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A System Model for Closed-circuit Inhalation Anesthesia

I. Computer Study

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Developing a custom computer program to simulate the uptake, distribution, and elimination of inhalational anesthetics allows the anesthesiologist to address specific problems, but extensive skills are required to translate the involved processes first into a set of mathematical equations and then into a satisfactory computer program. The first step is often facilitated by solutions offered in the literature. The second step demands computer proficiency that is often not available, but this problem can be obviated by means of a special-purpose simulation language (SPSL). We therefore constructed a model for closed-circuit inhalation anesthesia with the aid of the block-structured SPSL TUTSIM®. Noticeable differences with previous models are that the linear, 14-compartment basic model does not assume a constant alveolar concentration and mimics circulation times through the use of blood pools. Advanced features of the SPSL were used to develop variants of the basic model to simulate feedback-controlled isoflurane administration, nitrous oxide uptake, and the impact of a nonlinearity by incorporating the effect of enflurane on cardiac output. Two variants were concatenated to form a multiple model showing the concentration and second-gas effects. The model was capable of reproducing the anesthetic uptake from previous experimental studies for nitrous oxide. After its validation for other anesthetic agents, the model can be used for clinical, teaching, and research purposes. The SPSL freed the authors from the problems associated with computer programming and allowed them to concentrate on the structure of the model. (Key words: Anesthetic techniques: closed-circuit. Anesthetic gases: nitrous oxide. Anesthetics, volatile: isoflurane; enflurane. Computer: simulation; models; programming languages. Pharmacokinetics: uptake; distribution.)

MATHEMATICAL MODELS have been valuable scientific tools for studying the kinetics of respiratory and inert gases as well as inhaled anesthetic agents. For more than two decades, analogs, or mainframe analog, digital, and hybrid computers have been used to handle such models. Today, ready-to-run personal computer programs are capable of solving the differential equations involved.[1] We constructed our own model because these software packages did not allow us to address the problems of interest to us. The two major steps in developing a satisfactory computer model are: 1) formulation of a mathematical model that describes the processes involved; and 2) translation of this mathematical model into a computer program using a programming language. The second step requires computer proficiency that is generally not available. To bypass the second step we used a special-purpose simulation language (SPSL) developed at the Twente University of Technology (The Netherlands) and hence named TUTSIM®.§

The purposes of this study were 1) to construct a model to simulate the uptake and distribution of a single inhaled anesthetic agent during closed-circuit anesthesia; and 2) to extend this basic model to more elaborate models with additional features. In previous models of closed-circuit anesthesia, anesthetic uptake was calculated by assuming that the arterial and hence the alveolar concentration of an agent remains constant.[2–4] A model based on this assumption greatly simplifies the mathematical treatment but limits itself to the calculation of the amount of anesthetic needed to replace that consumed by a subject. Such a model is not able to predict the breath-by-breath alveolar concentrations after bolus injections of a liquid anesthetic agent into a closed system. The model presented here does not assume a constant alveolar concentration and therefore lends itself for validation by noninvasive measuring techniques such as respiratory mass spectrometry.

Materials and Methods

THE SPSL

We used TUTSIM® Professional Version 6.55 (Meerman Automation, Neede, The Netherlands) on an IBM AT personal computer system (640 kB RAM, 80287 coprocessor, 30-MB hard disk unit, Hercules graphics board). TUTSIM® is a toolbox with a large number of preprogrammed modules or building blocks that perform dedicated tasks. A typical block receives inputs, processes these inputs according to its function, and produces an output. The block function determines the name of the block: for example, a SUM block carries out a summation, and an INT block performs integration. Some blocks do not have inputs: for example a CON block allows one to

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introduce a constant in the model, and a PLS block creates a single-pulse or a step function. For each of the constants or the mathematical operations in a mathematical model a block with an appropriate function must be selected. The model structure is entered with one statement per block, such as in "3, SUM, 1, 2". This means that block 3 adds the outputs of blocks 1 and 2. Model parameters such as the initial value of an integration or a constant are entered separately.

An Example of Model Development

Figure 1A describes a system in which a solute is carried into and out of a compartment by a flow of fluid through the compartment. Formulating a mathematical model for this simple system is straightforward[5] (appendix A) and yields the differential equation shown in figure 1B. Figure 1C shows how the SPSL solves this equation by means of a nine-block model that includes one INT block. (See fig. 1 for symbols.) Because the input of the INT block is dC_W/dt, the output is C_W. Starting with the initial condition, $C_W = 0$; the simulation calculates C_W for a specified number of time steps dt. For illustrative purposes we chose $C_{in} = 0.6$ M, $\dot{V} = 1$ l·min^{-1}, $V_W = 10$ l, and $\dot{Q}_{other} = 1$ mol·min^{-1}. This example model was used, *mutatis mutandis,* to describe each of the compartments in the basic model.

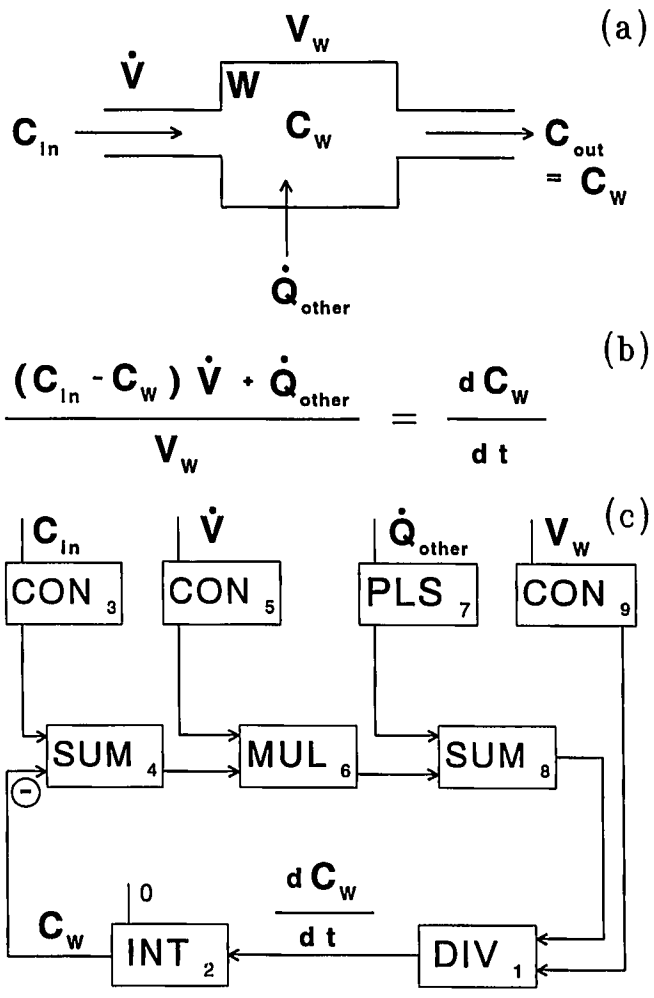

FIG. 1. Example of model development. *A:* Scheme. Compartment W with volume V_w is being washed through by a flow of fluid ($\dot{V}$) carrying a solute with concentration C_{in}. The outflowing concentration C_{out} equals the concentration in the compartment C_w. $\dot{Q}_{other}$ is an additional amount of solute entering the compartment per unit of time. *B:* Mathematical formulation. *C:* Block diagram. Reading the block diagram must preferably start at the input of the integration (INT) block 2 to reveal the resemblance to the mathematical formulation. The zero above the INT block indicates that its initial condition is $C_w = 0$. The CON blocks introduce constants, whereas the SUM, MUL, and DIV blocks represent summation, multiplication, and division, respectively. The PLS block is a pulse function.

The Basic Model

The basic model¶ for the uptake and distribution of a single inhalational anesthetic depicts the body and the closed anesthetic circuit as a system of 14 compartments (fig. 2). A merely nonmathematical account of the model is presented here; its mathematical formulation is given in Appendix B. Two hundred blocks translate the set of equations into a TUTSIM® model. Comprehensive quantification for the model is given in tables 1–4, which list the symbols and units, the assumed relationships between physiologic variables, and the default values used in the model, respectively. Data on isoflurane, enflurane, and nitrous oxide are given since only these anesthetics are used in the typical simulations.

The anesthetic agent is taken up from the lung–closed circuit compartment and is then distributed to these other tissue compartments: kidney, brain, heart, liver (including all other well-perfused organs), muscle, connective tissue, and adipose tissue. The model derives from the subject's age, body weight, height, and gender the other physiologic variables, including tissue volumes, blood volume, cardiac output, dead space, "alveolar space" (V_L), and tidal volume (table 2). For the typical simulations we model a 40-yr-old man of 70-kg body weight and 1.80-m height (1.88-m^2 body surface area).

The data source for total blood volume, cardiac output, tissue volumes, tissue blood flows, and partition coefficients was Lowe and Ernst[4] except where noted as follows (see tables 2–4 for details). The volume into which an anesthetic agent is distributed in the lung (V_L) not only includes the midinspiratory alveolar gas volume, *i.e.* the functional residual capacity plus half a tidal volume,[6] but also the lung tissue volume multiplied by its tissue–gas partition coefficient. The functional residual capacity is

¶ A list on paper of the basic model program is available from the author (JGCL).

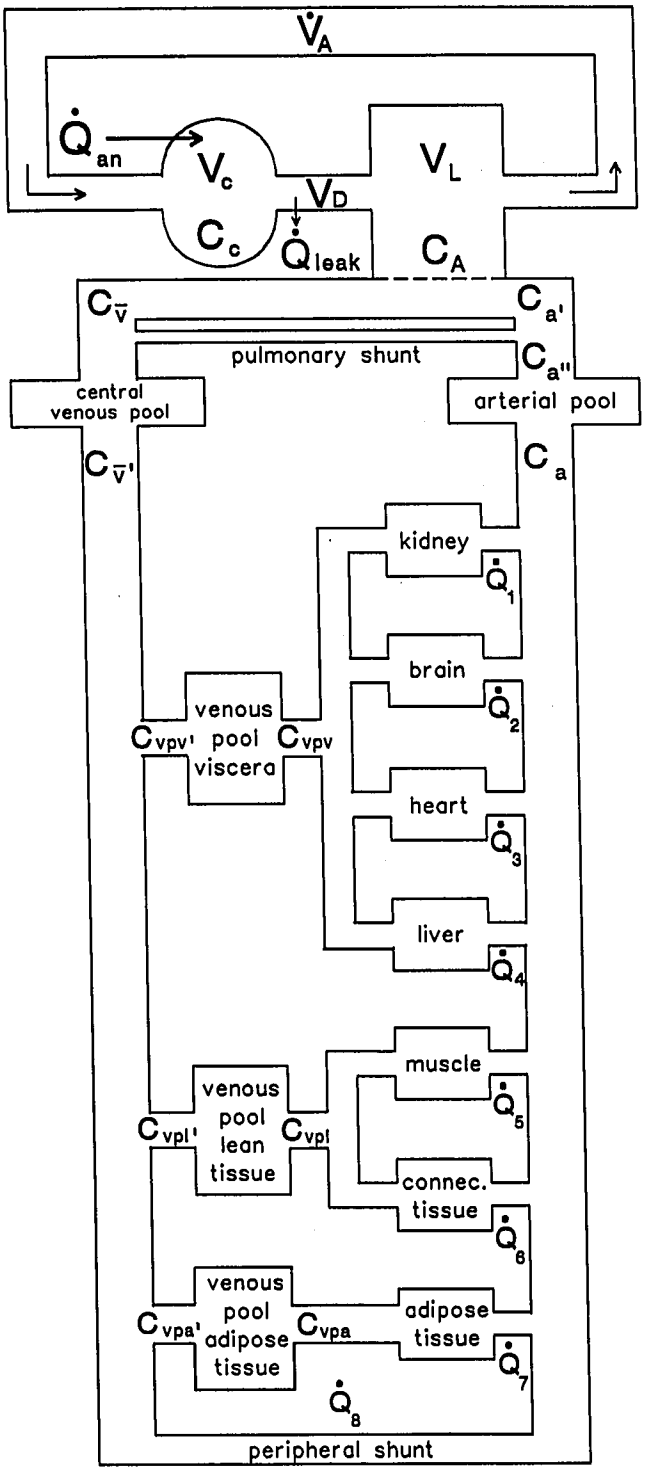

FIG. 2. The basic model, including closed breathing circuit and patient tissues. The symbols are listed in table 1.

calculated as a function of height, age, and gender with the aid of a regression equation for unanesthetized subjects in the sitting position[7] and subsequently adapted for a supine, anesthetized subject by a correction factor 0.65.[8]

All blood is stored in pools, thus simulating the differences in circulation times that exist in the body.[9,10] One fifth of the total blood volume is at arterial tension and is therefore stored in the arterial pool.[10] The rest of the blood is shared among the central venous pool and three venous pools associated with tissues and organs grouped into compartments, mainly on the basis of perfusion.[10]

The basic model is intended to operate with controlled

TABLE 1. Symbols and Units

A = age (yr)
BW = body weight (kg)
C_a = fractional concentration of agent in blood leaving arterial pool
$C_{a'}$ = fractional concentration of agent in blood exposed to alveolar gas
$C_{a''}$ = fractional concentration of agent in blood entering arterial pool
C_A = fractional concentration of agent in alveolar gas
C_C = fractional concentration of agent in anesthetic circuit
$C_{\bar{v}}$ = fractional concentration of agent in blood leaving central venous pool
$C_{\bar{v}'}$ = fractional concentration of agent in blood entering central venous pool
C_{vpa} = fractional concentration of agent in blood entering adipose-tissue venous pool
$C_{vpa'}$ = fractional concentration of agent in blood leaving adipose-tissue venous pool
C_{vpl} = fractional concentration of agent in blood entering lean-tissue venous pool
$C_{vpl'}$ = fractional concentration of agent in blood leaving lean-tissue venous pool
C_{vpv} = fractional concentration of agent in blood entering viscera venous pool
$C_{vpv'}$ = fractional concentration of agent in blood leaving viscera venous pool
C_{ω_i} = fractional concentration of agent in venous blood draining tissue i
f_s = shunt fraction of cardiac output
FRC = functional residual capacity (liter)
H = height (m)
$\dot{Q}$ = cardiac output ($l \cdot min^{-1}$)
$\dot{Q}_{an}$ = anesthetic agent administered as vapor ($l \cdot min^{-1}$)
$\dot{Q}_i$ = blood flow through tissue i ($l \cdot min^{-1}$)
$\dot{Q}_{leak}$ = anesthetic agent lost as vapor at BTPS through leaks ($l \cdot min^{-1}$)
t = time (min)
$\dot{V}_A$ = alveolar ventilation at BTPS ($l \cdot min^{-1}$)
V_{bl} = total blood volume (l)
$V_{bl,a}$ = arterial blood volume = blood volume in arterial pool (l)
$V_{bl,v}$ = venous blood volume (l)
V_c = volume of anesthetic circuit at BTPS (l)
V_D = volume of dead space at BTPS (l)
V_i = volume of tissue i (l)
V_L = "alveolar space" = lung volume into which the anesthetic agent is distributed at BTPS (l)
$\dot{V}_{leak}$ = gas volume lost from the closed circuit by mass spectrometry and/or other causes ($l \cdot min^{-1}$)
V_T = tidal volume at BTPS (l)
V_{vpa} = blood volume of the adipose tissue venous pool (l)
V_{vpc} = blood volume of the central venous pool (l)
V_{vpl} = blood volume of the lean tissue venous pool (l)
V_{vpv} = blood volume of the viscera venous pool (l)
$V_Z = V_c + V_D$ (l)
λ_b = blood–gas partition coefficient
λ_i = tissue–blood partition coefficient for tissue i

Symbols are given in alphabetical order.

TABLE 2. Relationships among Variables

$$FRC = 0.65(2.340H + 0.009A - 1.090)\ (man)*$$
$$FRC = 0.65(2.240H + 0.001A - 1.000)\ (woman)*$$
$$\dot{Q}_{leak} = \dot{V}_{leak}(C_c + C_A)/2.0$$
$$V_Z = V_c + V_D$$
$$V_{bl} = 0.07BW\dagger$$
$$V_{bl,a} = 0.2V_{bl}\ddagger$$
$$V_{bl,v} = 0.8V_{bl}\ddagger$$
$$V_D = 0.002BW$$
$$V_L = FRC + 0.5V_T + 0.008BW\ \lambda_b\ \lambda_{lung}$$
$$V_T = 0.01BW$$
$$\dot{V}_A = 10\ (V_T - V_D)$$
$$V_{vpc} = 0.126V_{bl,v} = 0.101V_{bl}\ddagger$$
$$V_{vpl} = 0.364V_{bl,v} = 0.291V_{bl}\ddagger$$
$$V_{vpv} = 0.399V_{bl,v} = 0.319V_{bl}\ddagger$$
$$V_{vpa} = 0.111V_{bl,v} = 0.009V_{bl}\ddagger$$
$$\dot{Q} = 0.2BW^{0.75}\dagger$$

* Data given by Quanjer and Tammeling.[7] The factor 0.65 reflects the impact of the supine position and the anesthetized state.[8]

† Lowe and Ernst.[4]

‡ Values are adapted from data of Mapleson[10] and Davis and Mapleson.[9]

ventilation and does not take the concentration and second-gas effects into account. Alveolar ventilation is the difference between total ventilation and dead space ventilation. The basic model has two versions. These differ in the size of their peripheral shunt: the shunt is 0 and 16% of the cardiac output for version A and B, respectively. The 16% peripheral skin shunt has been proposed by Mapleson.[10]

A liquid anesthetic agent injected directly into the closed system is assumed to mix uniformly after vaporization with the contents of the anesthetic system and to behave as an ideal gas. A bolus injection of liquid anesthetic was simulated by adding anesthetic vapor to the closed system over a period of 60 s. The conversion between liquid and vapor is given in appendix B.

EXTENSIONS OF THE BASIC MODEL

Using some of the more advanced features of TUTSIM®, we introduced extensions into the basic model (version A) and constructed three other models—a nonlinear, a feedback-controlled, and a multiple model.

TABLE 4. Miscellaneous Values Used in the Basic Model

$$f_s = 0.05$$
$$V_c = 6.5\ l$$
$$\lambda_b = 1.50\ (isoflurane)*$$
$$\lambda_b = 1.90\ (enflurane)*$$
$$\lambda_b = 0.47\ (nitrous\ oxide)*$$
$$\dot{V}_{leak} = 0.1\ l \cdot min^{-1}$$
1 ml liquid enflurane = 210 ml vapor (37° C)*
1 ml liquid isoflurane = 206 ml vapor (37° C)*

* Data given by H. J. Lowe and E. A. Ernst.[4]

Nonlinear Model

Adding one specialized block turns the linear basic model with its fixed cardiac output into a nonlinear model that incorporates the effect of an inhaled anesthetic agent on cardiac output. The cardiac output was regulated in inverse proportion to the actual enflurane concentration in the heart muscle according to the data from Calverley and co-workers,[11] who reported that during the first hour of anesthesia 1.0 and 1.5 MAC enflurane was associated with a decreased cardiac output by 26 and 32%, respectively. To compare the basic with the nonlinear model, 60 min of closed-circuit anesthesia using bolus injections of liquid enflurane (one bolus of 3 ml followed by 14 boluses of 0.75 ml) were simulated with each of both models.

Feedback-Controlled Model

Incorporating a proportional–integral–derivative (PID) controller block allowed us to simulate the feedback-controlled administration of an inhaled anesthetic agent into a closed circuit. Figure 3 shows how we implemented a proportional–integral (PI) control scheme with the aid of one PID block and one CON block for the desired target concentration (setpoint). The derivative element was omitted because it is not absolutely necessary in practice.[12]

TABLE 3. Default values for the Compartments of the Basic Model Version A and Version B

Compartment	Volume*	$\dot{Q}_i$†		λ_i		
		Version A	Version B	Isoflurane	Enflurane	Nitrous Oxide
Lung tissue	0.0080	—	—	1.80	1.30	1.00
Kidney	0.0040	0.250	0.2100	1.30	1.20	0.87
Heart	0.0040	0.050	0.0420	1.50	1.60	1.13
Brain	0.0210	0.160	0.1344	2.40	1.60	1.06
Liver	0.0570	0.300	0.2520	2.30	2.00	0.93
Muscle	0.4260	0.130	0.1092	1.50	1.60	0.86
Connective tissue	0.2600	0.060	0.0504	2.00	1.40	0.80
Adipose tissue	0.1500	0.050	0.0420	63.00	37.00	3.00
Peripheral shunt	—	0.000	0.1600	—	—	—

Values are data given by H. J. Lowe and E. A. Ernst,[4] except for the $\dot{Q}_i$ for version B.

* Expressed as fractions of the body weight. The remainder is the total blood volume (0.07BW).

† Blood flows through the compartments are expressed as fractions of the cardiac output.

Applying the scheme of figure 3 allowed the study of 1) the amount of isoflurane needed per unit of time to achieve and maintain a 1% alveolar concentration and 2) the nitrous oxide uptake rate—after priming the lung-breathing system compartment—at constant alveolar concentration (65%). The constants K_P and K_i were optimized during successive simulation runs for either isoflurane or nitrous oxide.

Multiple Model

TUTSIM® is capable of concatenating two or more submodels that could operate independently and thus generating a multiple model in which each submodel may interact with the others. Our multiple model consisted of the basic model with isoflurane as volatile agent and the extended model with feedback-controlled nitrous oxide administration. The controlled variable was the circuit nitrous oxide concentration, rather than the alveolar concentration. To simulate the concentration and second-gas effects, we incorporated the algorithm of Tanner and co-workers[1] into the multiple model. First, nitrous oxide in oxygen was administered with feedback control to maintain either a 70% or a 10% nitrous oxide circuit concentration. Second, these two simulation runs were repeated, but isoflurane vapor was also added to the closed system, at a rate of 25 ml · min^{-1}.

Results

Example Model

Figure 4 shows the concentration–time profile of the solute in the single compartment of the example model illustrated in figure 1. A constant inflowing concentration was disturbed by an additional input of solute from the 10th to the 30th min of the simulation run. The concentration in the compartment eventually equals the inflowing concentration. The calculation step size used was 0.1 min for 100 min total simulation time; thus, C_W was calculated 1,000 times during the simulation run. A step size of 0.05 min doubled the calculation time while enhancing the accuracy by only 0.02%.

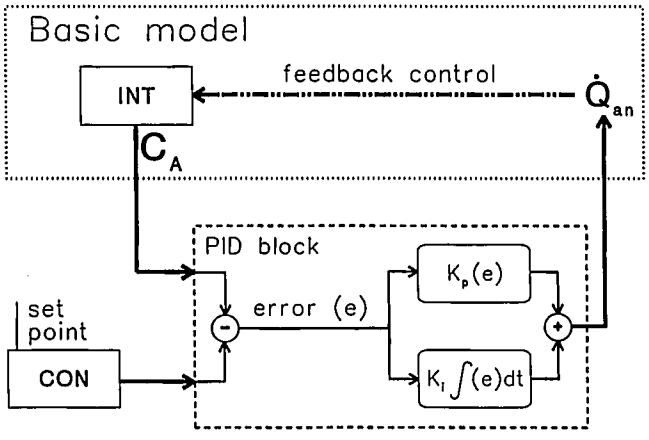

FIG. 3. Extension of the basic model with two extra blocks to simulate proportional-integral feedback control of the alveolar concentration C_A of an anesthetic agent. A constant (CON) block represents the set point or desired value. The error signal, *i.e.*, the difference between the set point and the actual value of C_A, passes to two feedback control elements. The first element is the proportional term, $K_p(e)$, and the second the integral term, $K_i\int(e)dt$, where K_P and K_i are proportionality constants. The sum of these elements forms the output of the controller, *i.e.*, the amount of anesthetic delivered to the closed system per unit of time ($\dot{Q}_{an}$).

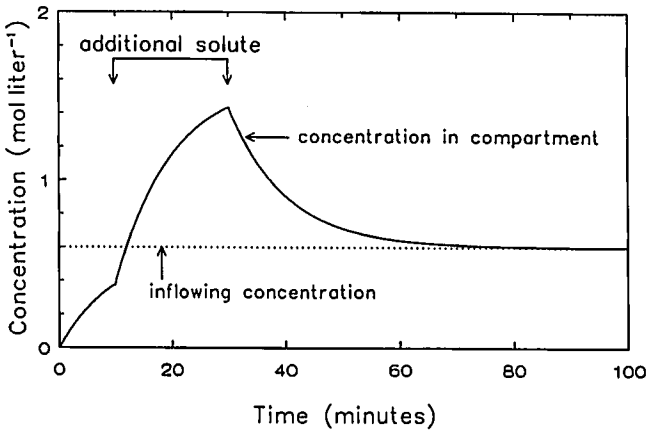

FIG. 4. Inflowing and compartment concentration for the one-compartment model shown in figure 1.

Basic Model

After 0.7-ml bolus injections of liquid isoflurane into the closed system, the time courses of the alveolar, arterial, and brain tissue concentrations have a sawtooth pattern. The boluses were injected at the times indicated by Lowe's "square root of time" model[4] (fig. 5). Version B generates alveolar concentrations up to 11% (9.44% on the average) higher than those obtained with version A. Figure 5 shows that the calculated arterial concentration is higher than

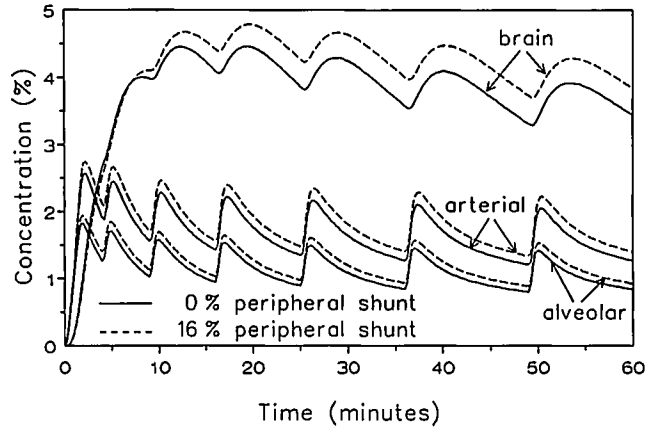

FIG. 5. Simulated time courses of the alveolar, arterial and brain concentrations after nine injections of 0.7 ml liquid isoflurane into the closed system. The first two boluses were injected at 0 min and were followed by one bolus each at 1, 4, 9, 16, 25, 36, and 49 min. Note the difference between the 0 and 16% peripheral shunts.

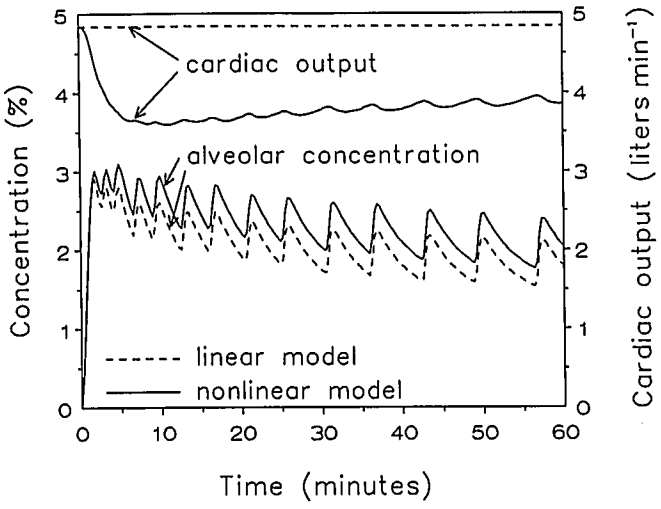

FIG. 6. Comparison of simulated results obtained with the basic linear model and those obtained with the nonlinear model after one injection of 3 ml liquid enflurane followed by 14 injections of 0.75 ml into the closed system. In the linear model the cardiac output is fixed, whereas in the nonlinear model the cardiac output is regulated in inverse proportion to the actual enflurane concentration in the heart muscle.

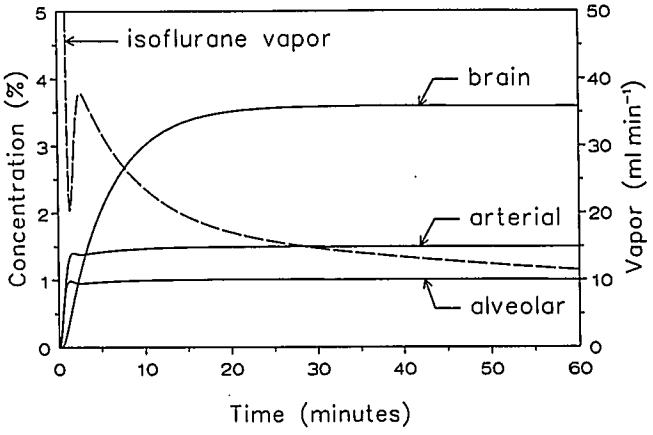

FIG. 7. Simulated time courses of the alveolar, arterial, and brain concentrations with feedback-controlled administration of isoflurane into the closed system. The output of the proportional-integral controller expressed in milliliters per minute isoflurane vapor achieves and maintains a target alveolar concentration of 1%.

the alveolar concentration and that the brain concentration is higher than the arterial concentration. These differences are related to the solubility of isoflurane in blood and brain tissue.[13]

EXTENSIONS OF THE BASIC MODEL

The differences in the time courses of alveolar enflurane concentrations in the basic linear and the extended nonlinear model can be appreciated in figure 6. The maximum depression of the cardiac output, *i.e.*, a decrease from 4.84 to 3.6 $l \cdot min^{-1}$, occurs 11 min after the start of the enflurane administration. The cardiac depression results in an alveolar enflurane concentration that is up to 14% greater than that of the linear model.

Figure 7 shows the capability of the PI controller to achieve an alveolar isoflurane concentration of 1.0% within 2 min without any noticeable overshoot. After 30 min the ratios of arterial to alveolar and of brain tissue to arterial concentrations are 1.5 and 2.4, respectively. Near equilibrium, these ratios reflect the blood–gas and brain–blood partition coefficients for isoflurane.**

Figure 8 shows that the rate of nitrous oxide uptake calculated by the extended model is in agreement with the experimental results of Barton and Nunn[14] and Severinghaus[15] between the 5th and the 55th min. However, the model predicts that after the 55th min there will be a tailing-off of the nitrous oxide uptake rate that is much more prominent than observed by these authors. Figure 8 also shows that the predictions of our model are less consistent with the experimental results of Beatty and co-workers, as compared to the agreement between our model and the results of Barton and Nunn[14] and of Severinghaus.[15,16]

Figures 9 and 10 show the results of four different simulations illustrating the concentration and second-gas effects. First, the ratio of alveolar to circuit concentration (C_A/C_c) of nitrous oxide is observed while its circuit concentration is maintained automatically at 10%. Second, the same observation is made with 70% nitrous oxide. The differences between the two C_A/C_c curves reflect the concentration effect: the ratio is 0.103 higher (0.895 *vs.* 0.792) after 2 min of 70% than after 2 min of 10% nitrous oxide inhalation (fig. 9). The third and fourth

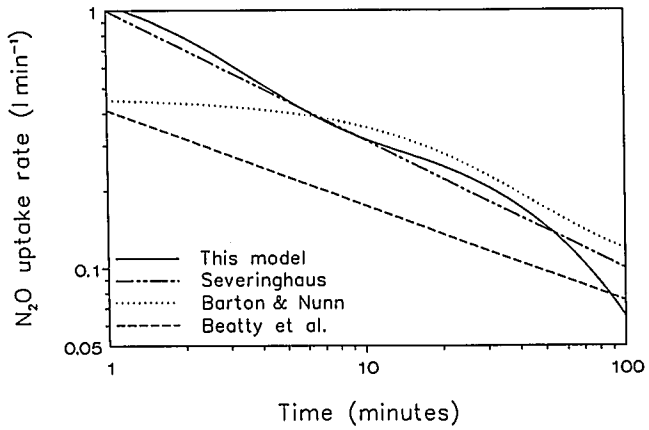

FIG. 8. Comparison of simulated results and experimental results from various authors (Severinghaus,[15] Barton and Nunn,[14] and Beatty *et al.*[16] for nitrous oxide uptake rates. Note the logarithmic scales.

** A volatile anesthetic moves from one phase to another under the action of a difference in partial pressure. At equilibrium the same anesthetic partial pressure exists in both phases; the concentrations, however, are different, and their ratio equals the partition coefficient.[4,13]

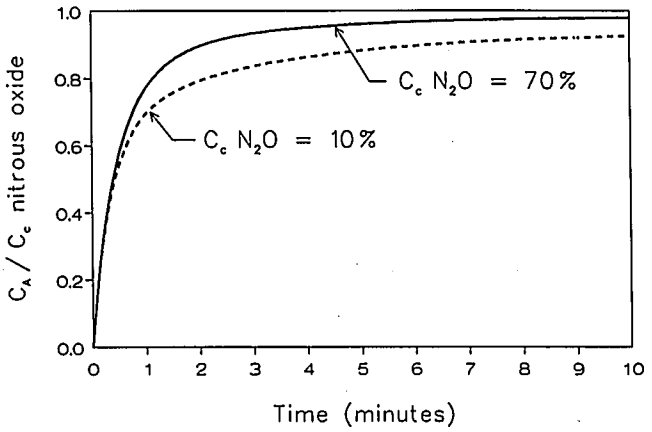

FIG. 9. Simulated influence of the feedback-controlled circuit concentration (C_c) of nitrous oxide (10 or 70%) on the alveolar to circuit concentration ratio (C_A/C_c) for nitrous oxide in oxygen. The alveolar rate of increase of nitrous oxide is more rapid with the higher nitrous oxide concentration (by the concentration effect).

simulation runs use the same conditions as the first and second runs, respectively, except that isoflurane is simultaneously added to the circuit (fig. 10). The differences between the two C_A/C_c curves for isoflurane now reflect the second-gas effect: the ratio is 0.04 higher (0.465 *vs.* 0.425) after 2 min of its simultaneous administration with 70% than with 10% nitrous oxide. Thus, the alveolar rates of increase of nitrous oxide and of isoflurane are more rapid with the higher nitrous oxide circuit concentration.[17]

Discussion

The Current Model *versus* Others

Our model has some important and unique features: 1) unlike the majority of the models of anesthetic uptake and distribution, it includes the breathing system and does not avoid the complexity of the closed system; 2) unlike earlier closed-circuit anesthesia models it does not assume constant arterial concentration or zero circulation time; and 3) it is written with the aid of an SPSL, thus allowing the user to profit from the programmers' knowledge hidden in the specialized blocks and to concentrate on the model's structure.

Several authors have discussed the simplifying assumptions on which mathematical models for inert gas exchange are based.[6,18–21] We therefore mention only those assumptions that determine the major differences between the various mathematical models published. Our basic model assumes that ventilation and circulation are continuous processes. Riggs and Goldstein reported that treating the ventilation as continuous is a legitimate simplification.[21] In contrast with most models, ours did not assume either that the circulation times are zero or that venous blood is part of each tissue compartment; rather, we followed Mapleson's suggestions by introducing his concept of blood pools that mimics circulation times in the human body.[10] Mapleson showed that the errors introduced by the failure to represent circulation times are of importance only in the first minutes of administration or recovery or after any other changes of inspired concentration.[10] The latter situation frequently is present during closed-circuit anesthesia that incorporates an intermittent bolus injection technique, and therefore we adopted Mapleson's concept.

In our basic model and its variants, the blood flows to the compartments are constant and do not depend on the anesthetic concentration as they do in some elaborate halothane models by other authors.[22–24] We were definitely more interested in modeling the uptake of the newer anesthetic isoflurane. However, data for organ weights and compartment blood flows already vary considerably from author to author,[4,9,10,25] and in addition, there exists little quantitative information about the impact of isoflurane on the cardiac output partitioning in the human circulation. The model lung has no subcompartments receiving different proportions of cardiac output and alveolar ventilation as in a model for gas exchange during the initial stages of nitrous oxide uptake and elimination.[26] We did not attempt to simulate changes in cardiac output partitioning and ventilation–perfusion mismatching until we had examined the predictive performance of the version of the model with fixed distribution and an ideal ventilation–perfusion relationship.

Our nonlinear model predicted that an average reduction of the cardiac output by 21.5% (maximum 25.7%) resulted in an average alveolar concentration of enflurane that was 12% higher than in the linear model (fig. 6). As

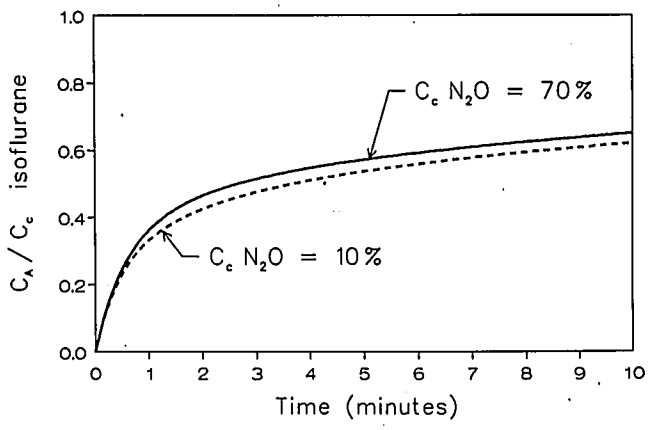

FIG. 10. Simulated influence of the feedback-controlled circuit concentration (C_c) of nitrous oxide (10 or 70%) on the alveolar to circuit concentration ratio (C_A/C_c) for isoflurane in nitrous oxide/oxygen. The curves for isoflurane are obtained by the administration of isoflurane vapor at a constant rate of 25 ml·min^{-1}. The alveolar rate of increase of isoflurane is more rapid with the higher nitrous oxide concentration (by the second gas effect).

a matter of comparison, we refer to the nonlinear model of Ashman and co-workers,[27] who simulated the impact of 1 h of halothane anesthesia with a constant inspired partial pressure of 1.0% atmosphere, resulting in an alveolar partial pressure of 0.6% halothane. They computed that as a result of the nonlinearity, the uniformly distributed cardiac output decreased gradually from 6.0 to 5.0 $l \cdot min^{-1}$, *i.e.*, a 16.6% reduction, and that the partial pressure of halothane in the lung was elevated by 6%.

The optimal number of compartments in a model for the uptake and distribution of volatile anesthetics has been a matter of discussion.[28] Models with one,[29] two,[30] or three[31] compartments have been considered. A 3-plus-1 model,[10,32,33] *i.e*, three body compartments and one lung compartment, and a 4-plus-1 model[19] have been described. Five,[27] seven,[24] twelve,[22] and eighteen[23] compartments have been used. These models can be classified in two types: physiologic models and empirical models. Physiologic models relate to known physiologic facts and mimic the normal human anatomy. Thus, each of the model's compartments represents a physically recognizable part of the body, such as the brain. The number of compartments is limited only by the anatomic, physiologic, and physicochemical knowledge about the system described. Empirical models are based on pharmacokinetic studies that lead—through the process of parameter estimation to fit a model to the experimental data—to the description of compartments that have no true anatomic interpretation. The compartmentalization in our physiologic basic model version A agrees with that of Lowe and Ernst,[4] with the alveolar space and the blood pools as noticeable exceptions. This helped us during the development process because we could have confidence in our model's predictions when anesthetic uptake grossly matched that of Lowe's model. The number of compartments in our model thus originates from the idea of constructing a physiologic model that combines the compartmentalization described by Lowe and Ernst[4] with Mapleson's[10] concept of blood pools.

Feedback Control

Simulating the feedback-controlled delivery of a volatile agent into a closed system may help to avoid time-consuming experiments in humans or animals. Simulation studies allow optimization of the proportionality constants K_p and K_i for the control elements in the PI control algorithm (fig. 3) while a feedback-controlled delivery system is designed. Simulation may also aid in developing a dose regimen for the induction and maintenance of closed-circuit anesthesia. The isoflurane vapor delivered by the controller (fig. 7) may be imitated during clinical practice by using different methods of administration of anesthetic agents, such as liquid injection to cover the high uptake rate at the start of anesthesia followed by the use of a vaporizer.

Feedback control of the alveolar nitrous oxide concentration enabled us to simulate the alveolar capillary nitrous oxide transfer (fig. 8). Beatty and co-workers[16] have already discussed the discrepancies between the nitrous oxide uptake rates measured by various authors and especially the discrepancies between their own results and those of others. They also have suggested that the predicted tailing-off in the rate of nitrous oxide uptake after 55–60 min of anesthesia is not observed in experimental studies because of the loss of nitrous oxide through surgical wounds.

Although the feedback control of the circuit concentration of nitrous oxide allowed us to simulate the concentration and second-gas effects, such a constant nitrous oxide concentration in a closed system must be regarded as barely attainable in practice (fig. 9).

Using an SPSL

Although simulation software may be written in virtually any language, such as BASIC,[1] Pascal,[34] or FORTRAN,[35] the block-structured SPSL has handled those parts of a computer simulation that would have required extensive programming. Designing an acceptable human–machine interface, as well as developing routines for visualizing the results (graphics), error handling, importing and exporting data, and mathematical operations such as integration are indeed time-consuming tasks, even for an expert. Tanner and co-workers state that two thirds of the source code of their anesthesia simulator contains graphic statements and trending procedures, whereas only one third consists of the model equations.[1] This detailed overhead of a simulation can be fully handled by an SPSL, of which TUTSIM® is only one.

In its present form, TUTSIM® has some general and specific limitations. Although an SPSL lets us avoid tedious computer programming, it does not free us from first formulating a mathematical model. Searching the literature, however, is often rewarding. For example, our system model implements a set of equations mainly based on the principle of the conservation of matter, for which numerous mathematical formulations are available (appendix A). Although an SPSL is optimized for certain tasks, it does this at the expense of flexibility. Moreover, TUTSIM®'s use of block numbers is an awkward means of entering the structure of a model into the computer. Thus, the prospect of rearranging the blocks of a large model requires careful consideration.

Validation

A new model must be validated before it can be used properly, such as for teaching or for designing a drug

administration scheme to achieve a desired target concentration. A model validation was performed for nitrous oxide by comparing the experimental rates of uptake of nitrous oxide reported by various authors[14–16] with the uptake rate predicted by our model (fig. 8). Another method of validation is the comparison of the predictions of the model with the predictions of a model already clinically validated. Although the anesthetic uptake in our model grossly matches the anesthetic uptake of the square root of time model, we predict slightly higher isoflurane uptake than did Lowe and Ernst.[4] Indeed, figure 5 shows that the average arterial isoflurane concentration decreases as a function of time, whereas the square root of time model assumes a constant arterial concentration (1.5%) after the same dose regimen. Moreover, we are not aware of any model for closed-circuit anesthesia that includes Mapleson's[10] concept of blood pools and at the same time allows prediction of breath-by-breath alveolar concentrations after bolus injections of liquid anesthetic agent into the closed system. Validation of the performance of our basic model is therefore mandatory and is presented in a separate study.[36]

We constructed a model for inhalation closed-circuit anesthesia. The use of an SPSL freed us from the problems associated with computer programming and allowed us to concentrate on the structure of the model. The model was capable of reproducing the anesthetic uptake of previous experimental studies for nitrous oxide. After clinical validation for other anesthetic agents, the basic model presented in this study may be used for clinical, teaching, and research purposes. Alternatively, it may be used as the basis for a more complete description of the patient–closed system entity by means of the multiple-model approach.

Appendices

Appendix A

The principle of the conservation of mass is applied to describe how a solute is carried into and out of a compartment by a flow of fluid through the compartment. Riggs has defined this principle as follows[5]: "During any interval of time, the quantity of solute entering a given compartment must be equal to the quantity of solute leaving the compartment by all routes, plus the quantity of solute accumulated in the compartment".

Figure 1A illustrates our example model, in which W represents the compartment. Assuming that both compartment volume and flow are constant and that the inflow and outflow of fluid are equal, we can formulate a mathematical model by looking at what will happen during an infinitesimal interval of time, dt. The quantity of solute entering W is equal to the infinitesimal volume of fluid, $\dot{V}dt$, multiplied by the inflowing solute concentration, C_{in}, plus the quantity of solute added to W, $\dot{Q}_{other}\,dt$:

$$dX_{in} = \dot{V}dt\ C_{in} + \dot{Q}_{other}dt \quad (1)$$

We assume that thorough mixing in the compartment occurs instantaneously, so that $C_{out} = C_W$. Thus the quantity of solute in the outflowing fluid is:

$$dX_{out} = \dot{V}dt\ C_{out} = \dot{V}dt\ C_W \quad (2)$$

The principle of conservation of mass implies that during any interval of time, dt, the quantity of solute accumulated in W is:

$$dX_W = dX_{in} - dX_{out} \quad (3)$$

Combining equations 1, 2, and 3 and letting $X_W = V_W C_W$, we obtain:

$$V_W dC_W = \dot{V}dt\ C_{in} + \dot{Q}_{other}\,dt - \dot{V}dt\ C_W \quad (4)$$

Dividing both sides by $V_W dt$ and rearranging yields:

$$\frac{dC_W}{dt} = \frac{(C_{in} - C_W)\,\dot{V} + \dot{Q}_{other}}{V_W}$$

Appendix B

Table 1 lists the symbols and table 2 the relationships between the variables used in the mathematical model development. Tables 3 and 4 show the default values used in the model. For the sake of clarity, the equations are expressed at BTPS conditions. (BTPS defines the following conditions of a gas: 37° C, 760 mmHg, and saturation with water vapor.) The concentration (C) of an inhaled anesthetic agent is therefore expressed as fraction of total gas rather than of the dry part.

A gas leak of 100 ml · min^{-1} from the anesthetic circuit is allowed for. The concentration of the anesthetic agent lost herein is the mean of the inspiratory and alveolar concentrations. The loss of anesthetic may be caused by the sample flow of a side-stream gas analyzer and uptake by the walls of the breathing system. The volume of the anesthetic circuit including the ventilator bellows is 6.5 l.

Describing each of the model's compartments in a similar way as the only compartment in the example model (appendix A) allows us to derive the following equations. Under the conditions illustrated in figure 2, we obtain for the circuit compartment:

$$\frac{dC_c}{dt} = \frac{\dot{V}_A}{V_Z}(C_A - C_c) + \frac{\dot{Q}_{an} - \dot{Q}_{leak}}{V_Z}$$

Notice that $\dot{Q}_{an}$ is the anesthetic agent administered as vapor per unit of time (l · min^{-1}). The administration of x ml liquid isoflurane or enflurane is simulated by letting

$\dot{Q}_{an} = 0.206x$ or $\dot{Q}_{an} = 0.210x$, respectively, over a period of 1 min (table B4).

We obtain for the lung compartment:

$$\frac{dC_A}{dt} = \frac{\dot{V}_A}{V_L}(C_c - C_A) - \frac{\dot{Q}(1 - f_s)(\lambda_b C_A - C_{\bar{v}})}{V_L}$$

Since $\lambda_b C_A = C_{a'}$, we find that:

$$C_{a''} = C_{a'}(1 - f_s) + C_{\bar{v}} f_s$$

For the arterial pool we obtain:

$$\frac{dC_a}{dt} = \frac{\dot{Q}}{V_{ap}}(C_{a''} - C_a)$$

while the rate of change of the concentration in the venous blood draining the tissue i (C_{ω_i}) is:

$$\frac{dC_{\omega_i}}{dt} = \frac{\dot{Q}_i}{V_i \lambda_i}(C_a - C_{\omega_i})$$

The concentration in the tissue i then equals $C_{\omega_i} \times \lambda_i$. The concentration of anesthetic agent in the venous blood draining the viscera (kidney, brain, heart, and liver compartments) is:

$$C_{vpv} = \sum_{i=1}^{4} \frac{C_{\omega_i}\dot{Q}_i}{\dot{Q}_1 + \dot{Q}_2 + \dot{Q}_3 + \dot{Q}_4}$$

For the viscera venous pool we obtain:

$$\frac{dC_{vpv'}}{dt} = \frac{\dot{Q}_1 + \dot{Q}_2 + \dot{Q}_3 + \dot{Q}_4}{V_{vpv}}(C_{vpv} - C_{vpv'})$$

Similarly treating the processes in the venous pool of the lean tissue (muscle and connective tissue), the venous pool of the adipose tissue, and the central venous pool yields the following six equations:

$$C_{vpl} = \sum_{i=5}^{6} \frac{C_{\omega_i}\dot{Q}_i}{\dot{Q}_5 + \dot{Q}_6}$$

$$\frac{dC_{vpl'}}{dt} = \frac{\dot{Q}_5 + \dot{Q}_6}{V_{vpl}}(C_{vpl} - C_{vpl'})$$

$$C_{vpa} = C_{\omega_7}$$

$$\frac{dC_{vpa'}}{dt} = \frac{\dot{Q}_7}{V_{vpa}}(C_7 - C_{vpa'})$$

$$C_{\bar{v}'} = C_{vpv'}\frac{\dot{Q}_1 + \dot{Q}_2 + \dot{Q}_3 + \dot{Q}_4}{\dot{Q}} + C_{vpl'}\frac{\dot{Q}_5 + \dot{Q}_6}{\dot{Q}} + C_{vpa'}\frac{\dot{Q}_7}{\dot{Q}} + C_a\frac{\dot{Q}_8}{\dot{Q}}$$

$$\frac{dC_{\bar{v}}}{dt} = \frac{\dot{Q}}{V_{vpc}}(C_{\bar{v}'} - C_{\bar{v}})$$

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