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Computational models for the study of heart-lung interactions in mammals

Alona Ben-Tal

Institute of Information and Mathematical Sciences, Massey University, Albany Campus, Auckland, New Zealand. a.bental@massey.ac.nz

Abstract

[The operation and regulation of the lungs and the heart are closely related. This is evident when examining the anatomy within the thorax cavity, in the brainstem and in the aortic and carotid arteries where chemoreceptors and baroreceptors, which provide feedback affecting the regulation of both organs, are concentrated. This is also evident in phenomena such as respiratory sinus arrhythmia where the heart rate increases during inspiration and decreases during expiration, in other types of synchronization between the heart and the lungs known as cardioventilatory coupling and in the association between heart failure and sleep apnea where breathing is interrupted periodically by periods of no-breathing. The full implication and physiological significance of the cardio-respiratory coupling under normal, pathological or extreme physiological conditions are still unknown and are subject to ongoing investigation both experimentally and theoretically using mathematical models. This paper reviews mathematical models that take heart-lung interactions into account. The main ideas behind low dimensional, phenomenological models for the study of the heart-lung synchronization and sleep apnea are described first. Higher dimensions, physiology-based models are described next. These models can vary widely in detail and scope and are characterized by the way the heart-lung interaction is taken into account: via gas exchange, via the central nervous system, via the mechanical interactions and via time delays. The paper emphasizes the need for the integration of the different sources of heart-lung coupling as well as the different mathematical approaches.]

[The lungs and the heart are nestled together in the closed cavity of the thorax, surrounded by the pleural fluid¹. Changes in the pleural pressure drive air in and out of the lungs and affect the cardiac output². As blood flows from the right ventricle of the heart into the lungs, gas exchange takes place and the levels of oxygen and carbon dioxide in the blood change. This essential process is highly dependent on the ratio between ventilation (which is a function of frequency and amplitude of breathing) and perfusion (blood flow, which is partly dependent on the cardiac output).

Chemosensors outside and within the central nervous system (CNS) sense the levels of oxygen and carbon dioxide in the blood and provide feedback signals to the CNS which in turn controls the lung ventilation via respiratory muscle movements that change the pleural pressure, as well as adjusts the activity of the heart (which has its own intrinsic pacemaker). The chemosensors outside the central nervous system, known as the peripheral chemoreceptors, are concentrated in the carotid bodies and the aortic bodies, in the same area where the baroreceptors are concentrated^{2, 3}. The baroreceptors which sense the arterial pressure also transmit feedback neural signals to the CNS which in turn adjusts the mean blood pressure using a combination of mechanisms including heart rate, contractility and systemic resistance^{2, 3}.

This intimate coupling between the respiratory and the cardiovascular systems at all levels of the control cycle results in complex interactions between the heart and the lungs. This is

perhaps most apparent in respiratory sinus arrhythmia (RSA), a phenomenon used as an index of cardiac vagal function, whereby the heart rate increases during inspiration and decreases during expiration. RSA is present from birth and is stronger in early adulthood. Its magnitude increases with lower respiratory frequency and higher tidal volume and decreases with age⁴⁻⁷. Synchronization between the heart rate and the respiratory cycle known as cardioventilatory coupling (CVC, also known as cardio-respiratory coupling) is another separate phenomenon seen usually during sleep, sedation and general anaesthesia where heart beats occur in constant timing in relation to the onset of inspiration^{8,9}. The coupling between the respiratory and the cardiovascular systems is also evident in Cheyne-Stokes Respiration (CSR) and in obstructive sleep apnea (OSA), both are breathing patterns associated with heart failure and seen usually during sleep, where breathing is interrupted periodically by periods of no-breathing. Unlike OSA where the interruption of breathing is caused by collapse of the upper airway, CSR is a form of central sleep apnea where the breathing pattern originates in the central nervous system¹⁰⁻¹².

All of the phenomena mentioned above are still not fully understood and are subject to ongoing investigation both experimentally and theoretically using mathematical models. The purpose of this paper is to review mathematical models that have been used (or can be used) to study the interactions between the heart and the lungs. As is often the case for biological systems, the cardio-respiratory system has been described by many mathematical models that take into account different features of the system. This results in mathematical models that range widely in size, each providing a different level of understanding. Low dimensional, phenomenological models are reviewed first. These models are characterised by the phenomenon they were designed to study, in this case synchronization (via RSA and CVC), or CSR. Physiology-based models differ widely in detail and can be used to study a variety of scenarios. These models are reviewed next and are characterised by the way the lung-heart interactions are taken into account: via gas exchange, via the central nervous system, via mechanical interactions and via time delays. Models that focus solely on the airways, heart or the circulatory system and do not take into account some form of lung-heart interaction are not reviewed here. Most of the models cited in this paper have been developed for a specific species depending on the experiment or phenomenon they have attempted to mimic. For example, most models of CSR have been developed for humans (adults or infants), breath-hold diving has been studied in humans as well as sea mammals and detailed models of the central nervous system have been developed for rats and cats. Nevertheless, the principles behind the modelling (on which this review is focused) are the same for all mammals and therefore it is often possible to swap one set of parameters for another and adapt a model for a different species in this way. Mathematical models are usually developed and grow over time (the other trend of reducing and simplifying models over time is currently less common). Several groups published a series of models and citing them all is impractical. Instead, only representative papers from each group are cited.]

[Phenomenological models]

[Many real-world systems that look complex when viewed in detail (this is termed the microscopic scale) exhibit a different, often simpler, behaviour when viewed at the macroscopic scale (this is sometimes called an emergent property). Phenomenological models attempt to capture the behaviour of a system as a whole and avoid modelling the different parts of a system in great detail¹³. This approach allows for easier comparisons with global measurements and the testing of hypotheses regarding the way the integrated system works. Because phenomenological models are often low dimensional, a wider range of mathematical tools can be used in comparison with high dimensional models, and this provides additional insights into the system. This section describes the main ideas behind

phenomenological models that have been used to study the synchronisation of the heart and the lungs via RSA and CVC, as well as CSR.]

[Models for RSA and CVC]

[Phenomenological models for the study of RSA and CVC treat the heart and the lungs as two oscillators. As such, each has its own natural frequency (this can be thought of as the intrinsic frequency, observed *in vitro*) but this is modulated by the interactions with the other oscillator and additional control mechanisms (so the frequency *in situ* is different from the frequency *in vitro*). If ω_1 and ω_2 are the two natural frequencies of the heart and the lungs respectively, and θ_1 and θ_2 are the respective phases (i.e. the position within a cycle defined on the interval $[0, 2\pi]$ or $[0, 1]$ in some cases¹⁴) then the rate of change of the phases is given by^{15, 16}:

$$\dot{\theta}_1 = \omega_1 + f_1(\theta_1, \theta_2) \quad (1)$$

$$\dot{\theta}_2 = \omega_2 + f_2(\theta_1, \theta_2) \quad (2)$$

where $f_1(\theta_1, \theta_2)$ and $f_2(\theta_1, \theta_2)$ are functions that describe the way by which the heart and the lungs interact. Different models define f_1 and f_2 in different ways^{17–20}, depending on the assumptions they make and the hypothesis they wish to test. In some cases f_1 and f_2 include the effects of other oscillating processes in the system¹³ either directly¹⁵, or as noise^{20, 21}. If system (2) is driven by system (1) (i.e. the heart is modulating the respiratory cycle), then Eq. (2) can be treated as a forced oscillator²¹ and analyzed using a Poincaré map (where the solution is sampled every period of the heart). This leads to the difference equation (also called a circle map): $\phi_{n+1} = g(\phi_n)$ where $g(\phi_n)$ is some periodic, nonlinear function^{14, 21}.

The formulations described above rely on and can be analyzed using tools from nonlinear dynamics²². All the models mentioned show the existence of several different regions of phase locking (i.e. n/m ratio between the heart and the respiratory rhythms). Interestingly, the calculation of Arnold tongues (regions where phase locking occurs)^{14, 23} could explain why phase locking is observed in a certain order (for example, a 4:1 phase locking will be followed by a 3:1 phase locking), as observed experimentally, and why certain ratios are observed more often (this is related to the size of the Arnold tongue). This formulation was also used to study the directionality of the coupling between the heart and the lungs^{14, 15} and influenced the way measurements are analyzed^{15–17, 19}.]

[Models for CSR]

[Most of the models that have been used to study CSR can be regarded as physiology-based and are reviewed in the following sections. However, the celebrated model by Mackey and Glass^{24, 25} is a nice example of a phenomenological model and is described in this section. The model is based on the observations that 1) the lung minute ventilation is a function of the partial pressure of carbon dioxide in the blood, and that 2) changes to the partial pressure of carbon dioxide in the lungs will be detected by the chemosensitive areas in the brain after some time has elapsed (this is called time delay and is denoted by τ). Taking $x(t)$ to be the instantaneous partial pressure of carbon dioxide in the pulmonary capillaries and assuming that the lung minute ventilation $\bar{V}$ is given by the Hill equation

$$\bar{V}(x) = \frac{\bar{V}_m x^n}{\theta^n + x^n} \quad (3)$$

where $\bar{V}_m$ is the maximum minute ventilation and θ and n are parameters, then the rate of change of $x(t)$ is given by the equation

$$\frac{dx(t)}{dt} = \lambda - \alpha x(t) \bar{V}(x(t - \tau)) \quad (4)$$

where λ is the carbon dioxide production rate and α is a parameter. It has been shown^{24, 25} that when the delay and the slope of Eq. (3) (also called the control gain) are small enough, Eq. (4) has a stable stationary solution which corresponds to normal breathing (constant minute ventilation). However, for increased delay or increased sensitivity to carbon dioxide in the brain (or both), the stationary solution becomes unstable and a stable periodic solution, which resembles CSR, exists. The importance of the Mackey and Glass model is that it illustrates how a simple model can support two of the hypotheses suggested for the appearance of CSR in patients who suffer from heart failure (HF). Increased delay could be caused due to the decrease in cardiac output while variation in sensitivity to carbon dioxide in the brain can explain why not all HF patients experience CSR. Fowler and Kalamangalam²⁶ later showed how the Grodins model (see discussion below), on which many cardio-respiratory models are based, can be reduced to the Mackey and Glass model.]

[Physiology-based models of the cardio-respiratory system]

[While phenomenological models can capture the essence of the dynamics qualitatively or coarsely, they are limited in their ability to provide accurate quantitative information. For example, in the Mackey and Glass model the CSR period is roughly four times the circulatory delay but the experimentally observed period is about half of this estimation²⁴. Physiology-based models are usually more detailed and can therefore provide better quantitative information. Many were developed to study specific aspects of the cardio-respiratory system such as gas exchange and gas transport or the respiratory rhythm generation in the brainstem. Others study the control of the integrated system over short or long periods of time. Therefore these models differ widely in detail and scope and will be characterized by the way the lung-heart interactions are taken into account. This is by no means the only way to characterize these models and other reviews^{27, 28} were done from a different perspective.]

[Modeling interactions via gas exchange]

Models that take gas exchange into account can be divided roughly into two groups according to the way air flow is included in the model. In “breathing lung” models, the instantaneous air flow is a variable, while in “mass balance” models the averaged air flow (minute ventilation) is a variable. In all the mass balance models and in some of the breathing lung models, cardiac output (averaged blood flow) is a variable. In other models the blood flow is continuous or pulsatile. This different choice of variables can be used to study the interactions between the heart and the lungs in different ways.

[“Mass balance” models]

[“Mass balance” models provide a rough understanding of how gas exchange in the lungs works and have been used extensively in clinical applications. These models include some form of the equation:

$$\frac{dV_x}{dt} = \bar{Q}(c_{ax} - c_{vx}) + \bar{V}(f_{lx} - f_{ax}) \quad (5)$$

where x is either CO_2 or O_2 , V_x is the alveolar volume of substance x , Q is the cardiac output, c_{ax} and c_{vx} are the arterial and venous content of substance x respectively, $\dot{V}$ is the alveolar minute ventilation and f_{Ix} and f_{Ax} are the inspired and alveolar concentrations of substance x respectively.

Eq. (5) helps understand why the alveolar gas concentrations are affected by both the lungs and the heart. Because of its simplicity, some form of Eq. (5) is used in many models that study the control of respiration and the appearance of CSR^{3, 29–39} as well as in theoretical studies of ventilation-perfusion mismatch^{40–42}.]

["Breathing lung" models]

[There are several arguments as to why breathing lung models should be used to study the cardio-respiratory system⁴³. Breathing lung models describe gas exchange in more detail and can therefore be used to study a wider range of phenomena. In some models the instantaneous air flow is a given function of time. Using this approach, it has been shown^{44, 45} that the ventilation pattern affects the partial pressure of carbon dioxide in the lungs (albeit this was more evident in multi-compartment models of the airways⁴⁴). In addition, an anatomically based structure of the airways was used to study gas exchange in human pulmonary acinus⁴⁶ and the respiratory control system was studied⁴⁷.

Other breathing lung models^{48–52} take lung mechanics into account (as well as gas exchange). That is, they include some interaction between the pleural pressure, lung compliance and the resistance to air flow. The simplest model that describes such a relationship is given by⁵¹:

$$R \frac{dV}{dt} + EV = \Delta P_l \quad (6)$$

where R is the airways resistance to flow, E is the lung elastance ($= 1/\text{lung compliance}$), ΔP_l is the pleural pressure (relative to the pressure outside the body) and V is the lung volume. This model assumes, among other things, that the air flow is equal to the rate of change of lung volume (this is not always the case⁵¹). Ben-Tal⁵¹ showed how Eq. (6) can be linked to models with gas exchange and how a breathing lung model can be reduced to a mass balance model. For a review of earlier breathing lung models see Khoo²⁷.]

[Modeling interactions via the central nervous system]

The central nervous system consists of several interacting populations of neurons in the brainstem and regulates the respiratory rhythm and the heart rate. Experimental evidence suggests that the regulation mechanisms of the heart and the lungs are integrated within the same neural network^{53–55}. Experimental and theoretical studies are still ongoing and models that truly integrate all the important aspects of the cardio-respiratory control at the level of the neural system do not exist yet. However, mathematical modelling of the central nervous system has come a long way (as described below).

Principles of control theory were first used to develop a mathematical model of the integrated respiratory system by Gray in 1945⁵⁶. His theory was developed further by Fred Grodins who, in 1963, recalled⁵⁶: *"The reception which Gray's theory received from respiratory physiologists in 1945–46 should perhaps have been expected. Few welcomed it as a valuable contribution, but many categorically denied the value of any such mathematical analysis in biology. Some demanded "more dogs and less talk", while others implied that there was nothing here that everyone didn't know already"*. The fact that, despite this initial reaction, the work of Gray and Grodins stimulated many experimental

studies of the cardio-respiratory regulation and greatly influenced the way people think and model the system today, is a testimony of the usefulness of mathematical modelling in general and Grodins' approach to the modelling in particular. Grodins^{29, 56} treated the control system as a "black box", where the output is an empirical function of the inputs. For example, in the case of the respiratory system the inputs could be partial pressures of oxygen and carbon dioxide and the output could be minute ventilation. Over time the Grodins model has been modified, simplified and extended⁵⁷ and new models that couple both the lungs and the heart have been developed^{3, 49, 58–61}. The controllers of the lungs and the heart in these models include some additional information about the neural system (so in part they can be regarded as "black box" and in part as neural-based models) and they interact indirectly via cerebral blood flow, gas concentrations or the lung stretch receptor, but they can be thought of as sitting side by side rather than being integrated at the level of the brainstem.

A model that studies the cardio-respiratory synchronization at the level of the central nervous system has been developed by Kotani et al.^{62, 63} who found regions of phase locking in their model. Several investigators^{55, 64, 65} have developed a large scale computational model of the brainstem respiratory network which includes interactions among respiratory neuron populations with input from baroreceptor cells^{55, 65} and output to the cervical vagus⁶⁴ (which affects the heart rate as well as the airways).]

[Modeling the mechanical interactions]

[As mentioned in the introduction, the lungs and the heart are nestled together in the closed cavity of the thorax subjecting the cardiac cavities and the pulmonary veins and arteries to the pleural pressure. In turn, the pleural pressure is affected by changes in the volume of the thoracic cavity caused by the respiratory muscles as well as the heart mechanical activity and external pressure^{66, 67}. Understanding how changes to the pleural pressure affect the cardio-respiratory function is particularly important under extreme physiological conditions such as diving and flying in combat aircraft where the human body is exposed to high external pressures.

Several models that include pressures which affect both the lungs and the heart function have been developed in recent years^{66–71}. These were used to study breath-hold diving⁶⁷, the valsalva maneuver⁶⁸, high-G protection⁷⁰ and cardiopulmonary resuscitation (CPR)⁷¹.]

[The role of delays in the circulatory system]

[Many of the models that study periodic breathing^{3, 24, 28–31, 35, 38, 72–74} include circulatory delays to represent the fact that it takes time for the blood to circulate around the body and in particular to move from the lungs, where gas exchange takes place, to the peripheral and central chemo sensitive areas where the sensing of oxygen and carbon dioxide takes place. In some cases^{24, 75}, the inclusion of delay in the model is the only way by which the heart-lung coupling is taken into account. The magnitude of the delay is directly related to cardiac output and, as has been demonstrated by the Mackey and Glass model²⁴, can explain the appearance of CSR in patients with heart failure. Therefore it comes as no surprise that models with delays can exhibit CSR. Nevertheless, physiology-based models were used to study specific questions in regard to the appearance of CSR such as the relative importance of circulatory delay versus controller gain²⁸, the role of hypocapnia²⁸, the effect of sleep^{28, 74} and the role of peripheral versus central chemoreceptors⁷³.

Most of the models that have been used to study CSR consist of a mass balance lung model coupled to a "black box" brain model. Ben-Tal and Smith⁷⁶ studied the question of circulatory transport versus neural feedback dynamics in a model that coupled neural-based

controller with a breathing lung model. The model predicted (among other things) that there could be two sources in the brainstem responsible for the appearance of periodic breathing and that the source of the circulatory delay (blood velocity versus distance from the chemoreceptors) is important.]

Conclusion

[Mathematical models that take heart-lung coupling into account have been developed at different levels of complexity and at different levels of operation. Low dimensional models have been developed to study specific phenomena such as synchronization between the heart and the lungs which was studied by treating these organs as two oscillators, and CSR which was studied by the Mackey and Glass model that consists of one differential equation with delay. Higher dimensional models take more information about the structure and function of the cardio-respiratory system into account and can be used to study several aspects of the system dynamics. In particular, the interactions between the heart and the lungs were studied at the level of gas exchange, via mechanical interactions and via time delays. Models that truly integrate all the important aspects of the cardio-respiratory control at the level of the neural system are still missing. However, some models have integrated the controllers of the lungs and the heart with gas exchange, time delays and lung and heart mechanics, while other large scale models of the neural circuitry in the brainstem have been developed.

The usefulness of studying the cardio-respiratory system as a whole using mathematical models was illustrated by the work of Grodins on the control of the respiratory system and by other studies that integrated different aspects of the cardio-respiratory system. Further integration of the neural circuitry in the brainstem with models of the lungs and the heart is expected to provide additional understanding of the operation and regulation of the system. At the same time, Grodins' approach to modelling the controller as a "black box" and the work of Mackey and Glass and others who study RSA and CVC, also illustrated that simpler models can provide powerful insights into the physiological system. It will therefore be beneficial to integrate the different modelling approaches as well as the different sources of heart-lung coupling. First steps in this direction were made by Fowler and Kalamangalam²⁶ who showed how the Grodins model can be reduced to the Mackey and Glass model and by Ben-Tal⁵¹ who showed how a hierarchy of lung models can be related to each other and to other models in the literature. More work on model simplification and on ways to link between simple and complex models is needed.]

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