Hemorrhage and transfusion regimen design: a modeling application

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1 Abstract

Hemorrhagic shock is the term used for the medical syndrome resulting from insufficient oxygen perfusion of key organs as a consequence of a significant loss of blood volume to the circulatory system. The initial reaction to blood loss is a drop in stroke volume (blood pumped by the heart in one beat) as a result of the Frank Starling mechanism and reduced filling pressure of the heart. This results in a drop in arterial pressure and (depending on the degree and duration of blood loss) may lead to a negative and worsening spiral of reactions of the cardiovascular system (CVS) if not compensated for by the CVS control system. The focus of this paper involves modeling CVS behavior and in particular the control system response to hemorrhage. We will consider a single feedback loop to study the impact of increased heart rate on stabilizing arterial blood pressure after an acute hemorrhage of various degrees. Future applications will involve implementing additional control elements and the exploration of transfusion mechanisms in clinical settings.

2 Physiology and statement of the problem

Hypovolemia and compensatory mechanisms

Hypovolemia refers to reduced blood volume which may be due to blood loss, fluid loss due to dialysis and other reasons. Hypovolemia affects blood pressure and other CVS variables. When P_{as} drops, vasoconstriction and increased heart rate are seen. In moderate hypovolemia, defined by a 20 - 40 % loss of blood volume, the drop in $P_{\rm as}$ begins to be significant and there is the potential for shock to set in. When greater than 40 % of blood volume is lost (severe hypovolemia), $P_{\rm as}$ may drop severely and organ failure begins. Figure 1 depicts the response of $P_{\rm as}$ to various blood loss levels due to hemorrhage (from [7]).

Hypovolemia can also occur in dialysis treatment where plasma water depletion can result in blood volume reduction of about 15 %. This can lead in some cases to a decrease in arterial pressure serious enough to terminate treatment. This is a serious complication of hemodialysis, as the drop in blood pressure can be so severe that it requires quick termination of the treatment in up to one-third of dialysis sessions and up to 60 % of sessions in critically ill patients [4]. Compensatory mechanisms available to stabilize the CVS after reduction in blood volume consist of a number of control loops among which the following are key:

- baroreceptor reflexes consisting of high pressure sensors responding to arterial blood pressure P_{as} and cardiopulmonary low pressure sensors which respond to central venous pressure;
- hormonal vasoconstrictors transported in circulation influencing primarily arterial and venous tone which influences pressure due to increased systemic resistance and reduced venous capacitance;
- chemoreceptor reflexes which respond to changes in CO_2 and O_2 and which play an important role when the arterial pressure drops below 60 mmHg – the point where the baroreflex becomes less effective;
- transfer (auto-transfusion) of tissue (interstitial) fluids into the blood which raises blood fluid volume - this can compensate for about 15 % of lost volume [11];
- reabsorption of sodium and water by kidney which raises blood fluid volume.

The sites at which the baroreflex and chemoreflex sensors are located are depicted in Figure 2. The sites for both are located in the carotid and aortic bodies (perhaps they even overlap) on the

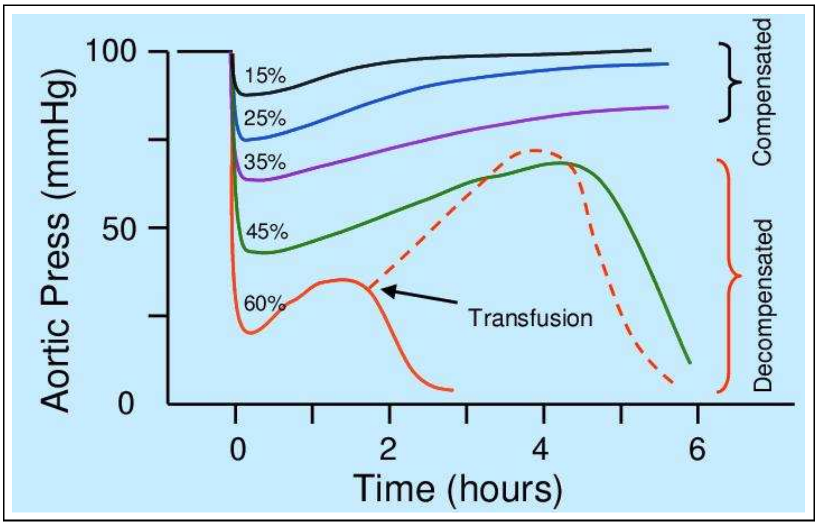

Figure 1: Blood pressure response to blood volume reduction (adapted from Guyton and Klaubundes).

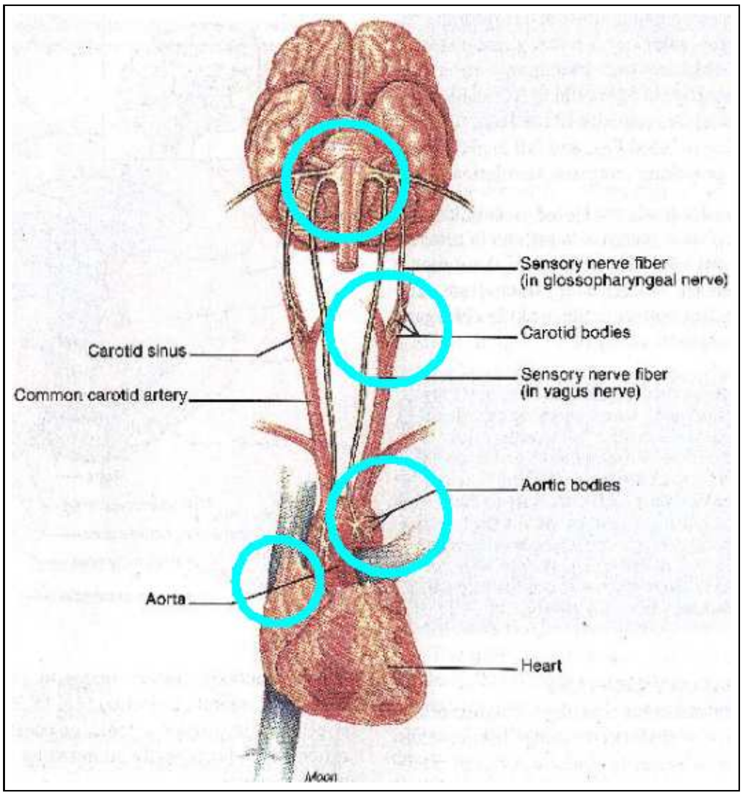

Figure 2: Sensory system diagram for the control loops

systemic arterial side while the cardiopulmonary sensors are near the region of the entrance and exit to the right heart. Figure 3 provides a schematic diagram of the cardiovascular-respiratory system indicating the baroreflex and respiratory feedback controls.

Baroreflex firing is reduced due to reduced arterial pressure. This leads to inhibition of the

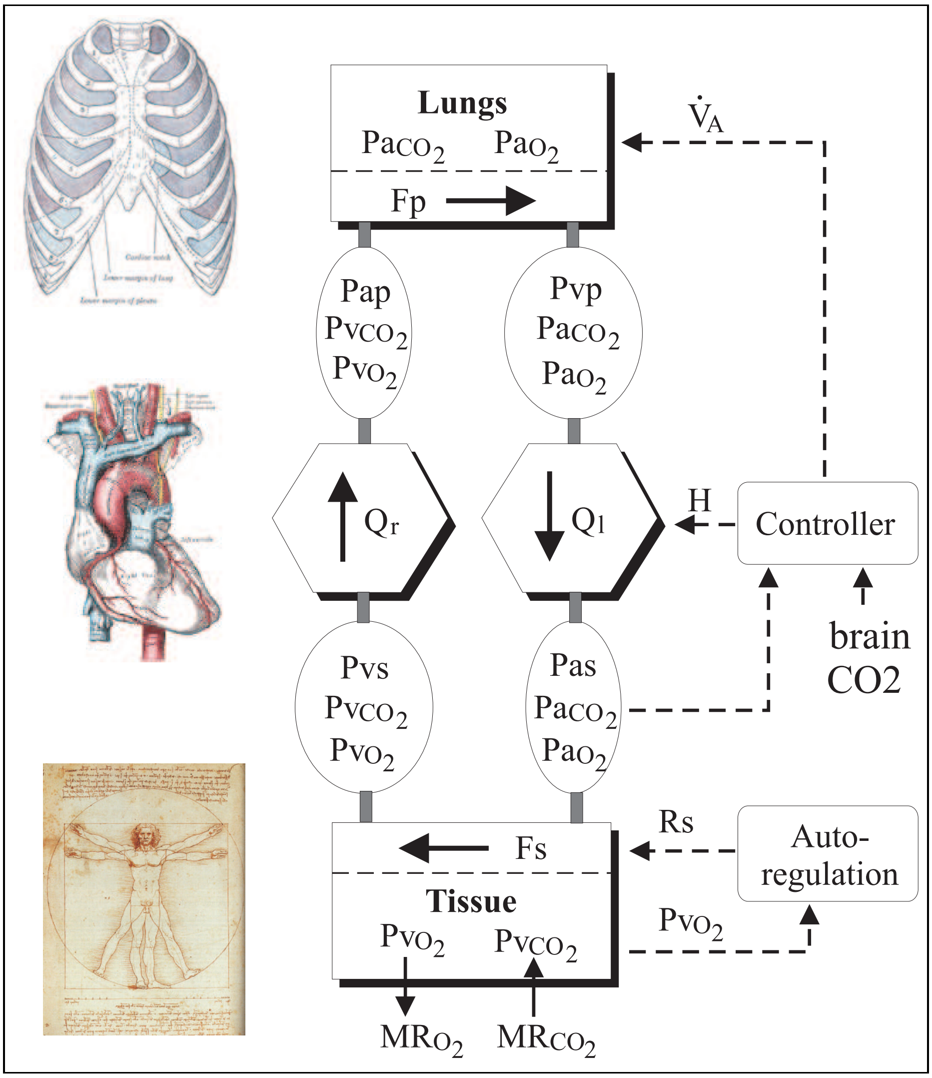

Figure 3: Block diagram for the model

cardioinhibitory area of the vasomotor center via parasympathetic output, as well as increased sympathetic activity from the vasomotor center. This results in increased vasoconstriction, and increased heart rate and contractility which raises cardiac output. Vascular constriction in splanchnic and skin tissue shifts blood to critical organs such as the brain and heart.

Hormonal control also acts to control cardiovascular function including heart rate and vasoconstriction. There are a number of feedback loops involving hormonal mechanisms including circulating catecholamines, the renin-angiotensin system, and vasopressin, among others. The chemoreceptor control loop is most important when $P_{\rm as}$ falls below 60 mmHg where baroreceptor sensitivity falls off. Chemoreceptors also stimulate respiration which may help mechanically to increase venous return. They also respond to acidosis.

Renal control responds to renal blood flow. When reduced, the response is increased production of renin which stimulates the production of angiotensin II which induces vasoconstriction. The renal control loop also contributes to the release of aldosterone from the adrenal cortex, which aids the reabsorption of salt and water. Water absorption is further induced by the increased production of vasopressin (ADH).

As a result of changes in capillary pressure and blood content ratios, fluid can be released from interstitial space into the blood. This is known as auto-infusion or auto-transfusion.

Figures 4, 5, and 6 provide schematic diagrams of the baroreceptor, vasoconstrictor, and renal control loops. It is interesting to note that one study showed that an 8 % drop in blood volume can result in a 12 % drop in aortic pressure when the compensatory mechanisms operate but can result in drops of 50 % or more if these mechanisms are impaired. Thus, understanding the action of these control loops is important and models describing the response to hemorrhage are of considerable medical and research interest.

Clearly, as can be seen from Figures 4, 5 and 6 and the discussion, the control processes are complex and interrelated and quantitative predictions for system performance depend on accurate models of the CVS and its control mechanisms. An excellent overview of these processes can be found in [2].

This paper will focus on studying how the CVS response to hemorrhage can be modeled. Mathematically the problem is formulated as a control problem. We adapt a model we have used previously to study the behavior of the CVS in other contexts such as transition from rest to aerobic exercise, orthostatic stress, and the transition from rest to quiet sleep. See, e.g., [1, 6, 8, 9, 15].

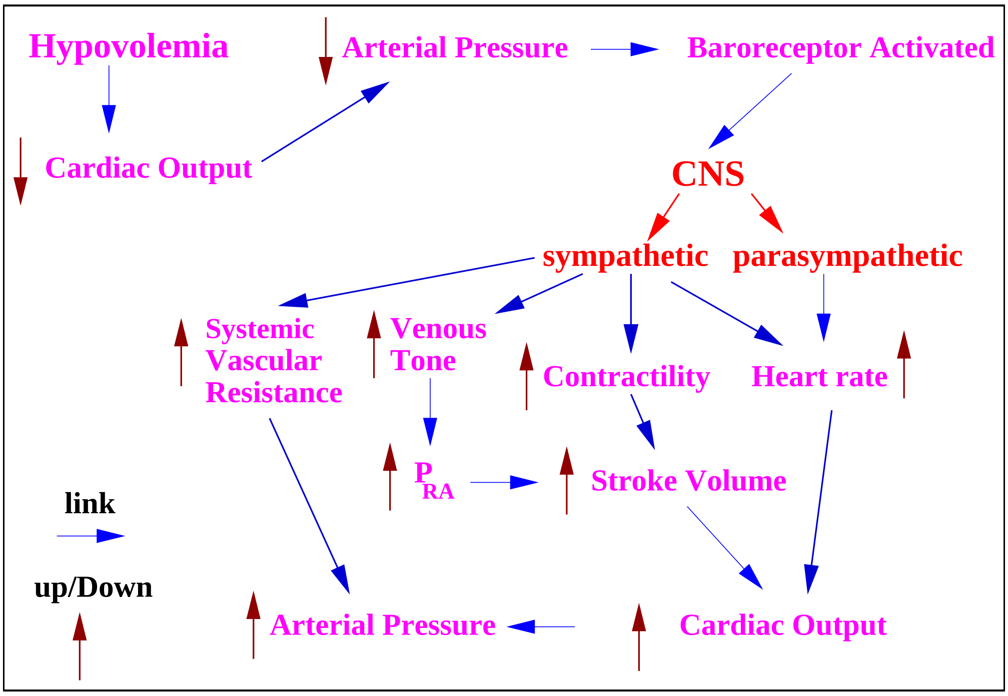

Figure 4: Baroreceptor reflex control loops

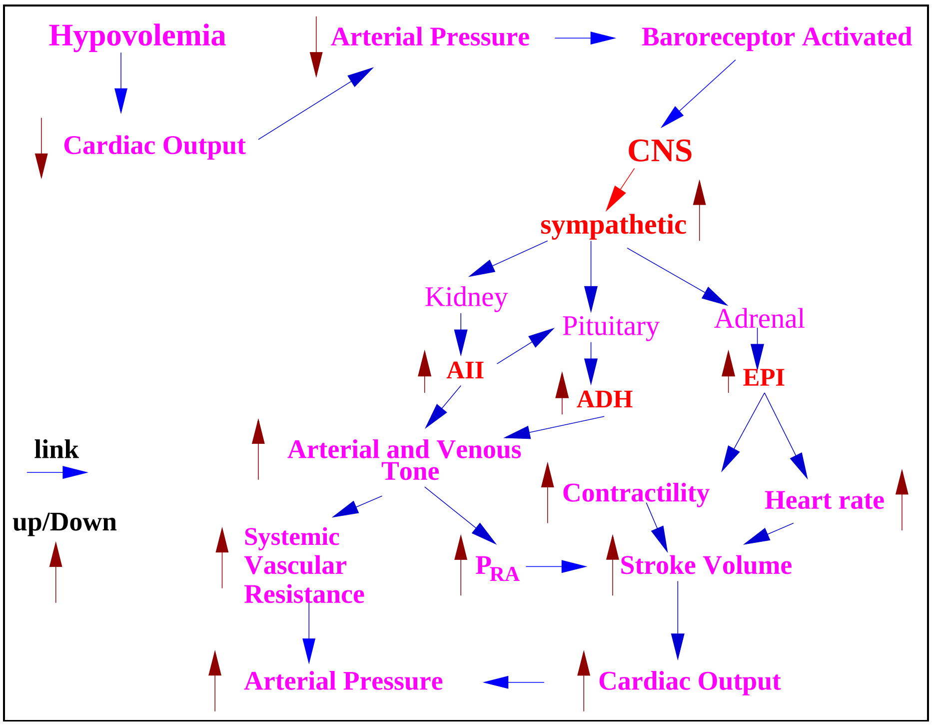

Figure 5: Vasoconstrictor reflex control loops

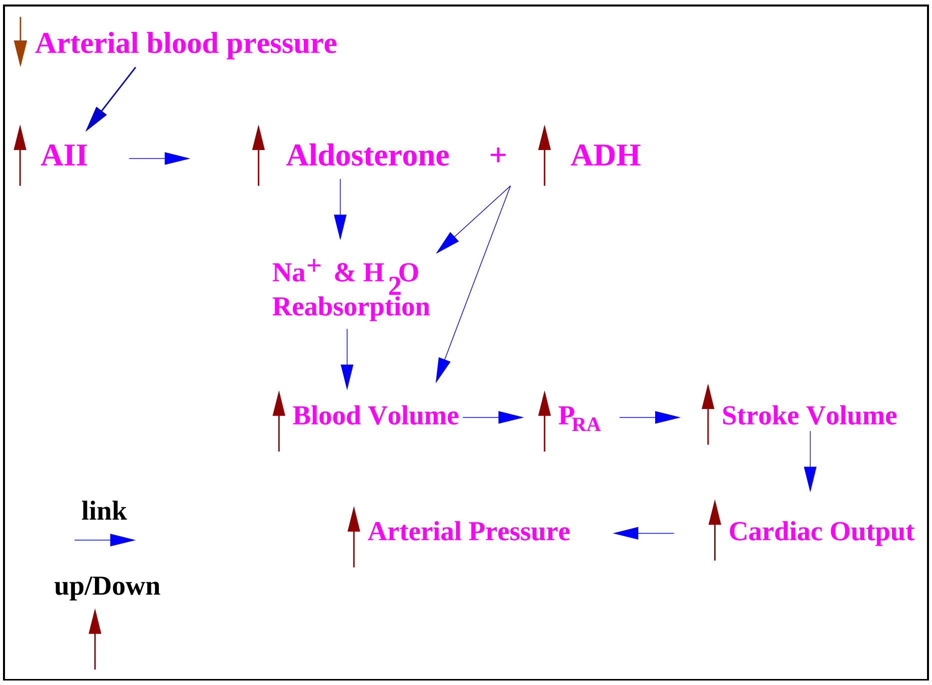

Figure 6: Renal reflex control loops

3 Mathematical model

Full details and description of the basic model can be found in the papers cited above (see especially [8]). We present here the basic model equations and the general basis for their derivation as well as aspects particular to modeling hypovolemia and hemorrhage. Other models which consider this problem can be found in [3, 4, 11]. Figure 3 provides a block diagram for the system. For current purposes, we only consider the cardiovascular system with the lungs and tissue compartments acting as resistances to flows F_{p} and F_{s} respectively. Equations for the respiratory component can be included in a manner similar to that found in Batzel et al. 2003, [1] and Fink et al. 2004 [6].

Basic mathematical model

The basic model consists of the following cardiovascular equations:

$$c_{\mathrm{as}}\dot{P}_{\mathrm{as}} = Q_\ell - F_{\mathrm{s}}, \tag{1}$$
$$c_{\mathrm{vs}}\dot{P}_{\mathrm{vs}} = -Q_{\mathrm{r}} + F_{\mathrm{s}}, \tag{2}$$
$$c_{\mathrm{ap}}\dot{P}_{\mathrm{ap}} = Q_{\mathrm{r}} - F_{\mathrm{p}}, \tag{3}$$
$$c_{\mathrm{vp}}\dot{P}_{\mathrm{vp}} = F_{\mathrm{p}} - Q_\ell, \tag{4}$$
$$\dot{S}_\ell = \sigma_\ell, \tag{5}$$
$$\dot{S}_{\mathrm{r}} = \sigma_{\mathrm{r}}, \tag{6}$$
$$\dot{\sigma_\ell} = -\gamma_\ell\sigma_\ell - \alpha_\ell S_\ell + \beta_\ell H, \tag{7}$$
$$\dot{\sigma_{\mathrm{r}}} = -\gamma_{\mathrm{r}}\sigma_{\mathrm{r}} - \alpha_{\mathrm{r}} S_{\mathrm{r}} + \beta_{\mathrm{r}} H, \tag{8}$$
$$\dot{H} = u_1, \tag{9}$$
$$\dot{c}_{\mathrm{vs}} = u_2. \tag{10}$$

Equations (1-4) are derived as mass balance equations for for the circuit elements consisting of the four lumped vascular volume compartments of arterial systemic (as), venous systemic (vs), arterial pulmonary (ap) , and venous pulmonary (vp). The right side of each of these equations (1-4) describe the blood inflow and outflow from the circuit element. The left side of each of these equations describe the change in volume in the compartment as calculated by pressure P multiplied by capacitance c. Thus, for example, in Equation (1) the left hand side describes the product $c_{\mathrm{as}}\dot{P}_{\mathrm{as}}$ of arterial systemic capacitance and rate of change of arterial blood pressure P_{as}. Equations (5-8) represent a model for the Bowditch effect which describes the effect of heart rate H on left and right heart contractility S_ℓ and S_{r}. The symbols Q_ℓ and Q_{r} denote cardiac outputs from the left and right heart respectively while c_{as} denotes capacitance of the arterial systemic compartment and similarly for the other symbols c_{vs}, c_{ap}, c_{vp}. Values for the parameters are given in Table 2. Auxiliary equations relating flow and pressure are given as:

$$F_{\mathrm{s}} = (P_{\mathrm{as}} - P_{\mathrm{vs}})/R_{\mathrm{s}}, \tag{11}$$
$$F_{\mathrm{p}} = (P_{\mathrm{ap}} - P_{\mathrm{vp}})/R_{\mathrm{p}}. \tag{12}$$

where R_{s} and R_{p} denote the vascular resistances of the systemic and pulmonary systems respectively. Cardiac outputs Q_ℓ and Q_{r} are defined in Equations (13-14) as the product of heart rate H and stroke volume V_{str}. Stroke volume depends upon filling pressure, time of diastole t_d, and other considerations. The expression for V_{str} can be seen as the remaining factors in Equations (13-14) excluding H. See [8] for the derivation of this expression for V_{str}. The formula f is used as a minimum function to exclude the possibility that V_{str} could be greater than the filling volume.

$$Q_\ell(t) = H \frac{c_\ell P_{\mathrm{vp}}(t) f\Big(S_\ell(t), P_{\mathrm{as}}(t)\Big)\Big(1-k_\ell\Big)}{P_{\mathrm{as}}(t)\Big(1-k_\ell\Big) + f\Big(S_\ell(t), P_{\mathrm{as}}(t)\Big)k_\ell}, \tag{13}$$

$$Q_{\mathrm{r}}(t) = H \frac{c_{\mathrm{r}} P_{\mathrm{vs}}(t) f\Big(S_{\mathrm{r}}(t), P_{\mathrm{ap}}(t)\Big)\Big(1-k_{\mathrm{r}}\Big)}{P_{\mathrm{ap}}(t)\Big(1-k_{\mathrm{r}}\Big) + f\Big(S_{\mathrm{r}}(t), P_{\mathrm{ap}}(t)\Big)k_{\mathrm{r}}}, \tag{14}$$

where k_ℓ, k_{r}, f, and t_d are defined as

$$k_\ell = \exp(-t_d/(R_\ell c_\ell)) \quad \text{and} \quad k_{\mathrm{r}} = \exp(-t_d/(R_{\mathrm{r}} c_{\mathrm{r}})), \tag{15}$$

$$f(s,p) = 0.5(s+p) - 0.5\left((p-s)^2 + 0.01\right)^{1/2}, \tag{16}$$

$$t_d = \frac{60}{H} - \kappa\left(\frac{60}{H}\right)^{1/2}. \tag{17}$$

The control equations in the above model set up appear as u_1 and u_2 in the last two equations (9-10):

$$\dot{H} = u_1, \quad , \quad \dot{c}_{\mathrm{vs}} = u_2.$$

These represent the change of heart rate H and venous capacitance c_{vs} due to the baroreflex response to levels of blood pressure P_{as}. The controls u_1 and u_2 are derived via the cost functional:

$$\int_0^\infty q_{\mathrm{a}}\left(P_{\mathrm{as}} - P_{\mathrm{as}}^f\right)^2 + q_{\mathrm{v}}\left(P_{\mathrm{vs}} - P_{\mathrm{vs}}^f\right)^2 + q_1\left(u_1\right)^2 + q_2\left(u_2\right)^2\, dt$$

which defines the optimal behavior of the system. The feedback control is defined by linearizing about a steady state and deriving the feedback gain matrix (algebraic Riccati equation) which drives the linear system to this steady state in an optimal way as defined by the cost function above. This control is used to stabilize the nonlinear system Eq. (1) to Eq. (10). This control will be suboptimal in the sense of Russell [12] and still stabilizing for the non linear system provided that specified deviations are sufficiently small.

In fact the sympathetic system also alters systemic resistance and contractility and hormonal influences also change some of these quantities as well as fluid retention. These effects can be included in the control or included as an exponential variation in these quantities to reflect these effects (by varying A_{pesk}, β_ℓ, and β_r). Further details on this approach are given in Section 5. For the preliminary simulations in this paper we only consider one control, namely the variation in heart rate.

Modeling hemorrhage

Basic considerations

In modeling hemorrhage and hypovolemia it is necessary to consider:

- where and how fast blood is lost from the system;
- how to model auto-transfusion from the interstitium;
- how to implement exterior (clinical) transfusion.
- which features of hemorrhagic shock and deterioration of system and organ function to model;
- how to implement the maximum sustainable heart rate as part of the control;

- how to reflect any inefficiencies in the system function due to reduced blood volume; filling pressure, or heightened heart rate produced only by the baroreflex response and hormonal effects.

Blood loss from an artery is a more serious matter than blood loss from a vein. Arterial blood loss should be modeled so that the loss rate is reduced as the blood volume and pressure are reduced. Exterior transfusion should be applied in the systemic venous compartment. There are a number of choices on type of fluid and regimen to be considered in exterior transfusion.

Even though auto-transfusion from the interstitium can only restore about 15 % of blood plasma volume it is a key element in stabilizing blood pressure and ultimately it should be modeled with an interstitial compartment.

One aspect of hemorrhagic shock is the deterioration in cardiac performance due to reduced blood flow to the heart. This can be a consequence of either tissue damage or inefficient performance due to disruption of normal CO_2 and O_2 levels. A reduction in contractility can reflect these features and there are several ways to model the reduction in contractility.

Obviously after the maximum sustainable heart rate (and cardiac output) is reached any further loss of blood volume will tend to imply a potential steady state with reduced P_{as}. Thus the system may stabilize at a lower P_{as} or continue to deteriorate if more volume is lost or system performance erodes due to the shock condition.

Animal data is readily available but clearly human data on hemorrhage is not easily obtained. Data from hypovolemia in dialysis can provide some human corroboration of simulated results and a current review by Cooke et al. 2004 [5] has justified the use of lower body negative pressure as a model to study acute hemorrhagic shock in humans.

Inefficiency in response

The Betzold-Jarisch reflex is a cardiovascular reflex which has a depressor effect on cardiovascular function. The reflex involves a significant increase in vagal parasympathetic discharge to the heart, elicited most likely by stimulation of chemoreceptors, primarily in the left ventricle. The reflex causes a slowing of the heart beat (bradycardia) and dilatation of the peripheral blood vessels with resulting lowering of the blood pressure.

According to Secher et al. (1992) [13] "Heart rate response to reversible central hypovolemia can be divided into three stages. In the first stage (corresponding to a reduction of the blood volume by approximately 15 %) a modest increase in heart rate ($<$ 100 beats/min) and total peripheral resistance compensate for the blood loss, and a near normal arterial blood pressure prevails (preshock). During the second stage, a reduction of the central blood volume by approximately 30 % results in a decrease in heart rate, total peripheral resistance and blood pressure due to activation of unmyelinated vagal afferents (C-fibres) from the left ventricle. In the third stage, blood pressure falls further as haemorrhage continues and tachycardia ($>$ 120 beats/min) is manifest".

Control strategy

The algorithm we use to model the impact of blood volume loss is given in Section 5, but as an overview the feedback controls are constructed according to the following requirements:

(i) At each time t the control tries to steer the system to an equilibrium, where the arterial systemic pressure $\bar{P}_{\mathrm{as}}$ equals the pressure $P_{\mathrm{as},0}$ before the hemorrhage occurred. There is one degree of freedom in the steady state calculation.

(ii) There is a maximal sustainable heart rate $H_{e,\max}$.

(iii) If at the calculated equilibrium with $\bar{P}_{\mathrm{as}} = P_{\mathrm{as},0}$ the heart rate is larger than $H_{e,\max}$, then the control tries to steer the system to the equilibrium picking $\bar{H} = H_{e,\max}$.

4 Steady state calculations

Steady state calculation are provided in this section. As noted above, there is one degree of freedom in the steady state calculation. It is shown that the steady state relations can be reduced to solving one equation in one unknown once a value for H or P_{as} is chosen. Calculations for both of these cases are given because the algorithm for the control requires that H be varied to drive the system back to the prescribed normal P_{as} level as long as $H \leq H_{e,\max}$. When the situation is such that the control requires that $H > H_{e,\max}$ then the control is set to $H_{e,\max}$ and the a level for P_{as} is derived from this assumption.

The reduction of the steady state relations to a single equation together with numerical analysis indicates that there is a unique equilibrium in the region of reasonable physiological values. Furthermore, using this simplified structure, the numerical calculation of the equilibrium is extremely successful, whereas when numerical solvers are applied to the steady state relations using more than one equation a solution is not always achievable.

The model without auto-regulation

In case of an equilibrium we have $F_{\mathrm{p}} = F_{\mathrm{s}} = Q_\ell = Q_{\mathrm{r}} =: F$, which gives the equations:

$$\frac{1}{R_{\mathrm{p}}}(P_{\mathrm{ap}} - P_{\mathrm{vp}}) = F, \tag{18}$$

$$\frac{1}{R_{\mathrm{s}}}(P_{\mathrm{as}} - P_{\mathrm{vs}}) = F, \tag{19}$$

$$H f(S_{\mathrm{r}}, P_{\mathrm{ap}}) \frac{c_{\mathrm{r}} a_{\mathrm{r}}(H) P_{\mathrm{vs}}}{P_{\mathrm{ap}} a_{\mathrm{r}}(H) + f(S_{\mathrm{r}}, P_{\mathrm{ap}}) k_{\mathrm{r}}(H)} = F, \tag{20}$$

$$H f(S_\ell, P_{\mathrm{as}}) \frac{c_\ell a_\ell(H) P_{\mathrm{vp}}}{P_{\mathrm{as}} a_\ell(H) + f(S_\ell, P_{\mathrm{as}}) k_\ell(H)} = F, \tag{21}$$

where

$$k_{\mathrm{r}}(H) = e^{-(c_{\mathrm{r}} R_{\mathrm{r}})^{-1} t_d(H)}, \quad a_{\mathrm{r}}(H) = 1 - k_{\mathrm{r}}(H),$$
$$k_\ell(H) = e^{-(c_\ell R_\ell)^{-1} t_d(H)}, \quad a_\ell(H) = 1 - k_\ell(H)$$

and

$$f(S, P) = \min(S, P).$$

In addition we have

$$c_{\mathrm{as}} P_{\mathrm{as}} + c_{\mathrm{vs}} P_{\mathrm{vs}} + c_{\mathrm{ap}} P_{\mathrm{ap}} + c_{\mathrm{vp}} P_{\mathrm{vp}} = V_0 \tag{22}$$

and

$$S_{\mathrm{r}} = \frac{\beta_{\mathrm{r}}}{\alpha_{\mathrm{r}}} H, \quad S_\ell = \frac{\beta_\ell}{\alpha_\ell} H. \tag{23}$$

H or *F* is given

We consider equations (18) – (22) as a linear system for $P_{\mathrm{as}}, \ldots, P_{\mathrm{vp}}$. In doing this we have to distinguish four cases:

Case 1: $S_{\mathrm{r}} < P_{\mathrm{ap}}$ and $S_\ell < P_{\mathrm{as}}$.
In this case we have $f(S_{\mathrm{r}}, P_{\mathrm{ap}}) = S_{\mathrm{r}}$ and $f(S_\ell, P_{\mathrm{as}}) = S_\ell$. Then equations (18) – (22) have the form

$$\begin{aligned} P_{\mathrm{ap}} - P_{\mathrm{vp}} &= R_{\mathrm{p}} F, \\ P_{\mathrm{as}} - P_{\mathrm{vs}} &= R_{\mathrm{s}} F, \\ a_{\mathrm{r}}(H) F P_{\mathrm{ap}} + S_{\mathrm{r}} k_{\mathrm{r}}(H) F &= H S_{\mathrm{r}} c_{\mathrm{r}} a_{\mathrm{r}}(H) P_{\mathrm{vs}}, \\ a_\ell(H) F P_{\mathrm{as}} + S_\ell k_\ell(H) F &= H S_\ell c_\ell a_\ell(H) P_{\mathrm{vp}}, \\ c_{\mathrm{as}} P_{\mathrm{as}} + c_{\mathrm{vs}} P_{\mathrm{vs}} + c_{\mathrm{ap}} P_{\mathrm{ap}} + c_{\mathrm{vp}} P_{\mathrm{vp}} &= V_0. \end{aligned} \tag{24}$$

With the notation

$$\begin{aligned}
\mu_{\mathrm{r}}(H) &= HS_{\mathrm{r}}c_{\mathrm{r}}a_{\mathrm{r}}(H) = \frac{\beta_{\mathrm{r}}}{\alpha_{\mathrm{r}}}c_{\mathrm{r}}a_{\mathrm{r}}(H)H^2,\\
\mu_\ell(H) &= \frac{\beta_\ell}{\alpha_\ell}c_\ell a_\ell(H)H^2,\\
\lambda_{\mathrm{r}}(H,F) &= S_{\mathrm{r}}k_{\mathrm{r}}(H)F = \frac{\beta_{\mathrm{r}}}{\alpha_{\mathrm{r}}}k_{\mathrm{r}}(H)HF,\\
\lambda_\ell(H,F) &= \frac{\beta_\ell}{\alpha_\ell}k_\ell(H)HF,\\
\nu_{\mathrm{r}}(H,F) &= a_{\mathrm{r}}(H)F, \quad \nu_\ell(H,F) = a_\ell(H)F
\end{aligned} \tag{25}$$

system (24) can be written as

$$\left(\begin{array}{cccc|c}
0 & 0 & 1 & -1 & R_{\mathrm{p}}F\\
1 & -1 & 0 & 0 & R_{\mathrm{s}}F\\
0 & \mu_{\mathrm{r}}(H) & -\nu_{\mathrm{r}}(H,F) & 0 & \lambda_{\mathrm{r}}(H,F)\\
\nu_\ell(H,F) & 0 & 0 & -\mu_\ell(H) & -\lambda_\ell(H,F)\\
c_{\mathrm{as}} & c_{\mathrm{vs}} & c_{\mathrm{ap}} & c_{\mathrm{vp}} & V_0
\end{array}\right).$$

If we solve the first four equations for P_{as}, P_{vs}, P_{ap} and P_{vp} we obtain

$$\begin{aligned}
P_{\mathrm{as}} &= \frac{\nu_{\mathrm{r}}(H,F)\lambda_\ell(H,F) + \mu_\ell(H)\big(\lambda_{\mathrm{r}}(H,F) + \nu_{\mathrm{r}}(H,F)R_{\mathrm{p}}F + \mu_{\mathrm{r}}(H)R_{\mathrm{s}}F\big)}{\mu_{\mathrm{r}}(H)\mu_\ell(H) - \nu_{\mathrm{r}}(H,F)\nu_\ell(H,F)},\\
P_{\mathrm{vs}} &= \frac{\mu_\ell(H)\lambda_{\mathrm{r}}(H,F) + \nu_{\mathrm{r}}(H,F)\big(\lambda_\ell(H,F) + \mu_\ell(H)R_{\mathrm{p}}F + \nu_\ell(H,F)R_{\mathrm{s}}F\big)}{\mu_{\mathrm{r}}(H)\mu_\ell(H) - \nu_{\mathrm{r}}(H,F)\nu_\ell(H,F)},\\
P_{\mathrm{ap}} &= \frac{\nu_\ell(H,F)\lambda_{\mathrm{r}}(H,F) + \mu_{\mathrm{r}}(H)\big(\lambda_\ell(H,F) + \nu_\ell(H,F)R_{\mathrm{s}}F + \mu_\ell(H)R_{\mathrm{p}}F\big)}{\mu_{\mathrm{r}}(H)\mu_\ell(H) - \nu_{\mathrm{r}}(H,F)\nu_\ell(H,F)},\\
P_{\mathrm{vp}} &= \frac{\mu_{\mathrm{r}}(H)\lambda_\ell(H,F) + \nu_\ell(H,F)\big(\lambda_{\mathrm{r}}(H,F) + \mu_{\mathrm{r}}(H)R_{\mathrm{s}}F + \nu_{\mathrm{r}}(H,F)R_{\mathrm{p}}F\big)}{\mu_{\mathrm{r}}(H)\mu_\ell(H) - \nu_{\mathrm{r}}(H,F)\nu_\ell(H,F)}.
\end{aligned} \tag{26}$$

System (24) is solvable if and only if

$$c_{\mathrm{as}}P_{\mathrm{as}} + c_{\mathrm{vs}}P_{\mathrm{vs}} + c_{\mathrm{ap}}P_{\mathrm{ap}} + c_{\mathrm{vp}}P_{\mathrm{vp}} = V_0$$

for P_{as}, P_{vs}, P_{ap} and P_{vp} given by (26). As a result we get the following equation:

$$\begin{aligned}
&(c_{\mathrm{as}} + c_{\mathrm{vs}})\big(\nu_{\mathrm{r}}(H,F)\lambda_\ell(H,F) + \mu_\ell(H)\lambda_{\mathrm{r}}(H,F) + \nu_{\mathrm{r}}(H,F)\mu_\ell(H)R_{\mathrm{p}}F\big)\\
&\quad + (c_{\mathrm{ap}} + c_{\mathrm{vp}})\big(\mu_{\mathrm{r}}(H)\lambda_\ell(H,F) + \nu_\ell(H,F)\lambda_{\mathrm{r}}(H,F) + \mu_{\mathrm{r}}(H)\nu_\ell(H,F)R_{\mathrm{s}}F\big)\\
&\quad + (c_{\mathrm{as}}R_{\mathrm{s}} + c_{\mathrm{ap}}R_{\mathrm{p}})\mu_{\mathrm{r}}(H)\mu_\ell(H)F + (c_{\mathrm{vs}}R_{\mathrm{s}} + c_{\mathrm{vp}}R_{\mathrm{p}})\nu_{\mathrm{r}}(H)\nu_\ell(H)F\\
&\qquad = \big(\mu_{\mathrm{r}}(H)\mu_\ell(H) - \nu_{\mathrm{r}}(H,F)\nu_\ell(H,F)\big)V_0.
\end{aligned} \tag{27}$$

This is a non-linear equation for F respectively H, if H respectively F is given. Once we have computed F respectively H, we get $P_{\mathrm{as}},\dots,P_{\mathrm{vp}}$ either from (26) or from

$$\begin{aligned}
P_{\mathrm{vs}} &= \frac{\mu_\ell(H)\lambda_{\mathrm{r}}(H,F) + \nu_{\mathrm{r}}(H,F)\big(\nu_\ell(H,F)R_{\mathrm{s}}F + \lambda_\ell(H,F) + \mu_\ell(H)R_{\mathrm{p}}F\big)}{\mu_{\mathrm{r}}(H)\mu_\ell(H) - \nu_{\mathrm{r}}(H,F)\nu_\ell(H,F)},\\
P_{\mathrm{as}} &= P_{\mathrm{vs}} + R_{\mathrm{s}}F,\\
P_{\mathrm{vp}} &= \frac{\mu_\ell(H,F)\lambda_{\mathrm{r}}(H,F) + \mu_{\mathrm{r}}(H)\big(\lambda_\ell(H,F) + \nu_\ell(H,F)R_{\mathrm{s}}F + \mu_\ell(H)R_{\mathrm{p}}F\big)}{\mu_{\mathrm{r}}(H)\mu_\ell(H) - \nu_{\mathrm{r}}(H,F)\nu_\ell(H,F)},\\
P_{\mathrm{ap}} &= P_{\mathrm{vp}} + R_{\mathrm{p}}F.
\end{aligned} \tag{28}$$

Of course, S_{r} and S_ℓ are given by (23).

Case 2: $S_{\mathrm{r}} < P_{\mathrm{ap}}$ and $S_\ell \geq P_{\mathrm{as}}$.
In this case we have $f(S_{\mathrm{r}}, P_{\mathrm{ap}}) = S_{\mathrm{r}}$ and $f(S_\ell, P_{\mathrm{as}}) = P_{\mathrm{as}}$. Then equations (18) – (22) have the form (using also the notation introduced in (25))

$$\begin{aligned} P_{\mathrm{ap}} - P_{\mathrm{vp}} &= R_{\mathrm{p}} F, \\ P_{\mathrm{as}} - P_{\mathrm{vs}} &= R_{\mathrm{s}} F, \\ \nu_{\mathrm{r}}(H,F) P_{\mathrm{ap}} + \lambda_{\mathrm{r}}(H,F) &= \mu_{\mathrm{r}}(H) P_{\mathrm{vs}}, \\ F &= c_\ell a_\ell(H) H P_{\mathrm{vp}}, \\ c_{\mathrm{as}} P_{\mathrm{as}} + c_{\mathrm{vs}} P_{\mathrm{vs}} + c_{\mathrm{ap}} P_{\mathrm{ap}} + c_{\mathrm{vp}} P_{\mathrm{vp}} &= V_0, \end{aligned} \tag{29}$$

which can be written as

$$\left(\begin{array}{cccc|c} 0 & 0 & 1 & -1 & R_{\mathrm{p}} F \\ 1 & -1 & 0 & 0 & R_{\mathrm{s}} F \\ 0 & \mu_{\mathrm{r}}(H) & -\nu_{\mathrm{r}}(H,F) & 0 & \lambda_{\mathrm{r}}(H,F) \\ 0 & 0 & 0 & c_\ell a_\ell(H) H & F \\ c_{\mathrm{as}} & c_{\mathrm{vs}} & c_{\mathrm{ap}} & c_{\mathrm{vp}} & V_0 \end{array}\right).$$

Solving the first four equations for P_{as}, P_{vs}, P_{ap} and P_{vp} we obtain

$$\begin{aligned} P_{\mathrm{as}} &= R_{\mathrm{s}} F + \frac{\nu_{\mathrm{r}}(H,F)}{\mu_{\mathrm{r}}(H)} R_{\mathrm{p}} F + \frac{\lambda_{\mathrm{r}}(H,F)}{\mu_{\mathrm{r}}(H)} + \frac{\nu_{\mathrm{r}}(H,F)}{\mu_{\mathrm{r}}(H)} \frac{F}{c_\ell a_\ell(H) H}, \\ P_{\mathrm{vs}} &= \frac{\nu_{\mathrm{r}}(H,F)}{\mu_{\mathrm{r}}(H)} R_{\mathrm{p}} F + \frac{\lambda_{\mathrm{r}}(H,F)}{\mu_{\mathrm{r}}(H)} + \frac{\nu_{\mathrm{r}}(H,F)}{\mu_{\mathrm{r}}(H)} \frac{F}{c_\ell a_\ell(H) H}, \\ P_{\mathrm{ap}} &= R_{\mathrm{p}} F + \frac{F}{c_\ell a_\ell(H) H}, \\ P_{\mathrm{vp}} &= \frac{F}{c_\ell a_\ell(H) H}. \end{aligned} \tag{30}$$

System (29) is solvable if and only if

$$c_{\mathrm{as}} P_{\mathrm{as}} + c_{\mathrm{vs}} P_{\mathrm{vs}} + c_{\mathrm{ap}} P_{\mathrm{ap}} + c_{\mathrm{vp}} P_{\mathrm{vp}} = V_0$$

for P_{as}, P_{vs}, P_{ap} and P_{vp} given by (30). As a result we get the following equation:

$$\begin{aligned} (c_{\mathrm{as}} + c_{\mathrm{vs}}) \Big(\lambda_{\mathrm{r}}(H,F) + \nu_{\mathrm{r}}(H,F) R_{\mathrm{p}} F + \frac{\nu_{\mathrm{r}}(H,F) F}{c_\ell a_\ell(H) H} \Big) + \mu_{\mathrm{r}}(H) c_{\mathrm{as}} R_{\mathrm{s}} F & \\ + (c_{\mathrm{ap}} + c_{\mathrm{vp}}) \frac{\mu_{\mathrm{r}}(H) F}{c_\ell a_\ell(H) H} + c_{\mathrm{ap}} \mu_{\mathrm{r}}(H) R_{\mathrm{p}} F = \mu_{\mathrm{r}}(H) V_0. & \end{aligned} \tag{31}$$

This is a non-linear equation for F respectively H, if H respectively F is given. Once we have computed F respectively H, we get $P_{\mathrm{as}}, \ldots, P_{\mathrm{vp}}$ either from (30) or from

$$\begin{aligned} P_{\mathrm{vp}} &= \frac{F}{c_\ell a_\ell(H) H}, \\ P_{\mathrm{ap}} &= R_{\mathrm{p}} F + P_{\mathrm{vp}}, \\ P_{\mathrm{vs}} &= \frac{\nu_{\mathrm{r}}(H,F)}{\mu_{\mathrm{r}}(H)} P_{\mathrm{ap}} + \frac{\lambda_{\mathrm{r}}(H,F)}{\mu_{\mathrm{r}}(H)}, \\ P_{\mathrm{as}} &= R_{\mathrm{s}} F + P_{\mathrm{vs}}. \end{aligned} \tag{32}$$

Of course, S_{r} and S_ℓ are given by (23).

Case 3: $S_\mathrm{r} \geq P_\mathrm{ap}$ and $S_\ell < P_\mathrm{as}$.
In this case we have $f(S_\mathrm{r}, P_\mathrm{ap}) = P_\mathrm{ap}$ and $f(S_\ell, P_\mathrm{as}) = S_\ell$. Then equations (18) – (22) have the form (using also the notation introduced in (25))

$$\begin{aligned} P_\mathrm{ap} - P_\mathrm{vp} &= R_\mathrm{p} F, \\ P_\mathrm{as} - P_\mathrm{vs} &= R_\mathrm{s} F, \\ F &= c_\mathrm{r} a_\mathrm{r}(H) H P_\mathrm{vs}, \\ \nu_\ell(H,F) P_\mathrm{as} + \lambda_\ell(H,F) &= \mu_\ell(H) P_\mathrm{vp}, \\ c_\mathrm{as} P_\mathrm{as} + c_\mathrm{vs} P_\mathrm{vs} + c_\mathrm{ap} P_\mathrm{ap} + c_\mathrm{vp} P_\mathrm{vp} &= V_0, \end{aligned} \tag{33}$$

which can be written as

$$\left(\begin{array}{cccc|c} 0 & 0 & 1 & -1 & R_\mathrm{p} F \\ 1 & -1 & 0 & 0 & R_\mathrm{s} F \\ 0 & c_\mathrm{r} a_\mathrm{r}(H) H & 0 & 0 & F \\ -\nu_\ell(H,F) & 0 & 0 & \mu_\ell(H) & \lambda_\ell(H,F) \\ c_\mathrm{as} & c_\mathrm{vs} & c_\mathrm{ap} & c_\mathrm{vp} & V_0 \end{array}\right).$$

Solving the first four equations for P_as, P_vs, P_ap and P_vp we obtain

$$\begin{aligned} P_\mathrm{as} &= R_\mathrm{s} F + \frac{F}{c_\mathrm{r} a_\mathrm{r}(H) H}, \\ P_\mathrm{vs} &= \frac{F}{c_\mathrm{r} a_\mathrm{r}(H) H}, \\ P_\mathrm{ap} &= R_\mathrm{p} F + \frac{\nu_\ell(H,F)}{\mu_\ell(H)} \frac{F}{c_\mathrm{r} a_\mathrm{r}(H) H} + \frac{\lambda_\ell(H,F)}{\mu_\ell(H)} + \frac{\nu_\ell(H,F)}{\mu_\ell(H)} R_\mathrm{s} F, \\ P_\mathrm{vp} &= \frac{\nu_\ell(H,F)}{\mu_\ell(H)} \frac{F}{c_\mathrm{r} a_\mathrm{r}(H) H} + \frac{\nu_\ell(H,F)}{\mu_\ell(H)} R_\mathrm{s} F + \frac{\lambda_\ell(H,F)}{\mu_\ell(H)}. \end{aligned} \tag{34}$$

System (33) is solvable if and only if

$$c_\mathrm{as} P_\mathrm{as} + c_\mathrm{vs} P_\mathrm{vs} + c_\mathrm{ap} P_\mathrm{ap} + c_\mathrm{vp} P_\mathrm{vp} = V_0$$

for P_as, P_vs, P_ap and P_vp given by (34). As a result we get the following equation:

$$\begin{aligned} &\mu_\ell(H) c_\mathrm{as} R_\mathrm{s} F + (c_\mathrm{as} + c_\mathrm{vs}) \frac{\mu_\ell(H) F}{c_\mathrm{r} a_\mathrm{r}(H) H} + c_\mathrm{ap} \mu_\ell(H) R_\mathrm{p} F \\ &\qquad (c_\mathrm{ap} + c_\mathrm{vp}) \Big(\lambda_\ell(H,F) + \nu_\ell(H,F) R_\mathrm{s} F + \frac{\nu_\ell(H,F) F}{c_\mathrm{r} a_\mathrm{r}(H) H} \Big) = \mu_\ell(H) V_0. \end{aligned} \tag{35}$$

This is a non-linear equation for F respectively H, if H respectively F is given. Once we have computed F respectively H, we get $P_\mathrm{as}, \ldots, P_\mathrm{vp}$ either from (34) or from

$$\begin{aligned} P_\mathrm{vs} &= \frac{F}{c_\mathrm{r} a_\mathrm{r}(H) H}, \\ P_\mathrm{as} &= R_\mathrm{s} F + P_\mathrm{vs}, \\ P_\mathrm{vp} &= \frac{\nu_\ell(H,F)}{\mu_\ell(H)} P_\mathrm{as} + \frac{\lambda_\ell(H,F)}{\mu_\ell(H)}, \\ P_\mathrm{ap} &= R_\mathrm{p} F + P_\mathrm{vp}. \end{aligned} \tag{36}$$

Again, S_r and S_ℓ are given by (23).

Case 4: $S_\mathrm{r} \geq P_\mathrm{ap}$ and $S_\ell \geq P_\mathrm{as}$.
In this case we have $f(S_\mathrm{r}, P_\mathrm{ap}) = P_\mathrm{ap}$ and $f(S_\ell, P_\mathrm{as}) = P_\mathrm{as}$. Then equations (18) – (22) have the form (using also the notation introduced in (25))

$$\begin{aligned} P_\mathrm{ap} - P_\mathrm{vp} &= R_\mathrm{p} F, \\ P_\mathrm{as} - P_\mathrm{vs} &= R_\mathrm{s} F, \\ F &= c_\mathrm{r} a_\mathrm{r}(H) H P_\mathrm{vs}, \\ F &= c_\ell a_\ell(H) H P_\mathrm{vp}, \\ c_\mathrm{as} P_\mathrm{as} + c_\mathrm{vs} P_\mathrm{vs} + c_\mathrm{ap} P_\mathrm{ap} + c_\mathrm{vp} P_\mathrm{vp} &= V_0, \end{aligned} \tag{37}$$

which can be written as

$$\left(\begin{array}{cccc|c} 0 & 0 & 1 & -1 & R_\mathrm{p} F \\ 1 & -1 & 0 & 0 & R_\mathrm{s} F \\ 0 & c_\mathrm{r} a_\mathrm{r}(H) H & 0 & 0 & F \\ 0 & 0 & 0 & c_\ell a_\ell(H) H & F \\ c_\mathrm{as} & c_\mathrm{vs} & c_\mathrm{ap} & c_\mathrm{vp} & V_0 \end{array}\right).$$

Solving the first four equations for P_as, P_vs, P_ap and P_vp we obtain

$$\begin{aligned} P_\mathrm{vs} &= \frac{F}{c_\mathrm{r} a_\mathrm{r}(H) H}, \\ P_\mathrm{as} &= R_\mathrm{s} F + \frac{F}{c_\mathrm{r} a_\mathrm{r}(H) H}, \\ P_\mathrm{vp} &= \frac{F}{c_\ell a_\ell(H) H}, \\ P_\mathrm{ap} &= R_\mathrm{p} F + \frac{F}{c_\ell a_\ell(H) H}. \end{aligned} \tag{38}$$

System (37) is solvable if and only if

$$c_\mathrm{as} P_\mathrm{as} + c_\mathrm{vs} P_\mathrm{vs} + c_\mathrm{ap} P_\mathrm{ap} + c_\mathrm{vp} P_\mathrm{vp} = V_0$$

for P_as, P_vs, P_ap and P_vp given by (38). As a result we get the following equation:

$$c_\mathrm{as} R_\mathrm{s} + c_\mathrm{ap} R_\mathrm{p} + (c_\mathrm{as} + c_\mathrm{vs}) \frac{1}{c_\mathrm{r} a_\mathrm{r}(H) H} + (c_\mathrm{ap} + c_\mathrm{vp}) \frac{1}{c_\ell a_\ell(H) H} = \frac{V_0}{F}. \tag{39}$$

This is a linear equation for F respectively a non-linear equation for H, if H respectively F is given. Once we have computed F respectively H, we get $P_\mathrm{as}, \ldots, P_\mathrm{vp}$ either from (38) or from

$$\begin{aligned} P_\mathrm{vs} &= \frac{F}{c_\mathrm{r} a_\mathrm{r}(H) H}, \\ P_\mathrm{as} &= R_\mathrm{s} F + P_\mathrm{vs}, \\ P_\mathrm{vp} &= \frac{F}{c_\ell a_\ell(H) H}, \\ P_\mathrm{ap} &= R_\mathrm{p} F + P_\mathrm{vp}. \end{aligned} \tag{40}$$

As before, S_r and S_ℓ are given by (23).

Once we have computed P_as, P_vs, P_ap, P_vp, S_r and S_ℓ in all four cases, we can decide which case is valid.

P_{as} is given

Case 1: $S_{\mathrm{r}} < P_{\mathrm{ap}}$ and $S_\ell < P_{\mathrm{as}}$.
Equations (18) and (19) imply

$$R_{\mathrm{p}} P_{\mathrm{vs}} + R_{\mathrm{s}} P_{\mathrm{ap}} - R_{\mathrm{s}} P_{\mathrm{vp}} = R_{\mathrm{p}} P_{\mathrm{as}}. \tag{41}$$

and equation (22) is written as

$$c_{\mathrm{vs}} P_{\mathrm{vs}} + c_{\mathrm{ap}} P_{\mathrm{ap}} + c_{\mathrm{vp}} P_{\mathrm{vp}} = V_0 - c_{\mathrm{as}} P_{\mathrm{as}} \tag{42}$$

and equations (19) and (21) imply (note that $\min(S_\ell, P_{\mathrm{as}}) = S_\ell$ and $\min(S_{\mathrm{r}}, P_{\mathrm{ap}}) = S_{\mathrm{r}}$ in this case)

$$\big(P_{\mathrm{as}} a_\ell(H) + S_\ell k_\ell(H)\big) P_{\mathrm{vs}} + H S_\ell R_{\mathrm{s}} c_\ell a_\ell(H) P_{\mathrm{vp}} = P_{\mathrm{as}} \big(P_{\mathrm{as}} a_\ell(H) + S_\ell k_\ell(H)\big). \tag{43}$$

We introduce the function

$$\delta(H) = \frac{R_{\mathrm{s}} S_\ell c_\ell a_\ell(H) H}{P_{\mathrm{as}} a_\ell(H) + S_\ell k_\ell(H)} = \frac{c_\ell \beta_\ell R_{\mathrm{s}} a_\ell(H) H^2}{\alpha_\ell a_\ell(H) P_{\mathrm{as}} + \beta_\ell k_\ell(H) H}$$

and write equations (41) – (43) as

$$\left(\begin{matrix} R_{\mathrm{p}} & R_{\mathrm{s}} & -R_{\mathrm{s}} \\ c_{\mathrm{vs}} & c_{\mathrm{ap}} & c_{\mathrm{vp}} \\ 1 & 0 & \delta(H) \end{matrix} \;\middle|\; \begin{matrix} R_{\mathrm{p}} P_{\mathrm{as}} \\ V_0 - c_{\mathrm{as}} P_{\mathrm{as}} \\ P_{\mathrm{as}} \end{matrix}\right),$$

which is transformed to

$$\left(\begin{matrix} 0 & R_{\mathrm{s}} & -R_{\mathrm{s}} - R_{\mathrm{p}}\delta(H) \\ 0 & c_{\mathrm{ap}} & c_{\mathrm{vp}} - c_{\mathrm{vs}}\delta(H) \\ 1 & 0 & \delta(H) \end{matrix} \;\middle|\; \begin{matrix} 0 \\ V_0 - (c_{\mathrm{as}} + c_{\mathrm{vs}}) P_{\mathrm{as}} \\ P_{\mathrm{as}} \end{matrix}\right).$$

From the first equation we obtain

$$P_{\mathrm{ap}} = \Big(1 + \frac{R_{\mathrm{p}}}{R_{\mathrm{s}}}\delta(H)\Big) P_{\mathrm{vp}}.$$

This and the second equation imply

$$\Big(c_{\mathrm{ap}} + c_{\mathrm{ap}}\frac{R_{\mathrm{p}}}{R_{\mathrm{s}}}\delta(H) + c_{\mathrm{vp}} - c_{\mathrm{vs}}\delta(H)\Big) P_{\mathrm{vp}} = V_0 - (c_{\mathrm{as}} + c_{\mathrm{vs}}) P_{\mathrm{as}}$$

respectively

$$P_{\mathrm{vp}} = \frac{V_0 - (c_{\mathrm{as}} + c_{\mathrm{vs}}) P_{\mathrm{as}}}{c_{\mathrm{ap}} + c_{\mathrm{vp}} + \Big(c_{\mathrm{ap}}\frac{R_{\mathrm{p}}}{R_{\mathrm{s}}} - c_{\mathrm{vs}}\Big)\delta(H)} =: \eta(H). \tag{44}$$

Then we get

$$P_{\mathrm{ap}} = \Big(1 + \frac{R_{\mathrm{p}}}{R_{\mathrm{s}}}\delta(H)\Big)\eta(H) \tag{45}$$

and

$$P_{\mathrm{vs}} = P_{\mathrm{as}} - \delta(H)\eta(H). \tag{46}$$

From equation (18) we get

$$F = \frac{1}{R_{\mathrm{s}}}\delta(H)\eta(H).$$

Using this in (20) gives

$$\frac{1}{R_{\rm s}}\delta(H)\eta(H) = HS_{\rm r}\frac{c_{\rm r}a_{\rm r}(H)P_{\rm vs}}{P_{\rm ap}a_{\rm r}(H)+S_{\rm r}k_{\rm r}(H)}$$
$$= \frac{HS_{\rm r}c_{\rm r}a_{\rm r}(H)\big(P_{\rm as}-\delta(H)\eta(H)\big)}{a_{\rm r}(H)\Big(1+\frac{R_{\rm p}}{R_{\rm s}}\delta(H)\Big)\eta(H)+S_{\rm r}k_{\rm r}(H)}$$

or, equivalently,

$$\frac{1}{R_{\rm s}}\delta(H)\eta(H) = \frac{\beta_{\rm r}}{\alpha_{\rm r}}\frac{c_{\rm r}a_{\rm r}(H)H^2\big(P_{\rm as}-\delta(H)\eta(H)\big)}{a_{\rm r}(H)\Big(1+\frac{R_{\rm p}}{R_{\rm s}}\delta(H)\Big)\eta(H)+\frac{\beta_{\rm r}}{\alpha_{\rm r}}k_{\rm r}(H)H}.$$

This is an equation for H. Once we have determined H, we get $P_{\rm vs}$, $P_{\rm ap}$, $P_{\rm vp}$ from (44) – (46) and S_ℓ, $S_{\rm r}$ from (23).

Case 2: $S_{\rm r} < P_{\rm ap}$ and $S_\ell \geq P_{\rm as}$.
Equation (21) implies $c_\ell a_\ell(H)HP_{\rm vp} = F$ respectively

$$P_{\rm vp} = \frac{F}{c_\ell a_\ell(H)H}. \tag{47}$$

From equation (19) we see that

$$P_{\rm vs} = P_{\rm as} - R_{\rm s}F. \tag{48}$$

and equation (18) implies

$$P_{\rm ap} = \Big(\frac{1}{c_\ell a_\ell(H)H} - R_{\rm p}\Big)F. \tag{49}$$

Using (47) – (49) in (42) we get

$$\Big(\frac{c_{\rm ap}+c_{\rm vp}}{c_\ell a_\ell(H)H} - c_{\rm vs}R_{\rm s} - c_{\rm ap}R_{\rm p}\Big)F = V_0 - (c_{\rm as}+c_{\rm vs})P_{\rm as}$$

respectively

$$F = \frac{\big(V_0-(c_{\rm as}+c_{\rm vs})P_{\rm as}\big)c_\ell a_\ell(H)H}{c_{\rm ap}+c_{\rm vp}-c_\ell a_\ell(H)H(c_{\rm vs}R_{\rm s}+c_{\rm ap}R_{\rm p})} =: \delta_0(H). \tag{50}$$

Using this and (48), (49) in equation (20) we get

$$\frac{\beta_{\rm r}}{\alpha_{\rm r}}c_{\rm r}a_{\rm r}(H)H^2(P_{\rm as}+R_{\rm p}\delta_0(H)) = \delta_0(H)\Big(\Big(\frac{1}{c_\ell a_\ell(H)H} - R_{\rm p}\Big)\delta_0(H)a_{\rm r}(H) + \frac{\beta_{\rm r}}{\alpha_{\rm r}}k_{\rm r}(H)H\Big). \tag{51}$$

This is an equation for H. Once we have determined H, we get F from (50) and then $P_{\rm vs}$, $P_{\rm ap}$, $P_{\rm vp}$ from (47) – (49) and, finally, S_ℓ, $S_{\rm r}$ from (23).

Case 3: $S_{\rm r} \geq P_{\rm ap}$ and $S_\ell < P_{\rm as}$.
We have $f(S_{\rm r}, P_{\rm ap}) = P_{\rm ap}$ and $f(S_\ell, P_{\rm as}) = S_\ell$. Then equation (20) implies

$$P_{\rm vs} = \frac{F}{c_{\rm r}a_{\rm r}(H)H}.$$

On the other hand we get from (19)

$$P_{\rm vs} = P_{\rm as} - R_{\rm s}F. \tag{52}$$

These two equations imply

$$F = \frac{c_{\rm r}a_{\rm r}(H)HP_{\rm as}}{1+c_{\rm r}a_{\rm r}(H)HR_{\rm s}} =: \delta_1(H). \tag{53}$$

From equations (21) and (18) we obtain

$$P_{\rm vp} = \frac{F\big(\alpha_\ell a_\ell(H)P_{\rm as} + \beta_\ell k_\ell(H)H\big)}{\beta_\ell c_\ell a_\ell(H)H^2} \tag{54}$$

and

$$P_{\rm ap} = R_{\rm p}F + P_{\rm vp} = R_{\rm p}F + \frac{F\big(\alpha_\ell a_\ell(H)P_{\rm as} + \beta_\ell k_\ell(H)H\big)}{\beta_\ell c_\ell a_\ell(H)H^2}. \tag{55}$$

The system (18) – (22) is solvable if and only if we have

$$(c_{\rm as} + c_{\rm vs})P_{\rm as} + (c_{\rm ap}R_{\rm p} - c_{\rm vs}R_{\rm s})\delta_1(H) + (c_{\rm ap} + c_{\rm vp})\frac{\delta_1(H)\big(\alpha_\ell a_\ell(H)P_{\rm as} + \beta_\ell k_\ell(H)H\big)}{\beta_\ell c_\ell a_\ell(H)H^2} = V_0. \tag{56}$$

this is a non-linear equation for H. Once we have computed H we get F from (53) and then $P_{\rm vs}$, $P_{\rm ap}$, $P_{\rm vp}$ from (52), (54) and (55). As usual, $S_{\rm r}$ and S_ℓ are obtained from (23).

Case 4: $S_{\rm r} \geq P_{\rm ap}$ and $S_\ell \geq P_{\rm as}$.
We have $f(S_{\rm r}, P_{\rm ap}) = P_{\rm ap}$ and $f(S_\ell, P_{\rm as}) = P_{\rm as}$. Then equations (20) and (21) imply

$$\begin{aligned} P_{\rm vs} &= \frac{F}{c_{\rm r}a_{\rm r}(H)H^2}, \\ P_{\rm vp} &= \frac{F}{c_\ell a_\ell(H)H^2}. \end{aligned} \tag{57}$$

From (19) we get

$$P_{\rm vs} = P_{\rm as} - R_{\rm s}F. \tag{58}$$

As in Case 3 we have

$$F = \delta_1(H). \tag{59}$$

From equation (18) we get

$$P_{\rm ap} = F(R_{\rm p} + \frac{1}{c_\ell a_\ell(H)H^2}.$$

The solvability condition for the system (18) – (22) is

$$(c_{\rm as} + c_{\rm vs})P_{\rm as} + (c_{\rm ap}R_{\rm p} - c_{\rm vs}R_{\rm s})\delta_1(H) + (c_{\rm ap} + c_{\rm vp})\frac{\delta_1(H)}{c_\ell a_\ell(H)H^2} = V_0. \tag{60}$$

This equation determines H. Then we get F from (59) and $P_{\rm vs}$, $P_{\rm ap}$, $P_{\rm vp}$ from (58), (57) and $P_{\rm ap} = P_{\rm vp} + R_{\rm p}F$. Again, $S_{\rm r}$ and S_ℓ are given by (23).

5 Simulation

Algorithm for control design

When designing a control that directs the transition from a single initial perturbation (which may be an initial steady state) x^i to the final state x^f the following steps are carried out:

- Compute the steady states "initial", x^i, and "final", x^f.
  where the steady states "initial" and "final are defined by parameter changes such as: change in blood volume over the interval due to hemorrhage, interstitial replacement or transfusion.
- The control functions u_i (depending on the number of controls modeled) which transfer the system (Eq. (1) to Eq. (10)) from the initial steady state to the final steady state are found as follows. We consider the linearized system around state x^f with initial condition $x(0) = x^i$, and the cost functional as given in Eq. (3). We then compute the control functions u_i such that the cost functional is minimized subject to the linearized system. These control functions are defined by the feedback gain matrix which is found by solving an associated algebraic matrix-Riccati equation. In particular, the u_i are given as feedback control functions.

- This control is used to stabilize the nonlinear system Eq. (1) to Eq. (10). This control will be suboptimal in the sense of Russell [12] and still stabilizing.

As hemorrhage continues, the change in blood volume implies that the control response must change. We adapt the one step control design described above as follows. We carry out the above control derivation process over small time steps, recalculating the control after a small time step in which the blood volume is altered by the hemorrhage. We use the final state of the system x_k at the kth step as the initial state for the simulation at the $k+1$ step. The control at the $k+1$ step is found using the equilibrium calculated using the volume at the end of the kth step. This implements a form of adaptive control using the following algorithm:

Algorithm for hemorrhage

As mentioned above, the feedback controls are constructed according to the following requirements:

(i) At each time t the control tries to steer the system to an equilibrium, where the arterial systemic pressure $\bar{P}_{\text{as}}$ equals the pressure $P_{\text{as},0}$ before the hemorrhage occurred.

(ii) There is a maximal heart rate $H_{e,\max}$ acceptable at an equilibrium.

(iii) If at the calculated equilibrium with $\bar{P}_{\text{as}} = P_{\text{as},0}$ the heart rate is larger than $H_{e,\max}$, then the control tries to steer the system to the equilibrium with $\bar{H} = H_{e,\max}$.

We introduce the following notation:

$\bar{x}_{e,t}$ ... equilibrium, which at time t is the goal of the control efforts.

$\bar{p}_t$ ... parameter vector at time t.

A_t ... system matrix for the linearized system around $\bar{x}_{e,t}$ and $A_t = \frac{\partial f}{\partial x}(\bar{x}_{e,t}, \bar{p}_t)$, where

$$\dot{x}(t) = f(x(t), \bar{p}_t) + Bu(t),$$
$$y(t) = Cx(t)$$

with $B = \operatorname{col}(0, \ldots, 0, 1)$ and $C = (1, 0, \ldots, 0)$ is the model for the cardiovascular system.

X_t ... solution of the Riccati equation $A_t^{\mathsf{T}} X + XA_t - XBB^{\mathsf{T}} X + C^{\mathsf{T}} C = 0$.

$H_{e,\max}$ ... maximal acceptable heart rate at an equilibrium ($\sim$ 130 beats/min)

,

The parameter vector changes in time. This is due to the following effects:

a) Change of V_0 as a consequence of hemorrhage, infusion and exchange processes with the interstitium (capillary refill, loss of crystaloid or colloid substitutes from plasma into the interstitium).

b) Change of R_s and R_p as a consequence of changing viscosity of blood.

The control $u(t)$ at time $t \geq 0$ is calculated as follows:

Step 1: Determine the parameter vector $\bar{p}_t$.

Step 2: Compute $\bar{x}_{e,t} = \operatorname{col}\left(\bar{P}_{\text{as}}, \ldots, \bar{H}\right)$ from $f(x, p) = 0$ with $\bar{P}_{\text{as}} = P_{\text{as},0}$ and $p = \bar{p}_t$.

Step 3: If $\bar{H} \leq H_{e,\max}$, then accept $\bar{x}_{e,t}$, compute X_t and set

$$u(t) = -B^{\mathsf{T}} X_t (x(t) - \bar{x}_{e,t}).$$

Step 4: If $\bar{H} > H_{e,\max}$, then calculate $\bar{x}_{e,t}$ with $\bar{H} = H_{e,\max}$ and $p = \bar{p}_t$. Compute X_t and set

$$u(t) = -B^{\mathsf{T}} X_t (x(t) - \bar{x}_{e,t}).$$

Simulation results

We model several levels of acute hemorrhage and consider the response of heart rate to the reduced blood volume. The heart rate control will act to restore arterial pressure P_{as} by increasing H up to the maximum sustainable rate $H_{e,\max}$ described above. Once $H_{e,\max}$ is reached the system will stabilize around a reduced steady state P_{as} consistent with this fixed control $H_{e,\max}$.

Figure 7 provides the state variable simulation for an acute hemorrhage of 20 % blood loss in one minute. Figure 8 provides the auxiliary variable simulations for the same case. The vertical line in the simulation of H increases to 100 bpm at the top of the graph which is the maximal heart rate.

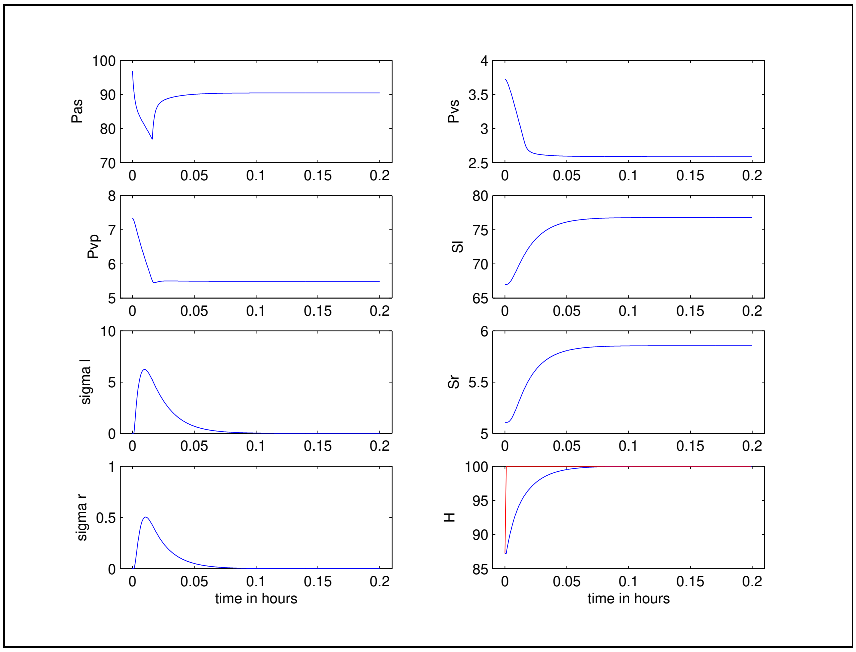

Figure 7: 20 % blood loss in 1 minute: state variables

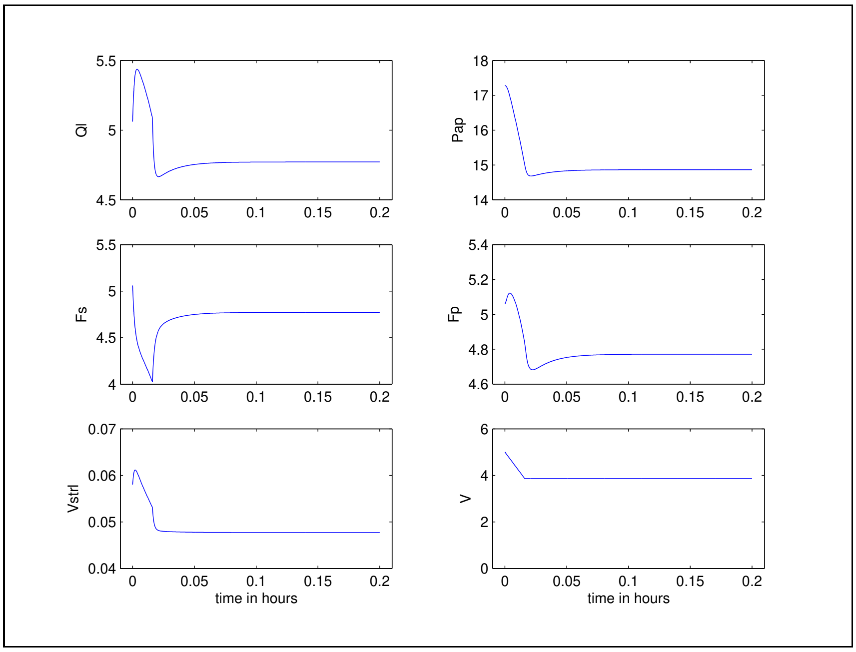

Figure 8: 20 % blood loss in 1 minute: auxiliary variables where V is blood volume

Figure 9 provides the state variable simulation for an acute hemorrhage of 45 % blood loss in one minute. Figure 10 provides the auxiliary variable simulations for the same case. Again, the vertical line in the simulation of H increases to 100 bpm which is the maximal heart rate. Figure 11 focuses on the key variables of P_{as}, Q_ℓ, S_ℓ, H, V and and V_{strl}. Comparison can be made to the data provided by Guyton and Crowell (1961) [7] in Figure 1 for animal experiments of acute hemorrhage.

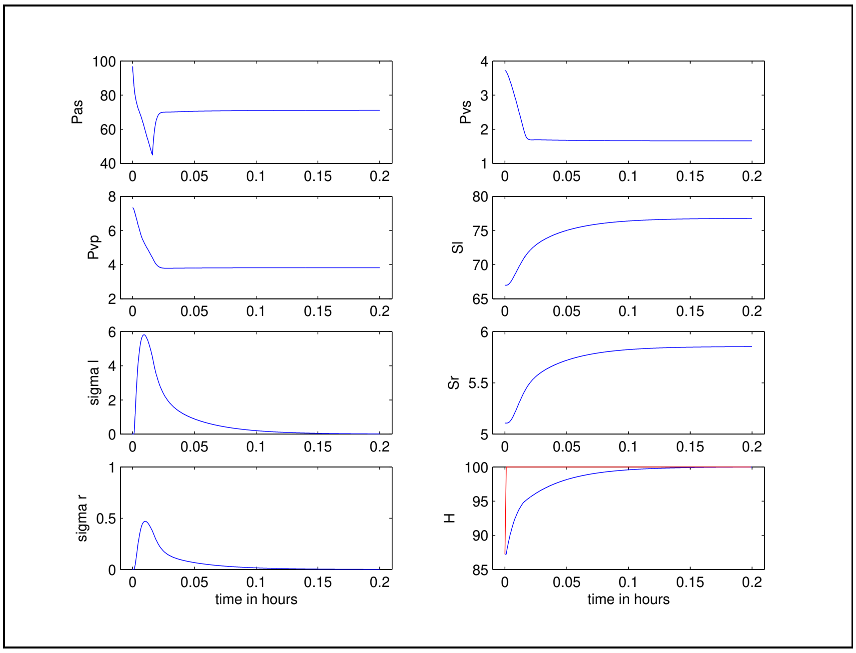

Figure 9: 45 % blood loss in 1 minute: state variables

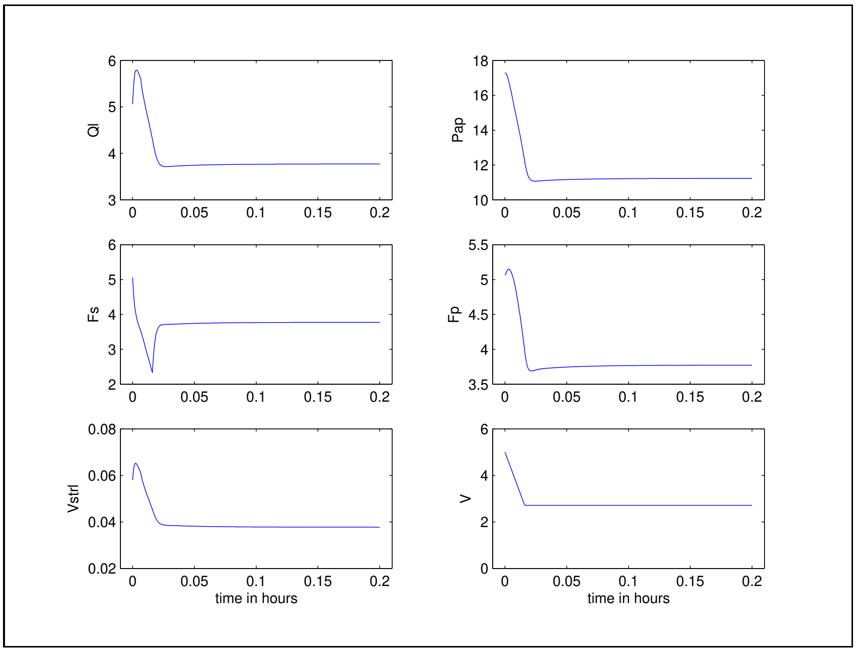

Figure 10: 45 % blood loss in 1 minute: auxiliary variables where V is blood volume

In these simulations the quick initial drop in $P_{\rm as}$ is consistent with the data provided in [7]. Also for the 45 % blood loss case, the fact that recovery to original $P_{\rm as}$ levels is consistent with the data and reflects the fact that a maximal sustainable heart rate exists which is lower than that for exercise because it is the response only of the baroreflex. There are a number of issues to be addressed in this model which will be discussed in Section 7.

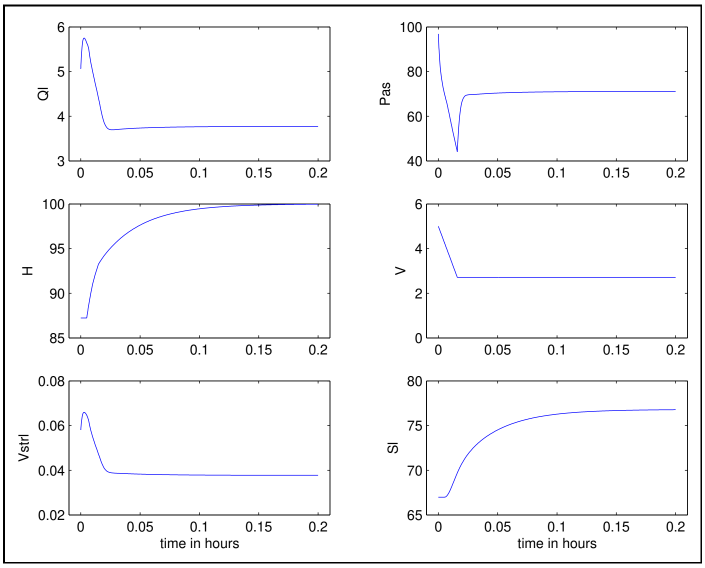

Figure 11: 45 % blood loss in 1 minute: key variables where V is blood volume

6 The transfusion problem

It is estimated that more than 4.9 million patients in the United States receive transfusion every year because of blood loss occurring in different situations such as accidents, transplants, cancer therapies, anemia, and other situations (National Blood Data Resource Center). It is relevant to point out that it was noted in an editorial in a recent issue of the New England Journal of Medicine [10] that "The art of fluid administration and hemodynamic support is one of the most challenging aspects of treating critically ill patients. Considering that every year in the United States over 11 million units of red cells are transfused in more than 3 million patients, there is a surprising paucity of data to guide decisions on transfusion."

This editorial goes on to note that there exists a transfusion algorithm developed by the American College of Physicians based on a consensus of experts, and not on quantitative analysis. It also notes that transfusion regimens in critically ill patients varies widely, with "an estimated 66 percent of transfusions are administered inappropriately." Thus a fuller understanding of the control interactions of the various control systems of the cardiovascular and respiratory systems as it relates to blood volume control and the development of mathematical models which describe these interactions is essential to developing optimal strategies for treatment. Acute hemorrhage treatment issues include the following areas:

- What fluid should be used in acute hemorrhage treatment? How administered?
  - isotonic vs hypertonic fluids,
  - whole blood vs packed blood,
  - crystaloid vs non-crystaloid fluids,
  - hemoglobin or perfluorocarbon-based solutions.
- What treatment is best for individuals who have medical conditions?
  - patients that are at risk for myocardial infarction,
  - patients with kidney disease,
  - patients with diabetes,
  - older individuals.

Information on types of fluids and transfusion protocol can be found at [16].

7 Future work on transfusion problem

This paper presents the issues to be examined in this area of research and some preliminary results. Qualitatively the model produces results consistent with clinical and experimental experience. The following points need to be addressed:

- The simulations at this point include only the response of H to volume loss. It is necessary to add to the model the other sympathetic effects of increased systemic resistance, effects on contractility, venous capacitance, and volume shifts. It will also be necessary to model interstitial fluid auto-transfusion as discussed in Section 2. This effect can act to replace about 15 % of lost volume and raise blood pressure.
- The simulations indicate that with the model as presented, the control H can act more effectively than data suggests ([7]). The recovery time in the simulations is much faster than it appears to be in reality suggesting that further mechanisms need to be included such as inefficiency in filling at high H, increased ventricular viscous resistance, or some manifestation of the Betzold-Jarisch reflex responsible for paradoxical bradycardia when the filling volume is very low.

- Comparison data from humans is hard to come by in this area and animal experiments often include denervation of feedback circuits. It is important also to consider where blood pressure is measured (aortic or femoral pressure) when comparing dynamics. The model generates MAP for a single mixed arterial compartment.
- Blood loss should be proportional to blood pressure (lower pressure reduces the flow out of the body). Transfusion will be modeled intravenously.

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Symbol	Meaning	Unit
α	coefficient of S in the differential equation for σ	min^{-2}
A_{pesk}	$R_s = A_{\mathrm{pesk}} C_{\mathrm{v,O_2}}$	$\mathrm{mmHg} \cdot \mathrm{min} \cdot \mathrm{l}^{-1}$
β	coefficient of H in the differential equation for σ	$\mathrm{mmHg} \cdot \mathrm{min}^{-1}$
frac	upper compartment fraction of basic total prone systemic volume	1
c_{as}	capacitance of the arterial part of the systemic circuit	$\mathrm{l} \cdot \mathrm{mmHg}^{-1}$
c_{ap}	capacitance of the arterial part of the pulmonary circuit	$\mathrm{l} \cdot \mathrm{mmHg}^{-1}$
c_{vs}	capacitance of the venous part of the systemic circuit	$\mathrm{l} \cdot \mathrm{mmHg}^{-1}$
c_{vp}	capacitance of the venous part of the pulmonary circuit	$\mathrm{l} \cdot \mathrm{mmHg}^{-1}$
F_{p}	blood flow perfusing the lung compartment	$\mathrm{l} \cdot \mathrm{min}^{-1}$
F_{s}	blood flow perfusing the tissue compartment	$\mathrm{l} \cdot \mathrm{min}^{-1}$
H	heart rate	min^{-1}
γ	coefficient of σ in the differential equation for σ	min^{-1}
P_{as}	mean blood pressure in arterial region: systemic circuit	mmHg
P_{ap}	mean blood pressure in arterial region: pulmonary circuit	mmHg
P_{vs}	mean blood pressure in venous region: systemic circuit	mmHg
P_{vp}	mean blood pressure in venous region: pulmonary circuit	mmHg
Q	cardiac output	$\mathrm{l} \cdot \mathrm{min}^{-1}$
R_{p}	resistance in the peripheral region of the pulmonary circuit	$\mathrm{mmHg} \cdot \mathrm{min} \cdot \mathrm{l}^{-1}$
R_{s}	peripheral resistance in the systemic circuit	$\mathrm{mmHg} \cdot \mathrm{min} \cdot \mathrm{l}^{-1}$
S	contractility of the ventricle	mmHg
$c_{\ell,\mathrm{r}}$	compliance of the respective relaxed ventricle	$\mathrm{l} \cdot \mathrm{mmHg}^{-1}$
$R_{\ell,\mathrm{r}}$	total viscous resistance of the respective ventricle	$\mathrm{mmHg} \cdot \mathrm{min} \cdot \mathrm{l}^{-1}$
σ	derivative of S	$\mathrm{mmHg} \cdot \mathrm{min}^{-1}$
u	control function	
V_{str}	stroke volume of the ventricle	l
V_0	total blood volume	l
VU	total unstressed volume	l
ℓ, r	left, right heart circuit respectively	

Table 1: Cardiovascular parameters

Parameter	Value
V_0	5.0–2.712
H_{max}	100
c_{as}	0.01002
c_{vs}	0.643
c_{ap}	0.03557
c_{vp}	0.1394
R_{s}	18.41
R_{p}	1.965
κ	0.4

Parameter	Value
α_ℓ	89.47
α_{r}	28.46
β_ℓ	68.71
β_{r}	1.66
γ_ℓ	37.33
γ_{r}	11.88
c_ℓ	0.01289
c_{r}	0.06077
R_ℓ	11.350
R_{r}	4.158

Table 2: Basic parameter values unchanged for all cases – Parameters were taken from [8] and [14].

State variable	Rest Supine	Hemorrhage
P_{as}	100.00	71.08
P_{vs}	3.72	1.66
P_{ap}	17.28	11.23
P_{vp}	7.33	3.82
S_ℓ	67.00	76.77
S_{r}	5.11	5.85
σ_ℓ	0.00	0.00
σ_{r}	0.00	0.00
H	87.23	100.00

Auxiliary variable	Rest Supine	LBNP
Q	5.06	3.77
F_{s}	5.06	3.77
F_{p}	5.06	3.77
V_{strl}	0.058	0.0377

Table 3: Steady states and auxiliary values

State variable	WeightsX
P_{as}	5.0
P_{vs}	1.0

Control variable	WeightsU
u_1	1.000

Table 4: Weights for the cost function