MACPUF

A Simulation of Human Respiration, Gas Exchange and Control

For anyone whose career may involve acute medicine, a superficial grasp of respiration is inadequate. *MacPuf* offers a classical physiological model from which students can gain familiarity with, for example, the management of shock or heart failure, hypoxia, breathlessness, the use of blood gas measurements, cardiopulmonary resuscitation or oxygen therapy. Especially useful for teaching is the possibility of following the complicated consequences of a failure in the delivery of oxygen in more detail than with a real patient. The main functions, the volumes of body spaces and gas concentrations and pressures in critical sites are all quantified in *MacPuf*, so that students can study the rates at which changes occur. This computer simulation therefore supplies a complementary approach to traditional laboratory exercises and clinical bedside experience.

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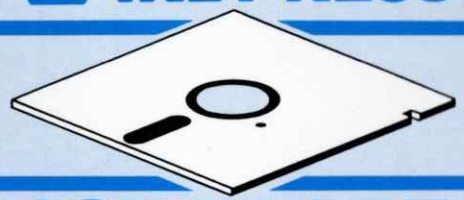

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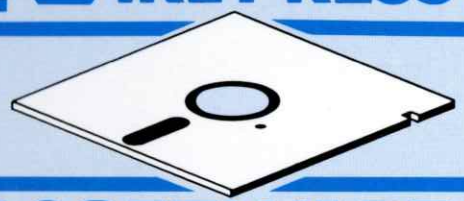
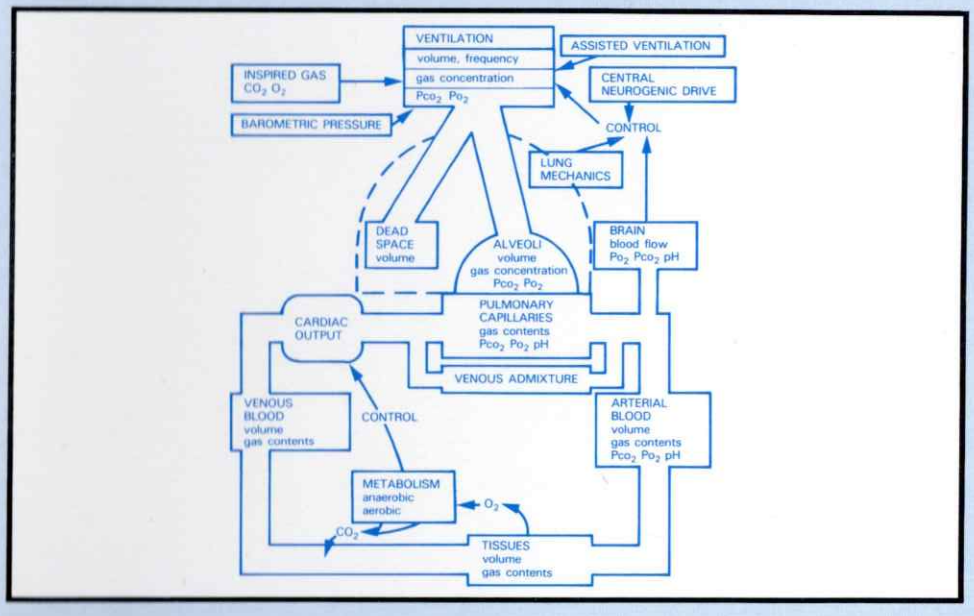


SOFTWARE

THE MAC SERIES OF MEDICAL AND PHYSIOLOGICAL SIMULATIONS

MACPUF

D Ingram, C J Dickinson
& K Ahmed



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PO Box 1,
Eynsham,
Oxford OX8 1JJ,
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ISBN 1-85221-043-5

CONTENTS

LIMITATION OF LIABILITY

Mathematical models cannot be expected to provide completely accurate descriptions of the systems under consideration; our aim is to make these models relevant and helpful to someone learning about the behaviour of the system. To this end, they have been revised and developed through many versions over a seventeen-year period and have been in continuous use at many centres during that time.

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1. The model

1.1 Introduction to *MacPuf*

Knowledge of the processes by which the body achieves exchange of oxygen and carbon dioxide in a variety of situations in health and disease is central to the intelligent practice of medicine. It is arguable that a simple descriptive knowledge is sufficient as part of a general scientific education, but for anyone whose career may involve acute medicine, superficial grasp is not enough. Management of shock, heart failure, hypoxia, breathlessness, use of blood gas measurements, cardiopulmonary resuscitation, oxygen therapy — all require a quantitative familiarity with respiration.

Traditionally, animal or human laboratory exercises and bedside clinical experience are used to attain this familiarity. They are not always very effective. Computer simulation represents another complementary approach.

MacPuf is not just a 'computer model' — *MacPuf* is a computer simulation of a classical physiological model. Its flexibility is such that you can develop your understanding of fundamental physiological and clinical situations without laboratory exercises, without endangering patients, and without understanding computers.

Two features make *MacPuf* particularly useful as a learning resource. First, the delivery of oxygen depends on the demand (set by tissue metabolism), on the capacity for storage in various sites, and on a chain of transport mechanisms. In this chain, malfunction of one part places a strain on others, which may or may not be able to adapt or compensate. *MacPuf* allows you to follow the consequences of this complex malfunction in a more detailed way than is possible in real life. Second, *MacPuf* can show you the rate at which changes occur. The main functions and also the volumes of various spaces and the gas concentrations and pressures in critical sites have all been quantified in *MacPuf*.

1.2 Brief description

The lungs and airways are simulated in mechanical terms and the pulmonary circulation and gas exchange are simulated by a simple three-compartment model. In one compartment, ventilation and blood flow are ideally matched; one is ventilated but not perfused (dead space); and one is perfused but not ventilated (venous admixture). (See Figure 1.) This model determines the transfer of oxygen into, and carbon dioxide out of, incoming venous blood, and thus determines arterial gas composition. Arterial blood passes round to the tissues, where oxygen is extracted and carbon dioxide produced; the blood then returns to the lungs. The carriage of gases in the blood is governed by accurate mathematical expressions describing the oxygen and carbon dioxide dissociation curves, taking account of temperature, barometric pressure, haemoglobin, packed cell volume, pH and bicarbonate concentration. The storage of gases in the tissues is based on the best available estimates of the mean tissue 'dissociation curves'. Ventilation can be either 'artificial', in which case rate, tidal volume and end-expiratory pressure can be specified, or 'natural', i.e. controlled

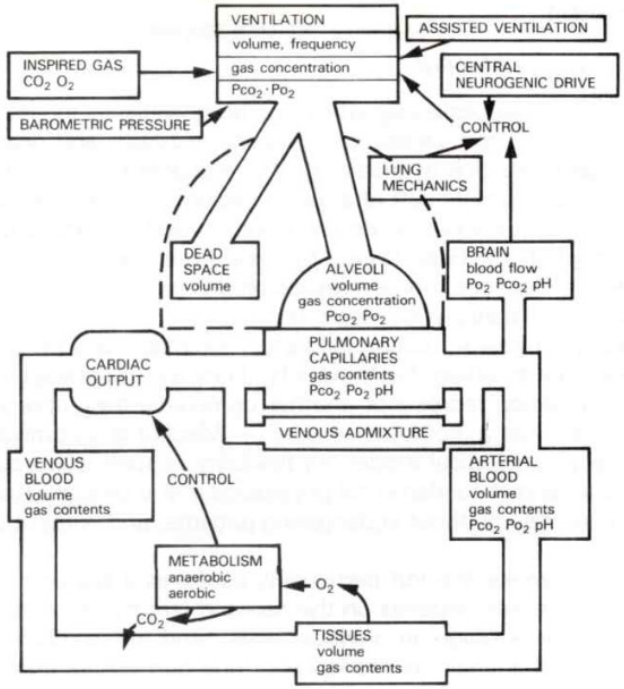


Figure 1. Block diagram of the model.

by known influences upon ventilation (PO_2 and PCO_2, with an additional central neurogenic drive which has been made arbitrarily proportional to tissue oxygen consumption, but which can be increased to simulate increased reflex drives from the lungs or reduced to simulate narcosis or anaesthesia).

If the tissues acquire an oxygen debt, proportional anaerobic respiration results in generation of lactic acid and CO_2, with appropriate changes in pH and with appropriate effects on related mechanisms.

We now consider how the model is used and the information obtained. Every parameter is initialized at the start to a value realistic for a normal 70 kg young adult, at rest, consuming about 250 ml oxygen per minute (STPD). A number of factors (see list in Appendix 1) can be changed by manual interaction at the end of each run (normally a simulated 3 minutes). The results appear in the form of a graph indicating total ventilation, respiratory rate, arterial PCO_2 and PO_2, but numerical output of any selected value, or even of all values, can be obtained (see Section 4). The normal iteration interval is the same as the standard time interval for output of results, i.e. 10 s, but it can also be reduced manually. (It should not be made longer because accuracy suffers and a steady state cannot be reached.) A 10-s interval represents a reasonable compromise between accuracy and computing time, but with high ventilation or cardiac output a smaller interval (e.g. 2 – 5 s) may be necessary to retain stability.

It is possible to change inspired oxygen percentage, inspired carbon dioxide percentage, nominal cardiac output as a percentage of resting value (the actual cardiac output is automatically altered by changes in gas tensions), the 'venous admixture' (shunt, wasted perfusion), the amount of added dead-space and dynamic dead-space dependent on capacity and many other things. This facility allows simulation of ventilatory defects, defects of ventilation – blood flow relationships, oxygen therapy, carbon dioxide inhalation, tracheostomy (negative added dead-space), muscular exercise (increased tissue metabolic rate), altered barometric pressure or blood volume, anaemia, changes in lung elastance, body temperature, and metabolic acid – base disturbances, either singly or in combination. For example, the effects of hyperbaric oxygen therapy can be studied by altering both inspired oxygen concentration and barometric pressure.

In addition to the standard printed values, the program computes at each 10-s (or smaller) interval the tensions, contents, and total amounts of oxygen and carbon dioxide in the alveoli, in idealized pulmonary capillary blood, in arterial blood, in the tissues generally, in the brain, and in mixed venous blood returning to the lungs. Arterial bicarbonate, alveolar ventilation, expired respiratory quotient, tidal volume, effective dead space, effective venous admixture, predicted cardiac output and cerebral blood flow are also computed. At the end of each simulated 3-minute period (which can be shortened or extended), the usual clinical measurements are printed, and the model awaits further instructions. A test is made for lethal changes in pH and blood gases at each iteration, and if these limits are transgressed, 'death' results, a necropsy report is printed and a new (intact) subject is generated. At the end of each run, appropriate symptoms and nursing reports are issued. At any stage, the present state of the simulated subject can be stored, and recalled later if needed for different experiments.

The model can be used at different levels of complexity or sophistication. It is suitable for the most elementary physiological experiments, but also accurate enough to be able realistically to simulate complex clinical disorders and practical clinical therapy.

1.3 Limitations – conceptual and procedural

MacPuf has two main limitations: conceptual and procedural.

1.3.1 Conceptual

All attempts to model physiological systems are limited either by gaps in our knowledge or by simplifications implicit in the concepts. Thus, *MacPuf* treats the lungs 'as if' there are three compartments with zero, normal and infinite ventilation/blood flow ratios, whereas there is really an infinite gradation. The model uses various empirical means to overcome the limitations of this oversimplification, and to improve the accuracy of its performance during changing conditions, but it will inevitably, at times, fail to match adequately real-life situations. (Incidentally, the originators of *MacPuf* will be most grateful for information about faults of behaviour so that they can aim to correct them in later editions.)

Our limited understanding of the non-chemical factors governing breathing can only be crudely quantified as 'central neurogenic drive'. Such limitations are in *MacPuf* simply because the concepts are in us.

1.3.2 Procedural

Considerable care and thought have been devoted to making *MacPuf* easy to use, and medical students all over the world who have tried it out as a learning resource have had no serious difficulty. You will still have to practise with *MacPuf* to be able to use it to its full capacity. Inevitably, since it works through a computer, there will be a certain amount of unfamiliarity for some people, but it needs emphasizing again that no knowledge of computers is needed.

After familiarizing yourself with *MacPuf* through the introductory Section 2, you will start to be aware of apparent limitations of speed and convenience. By reading Section 3 (for experienced users), you will find that *MacPuf* has additional resources available which give added flexibility, e.g. the ability to change type of output and timescale, to avoid repetitive interactive dialogue and to store and recall the current state of the subject. Section 4 contains an account of further resources embedded in *MacPuf* which allow clinical simulation of various kinds, rebreathing experiments and other possibilities. To get the best return from these resources you need to have mastered fully the Sections 2 and 3.

Section 5 contains some suggested 'physiological' experiments which you might try to examine with the model, and some more advanced clinical problems, which can also be examined, in a preliminary way at least, using *MacPuf*.

Appendix 1 contains a complete list of changeable factors and computed variables with their initial values and code numbers for easy reference.

1.4 Implementation

MacPuf is written in Fortran 77 and uses high-level graphics programming techniques. The technical description of the program is beyond the scope of this manual, but full details are available in the monograph 'A Computer Model of Human Respiration' (1977) by C.J. Dickinson, published by MTP Press Ltd, St. Leonard's House, Lancaster, England, or University Park Press, Chamber of Commerce Bldg, Baltimore, MD 21202, USA.

The graphics version of *MacPuf* is about 50% longer than the original published form. The basic physiological design has been altered little, except to improve the accuracy of representation of lung gas-exchange. The program has been rewritten to take advantage of the facilities of Fortran 77 and its structural design has been revised and clarified, an inevitable need with a program which has evolved gradually. Also, considerable revision was required to allow the graphical procedures to be satisfactorily incorporated.

2. Operating the program: beginners' guide

2.1 How to get started

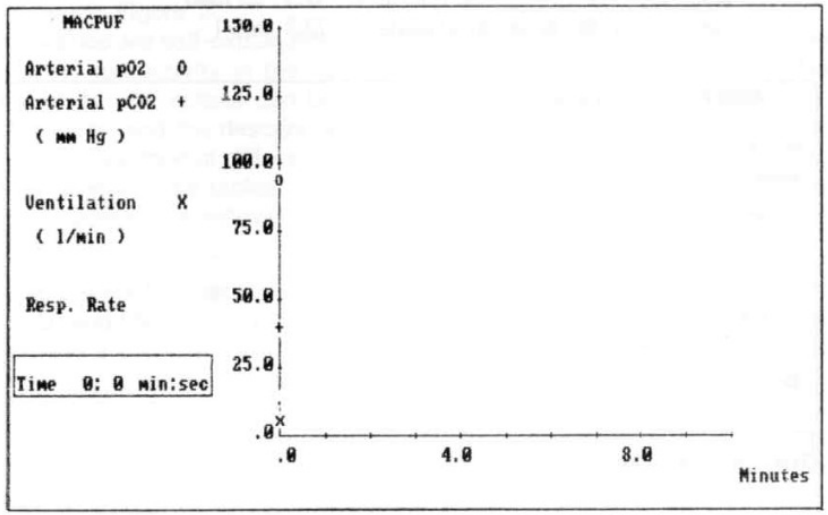
The procedure for installing and gaining access to the program on your computer is covered in separate installation notes. This handbook starts from the point where you call up the program. Operation is largely self-explanatory and makes use of straightforward menus of options. Brief explanatory messages are available at each stage of the dialogue.

On running the program, a title banner is displayed, followed optionally by a brief introduction for new users.

You will now be asked to specify the units to be used for gas pressures. The model allows for either mm Hg or kPa (SI units) but you cannot interchange the two without stopping and restarting the program.

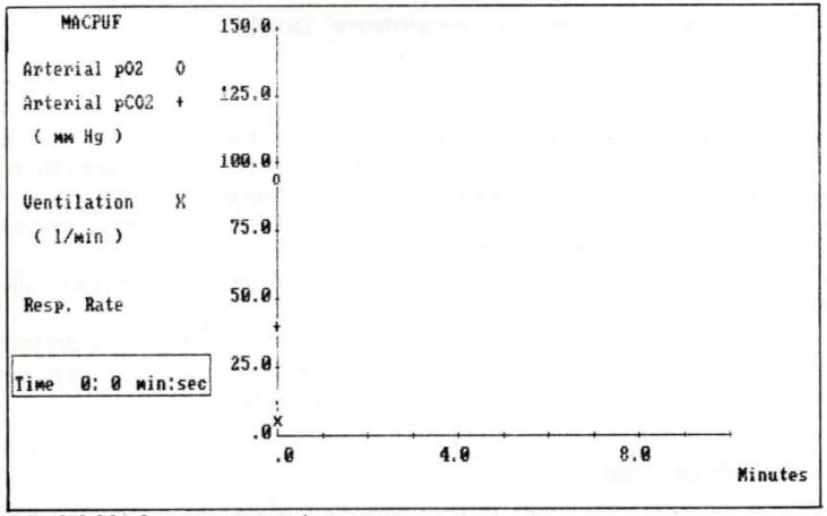
2.2 How to get help

The program is equipped with help facilities which may be invoked to explain the options available at key points in the interactive dialogue which sets up



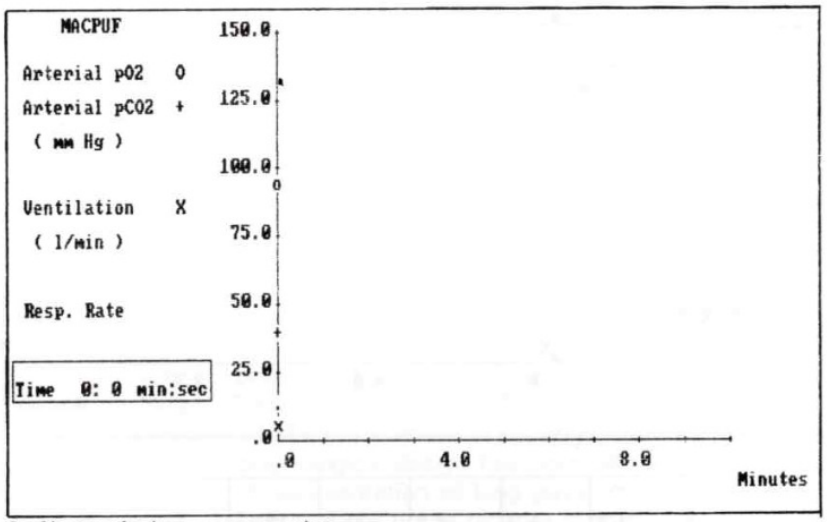
.3	7.4	6.1	4.4	23.8	101.7	93.6	40.1
Exp.RQ	Art.pH	Tot.-Vent.-Alv.		HCO3	Alv.pO2	pO2 -Art.-	pCO2

Figure 2. Baseline display for the standard subject.



Arterial blood gas measurements:

Arterial pO2	=	12.5 kPa	O2 content	= 19.5 cc/100ml	Satn. = 97.%
pCO2	=	5.3	CO2 content	= 47.4 cc/100ml	
pH	=	7.40(40.nm)	Bicarbonate	= 23.8 mmol/l	



Cardio-respiratory measurements:

Respiratory rate	= 12.7	Tidal volume	= 478. ml
Total ventilation	= 6.1 l/min	Cardiac output	= 5.0 l/min
Total dead space	= 131. cc	Venous admixture	= 2.4 percent

Figure 3. Standard display of blood gas measurements and cardio-respiratory data produced at the end of a simulation run.

a simulation run. The general procedure is to respond to a question which you don't understand by typing 'Q' (for 'Query'), and then pressing the ENTER key. A message will then appear on the screen and you should afterwards be able to respond immediately to the original question. Figure 4 (overleaf) shows an example of the use of this facility.

2.3 Example of an actual run: the main menu of options

Once the units of measurement have been selected, the program sets up a standard 70 kg male subject and produces on the screen a standard graphical display (Figure 2).

The standard graph is of arterial PO_2 and PCO_2, minute ventilation and respiratory rate. Notice also the clock, which displays simulated time, and the values, continually updated, of 8 key respiratory variables. This set includes the numerical values of the arterial blood gas tensions and is produced by default at the outset, but it can be altered subsequently by the user (see Section 3.5).

The bottom section of the screen, below the window containing the graph, is reserved for dialogue, explanatory messages and further numerical displays of results. When the program pauses, you press keys in succession to reveal current values for the blood gas results and other cardio-respiratory variables as shown in Figure 3.

The values are self-explanatory and are given in the usual clinical units, with arterial H^+ ion activity in the nano-molal scale, as well as in pH units. Note that such tabular output can be selected or omitted to suit the needs of individual users and the description here covers the operation which is selected by default. Selection of different kinds of output is covered in detail in Section 3.

Having viewed the tables of baseline results, the user is then offered a main menu of options as follows:

Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Plot, 6. Stop

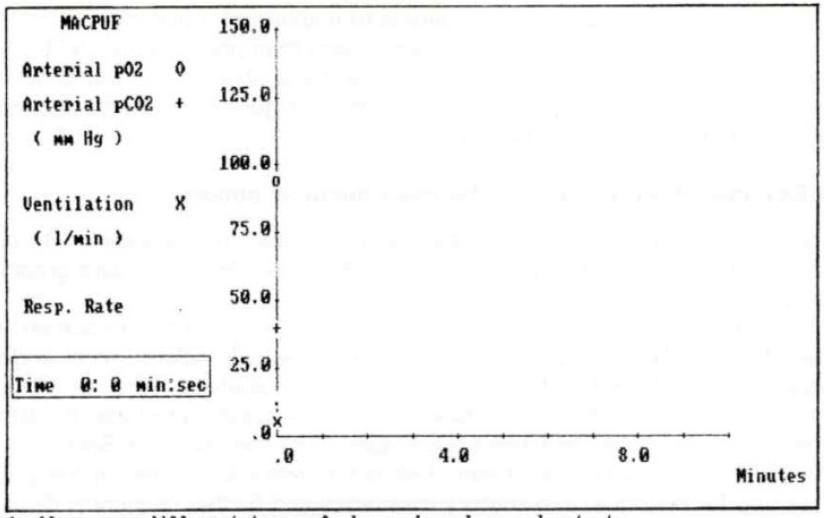
A message briefly describing these is obtained (Figure 4) if you ask for help (type 'Q' and ENTER at this point). Remember always to press the ENTER key to activate a command to the program. At any point typing '*' and ENTER will return you to the main menu.

The next example (Figure 5) was obtained when the user typed in '2', the instruction to 'Continue', i.e. proceed with no further change into (by default) another 3 minute run. At the end of this a new set of values would have been printed.

The plotting symbols on the graph are as follows:

'O———O'	for arterial PO_2 in mm Hg
'+———+'	for arterial PCO_2 in mm Hg
'X———X'	for total ventilation, i.e. volume of air in litres/min being breathed in or out
'.———.'	for respiratory rate, i.e. number of breaths/min
'*———*'	for nitrogen supersaturation index (if there has been recent reduction of barometric pressure in the model)

The time axis is set by default to cover 10 minutes of simulated time, but



1 allows many different types of change in values and output,
2 starts another run of standard (unless changed) 3 min.
3 starts again with a new subject, 4 prints a table of most useful values
5 allows results to be plotted, 6 stops the program

Figure 4. Example of help offered to explain the main menu of options.

in general this will vary according to the length of the simulation requested. The program sets up what appears to be the most satisfactory length of axis but this can be overridden by user command (see Section 3.5). When the time reaches the end of the axis, this display will be regenerated automatically with the same scale but a revised origin.

Certain operations such as the plotting of other model variables (Section 3.1) or inspection of numerical values throughout the modelled system (Section 3.2) have to overwrite the simulation results currently displayed. These results are always saved and regenerated automatically on the screen when the user subsequently requests a continuation of the current simulation.

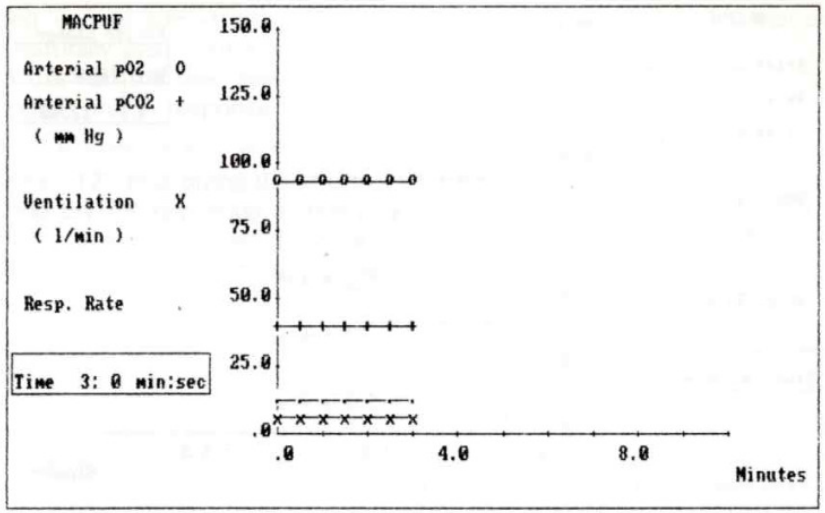
For the other options in the main menu:

1. Change	is described in Section 2.4.
3. Restart	simply creates a new standard subject and proceeds from the base-line values.
4. Inspect	is described in Section 3.2.
5. Plot	is described in Section 3.1.
6. Stop	stops the program.

2.4 How to change a model factor

On selecting the Change option, a subsidiary menu is offered as follows:

1. Change values, 2. Nat(ural)/Art(ificial) vent(ilation), 3. Store/B(ac)ktr(ac)k,
4. Run Change, 5. Presets



Exp.RQ	Art.pH	Tot.-Vent.-Alv.	HCO3	Alv.pO2	pO2 -Art.- pCO2
.8	7.4	6.1	4.4	23.8	101.6	93.6	40.1

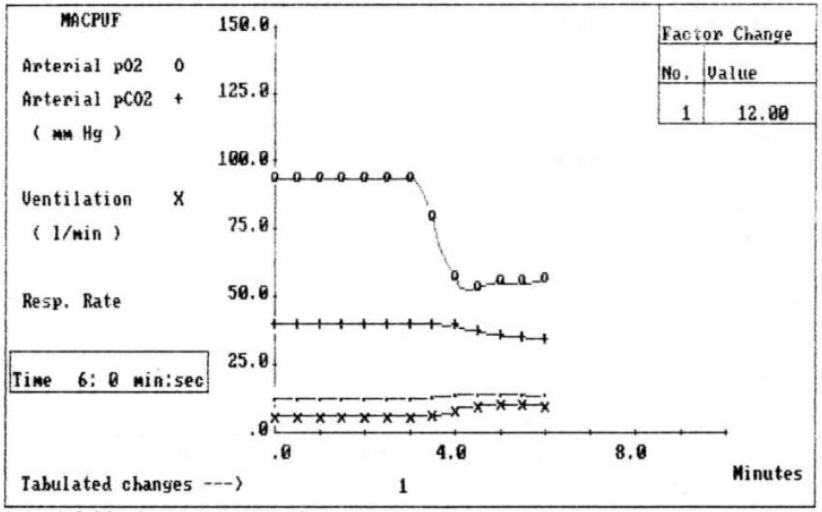
Figure 5. A standard 3-minute simulation run from the baseline steady state.

For the purposes of this elementary introduction we will concentrate on changes to model values, option 1.

The other options are dealt with elsewhere as follows:

2. Artifical ventilation	Putting the simulated subject on a ventilator	Section 2.5 (example)
3. Store/Backtrack	Saving the current state of the model for future use	Section 3.4
4. Run change	Allowing the user to specify the length of simulation and manner of output of results	Section 3.5
5. Preset subjects	Allowing the user to call up one of a number of special subjects or to specify basic data and measurements which enable the program to set up a suitable subject	Section 4.2

On choosing the option '1. Change values', type the number of the factor or factors you want to change. There are a large number of these, and a complete table of changeable variables appears in Appendix 1; the query option here lists the principal ones.



Arterial blood gas measurements:

Arterial pO2	=	7.4 kPa	O2 content	=	18.1 cc/100ml	Satn. =	90.%
pCO2	=	4.6	CO2 content	=	44.5 cc/100ml		
pH	=	7.44(37.nn)	Bicarbonate	=	22.6 mmol/l		

Figure 6. Simulation of an acute change from room air to breathing 12% oxygen in nitrogen.

You can change virtually every aspect of the model's anatomy and function, but for most experiments you will want to change a few main things, which are given 'factor numbers' as follows.

1. Inspired oxygen percent (normally 20.93).
2. Inspired CO_2 percent (normally 0.03).
3. Nominal cardiac output (percentage of normal value — around 5 litres/min).
4. Tissue metabolic rate (percentage of normal value) — equivalent to a resting value of about 250 ml/min oxygen consumed (an increase simulates exercise).
5. Extra right to left shunt of blood for 'venous admixture' — normally zero, but there is a small physiological shunt of blood of about 2% of the cardiac output, which is given as Venous admixture in the table in Figure 7 (units are percent cardiac output).
6. Extra 'dead space' or wasted ventilation — normally zero but there is a small normal dead space shown (in Figure 7) as total dead space of about 130 ml (units in ml).

At the start of the run illustrated below (Figure 7), the inspired oxygen was 21 percent (i.e. the subject was breathing room air); inspired CO_2 percentage was zero; the cardiac output was normal (nominal 5 litres/min); the tissue metabolic rate was '100%' of that normal for a resting adult; there was no

added 'venous admixture' and no extra dead space, over and above that present naturally (see normal values displayed in Figure 3).

In this run the user selected factor 1 (inspired oxygen percentage) to be changed, and in response to the request:

```
Factor 1 (current value = 20.93), Specify new value
```

typed in '12', thus giving the effect of breathing 12% oxygen in nitrogen. Pressing the ENTER key alone at this point would have the effect of leaving the current value unchanged (at 20.93).

The program then returns to the main menu of options:

```
Do you want to 1. Change, 2. Continue, 3. Restart, 4. Inspect, 5. Plot, 6. Stop
```

The user then asked for the run to 'Continue' by typing '2' and the computer responded by displaying a graph showing changes in ventilation and blood gases over the next three minutes and the values reached at the end of the run. Any appropriate symptoms and signs are displayed at this point as well. Note that the program has marked the change made to factor 1 — both its value (in the table in the top right hand corner) and its location in time (on the bar under the time axis).

Some changes to factors are assessed with respect to their physiological realism and comments may appear indicating likely outcomes. Some examples of such messages are to be found elsewhere in this handbook (e.g. impossible gas mixtures are commented on in the example in Section 3.3). In addition, the program checks whether a specified factor change is likely to cause instability in model calculations and, if so, the iteration interval will be automatically changed. The user can control this procedure as one of the 'Run Change' options mentioned above (see Section 3.5).

Take a good look at the example — you will see what is meant by a complex interaction. You will see that the fall in arterial oxygen tension stimulated breathing and this 'blew off' carbon dioxide and lowered arterial PCO_2, with a consequential rise in pH from 7.4 to 7.44.

2.5 Suggested preliminary experiments: artificial ventilation

Figure 7 illustrates a rather complex experiment. We suggest you might better start by observing the effects of altering (1) cardiac output and (2) total ventilation.

Cardiac output is manipulated by asking to change factor 3 and assigning a new value as a percentage of normal function.

Ventilation effects are studied most easily in isolation by using artificial ventilation. This is option 2 in the 'Change' subsidiary menu mentioned above. Invoking this option, the user is led through a dialogue to cut off normal ventilatory controls and to specify a rate and depth of ventilation and also end-expiratory pressure for the current subject.

It is wisest to fix the ventilation rate (e.g. at 14 breaths/min) and to change tidal volume (e.g. to 300 ml). Keep end-expiratory pressure zero unless you

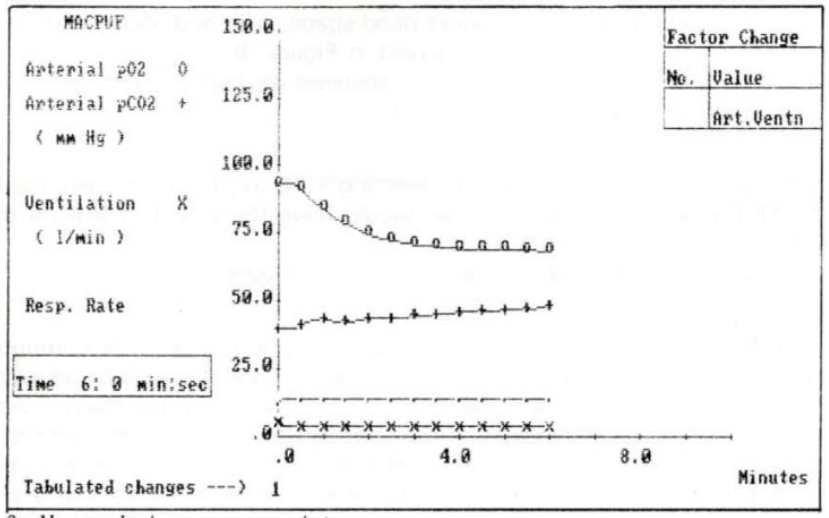


Figure 7. Controlling ventilation using the artificial ventilation option.

are an anaesthetist! The program confirms the values set with the message

*** ART.VENT. at 14./min., 300 ml Tid. vol., and 0.cm PEEP

Make sure you have reached a steady state by using the 'Continue' option if necessary. In the experiment summarized in Figure 7, inspection of the expired RQ (the first value in the boxed table of standard values displayed during the run) indicates that the model has not yet, after 6 minutes, reached a steady state. Note that PCO_2 rises only slowly because of the body's large CO_2 stores; this means that sometimes you have to be prepared to wait a long time, and perhaps to 'Continue' for three or more periods of 3 min, to get a properly steady state. Any time you want a new subject, choose main menu option '3. Restart' and at the end select option '6. Stop'.

This experiment will have given you some idea of *MacPuf's* capabilities and how to use it to do experiments. Section 3 explains how to extend your use of the program into more detailed areas of investigation.

3. Operating the program: further details

3.1 Storing and plotting results

The standard graphical display described in Section 2 is not suitable for all purposes. In some experiments we may wish to view the time course of different model variables or we may wish to cross-plot one variable against another.

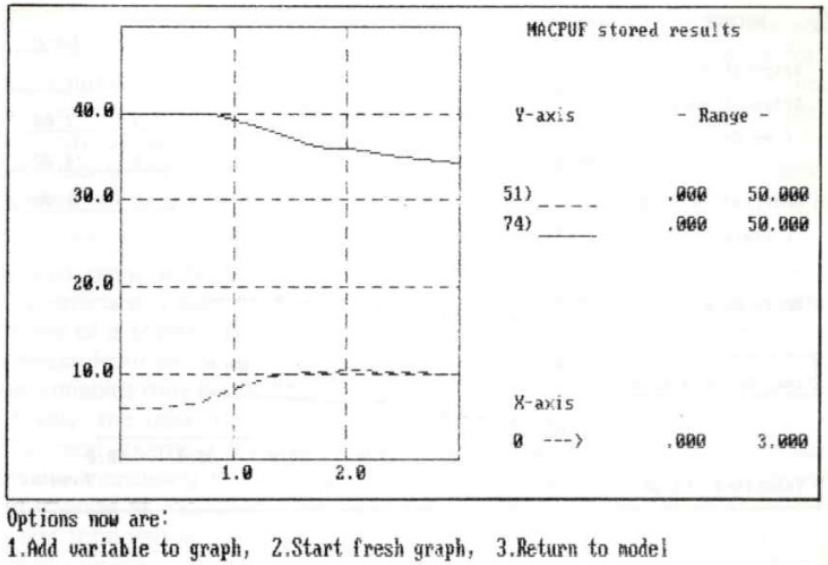


Figure 8. Illustration of the general plotting facility. Graphs of PCO_2 (factor 74) and total ventilation (factor 51) after inspired oxygen (factor 1) is reduced to 12% plotted against time in minutes. Note — Model variable numbers are as described in Appendix 1.

These facilities are provided in a general purpose graph-plotting module which can be selected as option 5 from the main menu.

The program preserves the calculated values of model variables for the last 100 points plotted or tabulated on the screen. Thus the standard plotted variables, PO_2, PCO_2, minute-ventilation, respiratory rate and nitrogen saturation index, and the currently specified set of 8 tabulated variables, continually updated during a run, may be replotted as functions of time or as cross-plots of one variable against another. (See Figure 8 and Section 3.3 for a description of how the list of tabulated variables can be changed.)

Specification of the graph to be plotted proceeds interactively. First the abscissa (x-axis) is defined in terms of the variable to be plotted (time by default).

Select x-axis variable using numeric code ( ) from: (default = time)
Time (0), PO2 (72), PCO2 (74), Ventn. (51), R.Rate (48), N2 index (83) or the tabular variables (69), (33), (51), (35), (60), (41), (72), (74).

The Query facility provides detailed description of this process and enables the user selectively to use the full model inspection facility to look up details of model factors and variables, their numeric codes, current and normal values. Variables are listed in physiological groupings and in numerical sequences.

Next the range of values to be displayed along the abscissa is defined.

Choose scaling: 1. automatic (range of values is 6.000 to 30.000) 2. to be specified
3. as specified previously (0.000 to 100.000)

Automatic scaling devotes the full width of plot available to the range of values

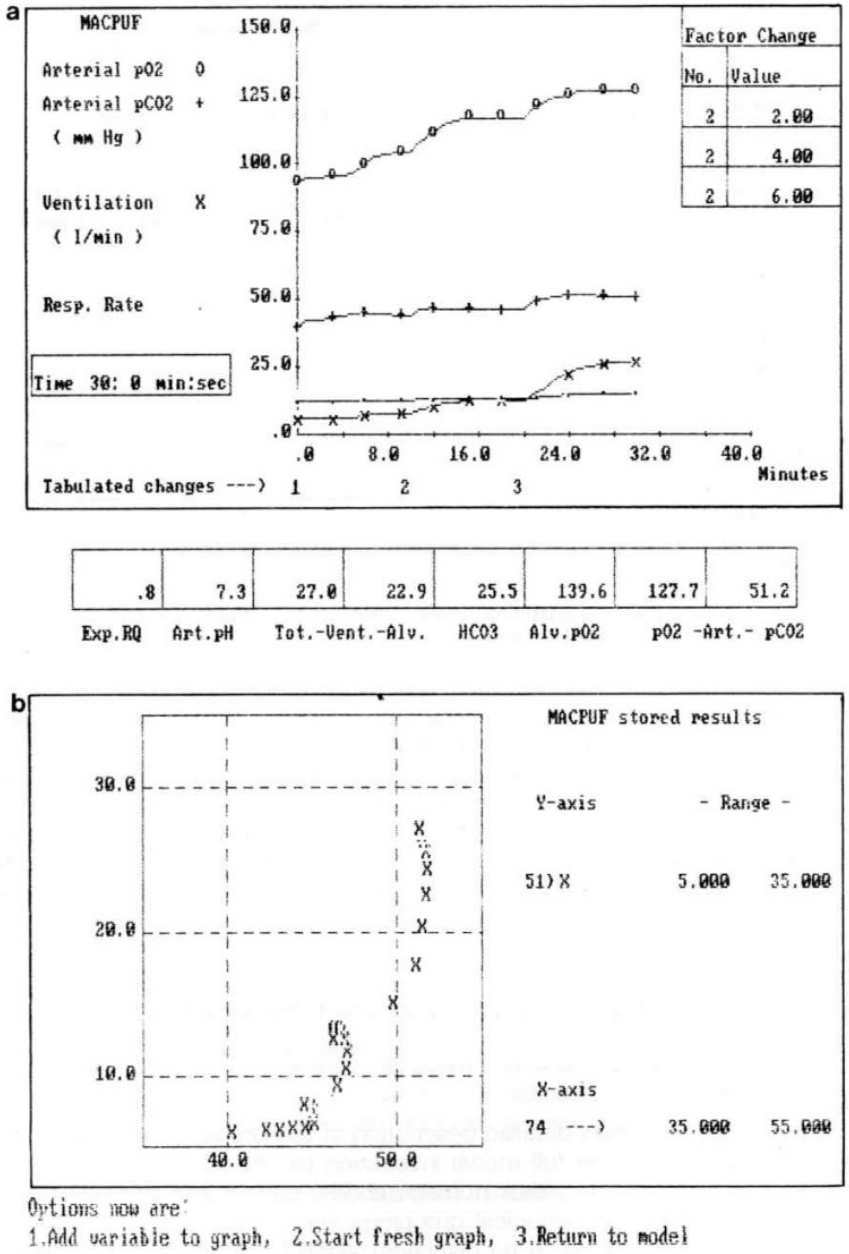


Figure 9. (a) Increase of factor 2 (inspired carbon dioxide level) to 6% over 30 minutes, and (b) relationship between PCO_2 and total ventilation over this period. (Note the gradual progress to steady state conditions.)

currently stored; the minimum and maximum of the values currently stored for the selected plot variable are shown. A different range of values for the plot may be specified by the user, or the range previously in operation [useful when constructing the ordinate (y-axis) for multiple plots on a single pair of axes] may be selected.

The user is now asked to specify a set of up to ten abscissa values defining a labelled set of grid lines parallel to the ordinate to be overlaid on the graph.

Specify (next) X-axis value at which bar to be plotted

(Allowed range is 6.000 to 30.000; <ENTER> alone to terminate list.)

The ordinate (y-axis) is specified in like manner and the user is then offered a choice of a scatter plot or a line graph with a variety of line-drawing modes to choose from (such as full or dashed lines). On completion of the plot, additional variables may be plotted on the same x-axis, a fresh graph may be started or, finally, the user may return to the main menu of options.

The next example (Figure 9) shows a standard display of the effect of gradually increasing the inspired CO_2 level to 6%, waiting 10 min between each change as indicated. The resulting relationship between PCO_2 (variable 74) and total ventilation in litres/min (variable 51) is plotted and illustrates the gradual convergence to steady-state conditions during each ten minute phase.

3.2 Use of the 'Inspect' option

Many more things have to be computed than are actually displayed in a normal run. Nearly everything you could possibly want to investigate can be displayed by selecting the 'Inspect' option from the main menu. The display requires the full screen and so the current graphical display is overwritten. It is, however, automatically recreated following the inspection, if the user chooses to 'Continue' the current simulation.

In Figure 10, the values for a normal subject are displayed. 'Pressures' are partial pressures in kPa; 'Contents ml%' are blood gas contents in ml/100 ml; 'Amounts' refers to the total amounts of gas in the compartments mentioned (STPD). (Note that the tables will give pressures in mmHg if you ask for this at the start.)

Other abbreviations are:

Alv./lung	alveolar compartment.
Pulm.cap.	'idealized' pulmonary capillary blood which has made perfect contact with alveolar gas.
Brain/CSF	values in brain, or, in the case of bicarbonate and pH, at the central chemoreceptor site (supposed to be part way between brain tissue and arterial blood).
Tissue/ECF	average values for all tissues lumped together.
Mixed Ven.	mixed venous blood.
O_2 uptake/ CO_2 output	instantaneous rates of O_2 consumption and CO_2 output prevailing at the end of the run. When conditions are changing fast or there is some oscillation in breathing, they cannot be representative of the whole run. The same applies to Expired RQ (below).

```
Time          P.pressures     Contents cc%    Amounts in cc    pH    HCO3-
  3. 0          O2     CO2      O2(STPD)CO2     O2(STPD)CO2

Arterial      12.5     5.3    19.5    47.4     195.    474.  7.397  23.8
Alv./lung     13.5     5.3 (Sat= 97.%)          347.    144.
(Pulm.cap)    13.5     5.3    19.7    47.3
Brain/CSF      3.9     7.0    10.2    56.5      18.    677.  7.330  22.7
Tissue/ECF     5.3 (  6.1)    14.4    51.5     178.  13390.  7.370
Mixed Ven. (  5.3) (  6.1)    14.5    51.4     435.   1543.  7.370  25.5
Plasma lactate conc.= 1.0 mmol/l

O2 uptake =  250. CO2 output =  200. cc/min (STPD)        Expired R.Q.=   .80
Tot.vent. =  6.1  Alv.vent.(BTPS) =  4.4   R.rate =12.7   Ven. admx. = 2.4 %
Dead space =  131. Tidal vol.= 477. cc(BTPS)              VD/VT ratio = .27
Card. O/P =  5.0  Cerebral blood flow=  53. ml/100g/min
```

Figure 10. An example of the use of the '4. Inspect' option.

Expired RQ respiratory quotient (CO_2 output divided by O_2 uptake).
Tot(al) and Alv(eolar) vent(ilation) are in litres/min.
R(espiratory) rate is in breaths/min.
Ven(ous) admix(ture) is expressed as percentage of cardiac output.
Dead space and Tidal vol(ume) in ml.
VD/VT (dead space to tidal volume) ratio as a fraction.

The 'Inspect' option also provides access to a more general facility which allows the user to view and 'browse through' the current state of model factors and variables, seeing also reference or standard values. Tables may be displayed grouping variables by physiological function or in numerical sequence. This general facility is also made available to assist choice of tabular variables in the 'Run Change' option (Section 3.5) and in choosing from these in the 'Plot' option (Section 3.1). Details of the tables are shown in Appendix 1.

3.3 More about changing variables

3.3.1 Inspecting single variables

The values of any of the 120 factors and variables listed at the end of this handbook may be interrogated by the following procedure. Specify first the '1. Change' option in the main menu, then '1. Change values'. Then type the factor number (see Appendix 1 for list). At this point, as described above, you can specify a new value for the variable; if instead you now just press ENTER without any number, the value will not be changed but its current value will nevertheless be displayed.

A quick way of doing this makes use of the 'slash separator' (see Section 3.6.1) to cut out the intervening dialogue. For example, in the main menu, the

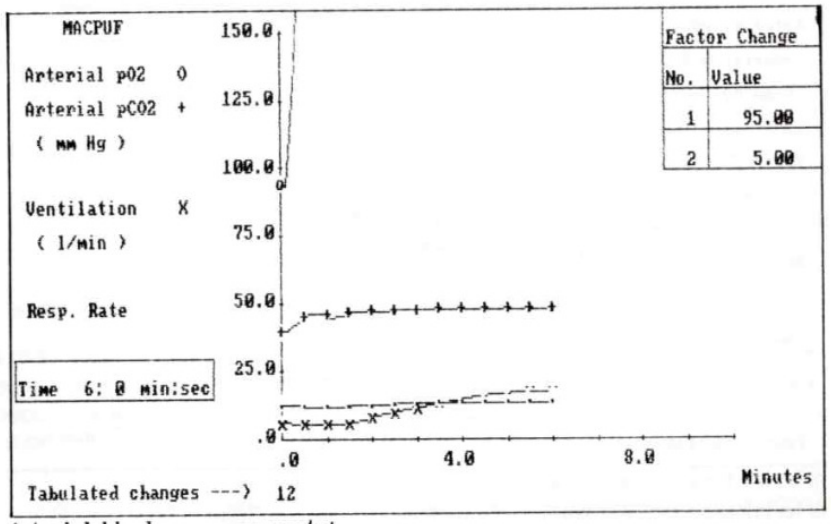
command '1/1/1' will display the current value of the inspired oxygen level (factor 1).

3.3.2 Changing more than one variable at once

Since no run starts until you select '2. Continue', you can always ask for '1. Change values' a second time and change further factors until you are ready to 'Continue'. However, *MacPuf* will accept a list of up to 10 factors to be changed one after the other (they should be separated by spaces).

In the following example the operator wanted to administer 5% CO_2 (factor 2) in oxygen but made a mistake in assigning the value 50 (to make a nonsensical gas mixture!) and so went back to make the correction. Study of the following sequence should make the whole process clear. The example shows checks and informative responses given to the user to help correct the error.

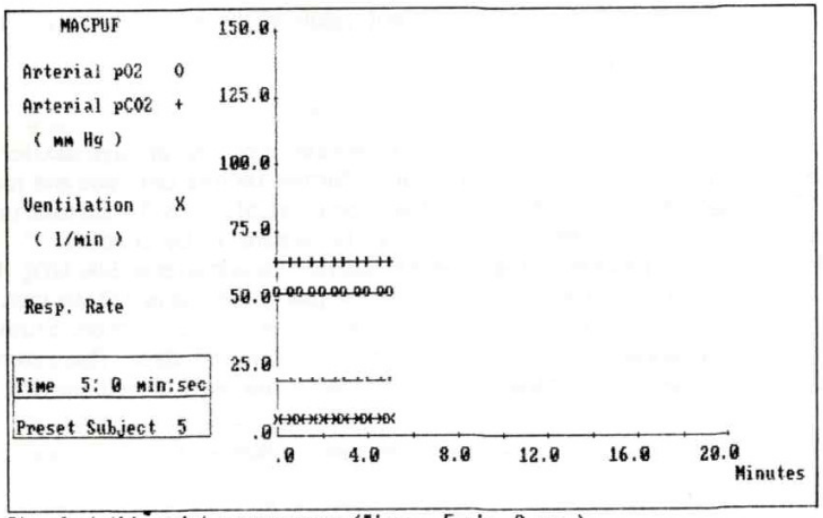
```
Do you want to 1. Change,  2. Continue,  3. Restart,  4. Inspect,  5. Plot  6. Stop
1
1. Change values,  2. Nat/Art vent,  3. Store/Bktrk,  4. Run change,  5. Presets
1
Type factor numbers (1-30) to change, or 100 for bag expts., etc.
1 2
Factor 1 (current value = 20.93), specify new value
95
Factor 1 = 95.0 (previously = 20.93)
```




```
Arterial blood gas measurements:
Arterial pO2 =   84.0 kPa      O2 content =  21.7 cc/100ml  Satn. =  100.%
       pCO2 =    6.4           CO2 content =  50.2  cc/100ml
         pH =   7.34( 46.nm)  Bicarbonate =  25.0 mmol/l
```

Figure 11. Breathing a mixture of 5% CO_2 and 95% O_2.

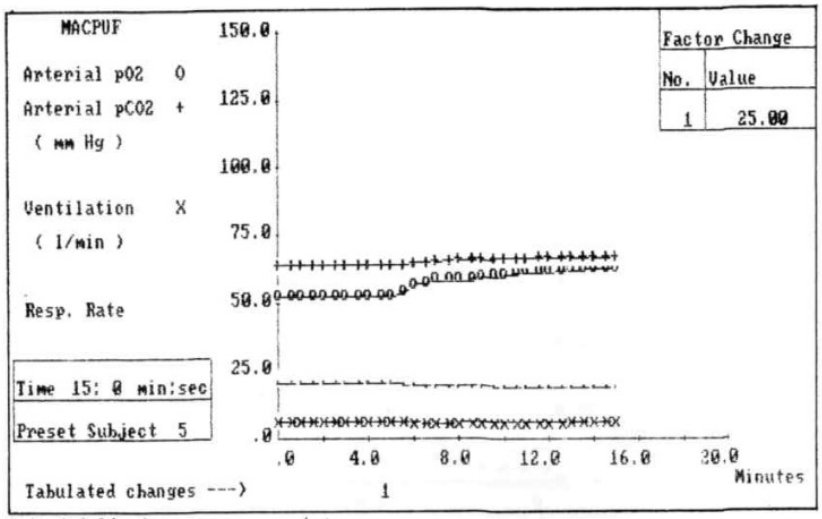
a



Stored at this point ********** (Time= 5 min. 0 sec.)

Do you want to 1.Change, 2.Continue, 3.Restart, 4.Inspect, 5.Plot, 6.Stop

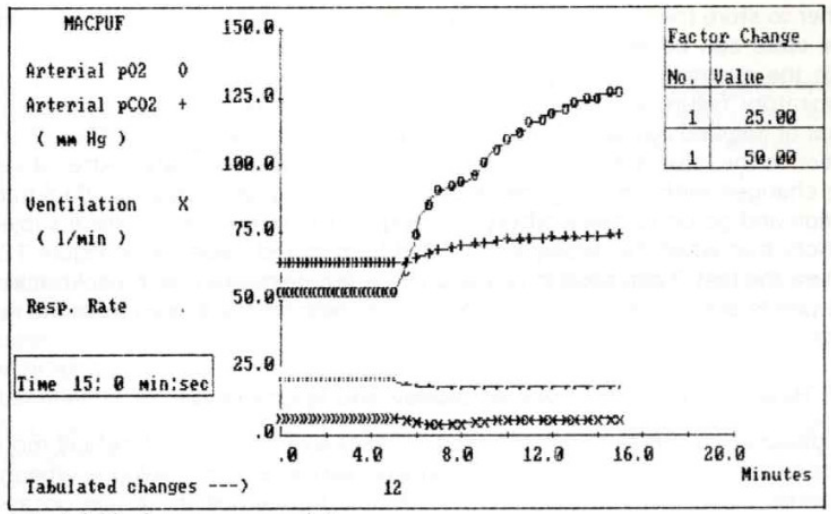
b



Arterial blood gas measurements:

Arterial pO2	=	8.4 kPa	O2 content	=	18.0 cc/100ml	Satn. =	90.%
pCO2	=	8.9	CO2 content	=	70.9 cc/100ml		
pH	=	7.34(45.nm)	Bicarbonate	=	35.2 mmol/l		

c



Arterial blood gas measurements:

Arterial pO2	=	16.9 kPa	O2 content	=	19.8 cc/100ml	Satn. =	98.%
pCO2	=	9.9	CO2 content	=	73.3 cc/100ml		
pH	=	7.31(49.nm)	Bicarbonate	=	36.3 mmol/l		

Figure 12. Store and Backtrack as described in the text: (**a**) storing a subject with ventilatory failure; (**b**) trying 25% oxygen therapy; (**c**) after backtracking and proceeding to try 50% oxygen.

Factor 2 (current value = 0.03), specify new value
50
Factor 2 = 50.00 (previously = 0.0)
This will be horrible
Impossible gas mixture — think again

The graph (Figure 11) shows the output when the mixture has been correctly set up.

3.4 Storing the current model state and recreating it later

You may wish to conduct a number of different experiments with a simulated subject you have set up in exactly the right state at the end of a series of manoeuvres, e.g., prolonged anoxia, cardiac arrest, simulated respiratory failure. It is then tedious to recreate these same conditions each time and much easier to be able to backtrack to where you were before. This is especially useful when you are about simulate something from which it may not be possible to recover.

At any stage, then, after selecting '1. Change' in the main menu of options, you can select from the corresponding submenu the '3. Store/Bktrk' option

either to store the current state or to backtrack to a previous stored state (only one state can be stored here but see also Section 4.2).

In the example (Figure 12) the user had created a simulated patient with respiratory failure and wished to observe the effects of different concentrations of inspired oxygen. The first command was to select the '3. Store/Bktrk' option in the main menu and then ask to '1. Store present state'. After observing changes with 25% O_2, he or she was able to select the '2. Backtrack' option and go on to make different changes next time to an identical subject.

Note that when the display is recreated from stored values (as in Figure 12(c) where the first 3-min section of the graph is reconstructed upon backtracking) the points are not joined up, to differentiate them on the screen from the new run.

3.5 How to change the type of display and length of run

As discussed in Section 2.3, the model makes extensive use of default modes of operation in order to cut down on unnecessary interactive dialogue wherever possible. However, you may want to be able to override these. On occasion it may be necessary to set a very small iteration interval for solution of the model equations in order to avoid instability. Alternatively, one may be interested in very short or very long periods of simulation and wish to tailor the operation and output of the run accordingly, e.g. to look in detail at events over less than a minute with intense muscular exercise, or to look intermittently at changes over many days with slowly accumulating changes in, say, body CO_2 stores.

Such alterations are handled in the 'Run change' section of the 'Change' menu of options which is first selected from the main menu. You will be asked to specify the number of seconds for the required run. A six-minute run (360 s) will be enough to achieve a steady state in most cases, and more is wasteful of computer time. The iteration interval (interval between computations) is initially set at 10 s. It cannot be lengthened, but may need to be shortened if odd oscillations develop in the output record. This is especially liable to occur with large cardiac outputs, large ventilations, or with severe hypoxaemia. In the example below the operator shortened the interval to 5 s. The ideal interval, providing the model does not oscillate (see above), is the number of seconds between each breath, i.e. for 12 breaths/min, the most accurate results would be given by an interval of 5 s. There is not much point in making the interval less than 2 s. This would use a lot of computer processing time so the program will not allow you to do it. Change of iteration interval can destabilize the model and you should always allow this to settle before making further changes. Pressing ENTER alone for the run length and iteration interval leaves these unchanged.

The next question concerns the time span of the experiment to be displayed in the standard graph. If you wish, this can be a value automatically calculated by the program from the run length, or you may specify a value independently. The default option, obtained by pressing the ENTER key, leaves the display scale unchanged.

The next question asked is:

Do you want 1. All, 2. Every 6th, or 3. Every 30th value printed

This is useful for speeding up graph-plotting when things are changing slowly. Computation is unaffected by this instruction. The command also controls the frequency of storage of values for subsequent replotting using the procedure described in Section 3.1.

The next question concerns type of output:

Do you want 1. Graphs + text, 2. Graphs only, 3. Selected values only

'Graphs + text' is recommended for new users; it plots graphs and gives the two tables of values at the end of the run.

Later on, you can economize on time and interactive control required by using the 'graphs only' option, making use of the 'Inspect' option in the main menu subsequently as required to get numerical values.

You can specify the 'selected values' mode of output which tabulates eight selected measurements at each iteration interval — Section 3.6.5. gives an example of this mode of output. The default set of values is:

	Variable	Code number
1.	Expired RQ	69
2.	Arterial pH	33
3.	Total ventilation	51
4.	Alveolar ventilation	35
5.	Arterial bicarbonate	60
6.	Alveolar PO_2	41
7.	Arterial PO_2	72
8.	Arterial PCO_2	74

This is the same set of values that is displayed under the graph during output types 1 and 2, overwritten at each successive iteration and also saved for subsequent plotting.

The next question allows selection of a suitable time scale for the graphical display options (1 and 2 only):

Do you want 1. Automatic timescale selection, or fixed timescale of 2. 1 min, 3. 5 min, 4. 10 min, 5. 20 min, 6. 40 min (ENTER alone = no change)

The selected variable numbers are entered in response to the question:

Selected values: Type up to 8 nos. (currently 69 33 51 35 60 41 72 74)
(To leave unchanged, press ENTER; 69 sets up standard list of variables)

to which the user responds with the list of values required, separated by spaces.

The Query facility here explains the procedure in detail and invokes a general inspection facility to allow the user to browse through tables of factors and calculated variables, displayed in physiological groupings or in numerical order. Current and normal values of variables are displayed.

A complete 'Run change' dialogue might look as follows – note that once

details of a run have been changed, they remain in force until the 'Run change' option is used again.

```
1. Change values,  2. Nat/Art vent,  3. Store/Bktrk,  4. Run change,  5. Presets
4
Type no. of seconds for run (1800 max. — current value = 90)
360
Type iteration interval in secs. (10 max. — current value = 5.0)
5
Do you want 1. All,  2. Every 6th, or  3. Every 30th value printed
2
Do you want 1. Graphs + text,  2. Graphs only,  3. Selected values only
1
Do you want 1. Automatic timescale selection, or fixed timescale of  2. 1 min,  3. 5 min,
 4. 10 min,  5. 20 min,  6. 40 min, (ENTER alone = no change)
1
Selected values: Type up to 8 nos. (currently 69 33 51 35 60 41 72 74)
(To leave unchanged, press ENTER; 69 sets up standard list of variables)
69
```

3.6 Some further hints on running the program

3.6.1 Abbreviating the dialogue

When you are very familiar with the interactive dialogue, it becomes tedious to wait for the prompts at each stage. Therefore, if you know what is coming, you can enter several responses in one line, separated by slashes ('/'), and when all the responses have been entered, press the ENTER key. The succeeding questions will be suppressed and the next instructions executed in order by the computer without interruption.

For example the command:

```
1/1/1 2/95/5/2
```

indicates the sequence: Change (1), Change values (1) of factors 1 and 2 (note separating space between these), assign a new value of 95 to factor 1 (% inspired O_2) and 5 to factor 2 (%CO_2), then instruct the computer to continue (2).

3.6.2 Simple inspection of values

To inspect the values of factors 1, 2, 45 and 46 you need only type 1/1/1 2 45 46 and press ENTER successively to reveal the current values; no changes will be made.

3.6.3 Suppressing output

If, in reply to the main menu of options

```
Do you want to 1. Change,  2. Continue,  3. Restart,  4. Inspect,  5. Plot,  6. Stop
```

you respond '0' (zero), this will continue for a further run without printing anything, though computing will still take place.


```
MacPuf Variables
  28.93    .03 100.00 100.00    .00    .003000.00   5.00   3.00 100.00
 100.00 100.00 101.23  37.00    .00  13.39  12.00  14.00  45.003000.00
    .00    .00   3.00 100.00  31.00    .40  35.00    .00   5.00    .00
  14.49 100.00   7.40   7.37   4.40   7.33    .00    .00 346.97 144.29
  13.54   5.32   7.40    .00   3.90   7.04 477.53  12.69  19.531543.01
   6.06   6.06  47.31  19.65  14.39  51.51  10.21  56.53   7.37  23.84
  51.44 195.30 474.01   8.881987.25  18.31 677.37  52.89    .00 130.73
3000.00  12.46 240.00   5.34    .00  97.07    .00  47.40 199.06   2.36
    .17   4.60    .00  45.72 317.41  71.41  25.52  25.52  34.00    .99
  22.70   1.00   4.95  19.53 177.58   5.32   6.09 434.78 733.43    .00
  47.40  76.06  75.99   4.00  75.25    .72    .00   7.22 713.01    .13
    .10 968.53 249.55    .00    .00    .00   1.00 170.00  70.00  40.00
```

Figure 13. Baseline model variables.

```
Model Variables
        96      97      95      16      45      46      47      48
2.55  5.751   6.140   192.1   13.4    3.6     7.2   434.9    12.3
3.0   5.763   6.150   192.4   13.4    3.6     7.2   434.0    12.3
3.5   5.773   6.160   192.8   13.4    3.6     7.2   433.3    12.3
3.10  5.783   6.170   193.1   13.4    3.7     7.2   432.6    12.3
3.15  5.792   6.180   193.4   13.4    3.7     7.2   431.9    12.3
3.20  5.801   6.190   193.7   13.4    3.8     7.2   431.4    12.3
3.25  5.809   6.199   193.9   13.4    3.8     7.2   430.9    12.3
3.30  5.816   6.209   194.2   13.4    3.8     7.2   430.5    12.3
3.35  5.823   6.218   194.4   13.4    3.9     7.3   430.1    12.3
3.40  5.829   6.227   194.6   13.4    3.9     7.3   429.7    12.3
3.45  5.835   6.236   194.8   13.4    4.0     7.3   429.4    12.3
3.50  5.841   6.244   195.0   13.4    4.0     7.3   429.1    12.3
```

Figure 14. The numerical output mode as described in the text.

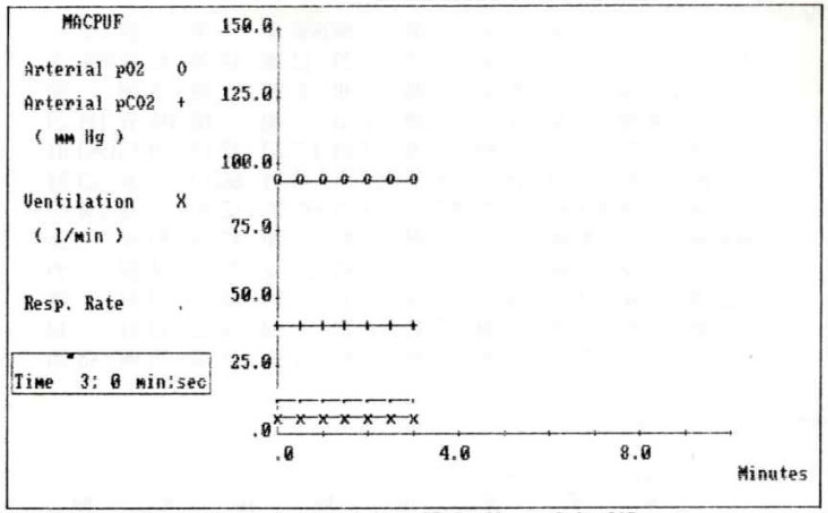
3.6.4 Storage of variables in the computer and output of all values

The table in Appendix 1 at the end of the handbook contains a list of 120 variables used in the model. Some of these (the earlier ones) are the main changeable factors. The later ones are mainly computed variables. Most important ones are listed by the use of the '4. Inspect' option (3.2). However, if in reply to the main menu

```
Do you want to 1. Change,  2. Continue,  3. Restart,  4. Inspect,  5. Plot,  6. Stop
```

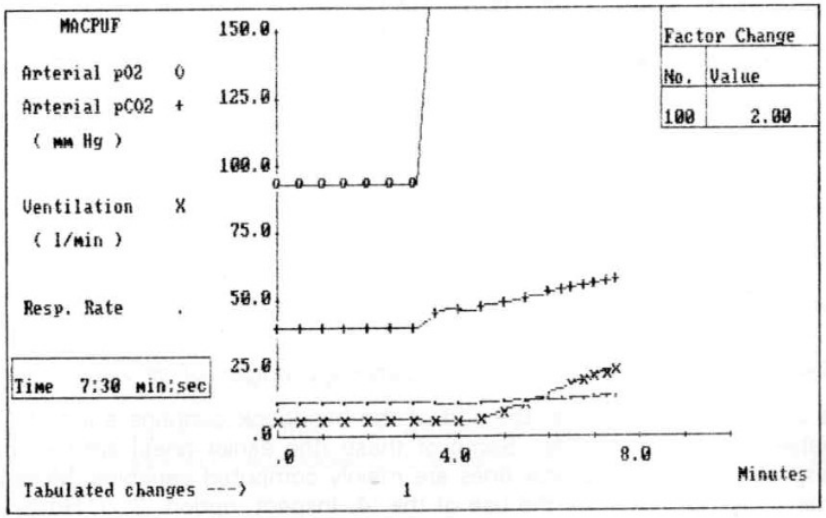
you type '7' (an option not offered in the list), you will get 15 lines of 8 columns which list, from left to right in sequence, the current values of all 120 variables. Figure 13 shows the baseline steady-state values obtained in this way.

a



*** 3000. cc bag connected, containing 95.0% O2 + 5.0% CO2

b



-.1	7.3	25.2	21.0	27.7	282.5	269.2	57.8
Exp.RQ	Art.pH	Tot.-Vent.-Alv.		HCO3	Alv.pO2	pO2 -Art.-	pCO2

c

Time 7.30	P.pressures O2	CO2	Contents cc% O2(STPD)	CO2	Amounts in cc O2(STPD)	CO2	pH	HCO3-
Arterial	35.9	7.7	20.5	56.1	206.	560.	7.385	27.7
Alv./lung	37.6	7.8 (Sat=100.%)			977.	203.		
(Pulm.cap)	37.6	7.8	20.6	56.2				
Brain/CSF	7.6	8.1	17.1	58.0	36.	776.	7.284	22.7
Tissue/ECF	6.1 (8.1)		14.8	56.8	205.	14144.	7.276	
Mixed Ven.	(6.1) (8.1)		15.0	56.1	450.	1696.	7.380	28.8
***** Bag.	35.6	7.2			550.	112.	*N2=	715.

* Bag vol. 1667. (cc BTPS) (O2= 40.% CO2= 8.% N2= 52.%)
Plasma lactate conc.= 1.0 mmol/l

O2 uptake = 161. CO2 output = -15. cc/min (STPD) Expired R.Q.= -.09
Tot.vent. = 25.2 Alv.vent.(BTPS) = 21.0 R.rate =14.7 Ven. admx. = 1.2 %
Dead space = 288. Tidal vol.=1718. cc(BTPS) VD/VT ratio = .17
Card. O/P = 4.7 Cerebral blood flow= 150. ml/100g/min

Figure 15. A bag rebreathing experiment for an initial 3 litre bag containing 95% oxygen and 5% carbon dioxide. (**a**) Initial state; normal subject with bag attached. (**b**) Rebreathing for several minutes (the program has reduced the iteration interval automatically. (**c**) Inspection of values after rebreathing.

Any of these 120 variables can be changed in value, though ridiculous changes may lead either to death of the subject or even to collapse of the program through arithmetic errors (in which case you will have to start again). To some extent, the program itself enforces realistic limits to the bounds within which you can set values of factors and indicates particularly absurd values.

In exceptional circumstances, you might wish the large table to be displayed at each iteration interval (although this takes a long time!). This can be obtained by selecting the '4. Run change' option, and, in answer to the question, 'Do you want.... 1. Graphs + text, 2. Graphs only, 3. Selected values', if you type '4' (an option not offered in the list), the complete output will continue until it is stopped by the use of the '4. Run change' option again.

3.6.5. Output of selected variables

This option is available if you type '3' in response to the question

Do you want 1. Graph + Text, 2. Graphs only, 3. Selected values

You will then obtain tabular output, pausing whenever the screen is full, of the set of variables entered in response to the question:

Selected values: Type up to 8 nos., - 69 is standard etc.

(see Section 3.5).

Thus, if you wanted to examine at each integration interval, let's say, tissue PO_2, tissue PCO_2, tissue O_2 stores, tissue CO_2 stores, brain PO_2, brain PCO_2, tidal volume and respiratory rate, you could type in:

96 97 95 16 45 46 47 48

(each number separated by a space). This display then remains unchanged until the '4. Run change' option is called again. The usual '4. Inspect' table is of course still available at the end of each run. Figure 14 shows numerical output of these values from a simulation in which inspired oxygen is changed acutely. For long simulation runs the program pauses after each screen-full is displayed, as illustrated here.

4. Special facilities

4.1 Bag collection, rebreathing and closed glottis experiments

If you specify that factor 100 is to be changed (it has an initial normal value of zero), then you will be offered a set of options as follows:

'1. Close the glottis' does what it says, and changes in lung volume (factor 7) will ensue at a rate proportional to the prevailing respiratory quotient and lung mechanical properties. You can follow the value of factor 7 by the use of the facility to output selected variables (see above), though lung volume will automatically appear if you use the '4. Inspect' option.

'2. Collect expired air in a bag' allows you to specify bag volume and content. If bag volume is made zero (ml) you can then '2. Continue' and follow bag volume (factor 23), bag oxygen (factor 37) and CO_2 (factor 38), or obtain bag volume, bag CO_2 and bag PCO_2 by using the '4. Inspect' option which prints the bag contents when a bag is in operation (see figure 15).

'3. Rebreathe from a bag' allows the same possibilities as above, but in this case either you will carry on by using a previously filled bag, or specify a new one (see figure 17) filled with the appropriate gas mixture. Once again, you can examine bag values as described above.

'4. Rebreathe, with CO_2 absorber attached' is self explanatory.

'5. Reset all to normal' — breathing air, glottis open, no bag, brings you back to normal conditions again.

Figure 17 shows a rebreathing experiment with a bag of 3 litres containing 95% oxygen and 5% carbon dioxide. The 'Inspect' table after a period of rebreathing is also shown. Note that extra lines automatically appear giving details of the bag contents.

Any time you get a new subject by selecting option 3 (Restart) or 5 (Presets), the glottis will be opened, and the bag will be automatically disconnected and emptied.

4.2 Preset simulated subjects

It is tedious to get conditions exactly right to simulate patients with chronic chest disease and some other conditions. By selecting option 1 in the main


```
The following preset patients are available
1. Normal fit subject exercising at 300 Kpm/min
2. Same, at 900 Kpm/min
3. Unfit normal subject exercising at 900 Kpm/min
4. Normal subject, compressed to 10 atmospheres for 25 minutes
5. Chronic airways obstruction with ventilatory failure
6. Same, but with acute exacerbation, eg. added bronchopneumonia
7. Cheyne-Stokes breathing due to brain stem damage and heart disease
8. Ventilated patient after open-heart surgery, breathing 50% O2
...Please type a number
```

Figure 16. List of preset subjects available.

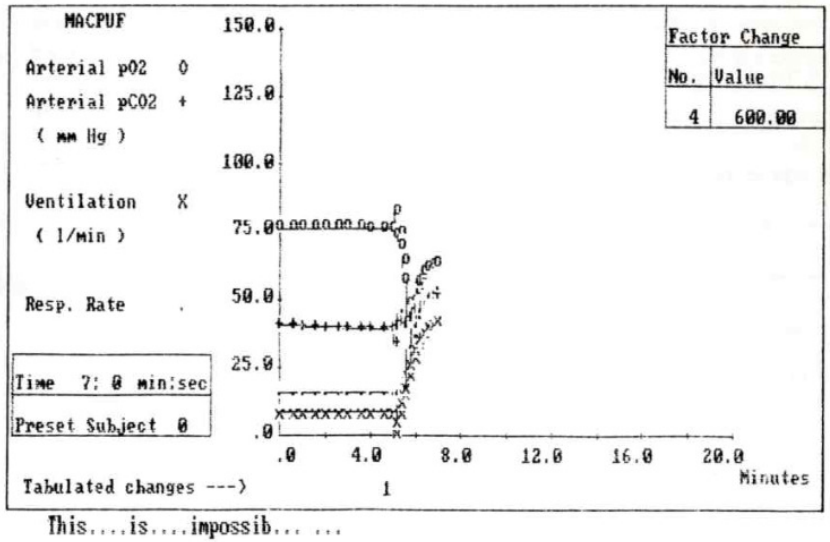


Figure 17. Dialogue creating an 80 kg female subject, aged 55 and of height 175 cm. The measured FEV1 and VC are entered. The resulting calculated steady state and exercise intolerance is illustrated.

menu (Change option) you are offered the submenu:

1. Change values, 2. Nat/Art vent, 3. Store/Bktrk, 4. Run change, 5. Presets.

On selecting option 5 you will be asked first whether you want:

1. Preset patients or subjects, 2. Specify your own patients or subjects

If you choose option 1 a list of available subjects is shown as in Figure 16.

When you select one of the subjects offered, your present subject is removed and a new one created with values appropriate for the conditions stated (this may take a short time and is therefore accompanied by a message indicating a delay). You can then use this subject for later experiments.

If you choose option 2, you will enter an interactive dialogue which will ask

for details of sex, age, body size, and for the results of pulmonary function testing (if you have them). This will always include forced expired volume (FEV) and vital capacity (VC), and may also ask for an estimate of diffusing capacity (if you have one). The program will then do its best to create an average subject having the pulmonary function test results you gave. You can then use this subject for later experiments. In this case, as after creating preset patients (above) the subject is automatically stored (see 3.2) so that you can backtrack to the corresponding base state at any time.

Figure 17 shows a section of the dialogue used to create a subject and illustrates the baseline steady state calculated by the program.

```
Setting up an individual subject
70 kg average man. Do you want to specify someone else ..1.Yes 2.No
1
Please specify..1.Male, 2.Female
2
Give me the height in cm (183 cm = 6 ft)
175
Now weight in kg
80
and age in years
55
Do you want to enter spirometry results ...1.Yes 2.No
1
Give me the value for FEV1 in litres
0.6
Now the value for VC
1.2
The FEV1/VC ratio is 0.50, i.e. 50 per cent
These values indicate airways obstruction
Is your patient 1. Acutely breathless  2. Not much changed in last week or so
2
Have you measured diffusing capacity 1.Yes 2.No
2
I shall assume that diffusing capacity is 7.6 ml/mm Hg/min.
This would be an average sort of figure for your subject
```

5. Experiments and problems which can be tackled

5.1 Suggested 'physiological' experiments and problems

1. Examine the effects of different levels of ventilation on arterial gas tensions, especially PCO_2. It will be best to use the artificial ventilation option, fix rate at, say 10 or 15/min, and vary tidal volume over the range 100 – 1000 ml. Does resultant PCO_2 relate best to total ventilation or to alveolar ventilation = (tidal volume − dead space) × respiratory rate?
2. Examine the effects of different amounts of venous admixture (factor 5 = fixed shunt %) on arterial gas tensions, especially PO_2. It is best to fix ventilation at a normal level (use artificial ventilation option). Plot PO_2 (and PCO_2) against % shunt. Why does PCO_2 reflect alveolar ventilation, and PO_2 largely reflect venous admixture?

3. Examine the effects of changing PO_2 on ventilation. (You can either give different concentrations of inspired CO_2, or use the bag-rebreathing system, the bag being filled with oxygen.) Plot PCO_2 against ventilation.
4. Examine the effects of changing PO_2 on ventilation. (You can give progressively smaller percentages of inspired oxygen, but to keep PCO_2 constant as well, you may also have to increase inspired CO_2%.)
5. You have seen in experiment 1 the effects of ventilation on PCO_2 and in experiment 3 of PCO_2 on ventilation. This constitutes a stable system of negative feedback. Using normal, natural ventilation (i.e. not artificial) produce acute changes in the whole *MacPuf* by some means (e.g. reduction of 'breathing capacity' (factor 24), increased dead space (factor 6), or decreased inspired oxygen %). Satisfy yourself that *MacPuf* can achieve a new steady state in which the relationships of problems 1 and 3 (above) are satisfied.
6. Examine the changes brought about by (a) mild, and (b) severe exercise. To simulate 300 kpm/min exercise increase metabolic rate (factor 4) to 400% normal, which corresponds to 1000 ml/min oxygen consumption. For very severe exercise (e.g. 200 metre dash) try increasing metabolic rate to 2800% (=9 litres/min oxygen consumption). What limits the maintenance of extremely strenuous exercise? What causes the ventilation and cardiac output to increase?

5.2 Suggested 'clinical' experiments and problems

1. An endo-tracheal tube slips into the right main bronchus, blocking off the whole left lung (not all that uncommon an accident). What happens? [Consider the likely effects on dead space, effective lung volume, venous admixture (shunt of blood) and lung 'stiffness' (called 'elastance' from now on)].
2. A patient throws off a large pulmonary embolus which blocks the right main pulmonary artery. What happens? (Consider cardiac output, dead space, lung elastance.) In practice, arterial PO_2 is commonly low and respiratory rate increased. What additional factors may play a part in the clinical syndrome? (When local PCO_2 in part of the lung falls, its elastance increases.)
3. What is the lowest level of haemoglobin compatible with life? (Remember to change packed cell volume in proportion to haemoglobin.) What adaptive changes take place (a) at once, and (b) in the course of a few days? How much lower could the haemoglobin level be if 50% oxygen inhalation was available?
4. What is the highest altitude (lowest barometric pressure) compatible with (a) life, and (b) sustained physical exercise at 600 kpm/min. What adaptive changes take place? (Consider oxygen supply to the tissues in relation to metabolic rate. You can simulate the addition of acid by making additional bicarbonate a negative value i.e. −50 for factor 21 will add 50 mmol strong acid to the body.)
5. Take two ready-made subjects (one at a time) with obstructive airways

disease and chronic CO_2 retention and hypoxaemia (ask for preset subjects 4 and 5). Calculate for each the possible maximum tissue oxygen delivery with (a) room air, (b) 23%, (c) 28%, (d) 60% and (e) 100% oxygen in the inspired air.

6. What series of events follow cardiac arrest? After, say, three minutes cardiac arrest, you start external cardiac massage and achieve a cardiac output of 2 litres/min for a further six minutes. The heart is now started again at 3 litres/min after defibrillation. How can you best secure the rapid recovery of your 'patient'?
7. Take preset subject 5 with severe ventilatory failure. How much benefit would tracheostomy *per se* bring? What are the additional (a) benefits, and (b) hazards of tracheostomy apart from those physiological changes which can be simulated by *MacPuf*?
8. Try to explain periodic (Cheyne–Stokes) breathing in terms of altered respiratory control mechanism (preset subject 6). (Consider central neurogenic drive to breathing, central CO_2 sensitivity and cardiac output.) Can you reproduce this effect by making changes in a normal subject, and why? What effects do the following have and why: (a) inhalation of 3% CO_2, (b) inhalation of 100% oxygen, and (c) altered cardiac output?
9. Examine the sequence of events in rapidly developing metabolic acidosis (e.g. in diabetic keto-acisosis or acute renal failure). Use factor 21 – addition of bicarbonate – to simulate generation of acid by giving a negative value. What happens to (a) arterial PCO_2 and (b) plasma bicarbonate, and why? What is the maximum acute load which the body can tolerate acutely?
10. Hyperbaric oxygen (e.g. 100% oxygen at 2 atmospheres pressure) has been used in medical treatment. How much extra oxygen is supplied to the tissues by this means? In what circumstances could this treatment be beneficial? What are its dangers?
11. Examine asphyxia (i.e. zero ventilation) for (a) 3 minutes and (b) 6 minutes, and the possibilities of recovery. What causes the acidaemia? How could it be treated? What would you have to do to restore normal conditions after prolonged asphyxia?
12. What happens, and how fast does it happen, when an anaesthetist's oxygen cylinder runs out and a patient is breathing, for example, pure nitrous oxide? What precautions do anaesthetists take to guard against this?
13. What proportion of one's airways can be blocked, compatible with life? (Consider first breathing capacity and elastance, and then what you might expect to happen in terms of venous admixture.)
14. In status asthmaticus there is hypersecretion of mucus. This blocks the airways. What effect will this have? (Consider elastance and venous admixture; perhaps try successive increments of 10% in venous admixture and of 5% in elastance.) If we tell you that in moderately severe asthma (e.g. FEV1 about 0.5) the PCO_2 is often below normal, what additional factors must be operating?

15. Consider a man with severe acute myocardial infarction with a cardiac output of, say 2.5 litre/min. What would happen if he developed pulmonary oedema [which increases both venous admixture (factor 9) and lung elastance (factor 8)]? How could the disorder be treated?

Appendix 1

Details of the *MacPuf* model factors and variables — the general inspection facility

The program incorporates a general inspection facility for 'browsing through' the current state of the model and for looking up details and numeric codes of model variables. This facility is made available when the user invokes the 'Inspect' option in the main menu of options (Section 3.4) and as part of the help offered, on typing 'Q', when specifying either the 8 tabular variables for the 'Run change' option (Section 3.5) or a variable to be plotted in the 'Plot' option (Section 3.1). Information is diplayed in the form of tables; the information in this appendix is based on tables created using the facility, with some additional annotation of details.

The lists and tables displayed are organized in groups since the lists of the principal changeable factors in the model and of the model variables fill more than one screen-full. For ease of use, the information is made available in tables grouped by physiological functions and by numerical sequence, all factors/variables being identified in the program by numeric codes.

The inspection facility in *MacPuf* is controlled by a submenu, which appears at the bottom of the screen beneath each table. This is:

```
R :RETURN to model/set up, P :Show PREVIOUS table, I :Show INSPECT table
For further details of model factors/variables choose:
1.FACTOR LIST, 2.RESP/CIRC, 3.ALVEOLI, 4.ARTERIES, 5.TISSUES, 6.VEINS, 7.BRAIN,
8.BAG, 9.VARIABLES LIST, Press <ENTER> key only for NEXT TABLE in group
```

When entered, the appropriate first page of information is displayed and the above menu of options is set up at the bottom of the screen. To see the next table in a group (e.g. the next set of variables in the numerically ordered list of variables), the user simply presses the ENTER key. On pressing ENTER after displaying the last table of a group, or on selecting the 'Return' option at any time ('R' then ENTER), the program returns to the place where the inspection was requested, re-establishing any necessary instructions on the screen. To move back through a group, pressing 'P' then ENTER repeats the previous table displayed (or the same table if the first table of the group is currently displayed).

Option 'I' displays the main 'Inspect' table described in Section 3.4, which summarizes the overall state of the model. This information, with some additional details, is broken down more simply in a set of tables covered in options as follows:

2. Breathing and Circulation
3. Alveolar Gases
4. Arterial Blood Pool

5. Lumped Tissue Compartment
6. Venous Blood Pool
7. Brain Compartment
8. Bag Collection of Rebreathed Air

These are available individually or as a group which may be scanned, pressing ENTER or 'P' then ENTER to move down or up through the group, as described above. The tables include description, units, and current and reference steady-state values for the variables.

Option 1 displays a group of tables detailing the principal model factors, with units and current and reference steady-state values, and Option 9 lists the model variables which may be of physiological interest, ordered by their numerical codes.

The tables diplayed below were generated for the standard reference subject (at the outset, when running the program in units of mm Hg rather than kPa).

Macpuf subject factors		[Reference]	Current
1.	Inspired O_2, %	[20.93]	20.93
2.	Inspired CO_2, %	[0.03]	0.03
3.	Cardiac pump performance, % normal	[100]	100
4.[a]	Metabolic rate, % normal resting value	[100]	100
5.[b]	Extra anatomical right-to-left shunt, % cardiac output	[0.0]	0.0
6.	Extra dead space (above normal value), ml BTPS	[0]	0
7.	Lung volume, (end-expiration), ml BTPS	[3000]	3000
8.[c]	Lung elastance, cm H_2O/litre	[5.0]	5.0
9.[d]	Venous admixture effect, as % cardiac output	[3.0]	3.0
10.	Ventilatory response to CO_2 or H^+, as % average normal	[100]	100
11.	Ventilatory response to falling PO_2, as % average normal	[100]	100
12.[e]	Central neurogenic (learnt) respiratory drive, % normal	[100]	100
13.[f]	Total barometric pressure, mm Hg or kPa	[760]	760
14.[g]	Body temperature, degrees centigrade	[37.0]	37.0
15.	Tissue respiratory quotient (CO_2 output/O_2 uptake)	[0.80]	0.80
16.	Tissue CO_2 stores, litres STPD	[13.39]	13.39
17.	Tissue ECF distribution volume, litres	[12.00]	12.00
18.	Haemoglobin, g/100 ml blood	[14.8]	14.8
19.	Packed cell volume	[45.0]	45.0
20.	Venous blood volume, ml	[3000]	3000
21.[h]	Addition of bicarbonate or acid, mmol standard bicarb.	[0]	0
22.[i]	Brain bicarbonate, deviation from normal (+/−), mmol/litre	[0.0]	0.0
23.	2,3-DPG concentration in red cells, mmol/litre	[3.8]	3.8
24.	'Breathing capacity', % normal average value	[100]	100
25.[j]	Index of state of physical fitness	[31.0]	31.0
26.	Inspiratory/total breath duration ratio	[0.40]	0.40
27.[k]	Maximum cardiac output litre/min	[35.0]	35.0
28.[l]	Left-to-right shunt, ratio to cardiac output	[0.0]	0.0
29.[m]	Vital capacity, litres BTPS	[5.00]	5.00
30.	Positive end-expiratory pressure, cm H_2O	[0]	0

[a]Factor 4 may be increased to simulate exercise, taking care to adjust the iteration interval appropriately.
[b]Factor 5 is a fixed shunt, as for example in congenital heart disease.
[c]Increases in factor 8 make breathing faster; stiffer lungs reduce the adverse circulatory effects of positive end-expiratory pressure.
[d]Factor 9 is a variable shunt, automatically modified by alveolar PO_2, characteristic, for example, of V/Q abnormalities.
[e]Factor 12 influences the 'central neurogenic' component of the ventilatory stimulus, which rises in proportion to metabolic rate and oxygen consumption.
[f]Factor 13: water vapour pressure is calculated as a function of temperature and used in gas calculations where necessary.
[g]Factor 14 does not permit values less than 30% or more than 44% to be entered.
[h]For factor 21, the addition of bicarbonate (positive values) or acid (negative values) specified is applied gradually over the succeeding run; then the factor is reset automatically to zero.
[i]Factor 22 is used in simulating chronic acid/base disturbances. Brain bicarbonate (variable 91) will adapt only slowly to an equilibrium value and this factor enables direct increments to be made to speed the process.
[j]Factor 25 controls the anaerobic threshold (mm Hg PO_2) below which anaerobic metabolism is switched on. This is set within the range 30–37. A value greater than 31 lowers the threshold, simulating unfitness.
[k]Factor 27 can be used to place an absolute upper limit on cardiac output. (A reduction in factor 4 — cardiac contractility — may be to some extent offset by increased sympathetic activity.
[l]A value for factor 28 of 2 will specify a 2:1 shunt.
[m]Maximum tidal volume is restricted to 60% of factor 29.

Breathing and circulation	[Reference]	Current
Ventilation: total, litres/min, BTPS (51)[a]	[6.1]	6.1
alveolar, litres/min, BTPS (35)	[4.4]	4.4
Respiratory rate, cycles/min (48)	[12.7]	12.7
Tidal volume, ml BTPS (47)	[477]	477
Total dead space, ml BTPS (70)	[131]	131
Respiratory exchange ratio, (69)[b]	[0.80]	0.80
Effective cardiac output, litre/min (93)	[4.9]	5.0
Effective venous admixture, % cardiac output (80)	[2.4]	2.4

[a]( ) signifies *MacPuf* variable/factor number.
[b]Respiratory exchange ratio is calculated as the CO_2 production divided by the O_2 consumption in the last calculation (iteration) interval. A normal value of 0.80 indicates steady-state conditions in the overall system.

Alveolar gases		[Reference]	Current
O_2	Amount, ml STPD (39)[a]	[347]	347
	Partial pressure, kPa or mm Hg (41)	[101.7]	101.6
	Content in idealized pulm. cap. blood, ml/100 ml (54)	[19.6]	19.7
CO_2	Amount, ml STPD (40)	[144]	144
	Partial pressure, kPa or mm Hg (42)	[40.0]	40.0
	Content in idealized pulm. cap. blood, ml/100 ml (53)	[47.3]	47.3
N_2	Amount, ml STPD (65)	[1987]	1987

[a]( ) signifies *MacPuf* variable/factor number.

Arterial blood pool		[Reference]	Current
O_2	Amount, ml STPD (62)[a]	[195]	195
	Partial pressure, kPa or mm Hg (72)	[93.6]	93.6
	Content, ml/100 ml (49)	[19.5]	19.5
	Content of blood leaving art. pool, ml/100 ml (94)	[19.5]	19.5
	Saturation, maximum, % (76)	[97]	97
CO_2	Amount, ml STPD (63)	[474]	474
	Partial pressure, kPa or mm Hg (74)	[40.1]	40.1
	Content ml/100 ml (78)	[47.4]	47.4
	Content of blood leaving art. pool, ml/100 ml (101)	[47.4]	47.4
N_2	Partial pressure, mm Hg (108)	[7.3]	7.2
	Content of blood leaving art. pool, ml/100 ml (106)	[0.7]	0.7
HCO_3^-	Content, mmol/litre (60)	[23.8]	23.8
Lactate	Concentration, mmol/litre (90)	[0.99]	0.99
pH	(33)	[7.40]	7.40

[a]( ) signifies *MacPuf* variable/factor number.

Lumped tissue compartment		[Reference]	Current
O_2	Amount, ml STPD (95)[a]	[178]	178
	Partial pressure, kPa or mm Hg (96)	[40.0]	40.0
	Content of blood leaving tissues, ml/100 ml (55)	[14.4]	14.4
CO_2	Amount, litre STPD (16)	[13.39]	13.39
	Partial pressure, kPa or mm Hg (97)	[45.7]	45.7
	Content of blood leaving tissues, ml/100 ml (56)	[51.5]	51.5
N_2	'fast compartment'		
	– amount, ml STPD (102)	[76]	76
	– p. pressure, kPa or mm Hg (105)	[570.6]	570.5
	'slow compartment'		
	– amount, ml STPD (112)	[969]	969
	– p. pressure, kPa or mm Hg (105)	[565.0]	565.0
	Excess nitrogen, ml STPD (107)	[0]	0
HCO_3^-	Content of blood leaving tissues, mmol/litre (87)	[25.5]	25.5
pH	of blood leaving tissues (59)	[7.37]	7.37
lactate	total amount in body, mmol (89)	[34.8]	34.8

[a]( ) signifies *MacPuf* variable/factor number.
[b]The description of nitrogen storage in tissues is intended only as a qualitative representation of the physiological mechanisms concerned. The excess nitrogen is the amount currently stored in excess of that which would be held at normal saturation, calculated for the current ambient conditions.

The empirical 'index' of susceptibility to decompression sickness (variable 83) is displayed on the standard graph when activated in the program. The steady state on starting the model is not absolutely in N_2 equilibrium, hence the slight PN_2 differences between fast and slow compartments.

Venous blood pool		[Reference]	Current
O_2	Amount in whole pool, ml STPD, (98)[a]	[435]	435
	Partial pressure, kPa or mm Hg (96)	[40.0]	40.0
	Content (blood in pulmonary artery), ml/100 ml (31)	[14.5]	14.5
CO_2	Amount in venous blood pool, ml STPD (50)	[1543]	1543
	Partial pressure, kPa or mm Hg (97)	[45.7]	45.7
	Content (blood in pulmonary artery), ml/100 ml (61)	[51.4]	51.4
HCO_3^-	Content of mixed venous blood, mmol/litre (88)	[25.5]	25.5
pH	of mixed venous blood (34)	[7.37]	7.37

[a]( ) signifies *MacPuf* variable/factor number.
[b]The contents of gases in mixed venous blood are computed with appropriate delay in transit through the venous blood pool. Partial pressures are not calculated to economize on computing time; time-shifted approximate values are displayed instead.

Brain compartment		[Reference]	Current
O_2	Amount, ml STPD (66)[a]	[18]	18
	Partial pressure, kPa or mm Hg (45)	[29.2]	29.3
	Content of blood leaving brain, ml/100 ml (57)	[10.2]	10.2
CO_2	Amount, ml STPD (67)	[677]	677
	Partial pressure, kPa or mm Hg (46)	[52.8]	52.8
	Content of blood leaving brain, ml/100 ml (58)	[56.5]	56.5
HCO_3^-	Content of blood leaving brain, ml/100 ml (58)	[22.7]	22.7
pH	at putative central chemoreceptor site (36)	[7.33]	7.33
Blood flow	ml/(100 g brain mass/minute) (68)	[53]	53

[a]( ) signifies *MacPuf* variable/factor number.
[b]Adaptation of brain bicarbonate is augmented by factor 22.

Bag collection of rebreathed air[a]		[Reference]	Current
Volume	ml BTPS (116)[b]	[0]	0
O_2	Amount, ml STPD (37)[c]	[0]	0
CO_2	Amount, ml STPD (38)	[0]	0

[a]Bag variables remain unchanged when the bag is disconnected from the subject.
[b]( ) signifies *MacPuf* variable/factor number.
[c]The amounts of gases are specified in STPD units, whereas bag volume is in ml, BTPS.

Variables of physiological interest in numerical order

31. Venous O_2 content, ml/100 ml of blood in pulmonary artery
33. Arterial pH
34. Venous pH (of mixed venous blood)
35. Alveolar ventilation, litres/min BTPS
36. Brain pH (at putative central chemoreceptor site)
37. Bag: amount of O_2, ml STPD
38. Bag: amount of CO_2, ml STPD
39. Alveolar O_2 amount, ml STPD
40. Alveolar CO_2 amount, ml STPD
41. Alveolar PO_2, kPa or mm Hg
42. Alveolar PCO_2, kPa or mm Hg
45. Brain PO_2 (of blood leaving brain), kPa or mm Hg
46. Brain PCO_2 (of blood leaving brain), kPa or mm Hg
47. Tidal volume, ml BTPS
48. Respiratory rate, cycles/min
49. Arterial O_2 content, ml/100 ml
50. Venous CO_2 amount, ml STPD
51. Total ventilation, litres/min BTPS
53. CO_2 content of idealized pulmonary cap. blood, ml/100 ml
54. O_2 content of idealized pulmonary cap. blood, ml/100 ml
55. Oxygen content of blood leaving tissues, ml/100 ml
56. CO_2 content of blood leaving brain, ml/100 ml
57. Oxygen content of blood leaving brain, ml/100 ml
58. CO_2 content of blood leaving brain, ml/100 ml
59. Tissue pH
60. Arterial bicarbonate content, mmol/litre
61. Venous CO_2 content (blood in pulm. artery), ml/100 ml

62. Arterial oxygen amount, ml STPD
63. Arterial CO_2 content, ml STPD
65. Alveolar N_2 amount, ml STPD
66. Brain O_2 amount, ml STPD
67. Brain CO_2 amount, ml STPD
68. Brain blood flow, ml/100 g brain per min
69. Respiratory exchange ratio
70. Dead space (total effective physiological), ml BTPS
72. Arterial PO_2, kPa or mm Hg
74. Arterial PCO_2, kPa or mm Hg
76. Arterial O_2 saturation (maximum), percent
78. Arterial CO_2 content, ml/100 ml
80. Venous admixture (total effective), as % cardiac output
83. Arbitrary index of risk of decompression symptoms
87. Bicarbonate content of blood leaving tissues, mmol/litre
88. Venous bicarbonate content (mixed venous), mmol/litre
89. Tissue lactate amount (body total), mmol
90. Arterial lactate concentration, mmol/litre
91. Brain bicarbonate content, mmol/litre
93. Cardiac output (actual effective), litre/min
94. Oxygen content blood leaving arterial pool, ml/100 ml
95. Tissue O_2 amount, ml STPD
96. Venous PO_2 (approx. values – time shifted), kPa or mm Hg
97. Venous PCO_2, kPa or mm Hg
98. Venous oxygen amount, ml STPD
101. CO_2 content of blood leaving arterial pool, ml/100 ml
102. Tissue N_2 amount in 'fast' compartment, ml STPD
103. Tissue N_2 partial pressure in 'fast' compt, kPa or mm Hg
105. Tissue N_2 partial pressure in 'slow' compt, kPa or mm Hg
106. Nitrogen content of blood leaving arterial pool, ml/100 ml
107. Excess N_2 held above normal max. saturation, ml STPD
108. Arterial N_2 partial pressure, mm Hg
112. Tissue N_2 amount in 'slow' compartment, ml STPD
116. Bag volume, ml BTPS
118. Subject height, cm
119. Weight, kg
120. Age, years

Error messages

Factor negative	Meaning of error	Probable cause	Suggested remedy
0	Tidal volume too large for bag or	Rebreathing bag too small	Use larger bag or shorten run
	Pulmonary capillary blood HCO_3^- fell too fast to allow equilibration	Sudden fall in alveolar PCO_2 (e.g. sudden hyperventilation)	Change CO_2 or ventilation more slowly. If this is impossible, shorten time interval and rerun
41	Alveolar O_2 less than zero	Sudden fall in alv. PO_2	Change O_2 or barometric pressure more slowly or shroten time interval
42	Alveolar CO_2 less than zero	Sudden fall in alv. PCO_2	Change CO_2 or ventilation or add HCO_3^- more slowly or shorten time interval
60	Arterial HCO_3^- less than zero	Sudden fall in alv. PCO_2 or too much acid given or made too quickly	Shorten time interval considerably and rerun and/or give acid more slowly
87	Tissue HCO_3^- less than zero	Very rapid addition of acid or too rapid generation of lactic acidosis	Add acid more slowly or rerun at much shorter time interval
88	Venous HCO_3^- less than zero	Too rapid addition of acid	Add acid more slowly
95	Tissue oxygen less than zero	Not enough time for anaerobic metabolism to get going	Shorten time interval and rerun

If any of these conditions occur, the program halts with a message indicating which factor has been found negative. Failure of the program should not be thought of as necessarily indicative of an attempt to model an 'unphysiological' situation. Certain possibly more extreme manoeuvres may simply be beyond its current powers of realistic representation and computation with the current design, which uses various shortcuts and approximations, especially in terms of circulation times, in order to allow a manageable overall performance.