VentSim: A Simulation Model of Cardiopulmonary Physiology

Geoffrey W. Rutledge, M.D.
Section on Medical Informatics, Department of Medicine
Stanford University, Stanford, California 94305-5479
rutledge@camis.stanford.edu

ABSTRACT

VentSim is a quantitative model that predicts the effects of alternative ventilator settings on the cardiopulmonary physiology of critically ill patients. VentSim is an expanded version of the physiologic model in VentPlan, an application that provides ventilator-setting recommendations for patients in the intensive care unit.

VentSim includes a ventilator component, an airway component, and a circulation component. The ventilator component predicts the pressures and airflows that are generated by a volume-cycled, constant-flow ventilator. The airway component has anatomic and physiologic deadspace compartments, and two alveolar compartments that participate in gas exchange with two pulmonary blood-flow compartments in the circulatory component. The circulatory component also has a shunt compartment that allows a fraction of blood flow to bypass gas exchange in the lungs, and a tissue compartment that consumes oxygen and generates carbon dioxide.

The VentSim model is a set of linked first-order difference equations, with control variables that correspond to the ventilator settings, dependent variables that correspond to the physiologic state, and one independent variable, time. Because the model has no steady state solution, VentSim solves the equations by numeric integration, which is computation intensive.

Simulation results demonstrate that VentSim predicts the effects of a variety of physiologic abnormalities that cannot be represented in less complex models such as the VentPlan model.

For a ventilator-management application, the time-critical nature of ventilator-setting decisions limits the use of complex models. Advanced ventilator-management applications may include a mechanism to select patient-specific models that balance the trade-off of benefit of model detail and cost of computation delay.

MODELS FOR VENTILATOR MANAGEMENT

Numerous researchers have developed computer programs to assist the monitoring and treatment of patients in the intensive care unit (ICU) who receive treatment with a mechanical ventilator. These programs implement various methods, including protocols [13, 22], rule-based expert systems [7, 14, 18], causal probabilistic models (belief networks) [3], and mathematical models [19].

All programs that interpret patient data and make recommendations for the settings of a mechanical ventilator must rely on some model of patient response to the ventilator. Programs that incorporate mathematical models or belief networks may allow the user to examine the models and determine if the assumptions and simplifications these models make are valid for a specific patient. The user may also inspect the model predictions to verify that they match her expectations.

By contrast, protocols and rule-based expert systems implement symbolic models of patient responses that are opaque to the user. Users cannot inspect or test such embedded physiologic models, and may not be able to verify that the program's interpretation of a patient's physiology is valid.

VENTPLAN

VentPlan is a prototype ventilator management advisor (VMA) that explores the ability of a patient-specific mathematical model to guide the selection of optimal ventilator settings for ICU patients. VentPlan implements a classical three-compartment physiologic model to predict the effect of changes in ventilator settings [19].

VentPlan's mathematical model makes accurate predictions for postoperative patients whose abnormalities are well represented by a three-compartment model. For these patients, VentPlan's recommendations for changes to the ventilator settings were compared with the actual changes that were implemented by physicians. VentPlan's recommendations matched the sign of the actual changes in settings and correlated with their magnitude.

VentPlan's architecture allows it to take advantage of uncertain model predictions by computing the expected utility of the predicted effects of alternative ventilator settings. For patients with physiologic abnormalities not representable by a three-compartment physiologic model, VentPlan makes accurate predictions for small changes in ventilator settings, but not for large changes.

0195-4210/94/$5.00

A clinically useful VMA should incorporate a model that is capable of representing the variety of physiologic abnormalities found in ICU patients.

VENTSIM

VentSim is a continuous time, continuous state simulation model that consists of a set of linked first-order differential equations that describe the circulation of oxygen and carbon-dioxide through compartments of the body.

VentSim expands the VentPlan model by including a detailed simulation model of a mechanical ventilator, and by increasing the number of circulation and airway compartments. The structures of VentSim and VentPlan are compared in Figure 1.

Ventilator component

VentSim's ventilator component simulates the constant mandated volume modes of a volume-cycled, constant-flow ventilator. The mechanical analog of the simulator is a rigid bellows with adjustable movement of a plunger during inspiration. In VentSim's default configuration, the plunger moves at constant velocity and compresses the desired tidal volume during the first part of the inspiration cycle. The simulator leaves a short inspiratory hold time after the plunger stops; during the inspiratory hold time, the bellows pressure equilibrates with the patient's airways.

During expiration, the ventilator pressure decreases to the value set for positive end-expiratory pressure, and outflow of air from the patient is limited by a variable outflow resistance (retard setting). Sample pressures and airflows during one cycle of ventilation of a simulated patient are shown in Figure 2.

Adjustable parameters of the ventilator component allow it to simulate most volume-cycled constant-flow ventilators. These adjustments include a maximum positive pressure, an inspiratory hold time, and an expiratory retard.

Differential equation modeling makes it straightforward to adapt the VentSim ventilator component to simulate any mechanical ventilator for which a complete description is available.

Airway component

VentSim's airway component has four compartments: a series anatomic deadspace, a parallel physiologic deadspace, and two alveolar compartments (Figure 1). Each compartment has an associated airway resistance

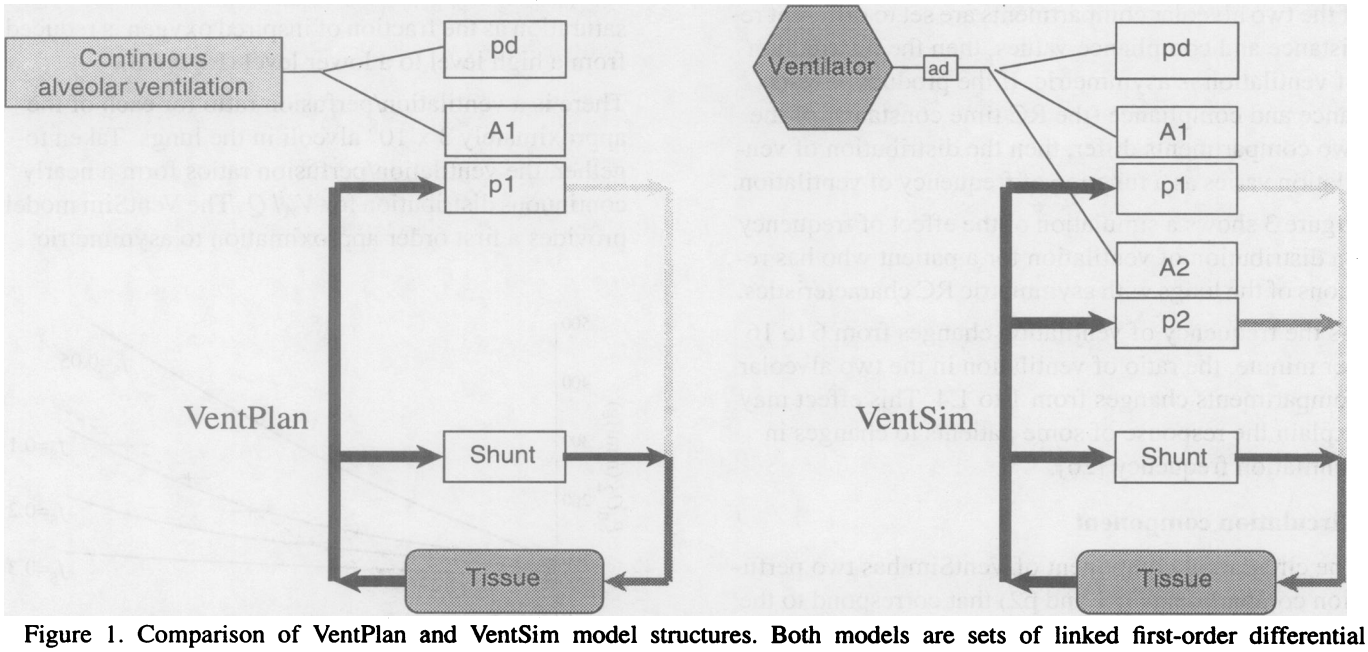

Figure 1. Comparison of VentPlan and VentSim model structures. Both models are sets of linked first-order differential equations. Blood carries oxygen and carbon dioxide in a circuit, as shown by arrows. VentPlan does not simulate the ventilator, but derives the total alveolar ventilation from the ventilator settings (the continuous alveolar ventilation assumption is indicated by the shaded rectangle). The compartments of VentPlan that correspond to the classic three-compartment model are (1) deadspace (pd), a compartment that receives ventilation but no blood flow, (2) a combined gas-exchange compartment with alveolar (A1) and pulmonary blood flow (p1) components, and (3) a compartment that corresponds to shunt. VentSim simulates a volume-controlled positive-pressure ventilator (indicated by a shaded hexagon) to compute airway pressures and airflows. The distribution of ventilation among the three ventilation compartments (pd, A1 and A2) depends on the resistance and compliance of each compartment, and varies with the frequency of ventilation. The VentSim model includes the components of the three-compartment model, plus a series anatomic deadspace (ad), and a second gas-exchange compartment (A2+p2). The presence of two gas-exchange compartments in VentSim allows it to predict the effects of asymmetric distribution of ventilation and perfusion.

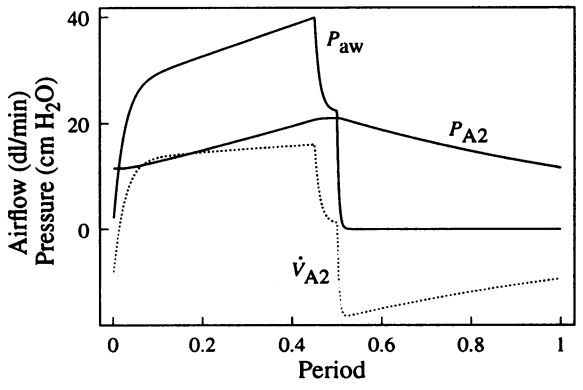

Figure 2. Sample ventilator simulation. The graph plots ventilator pressure at the mouth (P_{aw}), the pressure in one alveolar lung compartment (P_{A2}) and the airflow into one alveolar compartment ($\dot{V}_{A2}$) during one cycle of ventilation. Solid line, pressure; dotted line, airflow.

and a lung compliance. The airway component interacts with the ventilator component to predict the pressures, airflows, and volumes of ventilation at each point in the ventilator cycle. VentSim computes the tidal volumes for each airway compartment during the simulation, and, when all tidal volumes are unchanged during successive ventilator cycles, VentSim notes that the simulator has reached a cyclic steady state.

If the two alveolar compartments are set to different resistance and compliance values, then the distribution of ventilation is asymmetric. If the product of resistance and compliance (the RC time constants) of the two compartments differ, then the distribution of ventilation varies as a function of frequency of ventilation.

Figure 3 shows a simulation of the effect of frequency on distribution of ventilation for a patient who has regions of the lungs with asymmetric RC characteristics.

As the frequency of ventilation changes from 6 to 16 per minute, the ratio of ventilation in the two alveolar compartments changes from 1 to 1.4. This effect may explain the response of some patients to changes in ventilation frequency [26].

Circulation component

The circulation component of VentSim has two perfusion compartments (p1 and p2) that correspond to the two ventilation compartments (A1 and A2), in addition to shunt and tissue compartments (see Figure 1). The presence of a second perfused compartment that participates in gas exchange allows VentSim to represent asymmetric ventilation/perfusion distributions ($\dot{V}_A/Q$).

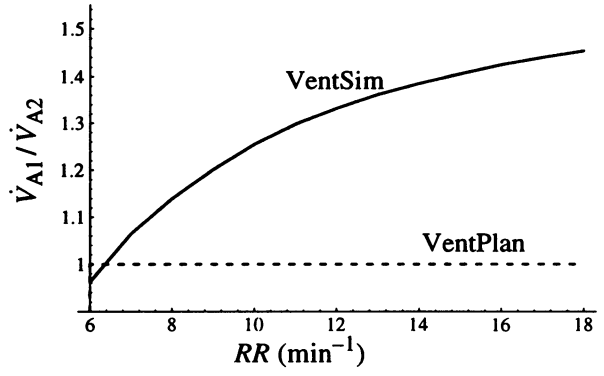

Figure 3. Simulation of the effect of asymmetric resistance-compliance (RC) on distribution of ventilation. The continuous line shows the ratio of ventilation in two alveolar compartments for a patient with asymmetric RC values. The dashed line shows the constant, symmetric ventilation of the single alveolar compartment of the VentPlan model. $\dot{V}_{A1}$, $\dot{V}_{A2}$, ventilation of the A1 and A2 alveolar compartments shown in Figure 1; RR, frequency of ventilation.

The ability to represent asymmetric $\dot{V}_A/Q$ is essential to describe accurately the effect of changes in inspired oxygen on the oxygen saturation. For example, in a simulation of a patient with severe asthma, the three-compartment model underestimates the fall in oxygen saturation as the fraction of inspired oxygen is reduced from a high level to a lower level (Figure 3).

There is a ventilation/perfusion ratio for each of the approximately 3 x 10^8 alveoli in the lungs. Taken together, the ventilation/perfusion ratios form a nearly continuous distribution for $\dot{V}_A/Q$. The VentSim model provides a first order approximation to asymmetric

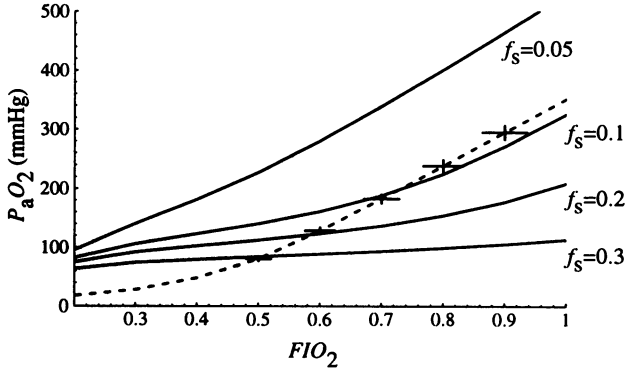

Figure 4. Effect of circulation compartments. The dashed line shows the VentSim model with parameters set to simulate a patient with a ventilation/perfusion mismatch (a moderate asymmetry in distribution of ventilation and perfusion, $\dot{V}_{A1}/Q_{p1} < \dot{V}_{A2}/Q_{p2}$). The continuous lines show the VentPlan model as the shunt fraction, f_s varies. Sampled data are shown as crosses on the dashed line. No value of f_s allows VentPlan to fit the data. (Variable names defined in legend to the Table.)

Table: VentSim and VentPlan variables

Model	Model parameters	Prediction variables	Control variables
VentPlan	$\dot{V}_{O_2}$, RQ, Q_T, f_s, V_{ds} HCO_2, Hb	P_aO_2, P_aCO_2, pH_a P_vO_2, P_vCO_2, pH_v, $\dot{V}_{A1}$	V_{Tset}, RR, FIO_2, $PEEP$
VentSim	$\dot{V}_{O_2}$, RQ, Q_T, f_s, f_{p1}, V_{ad} V_{pd}, R_{pd}, R_{A1}, R_{A2}, C_{A1} C_{A2}, C_{pd}, HCO_2, Hb	P_aO_2, P_aCO_2, pH_a, P_vO_2 P_vCO_2, pH_v, P_{aw}, V_{tidal} $\dot{V}_{A1}$, $\dot{V}_{A2}$, Q_{p1}, Q_{p2}, Q_s	V_{Tset}, RR, FIO_2, $PEEP$ P_{max}, $IEratio$

Variables: V, volume; $\dot{V}$, dV/dt; P, pressure; R, resistance; C, compliance; Q, blood flow; f: fraction; $\dot{V}_{A1}$, alveolar compartment ventilation; $\dot{V}_{O_2}$, metabolic rate; RQ, respiratory quotient; Q_T, cardiac output; f_s, shunt fraction; HCO_2, serum bicarbonate; Hb, hemoglobin concentration; V_{tidal}, delivered tidal volume; V_{Tset}, set tidal volume; RR, set rate of ventilation; FIO_2, set fraction of inspired oxygen; $PEEP$, set positive end-expiratory pressure; P_{max}, set maximum positive pressure; $IEratio$, set inspiratory/expiratory ratio. Subscripts: s, shunt; a, arterial; v, mixed venous; ds, total deadspace;, ad, anatomic deadspace; pd, physiologic deadspace; aw, airway; A1 and A2, ventilated alveolar compartments; p1 and p2, perfused pulmonary compartments.

V_A/Q by representing the distribution as $\{\dot{V}_{A1}/Q_{p1}, \dot{V}_{A2}/Q_{p2}\}$

IMPLEMENTATION

The author implemented the differential equations that describe VentSim as difference equations in a C program, then constructed a graphical user interface to study the behavior of the model. This interface allows a user to inspect model parameters, adjust ventilator settings, and observe the time-varying model predictions.

The VentSim model has 143 variables. A selection of the key model parameters, control variables, and prediction variables are shown in the Table.

Solution methods

The model equations are stiff—an airway component with very short time constants (due to low resistance and compliance of the anatomic deadspace) interacts with a circulation component that has much longer time constants. As a result, numeric integration of the full model is computation intensive. The initial implementation in C, on a desktop workstation (NeXT 68040/25Mhz), requires 53 seconds to simulate 20 minutes.

A second implementation reduced the computation delay by solving only for the steady state solutions to the model. The ventilator and airway components were first solved by numeric integration until a cycling steady state was achieved. Then, the circulation component was solved by searching for the roots of the equilibrium solutions [17], using values for the alveolar ventilation derived from the ventilator simulation. With this approach, VentSim now requires only 1.6 seconds to generate the steady-state solution to a change in ventilator settings.

The VentSim model is implemented as an external C routine that is separately compiled and linked to Mathematica, which provides symbolic and numeric manipulation methods in addition to graphical presentation tools [28].

DISCUSSION

Mathematical models are powerful tools for simulating the quantitative time-dependent behavior of complex, dynamic systems, such as the human cardiopulmonary system [5]. Quantitative models that focus on limited areas of physiology assist the study of individual physiologic concepts. For example, detailed models of the human airway led to insights on the distribution of airway resistance in normal and diseased lungs [26, 27], and to a better understanding of gas exchange in the respiratory system [24]. Detailed models of cardiovascular physiology allowed analysis of the effects of counterpulsation [1], of the effects of arterial grafts on cardiovascular function [10], and of the effects of therapeutic interventions on coronary sinus blood flow [20].

Models that include components from several areas of physiology allow the study of regulatory mechanisms and provide insight into the interactions among systems [2, 23]. An early and influential project in this area was a study by Guyton and colleagues of the behavior of a comprehensive model of renal and cardiovascular physiology, which led to new understanding of the mechanisms of blood pressure regulation [9].

Physiologic models also are useful to teach concepts to students of medicine and physiology. HUMAN is a comprehensive microcomputer-based model that allows students to perform a wide variety of physiologic experiments without performing animal or human experimentation [6]. Other examples of teaching models

were developed in the areas of cardiovascular and respiratory physiology [12], anesthesia treatments [8, 16, 21], and ventilator management [4, 15].

An important problem in applying detailed simulation models to patients is that it is difficult to assess all patient-specific model parameters. For example, Wagner developed a 50-compartment model of lung ventilation and perfusion, but this model requires an inconvenient and expensive multiple inert gas study to determine patient-specific values for the model parameters [25]. The many parameters of Wagner's ventilation/perfusion model are underdetermined in all cases. In another study, Kaufman and colleagues demonstrated that, if only arterial blood gas data are available, the maximum number of perfusion compartments that are distinguishable is three [11].

An implementation of VentSim to assist in clinical care of ICU patients would require a method to determine patient-specific values of model parameters. This problem is addressed by the VentPlan architecture, which combines a belief network with a mathematical model. The belief network is a semi-quantitative model of the effect of disease states on the probability distributions of physiologic parameters; it computes conditional distributions for the parameters of the mathematical model. When the quantitative observations for a patient do not determine the value of all physiologic parameters, the model parameters are based on the prior distributions that are computed by the belief network [19].

The VentSim model includes a set of physiologic interactions that are sufficient to explain a variety of patient abnormalities, but it is by no means complete. For example, VentSim contains no representation of the phenomenon of hypoxic pulmonary vasoconstriction, and does not predict changes in cardiac output that may occur with increases in mean airway pressure. These, and other unmodeled physiologic effects, make it essential that any computer-based ventilator-advice system maintain a cautious estimate of the degree of model-prediction uncertainty.

The time-critical nature of decision making in the ICU limits the computation time that is available for evaluating complex models. Future ventilator-management applications may assess the tradeoff of benefit of model detail and cost of computation delay. This assessment would allow an application to select a model that is detailed enough to represent a patient's physiologic abnormalities and make accurate predictions, but not so complex that it delays treatment recommendations unnecessarily.

Acknowledgment

I thank Ross Shachter, Lewis Sheiner, and Lawrence Fagan for helpful discussions. George Thomsen developed the first VentPlan model and numerous model-solving techniques. Nora Sweeney and Maria Tovar provided valuable comments. I especially thank Edward Shortliffe for providing the environment for research in Medical Informatics at Stanford. This research was supported in part by Grant IRI-9108359 from the National Science Foundation and Grants LM-07033 and LM-04136 from the National Library of Medicine. Computing facilities were provided by the CAMIS Resource, LM-05305.

References

[1] Bai, J., Ying, K. and Jaron, D. Cardiovascular responses to external counterpulsation: A computer simulation. *Medical & Biological Engineering & Computing,* **30**(3):317–23, 1992.

[2] Barnea, O. and Sheffer, N. A computer model for analysis of fluid resuscitation. *Computers in Biology and Medicine,* **23**(6):443-54, 1993.

[3] Beinlich, I.A., Suermondt, H.J., Chavez, R.M. and Cooper, G.F. The ALARM monitoring system: A case study with two probabilistic inference techniques for belief networks. *Proceedings of the Second European Conference on Artificial Intelligence in Medicine,* London, UK, 1989, pp. 247–256.

[4] Boyle, J. RESPSYST: An interactive microcomputer program for education. *Physiologist,* **28**(5):452–3, 1985.

[5] Cellier, F.E. *Continuous System Modeling.* New York: Springer Verlag, 1991.

[6] Coleman, T.G. and Randall, J.E. HUMAN – A comprehensive physiological model. The Physiologist, **26**(1):15–21, 1983.

[7] Fagan, L.M., Kunz, J.C., Feigenbaum, E.A. and Osborn, J.J. Extensions to the rule-based formalism for a monitoring task. In Buchanan, B. and Shortliffe, E.H. (eds), *Rule-Based Expert Systems: The MYCIN Experiments of the Stanford Heuristic Programming Project.* Reading: Addison-Wesley, 1984, pp. 397–423.

[8] Gaba, D.M. and DeAnda, A. A comprehensive anesthesia simulation environment: Re-creating the operating room for research and training. *Anesthesiology,* **69**(3):387-94, 1988.

[9] Guyton, A.C., Coleman, T.G. and Granger, H.J. Circulation: Overall regulation. *Ann Rev Physiol,* **34**:13–46, 1983.

[10] Helal, M.A., Watts, K.C. and Marble, A.E. Hydrodynamic simulation of arterial networks which include compliant and rigid bypass grafts. *Journal of Biomechanics,* **27**(3):277–87, 1994.

[11] Kaufman, R.D., Patterson, R.W. and Lee, A.S. Derivation of VA/Q distribution from blood-gas tensions. *Br J Anaesth,* **59**(12):1599–609, 1987.

[12] Lefevre, J., Roucou, D., Lambert, K. and Maes, B. Simulation and computer-aided instructions in cardiovascular physiology. *Proceedings of the Conference on Computers in Cardiology,* Washington, D.C., 1988, p. 597.

[13] Menn, S.J., Barnett, G.O. and Schmechel, D. A computer program to assist in the care of acute respiratory failure. *JAMA,* **223**(4):308–312, 1973.

[14] Miller, P.L. Goal-directed critiquing by computer: Ventilator management. *Comput Biomed Res,* **18**(5):422-38, 1985.

[15] Petrini, M.F. Distribution of ventilation and perfusion: A teaching model. *Comput Biol Med,* **16**(6):431-44, 1986.

[16] Philip, J.H. Gas Man—an example of goal oriented computer-assisted teaching which results in learning. *Int J Clin Monit Comput,* **3**(3):165–73, 1986.

[17] Press, W.H., Flannery, B.P., Teulokolsky, S.A. and Vetterling, W.T. *Numerical Recipes in C: The Art of Scientific Programming.* Cambridge: Cambridge University Press, 1988.

[18] Rudowski, R., Bokliden, A., Carstensen, A., Gill, H., Ludwigs, U. and Matell, G. Multivariable optimization of mechanical ventilation. A linear programming approach. *Int J Clin Mon Comput,* **8**:107–115, 1991.

[19] Rutledge, G.W., Thomsen, G., Farr, B., Beinlich, I., Tovar, M.A., Sheiner, L. and Fagan, L.M. The design and implementation of a ventilator-management advisor. *Art Intell Med,* **5**:67–82, 1993.

[20] Schreiner, W. Computer simulation of the coronary circulation. *Simulation,* **59**(1):15–23, 1992.

[21] Schwid, H.A. A flight simulator for general anesthesia training. *Comput Biomed Res,* **20**(1):64-75, 1987.

[22] Sittig, D.F. *COMPAS: A Computerized Patient Advice System to Direct Ventilatory Care,* Doctoral dissertation, Dept. Medical Informatics, University of Utah, 1988.

[23] Sun, Y. and Chiaramida, S. Simulation of hemodynamics and regulatory mechanisms in the cardiovascular system based on a nonlinear and time-varying model. *Simulation,* **59**(1):28–36, 1992.

[24] Tomlinson, S.P., Lo, J. and Tilley, D.G. Time transient gas exchange in the respiratory system. *IEEE Engineering in Medicine and Biology Magazine,* **12**(3):64–70, 1993.

[25] Wagner, P.D., Smith, C.M., Davies, N.J., McEvoy, R.D. and Gale, G.E. Estimation of ventilation-perfusion inequality by inert gas elimination without arterial sampling. *J Appl Physiol,* **59**(2):376-83, 1985.

[26] Weibel, E.W. Lung morphometry and models in respiratory physiology. In Chiang, H.K. and Paiva, M. (ed), *Respriatory Physiology: An Analytical Approach.* New York: Marcel Dekker, 1989, pp. 1–56.

[27] Wiggs, B.R., Moreno, R., Hogg, J.C., Hilliam, C. and Pare, P.D. A model of the mechanics of airway narrowing. *J Appl Physiol,* **69**(3):849-60, 1990.

[28] Wolfram, S. *Mathematica: A System for Doing Mathematics by Computer.* Redwood City: Addison–Wesley, 1991.