out2}^{Glc}$$

The 1:node flux equations are

$$v_{gi}^{H_2O}=k_{gi}^{H_2O}.\left(u_{vc}^{osmotic}-u_{gi}^{osmotic}\right)$$

$$v_{pt}^{H_2O}=k_{pt}^{H_2O}.\left(u_{vc}^{osmotic}-u_{pt}^{osmotic}\right)$$

$$v_{gl}^{H_2O}=k_{gl}^{H_2O}.\left(u_{ac}^{H_2O}-u_{pt}^{H_2O}\right)$$

$$v_{cc}^{H_2O}=k_{cc}^{H_2O}.\left(u_{ac}^{H_2O}-u_{vc}^{H_2O}\right)$$

$$v_{gi}^{SGLT1}=k_{gi}^{SGLT1}\frac{\left(\bar{q}_{gi}^{Na^+}\right)^2.\bar{q}_{gi}^{Glc}-\left(\bar{q}_{gi.epi}^{Na^+}\right)^2.\bar{q}_{gi.epi}^{Glc}.e^{2Fu_m^e/RT}}{\left\{1+\left(\bar{q}_{gi}^{Na^+}\right)^2\right\}.\left\{1+\bar{q}_{gi}^{Glc}\right\}.\left\{1+\left(\bar{q}_{gi.epi}^{Na^+}\right)^2\right\}.\left\{1+\bar{q}_{gi.epi}^{Glc}\right\}}$$

$$v_{pt}^{SGLT1}=k_{pt}^{SGLT1}\frac{\left(\bar{q}_{pt}^{Na^+}\right)^2.\bar{q}_{pt}^{Glc}-\left(\bar{q}_{pt.epi}^{Na^+}\right)^2.\bar{q}_{pt.epi}^{Glc}.e^{2Fu_m^e/RT}}{\left\{1+\left(\bar{q}_{pt}^{Na^+}\right)^2\right\}.\left\{1+\bar{q}_{pt}^{Glc}\right\}.\left\{1+\left(\bar{q}_{pt.epi}^{Na^+}\right)^2\right\}.\left\{1+\bar{q}_{pt.epi}^{Glc}\right\}}$$

$$v_{gl}^{Na^+}=k_{gl}^{Na^+}.\left(\bar{q}_{cvs}^{Na^+}-\bar{q}_{pt}^{Na^+}\right)=k_{gl}^{Na^+}.K^{Na^+}.\left(q_{cvs}^{Na^+}-q_{pt}^{Na^+}\right)$$

$$v_{gi}^{NKE}=k_{gi}^{NKE}.\frac{\left(\bar{q}_{gi.epi}^{Na^+}\right)^3.\left(\bar{q}_{cvs}^{K^+}\right)^2-\left(\bar{q}_{cvs}^{Na^+}\right)^3.\left(\bar{q}_{gi.epi}^{K^+}\right)^2.e^{2Fu_m^e/RT}}{\left\{1+\left(\bar{q}_{gi.epi}^{Na^+}\right)^3\right\}.\left\{1+\left(\bar{q}_{cvs}^{K^+}\right)^2\right\}.\left\{1+\left(\bar{q}_{cvs}^{Na^+}\right)^3\right\}.\left\{1+\left(\bar{q}_{gi.epi}^{K^+}\right)^2\right\}}$$

$$v_{pt}^{NKE}=k_{pt}^{NKE}.\frac{\left(\bar{q}_{pt.epi}^{Na^+}\right)^3.\left(\bar{q}_{cvs}^{K^+}\right)^2-\left(\bar{q}_{cvs}^{Na^+}\right)^3.\left(\bar{q}_{pt.epi}^{K^+}\right)^2.e^{2Fu_m^e/RT}}{\left\{1+\left(\bar{q}_{pt.epi}^{Na^+}\right)^3\right\}.\left\{1+\left(\bar{q}_{cvs}^{K^+}\right)^2\right\}.\left\{1+\left(\bar{q}_{cvs}^{Na^+}\right)^3\right\}.\left\{1+\left(\bar{q}_{pt.epi}^{K^+}\right)^2\right\}}$$

$$v_{gi}^{GLUT2}=k_{gi}^{GLUT2}.\frac{\bar{q}_{gi.epi}^{Glc}-\bar{q}_{cvs}^{Glc}}{1+\frac{\bar{q}_{gi.epi}^{Glc}}{k_1^{GLUT2}}+\frac{\bar{q}_{cvs}^{Glc}}{k_2^{GLUT2}}+\frac{\bar{q}_{gi.epi}^{Glc}.\bar{q}_{cvs}^{Glc}}{k_3^{GLUT2}}}$$

$$v_{pt}^{GLUT2}=k_{pt}^{GLUT2}.\frac{\bar{q}_{pt.epi}^{Glc}-\bar{q}_{cvs}^{Glc}}{1+\frac{\bar{q}_{pt.epi}^{Glc}}{k_1^{GLUT2}}+\frac{\bar{q}_{cvs}^{Glc}}{k_2^{GLUT2}}+\frac{\bar{q}_{pt.epi}^{Glc}.\bar{q}_{cvs}^{Glc}}{k_3^{GLUT2}}}$$

where the osmotic pressures are generated via concentrations by

$$c_{gi}^{Na^+}=\frac{q_{gi}^{Na^+}}{q_{gi}^{H_2O}}\ (\text{mol.L}^{-1});\quad u_{gi}^{osmotic}=RT.c_{gi}^{Na^+}=RT.\frac{q_{gi}^{Na^+}}{q_{gi}^{H_2O}}\quad (\text{J.L}^{-1})$$

$$c_{pt}^{Na^+}=\frac{q_{pt}^{Na^+}}{q_{pt}^{H_2O}}\ (\text{mol.L}^{-1});\quad u_{pt}^{osmotic}=RT.c_{pt}^{Na^+}=RT.\frac{q_{pt}^{Na^+}}{q_{pt}^{H_2O}}\quad (\text{J.L}^{-1})$$

$$c_{vc}^{Na^+}=\frac{q_{cvs}^{Na^+}}{q_{vc}^{H_2O}+q_{ac}^{H_2O}}\quad (\text{mol.L}^{-1});\quad u_{vc}^{osmotic}=RT.c_{vc}^{Na^+}=RT.\frac{q_{cvs}^{Na^+}}{q_{vc}^{H_2O}+q_{ac}^{H_2O}}\quad (\text{J.L}^{-1})$$

The hydrostatic pressures generated by the elastic stiffness of the compliant water containers (arteries, veins & kidney tubules) are based on the pole-zero law described above:

$$u_{vc}^{H_2O}=E_{vc}.\frac{q_{vc}^{H_2O}-\hat{q}_{vc}^{H_2O}}{\left(\bar{q}_{vc}^{H_2O}-q_{vc}^{H_2O}\right)^2}\quad (\text{kPa})$$

$$u_{ac}^{H_2O} = E_{ac}.\frac{q_{ac}^{H_2O} - \hat{q}_{ac}^{H_2O}}{\left(\bar{q}_{ac}^{H_2O} - q_{ac}^{H_2O}\right)^2} \quad \text{(kPa)}$$

$$u_{pt}^{H_2O} = E_{pt}.\frac{q_{pt}^{H_2O} - \hat{q}_{pt}^{H_2O}}{\left(\bar{q}_{pt}^{H_2O} - q_{pt}^{H_2O}\right)^2} \quad \text{(kPa)}$$

where E_{vc}, E_{ac} & E_{pt} have units of joules (so that the pressures $u_{vc}^{H_2O}, u_{ac}^{H_2O}$ & $u_{pt}^{H_2O}$ have units kPa).

Substituting the potentials into the fluxes gives

$$v_{gi}^{H_2O} = RTk_{gi}^{H_2O}.\left(\frac{q_{cvs}^{Na^+}}{q_{vc}^{H_2O}+q_{ac}^{H_2O}} - \frac{q_{gi}^{Na^+}}{q_{gi}^{H_2O}}\right)$$

$$v_{pt}^{H_2O} = RTk_{pt}^{H_2O}.\left(\frac{q_{cvs}^{Na^+}}{q_{vc}^{H_2O}+q_{ac}^{H_2O}} - \frac{q_{pt}^{Na^+}}{q_{pt}^{H_2O}}\right)$$

$$v_{gl}^{H_2O} = k_{gl}^{H_2O}.\left(E_{ac}.\frac{q_{ac}^{H_2O} - \hat{q}_{ac}^{H_2O}}{\left(\bar{q}_{ac}^{H_2O} - q_{ac}^{H_2O}\right)^2} - E_{pt}.\frac{q_{pt}^{H_2O} - \hat{q}_{pt}^{H_2O}}{\left(\bar{q}_{pt}^{H_2O} - q_{pt}^{H_2O}\right)^2}\right)$$

$$v_{cc}^{H_2O} = k_{cc}^{H_2O}.\left(E_{ac}.\frac{q_{ac}^{H_2O} - \hat{q}_{ac}^{H_2O}}{\left(\bar{q}_{ac}^{H_2O} - q_{ac}^{H_2O}\right)^2} - E_{vc}.\frac{q_{vc}^{H_2O} - \hat{q}_{vc}^{H_2O}}{\left(\bar{q}_{vc}^{H_2O} - q_{vc}^{H_2O}\right)^2}\right)$$

$$v_{gi}^{SGLT1} = k_{gi}^{SGLT1}\frac{\left(\bar{q}_{gi}^{Na^+}\right)^2.\bar{q}_{gi}^{Glc} - \left(\bar{q}_{gi.epi}^{Na^+}\right)^2.\bar{q}_{gi.epi}^{Glc}.e^{2Fu_m^e/RT}}{\left\{1+\left(\bar{q}_{gi}^{Na^+}\right)^2\right\}.\left\{1+\bar{q}_{gi}^{Glc}\right\}.\left\{1+\left(\bar{q}_{gi.epi}^{Na^+}\right)^2\right\}.\left\{1+\bar{q}_{gi.epi}^{Glc}\right\}}$$

$$v_{pt}^{SGLT1} = k_{pt}^{SGLT1}\frac{\left(\bar{q}_{pt}^{Na^+}\right)^2.\bar{q}_{pt}^{Glc} - \left(\bar{q}_{pt.epi}^{Na^+}\right)^2.\bar{q}_{pt.epi}^{Glc}.e^{2Fu_m^e/RT}}{\left\{1+\left(\bar{q}_{pt}^{Na^+}\right)^2\right\}.\left\{1+\bar{q}_{pt}^{Glc}\right\}.\left\{1+\left(\bar{q}_{pt.epi}^{Na^+}\right)^2\right\}.\left\{1+\bar{q}_{pt.epi}^{Glc}\right\}}$$

$$v_{gl}^{Na^+} = k_{gl}^{Na^+}.\left(\bar{q}_{vc}^{Na^+} - \bar{q}_{pt}^{Na^+}\right) = k_{gl}^{Na^+}.K^{Na^+}.\left\{q_{cvs}^{Na^+} - q_{pt}^{Na^+}\right\}$$

$$v_{gi}^{NKE} = k_{gi}^{NKE}.\frac{\left(\bar{q}_{gi.epi}^{Na^+}\right)^3.\left(\bar{q}_{cvs}^{K^+}\right)^2 - \left(\bar{q}_{cvs}^{Na^+}\right)^3.\left(\bar{q}_{gi.epi}^{K^+}\right)^2.e^{2Fu_m^e/RT}}{\left\{1+\left(\bar{q}_{gi.epi}^{Na^+}\right)^3\right\}.\left\{1+\left(\bar{q}_{cvs}^{K^+}\right)^2\right\}.\left\{1+\left(\bar{q}_{cvs}^{Na^+}\right)^3\right\}.\left\{1+\left(\bar{q}_{gi.epi}^{K^+}\right)^2\right\}}$$

$$v_{pt}^{NKE} = k_{pt}^{NKE}.\frac{\left(\bar{q}_{pt.epi}^{Na^+}\right)^3.\left(\bar{q}_{cvs}^{K^+}\right)^2 - \left(\bar{q}_{cvs}^{Na^+}\right)^3.\left(\bar{q}_{pt.epi}^{K^+}\right)^2.e^{2Fu_m^e/RT}}{\left\{1+\left(\bar{q}_{pt.epi}^{Na^+}\right)^3\right\}.\left\{1+\left(\bar{q}_{cvs}^{K^+}\right)^2\right\}.\left\{1+\left(\bar{q}_{cvs}^{Na^+}\right)^3\right\}.\left\{1+\left(\bar{q}_{pt.epi}^{K^+}\right)^2\right\}}$$

$$v_{gi}^{GLUT2} = k_{gi}^{GLUT2}.\frac{\bar{q}_{gi.epi}^{Glc} - \bar{q}_{cvs}^{Glc}}{1+\frac{\bar{q}_{gi.epi}^{Glc}}{k_1^{GLUT2}}+\frac{\bar{q}_{cvs}^{Glc}}{k_2^{GLUT2}}+\frac{\bar{q}_{gi.epi}^{Glc}.\bar{q}_{cvs}^{Glc}}{k_3^{GLUT2}}}$$

$$v_{pt}^{GLUT2} = k_{pt}^{GLUT2}.\frac{\bar{q}_{pt.epi}^{Glc} - \bar{q}_{cvs}^{Glc}}{1+\frac{\bar{q}_{pt.epi}^{Glc}}{k_1^{GLUT2}}+\frac{\bar{q}_{cvs}^{Glc}}{k_2^{GLUT2}}+\frac{\bar{q}_{pt.epi}^{Glc}.\bar{q}_{cvs}^{Glc}}{k_3^{GLUT2}}}$$

Substituting these fluxes into the mass balance equations gives:

$$\frac{dq_{gi}^{H_2O}}{dt} = v_{in}^{H_2O} - v_{gi}^{H_2O} - v_{out1}^{H_2O}$$

$$\frac{dq_{pt}^{H_2O}}{dt} = v_{gl}^{H_2O} - v_{pt}^{H_2O} - v_{out2}^{H_2O}$$

$$\frac{dq_{vc}^{H_2O}}{dt} = v_{cc}^{H_2O} + v_{gi}^{H_2O} + v_{pt}^{H_2O} - v_{lv}^{H_2O}$$

$$\frac{dq_{ac}^{H_2O}}{dt} = v_{lv}^{H_2O} - v_{cc}^{H_2O} - v_{gl}^{H_2O}$$

$$\frac{dq_{gi}^{Na^+}}{dt} = v_{in}^{Na^+} - 2v_{gi}^{SGLT1} - v_{out1}^{Na^+}$$

$$\frac{dq_{gi.epi}^{Na^+}}{dt} = 2v_{gi}^{SGLT1} - 3v_{gi}^{NKE}$$
$$\frac{dq_{pt}^{Na^+}}{dt} = v_{gl}^{Na^+} - 2v_{pt}^{SGLT1} - v_{out2}^{Na^+}$$
$$\frac{dq_{pt.epi}^{Na^+}}{dt} = 2v_{pt}^{SGLT1} - 3v_{pt}^{NKE}$$
$$\frac{dq_{cvs}^{Na^+}}{dt} = 3v_{gi}^{NKE} + 3v_{pt}^{NKE} - v_{gl}^{Na^+}$$
$$\frac{dq_{gi}^{Glc}}{dt} = v_{in}^{Glc} - v_{gi}^{SGLT1} - v_{out1}^{Glc}$$
$$\frac{dq_{gi.epi}^{Glc}}{dt} = v_{gi}^{SGLT1} - v_{gi}^{GLUT2}$$
$$\frac{dq_{pt}^{Glc}}{dt} = v_{gl}^{Glc} - v_{pt}^{SGLT1} - v_{out2}^{Glc}$$
$$\frac{dq_{pt.epi}^{Glc}}{dt} = v_{pt}^{SGLT1} - v_{pt}^{GLUT2}$$
$$\frac{dq_{cvs}^{Glc}}{dt} = v_{gi}^{GLUT2} + v_{pt}^{GLUT2} - v_{gl}^{Glc} - v_{sink}^{Glc}$$

Note that the reversal potential for SGLT1 is given by

$$u_m^e = \frac{RT}{2F}\ln\left\{\left(\frac{\bar{q}_{gi}^{Na^+}}{\bar{q}_{gi.epi}^{Na^+}}\right)^2 . \frac{\bar{q}_{gi}^{Glc}}{\bar{q}_{gi.epi}^{Glc}}\right\} = \frac{RT}{2F}\ln\left\{\left(\frac{c_{gi}^{Na^+}}{c_{gi.epi}^{Na^+}}\right)^2 . \frac{c_{gi}^{Glc}}{c_{gi.epi}^{Glc}}\right\}$$

For $c_{gi}^{Na^+} = 150$ mM, $c_{gi.epi}^{Na^+} = 10$ mM, $c_{gi}^{Glc} = 50$ mM, $c_{gi.epi}^{Glc} = 1$ mM, $u_m^e = \frac{25}{2}\ln(15^2.50) = 116$ mV.

The reversal potential for NKE is given by

$$u_m^e = -\frac{RT}{2F}\ln\left\{\left(\frac{\bar{q}_{cvs}^{Na^+}}{\bar{q}_{gi.epi}^{Na^+}}\right)^3 . \left(\frac{\bar{q}_{gi.epi}^{K^+}}{\bar{q}_{cvs}^{K^+}}\right)^2\right\} = -\frac{RT}{2F}\ln\left\{\left(\frac{c_{cvs}^{Na^+}}{c_{gi.epi}^{Na^+}}\right)^3 . \left(\frac{c_{gi.epi}^{K^+}}{c_{cvs}^{K^+}}\right)^2\right\}$$

For $c_{cvs}^{Na^+} = 140$ mM, $c_{gi.epi}^{Na^+} = 10$ mM, $c_{cvs}^{K^+} = 5$ mM, $c_{gi.epi}^{K^+} = 150$ mM, $u_m^e = -\frac{25}{2}\ln(14^3.30^2) = -150$ mV.

Note that the membrane potential for most epithelial cells is in the range -30 mV to -50 mV.

Need to track charge movement and membrane potentials.

12. A 50-compartment model of the cardiovascular circulation

We next extend the very simple circulation model above to include more vascular compartments. Figure 11 shows the bond graph model using red-outline 0:nodes (where mass is conserved, including the local storage/compliance relation between blood volume and blood pressure for a compartment) and green outline 1:nodes (where energy is conserved, including viscous dissipation and kinetic storage in the fluid inertia).

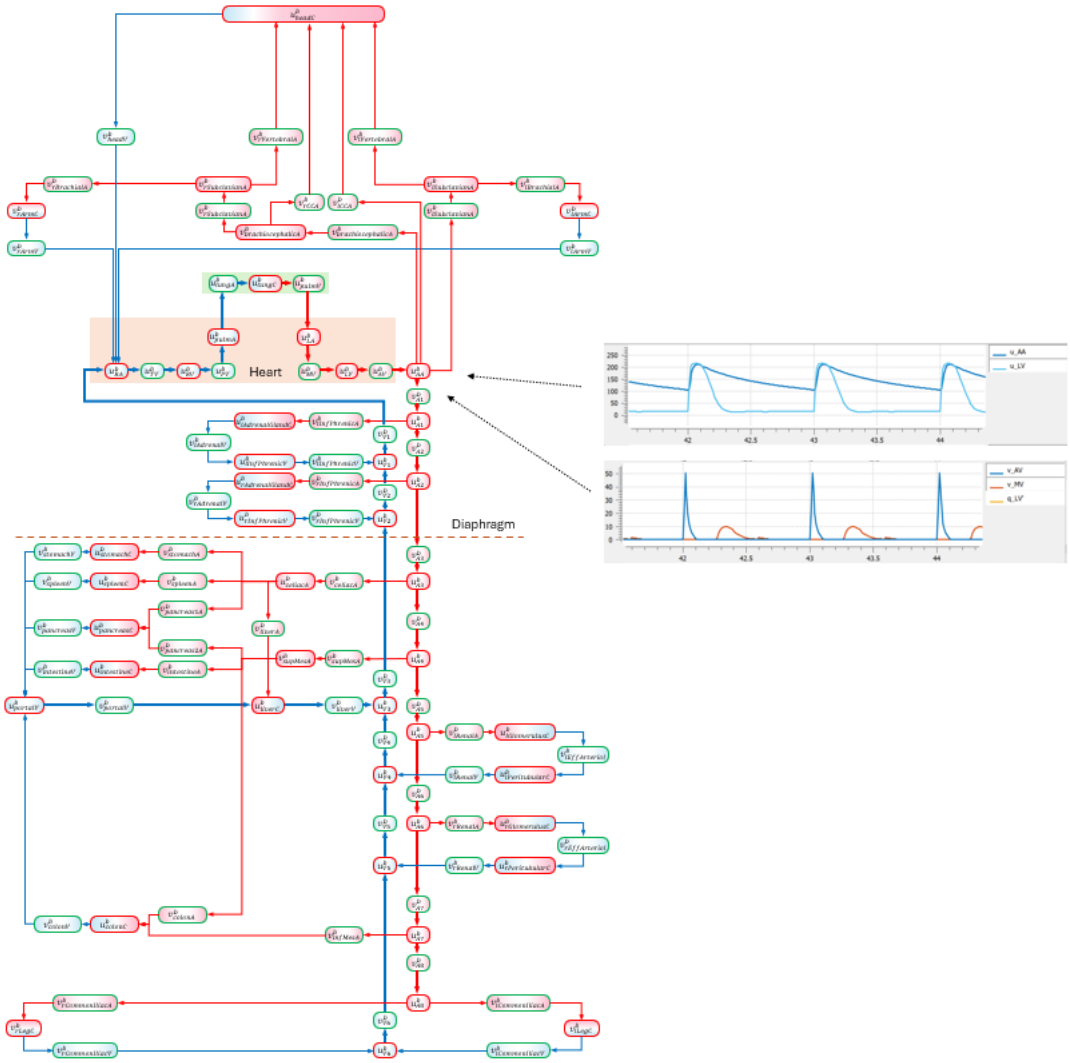
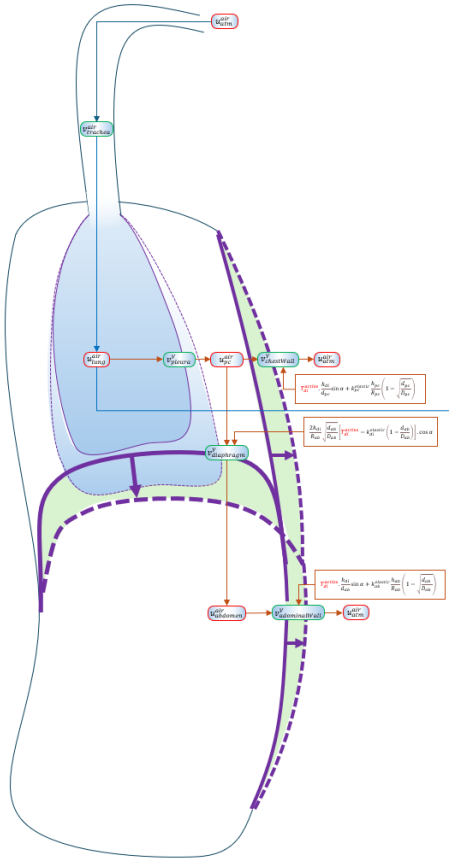


Figure 11. A cardiovascular system (CVS) model with about 50 vascular compartments. This model focusses on the visceral organs (heart, lungs, kidneys, adrenal glands, liver, pancreas, stomach, small intestines and colon). The plots shown on the top right illustrate pressures and flows in the left ventricle and aorta.

The model is available as a CellML model here. It is currently being used as a test case for interaction with Circulatory Autogen, which provides a Python environment for assembling CellML models with PDE solvers for solving 1D or 3D Navier-Stokes equations and/or finite element codes for solving mechanics.

13. A model of respiratory mechanics



Trachea flow

$$v^{air}_{trachea} = \left(u^{air}_{atm} - u^{air}_{lung}\right)/R_{trachea}$$

Lung compartment flow balance and compliance

$$\frac{d}{dt}q^{air}_{lung} = v^{air}_{trachea} - v^{V}_{pleura}$$

$$u^{air}_{lung} = q^{V}_{lung}/C_{lung}$$

Pleura energy balance (1: v^{V}_{pleura})

$$v^{V}_{pleura} = \left(u^{air}_{lung} - u^{air}_{pc}\right)/R_{pleura}$$

Pleural cavity (pc) flow balance and compliance

$$\frac{d}{dt}q^{air}_{pc} = v^{V}_{pleura} - v^{V}_{diaphragm} - v^{V}_{chestWall}$$

$$u^{air}_{pc} = q^{V}_{pc}/C_{pc}$$

Chest wall energy balance (1: $v^{V}_{chestWall}$)

$$v^{V}_{chestWall} = \left\{u^{air}_{pc} + T^{active}_{di}.\frac{h_{di}}{d_{pc}}\sin\alpha - k^{elastic}_{pc}\frac{h_{pc}}{R_{pc}}\left(1 - \sqrt{\frac{d_{pc}}{D_{pc}}}\right) - u^{air}_{atm}\right\}/R_{chestW}$$

Abdomen compartment flow balance and compliance

$$\frac{d}{dt}q^{V}_{abdomen} = v^{V}_{diaphragm} - v^{V}_{abdomenWall}$$

$$u^{air}_{abdomen} = q^{V}_{abdomen}/C_{abdomen}$$

Abdomen wall energy balance (1: $v^{V}_{abdomenWall}$)

$$v^{V}_{abdomenWall} = \left\{u^{air}_{abdomen} + T^{active}_{di}.\frac{h_{di}}{d_{ab}}\sin\alpha - k^{elastic}_{ab}.\frac{h_{ab}}{R_{ab}}\left(1 - \sqrt{\frac{d_{ab}}{D_{ab}}}\right) - u^{air}_{atm}\right\}/R_{abdomenWall}$$

Diaphragm energy balance (1: $v^{V}_{diaphragm}$)

$$v^{V}_{diaphragm} = \left\{u^{air}_{pc} + \frac{2h_{di}}{R_{ab}}\sqrt{\frac{d_{ab}}{D_{ab}}}\left[T^{active}_{di} - k^{elastic}_{di}\left(1 - \frac{d_{ab}}{D_{ab}}\right)\right].\cos\alpha - u^{air}_{abdomen}\right\}/R_{diaphragm}$$

Depth of abdomen (d_{ab}) and thorax (d_{th})

$$\frac{d}{dt}d_{ab} = -k.v^{V}_{diaphragm}/\pi R^{2}_{ab}$$

$$d_{pc} = D_{pc} + D_{ab} - d_{ab}$$

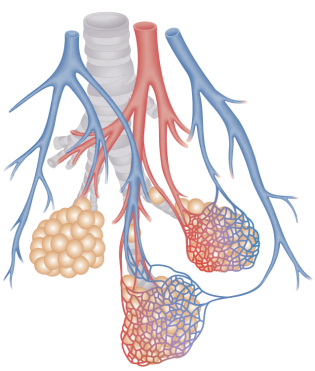
Note that d_{ab} and R_{ab} have units of metres, and $v^{V}_{diaphragm}$ is in L.s^{-1}, $k = 10^{-3}$ m^{3}.L^{-1}.

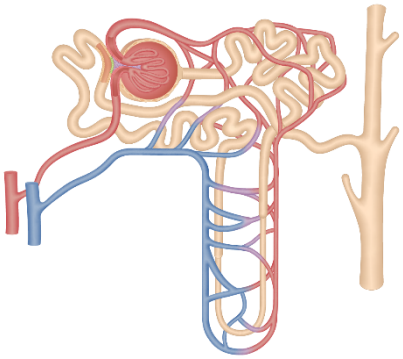
Active muscle contraction during inspiration

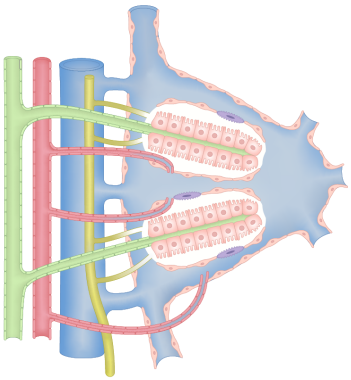
$$T^{active}_{di} = 70sin\left(\frac{t}{T_{inspire}}.\frac{\pi}{2}\right)$$ (amplitude 100 kPa)

For specified values of the kinetic parameters u^{air}_{atm} *and* T^{active}_{di}, the geometric parameters $h_{pc}, R_{pc}, D_{pc}, h_{di}, h_{ab}, R_{ab}, D_{ab}$, α, and material parameters $R_{trachea}, R_{pleura}, R_{chestWall}, R_{diaphragm}, R_{abdomenWall}, k^{elastic}_{di}, k^{elastic}_{th}, k^{elastic}_{ab}$, these 13 equations are solved for the 3 kinetic variables $u^{p}_{lung}, u^{p}_{pc}, u^{p}_{abdomen}$ and the 10 kinematic variables, $q^{air}_{lung}, q^{air}_{pc}, q^{V}_{abdomen}, v^{air}_{trachea}, v^{V}_{pleura}, v^{V}_{chestWall}, v^{V}_{diaphragm}, v^{V}_{abdomenWall}, d_{ab}, d_{pc}$.

14. FTUs for epithelial transport







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