Modeling congestive heart failure: a control system model with state delay

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Abstract. A global model of the human cardiovascular-respiratory control system is presented and applied to modeling congestive heart failure. In the model, one and two transport delays in the state equations of the respiratory system will be included. The intricate relationships between heart rate, blood pressure, cardiac output, and blood vessel resistance in the cardiovascular control process will be integrated via an optimal control approach. The control will act to minimize deviations of certain state variables. The model will consider the congestive heart condition where these transport delays are increased with consequences for stable functioning of the system.

1 The Model

The model which is presented here focuses on several aspects of control of the cardiovascular-respiratory system. System control is implemented via an optimal control approach which specifies heart rate and ventilation. The associated cost functional includes measurements of deviation in blood pressure, and arterial partial pressures of CO_2, and O_2 from a target steady state. Transport delay is included in the state equations. In congestive heart failure increased transport delay caused by reduced cardiac output also reduces the efficiency of the feedback control loop of ventilatory control resulting in potential instabilities. This issue will be discussed further in Section 3.

The model consists of two respiratory compartments (lung and tissue compartments) and four cardiovascular compartments (pulmonary and systemic arterial and venous volumes). Cardiac output Q is modeled for both left and right hearts. The model is represented by Figure 1 and equations (1) to (14). Arterial blood gas pressures are assumed to be equilibrated with alveolar pressures, the model is an average time model and non-pulsatile.

The system is described by 14 nonlinear ordinary differential equations reflecting, primarily, applications of mass balance relations. Equations (1)-(4) include expressions for the partial pressures of arterial carbon dioxide and oxygen ($P_{a_{CO_2}}$ and $P_{a_{O_2}}$), and venous CO_2 and O_2 concentrations ($C_{v_{CO_2}}$ and $C_{v_{O_2}}$). Concentrations can be related to partial pressures via dissociation laws. Brain carbon dioxide concentration ($C_{B_{CO_2}}$) is tracked via Equation 5.

Equations (6)-(8) include expressions for systemic arterial and venous pressures (P_{as} and P_{vs}) and pulmonary venous pressure P_{vp}. Pulmonary arterial pressure P_{ap} is found using these pressures assuming constant blood volume. Equations (9)-(12) describe a relation between heart rate H and contractility S (Bowditch effect). Equations (13)-(14) describe the controls influencing the system and are represented by heart rate H and ventilation rate $\dot{V}_A$.

Auxiliary equations relate systemic and pulmonary blood flow (F_s and F_p) to systemic and pulmonary resistances (R_s and R_p) respectively. Further, a relationship between stroke volume V_{str}, contractility S, and blood pressure is given in Kappel and Peer 1993 [3] based on the Frank-Starling mechanism. A relation between R_s and venous oxygen concentration $C_{v_{O_2}}$ describes the local control of systemic resistance. All other control features are subsumed under the action of the control equations which describe an optimal control process. This mechanism is discussed in section 2. Given the limited space available we refer the reader to Kappel and Peer 1993 [3] and Timischl et al. 2000 [8] for further details.

Delays τ_V, and τ_T, occur because it takes time for the blood to transfer the blood gases from the lungs to the tissue compartment and return from tissue to lungs. We will assume the delays τ_V and τ_T are equal. In this model, the brain is to be considered as part of the lumped tissue compartment in Figure 1 but it would not be difficult to model the brain as a separate compartment if desired. The brain CO_2 equation (5) merely tracks brain CO_2 and will be needed for the control equation in section 3.

$$V_{A_{CO_2}}\dot{P}_{a_{CO_2}}(t) = 863F_p(t)(C_{v_{CO_2}}(t-\tau_V) - C_{a_{CO_2}}(t)) + \dot{V}_A(t)(P_{I_{CO_2}} - P_{a_{CO_2}}(t)), \tag{1}$$

$$V_{A_{O_2}}\dot{P}_{a_{O_2}}(t) = 863F_p(t)(C_{v_{O_2}}(t-\tau_V) - C_{a_{O_2}}(t)) + \dot{V}_A(t)(P_{I_{O_2}} - P_{a_{O_2}}(t)), \tag{2}$$

$$V_{T_{CO_2}}\dot{C}_{v_{CO_2}}(t) = MR_{CO_2} + F_s(t)(C_{a_{CO_2}}(t-\tau_T) - C_{v_{CO_2}}(t)), \tag{3}$$

$$V_{T_{O_2}}\dot{C}_{v_{O_2}}(t) = -MR_{O_2} + F_s(t)(C_{a_{O_2}}(t) - C_{v_{O_2}}(t-\tau_T)), \tag{4}$$

$$V_{B_{CO_2}}\dot{C}_{B_{CO_2}}(t) = MR_{B_{CO_2}} + F_B(t)(C_{a_{CO_2}}(t-\tau_B) - C_{B_{CO_2}}(t)), \tag{5}$$

$$c_{as}\dot{P}_{as}(t) = Q_l(t) - F_s(t), \tag{6}$$

$$c_{vs}\dot{P}_{vs}(t) = F_s(t) - Q_r(t), \tag{7}$$

$$c_{vp}\dot{P}_{vp}(t) = F_p(t) - Q_l(t), \tag{8}$$

$$\dot{S}_l(t) = \sigma_l(t), \tag{9}$$

$$\dot{S}_r(t) = \sigma_r(t), \tag{10}$$

$$\dot{\sigma}_l(t) = -\gamma_l\sigma_l(t) - \alpha_l S_l(t) + \beta_l H(t), \tag{11}$$

$$\dot{\sigma}_r(t) = -\gamma_r\sigma_r(t) - \alpha_r S_r(t) + \beta_r H(t), \tag{12}$$

$$\dot{H}(t) = u_1(t), \tag{13}$$

$$\ddot{V}_A(t) = u_2(t). \tag{14}$$

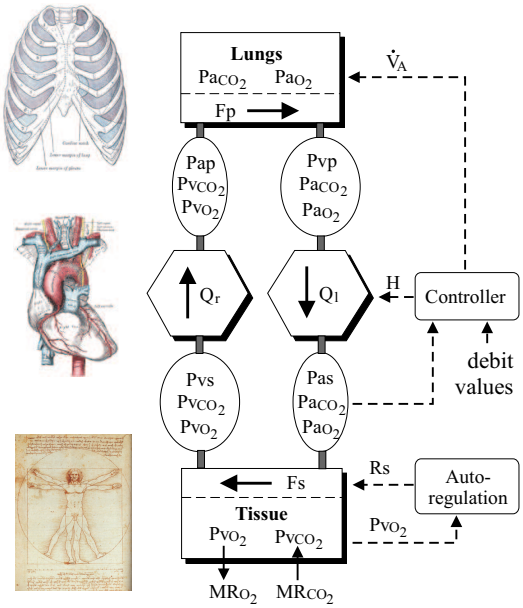

Fig. 1. Block diagram

2 Control mechanisms and optimal control

In this model the design of an optimal control determines control functions u_1 and u_2 that transfer the system from the steady initial condition *quiet awake* to the equilibrium state (ES) *NREM sleep* such that the cost functional

$$\int_0^\infty \Big(q_{as}(P_{as}(t) - P_{as}^{ES})^2 + q_c(P_{aCO_2}(t) - P_{aCO_2}^{ES})^2 + q_o(P_{aO_2}(t) - P_{aO_2}^{ES})^2 + q_1 u_1(t)^2 + q_2 u_2(t)^2 \Big)\, dt \tag{15}$$

is minimize subject to the constraints

$$\dot{x}(t) = f(x(t), x(t-\tau_T); W^s) + B\,u(t), \qquad x_0 = \phi. \tag{16}$$

The cost functional measures deviations in P_{as}, P_{aCO_2}, P_{aO_2}, as well as deviations in the controls u_1 and u_2. The optimal control is designed and numerically implemented using results found in Kappel and Propst 1984 [4] for control systems with state delay. Delay in the optimal control is not included. States *quiet awake* and *NREM sleep* are determined by parameters. For further details see Timischl et al. 2000 [8]. For a survey of applications of optimal control theory in biomedicine and motivations for this approach see, e.g., Swan 1984 [7].

The cardiovascular control system is quite complicated and involves among its features: the sympathetic and parasympathetic nervous systems influence

on H, S and systemic resistance; the baroreflex control of blood pressure; and local control of systemic resistance. Except for local control of systemic resistance, this model subsumes the cardiovascular control effects under the optimal control approach.

Besides venous O_2 influence on systemic resistance (local control), respiration influences cardiac output and heart rate. Here, the cardiovascular and respiratory systems can be linked via the cost function of the optimal control.

The mechanisms which control ventilation are somewhat simpler and better understood than the more intricate interactions in cardiovascular control. The ventilatory control system responds to deviations in partial pressures $P_{a_{CO_2}}$ and $P_{a_{O_2}}$ at sensory sites in the carotid artery ($\Rightarrow$ peripheral control) as well as brain tissue $P_{B_{CO_2}}$ ($\Rightarrow$ central control). These sensory sites send data to the ventilatory control processor in the medulla which modulates breathing. A reasonable descriptive representation of ventilatory control can be given (see Khoo et al. 1991 [6]) by

$$\dot{V}_A(t) = G_p e^{-0.05 P_{a_{O_2}}(t-\tau_p)}(P_{a_{CO_2}}(t-\tau_p) - I_p) + G_c(P_{B_{CO_2}}(t) - I_c). \tag{17}$$

In this equation the first term describes the peripheral control and the second term the central control. G_p and G_c are control gains and I_p and I_c are cutoff thresholds. The delay τ_p is the transport delay from lung to peripheral control.

One way the cardiovascular and respiratory systems interact is through cardiac output determination of the transport delay τ_p in the respiratory feed back control loop. This can effect the stability of the control (see, e.g., Batzel and Tran 2000 [1]). In the optimal control above, no delay is included but we will consider its implementation further below.

3 Application: congestive heart failure

Heart failure (HF) refers to the clinical condition of reduced heart pumping efficiency. Forward failure refers to the reduction in ability to deliver blood to the arterial system at a sufficient rate to meet metabolic needs and reflects the direct pumping ability of the heart or increased after-load.

Each of the possible combinations of left and right, forward and backward failure (systolic/diastolic) has different pressure implications as listed in table 1 (see Katz 1992 [5]). When left forward failure occurs excess blood accumulates in the pulmonary venous system because the left heart cannot effectively push blood to the systemic arterial system. This can result in fluid congestion in the lungs - hence the term congestive heart failure.

In heart failure there is progressive deterioration in heart function resulting from compensatory but damaging adjustments to maintain sufficient cardiac output via activity of the sympathetic system and fluid retention.

Cheyne-Stokes respiration (CSR) is common in heart failure patients during sleep. CSR is an unstable breathing pattern which is non-voluntary and

oscillates between rising and falling breath volumes interspersed with apneas. CSR is an important clinical condition because it contributes to the progressive deterioration in heart function seen in heart failure. Among a number of possible contributing factors to CSR is the increased delay in the respiratory control loop which affects feedback loop efficiency. This is due to the increased time needed for blood gases to move from the site where these blood gas levels are adjusted (the lungs) to the sensory sites where these levels are measured. Another factor may be increased control sensitivity to CO_2.

In the first simulation (Figure 2) we exhibit an optimal control defining both $\dot{V}_A$ and H and the system transition from quiet awake to NREM sleep implemented by that control. Only one delay occurs in the lung to tissue transport loop. Left forward heart failure is modeled by reducing the parameters which effect contractility. Total blood volume is also increased and systemic resistance is increased modeling compensatory behavior of the system. Note that the awake to NREM $\dot{V}_A$ and H transition is smooth.

In the second simulation described by Table 2 and Figure 3 we alter the model by taking $\dot{V}_A$ out of the optimal control and define $\dot{V}_A$ via Equation (17) utilizing Equation (5). This introduces a second delay in the state equations and implements a delay in the respiratory control loop (we assume τ_p equals τ_B). Table 2 and Figure 3 simulate severe left forward heart failure with some right heart deterioration as well (as is commonly seen). Increased control gain and rapid sleep transition are assumed (see Table 2) as well. Under these conditions the respiratory function is driven to CSR-like instability.

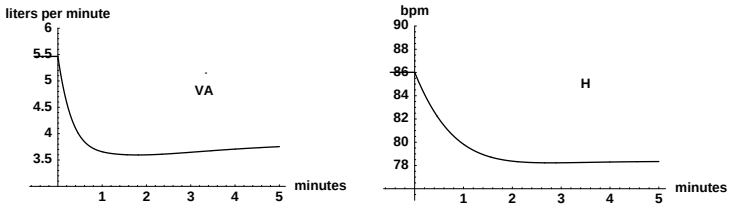

Fig. 2. Left heart failure transition to NREM sleep-optimal control

Table 1. Heart pressure changes

condition	P_{as}	P_{vs}	P_{ap}	P_{vp}
left forward	no change	↑ moderately	↑ moderately	↑ significantly
left backward	no change	no change	no change	↑
Right forward	no change	↑ significantly	small change	small change
Right backward	no change	↑ significantly	no change	no change

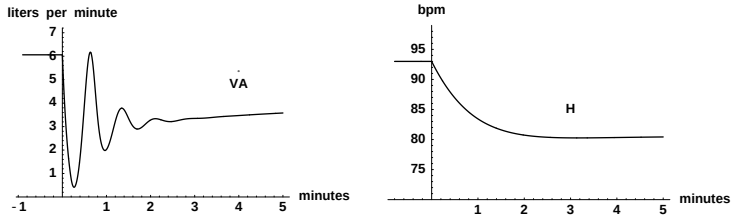

Fig. 3. Severe left-right Heart failure transition to NREM sleep

Table 2. Left-right forward failure sleep transition parameters and steady states

Parameter	Awake	Sleep
A_{pesk}	250.17	237.7
β_l	12.88	11.60
β_r	1.46	1.31
R_p	2.16	2.16
V_0	6.9	6.9
H	93.02	80.02
I_C	35.5	35.5
I_P	35.5	35.5
G_s	1.60	0.480
K_{shift}	0	5.2
τ_p	11.6	11.6
τ_T	36.0	36.0
S 4 transit	-	2 min

Steady State	Awake	Sleep
H	93.00	80.02
P_{as}	92.08	72.78
P_{ap}	26.80	25.17
P_{vs}	3.57	4.05
P_{vp}	19.58	19.14
P_{aCO_2}	37.87	44.15
P_{aO_2}	105.86	98.76
P_{vCO_2}	50.08	56.51
P_{vO_2}	25.92	25.49
P_{BCO_2}	45.95	51.81
Q_l, Q_r	3.35	2.79
R_s	26.40	24.67
S_l	13.39	10.37
S_r	4.76	3.69
$\dot{V}_A$	6.06	4.38
$V_{str,l}$, $V_{str,r}$	0.036	0.035

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