

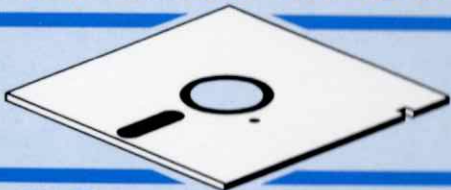
MACPEE

A Simulation of
Heart, Peripheral Circulation, Kidneys, Body Fluids,
Electrolytes and Hormones

The interaction between circulation, kidneys and body-fluid and electrolyte compartments is so complex that the influence of one factor on another is often not easy to predict. *MacPee* concentrates on illustrating those changes in haemodynamic function which are related to changes in the volume and distribution of the contents of the body's fluid spaces. *MacPee* allows students to perform physiological experiments, e.g. giving water loads, and to analyse clinical situations, such as the complex series of events that follow a renal leak of albumin or a large haemorrhage. It complements animal experiments, which are difficult in this area to translate accurately, and simulates human experiments which would be, at least, unethical.

IRL PRESS
OXFORD · WASHINGTON DC

IRL PRESS



SOFTWARE

MACPEE

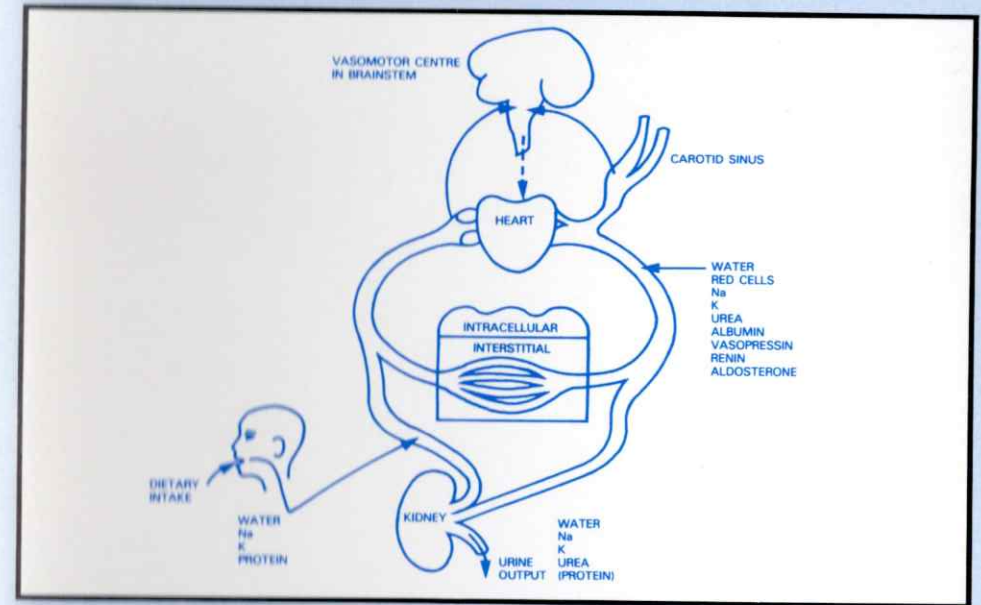
D Ingram, C J Dickinson & K Ahmed

IRL PRESS

THE MAC SERIES OF MEDICAL AND PHYSIOLOGICAL
SIMULATIONS

MACPEE

D Ingram, C J Dickinson
& K Ahmed



IRL PRESS



SOFTWARE

IRL PRESS SOFTWARE LICENCE AGREEMENT

In consideration of payment of the licence fee, which is part of the price that you paid for this product, IRL Press grants you a non-exclusive right to use this copy of an IRL Press software program on a single computer (i.e. with a single CPU) at a single location.

1. You may physically transfer the software from one computer to another provided that the software is used on only one computer at a time.
2. You may not electronically transfer any part of the software to another computer (e.g. over a network).
3. You may not distribute copies of the software or its written materials to others.
4. You may not modify, adapt, translate, reverse engineer, decompile, or disassemble this software or create derivative works based on it.
5. This software and the accompanying written materials are copyright. Unauthorized copying of the software, including software that has been modified, merged, or included with other software, is expressly forbidden without permission in writing from IRL Press. Subject to these restrictions, you may make one copy of the software solely for backup purposes.
6. Updates of this software may be produced by IRL Press from time to time. By returning the accompanying registration card you will be entitled to receive information on updates, and qualify for a discount on the price of any enhanced or improved versions of the software.

IRL Press Limited,
PO Box 1,
Eynsham,
Oxford OX8 1JJ,
UK

All rights reserved by the publisher. No part of this booklet may be reproduced or transmitted in any form by any means, electronic or mechanical including photocopying, recording or any information storage and retrieval system, without permission in writing from the publisher, except that photocopying for use with an authorized copy of the software is permitted.

ISBN 1-85221-044-3

© 1987 The Medical College of St Bartholomew's Hospital and Health Sciences Centre, McMaster University.

CONTENTS

1	The model	1
1.1	Introduction to <i>MacPee</i>	1
1.2	Brief description	1
1.3	Limitations – conceptual and procedural	3
1.4	Implementation	4
2	Operating the program – beginners' guide	4
2.1	How to get started	4
2.2	How to get help	4
2.3	Example of an actual run – the main menu of options	5
2.4	How to change model factors	8
2.5	How to prescribe parenteral or oral fluids	10
2.6	Some suggested initial experiments	11
3	Operating the program – further details	13
3.1	Storing and plotting results	13
3.2	The 'Inspect' option	15
3.3	Inspecting and changing model factors and variables	17
3.4	The Store/Backtrack option	20
3.5	Changing the type of display	21
3.6	Preset simulated subjects	25
3.7	Abbreviating repetitive dialogue	25
3.8	Display of all model variables	25
4	Specific simulations and <i>MacPee</i> problems	26
	Appendix 1	31

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.

The authors and publishers make no warranties, express or implied, that these programs are free of error, or are consistent with any particular standard of merchantability, or that they will meet your requirements for any particular application. It is a condition of use of the programs that persons acquiring or using them satisfy themselves of their relevance and accuracy for the uses they have in mind and take full responsibility for such use. They should not be relied on for solving a problem whose incorrect solution could result in injury to a person or loss of property. If you do use the programs in such a manner, it is at your own risk. The authors and publisher disclaim all liability for direct or consequential damages resulting from your use of the programs.

1. The model

1.1 Introduction to *MacPee*

The interaction between circulation, kidneys and body fluid and electrolyte compartments is so complex that it is not always intuitively obvious what the influence of one factor on another may be. This program gives you a means of performing experiments in this area which would be impossible, dangerous or unethical to perform on a patient or a volunteer. It can also substitute to a considerable degree for class experiments or demonstrations on animals. Apart from the ethical problems they raise, many such experiments are difficult to translate accurately to man. Furthermore, not only can you perform 'physiological' experiments (e.g. altering dietary sodium, giving water loads) but you can also analyse clinical situations (e.g. the complex series of events which follow a renal leak of albumin, a massive reduction in cardiac performance or a large haemorrhage). *MacPee* thus enables you to examine hypotheses and study problems in a way impossible to achieve by other means.

The *Mac Series of Medical and Physiological simulation programs* is a family of interactive digital computer models designed to help you learn about the physiology of major body systems in health and disease. The first of these models was *MacMan* and, in fact, *MacPee* was designed starting from the core of the *MacMan* program. *MacMan* has a heart inside a chest, systemic arteries and arterioles, a capillary bed and veins collecting blood from the capillary bed and returning it to the heart. Systemic arterial pressure in *MacMan* is under simulated nervous control — this is the baroreceptor reflex which is a major determinant of short term blood pressure regulation in man (see Figure 1).

While *MacMan* is designed to examine and simulate rapid fluctuations in haemodynamic function and has a two-second computing interval, *MacPee* is not concerned with such rapid fluctuations, and has a normal computing interval of 60 min (changeable between 5 and 120 min). It is designed to illustrate and allow you to study the much slower adaptations in haemodynamic function which take place when changes occur in body fluids and electrolytes, and it also allows you to see how changes in haemodynamic function exert long-term effects on body fluids. The arterial baroreceptor reflex still operates in *MacPee* but the emphasis has partly shifted from the rapid response needed to stabilize blood pressure to the slow 'resetting' which can result in abnormally high or low blood pressure becoming dynamically maintained.

1.2 Brief description

The output of the model is normally in the form of a graph of blood pressure and pulse rate plotted against time and a continuously updated display of the values of eight (user-selectable) circulatory variables. At the end of each run — normally a single day, but you can change this — tables of values are printed for plasma sodium, potassium, urea, creatinine and albumin concentrations, haemoglobin concentration and packed cell volume, right atrial pressure, body weight, and urinary water and solute excretion. A large number of other things

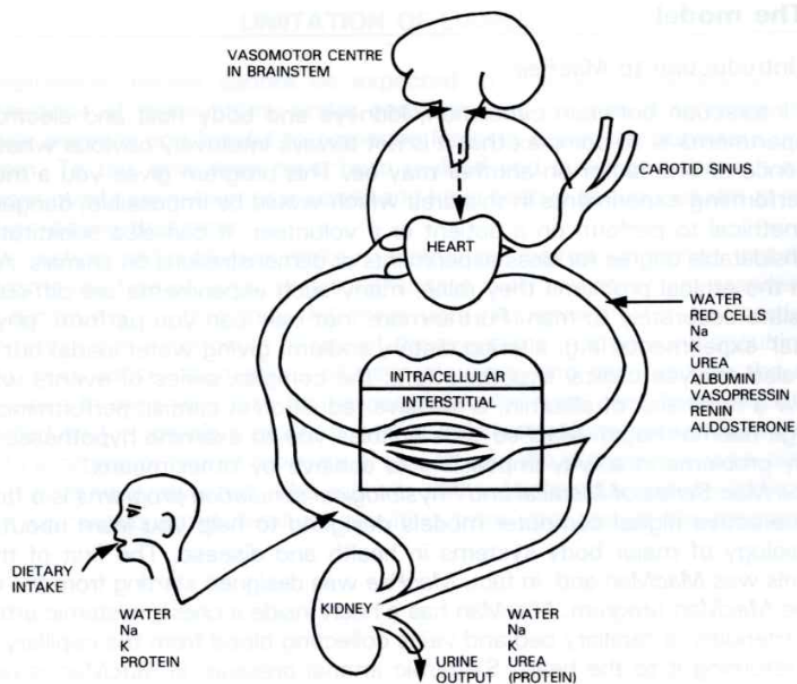


Figure 1. Main elements of the *MacPee* model.

— e.g. glomerular filtration rate, total body water, lean body mass, cardiac output, interstitial fluid pressure, the concentrations of various hormones — are being computed at each iteration interval, and these values are obtainable at any time by asking for the 'Inspect' table (Section 3.2) or by appropriate alterations in the type of output from the simulation (Section 3.5).

The model will perform as many simulated hours or days of operation as you direct, and can then be made to stop to await changes which the operator can bring about to any extent in any of a large number of variables (a complete list of which is given in the Appendix). Controllable factors include dietary sodium, dietary protein, potassium administration or withdrawal, cardiac contractility, general systemic arterial and venous resistance, renal artery pressure drop, total glomerular function, total tubular sodium re-absorptive function, urinary protein loss, vasopressin and aldosterone activity. In addition, any parenteral fluid normally available in hospital practice may be administered or withdrawn (e.g. 5% dextrose, saline, potassium chloride solution, blood, packed cells), and the oral consumption of fluids can be either restricted or augmented to any specified extent by simulated instructions to nursing staff.

Water intake is controlled by thirst (itself controlled by the known factors influencing thirst), and the urinary output of water, urea and electrolytes is also controlled in accordance with the best available knowledge of the influences upon the kidney of electrolyte concentrations, systemic arterial pressure, sym-

pathetic nervous activity, and the actions of angiotensin, vasopressin and aldosterone. Realistic sizes of body-fluid compartments for an average 70 kg young man are set up and supplied with appropriate contents of electrolytes, urea, etc. At each iteration interval, shifts of electrolytes and water take place in accordance with concentration gradients and colloid and crystalloid osmotic pressures at rates which have been given realistic values. In addition, tissue blood flow is governed by general body autoregulation, operating with a realistic time scale and gain, and systemic arterial baroreceptor resetting takes place at an appropriate rate.

The program is capable of simulating a very large range of clinical situations which can be examined over realistic periods of time. For example, if the model *MacPee* is given either gross proteinuria, gross reduction in cardiac contractility or a substantial haemorrhage, sodium virtually disappears from the urine and body weight increases, eventually with oedema. Administration of diuretics brings improvement, but too much results in potassium depletion. The hypertension of renal artery stenosis and of primary hyperaldosteronism can be simulated, and the time course of changes in cardiac output and total peripheral resistance can be examined. *MacPee* allows simulation of any degree of acute or chronic renal failure, with any specified coincident variation in sodium and protein content of the diet. Diabetes insipidus, inappropriate ADH secretion, Addison's disease, and a very large number of other well-known clinical conditions can also be realistically simulated. You can study interactions with many different combinations of physiological and pathological conditions.

The simulation will usually find its way into a steady state, providing no induced disturbance is unduly great. If it cannot do so, and any one of a large number of monitored essential functions move outside the range which the body can tolerate, *MacPee* will die and a necropsy report will be issued. To improve its clinical realism further, *MacPee* will also inform you of any appropriate symptoms, signs and nursing reports which might realistically be expected in severely abnormal conditions.

1.3 Limitations — conceptual and procedural

As in other simulation programs, there are inevitable conceptual limitations. These are due largely to our ignorance of fundamental physiology. For example, there is no agreed hypothesis to explain the tendency of both glomerular filtration rate and renal blood flow to remain relatively constant as blood pressure changes, and a truly realistic description of these functions cannot at present be given. Hence their operation in *MacPee* will often be inadequate or inaccurate. (Incidentally, it will be a great help to the designers if any examples of apparent unphysiological behaviour are noted and reported, so that these can be considered as part of the continuing process of correction and development in subsequent versions of the program.)

Procedural limitations are largely those of unfamiliarity. Do not think of *MacPee* as a computer model, but rather as an obliging individual who will allow all sorts of experiments to be performed on him. No knowledge whatever of computers is needed and the interactive system has been designed to make

it as easy as possible to run the program. (If you have any suggestions about improvements in the interactive dialogue technique, again please let us know.)

1.4 Implementation

The program is written in Fortran 77 and uses high-level graphics programming techniques. It is about 50% longer than the original form of the program and has been rewritten to take advantage of the facilities of Fortran 77 and to revise and clarify the program structural design, an inevitable need with a program which has evolved gradually. Considerable revision was also required to allow the graphical features 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.

To proceed type 1, then press the <ENTER> key

To get brief introduction, type 2 and then <ENTER>

You will now be asked to specify the units to be used — either g and mg or SI.

To use units of g and mg type 1. For SI units type 2

You cannot interchange between the two without stopping and restarting the program.

You then have the choice of having a normal-looking subject whose blood pressure is variable during the day, and whose intake of food and fluid is intermittent, or a more artificial subject in which, for more theoretical study, everything remains initially in a steady state throughout the 24 hours.

For normal display type 1. To suppress diurnal rhythm type 2

For most purposes you will find the 'normal' display is more realistic, though (like human beings) the lack of a completely steady baseline makes observations more difficult. Once again, you can only interchange between the 'normal' display and the artificially stable display by stopping and restarting the program.

2.2 How to get help

If you make a mistake in entering an instruction, on most microcomputers and terminals you can simply press the 'Backspace' or 'Delete' key, and re-enter your command. Remember, the computer will do nothing until you have pressed the ENTER key.

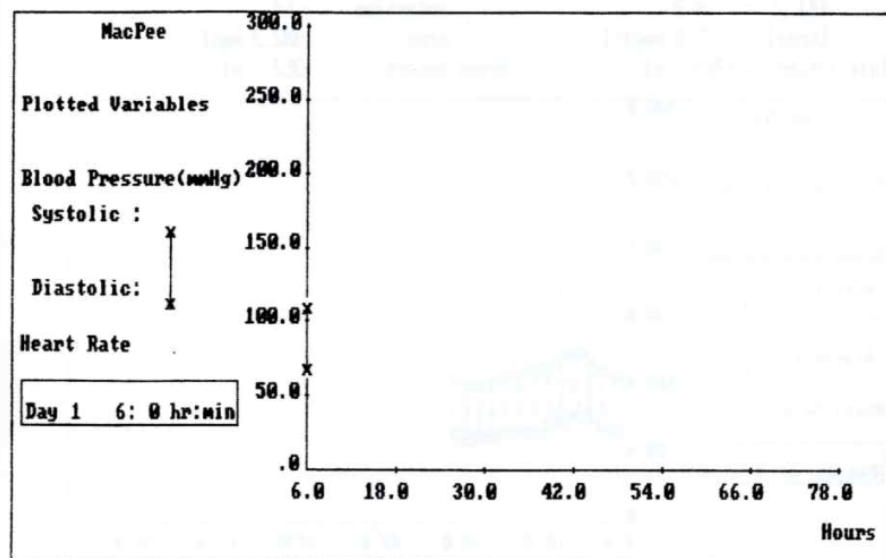
If you are not clear about a menu option or instruction type 'Q' (for Query),

and press ENTER, whereupon help and explanation will be given. The handbook shows examples of the use of this facility.

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

Once the initial questions concerning units of measurement and diurnal rhythm have been answered, the program sets up a standard male subject of ~70kg body weight and produces on the screen a standard graphical display (Figure 2). This display is largely self-explanatory. Its main feature is a chart of blood pressure (X—X bars running between systolic and diastolic pressures) and heart rate (represented as dots) at each iteration interval during the day. Unless changed deliberately, the graph will plot results every hour. Note also the clock giving the time in days, hours and minutes and the continually updated table of 8 key model variables. This set is shown initially by default, but can be subsequently altered by the user (see Section 3.5) to include any of the model variables listed in Appendix 1. The time axis of the display is set by default to cover 3 days, with the simulation starting at 6 a.m. on day 1.

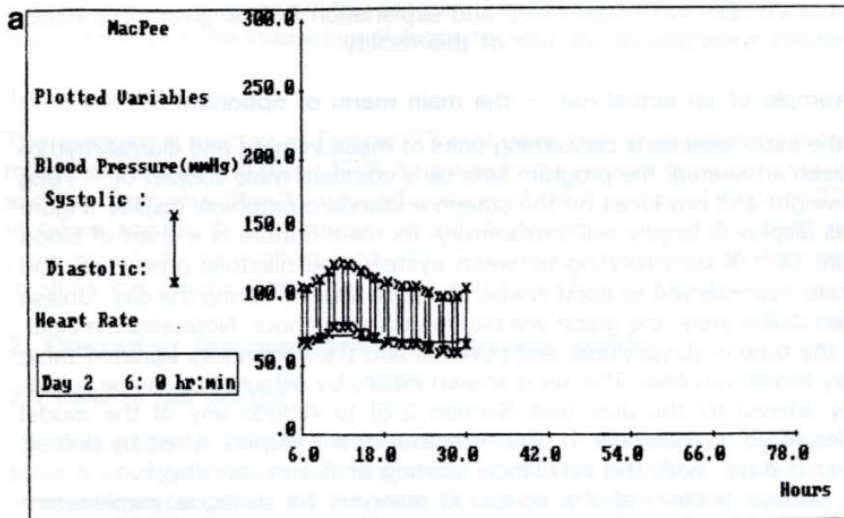
The bottom section of the screen is reserved for dialogue, explanatory messages and further tables of results. When the program pauses here, you press the ENTER key to reveal in succession two tables of things which are



1768.4	1353.5	78.8	144.3	4.3	140.4	63.3	5.1
--------	--------	------	-------	-----	-------	------	-----

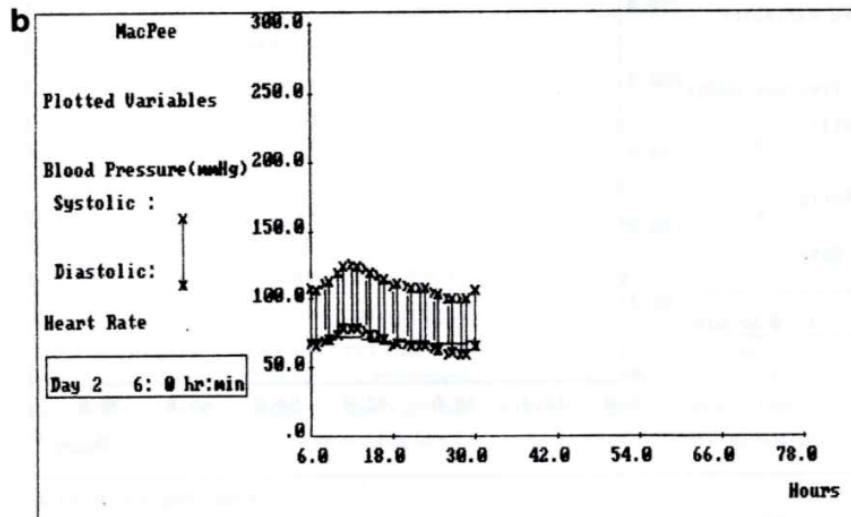
In -Fluid- Out Mean BP (Na)-Plasma-(K) (Na)-Urine-(K) Bl. Urea

Figure 2. The standard form of graphical display, before starting a run. A standard set of 8 tabular variables is displayed and continually updated. This set may be altered by the user.



Final values recorded (since 6 a.m.) were:

Plasma [Na] = 144. mmol/l	Urine sodium = 140. mmol
[K] = 4.3	potassium = 64.
[urea] = 5.0 mmol/l	urea = 482.3 mmol
Fluid intake = 1769. ml	Urine output = 1352. ml



Creatinine = .10 mmol/l	Haemoglobin = 14.0 g/dl	PCV = 45. %
Plasma alb. = 41.2 g/l	24 hr Ur.prot. = .1 g	Body weight = 67.2 kg
B.P. 104/ 63 (mean= 77.)	R.atrial press.= 2. mm Hg	Heart rate = 71.

Figure 3a. The standard subject exhibiting diurnal variations after a standard run of 24 hr with results displayed hourly and with the first table of results.

Figure 3b. As for Fig. 3a with the second standard table of results displayed at the end of the run.

commonly measured. These are shown in Figure 3, after an initial run of 24 hours (see below), where the display is that generated for the normal subject when exhibiting a diurnal rhythm. In the second table (Figure 3b) 'PCV' stands for 'packed cell volume'; 'Alb' for 'albumin concentration' and 'Ur.Prot.' for 'urinary protein loss'. The others should be clear. You will see that all values are about normal for an average adult male and are in SI units since in this case the user had asked for these (not g and mg) when starting up the program. You can obtain further values by pressing the ENTER key when you have noted the first table of results.

Having viewed the 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 options is obtained if you ask for help (type 'Q' then press ENTER at this point). Remember always to press the ENTER key to activate a command to the program. To return to the main menu of options at any time, type '*' then press ENTER.

Selection of the '2. Continue' option results in output of charts for the next day as shown in Figure 3. The other options, dealt with in detail below, are:

- | | | |
|------------|--|-------------|
| 1. Change | to make alterations e.g. to subject factors, to the mode of output and length of simulation run, to fluid therapy options or to make a selection from a range of 'preset' subjects. | Section 2.4 |
| 3. Restart | to start afresh with the standard 70 kg male subject. | |
| 4. Inspect | to view in detail the current state of the model in terms of, for example, haemodynamics, compartmental concentrations and amounts of fluid and electrolytes and levels of circulating hormones (renin, aldosterone, ADH). | Section 2.4 |
| 5. Plot | to plot results from a preceding simulation as functions of time or as cross-plots of one variable against another. | Section 3.1 |
| 6. Stop | to terminate the program. | |

Certain options, such as the 'Inspect' and 'Plot' options, will clear the current display of simulation results. These results are still stored and will be regenerated automatically when the user next selects the 'Continue' option. When the simulated time reaches the end of the displayed time axis, the program automatically generates a new graph using the same scale but a new origin.

2.4 How to change model factors

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

1. Change values, 2. Fluids (+/-), 3. Store/Bktrk, 4. Run change, 5. Presets

For the purposes of this elementary introduction we will concentrate on changes to model values (or factors) option 1.

The other options are dealt with elsewhere as follows:

Fluid Management	Section 2.5
Store/Backtrack	Section 3.4
Run Change	Section 3.5
Presets	Section 3.6

On choosing the option '1. Change values', you are invited to type the number of the factor or factors you want to change. There are many of these, and a complete list with further explanation is given in Appendix 1. To specify a factor to be changed, you respond to the prompt:

Type number of factors (1-25) to change

On entering the response 'Q' (Query) the principal factors are listed as follows:

Principal Changeable Factors in the Model:

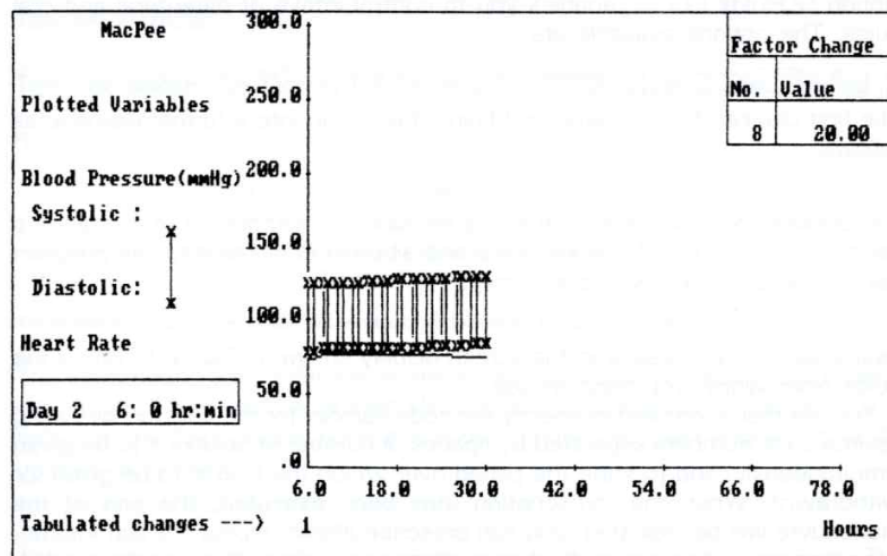
1. DIET: SODIUM INTAKE, mmol/day
2. DIET: PROTEIN, g/day
3. DIET: EXTRA POTASSIUM OR K WITHDRAWAL, mmol/day
4. CARDIAC 'CONTRACTILITY', as % normal average value
5. WHOLE BODY ARTERIAL RESISTANCE, as % average value
6. RENAL ARTERY PRESSURE DROP, in mm Hg across the renal arteries (arbitrary upper limit of 30 mm Hg set for this)
7. WHOLE BODY VENOUS RESISTANCE, % normal average value
8. KIDNEYS: GLOMERULAR FUNCTION, as % average normal (corresponding to about 120 ml/min GFR in average-sized subject)
9. TUBULAR SODIUM LOSS from any cause (factor value corresponds approximately to equiv. daily dose frusemide, mg)
10. VASOPRESSIN FUNCTION, % average normal
11. KIDNEYS: AVERAGE DAILY LOSS OF PROTEIN, g (assuming normal glomerular function: e.g. 30 gives daily loss of 30 g of albumin at GFR of 120, or 15 g/day at GFR of 60)
12. ALDOSTERONE FUNCTION, % average normal
13. INTRATHORACIC PRESSURE, mm Hg (average) - relative to atmospheric pressure
14. LIMITING CARDIAC FILLING PRESSURE, mm Hg (over mean intrathoracic press., above which no more output is obtainable)
15. MASS TOTAL EXCHANGEABLE SODIUM, mmol
16. QUANTITIES TOTAL EXCHANGEABLE POTASSIUM, mmol
17. IN THE BODY: TOTAL UREA MASS, mmol or mg
18. TOTAL ALBUMIN MASS, g (plasma only)
19. TOTAL RED CELL VOLUME, ml
20. LEAN TISSUE MASS, kg
21. TOTAL BODY WATER, litres
22. CAPACITANCE OF THE VENOUS SYSTEM, % of normal value
23. SET POINT FOR BARORECEPTOR SENSITIVITY, mm Hg above (+) or below (-) the normal average value for a normotensive subject. (The value slowly changes with sustained hypo- or, hypertension at an appropriate rate)
24. FLUIDS: MAXIMUM DAILY INTAKE ALLOWED, ml
25. EXTRA FLUID INTAKE, ml/day (above that normally determined solely by thirst)

The operator in the next example selected 'factor 8' (renal glomerular function) to be changed, and in response to the request

Factor 8 (Current value = 100.00). Specify new value

typed in '20' thus reducing glomerular function to one fifth its normal value (since the '100.00' refers to 'percent of normal function'). He then asked for the run to '2.Continue' and the program responded by displaying a graph, covering the next day's results and charts (Figures 4 and 5). Note here, the fall of urine volume and the rise in the blood urea and creatinine concentrations. Note also that the program has recorded on the screen the change in factor 8 and the time at which it occurred.

By comparing this run with Figures 2 and 3 (although these are based on the subject exhibiting diurnal rhythms) you will see what is meant by complex interactions - e.g. the fall in urinary potassium and displacement of potassium from cells raises plasma [K]; the water and sodium retention slightly expands plasma volume and lowers haemoglobin and plasma albumin concentration; the blood urea rises.



1666.1	474.6	97.9	141.3	4.9	23.1	17.5	9.3
In-Fluid-	Out	Mean BP	(Na)-Plasma-(K)	(Na)-Urine-(K)	Bl. Urea		

Figure 4. The standard 70 kg subject with diurnal rhythm suppressed showing alteration of renal glomerular function (factor 8) to 20% of normal after an initial run of 24 hr.

Final values recorded (since 6 a.m.) were:

Plasma [Na] = 141. mmol/l	Urine sodium = 23. mmol
[K] = 4.9	potassium = 17.
[urea] = 9.3 mmol/l	urea = 140.3 mmol
Fluid intake = 1666. ml	Urine output = 475. ml

Creatinine = .12 mmol/l	Haemoglobin = 14.3 g/dl	PCV = 43. %
Plasma alb. = 37.7 g/l	24 hr Ur.prot. = .8 g	Body weight = 68.1 kg
B.P. 129/ 82 (mean= 98.)	R.atrial press.= 2. mm Hg	Heart rate = 76.

Figure 5. Tables of results displayed following the 24-hr run with reduced glomerular function. Note the rise of plasma potassium and urea.

2.5 How to prescribe parenteral or oral fluids

Option '2.Fluids (+/-)' enables you to control intake of parenteral and oral fluids. The options available are:

1. Give instructions about parenteral fluids, 2. Push fluids, 3. Restrict fluids, 4. Give fluids ad lib, 5. give a water load

The first choice offered (parenteral fluids) takes you into a further dialogue as follows:

Do you want 1. Give new instructions, 2. Repeat last, 3. Cancel all?

Instructions can cover the intravenous infusions or withdrawal of all standard parenteral fluids, blood, packed cells and albumin concentrate. The program asks for your choice with the prompt

Type code number for therapy (Q for details, just press <ENTER> alone if none required)

Response 'Q' here results in the screen display shown in Figure 6, listing the fluids from which you may choose.

You are then prompted to specify the code number for the fluid (or, by typing several code numbers separated by spaces, a number of solutions to be given simultaneously) and to state the period over which the fluid is to be given (or withdrawn). When the 'prescription' has been executed, the end of the manoeuvre will be indicated; you can prescribe afresh, repeat the last instructions, or cancel all parenteral fluid instructions at any time after a run has ended.

Instructions given in the options 2 and 3 specify 'pushing' or restriction of fluids, and these continue in effect until rescinded. By the use of these options you can enforce any degree of fluid restriction, or instruct the nurses to 'push' fluids, i.e. make *MacPee* drink any specified amount, which might be more than he would wish to do to satisfy his thirst (real patients are usually harder to persuade!). To cancel either of these options specify '4.Give fluids ad lib'.

In the following example, *MacPee* was given 3 litres of isotonic saline over 12 hours. The dialogue was as follows:

Fluids which may be prescribed are:

1. Isotonic (0.9%) saline
2. Half-strength (0.45%) saline
3. Hypertonic 5% saline (5.5 X isotonic strength)
4. Dextrose (2/3) - saline (1/3) — isotonic
5. 5% dextrose (i.e. water)
6. 10% travasol (70 mmol Na + 60 mmol K/litre)
7. Potassium chloride, 2 mmol/ml
8. Whole blood
9. Packed red cells
10. Plasma (fresh or stored)
11. Concentrated albumin (salt-poor, 25 g/100 ml)

Type one or more option numbers, separated by spaces
Then press <ENTER>

Type code numbers for therapy (Q for details, <ENTER> alone if none required)

Figure 6. List of fluid management options.

Type code number for therapy (Q for details, just press <ENTER> alone if none required)

1

How much ISOTONIC SALINE do you want to give, or,
(if preceded by a negative sign) withdraw, in ml?

3000

Type period (in hours) over which fluid is to be given or withdrawn

12

The instructions are confirmed on the screen as shown in Figure 7. Complete restriction of oral fluids was then also applied, by using the '3.Restrict fluids' option in the fluid therapy submenu shown above and then responding to the prompt as follows:

Type maximum oral intake during each day, in ml

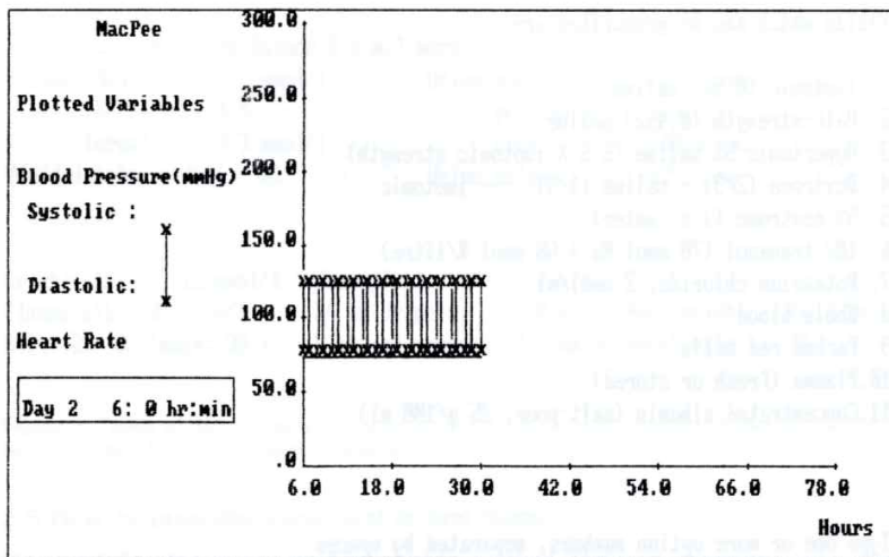
0

The run was then started by selecting the main menu option '2.Continue'. The display (Figure 8) is for the normal 70 kg subject with diurnal rhythm suppressed.

2.6 Some suggested initial experiments

You might start, as above, by examining the effects of progressively reducing renal glomerular function, and then observing the effects of changes in dietary sodium and dietary protein (factors 1 and 2 — see Appendix 1).

Another instructive example of complex interactions is to observe the way



*** 3000.0 ml ISOTONIC SALINE will be INFUSED
 *** over 12.0 hr

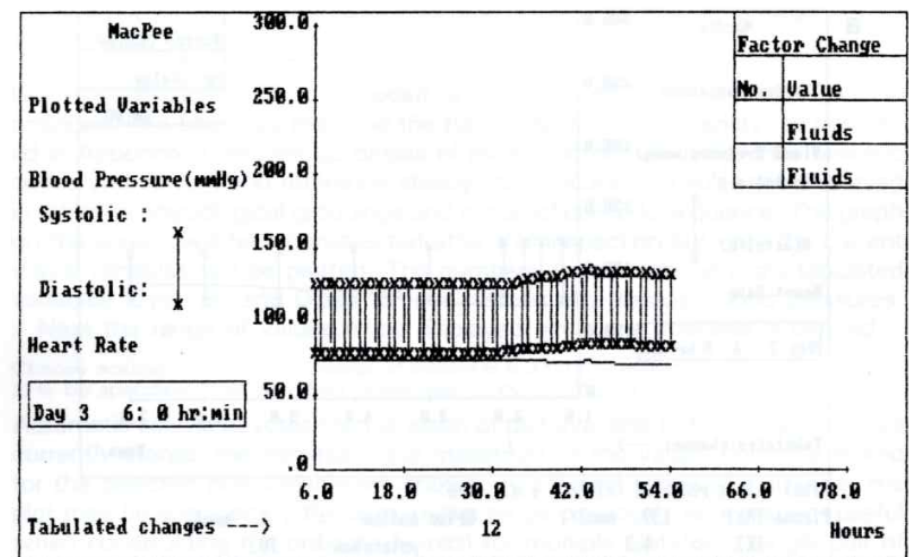
Figure 7. Confirmation of instructions to infuse 3 litres of isotonic saline over the next 12 hr.

in which the body can selectively conserve things in short supply. In the following example (Figure 9), sodium intake (factor 1) was reduced from 140 to 20 mmol/day and the situation followed for 5 days with results plotted every 24 hours (see Section 3.5 for details of the dialogue required to alter the length of run and format of output). Very little gross change has occurred other than the enormous reduction in urine sodium output. The situation could be studied in considerably more detail using the 'Inspect' option (see Section 3.2), as in Figure 9b. You can also check the body's ability to get rid of sodium on very high-sodium diets, and potassium when the diet is potassium-rich.

Any time you wish you can obtain a new subject by the use of the '3.Restart' option. If model 'death' should occur at any time you can similarly start afresh.

This exercise should have given you some idea of the capabilities of the program and how to use it to do experiments. More detailed guidance on experiments is given in Section 4.

The program is very flexible and there is thus an extremely large number of possible ways in which the user can configure and run the model. One of the prices paid for such flexibility is that occasionally the program will fail and issue an obscure error message when it is stressed abnormally in one direction or another. A large number of tests for such potential malfunctions are contained in the program, with corrective actions, but these cannot exhaust all possibilities. Should this type of failure occur, you will have to restart the program using different parameter values, or (in the case of some arithmetic errors) using a shorter iteration interval (e.g. 10 min instead of 60 min).



1800 hrs. Designated fluid has now all been infused

3000.0	2440.5	97.9	150.6	4.3	344.8	57.7	2.6
--------	--------	------	-------	-----	-------	------	-----

In -Fluid- Out Mean BP (Na)-Plasma-(K) (Na)-Urine-(K) Bl. Urea

Figure 8. Simulation of infusion of isotonic saline while disallowing oral intake of fluids. The total fluid intake over the 24-hr run is thus limited to the 3 litres of isotonic saline infused. The program displays symptoms of thirst.

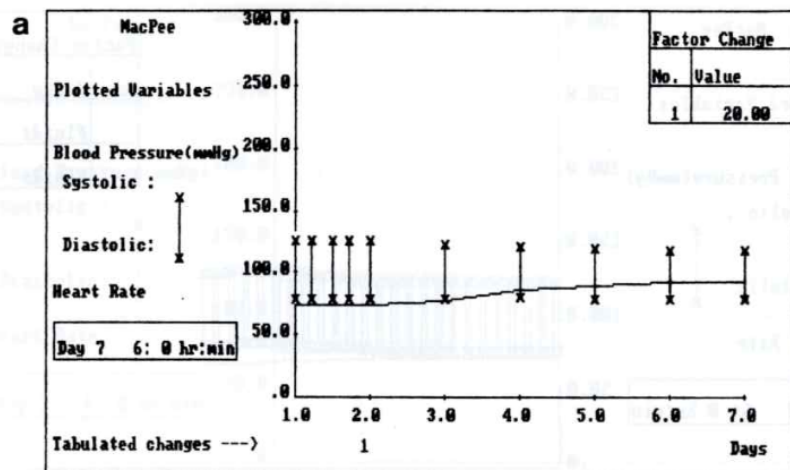
3. Operating the program — further details

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. These facilities are provided in a general purpose graph-plotting module which can be invoked at any time as option 5 in the main menu of options.

The program preserves the calculated values of selected model variables for the last 100 points plotted or tabulated on the screen. Thus the standard plotted variables, blood pressure and heart rate, 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 Section 3.5 for a description of how the set 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).



Final values recorded (since 6 a.m.) were:

Plasma [Na] = 139. mmol/l Urine sodium = 1. mmol
 [K] = 4.3 potassium = 78.
 [urea] = 4.6 mmol/l urea = 395.8 mmol
 Fluid intake = 1483. ml Urine output = 956. ml

Day 7 6: 0	WATER	SODIUM	POTASSIUM	UREA	OSM	ALBUMIN
	ml.	mmol	mmol/l	mmol	mmol/l	mmol
WHOLE BODY	41416.	(3291.	3375.	- both	total	exchangeable)
CELLS	27249.	1328.	49.	3313.	122.	189.
E.C.F.	14167.	1963.	139.	61.	4.3	
INT.FLUID	11352.	139.	4.3	5.	276.	7.9
BLOOD	5898.					
PLASMA	2815.	139.	4.3	5.	276.	111.
RED CELLS	2283.				5.	
CUM.INTAKE	1483.	28.	63.	(480.)		
CUM.URINE	956.	1.	1.	78.	81.	396.
(since 6 a.m.)				414.	234.	.1
	ART.	VEN.	CAP.	GLOM.	RENAL	INT.FL.
PRESSURES	115/ 76	1. 14.	44.		-4.	Heart rate = 93. /min
(mm Hg)	(89.2)					Haemoglobin= 14.8 g/dl
FLOWS	4.7(CO)	82.(GFR)	326.(RPF)			PCV = 45. %
(l or ml/min)						P.Creat. = .11mmol/l
RESISTANCES	16.5	2.8	25.(pre)	69.		Body weight= 67.7 kg
(mmHg/l/min)			43.(post)			

AUP= .3 pmol/l, PRA= 5.5 ng/ml/h, Aldo= 27.4 ng/dl, Symp.act.= 1.7

Figure 9a. Illustrating a very low sodium diet of 20 mmol/day. The model is run for 24 hr on a normal sodium diet with standard output every 6 hr. The dietary sodium is then set acutely to 20 mmol/day and the run continued for 5 days with standard of output every 6 hr. Note that the timescale for longer runs is displayed with day number.

Figure 9b. The 'Inspect' option display — described in Section 3.2 — produced after the 5 days of sodium depletion.

Select X-axis variable using numeric code () from: (<ENTER> alone = time)
 Time in hr (0), Syst.BP(1), Diast.BP(2), Heart Rate(56)
 or the tabular variables (78), (77), (48), (32), (34), (74), (71), (35).

By responding with 'Q' at this point, a detailed description of this process is provided. The user may then use the full model inspection facility, as described in Appendix 1, to look up details of model factors/variables, their numeric codes and current and reference steady-state values. Variables are displayed in tables in physiological groupings and in numerical code sequence. The graph on the screen will be reconstructed after this inspection but only the current y-axis variables will be plotted. The numbers shown are the eight tabulated variables. Syst. BP and Diast. BP are systolic and diastolic blood pressures.

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 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 150.000; <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). For scatter plots any character may be specified as the plotting symbol.

Having plotted the first graph, a submenu of options is offered as follows:

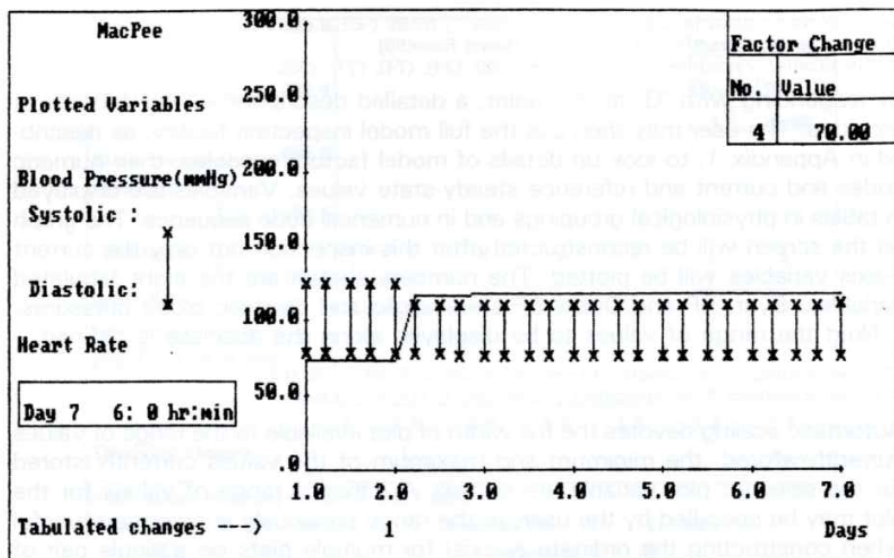
1. Add variable to graph, 2. Start fresh graph, 3. Return to model

To add a second variable to the graph, a new ordinate may be defined and scaling for this re-specified as required. Thus the user may construct multiple plots of model variables against time or multiple cross-plots against a single other variable.

Figure 10 shows a simulation over 5 days of myocardial infarction with reduction of cardiac pump performance to 70% normal (factor 4 = 70). Values are plotted and stored every 6 hr (see Section 3.5). Figure 11 shows of 3 stages in the plotting of mean blood pressure, heart rate and plasma urea concentration as functions of time, generated using the above described interactive procedure. During this time, an oedematous state is reached because of fluid retention. The scaling for abscissa and ordinate were specified to be in the ranges shown. A variety of plotting modes are illustrated.

3.2 The 'Inspect' option

This option allows you to display most of the variables computed in the model. Nearly everything you could possibly want to know is displayed by asking for



1576.1	642.4	87.5	140.5	4.1	4.8	54.2	4.5
In-Fluid	Out	Mean BP	(Na)-Plasma-(K)	(Na)-Urine-(K)	Bl. Urea		

Figure 10. Simulation of an acute myocardial infarction. The model is run for 24 hr and then myocardial performance is reduced to 70% of normal and kept at this value. Diurnal rhythm is suppressed and units of g and mg are in use.

'Inspect' in the main menu of options which appears at the end of any run. The display fills most of the screen and overwrites the current simulation output. This is regenerated automatically following the inspection, should the user then choose to 'Continue'.

Figure 12 shows the values in an 'Inspect' table for the normal subject (i.e. the 70 kg male subject exhibiting diurnal variations). Abbreviations in the table are as follows:

- OSMolarity in mmoles/litre,
- ECF = Extra Cellular Fluid,
- INTerstitial FLUID,
- SYStemic ARterial,
- Systemic VENous,
- Systemic CAPillary (whole body average value),
- Renal GLOmerular,
- INT.FL. = general body interstitial fluid pressure (normally negative to atmospheric pressure),
- Packed Cell Volume,
- GFR = Glomerular Filtration Rate,

PRE-glomerular,
 POST-glomerular,
 CARDIac CONtractility,
 CELL electrolyte concentrations are body averages — potassium and sodium concentrations are very variable in different tissues e.g. $[K^+]$ is high in muscle cells.
 AVP = arginine vasopressin,
 PRA = plasma renin activity,
 Aldo = aldosterone,
 Symp.act = index of sympathetic activity.

The units for the other values are the commonly used clinical units. The two figures at the top for whole body sodium and potassium are for 'total exchangeable' amounts, not true totals. The 24-hr intake of urea is shown in brackets, and shows the equivalent mass of urea derived from dietary protein. Cumulative values of urine sodium, potassium and urea concentrations and urine osmolarity indicate pooled values since 6 a.m., assuming 24-hr collections of urine from that time each day.

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

3.3 Inspecting and changing model factors and variables

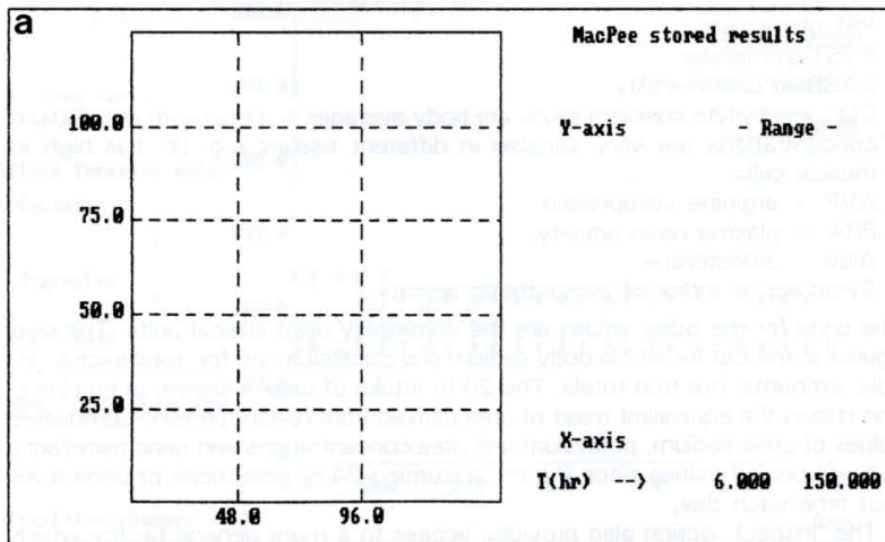
3.3.1 Inspecting single values

The values of any of the factors and variables listed in Appendix 1 may be interrogated by the following procedure. Specify first the 'Change' option in the main menu, then choose '1.Change values' in the subsidiary menu and type the factor number (see Appendix 1 for list). At this point, as described in Section 2.4, you can specify a new value for the variable. If instead you now just press ENTER (i.e. without any numeric input), the value of the variable will not be changed but its current value will, nevertheless, be displayed.

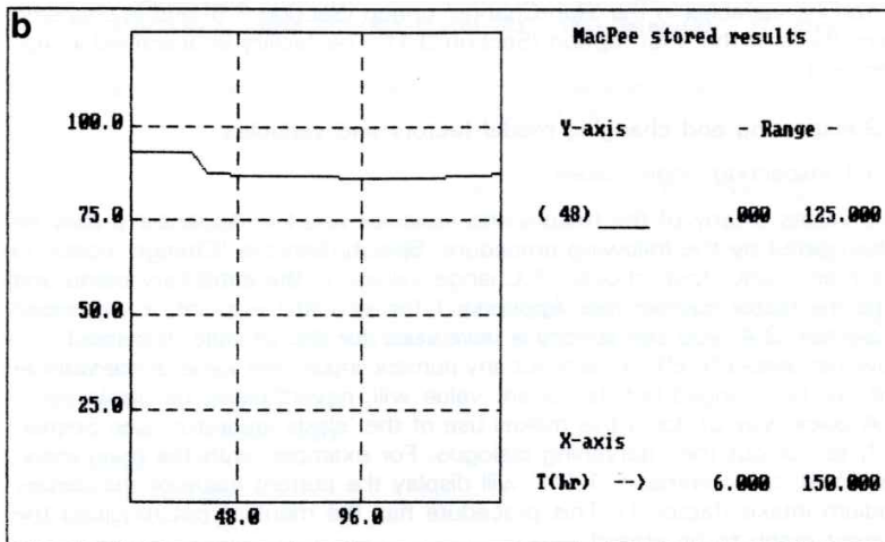
A quick way of doing this makes use of the 'slash separator' (see Section 3.7) to cut out the intervening dialogue. For example, with the main menu displayed, the command '1/1/1' will display the current value of the dietary sodium intake (factor 1). This procedure has the merit of not requiring the current graph to be erased.

3.3.2 Changing more than one factor at once

Since a new run is only commenced when the main menu option 'Continue' is selected, you can always ask for '1.Change values' a second time and change

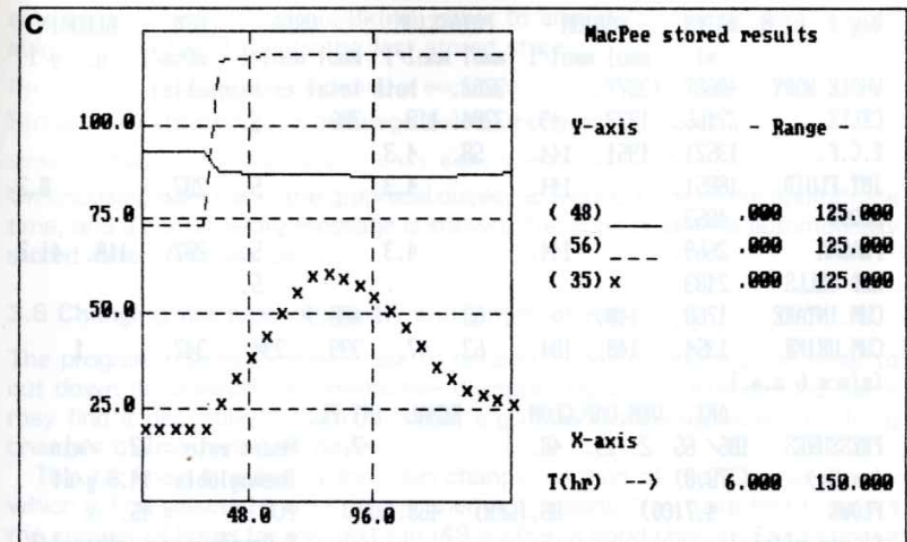


1. Scatter diagram,
2. Solid connecting line,
3. Dashed connecting line
4. Dot-dash line,
- 5,...,10 Other distinctive patterns



Options now are:

- 1.Add variable to graph,
- 2.Start fresh graph,
- 3.Return to model



Options now are:

- 1.Add variable to graph,
- 2.Start fresh graph,
- 3.Return to model

Figure 11a. Illustrating the use of the 'Plot' facility to display results from the simulation of myocardial infarction. The time axis with six-hourly data over 6 days has been selected with markers at 48 and 96 hours. The first plot is to be of mean blood pressure (variable 48) and the scale 0-125 has been marked out.

Figure 11b. Blood pressure (variable 48) has been plotting with a connected line.

Figure 11c. Heart rate (variable 56, dotted line) and blood urea (mg/100 ml, variable 35, symbol x) have been added to the plot on the same y-axis scale. Blood urea is seen to recover to only slightly above normal level after rising to three times its normal level following the acute infarction.

further factors until you are ready to 'Continue'. However, the model will accept a list of up to 10 factors to be changed one after the other (they are separated by spaces). Note that only the last ten factor changes are displayed on the table on the screen and this number of changes may interfere with the graphical display towards the end of the x-axis.

An example of the dialogue involved in changing dietary sodium and potassium is as follows:

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

1

1. Change values, 2. Fluids (+/-), 3. Store/Bktrk, 4. Run change, 5. Presets

1

Type number of factors (1-25) to change

1 2

Factor 1 (current value = 140.00), specify new value

20

Day 1 6: 0	WATER	SODIUM		POTASSIUM		UREA		OSM	ALBUMIN	
	ml.	mmol	mmol/l	mmol	mmol/l	mmol	mmol/l	mOsm/l	g.	g/l
WHOLE BODY	40687.	(3277.		3262. - both		total exchangeable)				
CELLS	27166.	1327.	49.	3204.	118.	206.	5.			
E.C.F.	13521.	1951.	144.	58.	4.3					
INT.FLUID	10851.		144.		4.3		5.	287.		8.2
BLOOD	4853.									
PLASMA	2669.		144.		4.3		5.	287.	110.	41.2
RED CELLS	2183.						5.			
CUM.INTAKE	1768.	140.		63.	(400.)					
CUM.URINE	1354.	140.	104.	63.	47.	399.	294.	347.		.1
(since 6 a.m.)										
	ART.	VEN.CAP.GLOM.		RENAL		INT.FL.				
PRESSURES	106/ 65	2. 13.	48.				-7.	Heart rate = 72.	/min	
(mm Hg)	(78.8)							Haemoglobin= 14.8	g/dl	
FLOWS	4.7(CO)		88.(GFR)	468.(RPF)				PCV = 45.	%	
(l or ml/min)								P.Creat. = .18	mmol/l	
RESISTANCES	14.4	2.4	26.(pre)	69.				Body weight= 67.2	kg	
(mmHg/l/min)			43.(post)							

AVP= 1.2 pmol/l, PRA= 3.3 ng/ml/h, Aldo= 24.6 ng/dl, Symp.act.= 1.0

Figure 12. The full 'Inspect' table for the normal subject. This is a 6 a.m. profile including results cumulative 24 hr urine studies over the previous day. SI units have been selected.

Factor 1 = 20.00 (previously = 140.00)
 Factor 2 (current value = 90.00), specify new value
 50
 Factor 2 = 50.00 (previously = 90.00)

In Figure 13 the operator has simulated diminished myocardial function (factor 4) and the administration of a vasoconstrictor, increasing arterial resistance (factor 5). The figure shows the situation after 24 hr (graphical display with boxed variables and then with symptoms) and after 48 hr (graphical display with symptoms and then the 'Inspect' table). Six-hourly output has been specified.

3.4 The Store/Backtrack option

You may wish to carry out a number of different simulations with a subject you have set up in exactly the right state at the end of a series of manoeuvres. It is then tedious to recreate these same conditions each time and much easier to be able to 'store' them and then be able at any subsequent time to 'backtrack' to where you were before. This is especially useful when you are about to do something which might prove to be irrecoverable.

On choosing the 'Change' option in the main menu, you can use the sub-

sidary menu option '3.Store/Bktrk', either to store the present state of your subject or to backtrack to the last stored state.

Do you want to 1. Store present state, 2. Backtrack to last stored state?

Storage is indicated by a message below the graph such as:

Stored at this point ***** (Time = 1 day 6 hrs 0 min)

On choosing backtrack, the graphical display is wound back to the appropriate time, and a confirmatory message is shown. The subject state is automatically stored when first set up.

3.5 Changing the type of display and length of run

The program makes extensive use of default modes of operation in order to cut down on unnecessary interactive dialogue. However, experienced users may find it desirable to override these, e.g. when following slowly evolving changes over a period of days.

This facility is handled in the 'Run change' section of the 'Change' menu which is first selected from the main menu of options. You have first to select the number of hours for the next run (48 is often a good choice). Then choose the iteration interval in minutes (60 is recommended). For each of these the current value is displayed and if you simply press the ENTER key, the value will be left as it is.

The next question is:

Do you want 1. All, 2. Every 6th, or 3. Every 24th value printed?

Normally all values are output but options 2 and 3 are important in keeping the screen uncluttered for the longer simulations.

In reply to the next question:

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

type 1 (for the standard format you have already seen), 2 (to suppress tables of lab. results at the end of each run), or 3 (to allow special tabular mode of output of the 8 selected values usually seen in the boxes below the graph).

For graphical display modes, the next question concerns the time scale to be adopted. The options are prompted in the form:

Do you want 1) Automatic timescale selection, or fixed timescale of 2) 12 hr, 3) 24 hr, 4) 3 day, 5) 6 day, 6) 12 day, 7) 24 day? (<ENTER> alone = no change)

The automatic selection is based on the run length selected, allowing space for at least two successive runs to be displayed on the screen.

Finally the program asks you to

Selected values: Type up to 8 nos. (currently 78 77 48 32 34 74 71 35)
 (<ENTER> alone leaves unchanged, 78 gives standard set of variables)

This specifies the set of model variables, using the code numbers listed in Appendix 1, which is to appear in the boxes under the graph (and be saved for subsequent replotting if desired) or to be tabulated in the numeric output mode. The standard set is as follows:

	In	Fluid	Out	Mean BP	(Na)-Plasma-(K)	(Na)-Urine-(K)	Urea
1.12.	0	438.5	75.5	87.9	141.9	4.4	.3 17.9 4.4
1.18.	0	863.3	131.9	87.6	141.2	4.5	.3 34.8 5.5
2. 0.	0	1274.9	189.5	87.3	140.5	4.5	.3 52.1 6.5
2. 6.	0	1675.7	248.3	87.2	140.0	4.6	.3 69.7 7.4
2.12.	0	392.0	59.9	87.0	139.6	4.7	.0 18.0 8.3
2.18.	0	776.7	120.8	86.9	139.2	4.7	.0 36.2 9.2
3. 0.	0	1155.3	186.8	86.9	138.9	4.8	.0 56.0 10.0
3. 6.	0	1529.6	277.7	86.9	138.7	4.8	.0 79.5 10.2

Figure 14. Numerical mode of output from the model, showing changes over two days, six-hourly, after reduction of cardiac pump performance (factor 4) to 70% of normal. The variables traced are as detailed in the text.

Model Variables (1-120),	Day 1	6: 0 hr:min
140.0 80.0 .0 100.0 100.0 .0 100.0 100.0 .0 100.0		
.1 100.0 -2.0 8.0 3315.5 3457.4 133.7 111.5 2286.5 26.3		
41.1 100.0 .124000.0 .0 3397.4 60.0 2.3 176.827221.0		
.9 142.6 41.6 4.3 3.3 1340.0 1975.5 49.2 124.8 1.0		
.8 .0 .0 .0 40.8 2729.9 111.8 93.013048.7 60.3		
644.8 13.2 1.6 5.0 45.6 74.7 3.0 16.6 105.3 55.4		
2.6 47.8 1.4 .9 67.3 1.3 5.8 5016.5 16.4 400.0		
63.6 140.0 63.2 140.1 .1 390.2 1330.5 1740.4 72.8 -6.0		
.0 1.0 12.5 133.7 2.1 1.0 15.0 621.911118.0 26.0		
-400.8 1.4 42.6 282.3 .0 394.1 .1 8.9 1.0 1.0		
2.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 183.4 1.0		
1.0 1.0 .0 .0 .0 .0 .0 .0 100.0 70.0		

Figure 15. Listing of all model variables (1 - 120).

Variable	Numeric code
Cumulative 24 hr fluid intake, ml	78
Cumulative 24 hr fluid output (excluding insensible losses), ml	77
Mean arterial blood pressure, mm Hg	48
Plasma sodium concentration, mmol/l	32
Plasma potassium concentration, mmol/l	34
Cumulative 24 hr urine sodium amount, mmol	74
Cumulative 24 hr urine potassium amount, mmol	71
Plasma urea concentration, mmol/l or mg/dl	35

The Query option here gives full instructions on how model variables are specified and gives access also to the general inspection facility (Appendix 1)

to allow the user to look up the details of model variables and their numeric codes. However, if you wanted to examine several selected variables, e.g. blood volume, interstitial fluid volume, total cell water, cardiac output, total exchangeable sodium, total exchangeable potassium, haemoglobin and packed cell volume, you could type

68 89 30 54 15 16 87 55

(each number separated by blanks). The chosen mode of display and run details remains in force 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 an example of the tabular mode of output of the set of variables described above. The myocardial function has been reduced to 70% of normal and the situation followed for 48 hr with output every 6 hr.

3.6 Preset simulated subjects

Option 5 in the 'Change' menu reached from the main menu of options concerns the setting up of different subjects according to age, sex, height and weight or selection from a range of preset simulated subjects. The following preset subjects are currently available:

1. Acute renal failure, 3 days duration, no therapy, normal diet
2. Chronic renal failure, normal diet
3. Congestive heart failure
4. Nephrotic syndrome

Following selection of a preset subject the program calculates the relevant values, stores them and then takes the user to the main menu.

3.7 Abbreviating repetitive dialogue

When you are very familiar with the interactive dialogue, it becomes tedious to wait for the computer to go through the whole sequence. 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 typed, press the ENTER key. The succeeding questions will be suppressed and the next instructions will be executed in order by the computer without interruption.

For example, to 'Change' factors 4 and 5 and then 'Continue', you might type, at the main menu prompt,

1/1/4 5/30/180/2

i.e. 'Change' (1), 'Change values' (1) of factors 4 and 5 to 30 and 180, respectively, (note separating space between 4 and 5) and finally 'Continue' (2).

3.8 Display of all model variables

The tables in Appendix 1 at the end of the handbook contain most of the lists of 120 variables used in the model and stored in the computer. The earlier ones are the main changeable factors. The later ones are mainly computed variables. Most of the important ones can be seen by the use of the 'Inspect' option

(Section 3.2) or the more general inspection facility described in Appendix 1. However, if in response to the main menu of options you type '7' (an option not offered in the list), you will get lines of 10 columns which list, from left to right in sequence, the current values of the 120 variables (Figure 15).

Any of these variables can be changed in value, although ridiculous changes may lead either to death of the subject or to the program aborting through arithmetic errors. There are some spare variables in the list available for research use of the program.

Under exceptional circumstances you might wish this large table to be printed at each iteration interval (although this produces a mass of output). This can be done by typing '4' (an option not listed) in response to the question about type of display in Section 3.5. Any type of output will continue until it is stopped by the use of the '4.Run change' option again.

4. Specific simulations and MacPee problems

This section outlines how the model may be used to explore many physiological and clinical situations of common interest. The problems given, which may be tackled with the aid of the program, are of considerable clinical relevance.

- Diet** Change factor 1 for High and Low Salt diets.
Change factor 2 for High and Low Protein diets (this will affect both lean body mass and the amount of potassium ingested).
- Potassium Administration** This can be simulated by increasing the value of factor 3 (extra potassium as mmol/24 hr). Potassium Exchange Resin Administration can be simulated by giving factor 3 a negative value (again, in mmol/day).
- Fluids** To simulate dehydration, restrict fluids to what you want, using the 'Fluids(+/-)' option.
For haemorrhage, use the 'Parenteral fluids' option (Section 2.5), ask for option 8 (whole blood) and type the amount of blood you want to remove, in ml, preceded by a minus sign. You will then be offered the period over which you would like the fluid withdrawn.
For plasma or serum loss (e.g. with extensive burns) use the same option, but ask to remove plasma (option 10), and proceed as above.
For post-operative water and electrolyte depletion (e.g. with intestinal fistulae or drains), use the same option, but ask to remove saline (option 1) or a saline/potassium mixture (option 6).
For overhydration ask for the 'Push fluids' option and specify what you want, or specify the administration of 5% dextrose (as described below).
For transfusion of blood or any other fluid, use the 'Parenteral fluids' option and specify your chosen fluid (from the list of 11 different fluids which can be given).

Heart To simulate a heart attack, reduce myocardial pump function (factor 4) to some figure less than the normal 100 (%). A 60% reduction would correspond to a very severe heart attack. Severe valvular heart disease and massive pulmonary embolism produce basically similar haemodynamic results, and are simulated in the same way.

Heart failure will automatically come about if cardiac function is reduced enough (see above). If you want to accelerate its development, you can give some extra parenteral saline!

Pericardial tamponade and constrictive pericarditis are slightly different, since the heart may function normally when its required output is small, but it may not be able to cope if output is required to increase (as in exercise). You can simulate tamponade by reducing factor 14 (which is the value for venous filling (right atrial) pressure, in mm Hg, above which no further output is obtainable, however high the right atrial pressure may be (normal value is around 8 mm Hg).

Heart transplant can be simulated by increasing the value for factor 4 again. It is also possible to simulate the transplant of a larger heart (e.g. by making factor 4, say, 150% — this is the basis of an interesting theoretical problem — see problems below).

Chest Severe airways obstruction and positive-pressure artificial ventilation can be simulated by increasing the intrathoracic pressure (factor 13, in mm Hg) from its normal mean value slightly negative to atmospheric pressure to a slightly positive one. [Hint: go easy here — any chronic elevation of 5 mm Hg or more will virtually bring the circulation to a standstill, unless the blood volume is much increased or circulatory capacitance (factor 22) much diminished.]

Arteries To simulate the infusion of a vasoconstrictor such as nor-adrenaline (norepinephrine), increase the value of factor 5 (systemic arterial resistance) above its normal 100 (% normal). Chronic systemic hypertension can be simulated by maintaining arterial resistance above normal for long enough to allow the arterial baroreceptors to reset, and pulse rate return towards normal.

For a vasodilator infusion reduce the value of factor 5.

To simulate renal artery stenosis increase the value of factor 6 (which is main renal artery pressure pressure drop). Because of the lack of representation in the model of various stabilizing systems which limit the speed of development of the vicious circle of malignant hypertension, the model is at present limited to modest increases in renal artery pressure drop (not to

	exceed 30 mm Hg). However, the changes are reasonably realistic, and blood pressure continues to rise with baroreceptor resetting, increased plasma renin, etc., and sodium retention.
Veins	To simulate inferior cava thrombosis, grossly restricting the return of blood to the heart, increase the value of venous resistance (factor 7) above its normal 100 (% normal). To simulate changed venous capacitance, alter factor 22 (e.g. gram-negative septicaemia may increase capacitance and lead to a shock state; noradrenaline may decrease capacitance considerably).
Exercise	Increase myocardial function (factor 4). Reduce both arterial and venous resistance (factors 5 and 7).
Kidneys	To simulate renal glomerular failure reduce renal glomerular function (factor 8) from 100 (% normal) to some lower value. Factor 8 = 0 simulates bilateral nephrectomy. To simulate administration of diuretics (or renal tubular sodium loss) increase the value of factor 9, which represents approximately the effect of a daily dose of frusemide, in mg/day — e.g. making factor 9 = 80 would simulate giving 80 mg/day of frusemide. Note, however, that the effect is evenly spread over the 24 hr, and therefore more resembles a renal tubular sodium leak rather than a bolus of oral or parenteral frusemide. To simulate nephrotic syndrome increase the daily urinary loss of albumin (factor 11). This is specified in grams, and is normally very small, but can be increased as desired. Note that the loss is specified as that which would occur at normal glomerular filtration rate. If this goes down, so also will the renal loss of albumin. For renal artery stenosis, see above under 'Arteries'.
Aldosterone	To simulate Conn's syndrome (primary hyperaldosteronism) increase factor 12 from its normal 100 (% normal). To simulate Addison's disease (hypoadrenalism) decrease factor 12. Factor 12 = 0 simulates bilateral adrenalectomy (as far as cortical mineralocorticoid function is concerned).
Vasopressin (ADH)	To simulate inappropriate ADH secretion increase factor 10 from 100 (% normal). For diabetes insipidus reduce factor 10, or make it actually zero.
N.B.	All the above simulations can be combined, simultaneously, to any degree of complexity — though the results may then become difficult to analyse and disentangle intellectually. It is generally best to stick to clinically realistic situations (e.g. to examine the deleterious combined effect of salt restriction and Addison's disease).

Problems

1. How well can the body conserve sodium and potassium? [Try stopping all food intake; make factor 1 (sodium intake) and factor 2 (protein intake) both zero and watch effects on electrolytes in blood and urine over the next, say, 6 days.] What mineral supplements might be desirable in starved obese patients?
2. Examine the effects of gross acute urinary protein loss causing nephrotic syndrome (see above), e.g. by increasing protein loss (factor 11) to, say, 40 g/day. Watch particularly urine sodium, fluid balance and body weight. Try to analyse the sequence of changes and ascribe a causal chain of probable events over, say, 8 days. In what respect do the changes in blood volume in *MacPee* not correspond to those found in patients? Can you suggest reasons for the discrepancy?
3. Examine the effects of a severe reduction in myocardial function (e.g. gross valvular heart disease or myocardial infarction) — by reducing myocardial contractility (factor 4) from its normal 100 (%) to, say, 60%. Analyse the sequence of changes over, say, 8 days and try to trace the sequence of events. What might eventually cause death? How might the symptoms be alleviated? What are the disadvantages of giving diuretics (factor 9)?
4. Examine the effects of the posterior pituitary by reducing vasopressin function (factor 10) from its normal 100 (%) to zero. Analyse the changes — what effect would fluid restriction to, say, 2000 ml/day have on the clinical condition? What electrolyte supplements would be desirable?
5. Simulate Conn's syndrome by increasing aldosterone function (factor 12) from its normal 100 (%) to, say, 500, 1000 or 2000%. What would be the symptoms, signs and biochemical effects? How might they be treated? You will have observed the phenomenon of 'aldosterone escape', i.e. continued aldosterone administration does not cause indefinitely prolonged sodium retention. What factors (at least those analysable in *MacPee*) might be concerned with 'aldosterone escape'?
6. Examine the situation of Addison's disease, with zero aldosterone function (factor 12 = 0). Why are such patients helped by sodium supplements, and why may they become ill or even die when sodium is restricted in the diet?
7. Examine the clinical and biochemical effects of a haemorrhage. 'Continue' for a few days and try to analyse the sequence of events. What physiological compensating mechanisms can you identify in action? Is the use of a vasoconstrictor agent such as noradrenaline [increasing factors 5 and 7 — general arterial and venous resistance — to, say, 150 or 200 (%)] good treatment? If not, why not? Pay special attention to the changes in haemoglobin and plasma albumin. Why are these not much changed originally but fall gradually over a few days? Why do they gradually return to normal over a period of a few weeks?
8. What would happen if there were to be a large arteriovenous shunt suddenly introduced (e.g. by a bullet wound)? You could simulate this

- by simultaneously decreasing factors 5 and 7 (arterial and venous resistance) to, say, 50–70% of normal; this is a similar situation to that of muscular exercise (except of course that body metabolic rate is not comparably increased). Why may a syndrome of 'high output heart failure' commonly develop in such conditions?
9. For how many days can you keep *MacPee* alive after removal of both kidneys [reduce factor 8 — renal glomerular function — from its normal 100 (%) to zero]. How can you keep the internal environment near normal and avoid as many symptoms as possible — i.e. what is the ideal conservative treatment of acute renal failure?
 10. Examine the effect of moderately severe renal glomerular failure (e.g. 20–30% normal function — factor 8) on sodium and potassium conservation and excretion. How are the permissible upper and low limits of dietary sodium intake affected by chronic renal failure? What are the clinical symptoms of (i) sodium depletion and (ii) sodium excess, and how are they produced? What are the effects of different amounts of dietary protein (factor 2, in g/day) on the patient's symptoms, and on the relative increases which occur in blood urea and serum creatinine? How can you explain the difference? Examine the effects of diuretics (frusemide dose, factor 9) in chronic renal failure. Why do you need to give so much more frusemide in chronic renal failure to achieve the same sodium loss that a smaller dose will produce in normal subjects?
 11. Put a larger heart into *MacPee* (see above: factor 4 increased, say, to 150% of normal). Why do things change remarkably little? What does this experiment show you about the control of cardiac output?
 12. Simulate positive pressure ventilation (or chronic airways obstruction) by increasing factor 13 (mean intrathoracic pressure) from its normally slightly negative value to a slightly positive value. Why can this have such a potentially disastrous effect on cardiac output and induce a state of shock?
 13. Simulate pericardial tamponade or constrictive pericarditis as described above [by reducing maximum cardiac output (factor 14)]. Then study the additional effect of muscular exercise (simulated as described above, also). Why are the effects so disastrous?
 14. Simulate gram-negative septicaemia with shock by increasing venous capacitance (factor 22) from its normal value (100%). Analyse the haemodynamic consequences. What might cause death? How could the circulatory collapse be treated?
 15. Simulate systemic essential hypertension by increasing arterial resistance (factor 5); and also the circulatory set point (factor 23), increasing the latter by the number of mm Hg you want to raise blood pressure. This should bring heart rate up to normal, and give you a fair simulation of chronic hypertension. You will also have to increase renal artery resistance to prevent the kidneys unloading too much salt and water. Having got your subject, store him with the '3.Store/Bktrk' option and have a look at his responses to haemorrhage, heart attack and other manoeuvres. Why is he so insistent on returning his BP to a hypertensive level? What can you infer about baroreceptor function in sustained hypertension?

Appendix 1

Details of the *MacPee* 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 3.2) 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 displayed 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 *MacPee* 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.SYST. HAEM., 3.KIDNEY, 4.BALANCES, 5.URINE, 6.BLOOD, 7.COMPTS,
8.WHOLE BODY, 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 3.2, 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. Systemic Haemodynamics
3. Renal Haemodynamics
4. Fluid and Electrolyte Balances
5. Urine
6. Blood/Blood Chemistry
7. Cellular/Extracellular Fluids
8. Whole Body

These are available individually or as a group which may be scanned, pressing ENTER or 'P' 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 list the model variables which may be of physiological interest, ordered by their numerical codes.

The tables displayed below were generated for the standard reference subject (at the outset), when running the program in SI units.

<i>MacPee subject factors</i>		[Reference]	Current
1.	Diet: Sodium intake, mmol/day,	[140]	140
2.	Protein, g/day	[80]	80
3. ^a	Extra potassium or K withdrawal, mmol/day	[0]	0
4. ^b	Cardiac 'contractility', % normal	[100]	100
5. ^c	Whole body arterial resistance, % normal	[100]	100
6. ^d	Renal artery pressure drop, mm Hg	[0]	0
7.	General whole body venous resistance, % normal	[100]	100
8. ^e	Kidney: Glomerular function, % normal	[100]	100
9.	Tubular sodium loss, (based on equiv. daily dose of frusemide, mg)	[0]	0
10.	Vasopressin function, % average normal	[100]	100
11. ^f	Average daily loss of protein at normal GFR	[0.1]	0.1
12.	Aldosterone function, % average normal	[100]	100
13. ^g	Intrathoracic pressure, mm Hg	[-2]	-2
14. ^h	Limiting cardiac filling pressure, mm Hg	[8]	8
15. ⁱ	Mass quantities in body: tot. exchangeable sodium, mmol	[3316]	3316
16.	total exch. potassium, mmol	[3457]	3457
17.	total urea mass, mmol or mg	[134]	134
18.	total albumin mass (plasma), g	[111]	111
19.	total red cell volume, ml	[2287]	2287
20.	lean tissue mass, kg	[26.3]	26.3
21.	total body water, litres	[41.1]	41.1
22. ^j	Capacitance of the venous system, % normal	[100]	100
23. ^k	Set point for baroreceptor sensitivity, mm Hg (+/-)	[0.1]	0.1
24.	Fluids: maximum daily intake allowed, ml	[24000]	24000
25.	extra intake (above that from thirst), mm/day	[0]	0

^aFactor 3: a positive value increments obligatory potassium intake from protein — normally 60–70 mmol/day. A negative value simulates potassium loss e.g. the use of potassium exchange resins.

^bFactor 4 controls the slope of the basic Starling cardiac function curve.

^cFactor 5: refers to an overall resistance between aorta and capillaries reflecting to an extent the renal arteries.

^dFactor 6: an arbitrary upper limit of 30 mm Hg is set for this.

^eFactor 8: a normal value of this factor corresponds to ~120 ml/min GFR in the standard subject.

^fThe effect of Factor 11 depends on prevailing glomerular function. Thus 30 will specify a daily loss of 30 g of albumin at 120 ml/min GFR and 15 g at 60 ml/min GFR.

^gFactor 13 is measured relative to atmospheric pressure.

^hFactor 14 is the cardiac filling pressure, relative to intrathoracic pressure, above which cardiac output is limited at a maximum value (plateau of the cardiac function curve).

ⁱFactors 15–21 are dynamically varying; the sum of factors 20 and 21 give the body weight of the subject.

^jFactor 22: The capacitance of the venous system, subject to adaptation through sympathetic innervation and stress relaxation, is ~170 ml/(mm Hg filling pressure). This figure is for filling over and above the obligatory volume of about 3000 ml at atmospheric pressure.

^kFactor 23 adapts with sustained hypo- or hypertension at an appropriate rate.

<i>Systemic haemodynamics</i>	[Reference]	Current
Heart rate, beats/min, (56) ^a	[75]	75
Systemic arterial blood pressure, mm Hg, (48)	[93]	93
Capillary pressure, average, mm Hg (52)	[13]	13 ^b
Cardiac filling (R.atrial) press., mm Hg, (53)	[1.6]	1.6
Cardiac output, l/min, (54)	[5.0]	5.0
Effective venous capacitance, ml/mm Hg, (29)	[177]	177 ^c
Systemic arterial resistance, mm Hg/(l/min), (69)	[16.4]	16.4
Systemic venous resistance, mm Hg/(l/min), (28)	[2.3]	2.3
Cardiac contractility, (l/min)/mm Hg, (66)	[1.3]	1.3

^a() Signifies *MacPee* variable/factor number.

^bCapillary pressure is applicable to the systemic circulation for a supine subject — the value is used in determining fluid transfers.

^cVenous capacitance varies dynamically with prevailing sympathetic activity and under 'stress relaxation'.

<i>Renal haemodynamics</i>	[Reference]	Current
Renal blood flow, ml/min, (51) ^a	[645]	645
Glomerular filtration rate, ml/min, (47)	[112]	112
Glomerular filtration pressure, mm Hg, (50)	[60]	60
Vascular resistance		
pre-glomerular, (ml/min)/mm Hg, (90)	[26]	26
post-glomerular, (ml/min)/mm Hg, (93)	[43]	43

^a() signifies *MacPee* variable/factor number.

<i>Fluid and electrolyte balances</i>	[Reference]	Current
Fluid Intake: cumulative 24hr, ml, (78) ^a	[1748]	1748 ^b
previous iteration, ml, (79)	[73]	73
Urine output: cumulative 24hr, ml, (77)	[1330]	1330
previous iteration, ml, (60)	[55]	55
Sodium output: cumulative 24hr, mmol, (74)	[140]	140
previous iteration, mmol, (67)	[5.8]	5.8
Potassium output: cumulative 24h, mmol, (71)	[64]	64
last iteration, mmol, (61)	[2.6]	2.6

Urea output:	cumulative 24h, mmol or g, (76)	[398]	398
	last iteration, mmol or g, (58)	[16.6]	16.1
Albumin output:	cumulative 24hr, g, (75)	[0.1]	0.1

^a() signifies *MacPee* variable/factor number.

^bRates of dietary intake and output of fluid and electrolytes are subject to wide diurnal variation. The full 'Inspect' table gives the best overall indication of the changing balance of the system (Section 3.2).

Urine ^a	[Reference]	Current
Sodium concentration, mmol/l, (59) ^b	[105]	105
Potassium concentration, mmol/l, (62)	[48]	48
Urea concentration, mmol/l or g/dl, (57)	[3.0]	3.0
Urine osmolality, mosm/l, (88)	[622]	622

^aValues here are for the current concentration/osmolality of urine produced. In the full 'Inspect' table (Section 3.2) cumulative average values are given based on pooled urine collections, starting each day at 6 a.m.

^b() signifies *MacPee* variable/factor number.

Blood/blood chemistry	[Reference]	Current
Blood volume, ml, (68) ^a	[5016]	5016
Red cell volume, ml, (19)	[2287]	2287
Plasma volume, ml, (46)	[2730]	2730
Haemoglobin concentration, g/100 ml, (87)	[15.0]	15.0
Haematocrit (PCV), percent, (55)	[46]	46
Plasma: Urea concentration, mmol/litre or mg/dl, (35)	[3.3]	3.3
Sodium concentration, mmol/l, (32)	[142.6]	142.6
Potassium concentration, mmol/l, (34)	[4.3]	4.3
Albumin concentration, g/l or g/dl, (45)	[40.8]	40.8
Albumin, total amount, g, (18)	[111]	111
Creatinine concn., mmol/l or mg/dl, (97)	[0.08]	0.08
Creatinine, total mass, g, (96)	[394]	394
Osmolality, mosmol/kg, (94)	[282]	282

^a() signifies *MacPee* variable/factor number.

Cellular/extracellular fluids	[Reference]	Current
CELLS: Volume (of water), ml, (30) ^a	[27221]	27221 ^b
Sodium concentration, mmol/l, (38)	[49.2]	49.2
total amount, mmol, (36)	[1340]	1340
Potassium concentration, mmol/l, (39)	[124.8]	124.8
total amount, mmol, (26)	[3397]	3397
EXTRACELLULAR FLUID: Volume, ml, (49)	[13849]	13849 ^c
Sodium concentration, mmol/l, (32)	[142.6]	142.6
total amount, mmol, (37)	[1976]	1976
Potassium concentration, mmol/l, (34)	[4.3]	4.3
total amount, mmol, (27)	[60]	60
INTERSTITIAL FLUID: volume, ml, (89)	[11119]	11119
Pressure, mm Hg, (80)	[-6.0]	-6.0

^a() signifies *MacPee* variable/factor number.

^bCellular values are averages and disguise wide variability between different body tissues e.g. potassium concentration is high in muscle cells.

^cExtracellular fluid volume (49) is the sum of plasma volume (46) and interstitial fluid volume (89).

Whole Body	[Reference]	Current
Weight, kg, (65)	[67.3]	67.3
Total body water, litres, (21)	[41.1]	41.1
Lean (Non-water) mass, kg, (20)	[26.3]	26.3
Total exchangeable sodium, mmol, (15)	[3316]	3316
Total exchangeable potassium, mmol, (16)	[3457]	3457
Hormones ^b :		
Renin, as Plasma Renin Activity, ng/ml/h, (92)	[1.4]	1.4
Vasopressin (AVP), pmol/litre, (41)	[0.8]	0.8
Aldosterone, ng/100 ml, (83)	[12.5]	12.5
Average sympathetic nervous activity, arbitrary index (31)	[0.9]	0.9
Autoregulation in whole body, arbitrary index (86)	[1.0]	1.0

^a() signifies *MacPee* variable/factor number.

^bHormonal factors show wide diurnal variation.

Variables of physiological interest in numerical order

26. Cellular potassium amount, mmol
27. Extracellular potassium amount, mmol
28. Systemic venous resistance, mm Hg/(l/min)

29. Effective venous capacitance, ml/mm Hg
30. Cell volume (of water), ml
31. Average sympathetic nervous activity, arbitrary index
32. Plasma/extracellular sodium concentration, mmol/l
34. Plasma/extracellular potassium concentration, mmol/l
35. Blood urea concentration, mmol/litre or mg/dl
36. Cellular sodium amount, mmol
37. Extracellular sodium amount, mmol
38. Cellular sodium concentration, mmol/l
39. Cellular potassium concentration, mmol/l
41. Vasopressin (AVP), pmol/l
45. Plasma albumin concentration, g/l or g/dl
46. Plasma volume, ml
47. Glomerular filtration rate, ml/min
48. Systemic arterial blood pressure, mm Hg
49. Extracellular fluid volume, ml
50. Glomerular filtration pressure, mm Hg
51. Renal blood flow, ml/min
52. Capillary pressure, average, mm Hg
53. Cardiac filling (R.atrial) pressure, mm Hg
54. Cardiac output, l/min
55. Haematocrit (PCV), percent
56. Heart rate, per minute
57. Urine urea concentration, mmol/l or g/l
58. Urea output in last iteration, mmol or g
59. Urine sodium concentration, mmol/l
60. Urine output in previous iteration, ml
61. Potassium output in last iteration, mmol
62. Urine potassium concentration, mmol/l
65. Body weight, kg
66. Cardiac contractility, (litre/min)/mm Hg
67. Sodium output in previous iteration, mmol
68. Blood volume, ml
69. Systemic arterial resistance, mm Hg/(l/min)
70. Cumulative 24-hr protein intake (urea equiv.), mmol or g
71. Cumulative 24-hr (from 6 a.m.) potassium output, mmol
72. Cumulative 24-hr sodium intake, mmol
73. Cumulative 24-hr potassium intake, mmol
74. Cumulative 24-hr sodium output, mmol
75. Cumulative 24-hr albumin output, g
76. Cumulative 24-hr urea output, mmol or g
77. Cumulative 24-hr urine output, ml
78. Cumulative 24-hr fluid intake, ml
79. Fluid intake in previous iteration, ml
80. Interstitial fluid pressure, mm Hg
83. Aldosterone, ng/100 ml

84. Body urea mass, mol or kg
 86. Autoregulation in whole body, index (normal = approx 1)
 87. Haemoglobin concentration, g/100 ml
 88. Urine osmolality, mosm/l
 89. Interstitial fluid volume, ml
 90. Pre-glomerular vascular resistance, (ml/min)/mm Hg
 92. Renin, as Plasma Renin Activity, ng/ml/h
 93. Post-glomerular vascular resistance, (ml/min)/mm Hg
 94. Plasma osmolality, mosmol/kg
 96. Plasma creatinine mass, mg
 97. Plasma creatinine concentration, mmol/l or mg/dl
 98. Urine creatinine amount in previous iteration, mg
-