A patient simulator for anesthesia training: a mechanical lung model and a physiological software model

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A Patient Simulator for Anesthesia Training: A mechanical lung model and a physiological software model

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J.J.M. Heffels

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A mechanical lung model and a physiological software model

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This report was submitted in partial fulfillment of the requirements for the degree of Master of Electrical Engineering at the Eindhoven University of Technology, The Netherlands. The work was carried out from January 1989 until December 1989 at the Department of Anesthesiology, College of Medicine, University of Florida, Gainesville, Florida, under supervision of Professor J.W.W. Beneken, Ph.D., and M.L. Good, M.D.
Abstract.

Anesthesia simulators and training devices are new educational tools which help anesthesiologists and students practice the management of common and uncommon clinical problem. A hybrid lung model consisting of mechanical bellows and a physiological software model for use in anesthesia simulation is described.

The mechanical portion of the model physically simulates all flows, pressures and gas mixing inside the lung. Gas substitution is used to simulate the uptake and delivery of gases by the patient.

The physiological software model is a multiple mathematical model consisting of a gas uptake and distribution model and a cardiovascular pressure and flow model. The physiological software model is programmed in Microsoft C and implemented on an IBM-AT compatible microcomputer. The physiological software determines the distribution of the gases in the blood and controls the exchange of gases in the mechanical lung. Physiological and pharmacological responses of the patient are included in the physiological software model.

The anesthesia simulator models the anesthesia work station in every detail, and can be used to train both anesthesiologists and students. The current patient model correctly simulates a variety of common and uncommon clinical situations and gives a firm basis for future expansions.
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Introduction.

Anesthesia is the practice of medicine that deals with the elimination of pain during surgery. The elimination of pain is accomplished by administration of anesthetic gases and intravenous drugs. In anesthesia, the complex concepts of gas and drug uptake and distribution play a major role. In order that anesthesiologists and students may practice the management of common and uncommon clinical situations, a simulator is needed. Anesthesiologists must be able to detect and rapidly correct rare and infrequent malfunctions of the complex anesthesia equipment, because these may harm the patient. In the current training programs, the resident waits for problems to come along, but there is no guarantee that a training resident gets exposed to all possible problems. An anesthesia simulator can provide the trainee with repeated exposure to rare and infrequent problems. The anesthesia simulator should resemble the anesthesia work station in every detail.

Since May 1986, Ohmeda Anesthesia Systems (Madison, WI) and the University of Florida Department of Anesthesiology (Gainesville, FL) have worked together to develop an anesthesia simulator. A current development goal is to model the patient's cardiopulmonary system. This model consists of two major parts i.e. a mechanical lung model and a physiological software model.

The mechanical lung model, developed in conjunction with the University of Alabama, physically simulates all flows, pressures and gas mixing inside the lung. As the mechanical lung uses real gas flows, it can be connected to a real anesthesia machine, which enhances the realism of the simulator.

The physiological software model, developed at the University of Florida, simulates the distribution of the gases in the blood and controls the exchange of gases in the lungs. The model consists of an uptake and distribution model (chapter 3), and a cardiovascular pressure and flow model (chapter 4). Pharmacological responses of
the patient model are included in the model (chapter 5). The anesthesia simulator can be initialized for different types of patients and for different clinical conditions (chapter 6). The physiological model is kept as simple as possible and one should bear in mind that we are trying to create a patient that could exist as opposed to an existing patient.
1 Anesthesiology and Anesthesia Simulators.

1.1 Introduction to Anesthesiology.

The practice of anesthesiology developed out of a need to prevent patients from experiencing pain during surgery. Pain, in fact, prevented early surgeons from doing little more than simple quick surgical procedures. The first anesthetics included chloroform, ether and nitrous oxide; all were inhaled by the patient. The vaporizing apparatus used in these days was simple but inaccurate and patients were often under or over anesthetized. The toxicity of chloroform and the flammability of ether were significant problems and thus, of the early anesthetics only nitrous oxide is still in use today. Halothane, enflurane and isoflurane are the inhaled volatile agents used today, and they are metered by complex but accurate vaporizers and gas delivery systems. Not only have the anesthetics changed, but the tasks of an anesthesiologist have become a lot more complex since then.

The American Board of Anesthesiology (ABA) defines anesthesiology as a practice of medicine dealing with, but not limited to:

a. the provision of insensibility to pain during surgical, obstetrical, therapeutic and diagnostic procedures, and the management of patients so affected,

b. the monitoring and restoration of homeostasis during the perioperative period, as well as homeostasis in the critically ill patient,

c. the diagnosis and treatment of painful syndromes,

d. the clinical management and teaching of cardiac and pulmonary resuscitation,
e. the evaluation of respiratory function and application of respiratory therapy in all of its forms,

f. the supervision, teaching, and evaluation of performance of both medical and paramedical personnel involved in anesthesia, respiratory and critical care,

g. the conduct of research at the clinical and basic science levels to explain and improve the care of patients insofar as physiologic function and response to drugs are concerned,

h. the administrative involvement in hospitals, medical schools, and outpatient facilities necessary to implement these responsibilities.

Although the number of tasks of an anesthesiologist has grown and become more complex, the main task is still eliminating the pain of surgery and blocking the human body’s response to stress. This is done by administering anesthetic agents and other drugs to the patient. There are many ways to administer these drugs; orally, intramuscularly, intravenously or by inhalation. In the operating room, pulmonary administration is commonly used to deliver anesthetics to the patient.

In the major operating room suite, most surgical procedures are performed under general anesthesia. General anesthesia means the patient is unconscious and unaware of what goes on around him. General anesthetics decrease the patient’s respiratory function and therefore, the patient’s respiration has to be assisted. Often this is accomplished with a mechanical ventilator. Artificial ventilation and the administration of anesthetics are delivered by an anesthesia machine. There are many different anesthesia machines, but their general operation is similar to the schematic given in figure 1.
Figure 1. An Anesthesia Machine.

The anesthesia machine is connected to the patient with a flexible breathing circuit (C + E). The patient's trachea is intubated with a special piece of tubing, an endotracheal tube (L). Some endotracheal tubes come with an inflatable balloon or cuff around the outside of its tip. Once the tube is positioned in the patient's trachea, the cuff is inflated. The cuff allows the mechanical ventilator to apply positive pressure to the lungs without leaking gas, and reduces the possibility of passage of foreign material into the lungs.

Gas is circulated through a breathing circuit by the mechanical ventilator (H). This allows for gas exchange with the patient's lungs, which is measured in terms of tidal volume, respiratory rate and expiratory to inspiratory ratio. The ventilator drives the bellows which in turn circulates the gases in the circuit. Most ventilators use oxygen to drive the bellows so that in case the bellows leak, the patient will still receive adequate oxygen.
Unidirectional valves create circular gas flows in the breathing circuit. In an open ended path gas flows from the fresh gas supply (A) through the inspiratory valve (B) and the inspiratory hose (C) into the lungs (D) and then via the expiratory hose (E) and expiratory valve (F) through the ventilator hose (G) to the bellows (H). Excess gas is vented from the bellows through the ventilator pressure relief or "spill" valve (I) into a scavenging system. The fresh gas flow is composed of a mixture of oxygen (O₂), nitrous oxide (N₂O) and volatile anesthetic agent (AGE). These gases are supplied either by a centralized hospital distribution system and transported via fixed pipelines, or by bottled gas mounted on the back of the anesthesia machine. The bottled gas supply is always available as a backup system in case the central distribution system fails. If the pressure of the central supply drops, check valves in the supply manifold (J) prevent gas from flowing from the bottled supply back into the central supply. When either oxygen supply fails, the oxygen failure safety mechanism (K) will close the nitrous oxide supply to prevent the patient from breathing 100% N₂O. The excess gas is led into a scavenging system to prevent anesthetics from leaking into the operating room. In a hospital, the scavenging system is centralized like the central gas supply. In active scavenging systems, a vacuum is maintained to create a continuous flow of gas away from the anesthesia machines.

The circular path of gas flow in the breathing circuit passes through the CO₂-absorber. In order to conserve gas, part of the expired gas is reused after carbon dioxide (CO₂) is removed by a CO₂-absorber. During expiration the gas flows from the lungs through the expiratory valve into the ventilator bellows. During inspiration, the gas flows from the bellows through the CO₂-absorber and the inspiratory valve back into the lungs.

In case the anesthesiologist requires a more direct control of the ventilation he can switch to a manual mode. In this mode, the ventilator is off and the anesthesiologist squeezes the breathing bag to generate positive pressure to ventilate the patient.
In addition to the anesthesia machine, the anesthesiologist uses several other instruments to monitor the patient. These monitors can vary from patient to patient, depending on the physical status of the patient and the type of surgery to be performed. The American Society of Anesthesiologists (ASA) considers the following monitors mandatory as part of its minimal monitoring standards: electrocardiograph (ECG), blood pressure, \( \text{O}_2 \) analyzer, airway pressure and patient temperature. Many anesthesiologists also routinely use spirometry, pulse oximetry, capnography, and respiratory gas analyzer.

An electrocardiograph measures the electrical activity of the heart using several electrodes placed on the patient’s skin. The ECG detects irregular heart rhythms, and in susceptible patients, inadequate blood flow to the heart muscle (myocardial ischemia).

The blood pressure monitor typically used in the operating room is an automated version of the traditional manual blood pressure cuff. With the manual system, a stethoscope is used to detect blood flowing under a pressure cuff that is wrapped around the patient’s arm. The automated blood pressure monitor measures oscillations in the cuff as cuff pressure is slowly decreased. At regular intervals, the monitor automatically measures the systolic, mean and diastolic blood pressures. This information is especially important if the patient loses a lot of blood during the operation.

The oxygen sensor is placed in the inspiratory side of the breathing system to make sure that the patient is getting adequate oxygen. Oxygen is one of the most important variables in anesthesiology, and is therefore checked at several places.

The gas flow and pressure sensors are normally placed on the expiratory side of the breathing circuit. These sensors help the anesthesiologist to detect obstructions or large leaks in the breathing circuit.

A pulse-oximeter non-invasively measures the oxygen saturation of hemoglobin in blood. This is done by connecting a clip-on probe to a thin, well-perfused part of the patient, like a finger or an ear-lobe. Its measurements are based on the fact that the optical properties of hemoglobin changes as its oxygen saturation changes.
The gas analyzer and the CO\textsubscript{2} monitor both measure gas concentrations at the endotracheal tube. A CO\textsubscript{2} monitor measures CO\textsubscript{2} concentration only whereas a gas analyzer measures the inspiratory and expiratory level of several other gases like O\textsubscript{2}, N\textsubscript{2}O and agents as well. Measuring the end expiratory gas concentration will give a good approximation of the concentrations in the alveoli and therefore in the patient’s blood.

All measurements mentioned above are obtained non-invasively. These measurements are preferred to invasive measurements, but in some cases the anesthesiologist will need additional, more frequent, or more precise information about the patient. In these cases catheters can be introduced into the patient’s arteries and veins to measure blood pressure, withdraw and analyze blood, or measure other variables like cardiac output.

All these instruments help the anesthesiologist to monitor the patient’s response to anesthetic gases and other drugs. The drugs are administered to block pain during surgery and to block the patient’s response to stress. Not only should the anesthesiologist know the effects of the administered drugs, but he should also know the restrictions and accuracy of the monitors used and the anesthesia machine. Therefore the anesthesiologist needs to be extensive training. In the next section, the use of anesthesia simulators in the training of anesthesiologists is described.
1.2 Introduction to Anesthesia Simulators.

The anesthesia machine is complex and thus prone to many possible malfunctions. Examples include incompetent unidirectional valves, an exhausted CO$_2$-absorber, crossed or failing gas supplies, leaks and disconnected tubes. Although these malfunctions are rare, they do occur [Cooper 1984] and can be very difficult to detect. Many malfunctions occur infrequently, but can severely injure or kill a patient. The anesthesiologist should understand the anesthesia machine well enough to detect even the rarest malfunctions and undertake the necessary steps to correct it, so that the patient will not be harmed.

The handling of these common and uncommon malfunctions is difficult to learn from a textbook. Studies of learning preference suggest that many anesthesiologists learn best by active experimentation [Baker 1987]. The problem is teaching someone how to handle a malfunction that is very rare and that could endanger the patient. There is no guarantee that a training resident gets exposed to all possible problems. A solution is to simulate these clinical problems on an anesthesia simulator to train students and other anesthesia personnel. An anesthesia simulator should resemble the normal working environment of the anesthesiologist in detail, and provide the trainee with the information normally available in the real operating room.

The disadvantage of anesthesia simulators to date has been that they are either completely implemented on a computer [Guyton 1972, Dickinson 1977, Schwid 1987], or built without software [Gaba 1988; Good 1988; Loughlin 1989]. A simulation that completely revolves on a computer screen does not create a realistic environment. A simulator without software can not simulate the patient at all [Gaba 1988], or not in enough detail [Good 1988]. The best features of each version are implemented in a hybrid model, that uses real gas flows, a real anesthesia machine and a mechanical lung model on one side and on the other side a software model to simulate the patient and to control the gas exchanges in the lung.
The anesthesia simulator recently developed by M.L. Good, S. Lampotang, G.L. Gibby and J.S. Gravenstein at the University of Florida [Good 1988], uses a standard anesthesia machine to ventilate a simple mechanical lung. A separate computer controls several mechanical actuators that are built into the anesthesia machine and the mechanical lung. These actuators cause a malfunction in the anesthesia machine or in the anesthesia breathing circuit. The computer also provides the blood pressure monitor and the pulse oximeter with simulated signals. Other monitoring devices such as a CO₂ monitor, pressure and flow meters measure directly from the breathing circuit.

The patient in this simulator is replaced by a mechanical lung model consisting of a mechanical bellows with a constant inflow of CO₂ to simulate CO₂ production. In some malfunction scenarios, this approach is too coarse. For example, in the case of an obstruction of the inspiratory hose, the lung is not ventilated sufficiently. In a real patient this results in an increased expired CO₂ concentration of about 0.5-0.8% per minute. The body will absorb the produced CO₂ and decrease the flow of CO₂ into the lungs. With the original lung model, the CO₂ concentration will keep increasing as long as the hose is obstructed and CO₂ continues to be infused into the lung bellows at a constant rate. Further, the original lung model could not consume O₂.

A new lung model that more realistically simulates gas exchange was required. This new model should be able to simulate physiologic CO₂ production, O₂ consumption, N₂, N₂O and volatile agent exchange.

In anesthesia, the complex concepts of gas and drug uptake and distribution play a major role. By including the uptake and distribution of N₂, N₂O and volatile agent in our model, we will be able to show the exchange of these gases in the lung and the distribution of these gases in the body compartments of the patient.
The hybrid character of the new model is shown in figure 2. The mechanical lung model uses real gas flows and therefore, creates a realistic environment for the trainee. The physiologic model consists of software models of the patient's body, and controls the exchange of gases in the mechanical lung. The mechanical lung model is connected to an anesthesia machine and ventilated like a patient's lungs. The patient data file contains the basic variables of a patient, such as age, weight, height and sex.

In the following chapters, the hardware that controls the exchange of gases in the lung is described and then the software models that simulate the patient are described.
2 The mechanical lung model.

The original mechanical lung model of the Gainesville Anesthesia Simulator used a constant inflow of CO₂ simulated CO₂ production by the patient. This lung model was adequate for generating the capnograms associated with malfunctions of the anesthesia machine, but did not quantitatively reflect physiologic changes in exhaled CO₂ during these malfunctions. Also, more complex scenarios were being developed which require the new lung model to exchange O₂, N₂, N₂O and volatile agent. This new mechanical lung model was designed at the University of Florida and developed at the University of Alabama by G. Ritchie, PhD. et al (see figure 3).

Figure 3. The mechanical lung.

An E-cylinder supply of each gas (O₂, CO₂, N₂, N₂O) is connected to the lung model (A). A cylinder pressure gauge indicates the supply pressure and a pressure regulator reduces the cylinder pressure to 20 psi (A). The flow of each gas is controlled by a solenoid valve which is electrically operated via relays as instructed by
the computer. A needle valve (B) upstream of the solenoid valve (C) allows adjustment of the flow through the open solenoid, and is used for calibration.

The gas exchange of each gas is accomplished by gas substitution. A constant gas flow flushes the lungs. The concentration of the different gases in the outflow is measured by an Ohmeda 5250 multi gas monitor. The multi gas monitor has an analog output signal for the concentration of $O_2$, $CO_2$, $N_2O$ and volatile agent. The remaining percentage is assumed to be $N_2$. Knowing the flow rate and these concentrations, the amount of each gas taken out of the lungs is calculated. The physiologic patient model determines the exchange for each gas. The difference between the desired uptake and the instantaneous outflow is the needed inflow of each gas. For example: when the alveolar volume concentration of oxygen is 20%, the uptake as determined by the model is 200 ml per minute and inflow and outflow are both 3 liter per minute (LPM), the oxygen concentration of the inflowing gas mixture should be:

\[
(\text{Alveolar } O_2 \text{ conc.} \times \text{Total Outflow}) - O_2 \text{ Uptake} = \\
\text{Inflow } O_2 \text{ conc.} \times \text{Total Inflow}
\]

so

\[
\text{Inflow } O_2 \text{ conc.} = ((0.2 \times 3 - 0.2) / 3) \times 100\% = 13\%
\]

The outflow can be selected by two parallel solenoid valves (D) at the pump. By opening one solenoid valve the outflow will be 3 LPM, and by opening both solenoid valves the outflow will be 5 LPM. The pressure difference over the solenoid valves created by the vacuum pump is too low to maintain a flow of 5 LPM through only one open solenoid valve. Therefore, both solenoids need to be opened for the high flow. The choice of 3 and 5 LPM flows is based on the flow needed to meet the greatest uptake or delivery of the gases and yet minimize the gas usage and scavenging requirements. In a steady state without anesthetics there will be a delivery of about 140 mL $CO_2$ per minute, and an uptake of about 200 mL $O_2$ per minute. In this case an outflow of 3 LPM is enough. But in the case of high uptake at low alveolar concentrations, as during induction of a patient with a volatile agent, an outflow of 5
LPM becomes necessary to achieve the desired uptake.

The 3 LPM outflow is calibrated by opening only one solenoid and adjusting the needle valve until the desired flow is obtained. Then both solenoid valves are opened and the remaining needle valve is calibrated until the total outflow is 5 LPM. The needle valves are located between the pump and the solenoid valves.

The inflow is regulated by one of two solenoid banks, one for the 3 LPM flows and one for the 5 LPM flows. The pressure difference over the solenoid valves at the inflow is much higher than at the outflow. Therefore, a flow of 5 LPM can be realized by opening only one solenoid valve. Each solenoid bank consists of five solenoid valves with matching needle valves, one for each gas. During operation only one of the gases is flowing into the lungs at any instant. The software that drives the solenoid valves updates the composition of the inflow every 1.37 seconds. The 1.37 seconds time period is divided into 100 time intervals of 0.0137 seconds. The inflowing gas is composed by opening each solenoid for a number of these 0.0137 second intervals, proportional to its concentration. If the total desired inflow is less than the selected inflow of 3 or 5 LPM, the excess number of time intervals are assigned to a state in which all solenoid valves are closed. After 100 time intervals or 1.37 seconds, the software calculates the new settings using updated alveolar gas concentrations from the gas monitor and new gas exchanges from the physiologic model.

In order to keep the gas usage as low as possible, the software will first try to realize the desired exchanges using an inflow and outflow of 3 LPM. If the desired exchanges can not be realized using the low flows, the same calculations are done with a 3:5, a 5:3 and a 5:5 inflow:outflow ratio. In some extreme cases, none of these flows will be able to realize the desired exchange. In these cases the 5:5 flows will be used, because they give the best approximation (see Table 1). During induction this situation lasts only a few seconds and the approximation will minimally affect the overall response of the model.
In Table 1, example calculations are shown. The upper part of the table gives an example of a normal steady state without anesthetics which can be handled with the low 3 LPM flows. The lower part gives an example at the beginning of induction at which even the high flows are not able to realize the desired exchanges. At a 3:5 ratio the total number of calculated time intervals exceeds 100 time intervals, which the model is unable to achieve.

**Table 1. Example of time interval calculation.**

<table>
<thead>
<tr>
<th>desired exchange ml/min</th>
<th>lung concentrations in %</th>
<th>calculated time intervals in:out flow rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂</td>
<td>-200</td>
<td>97</td>
</tr>
<tr>
<td>CO₂</td>
<td>+140</td>
<td>3</td>
</tr>
<tr>
<td>closed</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>O₂</td>
<td>-202</td>
<td>69</td>
</tr>
<tr>
<td>CO₂</td>
<td>+124</td>
<td>5.1</td>
</tr>
<tr>
<td>N₂O</td>
<td>-438</td>
<td>25.2</td>
</tr>
<tr>
<td>Age</td>
<td>- 62</td>
<td>0.7</td>
</tr>
</tbody>
</table>

The 12 needle valves are sensitive to shocks and changes in temperature. Therefore, all needle valves need to be recalibrated each time the simulator is transported. The gas flow through the inflow valves have a pulsating character and are therefore difficult to measure using a standard flow meter. These standard flow meters also have to be calibrated for use with different gases.

Another way of measuring these flows is using a volumetric flow meter. A volumetric flow meter uses an airtight float (e.g. a soap bubble) that moves through a transparent pipe with a given diameter. By directing the flow to be measured through the pipe and measuring the time that the float takes to travel over a known distance i.e. a
known volume, the mean flow can be obtained (figure 4a).

The main error with this calibration method is caused by the inaccuracy of measuring the time the floater needs to travel over the known distance. The flow meter should be able to measure flows up to 5 LPM ($F_{\text{max}}$). Assuming the time error using a stopwatch will be approximately 0.1 seconds ($dt_{\text{max}}$) and the maximum error in the flow may not exceed 0.055 LPM ($F_{\text{error}}$), the minimum measured volume ($V_{\text{min}}$) should be:

$$V_{\text{min}} = \frac{(F_{\text{max}} + F_{\text{error}}) \cdot F_{\text{max}} \cdot dt_{\text{max}}}{((F_{\text{max}} + F_{\text{error}}) - F_{\text{max}}) \cdot 60}$$

$$= 0.766 \text{ L.}$$

A volume of 800 ml is therefore enough for our purposes.

Only one flow rate is used for calibration as the relationship between duty cycle of the solenoid valve and the flow through the valve is assumed to be linear. The best flow at which to calibrate the needle valves is a flow in the mid-range of the anticipated flow rates (i.e. the solenoid valve switches at a 50% duty cycle). Measurements by Ritchie show that the relationship between the duty cycle of the solenoid valve and the obtained flow is not entirely linear. Therefore, the next version of the software driving the solenoid will use a calibration curve to describe the relation between duty cycle and flow.

The multi gas monitor uses a polarographic $O_2$-cell to measure the $O_2$ concentration. The response time of this type of $O_2$ sensor is approximately 45 seconds. This slow response causes the measured $O_2$ concentration to lag behind the alveolar $O_2$ concentration during rapid changes. Instead of a continuous increase, the gas monitor will show a discrete step every few seconds. Although the error is not
large enough to affect the overall response of the simulator, the replacement of this polarographic $O_2$-cell by a fast $O_2$ sensor (i.e. paramagnetic) should be considered in future versions of the lung model.

Figure 4. (a) A volumetric flow meter. (b) The VVR Calorimeter.

The gas analyzer has an autozero function that is automatically executed every hour. The autozero function is needed, because contaminants (e.g. secretions) in patient samples can accumulate in the optical detectors of the analyzer and thus, offset the zero baseline of the gas analyzer. The autozero function is used to compensate for this offset. During the autozero, the gas concentrations on the display and on the analog output port decrease rapidly and no longer represent the concentrations in the sample. The physiologic software model reads the analog signals continuously and detects the autozero functions if there is a decrease of more than 3% in the alveolar concentration of $CO_2$ between two samples (i.e. within 1 second).

If an autozero is detected the input to the physiologic model remains at the last measured values during and for 15 seconds after the termination of the autozero function. The last measured values are retained for 15 seconds after the autozero
function ends because the slow $O_2$ sensor needs this time to stabilize at the actual alveolar partial pressure of $O_2$. In the case of a high alveolar partial pressure of $O_2$, the $O_2$ sensor needs more than 15 seconds to equilibrate.

It must be appreciated that the autozero function can start at the moment that fast changing partial pressures, like $CO_2$, are at a minimum or maximum value. This causes an error in the physiologic model that increases with time. In figure 5 for example, the autozero function starts when alveolar $CO_2$ is at a maximum value, which causes a compensatory decrease in alveolar partial pressure of $CO_2$ (PACO$_2$) as long as the old $CO_2$ value is retained. Fifteen seconds after the autozero terminates, the current and low $CO_2$ value appears. The physiologic model compensates for this sudden decrease in alveolar $CO_2$ by delivering more $CO_2$ to the mechanical lung.

When the real $CO_2$ value appears, the $O_2$ analyzer has still not equilibrated at the actual alveolar $O_2$ partial pressure, causing the artificial appearance of N$_2$. Although the autozero function can not be disabled, most of the negative effects of autozero can be avoided by the use of a faster paramagnetic $O_2$ sensor, which should be incorporated in future versions of the mechanical lung model.
Figure 5. Effects of gas analyzer autozero function during real-time simulation. Alveolar partial pressures as received by the physiologic software model.

The accuracy of the exchange of gases in the lung was tested using a Biergy VVR Calorimeter (see figure 4b). The calorimeter measures oxygen uptake using a closed circuit, oxygen replenishment technique. A gas-tight connection is made between the patient and the closed circuit and as the patient breathes, the bellows will expand and contract. All the CO₂ produced by the patient is removed by a CO₂-absorber and as oxygen is used up by the patient, the volume in the circuit decreases. This decrease is detected and replenished by the calorimeter. In practice, several breaths are needed to measure the mean oxygen uptake. The system will not work if anesthetic gases are used, because if there is an uptake of these gases from the closed breathing circuit, the calorimeter will assume this to be the uptake of oxygen. In our case the patient is replaced by the mechanical lung and the uptake of oxygen is set to a fixed value.
By measuring the mean expired partial pressure of CO$_2$ in a mixing chamber on the expiratory side of the breathing circuit over several minutes, the CO$_2$ production of the lung can be determined. All expired CO$_2$ is produced by the lungs, because no CO$_2$ is present in the inhaled gas mixture. Therefore, the production of CO$_2$ by the lung is equal to the mean expired partial pressure of CO$_2$ multiplied by the minute ventilation of the lungs.

The results of these measurements are listed in appendix A. The measurements were done for an uptake of 150, 250, 350 and 450 ml O$_2$ per minute, with an equal CO$_2$ delivery. All other gas exchanges were fixed at 0 ml/min. The measurements were repeated for a fresh gas flow of 100% oxygen, and a fresh gas flow of air (20% O$_2$ and 80% N$_2$). Using air, the accuracy of the N$_2$ exchange is also tested. N$_2$O and agent exchanges are not tested by these experiments.

From these results we conclude that the lung model has errors of 10% to 20% between the requested and the measured uptake of oxygen and the delivery of carbon dioxide. The errors are not repeatable, and their cause is not yet determined. Although the cause of the errors must be determined and if possible eliminated, the lung model is accurate enough to simulate physiological processes.
3 The uptake and distribution model.

The physiological software model must calculate the gas exchanges that would occur in the lungs of a patient. The uptake and distribution of anesthetic gases involves complex interactions of the pulmonary and cardiac systems. It is not possible to measure real-time gas exchanges in patients under all possible clinical situations and thus, look up tables cannot be used in place of a physiologic mathematical model.

The use of multiple models in describing physiological events has been described [Beneken 1968; Zwart 1972]. The advantage of dividing a physiologic model into several smaller sub-models, is that these models are easier to specifically define and can be tested separately. The physiological software model should consist of an uptake and distribution model to simulate the distribution of gases in the human body, and a pressure flow model to simulate the blood flows in the cardiovascular system. This chapter describes the uptake and distribution sub-model.

The basic form of the uptake and distribution model is similar for all gases (figure 6).
The blood circulates through the pulmonary capillary compartment, the arterial blood compartment, the venous blood compartment, and three capillary compartments. Three capillary and tissue compartments are used to represent the different solubility and blood flow characteristics of different body tissues.

The model can be used to simulate the uptake and distribution of one gas in the human body, but the same general model can be expanded for the five gases (O₂, CO₂, N₂, N₂O, volatile agent) needed for anesthesia simulation. Partition coefficients are used by the general uptake and distribution model to describe the different physical and physiological properties of each gas. A partition coefficient of a gas between two different media is the ratio of the volume concentrations of that gas in these media when they are in equilibrium at a given temperature, usually 37 °C. In the human
body, two equilibrations exist for each gas. The first equilibration exists between alveolar gas and pulmonary capillary blood, and the second equilibration exists between blood and tissue in the capillaries of the tissue compartments.

In describing the uptake and distribution of anesthetic gases, the total body tissue can be divided into four tissue groups [Miller 1986, 628]: the vessel rich group (VRG), the muscle group (MG), the fat group (FG) and the vessel poor group (VPG).

The VRG is composed of the brain, splanchnic bed (including liver), kidneys, and endocrine glands. Muscle and skin make up the MG, and adipose tissue makes up the FG. The last group (VPG), is composed of ligaments, tendons, bone and cartilage. These latter tissues have little or no perfusion, and therefore do not take part, to any significant degree, in the uptake and distribution process. The different characteristics of each tissue group are listed in Table 2.
Table 2. Tissue characteristics (all partition coefficients at 37°C).

<table>
<thead>
<tr>
<th></th>
<th>VRG</th>
<th>MG</th>
<th>FG</th>
<th>VPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>percent of body mass</td>
<td>10</td>
<td>50</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>perfusion as percentage of cardiac output</td>
<td>75</td>
<td>19</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>half-equilibration time for N₂O</td>
<td>1 min.</td>
<td>20 min.</td>
<td>70 min.</td>
<td>--</td>
</tr>
<tr>
<td>half-equilibration time for Halothane and Isoflurane</td>
<td>3 min.</td>
<td>70 min.</td>
<td>20 hrs.</td>
<td>--</td>
</tr>
<tr>
<td>N₂O tissue-blood partition coeff.</td>
<td>1.0</td>
<td>1.2</td>
<td>2.3</td>
<td>--</td>
</tr>
<tr>
<td>HAL tissue-blood partition coeff.</td>
<td>2.6</td>
<td>3.5</td>
<td>6.0</td>
<td>--</td>
</tr>
<tr>
<td>ISO tissue-blood partition coeff.</td>
<td>2.6</td>
<td>4.0</td>
<td>4.5</td>
<td>--</td>
</tr>
<tr>
<td>N₂ tissue-blood partition coeff.</td>
<td>1.0</td>
<td>1.0</td>
<td>5.7</td>
<td>--</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N₂O</th>
<th>HAL</th>
<th>ISO</th>
<th>N₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>air-blood partition coeff.</td>
<td>0.47</td>
<td>2.5</td>
<td>1.4</td>
<td>0.015</td>
</tr>
</tbody>
</table>

where half-equilibration is the time at which the tissue anesthetic partial pressure equals half that in arterial blood.
Using only one capillary and tissue compartment, the following formulae describe the mass-balance equations:

\[ C_t[pulmonary] = \text{function(alveolar partial pressure)} \]  

\[ \text{Volume[arterial]} \times \frac{dC_t[arterial]}{dt} = (C_t[aorta] - C_t[arterial]) \times CO \]  

\[ (\lambda_{bl,t} \times \text{Volume[tissue]} + \text{Volume[capillary]}) \times \frac{dC_t[capillary]}{dt} = (C_t[arterial] - C_t[capillary]) \times CO - \text{Exchange} \]  

\[ \text{Volume[venous]} \times \frac{dC_t[venous]}{dt} = (C_t[capillary] - C_t[venous]) \times CO \]

where \( \lambda_{bl,t} \) is the blood-tissue partition coefficient of the gas in question, \( C_t \) is the volume concentration of the gas in the compartment between square brackets and \( CO \) is cardiac output.

Shunt fraction is the portion of blood flow that bypasses the lungs. The shunt fraction of blood mixes with the pulmonary blood before it enters the arterial blood pool. The shunt fraction is supplied as a constant for each patient in the patient file. The content of the mixed blood (\( C_t[aorta] \)) becomes:

\[ C_t[aorta](t+\Delta t) = C_t[pulmonary](t) \times \{1 - \text{shunt fraction}\} + C_t[venous](t) \times \text{shunt fraction} \]  

A digital computer cannot work with continuous signals. Therefore, continuous signals have to be converted into signals that are discrete with respect to time. This is done by sampling the continuous input signals at fixed time intervals (\( \Delta t \)). The derivatives with respect to time in formulae 4 to 6 will be held equal to the change in the variable divided by the time interval. The derivative in formula 4, for example, is evaluated as:
\[ Ct_{\text{arterial}}(t+\Delta t) = Ct_{\text{arterial}}(t) + \\
((Ct_{\text{aorta}}(t) - Ct_{\text{arterial}}(t)) \times \Delta t \times \frac{CO}{\text{Volume}_{\text{arterial}}}) \] (8)

Formula 4 shows that an increase in aortic content of a certain gas causes the arterial content of this gas to increase. The formulae describing the model form a continuous loop, as does the blood circulation in a patient. This implies that an increase in arterial content results in an increase in aortic content. If the time step (\(\Delta t\)) is too long with respect to the changes in the variables of the model, the system can become unstable. In a human, the physiologic signals that are simulated by the model will not change faster than the breath rate of the patient, which normally is about once every 5 seconds. On the other hand, a minimal value for the time interval is imposed by the time the program needs to update all the variables. The calculation in the physiological model can be done within 1 second on a 8 MHz IBM AT with coprocessor, and therefore, \(\Delta t\) is chosen to be 1 second.

The equilibration of \(O_2\) and \(CO_2\) in the lungs and the tissue can not be described with a partition coefficient as is done for \(N_2O\), \(N_2\), and volatile anesthetic agent. The transportation of \(O_2\) and \(CO_2\) from the lungs to the tissues and back takes place in several different ways. In fact, only a small part of \(O_2\) and \(CO_2\) is transported in the dissolved form.
3.1 O₂-circulation.

The majority of O₂ is transported in blood bound to hemoglobin. The relationship between pulmonary oxygen-hemoglobin saturation (S[pulmonary]O₂) and pulmonary partial pressure of oxygen (P[pulmonary]O₂) is described by the oxygen-hemoglobin dissociation curve (figure 7). This relationship can be described mathematically by the formula given by Kelman [Kelman 1966]. The dissociation curve shifts to the right by increasing pH (Bohr effect), temperature or carbon dioxide content. The pH can be calculated from the carbon dioxide partial pressure (P[pulmonary]CO₂). Kelman first calculates a virtual P[pulmonary]O₂ that would be obtained at a pH of 7.4, a P[pulmonary]CO₂ of 40 mmHg and a temperature of 37 °C:

\[
P[pulmonary]O₂,\text{virt} = P[pulmonary]O₂ * 10^{c1 * (37 - Temp) + c2 * (pH - 7.4) + c3 * (log(40 / P[pulmonary]CO₂))}
\] (9)

where c₁, c₂ and c₃ are constants.

Kelman then converts this virtual P[pulmonary]O₂ into percentage saturation using a standard dissociation formula, with oxygen tension as the only input. Figure 7 shows the dissociation curve as described by Kelman, including the effect that PCO₂ has on the pH as described by formulae 10 and 11 [Guyton 1986, 440].

\[
HCO_3^- = 24 + 0.3 * (PCO₂ - 40)
\] (10)

\[
pH = 6.1 + 10^{\log(HCO_3^- / (0.03 * PCO₂))}
\] (11)

where HCO₃⁻ is the concentration of bicarbonate ion in plasma.
Figure 7. The oxygen-hemoglobin dissociation curve.

We assume that the partial pressure of oxygen in blood that passes through the lungs equals the partial pressure of oxygen in the alveoli.

Guyton gives us a relationship between oxygen-hemoglobin saturation ($S_{O2}$) and oxygen content ($CtO_2$) [Guyton 1986, 497]:

$$CtO_2 \text{ in ml } O_2 \text{ per dl blood} = (1.34 \times Hb \times S_{O2} / 100) + (0.003 \times P_{O2}) \quad (12)$$

where Hb is the content of hemoglobin in g/dl blood and $P_{O2}$ is the partial pressure of $O_2$ in the sample. Hemoglobin content can be approximated by the hematocrit in percent divided by 3. The last part of formula 12 takes care of dissolved oxygen in the blood [Miller 1986, 1134], which is only a small part of the total oxygen content. Using this formula for
the pulmonary compartment, the new $C_{t[pulmonary]}O_2$ can be determined. For the uptake of oxygen by the blood:

$$Uptake[O_2](t+\Delta t) = (C_{t[pulmonary]}O_2(t+\Delta t) - C_{t[pulmonary]}O_2(t))\times\frac{Volume[pulmonary]}{\Delta t} +$$

$$(C_{t[pulmonary]}O_2(t+\Delta t) - C_{t[venous]}O_2(t))\times CO$$

(13)

In the tissue, oxygen is not bound to hemoglobin and exists in a dissolved state. This implies that with an equal partial pressure of oxygen, the oxygen content in the tissue is very low compared to the oxygen content in the blood. Therefore, it is justified to disregard the buffering of oxygen in the tissue and use no tissue compartments for oxygen.

The mass-balance equations of the general model (formulae 4-6), convert into formulae 14-16 for the $O_2$-circulation. From the capillary compartment oxygen is extracted according to the rate of oxygen consumption ($consO_2$).

$$C_{t[arterial]}O_2(t+\Delta t) = C_{t[arterial]}O_2(t) +$$

$$(C_{t[aorta]}O_2(t) - C_{t[arterial]}O_2(t))\times\Delta t\times CO / Volume[arterial]$$

(14)

$$C_{t[capillary]}O_2(t+\Delta t) = C_{t[capillary]}O_2(t) + ((C_{t[arterial]}O_2(t) -$$

$$C_{t[capillary]}O_2(t))\times CO - consO_2)\times\Delta t / Volume[capillary]$$

(15)

$$C_{t[venous]}O_2(t+\Delta t) = C_{t[venous]}O_2(t) +$$

$$(C_{t[capillary]}O_2(t) - C_{t[venous]}O_2(t))\times\Delta t\times CO / Volume[venous]$$

(16)
3.2 CO₂-circulation.

The carbon dioxide dissociation curve describes the content of CO₂ in blood in its three major forms i.e. the dissolved state (7%), the bicarbonate ion (70%) and bound to hemoglobin (23%). The curve shifts to the right with increasing PO₂ (Haldane effect), pH or temperature. Kelman gives a function to calculate CtCO₂ as a function of PCO₂, pH, SO₂, hematocrit and temperature [Kelman 1967]. The result of Kelman’s approximation is shown in figure 8.

The different values of oxygen saturation do not result in significant differences between the curves, and the curves can be approximated by a single straight line. Therefore, we will not use Kelman’s approximation, which is rather computational, but a linear approximation, which does not include the small effects of pH, SO₂, hematocrit
and temperature:

\[ CtCO_2 = 23.37 + 0.66 \times PCO_2 \quad (17) \]

The partial pressure of \( CO_2 \) in the pulmonary capillaries is equal to the alveolar partial pressure of \( CO_2 \), as in the \( O_2 \)-circulation model.

The buffering of carbon dioxide in the tissue cannot be omitted as in the oxygen circulation, because significant amounts of \( CO_2 \) exist in the tissues in the dissolved state and as bicarbonate ion. Tissue \( O_2 \) and \( CO_2 \) exchange can both be explained by passive diffusion, because the diffusion coefficients of \( O_2 \) and \( CO_2 \) are of the same order of magnitude and the solubility coefficient of \( CO_2 \) is about 20 times that of \( O_2 \) at 37 °C. Therefore, there is no tension gradient for \( CO_2 \) in the tissue, and the concentration of dissolved \( CO_2 \) in the tissue is equal to the concentration of dissolved \( CO_2 \) in the plasma. The concentration of bicarbonate ion in the tissue will also be equal to that in the plasma [Miller 1986, 1296].

The only difference between \( CO_2 \) transportation in the blood and in the tissue is the absence of hemoglobin in the tissue, therefore the concentration of \( CO_2 \) in the tissue will be 100% - 23% = 77% of the concentration in the plasma.

\[
1 \quad Ct[capillary]CO_2(t+\Delta t) = (Ct[capillary]CO_2(t) + ((Ct[arterial]CO_2(t+\Delta t) - Ct[capillary]CO_2(t)) \times CO \times \Delta t + prodCO_2 \times \Delta t)) / (Volume[capillary] + 0.77 \times Volume[tissue]) \quad (18)
\]

Table 2 lists the average blood flows through the different tissue compartments.

---

1 In all formulae we use the last calculated variables for each variable. Another approach is to record all variables at the beginning of an iteration loop, and use these variables in the formulae. This method implies that there are no variable(t+\Delta t) in the right part of the formulae.
In the human body these flows are highly dynamic, and depend upon $\text{O}_2$, $\text{CO}_2$ and agent levels in the tissue groups. The total cardiac output also changes continuously. Therefore, a second model must be used to determine cardiovascular pressures and flows.
4 The pressure and flow model.

A cardiovascular pressure and flow model is needed to determine the simulated patient's cardiac output, heart rate and blood pressure. The pressure and flow model must have the following characteristics:

- It must calculate total systemic blood flow and the blood flow and blood pressures the three tissue compartments of the uptake and distribution model.

- It must include the effects of the autonomic regulation, vascular autoregulation and the cardiovascular effects of inhaled anesthetics.

- It must run at least twice as fast as real-time (The other half of the computer time is needed for the uptake and distribution model).

Several cardiovascular pressure and flow models have previously been described. Some of these models simulate real-time blood pressure and flow waveforms [Beneken 1967]. For our purposes, however, the exact waveforms of these signals are not critical. For the purpose of the current simulator scenarios, knowing the systolic, diastolic and mean blood pressures is sufficient. The contour of the blood pressure waveform is shaped by a commercial waveform generator (Datasim 6000, Medical Data Electronics, Arleta CA), which takes systolic blood pressure and heart rate as input.

A model that simulates mean blood flows and pressures has been described by A.C. Guyton [Guyton 1972; Guyton 1980]. Unlike many models designed to simulate specific phenomena, Guyton's model was designed to give a system analysis of the human circulation based almost entirely on experimental data. Therefore, this model can be used to study both normal and abnormal physiological states. Although the model was used by Guyton to study chronic hypertension, which is caused by derangement of long-term (up to several months) pressure control systems, it also
incorporates short-term control systems. We are only interested in these short-term effects, because the anesthesia cases to be simulated last hours rather than days or months. Therefore, by omitting the long-term control systems, the model can be simplified substantially.

**Table 3. Major cardiovascular control systems.**

<table>
<thead>
<tr>
<th>System</th>
<th>Time constant (remarks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Circulatory dynamics</td>
<td>33 min.</td>
</tr>
<tr>
<td>* Vascular stress relaxation</td>
<td></td>
</tr>
<tr>
<td>- Capillary membrane dynamics</td>
<td>(not significant)</td>
</tr>
<tr>
<td>- Tissue fluids, pressures, and gel</td>
<td>several hours</td>
</tr>
<tr>
<td>- Electrolytes and cell water</td>
<td>(not significant)</td>
</tr>
<tr>
<td>- Pulmonary dynamics and fluids</td>
<td>(no lung circulation)</td>
</tr>
<tr>
<td>- Angiotensin control</td>
<td>(not significant)</td>
</tr>
<tr>
<td>- Aldosterone control</td>
<td>(not significant)</td>
</tr>
<tr>
<td>- Antidiuretic hormone control</td>
<td>(not significant)</td>
</tr>
<tr>
<td>- Thirst and drinking</td>
<td>(not significant)</td>
</tr>
<tr>
<td>- Kidney dynamics and excretion</td>
<td>(not significant)</td>
</tr>
<tr>
<td>* Muscle blood flow control and $PO_2$</td>
<td>5 min.</td>
</tr>
<tr>
<td>* Non-muscle oxygen delivery</td>
<td></td>
</tr>
<tr>
<td>* Non-muscle, non-renal local blood flow control-autoregulation</td>
<td>1, 20, 11520 min.</td>
</tr>
<tr>
<td>* Autonomic control</td>
<td>10 sec.</td>
</tr>
<tr>
<td>* Heart rate and stroke volume</td>
<td>immediate</td>
</tr>
<tr>
<td>- Red cells and viscosity</td>
<td>several days</td>
</tr>
<tr>
<td>- Heart hypertrophy and deterioration</td>
<td>40 days</td>
</tr>
</tbody>
</table>

The model is comprised of 18 different major systems that take part in circulatory control (see table 3). The control systems marked with a dash have long-term effects or do not play a significant role in the minute-to-minute determination of blood pressure and flow. Therefore, these systems are omitted from the model. The control systems marked with an asterisk are used in our version of the pressure and flow model. The control systems affect the circulatory dynamics system by means of
multipliers. Each affected variable in the circulatory dynamics system will be multiplied with one of these multipliers. In normal circumstances these multipliers will not affect the circulatory dynamics system, in other words, they are equal to 1. The major systems used in our version of the model are described in the following two paragraphs.

4.1 The circulatory dynamics.

The circulatory dynamics component of the cardiovascular pressure and flow model is the primary controller of the blood pressure and flow. Guyton's model simulates both the pulmonary and the systemic circulation of the blood. The circulatory dynamics can be simplified considerably by omitting the pulmonary blood circulation. This can be done by assuming the blood flow returning from the tissues to be equal to the blood flowing to the lungs, which results in the schematic shown in figure 9.

The total blood volume is distributed among three capacitive compartments: the arterial compartment, the venous compartment and the atrial compartment. Blood pressure in a compartment is calculated from the compartment's difference in current blood volume and unstressed blood volume divided by its capacitance (formula 19). Flow from each compartment to the next compartment is calculated from the blood pressure difference between the compartments, divided by the vascular resistance between the compartments (formula 20).

\[
\text{Pressure}[\text{comp}] = \frac{(\text{Volume}[\text{current}] - \text{Volume}[\text{unstressed}])}{\text{Capacitance}[\text{comp}]} \quad (19)
\]

\[
\text{Flow}[\text{tissue1}] = \frac{(\text{Pressure}[\text{arterial}] - \text{Pressure}[\text{venous}])}{\text{Resistance}[\text{tissue1}]} \quad (20)
\]
The pressure and flow model (PFM) divides the total body tissue in a renal, a muscle and a non-muscle group, whereas the uptake and distribution model (UDM) divides the total body tissue in a vessel rich (VRG), a muscle (MG) and a fat group (FG). The PFM has to supply the UDM with its local blood flows. Therefore, the blood flow through the tissue groups used by PFM has to be translated into the blood flow through the tissue groups used by the UDM. First, the perfusion of the fat group in the UDM is fixed at 6 percent of the total tissue perfusion (see table 2 in chapter 3). Next, the perfusion of the vessel rich group in the UDM is proportional to the sum of the blood flows through the kidney and the non-muscle group in the PFM. Finally the perfusion of the muscle group in the UDM and the PFM are proportional. Thus, the blood flow through a compartment is equal to:
Flow[VRG] = 0.94 \times (\text{Pressure[arterial]} - \text{Pressure[venous]}) \times \\
(1/\text{Resistance[renal]} + 1/\text{Resistance[non-muscle]}) \tag{21}

Flow[MG] = 0.94 \times (\text{Pressure[arterial]} - \text{Pressure[venous]}) / \\
\text{Resistance[muscle]} \tag{22}

Flow[total tissue] = (\text{Flow}[VRG] + \text{Flow}[MG]) \times 100 / 94 \tag{23}

Flow[FG] = \text{Flow}[total tissue] - \text{Flow}[VRG] - \text{Flow}[MG] \tag{24}

where Flow[compartment] stands for the blood flows used in the UDM.

The blood flow generated by the heart (cardiac output) is, in part, determined by the right atrial pressure. This implies that cardiac output is partially regulated by the amount of blood returning to the heart from the peripheral tissues of the body. The relationship between right atrial pressure and cardiac output is called a cardiac function curve (see Figure 10).
Guyton's model does calculate a value for the mean arterial blood pressure (MAP), heart rate (HR) and stroke volume (SV), but does not calculate a systolic or diastolic pressure. To be able to produce a blood pressure waveform with the blood pressure monitor stimulator (Datasim 6000) a value for systolic and diastolic pressure is needed. There is a relationship between stroke volume (SV), which is supplied by Guyton's model, and the pressure rise and fall during systole and diastole [Guyton 1986, 225]. The greater the stroke volume, the greater the amount of blood that is pressed into the arterial tree and therefore, the greater the pressure difference between systole and diastole (pulse pressure). Assuming that the compliance of the arterial tree does not change, the pulse pressure is proportional to the stroke volume (see formulae 25 and 26).
SV = Constant \times \{ \text{Systolic Pressure - Diastolic Pressure} \} \quad (25)

MAP = \{ 2 \times \text{Diastolic Pressure} + \text{Systolic Pressure} \} / 3 \quad (26)

therefore,

\text{Diastolic Pressure} = \frac{\text{MAP} - \text{SV}}{(3 \times \text{Constant})} \quad (27)

\text{Systolic Pressure} = 3 \times \text{MAP} - 2 \times \text{Diastolic Pressure} \quad (28)

With formulae 27 and 28 and the heart rate, which is also determined by the model, a blood pressure waveform can be created by the Datasim.

As contrasted with the circulatory dynamics system, the other control systems can be used without major changes. In the next paragraph the other control systems that are used in our version of the model are described.

4.2 The major control systems.

Vascular stress relaxation

Vascular stress relaxation is one of the methods by which the body can control blood pressure. By straining or relaxing the muscles around the veins, the unstressed volume of the veins can be decreased or increased. Stress relaxation is operated by excess blood volume in the veins, i.e. the current blood volume minus the unstressed blood volume in the veins. The overall response time of this control system is 33 minutes, and if given enough time the system is capable of canceling all increases in venous blood pressure caused by an increase in venous blood volume.

\footnote{The constant used in formula 25 is not really constant for a patient. In a patient this constant is a function of heart rate or more precisely of T_{systolic}.}
**Muscle blood flow control and $PO_2$**

In order to maintain a sufficient oxygen supply to the muscles, muscle blood flow is regulated at the local tissue level. This is done by adjusting the local vascular resistance by closing or opening the capillaries in the muscles (vasodilation). The control system is operated by the oxygen partial pressure in the muscles, and has a time constant of 1.5 seconds.

Oxygen partial pressure ($PO_2$) in the muscle cells is calculated from the $PO_2$ in the muscle capillaries and the $O_2$ utilization by the muscles. The $PO_2$ in the muscle capillaries is a variable that is supplied by the UDM. The $O_2$ utilization by the muscle cells, in turn, is regulated by the autonomic regulation system.

**Non-muscle oxygen delivery**

In the non-muscle oxygen delivery system the partial pressure of oxygen in the cells of the vessel rich group is calculated from the $PO_2$ in the vessel rich capillaries and the utilization of oxygen in this tissue group. The $PO_2$ in the vessel rich capillaries is generated by the UDM. The same autonomic regulator that influences the oxygen utilization in the muscles also influences the oxygen utilization by the vessel rich group. The $O_2$ utilization determined in Guyton's model is used to determine the $O_2$ consumption and the $CO_2$ production in the uptake and distribution model.

**Non-muscle, non-renal local blood flow control-autoregulation**

The blood flow through the vessel rich group can be controlled by changing its vascular resistance (vasodilation). The vasodilation is controlled by the $PO_2$ in the vessel rich group, as calculated in the non-muscle oxygen delivery system. The vasodilation system is composed of a rapid, an intermediate and a long-term effect. The time constants of the three effects are 1, 20 and 11520 minutes. The long-term
effect can be omitted, because we will never model cases longer than 600 minutes.

**Autonomic control**

The autonomic control system calculates the effects that chemoreceptor, baroreceptor and the central nervous system have on vascular compliance, the heart function, peripheral arteriolar vasoconstriction and venous vasoconstriction. First, a general autonomic state is calculated from the arterial pressure, non-muscle, non-renal PO$_2$ and muscle PO$_2$. From this autonomic state, a chemoreceptor output, baroreceptor output, and an output resulting from ischemia of the central nervous system is calculated. The baroreceptor output calculation includes baroreceptor adaptation, with a time constant of 2000 minutes. The three outputs are then combined into an overall autonomic output.

**Heart rate and stroke volume**

The calculation of heart rate and stroke volume includes the effects of autonomic stimulation, right atrial pressure, and cardiac deterioration caused by hypoxia.

**4.3 Iteration interval and timing.**

Some of the variables used in the algorithms of the pressure and flow model are, like the ones in the uptake and distribution model, discrete with respect to time. If the iteration interval ($\Delta t$) used to calculate the derivatives of these variables with respect to time is too long, the system may become unstable when the variables change rapidly. During simulation, the circulatory dynamics system proved stable using an iteration interval equal to or shorter than 0.05 seconds. This was tested by imposing step changes in cardiac output and vascular resistances. In the uncommon situation of severe hypoxia, near the point of cardiac arrest, the pressure and flow model showed
oscillations. All other control systems have time constants longer than 1 second, so these systems will be stable using an iteration interval of 1 second.

The iteration interval for the circulatory dynamics system is 0.05 seconds, whereas the iteration interval of the uptake and distribution model is 1 second. An exchange of variables between the UDM and the PFM takes place every second. Therefore these exchanged variables are only a presentation of the variables at the time of exchange. Since there is no accumulation or depletion of blood in the heart, over a longer period, the differences between the blood flow in the veins and arteries must add up to zero. If we only exchange the blood flow variables once per second, it can not be guaranteed that the differences between the two blood flows will add up to zero. To avoid an increase or decrease in the blood volume because of this difference in iteration interval, venous, arterial and total peripheral blood flow are made equal every time these variables are exchanged with the UDM.

The pressure and flow model and the uptake and distribution model can not yet model an anesthetized patient, because the cardiovascular side effects of anesthetics have not yet been included. These side effects will be described in chapter 5.
The effects of Anesthetics.

Equal potent doses of the different inhaled anesthetics produce a wide and variable range of side effects, especially the cardiovascular parameters. For example, halothane maintains the heart rate and decreases cardiac output, while isoflurane tends to increase the heart rate and maintain the cardiac output. Measurements obtained from volunteers exposed to inhaled anesthetics during controlled mechanical ventilation provided the basis of comparison for pharmacologic effects of these drugs on various organ systems [Eger 1985; Stoelting 1987]. The scale used to evaluate equal potent doses of anesthetics is the minimum alveolar concentration or MAC. MAC is the minimum alveolar concentration of an anesthetic that causes immobility in 50% of patients undergoing surgical incision. In our model we decided to include the effects of nitrous oxide and either halothane or isoflurane because these are the most commonly used anesthetics and halothane and isoflurane are never used at the same time. The MAC of nitrous oxide is 110% and can only be attained in a hyperbaric chamber. The MAC of halothane is 0.75% and, thus, far more potent than nitrous oxide. The MAC of isoflurane changes slightly with age (Table 4) [Eger 1985].

The cardiovascular side effects of anesthetic agents are caused by the agents acting on the vascular smooth muscle and on the heart. Thus, it is the concentration of agent in the vessel rich group which correlates with these cardiovascular side effects. In clinical practice, measuring the concentrations of the anesthetic agent in the vessel rich group is not practical. The alveolar concentrations of anesthetic agents can be easily measured with airway gas analyzers. Because these data correlate well with the blood concentrations, alveolar concentrations can also be correlated with the cardiovascular side effects. In our model, however, the alveolar agent concentrations can change rapidly and, therefore, do not correlate with the agent concentrations in the vessel rich group. Furthermore, the agent concentrations in the vessel rich group are always available in our model. The cardiovascular side effects of anesthetic agents in our model will,
therefore, be a function of the agent concentrations in the vessel rich group. The second column in Table 4, shows the volume concentration of the anesthetic agent in blood that correspond with the MAC of that anesthetic agent.

<p>| Table 4. MAC of nitrous oxide, halothane and isoflurane. |
|------------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Age</th>
<th>MAC (% atm)</th>
<th>matching blood volume conc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous Oxide</td>
<td>110</td>
<td>51.7</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.75</td>
<td>1.875</td>
</tr>
<tr>
<td>Isoflurane (age)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonates</td>
<td>1.60</td>
<td>2.24</td>
</tr>
<tr>
<td>1-6 months</td>
<td>1.87</td>
<td>2.62</td>
</tr>
<tr>
<td>7-11 months</td>
<td>1.80</td>
<td>2.52</td>
</tr>
<tr>
<td>1-2 years</td>
<td>1.60</td>
<td>2.24</td>
</tr>
<tr>
<td>3-5 years</td>
<td>1.62</td>
<td>2.27</td>
</tr>
<tr>
<td>19-30 years</td>
<td>1.28</td>
<td>1.79</td>
</tr>
<tr>
<td>31-55 years</td>
<td>1.15</td>
<td>1.61</td>
</tr>
<tr>
<td>Over 55 years</td>
<td>1.05</td>
<td>1.47</td>
</tr>
</tbody>
</table>

It is impossible to include all drug related effects on the circulation, simply because it is not possible to experimentally measure all these effects. This problem becomes even more complex when we try to determine what exactly causes, for example, the cardiac output to increase. Is it a decrease in vascular resistance, or is it caused by stimulation of the heart, and are these changes caused by the autonomic output, autoregulation or stress relaxation? Therefore a choice has to be made as to which effects will be simulated and how to include these effects in the model.

In the operating room, the anesthesiologist can monitor heart rate, blood pressure and, in some cases, cardiac output. If a closed circuit anesthesia technique is
used, \( O_2 \) consumption can also be measured. These are the variables that should be calculated primarily. Based on this concern and on what experimental data is available [Eger 1985], we choose to mathematically model the anesthetic agent related changes in cardiac output, peripheral vascular resistance, heart rate, arterial blood pressure and metabolism [Eger 1985]. Changes in metabolism cause corresponding changes in \( O_2 \) consumption and \( CO_2 \) production. Therefore, experimental data that describes the effects on \( O_2 \) consumption can be used to describe the effects on metabolism.

The easiest way to impose the desired effects on our circulation model is by using a multiplier to describe the relationship between the anesthetic concentration in the vessel rich group and the observed side effects. The problem with this approach is that we take no account of the control systems in the pressure flow model. These control systems are always trying to cancel any deflection from equilibrium. If, for example, the cardiac output multiplier decreases due to an increasing halothane concentration this also means that the oxygen concentration in the blood and the arterial blood pressure will increase. This, in turn, causes the autonomic system to increase its stimulation of the heart. So even though the agent related multiplier imposes a decrease in cardiac output, the side effect tends to be negated by the autonomic multiplier (control system).

The effect of nitrous oxide on the circulation is small, and is omitted from the model. For halothane and isoflurane, the overall effects on cardiac output, blood pressure, metabolism, peripheral vascular resistance and heart rate are known (see figure 11) [Eger 1985].
These graphs compare the cardiovascular effects as determined by Eger and the results obtained from the pressure flow model. The points in these graphs represent the overall effect of isoflurane including the cardiovascular control systems as simulated by the physiological software model. The effects we are especially interested in, like heart rate, cardiac output, arterial blood pressure and metabolism, are qualitatively correct, but tend to slightly deviate quantitatively from the experimental data. For our
purposes in anesthesia simulation, this approximation is adequate, especially considering the natural difference in drug related effects between different patients. More over, when running simulation scenarios, the model presents realistic cardiovascular data to the simulator user.
6 Initialization of the two models.

Each time the program is started, the physiological software model and the mechanical lung model have to be initialized. The initialization procedure depends on the type of patient to be simulated (see paragraph 6.1), and on the starting conditions of the simulation scenario (see paragraph 6.2).

6.1 Patient dependent parameters.

Physiologic parameters, like the volume of the tissue and blood compartments and the basic metabolic rate differ with each patient. To include some of this diversity in our model, the model can be initialized according to patient dependent variables. These variables are: height, weight, age, sex, tidal volume, dead space and shunt fraction. The patient dependent variables are read from a patient data file, which is specified at the beginning of the program. The format used by the patient description file is fixed and must be followed exactly. To ensure that the format is followed exactly, an existing file template is edited and saved on disk under a new file name.

Tidal volume and dead space are needed to calculate an initial alveolar ventilation in case we decide not to use the hardware lung model, but instead to simulate the hardware components of the model mathematically (i.e. to calculate rather than measure alveolar gas concentrations). The advantage of simulating the lung in software is that simulations can run faster than real-time. This means that if we want to demonstrate the equilibration of the slow compartments, like the fat group, we do not have to wait several hours. Without the hardware lung model, the model is capable of running ten times as fast as real-time on a 8 MHz IBM AT with co-processor.
Height, weight, age, sex and fractional shunt are used to calculate basal metabolism, \( O_2 \) consumption, \( CO_2 \) production, cardiac output, blood and tissue volumes and blood pressures. These parameters are later modified during the simulation by the multipliers and cardiovascular control systems discussed in chapter 4 and 5.

**Metabolism, oxygen consumption and carbon dioxide production**

In order to calculate an initial metabolic rate for a given patient, the formulae and curve given by Guyton are used [Guyton 1986, 847]. First the basal metabolic rate (BMR) as a function of sex and age is calculated. The curve given in figure 12 and formulae 29 through 33, are linear approximations based on statistical data given by Guyton:

![Figure 12. Basal metabolism as a function of sex and age.](image-url)
BMR in cal. per hour per sq. meter. =

\[
\begin{align*}
\text{(0-2)years:} & \quad 51.2 + 0.9 \times \text{age} \\
\text{Male:} \quad \text{(2-20)years:} & \quad 54.68 - 0.84 \times \text{age} \\
& \quad 39.14 - 0.063 \times \text{age} \\
\text{Female:} \quad \text{(2-15)years:} & \quad 55.54 - 1.27 \times \text{age} \\
& \quad 37.48 - 0.066 \times \text{age}
\end{align*}
\]

To get the metabolic rate of a patient, the BMR has to be multiplied by the body surface area (BSA) of the patient. The BSA is calculated as function of weight and height of the patient from formula 34 [Guyton 1986, 848]:

\[
\text{BSA in sq. meter} = \text{weight}_{\text{in kg}}^{0.425} \times \text{height}_{\text{in cm}}^{0.725} \times 0.007184
\]

Thus, the mean metabolic rate at 37 °C (MMR37) can be calculated.

\[
\text{MMR37 in cal. per hour} = \text{BMR} \times \text{BSA}
\]

With every ten degree increase in body temperature, regardless of its cause, the metabolic rate will increase by 120% [Guyton 1986, 847].

\[
\text{MMR(T) in cal. per hour} = \text{MMR37} \times \{1.082(T - 37)\}
\]

For the average diet, the quantity of energy liberated per liter of oxygen consumed is 4.825 calories. Therefore, oxygen consumption can be approximated by:

\[
\text{consO}_2 \text{ in liter per hour} = \frac{\text{MMR(T)}}{4.825}
\]

The ratio of carbon dioxide production to \(O_2\) consumption is the respiratory quotient (RQ). For a person on a typical diet consuming average amounts of carbohydrates, fats and proteins, the value for the RQ is 0.825. So, the carbon dioxide
production can be approximated by:

\[ \text{prodCO}_2 \text{ in liter per sec.} = RQ \times \text{consO}_2 \]  

(38)

**Cardiac output**

Another important patient dependent variable in the model is the cardiac output. The cardiac output is calculated from the cardiac index (ci), the latter is derived from the curve given by Guyton [Guyton 1986, 273]. The curve can be divided into two parts, persons younger and persons older than 5 years. The two parts can be approximated with two second order polynomials (see figure 13 and formulae 39 and 39).

under 5 years:

\[ \text{ci} = -0.077 \times \text{age}^2 + 0.77 \times \text{age} + 2.5 \]  

(39)

over 5 years:

\[ \text{ci} = 2.72E-4 \times \text{age}^2 - 5.05E-2 \times \text{age} + 4.68 \]  

(40)

The cardiac index is multiplied by the body surface area to get the cardiac output.
Blood volume and tissue volumes

An approximation of total blood volume as a function of sex and weight is given in figure 14 [Guyton 1986, 384]. Again the curve is approximated by linear parts, which results in formulae 41-44.
Total blood in liter =

Male: ( <65 kg): \(0.08 \times \text{Weight}\) \hspace{1cm} (41)

( >65 kg): \(1.56 + (0.056 \times \text{Weight})\) \hspace{1cm} (42)

Female: ( <55 kg): \(0.074 \times \text{Weight}\) \hspace{1cm} (43)

( >55 kg): \(4.07\) \hspace{1cm} (44)

The total blood volume is distributed over the different blood compartments. Guyton gives the blood volumes of these compartments as a fraction of the total blood volume:

\[
\begin{align*}
\text{Volume[pulmonary capillaries]} &= 1.4\% \text{ of total [Guyton 1986, 288]} \\
\text{Volume[arteries]} &= 15\% \text{ of total} \\
\text{Volume[tissue capillaries]} &= 5\% \text{ of total} \\
\text{Volume[venous]} &= 64\% \text{ of total [Guyton 1986, 218]}
\end{align*}
\]

From the weight and total blood volume, an approximation of the tissue volumes can be made. The ratio of the different tissue volumes is approximately 10\% vessel rich group, 50\% muscle group, 20\% fat group and 20\% vessel poor group. We assume that the specific gravity of a human body is 1 kg. per liter. Thus, the volume of the tissues equals the total body weight minus the total blood volume of the patient. The volume of each tissue compartment can now be derived from the given ratios.

**Blood pressures**

Finally, the initial systolic, diastolic and mean arterial blood pressure are described by the following formulae [approximation of Guyton 1986, 244]:
Blood Pressure [systolic] = 100 + age  
Blood Pressure [diastolic] = 50 + (age * 0.9375)  
Blood Pressure [mean arterial] = ((2 * BP[diastolic]) + BP[systolic]) / 3

Pressure flow model

After the initial cardiac output and the arterial pressure are calculated according to the patient dependent variables, the resistances and initial volumes of the pressure flow model are chosen to realize these initial conditions. The capacitances and the unstressed volumes of the three compartments are not patient dependent.

6.2 Scenario dependent parameters.

At the beginning of each simulation, the initial alveolar pressures have to be entered by the user. This allows the user to start the model with the alveoli full of air, oxygen or any mixture of anesthetic gas. The gas contents in each body compartment are then calculated at an equilibrated state. This means that the contents of each gas in each compartment is equal to what they would be if the alveolar partial pressures were constant for an infinite period of time. This "flushing" of the compartments can also be used to skip (fast forward) to clinical situations that would take hours to reach in real-time. For instance, if we are only interested in the induction of and emergence from general anesthesia, we can skip the maintenance phase of the anesthetic by re-initializing the patient with the alveolar partial pressures that are expected at the end of the maintenance phase.

After the software model is initialized, the mechanical lung model needs to be initialized. The software model directs the hardware model to fill the lung bellows with the requested initial partial pressures of each gas, until all measured partial pressures are within 10 mmHg of their requested initial values.
The physiologic software model was tested by evaluating its response to changing alveolar gas concentrations such as those seen during the induction of or emergence from general anesthesia. A comparison was made (figure 15) between the response of the physiologic software model with the mechanical lung model, and the physiologic software model with a software lung model (i.e. the fast forward mode of the hybrid lung model). The induction sequence consisted of de-nitrogenation of the lungs with 100% oxygen, followed by the administration of 5% isoflurane plus 65% nitrous oxide in oxygen. For emergence, the isoflurane and nitrous oxide were discontinued and 100% oxygen was given.

The first difference observed between the two models is that the software lung model does not simulate the changes in alveolar partial pressures that occur with each ventilatory cycle. The software lung model calculates the mean gas exchange rates between the pulmonary capillaries and the alveoli. Thus, the graphs from the software lung model are smooth while those from the mechanical lung model contain small ventilatory oscillations. These are caused by fresh gas diluting the alveolar gas during inspiration, and accumulation of the alveolar gases during the respiratory pause.

Another difference between the two lung models is the sudden apparent inflow of \( N_2 \) in the alveoli at the start of the emergence phase in the mechanical lung model. This artificial measurement of \( N_2 \) is caused by the slow response of the polarographic \( O_2 \) sensor. The partial pressure of \( N_2 \) in the alveoli is not measured by the gas analyzer, but calculated from the difference in atmospheric pressure and the sum of partial pressures of the measured gases (\( O_2, CO_2, N_2O \) and agent). During a rapid increase in the partial pressure of \( O_2 \), the measured \( O_2 \) partial pressure will lag behind the real pressure. The difference in real and measured partial pressure of oxygen is added to the partial pressure of \( N_2 \). This error can be avoided by using a faster paramagnetic \( O_2 \) sensor.
In chapter 2, it was mentioned that the relationship between duty cycle of the solenoid valve and the gas flow through the valve is not entirely linear. Although this is only a minor error, it can easily be avoided by introducing a calibration table for this relationship to the software that drives the solenoid valves. This may further improve the agreement of the hybrid model (with mechanical lung) and the software calculations.
**Figure 15.** Induction and emergence, simulated with and without the mechanical lung.
The gas analyzer has an autozero function that is automatically executed every hour. The autozero function is needed, because contaminants (e.g. secretions) in patient samples can accumulate in the optical detectors of the analyzer and thus, offset the zero baseline of the gas analyzer. The autozero function is used to compensate for this offset. During the autozero, the gas concentrations on the display and on the analog output port decrease rapidly and no longer represent the concentrations in the sample. Although the autozero function can not be disabled, most of the negative effects of autozero can be avoided by the use of a faster paramagnetic O_2 sensor.

The fast forward mode of the physiologic model, i.e. running simulations faster than real-time using the software lung model, was originally developed as a debugging tool for the physiologic software model, until the mechanical lung model became available. However, the fast forward mode proved to be helpful for the simulation of long scenarios. One problem, though, was that the software model of the lung and the anesthesia machine had to be made more realistic to be used for fast forward simulations.

The model can simulate the uptake and distribution of five gases simultaneously. Either isoflurane or halothane can be used as the volatile agent, because of similar vapor pressures. The physiologic software model is modified by changing the partition coefficients. It is more difficult to change the model so that it will simulate the cardiovascular side effects of the different agents. With sufficient experimental data, however, a good approximation of these effects can be made. In addition to the cardiovascular effects of inhaled anesthetic agents, the effects of other drugs, e.g. intramuscular or intravenous drugs, can be included in a future version of the model.

One control system that could be included in a new version of the physiologic software model is the cardiovascular effects of CO_2. These effects are of importance in scenarios that result in hyper or hypocapnia.
In summary, the physiologic software model responds like a real patient in the scenarios that were tested. This does not mean that the model will behave correctly in all possible scenarios. If the lung model does not behave correctly for a new scenario, this can be caused by an error in one of the existing cardiovascular control systems, or by the absence of one or more other control system (for example, CO$_2$ related cardiovascular effects). If the misbehavior is caused by the absence of one or more control systems, extending the model with one or more new control system should be considered.

The new patient model results in a far more realistic simulation of the anesthesia work station than anesthesia simulators up to now. For the trainee, there is hardly any difference with the real operating room. The current patient model correctly simulates most common and uncommon clinical situations and gives a firm basis for future expansions.
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APPENDIX A  
Mechanical lung model measurements.

<table>
<thead>
<tr>
<th>set rate O₂ consumption and CO₂ production</th>
<th>measured rate of O₂ consumption in 100% O₂ air</th>
<th>measured rate of CO₂ production in 100% O₂ air</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>155</td>
<td>161</td>
</tr>
<tr>
<td>150</td>
<td>186</td>
<td>155</td>
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<td>459</td>
</tr>
<tr>
<td>450</td>
<td>475</td>
<td>483</td>
</tr>
</tbody>
</table>

All values in ml/min, and are the mean of three different trials.
APPENDIX B  Flow diagram of the software model

Figure 16. Flow diagram of the patient simulator.
APPENDIX B

patient file *.pat

Purpose

The patient description file contains the patient characteristics. These characteristics are used during the initialization to calculate metabolic rate, cardiac output, blood volume, blood pressure, heart rate and MAC-levels.

Format

*.pat =

"Height [in] = " float "CR"
"Weight [kg] = " float "CR"
"Age [years] = " integer "CR"
"Sex [ 0=fem, 1=mal ] = " integer "CR"
"Tidal volume [l] = " float "CR"
"Dead space [l] = " float "CR"
Fractional shunt [] = float "EOF"

integer = digit {digit}.
float = digit [",", digit {digit} ].
digit = "0" .. "9".

Description

The shunt fraction is the fraction of the blood that does not pass through the lungs, and therefore does not reach equilibrium with the alveolar gases.
APPENDIX B

Example

pat1.pat:

Height [in] = 70.000
Weight [kg] = 70
Age [years] = 40
Sex [ 0=fem, 1=mal ] = 1
Tidal volume [l] = 0.50
Dead space [] = 0.150
Fractional shunt [] = 0.0300
<EOF>
APPENDIX B

scenario file *.scn

Purpose

In fast forward mode, the program simulates the mechanical lung model and the anesthesia machine. The settings of the mechanical lung and the anesthesia machine can be changed during simulation, using this file as a controller.

Format

*.scn = { act } "EOF"

act = commentstring"CR" {Setting}

commentstring = "*" string.

Setting = "Fi[CO2] = " float "CR" | "Fi[O2] = " float "CR" |
          "Fi[N2] = " float "CR" | "Fi[N2]O = " float "CR" |
          "Fi[AGE] = " float "CR" | "fgf = " float "CR" |
          "CO = " float "CR" | "Avent = " float "CR" |
          "T = " float "CR" | "Duration = " long integer.

long integer = digit {digit}.

float = digit [ "." digit {digit} ].

digit = "0" .. "9".

string = { character } "CR".

character = "a" .. "z" | "A" .. "Z" | " " | "." | "," | digit.

Description

The order in which the new variables are listed does not matter. Only variables that are changed need to be listed.
APPENDIX B

Example

hypoxia.scn:

* start with room air.
Fi[CO2] = 0
Fi[O2] = 0.2
Fi[N2] = 0.8
Duration = 300

* start with hypoxia.
Fi[N2] = 0.9
Fi[O2] = 0.1
Duration = 600
<EOF>
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