Modeling and analysis of instability in the control system for human respiration

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Mathematical models of the human respiratory control system have been developed since 1940 to study a wide range of features of this complex system. In the absence of voluntary or neurological control, the respiratory control system in which we are concerned, varies the ventilation rate in response to the levels of CO_2 and O_2 in the body (chemical control). The model we are studying was proposed by Khoo et al. (1983) [9] and consists of a nonlinear system of delay differential equations with multiple delays building on the work of Grodins et al in 1954 [6]. Into this basic model we have:

- incorporated variable cardiac output using a model given in [5] thereby allowing the inclusion of variable delay in the feedback control loop;
- extended the model to study infant sleep respiratory patterns including apnea apnea which may play a role in sudden infant death syndrome (SIDS);
- studied stability analytically using a submodel criteria for delay induced instability.

The respiratory control system mechanism acts by means of negative feedback. Deviations in blood gas partial pressures P_{CO_2}, P_{O_2}, from their physiological set points induce changes in ventilation rates which tend to compensate for these deviations. As chemosensors are a physical distance from the lungs, delays in this feedback can induce instabilities.

Periodic breathing (PB) is the generic name given to a number of breathing patterns which are involuntary and have a regular pattern. These patterns appear in patients with brain stem lesions, patients with congestive heart problems, normal individuals during sleep and at high altitudes, and newborn infants (which may be related to SIDS).

Perhaps the most widely held theory, introduced by Haldane and Douglas in 1909 holds that PB is caused by instability in the respiratory control system. It appears that PB is mediated by the peripheral sensory mechanism and is effected by delay in the feedback control loop and large deviations in controller gain. Furthermore, apnea (lack of ventilation) can occur when the oscillations in the ventilatory control signal drive the signal to the cutoff point.

Delay is introduced into the control system due to the physical distance which CO_2 and O_2 levels must be transported to the sensory sites before the ventilatory response can be adjusted. The delay in transfer of partial pressure information for carbondioxide

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(P_{CO_2}) and oxygen (P_{O_2}) from lung to chemosensors depends on cardiac output $\dot{Q}$ in general and blood flow rate to the brain $\dot{Q}_B$ in particular. Considered as a dynamical system with delay, well known mathematical results such as given in [3] show that long delay times in the feedback control loop will destabilize a system and produce oscillations. Figure (1) shows a schematic diagram of three compartments with the delays incorporated into the model. These delays vary with blood flow. The compartments track arterial and venous partial pressures ($P_{a_{CO_2}}$, $P_{a_{O_2}}$, $P_{V_{CO_2}}$ $P_{V_{O_2}}$, and $P_{B_{CO_2}}$). Hence this model represents a system of five nonlinear differential equations with four delays which are state dependent and distributed. Such a system can be studied numerically - analytical results for such are difficult to obtain. See, e.g., [11]. The equations arise from straight-forward development of mass balance equations which are rearranged through the application of basic physical laws and are given by:

$$\frac{dP_{a_{CO_2}}(t)}{dt} = \frac{863\dot{Q}K_{CO_2}[P_{V_{CO_2}}(t-\tau_V) - P_{a_{CO_2}}(t)]}{M_{L_{CO_2}}} + \frac{E_F\dot{V}_I[P_{I_{CO_2}} - P_{a_{CO_2}}(t)]}{M_{L_{CO_2}}}, \tag{1}$$

$$\frac{dP_{a_{O_2}}(t)}{dt} = \frac{863\dot{Q}[m_v P_{v_{O_2}}(t-\tau_V) - m_a P_{a_{O_2}}(t) + B_v - B_a]}{M_{L_{O_2}}} + \frac{E_F\dot{V}_I[P_{I_{O_2}} - P_{a_{O_2}}(t)]}{M_{L_{O_2}}}, \tag{2}$$

$$\frac{dP_{B_{CO_2}}(t)}{dt} = \frac{MR_{B_{CO_2}}}{M_{B_{CO_2}}K_{B_{CO_2}}} + \frac{[\dot{Q}_B(P_{a_{CO_2}}(t-\tau_B) - P_{B_{CO_2}}(t))]}{M_{B_{CO_2}}}, \tag{3}$$

$$\frac{dP_{V_{CO_2}}(t)}{dt} = \frac{MR_{T_{CO_2}}}{M_{T_{CO_2}}K_{CO_2}} + \frac{[\dot{Q}_T(P_{a_{CO_2}}(t-\tau_T) - P_{V_{CO_2}}(t))]}{M_{T_{CO_2}}}, \tag{4}$$

$$\frac{dP_{V_{O_2}}(t)}{dt} = \frac{\dot{Q}_T[m_a P_{a_{O_2}}(t-\tau_T) - m_v P_{V_{O_2}}(t) + B_a - B_v] - MR_{T_{O_2}}}{M_{T_{O_2}}m_v}. \tag{5}$$

The control equation is derived based on the following observations (among others):

- The central controller responds exclusively to P_{CO_2} [12].
- The peripheral controller responds to P_{CO_2} and P_{O_2} [12].
- The effect of P_{O_2} on $\dot{V}_I$ for fixed P_{CO_2} is exponential [12].
- Berger and West [2, 12] indicate that the peripheral P_{O_2} interacts multiplicatively with the peripheral P_{CO_2} effect.
- The peripheral and central control effects are additive [4].

Reflecting these facts, the control takes the form:

$$\dot{V}_I = G_P \exp(-.05P_{a_{O_2}}(t-\tau_a))(P_{a_{CO_2}}(t-\tau_a) - I_P) + G_C(P_{B_{CO_2}}(t) - \frac{MR_{B_{CO_2}}}{K_{CO_2}\dot{Q}_B} - I_C).$$

where $\dot{V}_I$ is minute ventilation, I_C and I_P are apneic thresholds, G_C and G_P are controller gains. See [1] for more details on this and other aspects of the model.

The sleep condition involves a number of different states and stages with different physiological profiles. As one passes from stage 1 sleep (S1) to stage 4 sleep (S4) non-rem sleep the CO_2 response curve shifts rightward, response to overall ventilatory drive diminishes, and muscle resistance to the upper airways and other muscle groups related to breathing increases. These effects are referred to as loss of the "wakefulness stimulus" [8]. Metabolic rates and cardiac output are also diminished. Once stage 4 is reached the sleeper shifts between non rapid eye movement sleep (NREM) and rapid eye movement sleep (REM). These physiological changes affect the stability of the respiratory control system. In 1991, Khoo [8] extended the basic model to simulate respiration during sleep reflecting these transitional features. We use this model for infant sleep respiration simulation.

The occurrence of PB and apnea during sleep is related to the number of changes in the control response which occur during sleep as described above.

In this model we consider only the withdrawal of the wakefulness stimulus sufficient to produce transient reduction in ventilatory drive past a minimal threshold. This will be interpreted as a central apnea. We will assume that this apneic episode will terminate only with arousal. Arousal will be triggered by the chemical ventilatory stimulus rising above an arousal threshold level. Arousal will reset the control mechanism to its awake parameter values.

In modeling the respiratory processes of full term infants in the age range of 3-4 months we use allometric scaling for physical parameters. Allowance is made for an alveolar-capillary gradient $D_{A\text{-}cap}$ for P_{O_2} [10], shunted blood flow from the systemic venous return to systemic arterial blood flow, and changes in hemoglobin loading characteristics (via dissociation laws).

These modeling studies looked at the effects on respiratory stability of arousal thresholds, rightward shifts in ventilatory drive due to the withdrawal of the awake stimulus, increase in the minimal threshold for ventilation, and loss of ventilatory drive during sleep.

Figure (2) reflects blood gas variation when apnea occurs due to ventilatory drive dropping to a level sufficiently low such that respiratory muscle response is absent and a central apneic episode begins. A fast transition time to the sleep state and increased maximal shift S_w (approximately equal to the awake ventilatory drive [8]) and an increase in arousal threshold produces this case. The resulting apnea causes ventilatory drive to rise until arousal occurs. The disturbance to blood gas levels is sufficient to produce new cycles of apnea.

Three-Dimensional State Space Model Stability Analysis

To consider analytically the stability of this model we considered a three dimensional submodel based on the following assumptions:

(i) $P_{V_{CO_2}}$ = constant.

(ii) $P_{V_{O_2}}$ = constant.

(iii) $\dot{Q}$ = constant.

(iv) Only one constant delay is considered: $\dot{\mathrm{Q}}$ is held constant, while the peripheral and central delay are assumed equal.

The three equation represent lung and brain $\mathrm{P}_{\mathrm{CO}_2}$ and $\mathrm{P}_{\mathrm{O}_2}$ as in equations (1)-(3) while the tissue equations are replaced by assumptions (i) and (ii) above. With $\mathrm{x}(t)$ and $\mathrm{y}(t)$ representing respectively $\mathrm{P}_{\mathrm{a}_{\mathrm{CO}_2}}$ and $\mathrm{P}_{\mathrm{a}_{\mathrm{O}_2}}$ deviations from ambient level, $\mathrm{z}(t)$ representing $\mathrm{P}_{\mathrm{B}_{\mathrm{CO}_2}}$, and V ventilation, the equations take the form:

$$\frac{d\mathrm{x}(t)}{dt} = \mathrm{a}_1 - \mathrm{a}_2\mathrm{x}(t) - \mathrm{a}_3\mathrm{V}\mathrm{x}(t), \tag{6}$$

$$\frac{d\mathrm{y}(t)}{dt} = \mathrm{b}_1 - \mathrm{b}_2\mathrm{y}(t) - \mathrm{b}_3\mathrm{V}\mathrm{y}(t), \tag{7}$$

$$\frac{d\mathrm{z}(t)}{dt} = \mathrm{c}_1 + \mathrm{c}_2\mathrm{x}(t-\tau) - \mathrm{c}_2\mathrm{z}(t), \tag{8}$$

where the a_i, b_i, and c_i, are accumulated constants. Some analytical results are as follows:

Theorem 1 *The system (6), (7) and (8) has a unique solution for initial point* $\sigma \in \mathbb{R}$ *and initial function* $\phi \in C$. Furthermore, from Theorem 2.2.2 in [7], we are also guaranteed that the solutions are continuously dependent on initial data so that the model is well-posed.

Theorem 2 *The above system described by (6),(7) and (8) has a unique positive equilibrium* $(\bar{x}^*, \bar{y}^*, \bar{z}^*)$.
We linearize equations (6),(7) and (8) about the equilibrium solution. and derive the characteristic equation:

$$\Delta(\lambda, \tau) = \mathrm{P}(\lambda) + \mathrm{Q}(\lambda)e^{-\tau\lambda} = 0 \tag{9}$$

which will be very complicated. Solving numerically, we may apply Theorem 3.5 described in Cooke and van den Driessche [3] to look for τ which will produce instability. There will be one cross over from stable to unstable behavior. The overall structure of instability is illuminated by the three-dimensional model while the actual state variables were in good agreement with the five-dimensional model.

Based on the foregoing development, we can show that:

1. The central control acts to reduce the instability inherent in the peripheral control mechanism. The peripheral control responds quickly to changes in the blood gases while the central control responds more slowly and with less variation due to the process of transforming $\mathrm{P}_{\mathrm{a}_{\mathrm{CO}_2}}$ levels into $\mathrm{P}_{\mathrm{B}_{\mathrm{CO}_2}}$ levels.

2. The lung compartments act to dampen oscillations and contribute to stability, as Table 1 indicates.

3. Variations in controller gain are critical to the stability of the system.

4. A control which varies depth of breathing is more unstable than one which varies rate of breathing.

Tables (1) and (2) provide numerical results for this analysis. In these tables the **critical values** are defined as multiples of **normal values** which produce instablilty. For example, "control multipliers" refer to multiples of normal gains and "τ multipliers" represent multipliers of the nominal case delay time τ. Thus a τ multiplier of 5.5 says we must increase the normal case delay τ five times for instability in the studied case. Table 1 compares the impact of controlling minute ventilation by changes rate and depth of breathing. Table 2 compares the impact of reduced cardiac output (increased delay) as found in congestgive heart failure. Note that, as Figure (3) indicates, the increased delay produces oscillations. For control gain 2.5 x normal, the destabilizing delay is less than the normal delay. Chenyne-Stokes type respiration occurs.

Table 1: Stability results of parameter changes for 3-D model

3-D with $E_F = 0.7$ (modulate rate of breathing)		
Quantity	parameter multiplier	τ multiplier
G_P and G_C	1.0	11.26 x
G_P and G_C	2.0	5.5 x
$M_{L_{co_2}}$ and $M_{L_{o_2}}$	0.5	10.99 x
$M_{L_{co_2}}$ and $M_{L_{o_2}}$	2.0	12.6 x
3-D with $V_D = 2.0$ l/min (modulate depth of breathing)		
Quantity	parameter multiplier	τ multiplier
G_P and G_C	1.0	5.67 x
G_P and G_C	2.0	3.09 x
$M_{L_{co_2}}$ and $M_{L_{o_2}}$	0.5	4.5 x
$M_{L_{co_2}}$ and $M_{L_{o_2}}$	2.0	7.05 x

Table 2: Stability calculation model parameter base values for Fig. 3

Figure 3	Quantity	Unit	Value
	G_P	l/min/mm Hg	112.5
	G_C	l/min/mm Hg	3.0
	$\dot{Q}$	l/min	3.5
	normal τ	sec	14.6
	unstable τ multiple at normal gain	...	1.76
	unstable τ multiple at 2.5 x normal gain	....	0.77
	$\dot{V}_D$	l/min	2.00

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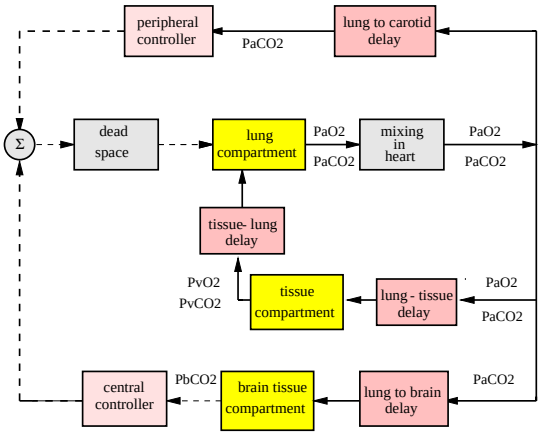

Figure 1: Block diagram of the respiratory system model

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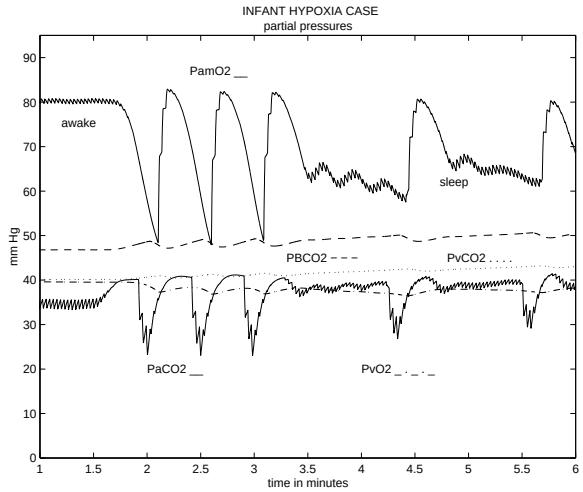

Figure 2: Infant blood gas level destabilized by sleep transition

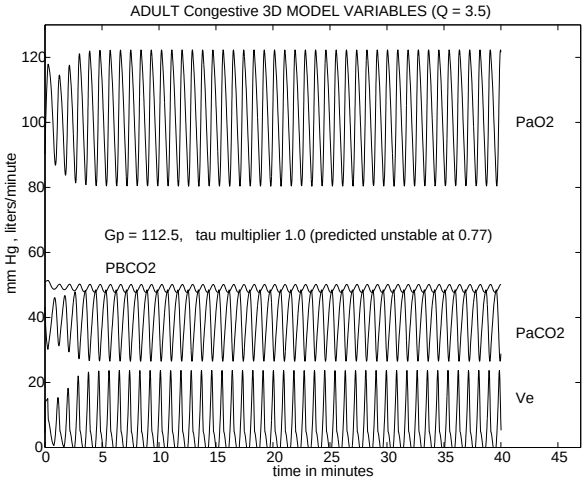

Figure 3: Congestive heart condition: cardiac output 3.5 l/min and high gain