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ABSTRACT

A Multicompartmental Model for the Simulation of Soluble Gas Exchange in the Lungs

by
Chitaranjan Varadhan

A dynamic multicompartmental model for respiratory exchange of soluble gas is described. The motivation for this new model is the continuing interest in estimating pulmonary system parameters during anesthesia and under diseased conditions.

Here a four compartment model for the blood-tissue gas exchange is described, which will be coupled to a whole body hemodynamic model developed earlier. With this pulmonary model we can simulate the pharmacokinetics of inhaled anesthetic agents at any instant of time. Simulations are computed using the TUTSIM software package. Values for the physiological parameters used in the simulation are estimated from standard physiological sources. Where necessary, parameter values reported for animal studies were adjusted to reflect normal human physiology.

A MULTICOMPARTMENTAL MODEL FOR THE SIMULATION OF SOLUBLE GAS EXCHANGE IN THE LUNGS

by

Chitaranjan Varadhan

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A Multicompartmental Model for the Simulation of

Soluble Gas Exchange in the Lungs

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This thesis is dedicated to my Parents

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CHAPTER 1
INTRODUCTION

The lung is exquisitely designed to facilitate gas exchange. Its prime function is to allow oxygen to move from the air into the venous blood and carbon dioxide to move in the opposite direction. The lung does other jobs as well. It metabolizes some compounds, filters toxic materials from the circulation, and acts as a reservoir for blood. But its cardinal function is gas exchange.

Exchange of gases such as oxygen in the lungs involves several physico-chemical processes:

a. Convective transport in the conducting pathways on the gas side of the lungs.

b. Molecular diffusion in the gas phase in the conducting pathways and alveoli on the gas side of the lungs.

c. Molecular diffusion across the surfactant layer and tissue space between the gas side and blood side of the lungs.

d. Possibly uptake by specialized transporters on the blood side of the lungs (e.g. hemoglobin transport of O_2 and CO_2 in the red cell).

e. Convective transport of the gas by the blood stream and distribution of the gas in various organs and tissues.

If the gas is soluble in lung tissue, blood or any other tissue or is metabolized at a particular site, these processes must also be taken into account. Inspiration, excretion, uptake and metabolism are spatially and temporally separated phenomena. Convective transport (blood flow) is the process that allows coupling among these processes and the proper physiological functioning of all organs and tissues, since they are each dependent on gas exchange.

A model of the lung involves three distinct elements.

a. Pulmonary Mechanics. This is a mathematical description of the mechanical motion of chest wall and abdomen or diaphragm to achieve inspiration and expiration of the tidal volume of gas.

The Diaphragm is the most important muscle of inspiration. This consists of a thin dome-shaped sheet of muscle which is inserted into the lower ribs. When it contracts, the abdominal contents are forced downward and forward, and the vertical dimension of the chest cavity is increased. In addition the rib margins are lifted and moved out, causing an increase in the transverse diameter of the thorax. In normal tidal breathing, the level of the diaphragm moves about 1 cm or so, but on forced inspiration and expiration, a total excursion of up to 10 cm may occur. When the diaphragm is paralyzed, it moves up rather than down with inspiration because the intrathoracic pressure falls.

b. Transport Function. This is a mathematical description of gas transport from inspiration/expiration through the conducting vessels, into the alveoli, exchange across the lung tissue, uptake by the blood and distribution throughout the various organ and tissue compartments.

The transfer of gas across the blood-gas barrier occurs by diffusion. Diffusion through tissues is described by Fick's law. This states that the rate of transfer of gas through a sheet of tissue is proportional to the tissue area and the difference in gas partial pressure between the two sides and inversely proportional to the tissue thickness. The area of the blood-gas barrier is enormous and barrier thickness is of the order of 1 micron, so the dimensions of the barrier are ideal for diffusion. In addition, the rate of transfer is proportional to a diffusion constant which depends on the properties of the tissue and the particular gas. The constant is proportional to the square root of the molecular weight. This means that CO_2 diffuses about 20 times more rapidly than O_2 through the tissue sheet since it has much higher solubility and similar molecular weight.

c. Regulation of Respiration. This is a mathematical description of those factors such as exercise, increased organ metabolism or pathologies which act to change the rate

and depth of respiration (Ventilation) through neural pathways (e.g. peripheral chemoreceptors).

Expiration is passive during normal quiet breathing. The lung and chest wall are elastic and tend to return to their equilibrium position after being actively expanded during inspiration. During exercise and voluntary hyperventilation, expiration becomes active. The most important muscles of expiration are those of the abdominal wall, including the rectus abdominus, internal and external oblique muscles, and transversus abdominus. When these muscles contract, intra-abdominal pressure is raised, and the diaphragm is pushed forward. They also contract forcefully during coughing, vomiting and defecation.

1.1 Review of Models

The uptake of oxygen occurs in one particular organ, the lung, and the oxygen is carried by the arterial blood from the site of uptake to the site of consumption, the tissues. The situation concerning the release of oxygen to and its consumption by the cells in various tissues and organs is much more complicated in so far as there are many kinds of tissue with widely different characteristics. Experimental studies of tissue oxygen supply and demand are numerous but have met with many methodological difficulties and are often not easy to interpret. This is the reason why numerous investigators have taken recourse to modeling and mathematical analysis of tissue oxygen supply and demand.

Kety et al.(1951)[1] developed a dynamic model for respiratory exchange of blood soluble gas, which was based on a well known mathematical model of soluble gas exchange. It was developed as a quantitative description of the pharmacokinetics of inhaled anesthetic agents. Most of its applications, therefore, have addressed the time course of anesthetic uptake with specific attention to concentration in body tissues. The validity of the model for this purpose, as well as for the related problem of inhalation exposure to environmental vapors, has been well established. However, its suitability as

a basis for a pulmonary perfusion was poorly established. Also, his work described the uptake and distribution of an inhaled gas in terms of an equation which is relatively simple but which gives an imperfect fit to experimental data. This is because it assumes in effect that the blood flow per unit volume of tissue is the same throughout the body.

The model developed by Jenkins et al.(1989)[2] described a general treatment of tidal breathing, in an inhomogeneous lung comprising distensible compartments, and multiple-gas effects. Here the lung was modeled as a set of parallel homogeneous distensible ideal mixing chambers(alveoli), each ventilated through a common series dead space and perfused by a blood flow that is constant within a breath. The body was modeled as a homogeneous ideal mixing chamber(tissue compartment), perfused by a blood flow that is constant within a breath. According to this model, each lung compartment received a constant fraction of the total inspired volume from one breath to another. Hence estimation of the distribution of ventilatory flow to the various lung compartments and changes thereto is a difficult problem.

In the model presented by Mapleson (1963)[3] the body is divided into the lungs and a number of tissue compartments such that the blood supply per unit volume is the same throughout each compartment. In this model, ventilation is regarded as continuous instead of cyclic. Failure to consider the effects of cyclic breathing may result in significant errors in the determination of cardiac output. Also in this model the Ostwald tissue-to-gas partition coefficient, which may be defined as the ratio between the volume of agent contained in an equal volume of gas with which the tissue is in equilibrium, for any tissue for any gas, or other agent, is assumed to be independent of concentration. This assumption will generally cease to be true if the concentration is high enough.

The 18-compartment hybrid computer multiple model developed by Fukui et al.(1981)[4] for the uptake and distribution of halothane is the basis of our present study. This study uses 88 equations and 124 parameter settings which is very complicated and cumbersome to use.

Krogh in association with Danish mathematician Erlang in 1919, developed a theoretical mathematical model for the analysis of tissue oxygen supply (Kreuzer, 1982)[5]. The Krogh-Erlang model is based on a number of simplifying and often unrealistic assumptions. There is an impressive list of 15 assumptions, which in turn raises the question as to how realistic and meaningful the calculations according to the Krogh model might be. For example, one assumption is that of homogeneous oxygen consumption. On the microscopic level there are always discontinuities in the tissue in that the mitochondria are the discrete oxygen sinks. This assumption implies that these minute sinks are evenly distributed in the volume of the tissue. However, the mitochondria must also be viewed in their relationship to the capillaries. Mainwood and Rakusan(1982)[27] showed that when the mitochondria are clustered around the capillaries, the Krogh cylinder radius shrinks from the anatomical value to that of the cluster. These authors assumed a lattice of 30-micrometer cells with a 1:1 cell to capillary ratio and a mitochondrial aggregation within 3-micrometers from the capillaries. They calculated a necessary oxygen pressure gradient of 24 mmHg for an homogeneous mitochondrial distribution as against 7.9 mmHg in the presence of mitochondrial aggregation. Thus, in the latter case the capillary oxygen pressure required for an adequate oxygen supply to the tissue was reduced to one third of that in the homogeneous situation.

A model of pulmonary transport was developed by Borovetz et al.(1981)[6] in which the lung is assumed to consist of four parallel tissue layers. Using a finite difference representation of the governing equations, the concentration distribution of Xenon gas in each of the layers of tissue is obtained for a step change in the Xe concentration in the inspired air space. Although this model gives good agreement with the experimental values it is a bit complicated, i.e. simulation could have been made simpler by using ordinary differential equations rather than partial differential equations.

A one compartment, continuous-time model was proposed for investigation of dynamic gas exchange in the lungs, by Poon et al.(1981)[7]. The main purpose of this

investigation was to demonstrate quantitatively and analytically the underlying mechanism responsible for the concentration and second gas effects during dynamic gas exchange in the lungs. In view of the complexity of the system, several simplifying assumptions were made to facilitate analysis and computation. For example, the effects of dead space ventilation and perfusion, and the storage capacity of lung tissue have been neglected. Likewise, the nonlinear dissociation characteristics of O_2 and CO_2 had been approximated in a linear fashion. Due to these assumptions it should be recognized that the model is unlikely to be applicable to clinical conditions which are characterized by extreme ventilation-perfusion maldistribution or by a significant diffusion limitation across the lungs.

A general dynamic model of ventilation, perfusion, and mass transfer in the lung has been developed by S.A.Barton et al.(1988)[8], as the theoretical basis for a clinical technique for monitoring on a continuous basis pulmonary performance in terms of the distribution of ventilation and perfusion through the lung. A set of describing equations has been set down with due regard to the conceptual modelers and experimental workers of the past in the field. But this is of no practical use. Before the model can be used as the basis of clinical measurements it must be tested experimentally. Its description and predictions must be compared with experimental observations in a suitable animal or human model. In addition, it must be determined what measurements of clinical interest can be made using the model, and how much the model can be simplified if it is still to yield useful information. If the working model is simple and can be described quantitatively by a small number of parameters then a small number of measurements will be required to yield those parameters. Another drawback of this model is that it does not address the general problem of multiple soluble gas exchange in parallel arrangement of tidally ventilated distensible ideal mixing boxes.

While most analyses of pulmonary gas exchange are based on models in which all of the abnormalities are taken to occur on a parallel basis, the possibility that series

inhomogeneity may be of significance has received serious consideration in recent years. P.D.Wagner and J.W.Evans (1977)[9] developed conditions for equivalence of gas exchange in series and parallel models of the lung. The Fick principle was applied to series and parallel compartmental lung models to determine whether conditions existed under which their differentiation was theoretically possible. Respiratory and inert gases were examined under assumptions of steady-state gas exchange, continuous ventilation and blood flow, perfect mixing within each compartment and alveolar-endcapillary diffusion equilibration. All of these analyses gave us invaluable information for our multiple compartmental model for soluble gas exchange.

Although the uptake and distribution of soluble gases in the lungs have been modeled by several workers, the characterization of the associated system dynamics has received little attention. This led us to develop a multicompartmental model with lesser number of equations and parameters for gas exchange and system dynamics in the lungs. The advantage of this model is that all parameters required for dynamic simulation can be estimated from standard physiological reference materials.

1.3 Terms and Definitions

1.3.1 Anatomic Dead Space and Alveolar Ventilation.

The volume of air entering and leaving the nose or mouth per minute, the minute volume, is not equal to the volume of air entering and leaving the alveoli per minute. Alveolar ventilation is less than the minute volume because the last part of each inspiration remains in the conducting airways and does not reach the alveoli. Similarly, the last part of each expiration remains in the conducting airways for several anatomic reasons. First, the walls of the conducting airways are too thick for much diffusion to take place; and next, mixed venous blood does not come into contact with air. The conducting airways are, therefore, referred to as the anatomic dead space. The anatomic dead space plus the alveolar dead space is known as the physiological dead space.

Thus for any respiratory cycle, not all of the tidal volume reaches the alveoli because the last part of each inspiration and expiration remains in the dead space. The relationship between the tidal volume (V_T) breathed in and out through the nose or mouth, the dead space volume (V_D), and the volume of gas entering and leaving the alveoli per breath (V_A) is

$$V_A = V_T - V_D$$

By multiplying both sides of the above equation by the breathing frequency (n) in breaths per minute,

$$n(V_A) = n(V_T) - n(V_D)$$

This means that the alveolar ventilation ($\dot{V}_A$) in liters per minute is equal to the minute volume ($\dot{V}_E$) minus the volume wasted ventilating the dead space per minute ($\dot{V}_D$).

$$\dot{V}_A = \dot{V}_E - \dot{V}_D$$

Where: $\dot{V} = nv$

1.3.2 Partial Pressures of Respiratory Gases.

According to Dalton's law, in a dilute gas mixture, the pressure exerted by each individual gas in a space is independent of the pressures of other gases in the mixture. The partial pressure of a particular gas is equal to its fractional concentration times the total pressure of all the gases in the mixture. Thus for any gas, a, in a mixture its partial pressure

$$Pa = \% \text{ of total gas} \times P_{total}$$

Oxygen constitutes 20.93% of dry atmospheric air. At a standard barometric pressure of 760 mmHg

$$PO_2 = 0.2093 \times 760 \text{ mmHg} = 159 \text{ mmHg}$$

Carbon dioxide constitutes only about 0.04% of dry atmospheric air, and so

$$PCO_2 = 0.0004 \times 760 \text{ mmHg} = 0.3 \text{ mmHg}$$

1.3.3 Airway Resistance

Generally, the relationship between Pressure, Flow and Resistance is stated as

$$\text{Pressure Gradient} = \text{Flow} \times \text{Resistance}$$

Therefore,

$$\text{Resistance} = \frac{\text{Pressure Gradient (cm } H_2O)}{\text{Flow (liters/s)}}$$

This means that resistance is a meaningful term only during flow. When airflow is considered, the units of resistance are usually cm H_2O/liter/s.

The resistance to airflow is analogous to electrical resistance in that resistance in series add as sums:

$$R_T = R_1 + R_2 + \ldots$$

Resistances in parallel add as reciprocals:

$$1/R_T = 1/R_1 + 1/R_2 + \ldots$$

1.3.4 Compliance of the lung and chest wall

The slope between two points on a pressure-volume curve of a vessel or organ is known as the compliance of that vessel or organ. Compliance is defined as the change in volume divided by the change in pressure. It is important to remember that compliance is the inverse of elasticity or elastic recoil. Compliance denotes the ease with which something can be stretched or distorted; elasticity refers to the tendency for something to oppose stretch or distortion, as well as to its ability to return to its original configuration after the distorting force is removed.

Compliance of the lung and chest wall provides useful data for the clinical evaluation of a patient's respiratory system, because many diseases or pathological states affect either the compliance of the lung or chest wall or both. The lung and chest wall are physically in series with each other and therefore their compliances add as reciprocals:

$$\frac{1}{\text{Total Compliance}} = \frac{1}{\text{Compliance of the lung}} + \frac{1}{\text{Compliance of the chest wall}}$$

CHAPTER 2
METHODS AND MATERIALS

The objective of this study is to develop a lung model for soluble gas exchange which will allow us to quantitatively estimate the pharmacokinetics of inhaled anesthetic agents.

2.1 Compartmental Model

Theoretically, a compartmental description of a distributed process such as gas exchange/distribution would require many (non-unique) arrangements of series/parallel compartments to provide accurate quantitative assessment. In practice, however, values for many of the parameters in such a model and estimates of initial and boundary conditions would be unavailable. With this in mind, we have used a four compartment model for the blood-tissue exchange with the following elements. On the blood side we have the right ventricles feeding the pulmonary artery which feeds three zones (lower one third, middle one third and upper one third) of pulmonary capillaries and a small shunt flow. This is collected by the pulmonary veins and drained into the left ventricle. On the gas side, we have the airways, the trachea and the alveolar ducts. The airways consist of a series of branching tubes which become narrower, shorter and more numerous as they penetrate deeper into the lung. The trachea divides into right and left main bronchi, which in turn divide into lobar, then segmental bronchi. This process continues down to the terminal bronchioles, which are the smallest airways without alveoli. All these bronchi make up the conducting airways. Their function is to lead inspired air to the gas exchanging regions of the lung. Since the conducting airways contain no alveoli and therefore themselves take no part in gas exchange, they constitute the anatomic dead space. According to the rule of thumb, the amount of gas in ml which remains in the dead space is equal numerically to the total body weight in pounds. In our model it is assumed to be 150 ml (standard body weight of 70 kg).

The terminal bronchioles divide into respiratory bronchioles which have occasional alveoli budding from their walls. Finally, we come to the alveolar ducts completely lined with alveoli. This alveolated region of the lung where the gas exchange occurs is known as the respiratory zone, which makes up most of the lung. Blood-airway gas exchange only takes place in the alveolar-capillary zones.

In our model the capillaries and the alveoli are divided into three compartments corresponding to the 3 physiological zones of the lung[14] to get a better quantitative assessment of gas transport. Mass balances for soluble gas exchange are written for each of the compartments. Parameters and initial conditions for each of the mass balance equations were estimated from various sources[17-25]. Respiratory mechanics were simulated by a periodic function which described inspiratory and expiratory pressure and flow around normal tidal volume.

The equations were solved on a personal computer using the TUTSIM simulation language.

2.2 Development of the Model

The first step in the development of any model is to define our problem, i.e. to identify what we exactly want to do. For example, in our case we are trying develop a multicompartmental model for soluble gas exchange in the lungs. This involves several steps and procedures. These are described in detail below.

2.2.1 Mass Balance Equations

Mass balance equations for soluble gas exchange were written (see Chapter 3) for:

(a) Blood flow in the three capillary zones perfusing the alveoli.

(b) Blood side soluble gas exchange in the three capillary zones.

(c) Alveolar side soluble gas exchange in the three zones.

(d) Soluble gas exchange in the large airways, dead zone, pulmonary venous systems and pulmonary arterial system.

(e) Shunt flow.

2.2.2 TUTSIM Block Diagrams

Block diagrams (see Appendix II) for all of the above models were constructed so as to comply with the requirements of TUTSIM. The functions of the blocks used as well as commands used are listed in Appendix II.

2.2.3 Model Data

Parameters and Initial conditions were extracted from standard physiological references (Particularly references numbered 11-20). All parameters and initial conditions are listed in Chapter 3.

2.2.4 Model Simulation

The model output was simulated on a personal computer using the TUTSIM simulation language. The results are shown in Appendix I.

2.3 TUTSIM

TUTSIM simulation software allows the user to simulate the time response of a process which consists of coupled sets of ordinary differential equations without programming a numerical integration algorithm.

It is a very simple simulation program designed to give transient, time response of linear or non-linear systems. It also has a very simple block diagram syntax. It has 93 defined blocks. Only a few of them are used in our model. The function of all these 93 blocks of TUTSIM and the commands are listed in APPENDIX I. Also, when need arises for functions beyond the capability of TUTSIM, we can write our own functions in C language or FORTRAN and assign it to the USR blocks of TUTSIM.

TUTSIM block diagrams may be written from the equations term by term, or sometimes by direct inspection of the real system.

The flow is simply:

Problem:—>Mathematical Model—>Block Model—>Results

Model parameters such as the initial values of an integration are easily entered and changed. Results are usually time dependent values and are available in graphical display or numerical tables on the screen.

ADVANTAGES OF TUTSIM

The advantage of TUTSIM is that:

1. It is supplied as a run module that can be executed on the IBM compatible class of computers.
2. We can use particular input functions derived from experimental data (ASCII format) for the simulations.
3. We can estimate the parameters from published data.

4. Any or all blocks may be monitored or changed in the course of simulation and the simulation may also be frozen at any moment and interrogated for their output values at that moment.

5. The core of TUTSIM is written in Assembly Language. This allows for the fastest possible program execution and thus achievement of "continuous simulation" of real time systems.

6. It has the convenience of an analog computer and the speed and accuracy of a digital computer.

The only drawback of TUTSIM is its poor graphical resolution.

The most common output of TUTSIM is the graphical output to the screen. Printer plots can be made from the screen output or results may also be sent to a file (ASCII format).

Figures 7-11 show the block diagram used in the simulation.

CHAPTER 3

SIMULATIONS AND RESULTS

3.1 Mass Balance Equations

3.1.1 Mass Balance Equation for Blood Flow

$$\frac{dP_{pc_1}}{dt} = \frac{[P_{pa}-P_{pc_1}]}{C_{pc_1} * R_{pc_1(a)}} - \frac{[P_{pc_1}-P_{pv}]}{C_{pc_1} * R_{pc_1(v)}}$$

$$\frac{dP_{pc_2}}{dt} = \frac{[P_{pa}-P_{pc_2}]}{C_{pc_2} * R_{pc_2(a)}} - \frac{[P_{pc_2}-P_{pv}]}{C_{pc_2} * R_{pc_2(v)}}$$

$$\frac{dP_{pc_3}}{dt} = \frac{[P_{pa}-P_{pc_3}]}{C_{pc_3} * R_{pc_3(a)}} - \frac{[P_{pc_3}-P_{pv}]}{C_{pc_3} * R_{pc_3(v)}}$$

3.1.2 Mass Balance Equation for Blood Side Soluble Gas Exchange

$$\frac{dP_{po_2\,c_1}}{dt} = \frac{F_1[P_{po_2\,a} - P_{po_2\,v}] - PS_{o_{21}}[P_{po_2\,c_1} - \gamma_1 P_{po_2\,al_1}]}{C_{pc_1} * P_{t_1}}$$

$$\frac{dP_{po_2\,c_2}}{dt} = \frac{F_2[P_{po_2\,a} - P_{po_2\,v}] - PS_{o_{22}}[P_{po_2\,c_2} - \gamma_2 P_{po_2\,al_2}]}{C_{pc_2} * P_{t_2}}$$

$$\frac{dP_{po_2\,c_3}}{dt} = \frac{F_3[P_{po_2\,a} - P_{po_2\,v}] - PS_{o_{23}}[P_{po_2\,c_3} - \gamma_3 P_{po_2\,al_3}]}{C_{pc_3} * P_{t_3}}$$

3.1.3 Mass Balance Equation for Alveolar Side Gas Exchange

$$\frac{dP_{po_2\,al_1}}{dt} = \frac{Q_{i_1} * P_{po_2(LA)} - Q_{e_1} * P_{po_2\,al_1} + PS_{o_{21}}(P_{po_2c_1} - \gamma_1 P_{po_2\,al_1})}{C\,al_1 * Pt\,al_1}$$

$$\frac{dP_{po_2\,al_2}}{dt} = \frac{Q_{i_2} * P_{po_2(LA)} - Q_{e_2} * P_{po_2\,al_2} + PS_{o_{22}}(P_{po_2c_2} - \gamma_2 P_{po_2\,al_2})}{C\,al_2 * Pt\,al_2}$$

$$\frac{dP_{O_2\,al_3}}{dt} = \frac{Q_{i3} * P_{O_2}(LA) - Q_{e3} * P_{O_2\,al_3} + PS_{O23}(P_{O_2 c3} - \gamma_3 P_{O_2\,al_3})}{C_{al_3} * Pt_{al_3}}$$

3.1.4 Shunt Flow

$$\frac{dPpo2_{sh}}{dt} = \frac{F_{sh} * Ppo2(a)}{C_{sh} * Pt_{sh}}$$

3.1.5 Gas Exchange in Large Airways

$$\frac{dP_{O_2}(LA)}{dt} = \frac{Qi(LA)\,[P_{O_2}(DZ) - P_{O_2}(LA)] - Qe(LA)\,[P_{O_2}(LA) - \gamma_1 * P_{O_2\,al_1} - \gamma_2 * P_{O_2\,al_2} - \gamma_3 * P_{O_2\,al_3}]}{C_{al_1} * Pt_{al_1}}$$

3.1.6 Gas Exchange in Dead Zone

$$\frac{dP_{O_2}(DZ)}{dt} = \frac{Qi[P_{O_2}(Room) - P_{O_2}(DZ)] - Qe[P_{O_2}(DZ) - P_{O_2}(LA)}{C_{DZ} * P_{DZ}}$$

3.1.7 Gas Exchange in Pulmonary Veins

$$\frac{dP_{O_2\,v}}{dt} = \frac{F_{10} * P_{O_2}\,C_1 + F_{20} * P_{O_2}\,C_2 + F_{30} * P_{O_2}\,C_3 - FPV * P_{O_2\,v} + Fsh * P_{O_2\,a}}{Cv * Ptv}$$

3.1.8 Gas Exchange in Pulmonary Arteries

$$\frac{dP_{O_2\,a}}{dt} = \frac{F_{RV} * P_{O_2\,RV} - Fa * P_{O_2\,a}}{Ca * Pta}$$

3.2 Parameters and Initial Conditions

3.2.1 Pulmonary Blood Flow

$Rpc_1(a)$ = Pulmonary Capillary Resistance in the arterial side of Zone 1 = 2.5 mmHg/ml-sec

$Rpc_1(v)$ = Pulmonary Capillary Resistance in the venous side of Zone 1 = 2.0 mmHg/ml-sec

$Rpc_2(a)$ = Pulmonary Capillary Resistance in the arterial side of Zone 2 = 1.8 mmHg/ml-sec

$Rpc_2(v)$ = Pulmonary Capillary Resistance in the venous side of Zone 2 = 1.7 mmHg/ml-sec

$Rpc_3(a)$ = Pulmonary Capillary Resistance in the arterial side of Zone 3 = 1.7 mmHg/ml-sec

$Rpc_3(v)$ = Pulmonary Capillary Resistance in the venous side of Zone 3 = 1.6 mmHg/ml-sec

$Cpc_1(a)$ = Pulmonary Capillary Compliance in the arterial side of Zone 1 = 3.0 ml/mmHg

$Cpc_1(v)$ = Pulmonary Capillary Compliance in the venous side of Zone 1 = 2.0 ml/mmHg

$Cpc_2(a)$ = Pulmonary Capillary Compliance in the arterial side of Zone 2 = 4.0 ml/mmHg

$Cpc_2(v)$ = Pulmonary Capillary Compliance in the venous side of Zone 2 = 3.0 ml/mmHg

$Cpc_3(a)$ = Pulmonary Capillary Compliance in the arterial side of Zone 3 = 5.0 ml/mmHg

$Cpc_3(v)$ = Pulmonary Capillary Compliance in the venous side of Zone 3 = 4.0 ml/mmHg

$Ppc_1(0)$ = Partial pressure of blood in the capillary of Zone 1 at time zero = 10 mmHg

$Ppc_2(0)$ = Partial pressure of blood in the capillary of Zone 2 at time zero = 8.0 mmHg

$Ppc_3(0)$ = Partial pressure of blood in the capillary of Zone 3 at time zero = 7.0 mmHg

Rc = Total Pulmonary Capillary Resistance = 0.6 mmHg/ml-sec

Cc = Total Pulmonary Capillary Compliance = 12 ml/mmHg

3.2.2 Alveolar and Capillary Gas Exchange

F_1 = Blood Flow into Capillary Zone 1 = 1.25 ml-min

F_2 = Blood Flow into Capillary Zone 2 = 1.75 ml-min

F_3 = Blood Flow into Capillary Zone 3 = 2.0 ml-min

Pso_{21} = Diffusing Capacity of Oxygen in Zone 1 = 105 ml/min

Pso_{22} = Diffusing Capacity of Oxygen in Zone 2 = 125 ml/min

Pso_{23} = Diffusing Capacity of Oxygen in Zone 3 = 150 ml/min

λo_{21} = Partition coefficient for Zone 1 = 0.381

λo_{22} = Partition coefficient for Zone 2 = 0.524

λo_{23} = Partition coefficient for Zone 3 = 0.60

Cpc_1 = Pulmonary Capillary Compliance in Zone 1 = 3.0 ml/mmHg

Cpc_2 = Pulmonary Capillary Compliance in Zone 2 = 4.0 ml/mmHg

Cpc_3 = Pulmonary Capillary Compliance in Zone 3 = 5.0 ml/mmHg

$Calv_1$ = Compliance of Alveolar Zone 1 = 5.44 ml/mmHg

$Calv_2$ = Compliance of Alveolar Zone 2 = 8.16 ml/mmHg

$Calv_3$ = Compliance of Alveolar Zone 3 = 13.6 ml/mmHg

QI_1, QI_2, QI_3 = Inspiratory Flow of Oxygen in Zone 1, 2, &3 = 6000 ml/min

QE_1, QE_2, QE_3 = Expiratory Flow of Oxygen in Zone 1, 2, &3 = 6000 ml/min

$Ppo_2AL_{1,\ 2,\ \&3}(0)$ = Partial Pressure of Oxygen in alveolar Zone 1, 2, &3 at time Zero = 8.0 mmHg

$Ppo_2C_{1,\ 2,\ \&3}(0)$ = Partial Pressure of Oxygen in Capillary Zone 1, 2, &3 at time Zero = 40.0 mmHg

$Pt_{1,\ 2,\ \&3}$ = Total Pressure in Capillary Zone 1, 2, &3 = 90 mmHg

PAL_1 = Total Pressure of Oxygen In alveolar Zone 1, 2, &3 = 100 mmHg

$Ppo_2A(0)$ = Partial Pressure of Oxygen in Arteries at time Zero = 40 mmHg

$Ppo_2V(0)$ = Partial Pressure of Oxygen in Veins at time Zero = 104 mmHg

$Ppo_2LA(0)$ = Partial Pressure of Oxygen in Large Airways at time Zero = 100 mmHg

3.2.3 Large Airways and Dead Zone

γ_1 = Mixing (Blood & Gas) Coefficient for Zone 1 = 0.2

γ_2 = Mixing (Blood & Gas) Coefficient for Zone 2 = 0.3

γ_3 = Mixing (Blood & Gas) Coefficient for Zone 3 = 0.5

QE LA = Amount of Expired Air From Large Airways = 800 ml/min

QI LA = Amount of Inspired Air into Large Airways = 200 ml/min

CLA = Compliance of Large Airways = 4.32 ml/mmHg

PtLa = Total Pressure in Large Airways = 100 mmHg

QE DZ = Amount of Expired Air From Dead Zone = 150 ml/min

QI DZ = Amount of Inspired Air into Dead Zone = 300 ml/min

P_{O_2} Room = Partial pressure of Oxygen at Room conditions = 159 mmHg

CDZ = Compliance of Dead Zone = 0.3 ml/mmHg

PDZ = Partial Pressure of Oxygen In Dead Zone = 60 mmHg

3.2.4 Arteries and Veins

F_{1O} = Blood Flow out of Capillary Zone 1 = 500 ml/min

F_{2O} = Blood Flow out of Capillary Zone 2 = 300 ml/min

F_{3O} = Blood Flow out of Capillary Zone 3 = 200 ml/min

Fpv = Blood Flow into Pulmonary Veins = 2000 ml/min

Cpv = Compliance of Pulmonary Veins = 105 ml/mmHg

Ptpv = Total Pressure in Pulmonary Veins = 40 mmHg

Frv = Blood Flow from Pulmonary Veins = 1600 ml/min

Fpa = Blood Flow from Pulmonary Arteries = 1800 ml/min

Cpa = Compliance of Pulmonary Arteries = 8.4 ml/mmHg

Ptpa = Total Pressure in Pulmonary Arteries = 100 mmHg

Fs = Shunt Flow = 100 ml/min

3.3 Results

Figure 1 shows the partial pressure of blood in the pulmonary arteries, veins, and the capillaries. The systolic pressure in the right ventricle of the normal human being averages approximately 25 mmHg, and the diastolic pressure averages about 0 to 1 mmHg, values that are only one fifth those for the left ventricle.

Pressures in the Pulmonary Artery. During systole, the pressure in the pulmonary artery is essentially equal to the pressure in the right ventricle as shown in figure 1. However, after the pulmonary valve closes at the end of systole, the ventricular pressure falls precipitously, whereas the pulmonary arterial pressure falls slowly as blood flows through the capillaries of the lungs. As shown in the figure 1, the systolic pulmonary arterial pressure averages approximately 25 mmHg in the normal human being; the diastolic pulmonary arterial pressure, approximately 15 mmHg.

Pulmonary Capillary and Venous Pressures. The capillary pressure as shown in the figure 1 is approximately 11 mmHg and the pulmonary veins average approximately 8 mmHg. For a normal human being the venous pressure varies from as low as 1 mmHg to as high as 8 mmHg.

The actual transfer of gases occurs in the 250 million or so tiny sacs called alveoli which comprise the terminal ends of the whole branched network of flow passages. The time averaged oxygen and carbon dioxide concentrations in the alveoli are 104 mmHg and 40 mmHg respectively versus 149 mmHg and 0.3 mmHg in the humidified air.

Figure 2 shows the partial pressure of oxygen in the three alveolar zones with respect to time. Because higher ventilation rates and higher metabolic rates usually occur together, we can deduce that on balance oxygen and carbon dioxide partial pressures in the alveoli will stay nearly constant over a wide range of conditions.

Figure 3 shows that the P_{O_2} in a red blood cell entering the capillary is normally about 40 mmHg. Across the blood-gas barrier, less than 1/2 micron away, is the alveolar P_{O_2} of

100 mmHg. Oxygen is transported down this large pressure gradient, and the P_{O_2} in the red blood cell rapidly rises; it nearly reaches the P_{O_2} of alveolar gas by the time the red blood cell is only one-third of its way along the capillary. Thus, under normal circumstances, the difference in P_{O_2} between alveolar gas and end-capillary blood is immeasurably small-a mere fraction of a mmHg. In other words, the diffusion reserves of the normal lung are enormous.

In all the models so far developed for gas exchange in the lungs, the large airways were simply considered as tubes for air to move from the mouth into the alveoli. But in reality there is some gas exchange in the large airways. Figure 4 shows the partial pressure of oxygen in the large airways with respect to time.

At the end of inspiration, the upper airways are filled with inspired gas that has undergone no gas exchange, and alveolar units contain gas that approximates pulmonary capillary blood in composition. Between these two sites, in large airways, the gas partial pressure must vary between these two extremes (between 100 mmHg and 149 mmHg). In our model it stays nearly constant at 105 mmHg.

Not all the air that passes through the mouth reaches the alveoli. Some of the air remains in the dead space where no gas exchange occurs. Figure 4 shows the partial pressure of oxygen during inspiration and expiration. Since no gas exchange occurs in this region the partial pressure also remains constant at 135 mmHg.

Figure 5 shows the partial pressures of oxygen in the arteries and the veins. Under equilibrium conditions, the partial pressure of the gas in the gas phase and in the liquid phase are equal[23]. This is because the number of gas molecules leaving the liquid per unit time is equal to the number entering the liquid. So the partial pressure of oxygen in the arteries (Figure 5) is almost equivalent to the blood pressure in pulmonary arteries and veins (Figure 1).

Figure 6 shows the blood pressure in the three capillary zones, which ranges between 9 mmHg and 13 mmHg.

CHAPTER 4
CONCLUSION

The Model developed in this thesis is a physiologically based pharmacokinetic model of inhaled gases in the lung. The model can be used to simulate the blood-alveolar exchange of gases such as oxygen and carbon dioxide as well as a wide variety of anesthetic gases of varying solubility in blood and lung tissue.

The major advantages of the model developed in this work are as follows:

1. The lung compartments are physiologically based. Under normal resting conditions alveolar-blood gas exchange takes place in three physiologically defined zones from the apex to the base of the lung. These are defined as follows:

Zone 1: Approximately, the top 1/3 of lung. No open capillaries. Well ventilated but not perfused.

Zone 2: Approximately, the middle 1/3 of lung. Capillaries only open about half the time. Poorly perfused but well ventilated.

Zone 3: Approximately, the lower 1/3 of lung. All capillaries open all the time. Well perfused and well ventilated.

2. The proportion of the lung which operates in zones 1, 2 and 3 changes with exercise and trauma. The model developed in this thesis simulates these adaptations by changing the proportion of the total blood flow perfusing each zone.

3. Also under normal resting conditions a small proportion of the total blood flow through the lungs occur as an arterial-venous shunt. This proportion can change with various pathologies. The model can readily simulate these changes by changing one variable.

4. Changes in other physiological lung compartments (for example, dead space) can readily be accomplished to simulate other pathologies.

5. Anesthetic gases of varying degrees of blood-tissue solubility can be simulated by changing the solubility coefficient in the mass balance equations.

6. The model can readily be coupled to a whole body hemodynamic model developed earlier to simulate distribution, uptake and metabolism of the inhaled gases by a variety of tissues and organs.

7. The model is implemented using TUTSIM simulation software. This software package runs on a PC and requires no programming experience. Equations are built up using functional blocks. The blocks are symbolic and the software for implementation of each function is transparent to the user. The blocks are interconnected to form the inputs and outputs for each equation. Parameters and initial conditions are associated with each block and can be easily altered to change simulation conditions. The output from the simulation can be sent to a file which can be easily imported by a wide variety of graphics software for preparation of graphs and reports.

APPENDIX I

This section contains the results of TUTSIM simulation program.

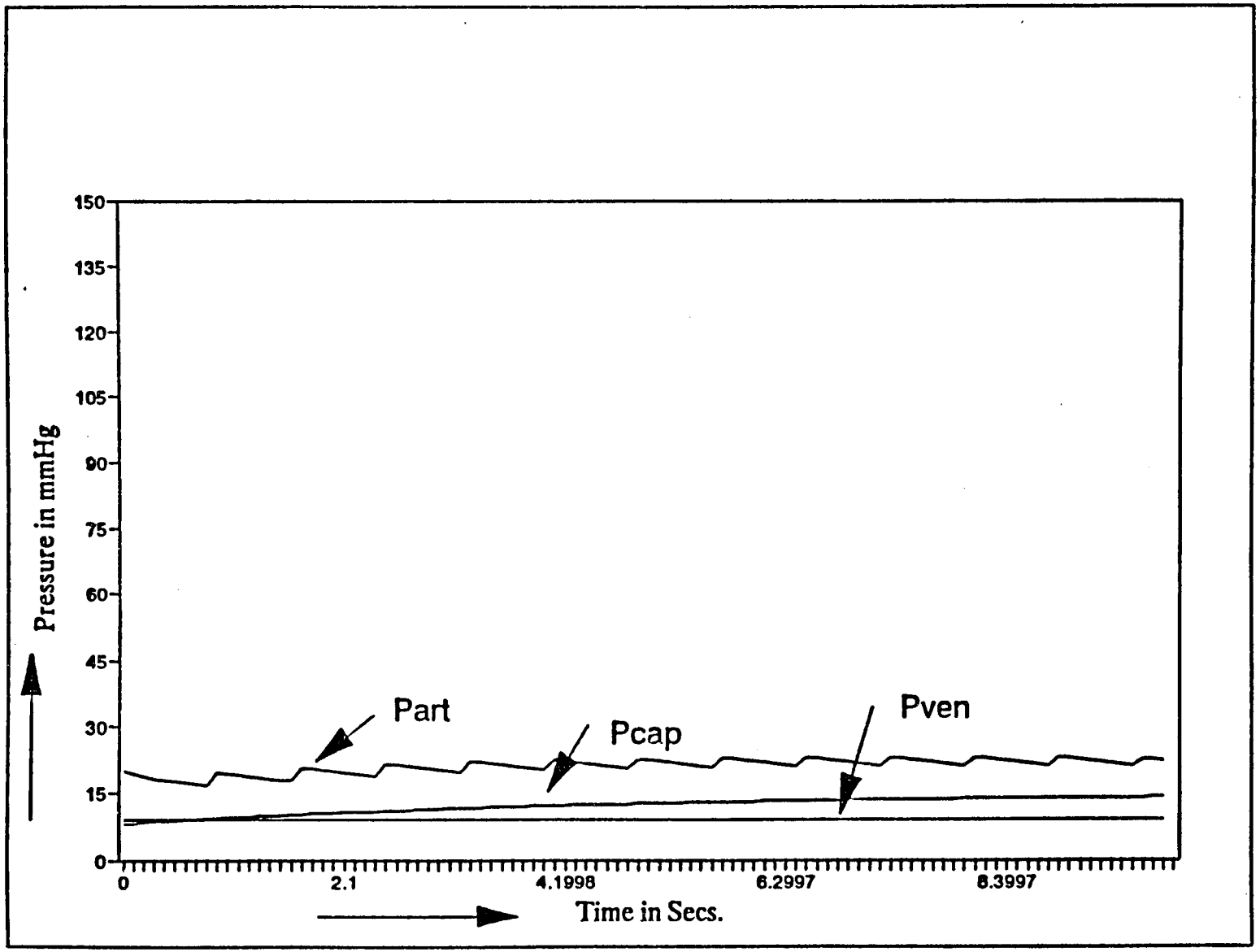

Figure 1 Blood Pressure in Pulmonary Arteries, Veins and Capillaries

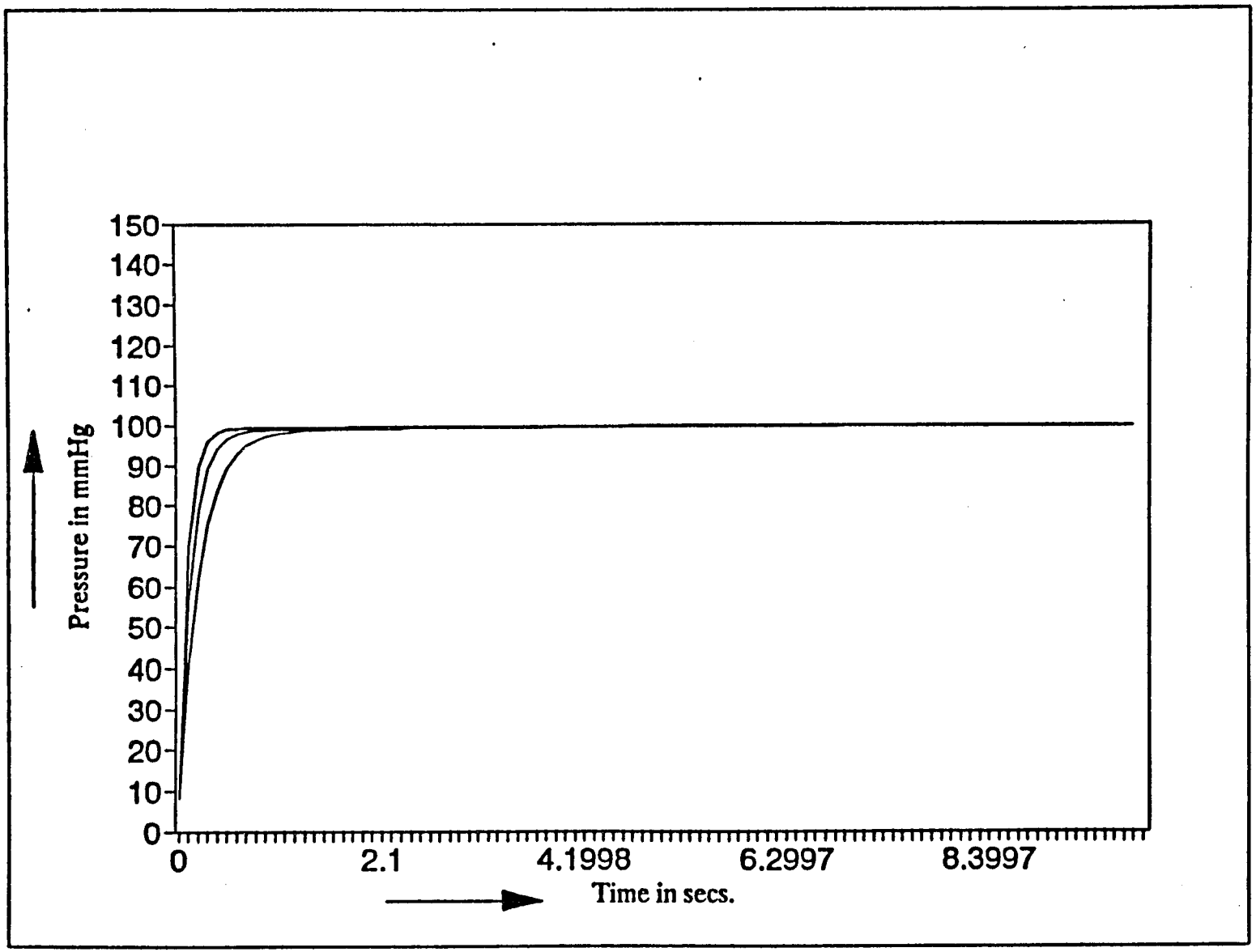

Figure 2 Partial Pressure of Oxygen in Alveolar Zones

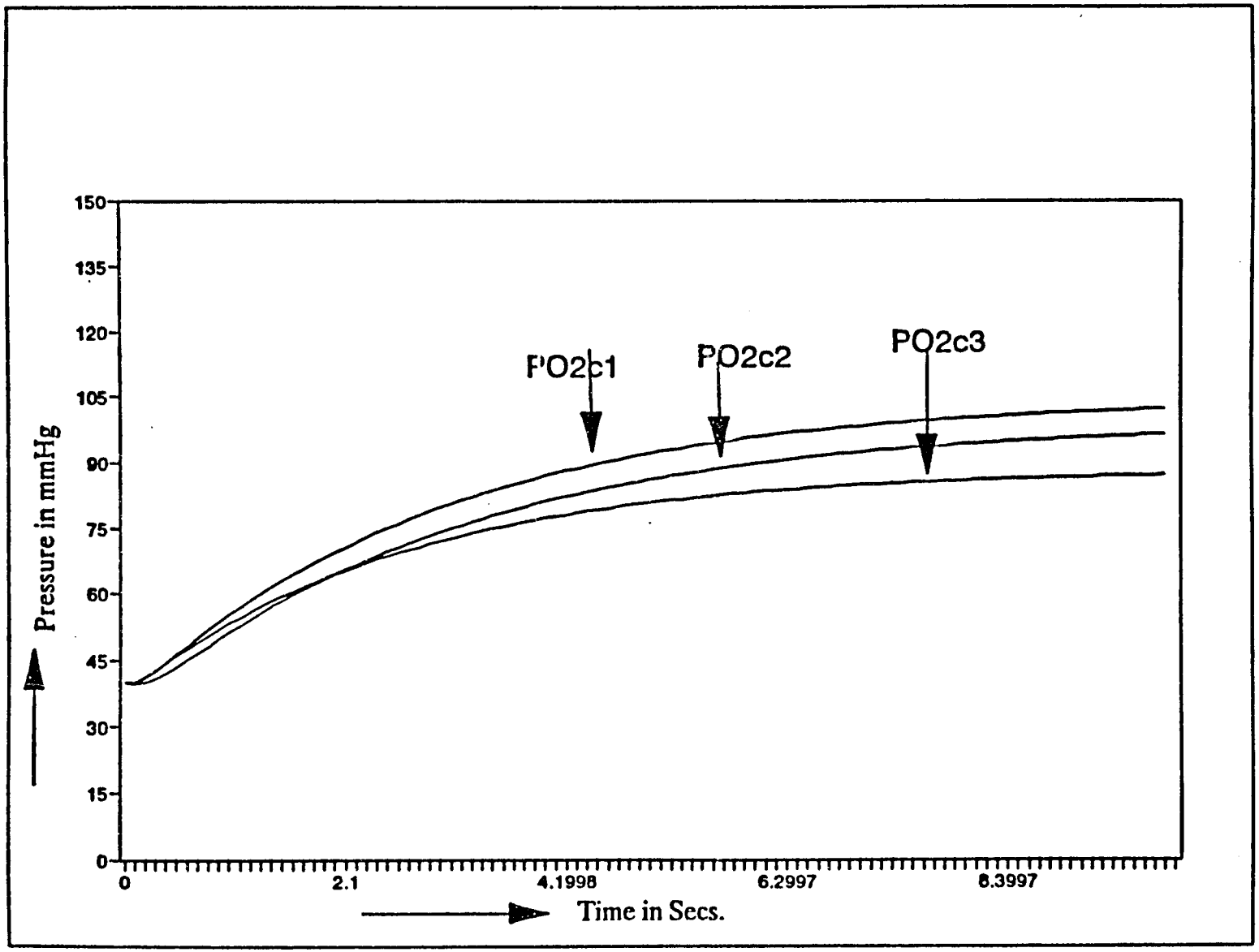

Figure 3 Partial Pressure of Oxygen in Capillary Zones

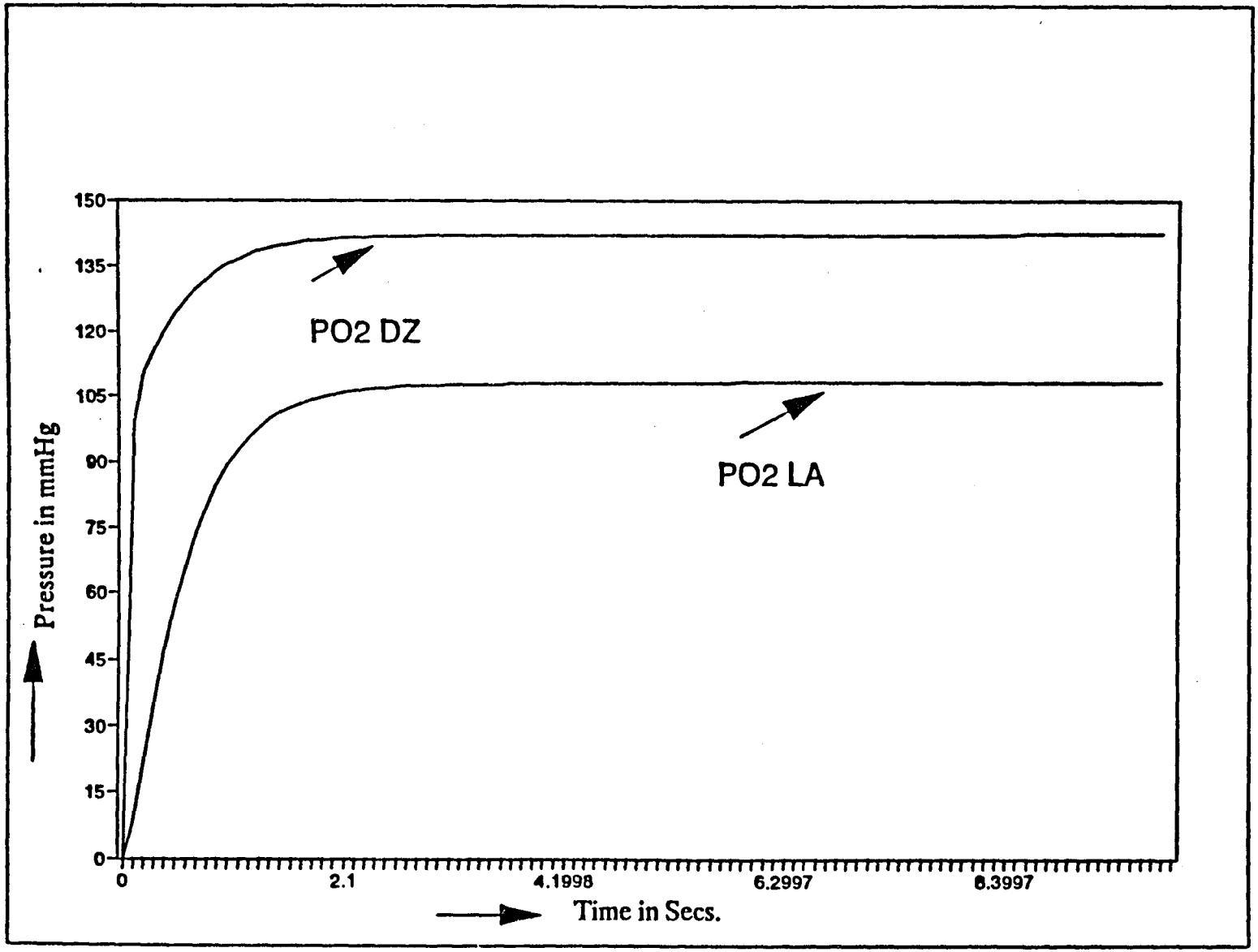

Figure 4 Partial Pressure of Oxygen in Large Airways and Dead Zone

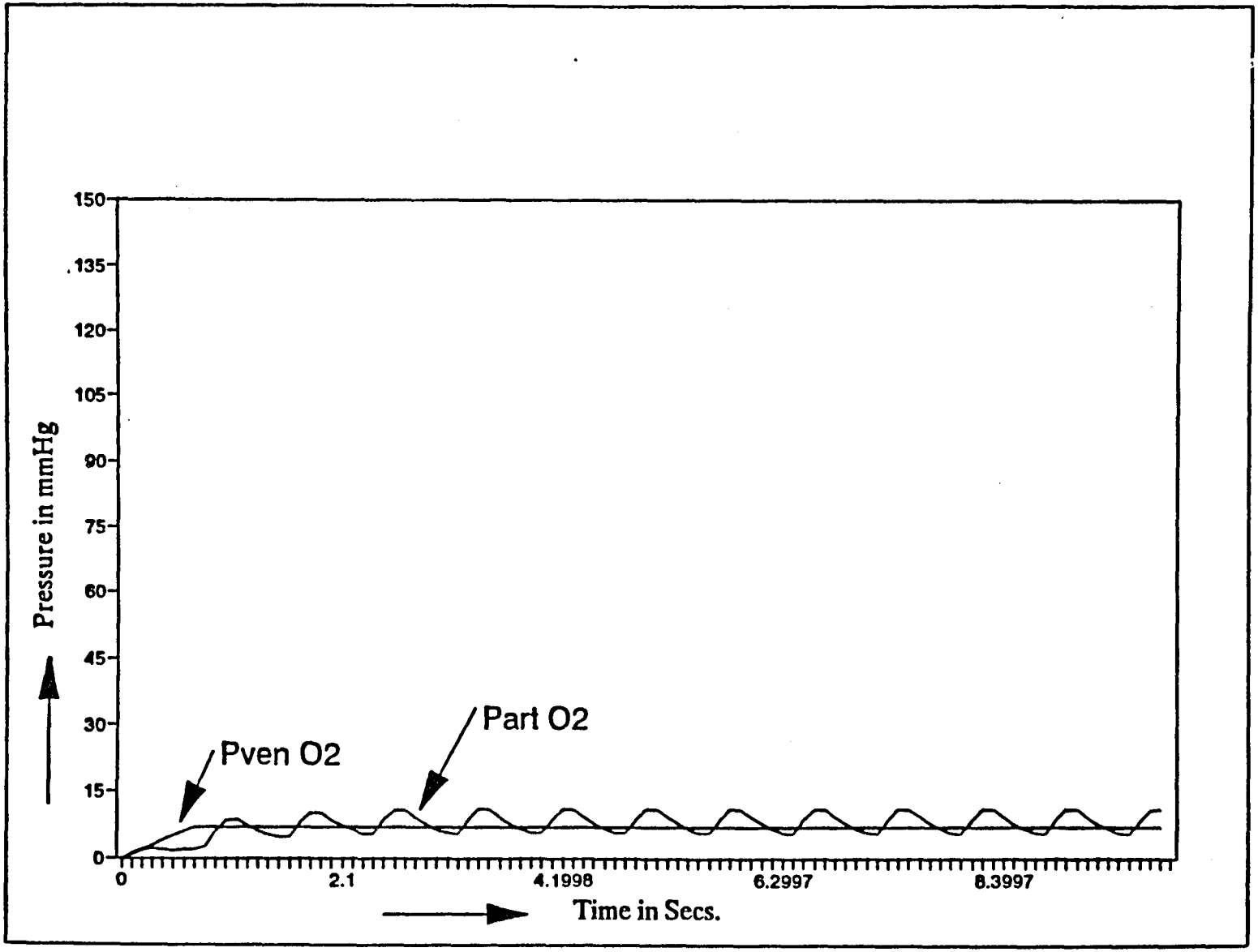

Figure 5 Partial Pressure of Oxygen in Arteries and Veins

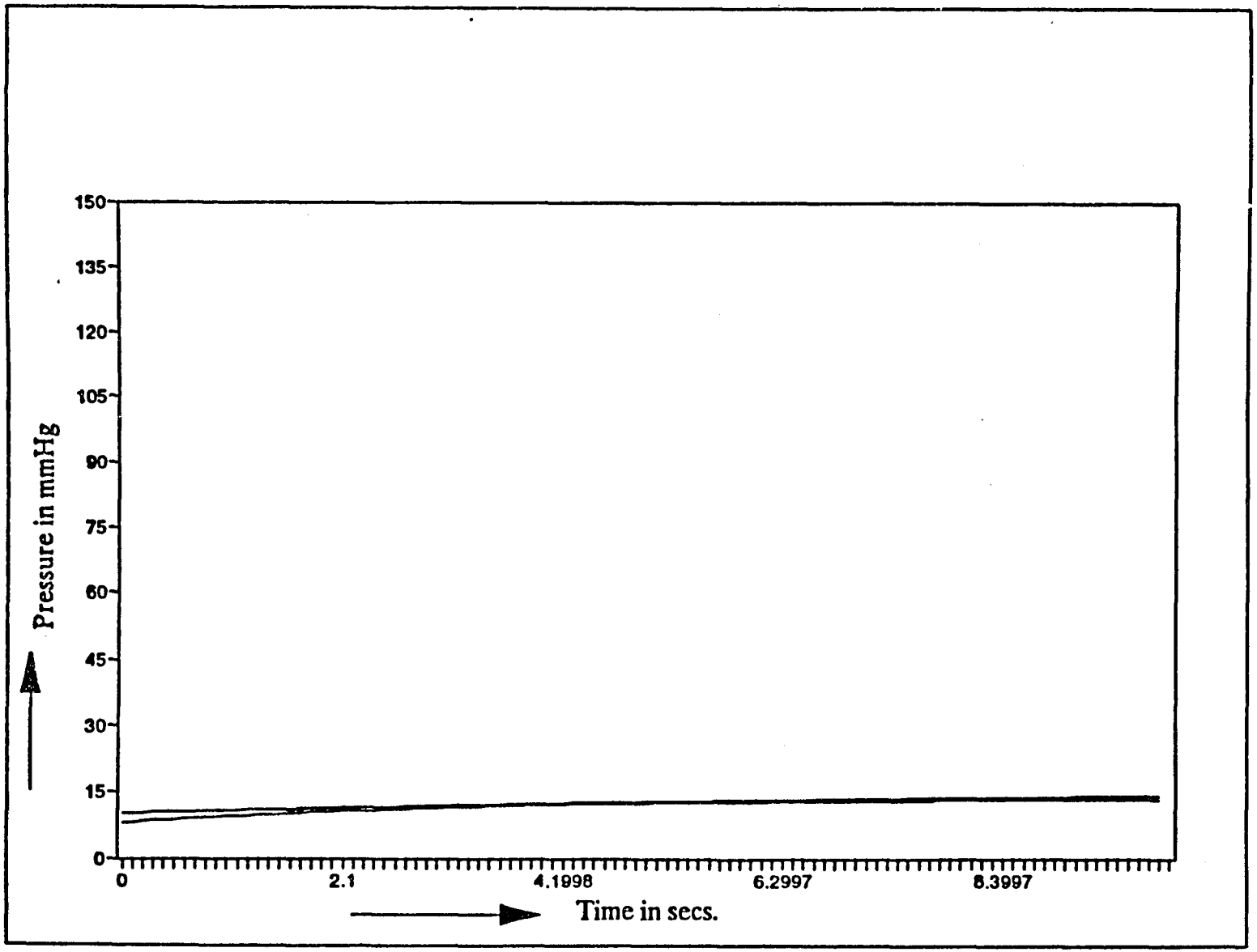

Figure 6 Blood Pressure in Capillary Zones

APPENDIX II

This section contains TUTSIM Block functions, Commands, Simulation Program and the Block diagrams used for Simulation.

TUTSIM BLOCKS

NAME	I	PARAMETERS	FUNCTION	(H)-History Block
ABS	1	none	Absolute Value	
ACC	1	Ic	Accumulate Sums of Inputs	(H)
ADL	1	Ic	Delay One Step	(H)
AND	2	none	Logical AND of Inputs	
ATN	1	none	Arctangent	
ATT	1	P	Attenuate/Divide by Parameter	
BKL	1	W,Ip	Backlash	
C	1	C,Ic	Electrical Capacitance	(H)
CLK	Ø	P	Clock/Square Wave Source	
CON	Ø	C	Constant Source	
COS	1	none	Cosine of Sum of Inputs	
CRP	Ø	T1,T2,F1,F2	Chirp Source/Swept Frequency	
DAT	Ø	Vn	Filed Data Input Source	
DEL	1	N,Td,Ic	Delay Td Time Units	(H)
DFF	2	Ilc	"D" Type Flip-Flop	
DIF	1	Ic,Ic	Differentiator	(H)
DIV	2	none	Divide Input1 by Input2	
DLT	Ø	none	Current Delta Time Output	
DTM	Ø	none	DOS Time/Stop Watch	
EUL	1	Ic	Euler Integrator	(H)
EXP	1	none	Exponential (e)	
FIO	1	K,T,Ic	First Order Block	(H)
FIX	1	none	Fix/Truncate Fractional Part	
FNC	1	n,Xn,Yn	Function Generator	
FND	1	blkØ	FNC Duplicator	
FRQ	Ø	F,A	Frequency Source/Sine Wave	
GAI	1	P	Gain/Multiply by Parameter	
GER	1	Th,R	Geared Delta Time	
GSQ	1	F	Signed Square Root	
HIS	1	Ic	History	(H)
HLT	1	none	Halt	
HYS	1	W,Ip,h	Magnetic Hysteresis	
IFE	3	none	If Input$_C$ Then In$_1$ Else In$_2$	
INT	1	Ic	Adams-Bashford Integrator	(H)
INV	1	none	Logical Inverter	
IWZ	1	Ic,Fz,K,Ic	LaPlace Integrator /w Zero	(H)

TUTSIM BLOCKS

NAME	I	PARAMETERS	FUNCTION	(H)-History Block
L	1	L,Ic	Electrical Inductance	(H)
LIM	1	min,max	Min/Max Limit	
LLG	1	Ic,Fz,Fp,Ic	LaPlace Lead/Lag	(H)
LME	1	Ic,min,max	Min/Max EUL	(H)
LMI	1	Ic,min,max	Min/Max INT	(H)
LOC	2	Ic	Latch On Condition	
LOG	1	none	Natural Logarithm	
MAX	2	none	Maximum Input	
MIN	2	none	Minimum Input	
MUL	2	none	Multiply Inputs	
NAN	2	none	Logical NOT AND	
NOI	Ø	none	Random Noise Source	
NOR	2	none	Logical NOT OR	
OP2	1	none	Second Output of BKL or HYS	
ORR	2	none	Logical OR	
PID	1	K,Ti,Td,t,Ic,Icd	PID Controller	
PLS	Ø	T1,T2,Ap	Pulse/Step Input Source	
PWR	1	P	Raise to P Power	
R	1	R	Electrical Resistance	
REL	4	Vc	Relay/Conditional	
REM	Ø	none	Remark/Listing Comments	
RIN	2	Ic	Resetting Integrator	(H)
RSQ	1	F	Signed Square	
SEO	1	Ic,Z,F,Ic	LaPlace Second Order Block	(H)
SGN	1	none	Sign of Inputs	
SIN	1	none	Sine of Inputs	
SOC	2	Ic	Strobe On Condition	
SPL	1	SI	Sample and Hold	
SQT	1	none	Square Root of Inputs	
SRS	2	Ilc	Set/Reset Flip-Flop	
SUM	2	none	Sum of Inputs	
SYC	Ø	none	Synchronize with DOS Time	
TFF	1	Ilc	Trigger Flip-Flop	
TIM	Ø	none	Time Source	
VDL	2	An,Im,Ic	Variable Delay	(H)
VDT	Ø	T1,T2,R	Variable Delta Time	
XNR	2	none	Logical EXCLUSIVE OR	

TUTSIM BLOCKS

NAME	I	PARAMETERS	FUNCTION	(H)-History Block
ZAC	1	Ts,a,Ic	Z Accumulator	
ZCC	1	aØ-aØ	Z Cross Correlation	
ZDF	1	Ts,K,Ic	Z Difference	
ZDL	1	Ts,Dm,Ic	Z Delay	(H)
ZDT	Ø	Ts,Pz,dz	Z Delta Time	
ZGC	1	Ts,aØ-aA,Ic	Z General Correlation	
ZGN	1	Ts,K	Z Gain	
ZHS	1	Ts,Ic	Z History	(H)
ZIR	1	Ts,K,a,Ip	Z Infinite Response	
ZSE	1	Ts,Bl	Z See Display Function	
ZSP	1	Ts,K,Ic	Z Sample and Hold	
ZUD	1	Ts,Ic	Z Unit Delay	(H)

TUTSIM OPTIONS BLOCKS

NAME	I	PARAMETERS	FUNCTION	(H)-History Block
IN	Ø	P1,P2	RTIO User Defined Input	
INI	1	P1,P2	RTIO IN with Forced Order	
OUT	1	P1,P2	RTIO User Defined Output	
USA	1	P1,P2	User Defined Algebraic Block	
USR	1	P1,P2,Ic	User Defined History Block	(H)
ZIN	Ø	Ts,P1	Z Real Time I/O IN block	
ZNI	1	Ts,P1	Z Real Time I/O INI Block	
ZOT	1	Ts,P1	Z Real Time I/O OUT Block	

THE TUTSIM COMMANDS

Change Commands

CS	Change the Structure of the model
CC	Change the Comments on a structure line
CP	Change the Parameters of the model
CB	Change the PlotBlocks and Ranges
CT	Change the Timing parameters

Change Structure Subcommands

D	Delete a Range of Blocks
E	Exit to Command Mode Without Sorting
L[P][:n,m]	List [Print][a Range of] Blocks
N[P][:n,m]	List [Print][a Range of] Unused Blocks
R	Repeat a Range of Blocks

Starting Simulation

SD	Start Simulation, Results to Display
SN	Start Simulation with Numerical Results
SNP	Start Simulation /w SN Results to Printer
SP	Start Simulation /w Print-Plot Output
SPP	Start Simulation /w SP Output to Printer
MR	Start Simulation /w Multi-Run Feature
SF	Start Simulation Output to ASCII File
MF	Start Simulation Output to Matlab File
PE	Parameter Estimation Simulations

Proceeding with Simulation after an Interrupt

PD	Proceed with Results to Display
PN	Proceed with Numerical Output
PNP	Proceed with Numerical Output to Printer
PP	Proceed with Print-Plot Output
PPP	Proceed with Print-Plot Output to Printer

List Commands

L	List the Model File
LP	List the Model File on the Printer
L:n,m	List a Range of Blocks
LP n,m	List a Range of Blocks on the Printer
LM	List a Macro
LMP	List a Macro on the Printer

Typing Commands

TT	Type Timing Data
TTP	Type Timing Data on Printer
TH	Type Model Heading Information
THP	Type Model Heading Information on Printer
TS	Type a Structure Line
TSP	Type a Structure Line on Printer

Model and Macro Filing Commands

DF	Save a Model File on Disk
K	Concatenation of Model Files
SM	Save Macro File on Disk
IM	Import Macro into Current Model

THE TUTSIM COMMANDS CONT'D

Simulation Set Up Commands

CO	Math Coprocessor Toggle (on/off)
I	Replace Initial Conditions with Outputs
IC	Iteration Counter
MR/MP	Set MCI Block (Random or Repetitive)
RO	Reset OUT Blocks (RTIC Option)
S	Signal Simulation Steps
(space bar)	Interrupt Model Simulation

Utility Commands

CN	Compress Block Numbers
RN	Renumber Individual Blocks in a Model
RN:n,m	Renumber a Range of Blocks in a Model
V	Verify Last Block Output Value
VP	Verify Last Block Output Value on Printer
V:n,m	Verify a Range of Output Values
VP:n,m	Verify a Range of Output Values on Printer
E	REstart the TUTSIM Program
DOS	Return to DOS. Leave TUTSIM Resident.
Q or A	Quit the TUTSIM Program (return to DOS)
H	Help on the Available Commands
FF	Send a Form Feed to the Printer
(carriage return)	Escape from Current Command

Graphic Screen Commands

GD	Draw a Grid
CL	Clear the Graphical Screen
HC	Print Hard Copy of the Graphical Screen
Shift-PrtSc	Hard Copy for Hercules Graphics
RG	Return Display in Graphic Mode
CD	Toggles Display, Dot to Line
X, Y	Draw X or Y Center Lines

Function Key Screen Labels

F1	Labels the Y1 curve and displays the structure line comment from that Block.
F2	Labels the Y2 curve.
F3	Labels the Y3 curve.
F4	Labels the Y4 curve.
F5	Labels the horizontal scale.
F6	Super-imposes the last screen saved with F7 on the present screen.
F7	Saves the present screen. No other screen will be saved until this screen is restored with F6.
F8	Clears the screen.
F9	Gives a 10 point summary of the simulation values.
F10	Allows the user to enter a title on the present graph.

Graphics Mode Subcommands

C	Clear Graph at End of Simulation Run
E	Echo Numeric Output to Printer
N	Turn Off Echo

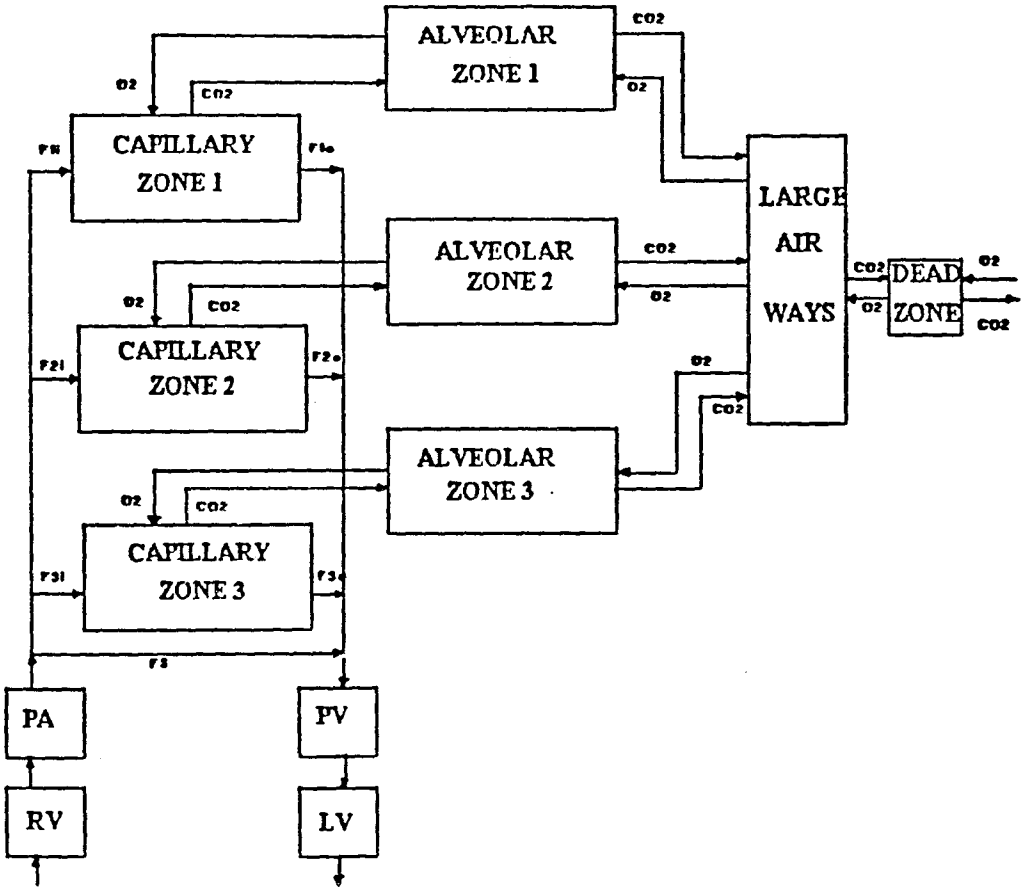

Figure 7 Basic Model for Gas Exchange in Lungs

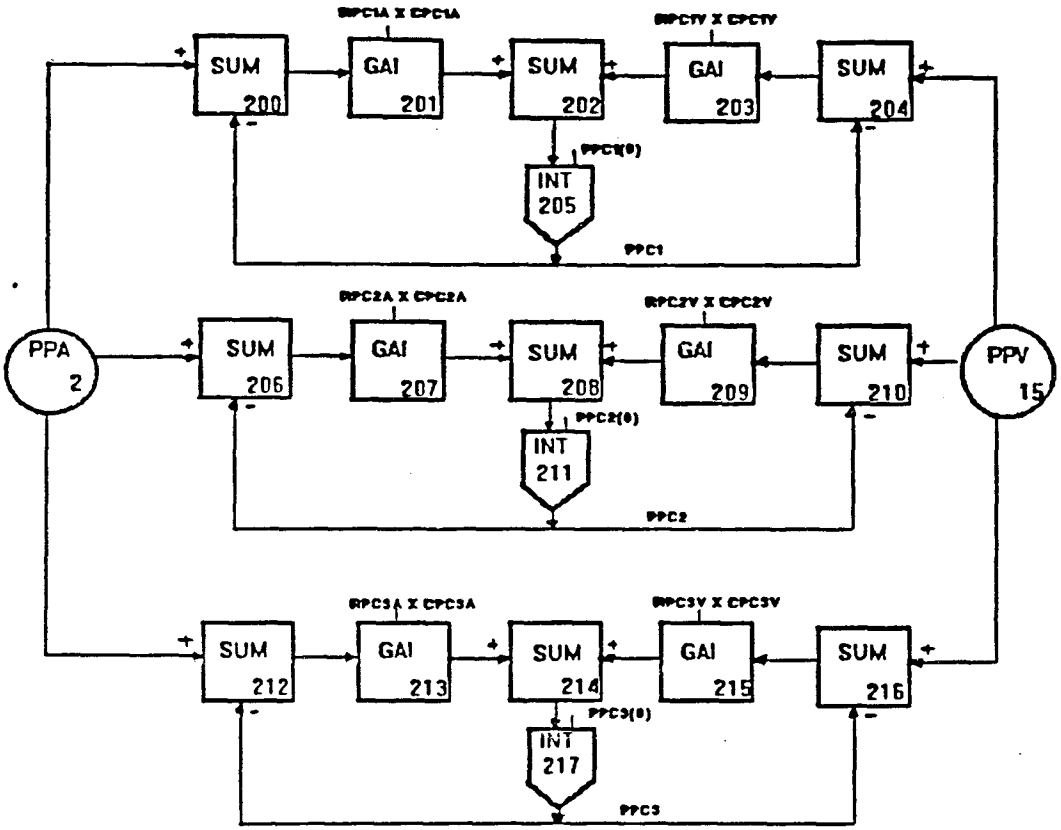

Figure 8 Tutsim Block Diagram for Pulmonary Blood Flow

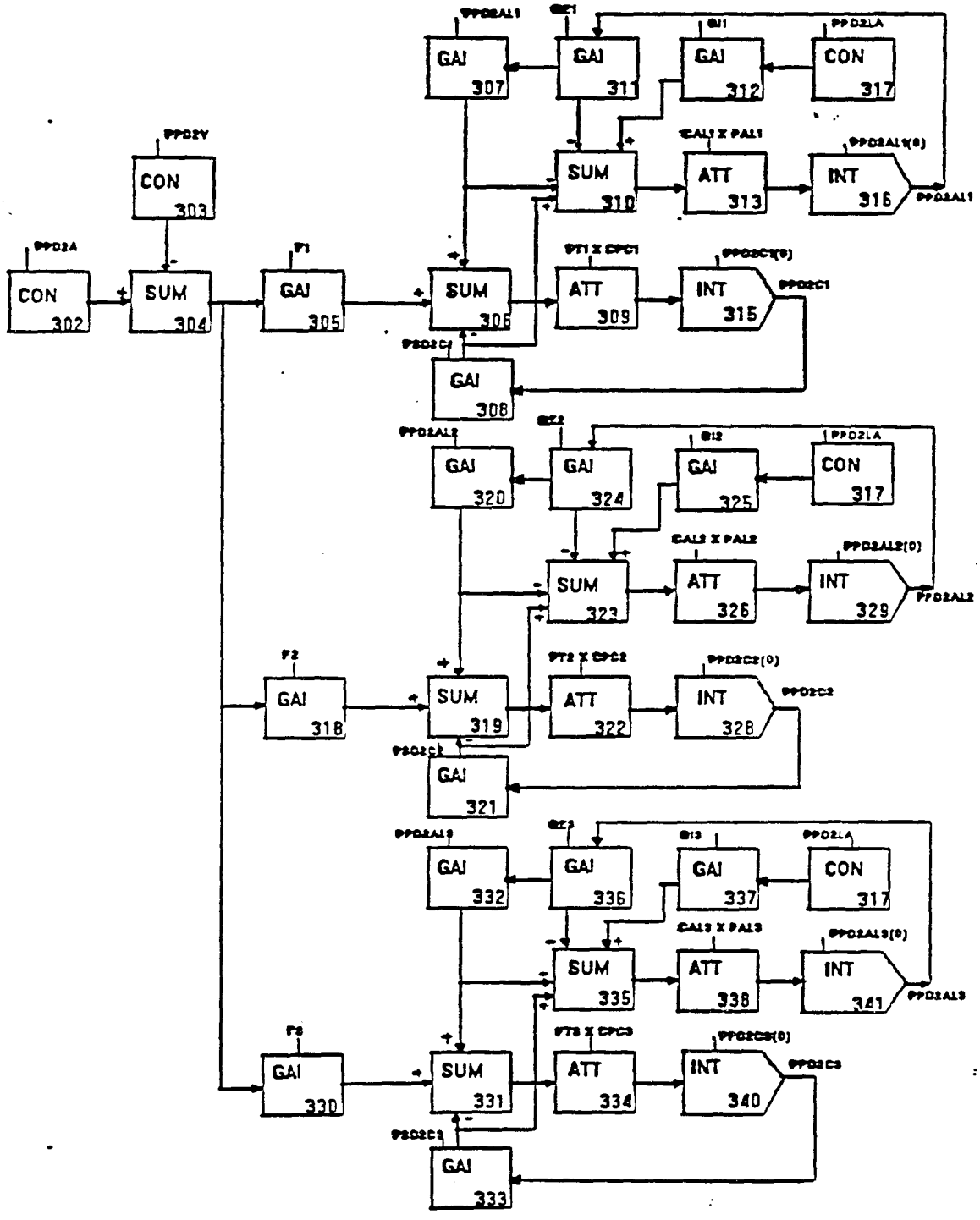

Figure 9 Tutsim Block Diagram for Alveolar and Capillary Gas Exchange

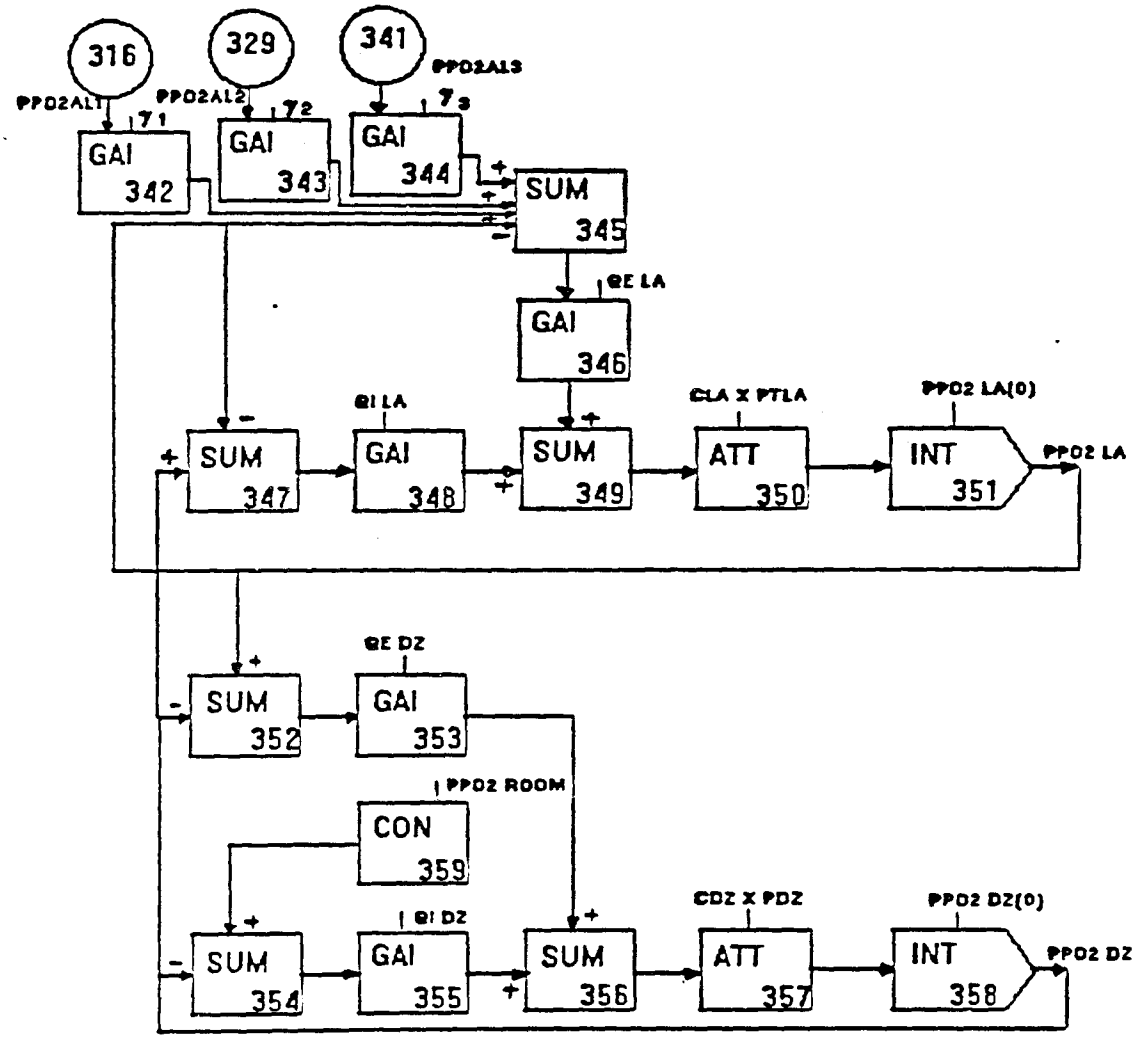

Figure 10 Tutsim Block Diagram for Large Airways and Dead Zone

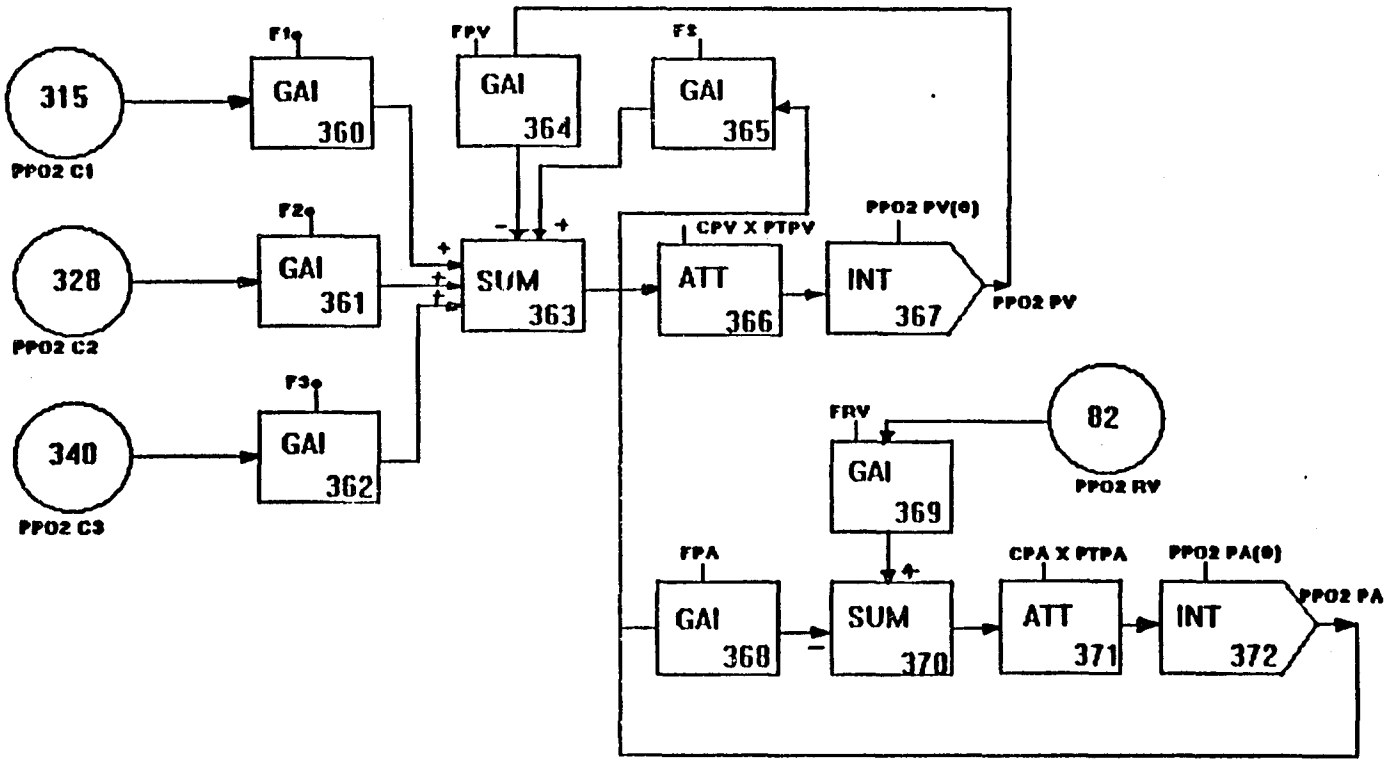

Figure 11 Tutsim Block Diagram for Arterial and Venous Pressures

```
=Model File: tot1
=Date:     4 /    11 / 1993
=Time:    15 :    31
=Timing:   0.0010000  ,DELTA  ;  10.0000     ,RANGE
=PlotBlocks and Scales:
=Format:
=     BlockNo,  Plot-MINimum,  Plot-MAXimum;  Comment
=Horz:     0 ,    0.0000     ,  10.0000     ; Time
= Y1:    373 ,    0.0000     , 150.0000     ;
= Y2:    372 ,    0.0000     , 150.0000     ;

     1 TIM
     2 INT      6
                                    P1=   20.0000
     3 SUM     -2     82
     4 LIM      3
                                    P1=    0.0000
                                    P2=  999.980E+03
     5 GAI      4
                                    P1=  200.0000
     6 GAI     -9      5
                                    P1=    0.0325000
     7 SUM    -10      2
     8 LIM      7
                                    P1=    0.0000
                                    P2=  999.980E+03
     9 GAI      8
                                    P1=   20.0000
    10 INT     14
                                    P1=   10.0000
    11 SUM    -15     10
    12 LIM     11
                                    P1=    0.0000
                                    P2=  999.980E+03
    13 GAI     12
                                    P1=   10.0000
    14 GAI    -13      9
                                    P1=    0.0450000
    15 INT     19
                                    P1=    9.0000
    16 SUM    -21     15
    17 LIM     16
                                    P1=    0.0000
                                    P2=  999.980E+03
    18 GAI     17
                                    P1=   25.0000
    19 GAI    -18     13
                                    P1=    0.0020000
    20 INT     25
                                    P1=    8.0000
    21 MUL     20     38
    22 SUM    -26     21
    23 LIM     22
```

```
                                                P1=    0.0000
                                                P2=  999.980E+03
    24 GAI    23
                                                P1=   25.0000
    25 GAI   -24     18
                                                P1=    1.0000
    26 INT    30
                                                P1=  100.0000
    27 SUM   -42     26
    28 LIM    27
                                                P1=    0.0000
                                                P2=  999.980E+03
    29 GAI    28
                                                P1=   17.1820
    30 GAI   -29     24
                                                P1=    5.0000
    31 GAI     1
                                                P1=    1.2500
    32 FIX    31
    33 GAI   -32     31
                                                P1=    0.8000000
    34 GAI     1
                                                P1=    1.0000
    35 FNC    34
X,Y-     1    0.0000          0.0800000
X,Y-     2    0.0200000       0.1620000
X,Y-     3    0.0400000       0.2170000
X,Y-     4    0.0600000       0.2550000
X,Y-     5    0.0800000       0.3000000
X,Y-     6    0.1000000       0.3240000
X,Y-     7    0.1200000       0.3490000
X,Y-     8    0.1400000       0.3450000
X,Y-     9    0.1600000       0.3410000
X,Y-    10    0.1800000       0.3380000
X,Y-    11    0.2000000       0.3080000
X,Y-    12    0.2200000       0.2860000
X,Y-    13    0.2400000       0.2500000
X,Y-    14    0.2600000       0.1600000
X,Y-    15    0.2800000       0.1070000
X,Y-    16    0.3000000       0.0400000
X,Y-    17    0.3200000       0.0133333
X,Y-    18    0.3400000       0.0132000
X,Y-    19    0.3600000       0.0102000
X,Y-    20    0.3800000       0.0084700
X,Y-    21    0.4000000       0.0123000
X,Y-    22    0.4200000       0.0117000
X,Y-    23    0.4400000       0.0152000
X,Y-    24    0.4600000       0.0149000
X,Y-    25    0.4800000       0.0184000
X,Y-    26    0.5000000       0.0183000
X,Y-    27    0.5200000       0.0217000
X,Y-    28    0.5400000       0.0216000
X,Y-    29    0.5600000       0.0214000
X,Y-    30    0.5800000       0.0213000
X,Y-    31    0.6000000       0.0211000
X,Y-    32    0.6200000       0.0210000
X,Y-    33    0.6400000       0.0208000
X,Y-    34    0.6600000       0.0207000
X,Y-    35    0.6800000       0.0205000
X,Y-    36    0.7000000       0.0204000
```

```
X,Y-    37    0.7200000     0.0202000
X,Y-    38    0.7400000     0.0201000
X,Y-    39    0.7600000     0.0233330
X,Y-    40    0.7800000     0.0600000
X,Y-    41    0.8000000     0.0800000
    36 FND     33
                                  P1=   35.0000
    37 FNC     34
X,Y-     1    0.0000        0.5333330
X,Y-     2    0.0200000     0.7100000
X,Y-     3    0.0400000     0.7970000
X,Y-     4    0.0600000     1.0090
X,Y-     5    0.0800000     1.2740
X,Y-     6    0.1000000     1.4090
X,Y-     7    0.1200000     1.5370
X,Y-     8    0.1400000     1.6000
X,Y-     9    0.1600000     1.5950
X,Y-    10    0.1800000     1.5900
X,Y-    11    0.2000000     1.5840
X,Y-    12    0.2200000     1.5260
X,Y-    13    0.2400000     1.3333
X,Y-    14    0.2600000     0.8133300
X,Y-    15    0.2800000     0.4000000
X,Y-    16    0.3000000     0.1600000
X,Y-    17    0.3200000     0.0533000
X,Y-    18    0.3400000     0.0395000
X,Y-    19    0.3600000     0.0204000
X,Y-    20    0.3800000     0.0254000
X,Y-    21    0.4000000     0.0246000
X,Y-    22    0.4200000     0.0312500
X,Y-    23    0.4400000     0.0341000
X,Y-    24    0.4600000     0.0373000
X,Y-    25    0.4800000     0.0404000
X,Y-    26    0.5000000     0.0438000
X,Y-    27    0.5200000     0.0435000
X,Y-    28    0.5400000     0.0432000
X,Y-    29    0.5600000     0.0429000
X,Y-    30    0.5800000     0.0426000
X,Y-    31    0.6000000     0.0423000
X,Y-    32    0.6200000     0.0420000
X,Y-    33    0.6400000     0.0451000
X,Y-    34    0.6600000     0.0483000
X,Y-    35    0.6800000     0.0445000
X,Y-    36    0.7000000     0.0408000
X,Y-    37    0.7200000     0.0405000
X,Y-    38    0.7400000     0.0403000
X,Y-    39    0.7600000     0.0400000
X,Y-    40    0.7800000     0.4000000
X,Y-    41    0.8000000     0.5333300
    38 FND     33
                                  P1=   37.0000
    39 SUM    -76     26
    40 LIM     39
                                  P1=    0.0000
                                  P2=  999.980E+03
    41 GAI     40
                                  P1=    0.0427350
    42 INT     46
                                  P1=   60.0000
    43 SUM    -47     42
```

```
-44 LIM     43
                                    P1=    0.0000
                                    P2=  999.980E+03
45 GAI      44
                                    P1=    2.0953
46 GAI     -41     -45      29
                                    P1=    1.0000
47 INT      58
                                    P1=   30.0000
48 SUM     -54      47
49 LIM      48
                                    P1=    0.0000
                                    P2=  999.980E+03
50 GAI      49
                                    P1=    3.1818
51 SUM     -71      42
52 LIM      51
                                    P1=    0.0000
                                    P2=  999.980E+03
53 GAI      52
                                    P1=    0.3836200
54 INT      62
                                    P1=   20.0000
55 SUM     -63      54
56 LIM      55
                                    P1=    0.0000
                                    P2=  999.980E+03
57 GAI      56
                                    P1=   21.4770
58 GAI     -66     -50     -53
                                       45
                                    P1=    1.1500
59 SUM     -63      47
60 LIM      59
                                    P1=    0.0000
                                    P2=  999.980E+03
61 GAI      60
                                    P1=    0.1275500
62 GAI     -61     -57      50
                                    P1=    0.0700000
63 INT      70
                                    P1=   15.0000
64 SUM     -63      42
65 LIM      64
                                    P1=    0.0000
                                    P2=  999.980E+03
66 GAI      65
                                    P1=    0.1923070
67 SUM     -71      63
68 LIM      67
                                    P1=    0.0000
                                    P2=  999.980E+03
69 GAI      68
                                    P1=  433.6800
70 GAI     -69      61      57
                                    P1=    0.0500000
71 INT      75
                                    P1=    8.0000
72 SUM     -76      71
73 LIM      72
                                    P1=    0.0000
```

```
                                                P2= 999.980E+03
 74 GAI     73
                                                P1=  11.4800
 75 GAI    -74     69     66     53
                                                P1=   0.0030000
 76 INT     80
                                                P1=   6.0000
 77 SUM    -82     76
 78 LIM     77
                                                P1=   0.0000
                                                P2= 999.980E+03
 79 GAI     78
                                                P1=  78.0000
 80 GAI    -79     74     41
                                                P1=   0.0040000
 81 INT     83
                                                P1=   4.0000
 82 MUL     81     36
 83 GAI     -5     79
                                                P1=   1.0000
 84 LIM     35
                                                P1=   0.0000
                                                P2= 999.980E+03
 85 GAI      2
                                                P1=  30.7692
 86 GAI     10
                                                P1=  11.1111
 87 GAI     15
                                                P1= 200.0000
 89 GAI     26
                                                P1=   1.0000
 90 GAI     42
                                                P1=   4.1666
 91 GAI     47
                                                P1=   0.8695650
 92 GAI     54
                                                P1=  14.2857
 93 GAI     63
                                                P1=  20.0000
 94 GAI     71
                                                P1= 166.6670
 95 GAI     76
                                                P1= 250.0000
100 SUM     82   -101    102    103
101 GAI    105
                                                P1=   2.8200
102 GAI    110
                                                P1=   1.7500
103 GAI    107
                                                P1=   0.0660000
104 ATT    100
                                                P1=   0.0341250
105 INT    104
                                                P1=   8.0000
106 GAI    107
                                                P1=   3.0000
107 GAI    115
                                                P1=   1.0000
108 GAI    110
                                                P1=   4.0000
```

```
109 SUM   -108    105    106
110 GAI    113
                                P1=    1.0000
111 ATT    105
                                P1=   16.0000
112 ATT    109
                                P1=    0.0540000
113 INT    112
                                P1=    5.0000
114 ATT    113
                                P1=    0.2000000
115 INT    118
                                P1=    4.0000
116 GAI    115
                                P1=    5.0600
117 SUM    111    114   -116
118 ATT    117
                                P1=    0.0500000
119 GAI    105
                                P1=    0.0325000
120 GAI    113
                                P1=    0.0900000
121 GAI    115
                                P1=    0.0500000
122 GAI    105
                                P1=    1.0000
123 GAI    113
                                P1=    0.6000000
124 GAI    115
                                P1=    0.2000000
200 SUM      2   -205
201 GAI    200
                                P1=    0.1330000
202 SUM    201    203
203 GAI    204
                                P1=    0.2500000
204 SUM   -205     15
205 INT    202
                                P1=   10.0000
206 SUM      2   -211
207 GAI    206
                                P1=    0.1390000
208 SUM    207    209
209 GAI    210
                                P1=    0.1960000
210 SUM   -211     15
211 INT    208
                                P1=    8.0000
212 SUM      2   -217
213 GAI    212
                                P1=    0.1180000
214 SUM    213    215
215 GAI    216
                                P1=    0.1560000
216 SUM   -217     15
217 INT    214
                                P1=   10.0000
218 SUM    204    210    216
302 CON
                                P1=   40.0000
```

```
303 CON
                                        P1=  104.0000
304 SUM    302   -303
305 GAI    304
                                        P1=    5.0000
306 SUM    305    307   -308
307 GAI    316
                                        P1=   96.0000
308 GAI    315
                                        P1=  105.0000
309 ATT    306
                                        P1=  270.0000
310 SUM   -307    308   -311    312
311 GAI    316
                                        P1=    6.000E+03
312 GAI    317
                                        P1=    6.000E+03
313 ATT    310
                                        P1=  544.0000
315 INT    309
                                        P1=   40.0000
316 INT    313
                                        P1=    8.0000
317 CON
                                        P1=  100.0000
318 GAI    304
                                        P1=    1.7500
319 SUM    318    320   -321
320 GAI    329
                                        P1=  132.0000
321 GAI    328
                                        P1=  125.0000
322 ATT    319
                                        P1=  360.0000
323 SUM   -320   -324    321    325
324 GAI    329
                                        P1=    6.000E+03
325 GAI    317
                                        P1=    6.000E+03
326 ATT    323
                                        P1=  816.0000
328 INT    322
                                        P1=   40.0000
329 INT    326
                                        P1=    8.0000
330 GAI    304
                                        P1=    2.0000
331 SUM    330    332   -333
332 GAI    341
                                        P1=  150.0000
333 GAI    340
                                        P1=  150.0000
334 ATT    331
                                        P1=  450.0000
335 SUM   -332   -336    333    337
336 GAI    341
                                        P1=    6.000E+03
337 GAI    317
                                        P1=    6.000E+03
338 ATT    335
```

```
                                        P1=    1.360E+03
340 INT    334
                                        P1=   40.0000
341 INT    338
                                        P1=    8.0000
342 GAI    316
                                        P1=    0.2000000
343 GAI    329
                                        P1=    0.3000000
344 GAI    341
                                        P1=    0.5000000
345 SUM    342    343    344   -351
346 GAI    345
                                        P1=  800.0000
347 SUM   -351    358
348 GAI    347
                                        P1=  200.0000
349 SUM    346    348
350 ATT    349
                                        P1=  432.0000
351 INT    350
                                        P1=    0.0000
352 SUM    351   -358
353 GAI    352
                                        P1=  150.0000
354 SUM    359   -358
355 GAI    354
                                        P1=  300.0000
356 SUM    353    355
357 ATT    356
                                        P1=   18.0000
358 INT    357
                                        P1=    0.0000
359 CON
                                        P1=  159.0000
360 GAI    315
                                        P1=  500.0000
361 GAI    328
                                        P1=  300.0000
362 GAI    340
                                        P1=  200.0000
363 SUM    360    361    362
364 GAI    367
                                        P1=    2.000E+03
365 GAI    372
                                        P1=  100.0000
366 ATT    363
                                        P1=    4.200E+03
367 INT    366
                                        P1=    0.0000
368 GAI    372
                                        P1=    1.800E+03
369 GAI     82
                                        P1=    1.600E+03
370 SUM   -368    369
371 ATT    370
                                        P1=  840.0000
372 INT    371
                                        P1=    0.0000
373 LIM    367
```

P1= 0.0000
P2= 7.0000

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