The Pathway for Oxygen: Tutorial Modelling on Oxygen Transport from Air to Mitochondrion

The Pathway for Oxygen

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Abstract The 'Pathway for Oxygen' is captured in a set of models describing quantitative relationships between fluxes and driving forces for the flux of oxygen from the external air source to the mitochondrial sink at cytochrome oxidase. The intervening processes involve convection, membrane permeation, diffusion of free and heme-bound O_2 and enzymatic reactions. While this system's basic elements are simple: ventilation, alveolar gas exchange with blood, circulation of the blood, perfusion of an organ, uptake by tissue, and consumption by chemical reaction, integration of these pieces quickly becomes complex. This complexity led us to construct a tutorial on the ideas and principles; these first PathwayO_2 models are simple but quantitative and cover: 1) a 'one-alveolus lung' with airway resistance, lung volume compliance, 2) bidirectional transport of solute gasses like O_2 and CO_2, 3) gas exchange between alveolar air and lung capillary blood, 4) gas solubility in blood, and circulation of blood through the capillary syncytium and back to the lung, and 5) blood-tissue gas exchange in capillaries. These open-source models are at Physiome.org and provide background for the many respiratory models there.

1 Introduction

Physiological models tend toward complexity. Carlson et al. [1] modeled ventilatory and alveolar-capillary exchanges showing that transport of O_2 and CO_2 to tissue was influenced not only by respiration rate, composition of inspired gas, tissue pH and CO_2 production, but also by the 1.5 times higher velocity of RBC than plasma [2], which increases alveolar-arterial (A-a) differences in P_{O2}. This minor effect is one of many that influence O_2 delivery and complicate attempts to quantitate physiology. A more important, particularly useful development was an efficient method for calculating the hemoglobin binding of oxygen and carbon dioxide using invertible Hill-type equations [3, 4] accounting for intracapillary gradients as the RBC progressed along the capillary-tissue exchange region. That made it practical to combine these events with convective transport, axial diffusion in the capillary, and with exchange and metabolism in the surrounding tissue region [5].

Such models exemplify some of the complexity of modeling ventilatory, circulatory and metabolic gas exchange, but the price of physiological accuracy was

the difficulty in learning how to use the models. So, in the interests of assisting people through the learning process, we are developing sets of relatively simple models that extend from a one-alveolus mechanical 'lung' step-by-step to account for the physiological behavior and lay a framework for the pathophysiology of disease and the pharmacology of therapies. These models are a part of our lab's contribution to the Physiome Projects, a world-wide grass roots consortium of efforts, including the European Union's Virtual Human Project and NIGMS's Virtual Physiological Rat program, to define integrative physiology quantitatively. The logic is that quantitative models are explicit hypotheses, but are inherently wrong in the sense of being incomplete, inexact, or truly erroneous. The precise nature of quantitative model hypotheses encourages their disproof, and so leads to the advancement of the science. Models are merely transient stepping-stones.

Pursuant to this cause, the models that we provide are public, open source, freely downloadable and reproducible. The language we use to define the models is human readable, an XML variant called MML (Mathematical Modeling Language) and the programs run under a freely downloadable simulation analysis system, JSim [6], that uses a declarative language (rather than a procedural one) so the code is easily readable and convertible to other languages. This system is designed to serve an investigator through the steps of a project, from hypothesis and experiment design to experimental data analysis, sensitivity analysis, verification testing, optimization for data fitting and validation testing, parameter confidence evaluation by covariance and Monte Carlo analysis, and uncertainty quantification. The 'Project File' nature of JSim project allows all the data, the model and the setups for the analysis to be retained for personal retention and for public dissemination in what we call "The Reproducible Exchangeable Package (REP)", which is simply the operational project file, '*model*.proj', for each of the models. The primitive examples in this first section are lacking a central aspect of modeling, namely the data and the relationships between the model and the data, but do portray fundamental principles underlying the real physiology.

2 The one-alveolus lung: Ventilation and alveolar-blood exchange

This first set of models, PathwayO_2.1, provides a generic overview of the processes from inhaled air to consumption in the tissue, a grossly oversimplified view composed of the main elements of the processes. Five models of gradually increasing complexity illustrate elementary lung mechanics, flow of air, inhalation of a gas dissolved in air, transport into the blood, and distribution and reaction in the body. The models (labeled Physiome #0xxx) can be run over the web or downloaded at physiome.org. The simulation analysis system, JSim, is free also. The models are developed to answer questions that are posed as a part of the tutorial.

Here is the code for model 1. The first and simplest in the series:

```
import nsrunit; unit conversion on;
math OneAlvLung.Assist
    { realDomain t sec; t.min = 0; t.max = 9; t.delta = 0.1; // independent variable, time
real Com   = 50    ml/mmHg,          // Compliance of the lung, linear
```

```
    Res    = 0.01  mmHg*sec/ml,   // Resistance of airway, a constant
    Patmo  = 0     mmHg,          // Reference atmospheric  pressure external to body and ventilator
    VFRC   = 3000  ml,            // Volume at rest, Functional Residual Capacity, open glottis
 extern real Pvent(t) mmHg,       // Driving Pressure from Ventilator. Set generator at Run Time
    Fair(t)   ml/sec,             // Flow of air at mouth
    Pmouth(t) mmHg,               // Pressure at the mouth
    Plung(t)  mmHg,               // Pressure in the lung
    Vlung(t)  ml;                 // Volume of air in lung, total
 when(t = t.min)  Vlung = VFRC;   // Initial Conditions
// Equations, Algebraic and ODEs
    Pmouth  = Pref +  Pvent;      // Pressure at mouth: Pvent set to 2 sec at 10 mmHg, zero for 4 sec
    Fair    = (Pmouth - Plung) / Res;   // Ohm's Law : current = driving force / resistance
    Vlung:t  = Flow;                    // Assumes incompressible air
    Plung    = Patmos + (Vlung-VFRC)/Com; // Linear Pressure/Volume relation around VFRC
} // program end
```

The human-readable syntax above declares variables, parameters, governing equations, and physical units for ventilation: pressure, flow (dV_{lung}/dt), and volume,

$$\frac{dV_{lung}}{dt} = \frac{P_{mouth} - P_{lung}}{Res};$$

$$P_{mouth}(t) = P_{ref} + P_{drive}(t);$$

$$P_{lung}(t) = P_{ref} + \frac{V_{lung} - VFRC}{Com}.$$

Model 1. OneAlvLung.Assist (Physiome #0001). The code above is for a one- alveolus lung, a compliant stirred-tank, driven to expand by a positive pressure ventilator. The model lung is purely elastic (stretches instantly like a spring), it returns to its rest volume, functional reserve capacity, when the pressure falls to zero. The airway resistance makes volume changes slower than pressure changes. The tidal volume is proportional to the pressure because the elasticity is constant. (Real lungs are stiffer at higher volumes, i.e. the pressure-volume curve is concave upward.)

Question: With a linear compliance of 50 ml/mmHg, what is the tidal volume with a ventilator pressure excursion of 10 mmHg?

FIGURE 1 HERE

Figure 1. Model 1 variables versus time. The forcing ventilator pressure Pmouth is the solid square wave repeated each 6 seconds. The numerical solutions: Flow: triangles; Volume of lung: circles; Pressure in lung, Plung, dashes. Test is black line exp(-t/(Res*com)), a verification test exactly fitting Flow(t). Model can be run at www.physiome.org Model #1.

Model 2. OneAlvLung.Chest (Physiome #0002). A one-alveolus lung is driven periodically by chest expansion, not the ventilator. Expansion of the chest reduces the pressure in the intrapleural space sucking in air from the mouth. An intrapleural pressure drop of 10 mmHg gives the results as in Model 1.OneAlvLung.Assist.

Question: In this model code one can also use the positive pressure ventilator to assist. Describe the airflow and volume changes if the period of the mechanical ventilator were out of synchrony with the patient's chest-driven breathing.

Model 3. OneAlvLung.IronLung (Physiome #0195). The Iron Lung was used for ventilating polio patients with paralyzed chest muscles. It is a rigid iron tank surrounding the chest and body but leaving the head outside. Exhausting air

from the tank every few seconds produced a negative pressure in the tank and expanded the chest passively, so creating a cycling negative intrapleural pressure.

Questions: Is the tidal volume with a tank pressure, Ptank, excursion of -10 mmHg the same as with an external positive pressure ventilator with a ventilator pressure of + 10 mmHg? What happens when the patient breaths in synchrony with the exhaust phase of the iron lung? Given an initial volume of 20 litres in the tank surrounding the patient's body, and a total chest compliance of 50 ml/mmHg, how much air must be exhausted from the tank to give a normal 500 ml tidal volume on each breath? (Boyle's Law is PV = nRT, where n = no. of moles of gas)

Model 4. OneAlvLung.GasExch (Physiome #0003): Inhalation carries a solute gas such as oxygen in the external air, and exhalation carries some of the alveolar contents back to the external air where it is lost. The gases, air and oxygen, have equal velocities. In the model code a reversible switch is set so the gaseous solute flows in the same direction as the ventilatory airflow. If there is no solute gas in the 'lung' initially, then it takes some time for the alveolar concentration to reach an oscillatory steady state; it takes less time at higher cycle rates and higher 'tidal volume' (the size of a breath). Passive oxygen uptake into the body with conductance 'PSO2lung' reduces the alveolar concentration, and would decrease the alveolar volume if the oxygen were not replaced by another gas.

Questions: Why are the switches needed in the computation? What happens if the 'valve' were leaky? How would you change the equations to do this? If inspiration were prolonged with a constant intrapleural pressure, oxygen is taken up into the body, but the alveolar volume is constant, and its pressure is the same as outside the body. What gases replace oxygen? Where do they come from?

Model 5. OneAlvLung.ExchBody.proj (Physiome #0206) Oxygen in the alveolar air exchanges with the pulmonary capillary blood VblLung, and is distributed by cardiac output, Fblood, to the body, here represented by a blood pool, Vbl ml, exchanging (PSO2tiss, ml/min) with a volume of body tissue, Vtiss ml, with consumption Gtiss, ml/min. Gtiss represents the concentration-dependent utilization of mitochondrial O_2 at cytochrome oxidase with an apparent Michaelis Km of about 0.5 mmHg [11]. Ventilation leads to a pseudo-steady-state in which the alveolar concentration PO2lung is less than in the outside air, PO2atmos, because of the consumption and there is no equilibration.

Questions: What parameter can be set so there is no gas uptake and alveolar gases equilibrate with outside air? With PS lung > 0 but no blood flowing, what regions equilibrate? With flow greater than 0, and PStiss > 0, but with Gtiss = 0, the concentrations in all of the regions equilibrate, PO2atmos = PO2lung = PO2pulcap = PO2tisscap = PO2tiss. Calculate the unidirectional flux of gas in nanomoles/min across the alveolar barrier when Gtiss = 100 ml/min? What are the flux-limiting factors? With the default parameters provided, what is the ratio of airway impedance to membrane impedance, working this out from either a mathematical point of view or by changing the model parameters to minimize one impedance or the other?

3 Next levels of models

These five elementary models, although so over-simplified that they are almost useless for describing real data, do cover the types of processes involved in delivering an external gas to a site of metabolism: convection in air, permeation to enter blood, convection in the circulation, permeation to enter cells, and reaction. Where they fail is in the details or nuances: the driving forces have the wrong shape, the anatomy is not sufficiently complex, the structures and the processes are heterogeneous, and the domains for exchange are spatially distributed rather than instantaneously mixed lumped compartments. But they are coded in unit-balanced equations (the first step in code verification) and illustrate logically sequenced structuring of the system. They represent particular aspects of functional systems and provide a basis for considering gases inhaled each day, O2 and CO2, NH3, ozone, CO, toluene, etc.

In subsequent models being made available at Physiome.org we provide more detailed and practical descriptions of oxygen transport [3-5,7-12], substrate transport and metabolism [13, 14]. Next comes mitochondrial consumption of O_2 to form CO_2 with stoichiometry dependent upon the RQ (respiratory quotient). The next set, **PathwayO_2.2** has a multi-segment airway, humidifies the air, has red blood cells with haemoglobin to bind O_2 and CO_2, bicarbonate to buffer CO_2, O_2 gradients and pH shifts within capillaries, and diffusional resistance to exchange. **PathwayO_2.3mech** adds dichotomous branching and axially distributed properties of airways, intra-pleural space (even pneumothorax) to provide more realistic mechanics (FEV, normal compliances and volume fractions), and allow pendel-luft and other asymmetric situations. **PathwayO_2.3metab** adds the interactions of O_2 and CO_2, pH, 2,3-DPG and temperature on binding to Hb and Mb, and a simplified oxidative phosphorylation with dependence on P_{O2} and pH. Level 3 teaching models are closer to the advanced research models [15], and reflect the ideas expressed long ago by incorporating spatially distributed exchange at the capillary level [1, 2, 16] and the dispersive nature of convective processes [17] . The design with modular components fosters the use of computationally fast components and allows substituting detailed complex components for the simple ones illustrating the principles. At higher level the models diverge, focusing on specific topics.

4 Conclusions: Teaching, training, and researching with Models

For physiologically realistic systems models to be comprehended and used effectively it is critical to convey not only code and instructions in usage but an understanding of the fundamentals. Sequences of models of increasing complexity are useful as open-source tutorials using reproducible component modules. They serve well in introductory classes in quantitative approaches to biology, biochemistry, physiology and pharmacology, and also in designing experiments and testing hypotheses in research.

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and the models, which can be downloaded from www.physiome.org. The inspiration for the title comes from the pioneering works of Professor Ewald Weibel, University of Bern [18].

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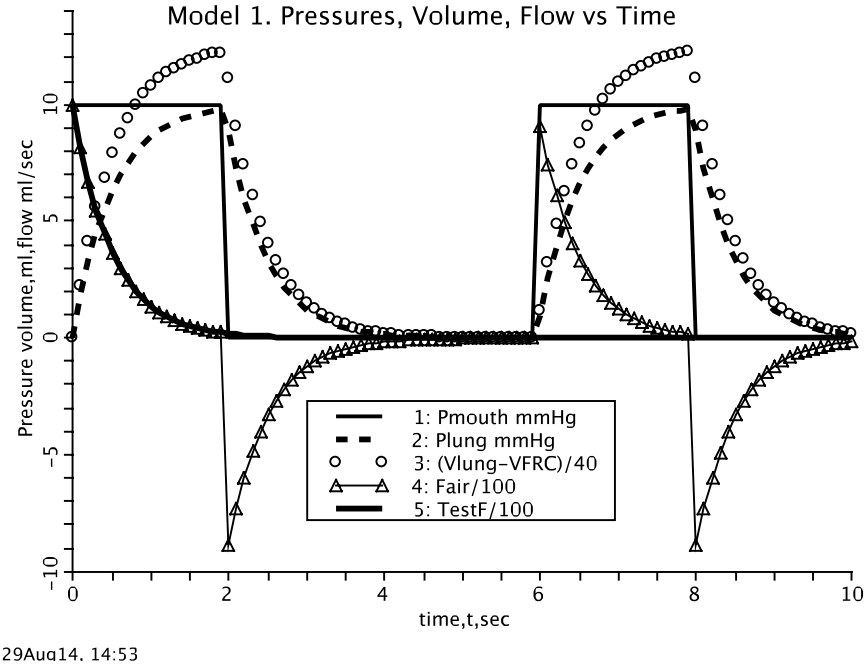

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Figure 1, to be printed in grey shade, NOT Colour.