Modeling the clearance of hyaluronan: an approach to estimating lymph flow

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April, 2004

Abstract

One of the important factors in long term blood pressure regulation is the maintenance of the blood volume. This may be done by changing the level of ADH. Another important issue in regulating blood volume (for instance at dialysis and orthostatic stress) is the flow from the interstitial to the plasma. To get an estimation on the fluid volume distribution and the dynamics it would be necessary to know the lymph flow dynamics.

This model is an approach to estimate the lymph flow by measurements of the substance hyaluronan (hyaluronic acid), which is transported by the lymph flow from the interstitial to the plasma. A four compartment model is presented in this paper, which is able to emulate the steady state relationships and qualitatively the dynamics.

To match the dynamics qualitatively it is necessary to decrease the lymph flow during orthostatic stress and ultrafiltration.

Sensitivity analysis shows, that during ultrafiltration the lymph flow is one of the main parameters which influences the total hyaluronan level. This suggests, that the model may produce good results in estimating the lymph flow.

Further investigations and parameter estimation will be done with data showing the dynamics of small and large HA molecules.

1 Physiology

1.1 Long-term blood volume regulation

Whereas in the first five to ten minutes of exercise and orthostatic stress the main control feature of the cardiovascular system is the baroreflex loop, long-term blood pressure control is exhibited by blood volume regulation.

Hemorrhage (blood loss) and also long term volume changes can lead to instability of the cardiovascular system, because the blood pressure can't be maintained with too little fluid in the circulation.

Though 60–70 % of the body mass is water, only a small part of it is located in the blood circulation. The main part is in the cells and about 12 L are in the interstitium. Only about 3 L of water and a huge amount of red blood cells make up for 5 L of blood circulating in our vessels.

Drinking, renal excretion, ultrafiltration at dialysis, and also orthostatic stress change the amount of plasma volume. The fluid balance between interstitium and plasma is maintained by two mechanisms: the lymph flow and the microvascular filtration. The lymph flow is a slow flow from the interstitium to the plasma at about 2 ml/min, which can be controlled by adapting the lymphatics (small lymph vessels).

Starling found that microvascular filtration Q_f, i.e. the exchange of water between capillaries and interstitium, can be determined by the net effect of four pressures

$$Q_\mathrm{f} = K_\mathrm{f}(p_\mathrm{c} - p_\mathrm{i} - \pi_\mathrm{p} + \pi_\mathrm{i}),$$

where K_f the capillary filtration coefficient reflects the membrane conductivity, p_c is the capillary pressure, p_i the interstitial pressure, and π_p and π_i are the colloid osmotic pressures for plasma and interstitium, respectively.

This represents a passive effect which depends on the pressures (and thus on the volumes) and on the protein concentrations of the interstitium and the plasma.

A possibility for an active change of the amount of blood plasma is by changing the concentration of the antidiuretic hormone (ADH), which mainly influences the reabsorption of water by the kidney back into the circulation.

A key element to understanding the dynamics is the lymphatic flow. Thus the long term goal of the model presented in this paper is to be able to estimate the dynamics of the lymph flow from the interstitium to the plasma, which is an important quantity in maintaining the blood volume in dialysis and orthostasis.

1.2 Hyaluronan

Hyaluronan is a substance which is degraded at the lymph nodes and as it is transported by the lymph flow to the blood plasma. It has been shown lately by Rössler and Hinghofer [1] that the degraded molecules can be split into a low and a high molecular weight group which act differently on the system. The shredding is depending on the time the molecules need to reach the plasma, where the shredding is stopped and the molecules are preserved in the state they are until they are excreted.

There are several differences between the two molecule groups. The low weight molecules for instance have the ability to tunnel through capillary walls, which is impossible for the large ones.

Another big difference is that low weight molecules are cleared by the kidney and though both weighting groups bind to the liver only the large ones are excreted by the liver.

Note that the number of small molecules is also depending on the state of the immune system, so it is difficult to draw conclusions from the absolute numbers, but relative changes during treatments should be expressive.

The normal concentration of hyaluronan in the blood plasma is between 30 and 40 μg/L, but it may vary from 10 to 100 μg/L.

2 Model

The model we developed to describe the hyaluronan dynamics consists of a system of four ordinary differential equations:

$$\frac{d}{dt}m_{\mathrm{m}} = J_{\mathrm{L,m}} - J_{\mathrm{hep}}, \tag{2.1}$$

$$\frac{d}{dt}m_{\mathrm{o}} = J_{\mathrm{L,o}} - J_{\mathrm{dia}} - J_{\mathrm{ren}} - J_{\mathrm{pt}}, \tag{2.2}$$

$$\frac{d}{dt}V_{\mathrm{P}} = Q_{\mathrm{L}} - Q_{\mathrm{f}} - Q_{\mathrm{uf}}, \tag{2.3}$$

$$\frac{d}{dt}V_{\mathrm{I}} = Q_{\mathrm{f}} - Q_{\mathrm{L}}, \tag{2.4}$$

where m_{m} and m_{o} are the masses of big resp. small molecules in the blood plasma, and $J_{\mathrm{L,m}}$ and $J_{\mathrm{L,o}}$ the respective molecule flow through the lymph. J_{hep}, J_{dia} and J_{ren} denote the excretion of the respective molecule by liver, dialysis and kidney. And V_{P} and V_{I} are the volumes of the plasma and the interstitial fluids resp. and Q_{L} is the lymph flow, Qf the microvascular filtration, and Q_{uf} the amount of ultrafiltration.

We will first describe the auxiliary equations for the hyaluronan modeling part and afterwards the auxiliary equations for the fluid volumes.

2.1 Hyaluronan auxiliary equations

Hyaluronan flow through the lymph

Hyaluronan is floating with the lymph flow from the interstitium to the plasma – along the way it is shredded into smaller molecules. When it reaches the plasma this process stops and no further conversion is done.

Thus the size of the molecules is depending on the time it floats through the lymph vessels, which mainly depends on the lymph flow Q_{L}.

$$J_{\mathrm{L,m}} = c_{\mathrm{m,L_0}} \left(1 - e^{-K_{\mathrm{L}}Q_{\mathrm{L}}}\right) Q_{\mathrm{L}}, \tag{2.5}$$

$$J_{\mathrm{L,o}} = c_{\mathrm{m,L_0}} \left(e^{-K_{\mathrm{L}}Q_{\mathrm{L}}}\right) Q_{\mathrm{L}}, \tag{2.6}$$

where Q_{L} is the actual lymph flow, K_{L} determines how fast molecules are shredded and $c_{\mathrm{m,L_0}}$ represents the concentration of hyaluronan in the lymph – which is assumed to be constant.

Enzyme kinetics in the kidney

The enzyme kinetics at the kidney are described by the approximation according to the Michaelis–Menten excretion rate. The enzyme E converts substrate S into the product P. First it combines with S to complex C and then breaks down into P and E:

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k_{-1}}}{\overset{\mathrm{k_1}}{\rightleftarrows}} \mathrm{C} \xrightarrow{\mathrm{k_2}} \mathrm{P} + \mathrm{E}. \tag{2.7}$$

The quasi-steady-state and the equilibrium approximation of these dynamics lead both to a reaction velocity v of

$$v = \frac{\bar{v}s}{K_s + s}, \tag{2.8}$$

with $\bar{v}$ the maximal reaction velocity, s concentration of the substrate S and K_s the Michaelis–Menten constant (see [2]).

Thus the excretion rate of the small hyaluronan molecules is given by

$$\tilde{J}_{\text{ren}} = \frac{\bar{v}_{\text{ren}} c_{\text{o}}}{K_{\text{o,ren}} + c_{\text{o}}}, \quad \text{with } c_{\text{o}} = \frac{m_{\text{o}}}{V_{\text{P}}}, \tag{2.9}$$

where c_{o} is the plasma concentration of oligomeric hyaluronan molecules and V_{P} denotes the blood plasma volume.

Competitive binding at the liver

The kinetics of the larger hyaluronan molecules at the liver can be described by a similar approach. Though the difference is that not only the large molecules bind to the liver, but also the small molecules, but without being excreted.
Adding a competitive inhibitor to the kinetics of 2.7 we get (see [2])

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftarrows}} \mathrm{C} \xrightarrow{\mathrm{k}_2} \mathrm{P} + \mathrm{E}, \tag{2.10}$$

$$\mathrm{I} + \mathrm{E} \underset{\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftarrows}} \mathrm{C}_2, \tag{2.11}$$

where I denotes the inhibitor (in our case the small molecules, which inhibit the binding of the big molecules to the liver), we get

$$v = \frac{\bar{v} s}{K_s + s\left(1 + \frac{i}{K_i}\right)}, \tag{2.12}$$

where i is the concentration of the inhibitor and $K_i = k_{-3}/k_3$.
For our model this is

$$\tilde{J}_{\text{hep}} = \frac{\bar{v}_{\text{hep}} c_{\text{m}}}{K_{\text{m,hep}} + c_{\text{m}}\left(1 + \frac{c_{\text{o}}}{K_{\text{o,hep}}}\right)}, \quad \text{with } c_{\text{m}} = \frac{m_{\text{m}}}{V_{\text{P}}}, \tag{2.13}$$

where c_{m} and c_{o} are the plasma concentrations of the larger resp. smaller hyaluronan molecules.

Dependency on blood flow to liver and kidney

The amount of excretion depends also on the blood flow to the organs, thus we get the relations

$$J_{\text{ren}} = Q_{\text{ren}} \tilde{J}_{\text{ren}} = \frac{Q_{\text{ren}} \bar{v}_{\text{ren}} c_{\text{o}}}{K_{\text{o,ren}} + c_{\text{o}}}, \tag{2.14}$$

$$J_{\text{hep}} = Q_{\text{hep}} \tilde{J}_{\text{hep}} = \frac{Q_{\text{hep}} \bar{v}_{\text{hep}} c_{\text{m}}}{K_{\text{m,hep}} + c_{\text{m}}\left(1 + \frac{c_{\text{o}}}{K_{\text{o,hep}}}\right)}. \tag{2.15}$$

2.2 Diffusion of small molecules through the vessel walls

Small molecules are not only going by the lymph flow, but can also filtrate through the capillary vessel walls. A possible approach to model just this exchange would be

$$\frac{d}{dt} m_{\text{o}} = -K_{\text{pt}} c_{\text{o}} + K_{\text{tp}} C_{\text{o}}, \tag{2.16}$$

where "pt" denotes plasma to tissue, "tp" tissue to plasma and C_{o} the tissue concentration of small molecules.

We approximate this equation using the assumption that the concentration of the small molecules in the tissue is somehow related to the crushing in the lymph and thus we model this additional flow from the tissue to the plasma by increasing the flow of the small molecules through the lymph to m_f times the original.

$$J_{\mathrm{L,o}} = m_\mathrm{f} J_{\mathrm{L,o}}^{\mathrm{orig}}. \tag{2.17}$$

The backflow from the plasma to the tissue is modeled as proposed above by

$$J_{\mathrm{pt}} = K_{\mathrm{pt}} c_\mathrm{o}. \tag{2.18}$$

Dialysis filter

The dialysis filter at ultrafiltration is assumed to filter a constant proportion of the small molecules, thus

$$J_{\mathrm{dia}} = Q_{\mathrm{uf}} K_{\mathrm{dia}} c_\mathrm{o}, \tag{2.19}$$

where Q_{uf} is the ultrafiltration rate.

2.3 Fluid volume auxiliary equations

Microvascular filtration

A simple model to describe the microvascular filtration between plasma and interstitial volume was proposed in [3]. We used this approach with the parameters given in the report. For calculating the colloid osmotic pressure we also used a variation [4] to compare these two approaches.

The fluid dynamics model given in [3] uses the starling equation to calculate the microvascular filtration Q_f

$$Q_\mathrm{f} = K_\mathrm{f}(p_\mathrm{c} - p_\mathrm{i} - \pi_\mathrm{p} + \pi_\mathrm{i} + p_{\mathrm{off}}), \tag{2.20}$$

where K_f is the capillary filtration coefficient, p_c and p_i are the pressures in the capillaries and the interstitium, π_p and π_i are the colloid osmotic pressures in the plasma and the interstitium, respectively, and p_{off} is an offset pressure.

The relationships between dynamic pressures in the capillaries and the interstitium and the fluid volumes of interstitium resp. the plasma were approximated by

$$p_\mathrm{i} = aV_\mathrm{I} + b/(V_\mathrm{I} + c), \tag{2.21}$$

$$p_\mathrm{c} = d(V_\mathrm{P} + V_{\mathrm{RBC}} + e)^f. \tag{2.22}$$

The colloid osmotic pressures were calculated according to [3] by the Landis-Pappenheimer equation [5]:

$$\pi_\mathrm{p} = k_1 c_\mathrm{p} + k_2 c_\mathrm{p}^2 + k_3 c_\mathrm{p}^3, \tag{2.23}$$

$$\pi_\mathrm{i} = k_1 c_\mathrm{i} + k_2 c_\mathrm{i}^2 + k_3 c_\mathrm{i}^3, \tag{2.24}$$

where $c_\mathrm{p} = m_\mathrm{p}/V_\mathrm{P}$ is the protein concentration in the plasma and $c_\mathrm{i} = m_\mathrm{i}/V_\mathrm{I}$ the protein concentration in the interstitium.

As mentioned above, we also used a second approach to calculate the colloid osmotic pressures by Geranton *et al.* [4]:

$$\pi_\mathrm{p} = k_{\mathrm{var}} c_\mathrm{p} + c, \tag{2.25}$$

$$\pi_\mathrm{i} = k_{\mathrm{var}} c_\mathrm{i} + c, \tag{2.26}$$

with the constant c disappearing in the starling equation (2.20).

3 Results

We show four different cases – healthy persons which undertake orthostatic stress and dialysis patients at ultrafiltration, both with either increasing or decreasing lymph flow during the treatment.

Healthy subjects under orthostatic stress

For modeling orthostatic stress, we assume, that the blood flow to the kidney is decreased by 1/6th and to the liver by 1/3rd. The capillary pressure is increased to three times its original value. The basic lymph flow was set to 0.02 L/min and was constant for Fig. 1 and decreased to 0.012 L/min during the orthostase treatment in Fig. 2.

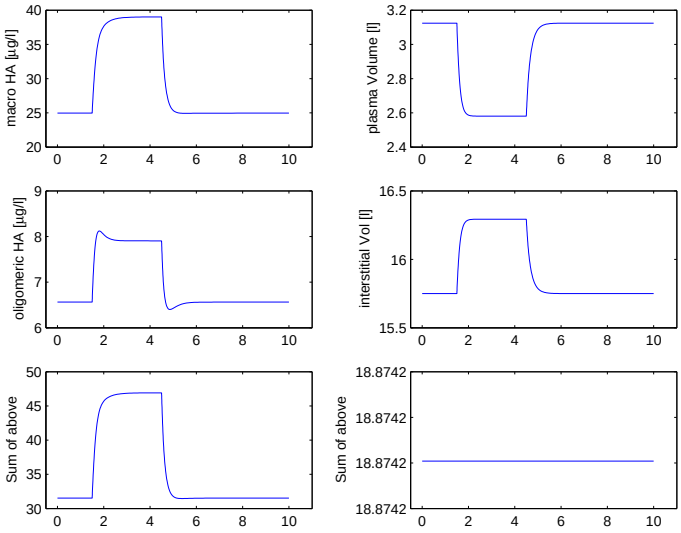

Figure 1: Model output: Healthy person with constant lymph flow at orthostatic stress

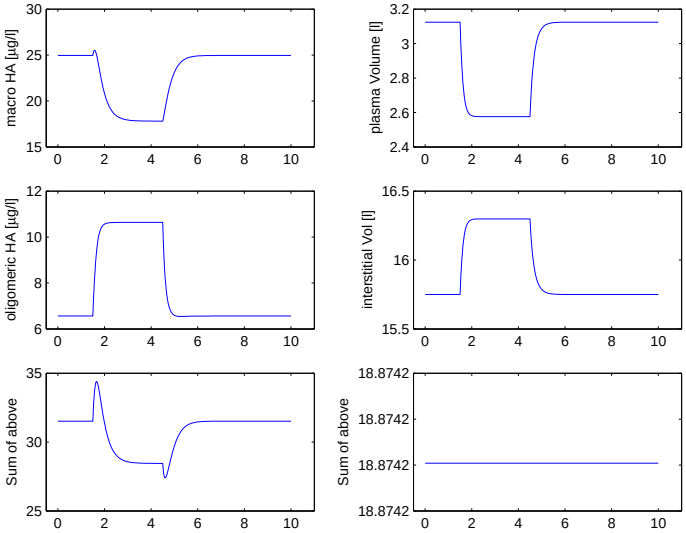

Figure 2: Model output: Healthy person with decreasing lymph flow at orthostatic stress

Dialysis patients at ultrafiltration

Ultrafiltration was modeled as a square pulse in a specified interval. The rate of ultrafiltration was assumed to be $Q_{\mathrm{uf}} = 0.03$ L/min. The lymph flow Q_{L} is set to 0.08 L/min for dialysis patients (see [3]), but was increased or decreased during ultrafiltration by 25 % for the Figures 3 and 4, respectively.

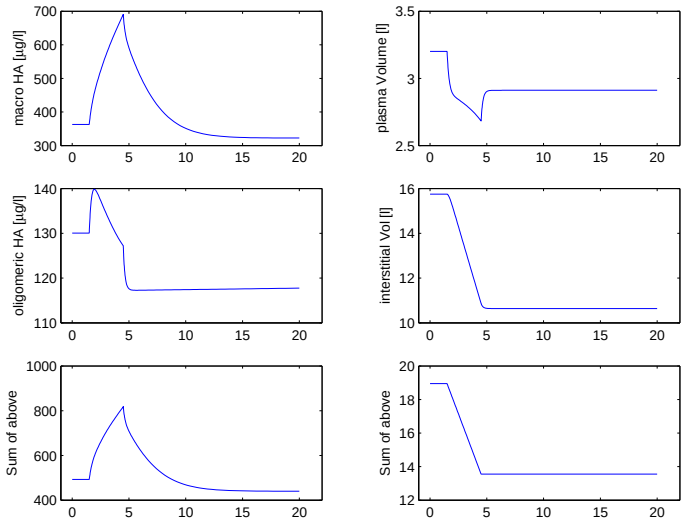

Figure 3: Model output: Dialysis patient with increasing lymph flow at ultrafiltration

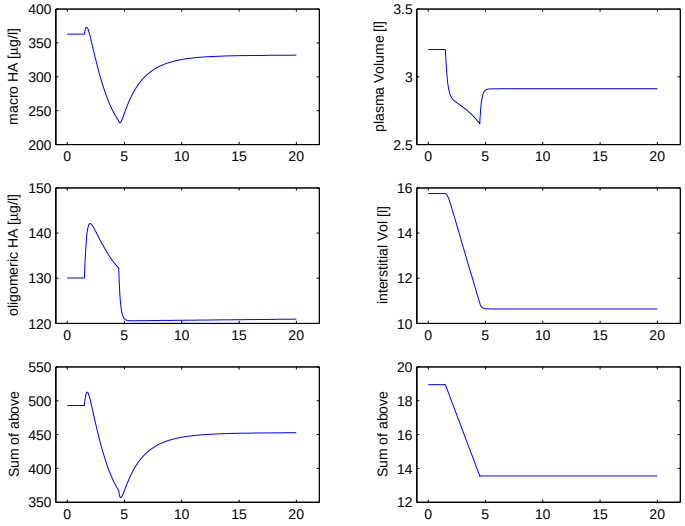

Figure 4: Model output: Dialysis patient with decreasing lymph flow at ultrafiltration

At the case of dialysis the simulation with decreasing lymph flow (Fig. 4) seems to be very reasonable according to what is known from experiments.

3.1 Sensitivity analysis

Given is the system of ODEs

$$\frac{d}{dt}x(t) = f(x(t), t, p), \tag{3.1}$$

where x is a vector of the states of the system, t is the time variable, and p is a vector of system parameters.

Sensitivity analysis then provides the sensitivity $S_{i,j}$ of a state x_i in dependence of the parameter p_j

$$S_{i,j} = \frac{\partial x_i}{\partial p_j}. \tag{3.2}$$

Though at steady state there exist some data sets distinguishing between small and large molecules, most dynamical data sets available provide the time course of total concentration of hyaluronan and also for clinical applications this would be the measurement to rely on.

As examples we present a case with renal failure including a dialysis treatment from 1.5 to 4.5 hours, where the lymph flow is decreasing to 0.8 times its original value.

We calculated the sensitivities of the plasma volume and the total hyaluronan concentration in the plasma at ultrafiltration – these sensitivities are plotted in Figures 5 and 6, respectively. The sensitivities may be interpreted as "necessary accuracy" for the parameters. A change in the parameter p_j by the amount of 1 changes the state x_i approximately by $S_{i,j}$.

To compare the sensitivities of several parameters it is more useful to compare the normalized sensitivities given by

$$S^n_{i,j} = p_j \frac{\partial x_i}{\partial p_j}. \tag{3.3}$$

This value is an approximation to the state change according to a 100 % change of the parameter. The numbers in the boxes denote mean normalized sensitivity over the plotted interval.

In the upper left edge of Figure 5 there is a plot of the volume over the given time interval. The sensitivity of this output depending on the respective parameter is represented by the other plots. It is obvious that the volume does not depend on the parameters of the hyaluronan auxiliary equations.

If the shape of the curves of two parameters are the same the volume has a similar dependency on these two parameters – regarding parameter estimation this means that they can not be distinguished using this set of data.

The numbers in the boxes show, that the mass of proteins in the plasma m_{p} determines the plasma volume at most. By a factor four less sensible reacts the plasma volume to the constants f and k_1. (The varied osmotic pressure calculation makes the m_{p} much less important.)

Figure 6 shows the sensitivities of total hyaluronan concentration in the plasma in respect to the model parameters. The output is most sensible to the parameters $c_{\mathrm{m,L_0}}$, $\bar{v}_{\mathrm{hep}}$, and Q_{hep}. The next sensitive parameter is Q_{L}, which is the parameter we would like to identify with this model.

$c_{\mathrm{m,L_0}}$ and $\bar{v}_{\mathrm{hep}}$ are assumed to be constant during ultrafiltration. Consequently we have to have data or at least a good approximation for the dynamics of Q_{hep} if we want to identify Q_{L}.

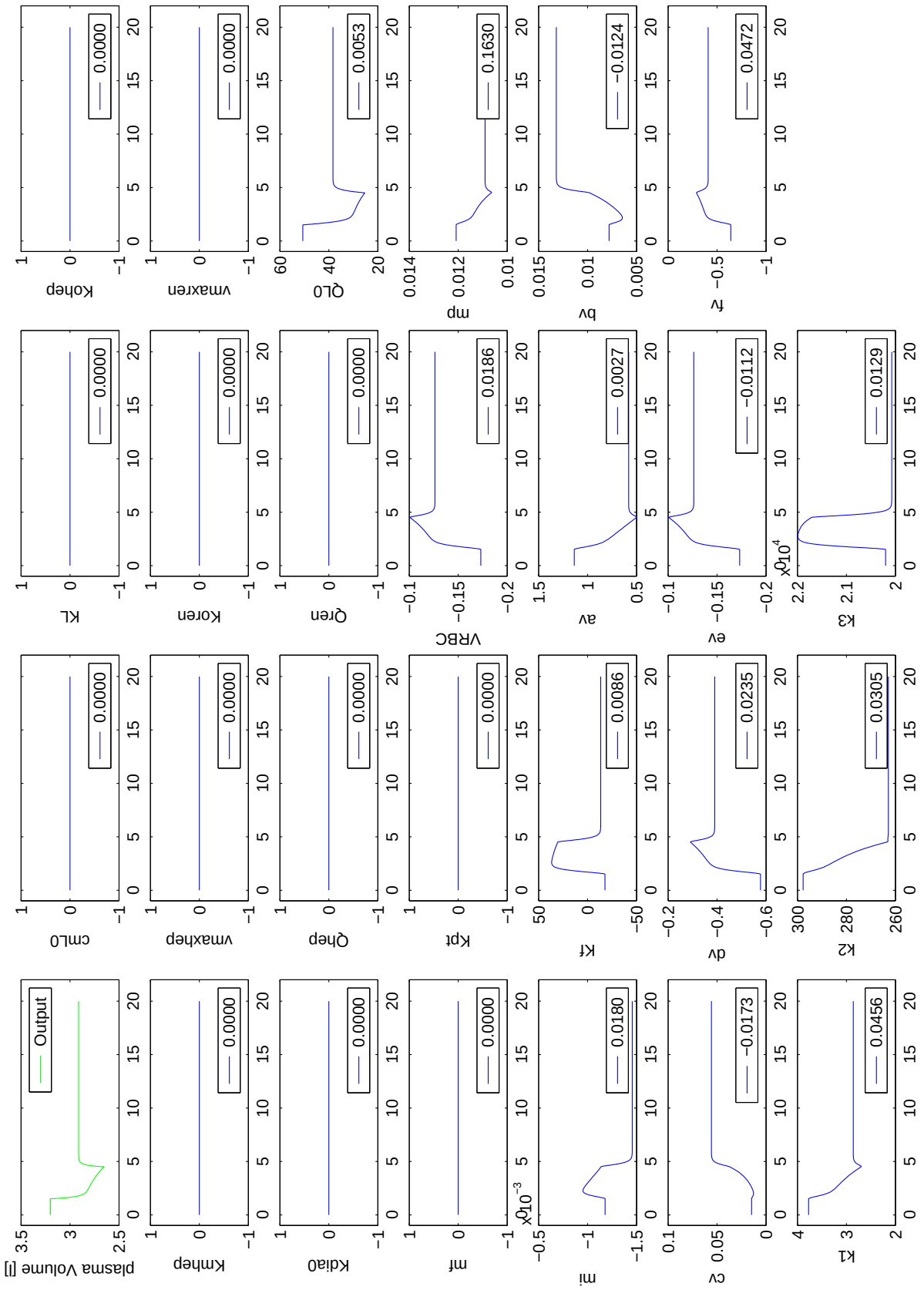

Figure 5: Sensitivity analysis for a dialysis patient with decreasing lymph flow at ultrafiltration: Sensitivity of plasma volume in respect to the model parameters

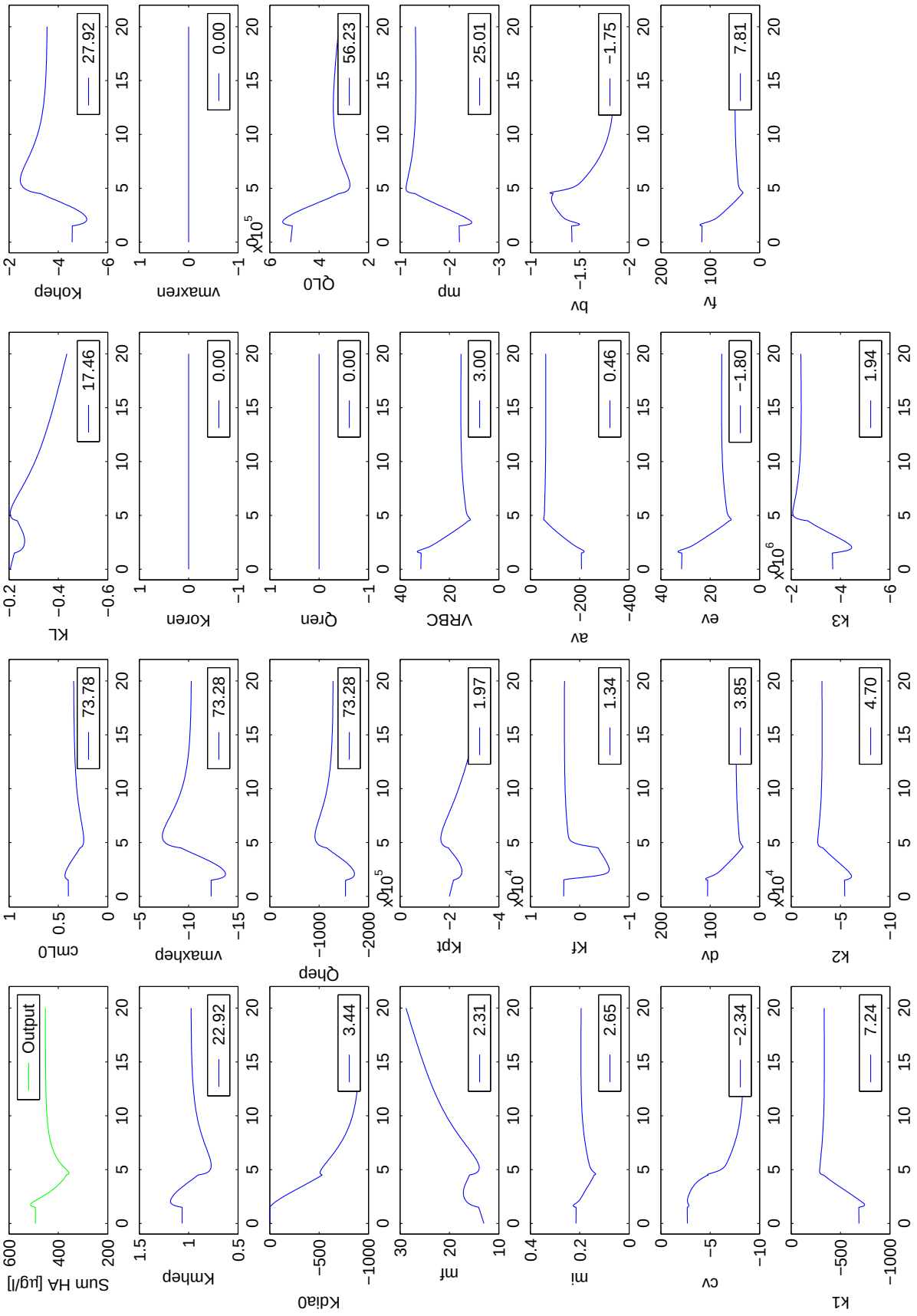

Figure 6: Sensitivity analysis for a dialysis patient with decreasing lymph flow at ultrafiltration: Sensitivity of total hyaluronan concentration in the blood in respect to the model parameters

A Model equations

The ODEs

$$\frac{d}{dt}m_{\mathrm{m}} = J_{\mathrm{L,m}} - J_{\mathrm{hep}}, \tag{A.1}$$
$$\frac{d}{dt}m_{\mathrm{o}} = J_{\mathrm{L,o}} - J_{\mathrm{ren}} - J_{\mathrm{pt}} - J_{\mathrm{dia}}, \tag{A.2}$$
$$\frac{d}{dt}V_{\mathrm{P}} = Q_{\mathrm{L}} - Q_{\mathrm{f}} - Q_{\mathrm{uf}}, \tag{A.3}$$
$$\frac{d}{dt}V_{\mathrm{I}} = Q_{\mathrm{f}} - Q_{\mathrm{L}}. \tag{A.4}$$

The hyaluronan auxiliary equations

$$J_{\mathrm{L,m}} = c_{\mathrm{m,L_0}}\left(1 - e^{-K_{\mathrm{L}}Q_{\mathrm{L}}}\right)Q_{\mathrm{L}}, \tag{A.5}$$
$$J_{\mathrm{L,o}} = m_{\mathrm{f}}c_{\mathrm{m,L_0}}\left(e^{-K_{\mathrm{L}}Q_{\mathrm{L}}}\right)Q_{\mathrm{L}} \tag{A.6}$$
$$J_{\mathrm{ren}} = Q_{\mathrm{ren}}\tilde{J}_{\mathrm{ren}} = \frac{Q_{\mathrm{ren}}\bar{v}_{\mathrm{ren}}c_{\mathrm{o}}}{K_{\mathrm{o,ren}} + c_{\mathrm{o}}}, \tag{A.7}$$
$$J_{\mathrm{hep}} = Q_{\mathrm{hep}}\tilde{J}_{\mathrm{hep}} = \frac{Q_{\mathrm{hep}}\bar{v}_{\mathrm{hep}}c_{\mathrm{m}}}{K_{\mathrm{m,hep}} + c_{\mathrm{m}}\left(1 + \frac{c_{\mathrm{o}}}{K_{\mathrm{o,hep}}}\right)}, \tag{A.8}$$
$$J_{\mathrm{pt}} = K_{\mathrm{pt}}c_{\mathrm{o}}, \tag{A.9}$$
$$J_{\mathrm{dia}} = Q_{\mathrm{uf}}K_{\mathrm{dia}}c_{\mathrm{o}}, \tag{A.10}$$

with $c_{\mathrm{o}} = m_{\mathrm{o}}/V_{\mathrm{P}}$ and $c_{\mathrm{m}} = m_{\mathrm{m}}/V_{\mathrm{P}}$.
The fluid volume auxiliary equations

$$Q_{\mathrm{f}} = K_{\mathrm{f}}(p_{\mathrm{c}} - p_{\mathrm{i}} - \pi_{\mathrm{p}} + \pi_{\mathrm{i}} + p_{\mathrm{off}}), \tag{A.11}$$
$$p_{\mathrm{i}} = aV_{\mathrm{I}} + b/(V_{\mathrm{I}} + c), \tag{A.12}$$
$$p_{\mathrm{c}} = d(V_{\mathrm{P}} + V_{\mathrm{RBC}} + e)^f, \tag{A.13}$$
$$\pi_{\mathrm{p}} = k_1c_{\mathrm{p}} + k_2c_{\mathrm{p}}^2 + k_3c_{\mathrm{p}}^3, \tag{A.14}$$
$$\pi_{\mathrm{i}} = k_1c_{\mathrm{i}} + k_2c_{\mathrm{i}}^2 + k_3c_{\mathrm{i}}^3, \tag{A.15}$$
$$\pi_{\mathrm{p}} = k_{\mathrm{var}}c_{\mathrm{p}} + c, \tag{A.16}$$
$$\pi_{\mathrm{i}} = k_{\mathrm{var}}c_{\mathrm{i}} + c. \tag{A.17}$$

Symbol	Description	Value	Unit
$c_{\mathrm{m,L_0}}$	concentration of HA in the lymph	3150	μg/L
K_{L}	shredding speed	1000	min/L
$K_{\mathrm{o,hep}}$	Michaelis constant for small HA at liver	105	μg/L
$K_{\mathrm{m,hep}}$	Michaelis constant for large HA at liver	340	μg/L
$\bar{v}_{\mathrm{hep}}$	maximal clearance of large HA by the liver	100	μg/L
$K_{\mathrm{o,ren}}$	Michaelis constant for small HA at kidney	340	μg/L
$\bar{v}_{\mathrm{ren}}$	maximal clearance of small HA by the kidney	150	μg/L
K_{dia}	clearance of small HA by ultrafiltration	0.10	μg/μg
Q_{hep}	blood flow to liver	0.8	L/min
Q_{ren}	blood flow to kidney	0.6	L/min
$Q_{\mathrm{L_0}}$	basic lymph flow (normal/dialysis)	0.002/0.008	L/min
m_{f}	const. for small HA flow through vessel walls	2.0	
K_{tp}	const. for small HA flow interst. to plasma	–	μgL/μg
K_{pt}	const. for small HA flow plasma to interst.	0.00013	μgL /μg

Table 1: Parameters of the hyaluronan part of the model

Symbol	Description	Value	Unit
V_{I0}	initial interstitial volume (normal/dialysis)	12/15.75	L
V_{RBC}	volume of red blood cells in blood	2	L
m_{p}	mass of proteins in plasma	210	g
m_{i}	mass of proteins in interstitium	210	g
K_{f}	capillary filtration coefficient	0.0057	L/min mmHg
a	constant for calc. interstitial fluid pressure	0.05	mmHg/L
b	constant for calc. interstitial fluid pressure	-17.5	mmHg L
c	constant for calc. interstitial fluid pressure	-6.5	L
d	constant for calc. capillary pressure	0.8	mmHg/L^f
e	constant for calc. capillary pressure	-1.2	L
f	constant for calc. capillary pressure	1.5	
k_1	constant for calc. COP (V1)	0.21	mmHg/ (g/L)
k_2	constant for calc. COP (V1)	0.0016	mmHg/ (g/L)^2
k_3	constant for calc. COP (V1)	9e-6	mmHg/ (g/L)^3
p_{off}	offset pressure for volume changes (V1)	14.0	mmHg
$k_s ubv$	constant for calc. COP (V2)	0.0689	mmHg/ (g/L)
p_{off}	offset pressure for volume changes (V2)	-3.0	mmHg

Table 2: Parameters of the fluid volume part of the model. V1 is calculating the colloid osmotic pressure (COP) according to [3], V2 according to [4]

			ESRD patients	
	absolute (μg/L)	Healthy subjects	Pre dialysis	Post dialysis
measured	Low molecule weight HA	6.7 ± 0.2	135.2 ± 14.4	124.4 ± 13.1
	High molecule weight HA	24.6 ± 1.4	386.0 ± 58.7	237.4 ± 37.7
	Total protein	62.9 ± 0.5	61.2 ± 0.5	66.3 ± 0.7
model	Low molecule weight HA	6.7	130.1	118.4
	High molecule weight HA	25.0	362.8	E: 232.0 S: 324.1

Table 3: Measured steady state values from Rössler (! CITE !) and model simulation steady states (E: end of dialysis treatment, S: steady state – see Fig. 4)

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