3.4 INDICATOR DILUTION: MODELING AND COMPUTER SIMULATION

Indicators such as cool saline solutions or inert dyes may be introduced into the cardiovascular system to determine the cardiac output (CO) or average blood flow (F) or to study heart defects (Zierler-63; Bassingthwaighte-74,77). A common procedure is to introduce a bolus of cold saline into the right ventricle by means of a catheter, after which thermocouple measurements are made to determine the concentration versus time of the cold liquid in the blood of the radial artery (Roselli-75). An inert dye was formerly used for these measurements; radio-opaque dyes are still used, together with X rays, to analyze coronary artery and other heart defects. Radionuclide substances are often used (Flaherty-67) to study heart defects such as ventricular septal defects that give rise to left-to-right shunts.

Computer simulation of indicator transport in the cardiovascular system may be important in studying indicator techniques. It should be noted that because the transients of interest encountered in indicator dilution are much faster than those in most pharmacokinetic (PK) studies, models of indicator dilution must be more detailed. Thus, if a satisfactory model of indicator dilution can be set up, it should be satisfactory as a basis for design of PK models.

Simulation study of indicator dilution can be accomplished with a model that combines delay and perfect mixing compartments as described for simple cases in Section 3.3; the compartments in this case must be connected in a complete loop, corresponding to the cardiovascular loop. Figures 3.4.1a and 3.4.1b show typical measured concentrations for radial artery output, with input to the right heart. Note that the measured concentration in the normal case (Fig. 3.4.1a) shows a small second peak, corresponding to a recirculation of the original bolus around the cardiovascular loop; it also shows an initial zero response up to the "appearance time" when response is first seen. With a VSD, or ventricular septal defect (an opening between the ventricles), particularly for the larger defect (Fig. 3.4.1c), a fast recirculation through the VSD and the right ventricle and lungs gives rise to a new peak just after the initial pulse. Also, the main recirculation peak is flattened and delayed.

In order to set up a compartment model using only delay and mixing compartments, it is necessary to know the following data:

1. *Total transport time* T_t around the loop. This time, which is about 39 sec in the healthy human adult, is approximately given by the peak-to-peak time, (if the second peak can be distinguished).
2. *Appearance time* T_a around the loop. This time, about 13 sec in the human adult, may be represented by delay compartments, leaving approximately $T_t - 13 = 27$ sec for the total of the time constants of the mixing compartments.
3. *Cardiac output* or average loop flow F.
4. *Blood volumes* in the principal parts of the CV system.

Knowledge of these data will not tell us how many compartments of each kind are needed. However, some experimentation will show that too few mixing chambers will cause the simulated thermal dilution curves to be too low and flat, whereas too many will cause them to be too sharply peaked.

Because the plug flow simulated by delay compartments is distributed throughout the cardiovascular system, some detailed simulations might require a number of such delays, perhaps one for each mixing compartment. Here we will compromise by arbitrarily assigning one delay compartment to the approximate 5 sec of appearance time delay in the pulmonary circulation, and one of 8 sec in the systemic circulation.

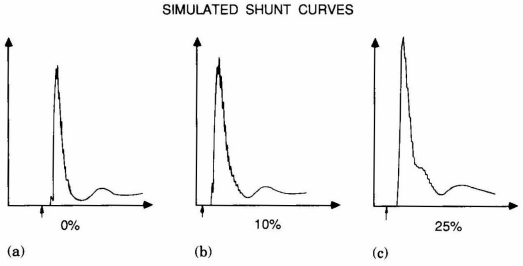


Figure 3.4.1. Canine indicator curves measured at the femoral artery (from (Castillo-66), with permission).
(a) Normal heart
(b) With 10% ventricular septal defect (simulated by injecting the major amount of dye into the left ventricle and the indicated fraction into the right ventricle simultaneously).
(c) With 25% ventricular septal defect, also simulated.

These values may be obtained from an assumed delay compartment volume of 500 ml in the pulmonary and 800 ml in the systemic system, according to the following equations:

$$T_p = V_p/F = 500/100 = 5 \text{ sec}$$
$$T_s = V_s/F = 800/100 = 8 \text{ sec} \qquad (3.4.1)$$

where the cardiac output is $F = 100$ ml/sec.

Experimentation has shown that eight mixing compartments in addition to the two delay compartments give a fair match to the observed thermal or dye dilution curves in the healthy adult human. Let us select one mixing compartment for each of the ventricles and assign other compartments, as shown in Fig. 3.4.2 and Table 3.4.1. Note that the total blood volume is 4000 ml, corresponding, for $F = 100$, to a total delay time of 40 sec.

Figure 3.4.2 shows a complete model of the cardiovascular system using ten compartments, and includes an input flow, FD (of dye or cold saline), to the pulmonary artery compartment. It includes a ventricular septal defect (VSD), with left-to-right average blood flow shunt, F_{VSD}. This defect will not be present, in effect, if F_{VSD} is set to zero.

A third kind of compartment that slightly skews the response has sometimes been included in other simulation studies but is not used here.

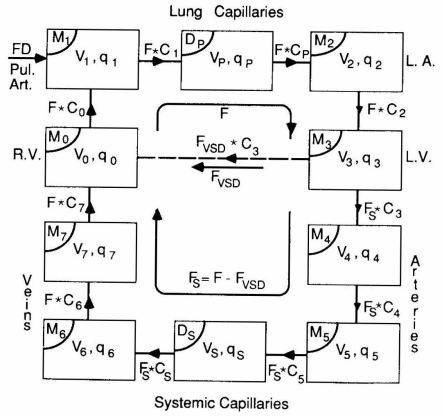


Figure 3.4.2. Ten-compartment model used to study indicator transport in the cardiovascular system.

Also, the loop is rather simple with no parallel paths. If parallel paths were used in a more detailed model, some skewing and flattening of the output peak would result if the parallel paths were of different lengths.

Before writing a simulation program for the model of Fig. 3.4.2, we must adapt the compartment equations developed in Section 3.2 to the needs of this model. Beginning with compartment 1 (pulmonary artery), into which the bolus of indicator is injected, (3.3.3) with indicator input flow included becomes

$$q_1 = \int_0^t (f_0 - f_1 + f_d)\, dt + q_1(0) \tag{3.4.2}$$

In terms of concentrations, as in (3.3.3)

$$\gamma_1 = (F/V_1) * \int_0^t (\gamma_0 - \gamma_1 + f_d/F)\, dt + \gamma_1(0) \tag{3.4.3}$$

where F/V_1 is $1/T_1$, the reciprocal of the time constant of compartment 1. Thus, in the ACSL program nomenclature

```
C1 = INTEG ((C0 - C1 + FD/F)/T1, 0.0)                    (3.4.4)
```

if the initial condition is zero.

A simple ACSL program for the model of Fig. 3.4.2 may now be written for the case of no VSD (flow FVSD = 0.0), using the typical time constants for an adult male given in Table 3.4.1; this program, IND-DIL1, is shown here.

TABLE 3.4.1

Compartment No.	Kind	Anatomy Represented	Volume (ml)	T_n (sec) (for F = 100 ml/s)
0	(M)	Right ventricle	125	1.25
1	(M)	Pulmonary artery	250	2.5
P	(D)	Pulmonary capillaries and veins	500	5.0
2	(M)	Left atrium	125	1.25
3	(M)	Left ventricle	125	1.25
4	(M)	Aorta, large arteries	750	7.5
5	(M)	Small arteries	200	2.0
S	(D)	Systemic capillaries and small veins	800	8.0
6	(M)	Systemic veins	1000	10.0
7	(M)	Right atrium	125	1.25
		Totals	4000 ml	40 sec


```
PROGRAM  IND-DIL1
 DYNAMIC
   Cinterval CINT=0.2
    Constant TF=80.0

  DERIVATIVE
   Maxterval MAXT = .02       $ Nsteps NSTP = 1
   FD = A*PULSE(0.0,1.E6,PW)  $'Single pulse, Amp. A, width PW'
    Constant A = 0.5, PW = 0.5
   C1 = INTEG ((C0 + FD/F - C1)/T1,0.0) $'Pulm.   Art.'
Constant F=100., T1=2.5
   CP = DELAY (C1, 0.0, TP, 1000)      $'Pulm. delay'
    Constant   TP=5.
   C2 = INTEG ((CP - C2)/T2, 0.0)      $'Pulm. veins,L.atrium'
    Constant   T2=1.25, T3=1.25, T4=7.5, T5=2.0
   C3 = INTEG ((C2 - C3)/T3, 0.0)      $'L. ventricle'
   C4 = INTEG ((C3 - C4)/T4, 0.0)      $'Aorta, large Arts.'
   C5 = INTEG ((C4 - C5)/T5, 0.0)      $'Small arteries'
   CS = DELAY (C5, 0.0, TS, 1600)      $'Systemic delay'
    Constant   TS=8.0
   C6 = INTEG ((CS - C6)/T6, 0.0)      $'Small veins'
    Constant   T6=10., T7=1.25, T0=1.25
   C7 = INTEG ((C6 - C7)/T7, 0.0)      $'Large veins,Rt.atrium'
   C0 = INTEG ((C7 - C0)/T0, 0.0)      $'Rt. ventricle'
  END    $ 'of Deriv'
    TERMT (T .GE. TF)
 END     $ 'of Dynamic'

END      $ 'of Program
```

The waveforms obtained with this program (see Fig. 3.4.3) resemble those obtained from normal adult humans; closer resemblance might require the use of many more compartments in the model. But it should be more than adequate for most pharmacokinetic simulations with their narrower-band frequency content, as pointed out in Section 3.3.

Note that the peak-to-peak time in C5 is about 37 sec, which is close to the sum (40 sec) of all time constants given in program IND-DIL1. With some checks of this sort and evidence of self-consistency in the model, we can go ahead and use it to give at least approximate answers for the effects of various defects on the indicator curves. Note that although "eyeball" checks are encouraging and helpful, the fine-tuning of a model to fit real data better may require formal parameter estimation methods (see Chapter 9).

A single defect (a VSD, as shown in Fig. 3.4.2) will be included in the next study. In order that the size of the VSD can be conveniently

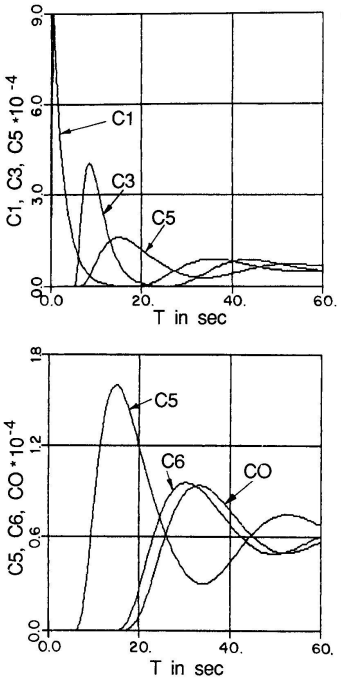


Figure 3.4.3. Indicator dilution (concentration) waveforms for C1, C3, C5, C6 and C0 obtained with program IND-DIL1, simulating the model of Fig. 3.4.2; note the recirculation peaks and the smoothing (lowering and widening) of all peaks after passage through mixing compartments.

changed from run to run, F_{VSD} will now be included in the system constants. The systemic flow F_S is given in (3.4.5), and is used in place of F in the equations for C_4 through C_7 in the systemic circuit.

$$F_S = F - F_{VSD} \tag{3.4.5}$$

The equation for compartment zero with its two inflows is based on

$$q_0 = \int_0^t (f_7 + \gamma_3 * F_{VSD} - f_0)\, dt + q_0(0)$$
$$= \int_0^t (\gamma_7 * F_S + \gamma_3 * F_{VSD} - \gamma_0 * F) dt + q_0(0)$$

The concentration in this compartment is q_0/V_0; therefore

$$\gamma_0 = (1/V_0) * \int_0^t (\gamma_7 * F_S + \gamma_3 * F_{VSD} - \gamma_0 * F) dt + \gamma_0(0) \tag{3.4.6}$$

It will now be interesting to examine the effects of the VSD in this compartment model; in order to do this, a better program has been written that includes not only the VSD effects but also the determination of time constants in the INITIAL part of the program, so that new time constants are automatically determined when blood flow F or F_{VSD} is changed. Two convenient constants are defined and calculated in INITIAL,

$$K_7 = F_S/F \text{ and } K_3 = F_{VSD}/F \tag{3.4.7}$$

The program, entitled IND-DIL2, is shown below (except for run-time commands). In Fig. 3.4.4 are shown various model output concentration curves versus time, with and without a VSD.

```
PROGRAM  IND-DIL2
  Constant F=100.,FVSD=0.0,V1=250.,...
  V2=125.,VP=500.,V3=125. ,V4=750.,...
  V5=200.,VS=800.,V6=1000.,V7=125.,...
  V0=125.

 INITIAL
  FS= F-FVSD $ T1= V1/F    $ TP=VP/F
  T2=V2/F    $ T3=  V3/F   $ T4=V4/FS
  T5=V5/FS   $ TS=  VS/FS  $ T6=V6/FS
  T7=V7/FS   $ T0= V0/F    $ K7=FS/F
  K3=FVSD/F
 END   $ 'of Initial'

 DYNAMIC
  Constant TF=80.
  Cinterval CINT=0.5

  DERIVATIVE
   Algorithm IALG= 4
   Maxterval MAXT= 0.25
   Nsteps NSTP= 1
  Constant PW = 0.5, A = 0.5
   FD= A*PULSE(0.0,1.E6,PW)
   C1= INTEG((C0+FD/F-C1)/T1,0.)
   CP= DELAY(C1,0.,TP,1000)
   C2= INTEG((CP-C2)/T2,0.)
   C3= INTEG((C2-C3)/T3,0.0)
   C4= INTEG((C3-C4)/T4,0.0)
   C5= INTEG((C4-C5)/T5,0.0)
```

```
      CS= DELAY(C5,0.,TS,1600)
      C6= INTEG((CS-C6)/T6,0.0)
      C7= INTEG((C6-C7)/T7,0.0)
      CO= INTEG((K7*C7+K3*C3-CO)/TO,0.)
    END $'of Derivative'

    TERMT (T.GE.TF)
  END $ 'of Dynamic'

END $ 'of Program'
```

The effects of the VSD, as shown in Fig. 3.4.4, again give concentration waveforms that have a fair resemblance to corresponding waveforms obtained clinically. Particularly noteworthy is the early peak of C0 due to VSD flow. The model can also be used to give approximate indicator-dilution responses for various other defects, such as an atrial septal defect, patent ductus arteriosus, or combinations of such defects (see the problems at the end of this chapter).

It is not easy to study the effects of a VSD by comparing the case of no VSD to a single case with a VSD of assumed size, so a program has been written using a parameter sweep scheme (see Appendix A) to show the effect of varying FVSD from 0 to 30 in 6 ml/s steps. This required that the program be modified by removing the constant FVSD and introducing three new constants, plus a modified Initial and a new Terminal portion, in program IND-DIL2, as shown below:

```
'New Initial program and Constants for FVSD sweep'

CONSTANT FVSDI=0.,DFVSD=6.,MFVSD=30.

INITIAL
  FVSD=FVSDI    $ T1=V1/F   $ TP=VP/F
  T2=V2/F       $ T3=V3/F   $ TO=VO/F
  L1..CONTINUE

  FS = F-FVSD     $    K3 = FVSD/F
  T5=V5/FS $  TS=VS/FS      $ T6=V6/FS
  T7=V7/FS $  T4=V4/FS      $ K7=FS/F
END $'Of Initial'

'New Terminal program (after End of Dynamic) for sweep'
TERMINAL
  CALL LOGD(.TRUE.)
  FVSD=FVSD+ DFVSD
  IF(FVSD .LE. MFVSD) GO TO L1
END $'Of Terminal'
```

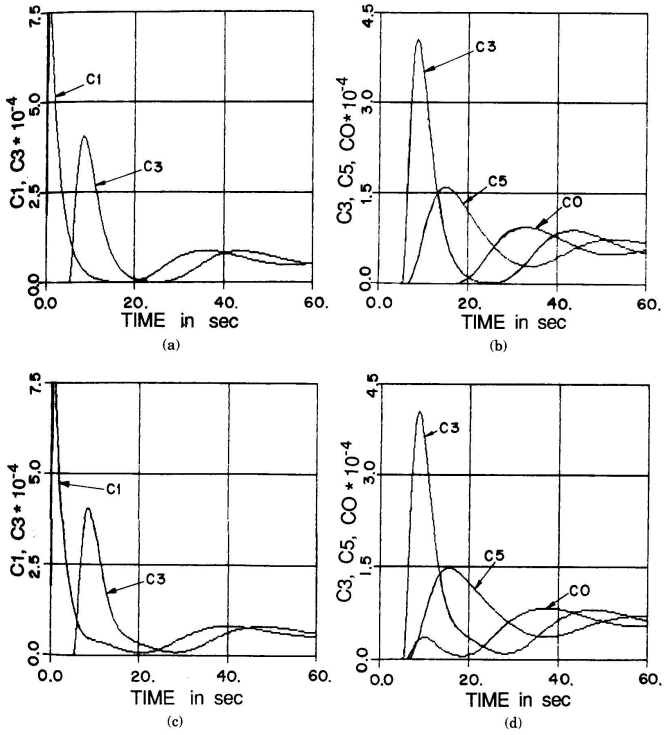



Figure 3.4.4. (a) Plots of concentrations C1 and C3 for the case of no VSD in response to an input pulse FD of length 0.5 sec.
(b) Plots of C3, C5, and C0 (no VSD). Note the new ordinate scale.
(c) Plots of C1 and C3 with VSD, for FVSD = 10.
(d) Plots of C3, C5, and C0 with VSD. Note that the early VSD recirculation pulse is quite evident in C0 but is more difficult to detect in C1 and C3 in (c). Its only visible effect on C5 is to delay the second peak.

The results of using this parameter sweep program (which will be named IND-DIL3) are as shown in Fig. 3.4.5 for concentrations C3, C7, and C0. Note that the concentration curves tend to have lower peaks that occur later in time as the VSD aperture size and flow increase. These effects are caused by the larger time constants in the systemic circuit as FS gets smaller, and by the later addition of the peak due to the VSD flow to the original first peak caused by indicator injection.

The single-loop model of Fig. 3.4.2 used in the programs given above is more than adequate for reproduction of transients in pharmacokinetic studies, in which the drug is introduced into the blood stream rather slowly, and is taken up still more slowly by diffusion into tissues. The

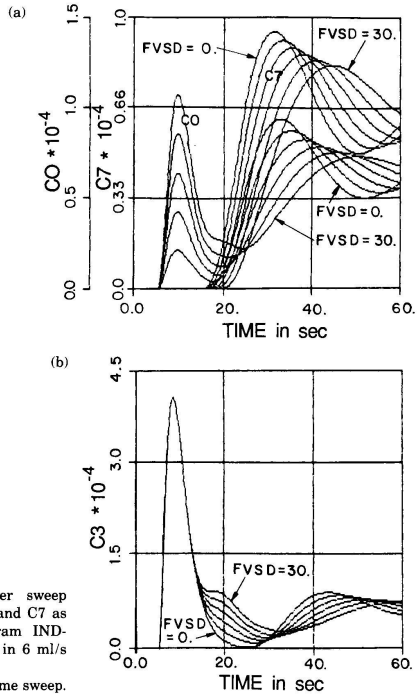


Figure 3.4.5. (a) Parameter sweep plots of concentrations C0, and C7 as FVSD is varied (in Program IND-DIL3) from zero to 30 ml/s in 6 ml/s steps.
(b) Plots of C3 during the same sweep.

physical, or structural, models used by such modelers as Bischoff and Dedrick do not require as many compartments in the main loop, but may need several systemic compartments in parallel to represent tissue beds in various organs (Bischoff-66,71, Dedrick-68, and Morrison-75). The combination of flow and diffusion transport required in pharmacokinetic studies is discussed in Section 3.5.

The transport model of Fig. 3.4.2 may also be used to simulate and study the use of indicator-dilution methods for measurement of cardiac output and system volume (Zierler-63,62, Bassingthwaighte-74,77). If a chain of compartments is not connected in a loop or if the effects of recirculation can be subtracted off in some way, then by conservation of mass

$$Q_I = F*\int_0^\infty \gamma_{AO}(t)dt = F*\int_0^\infty \gamma_n(t)dt \tag{3.4.8}$$

where F is cardiac output and Q_I is the total indicator volume injected into the right heart. This assumes that γ_{AO} (in the aorta) equals γ_n anywhere in the arterial system, because complete mixing has occurred in the left ventricle before the blood divides into its various channels. Thus the average cardiac output or blood flow F from the left heart is the total amount Q_I of indicator injected divided by the integral of concentration in any compartment n in the arterial system:

$$F = Q_I \div \int_0^\infty \gamma_n(t)\, dt \tag{3.4.9}$$

This is the Stewart-Hamilton expression for cardiac output, widely used clinically for cardiac output (CO) measurement, particularly with cold saline indicator (Roselli-75). The ACSL model IND-DIL2 given earlier in this section (now to be called IND-DIL4) may be used to illustrate the use of (3.4.9) by first eliminating recirculation altogether in the model and then examining methods for eliminating its effects in model or living subject tests. Recirculation elimination in the model becomes quite simple if a constant X, which may be set at zero or one, is introduced into the recirculation term in the C1 equation in the program referred to above, as follows:

```
C1 = INTEG((C0*X + FD/F - C1)/T1, 0.0)          (3.4.10)
```

Recirculation will be normal if X is set to unity at run time, but if it is set to zero, it will be eliminated.

In addition to using this new equation for C1 in the indicator program, we also need to add to the Derivative section the integral required in (3.4.9), which we will choose to determine for compartments 4 and 0; in ACSL form these are

```
INT4 = INTEG (C4, 0.0)
INT0 = INTEG (C0, 0.0)                          (3.4.11)
```

Because we need only the final values of these integrals, we choose some adequate length of run, TF = 100., and add to the program a Terminal section, using ACSL versions of (3.4.9) to find estimates of average flow F, such as FM4 and FM0, as follows:

```
TERMINAL
'Cardiac output may be found using integrals of C4 and C0'
  FM4 = QI/INT4                                              (3.4.12)
  FM0 = QI/INT0
End  $ 'Of Terminal'
```

With these additions in IND-DIL4, the run-time commands will yield various concentration and other curves of interest and will give the cardiac output as determined by sampling output concentration at compartment 4 (FM4) and compartment 0 (FM0). The initial run-time commands are

```
SET TF=100., X=0.0
OUTPUT T,INT4,INT0, 'NCIOUT'=20
PREPAR T,C4,C0,INT4,INT0
START
```

As the run is in progress, the output can be checked to see that TF is adequately long by noting if INT4 and INT0 reach steady maximum values. It is then possible to call for plots of C4, INT4, C0, and INT0, as shown in Fig. 3.4.6. Also, we can make a run-time display command (DISPLY) that calls for the final values; this command and the resultant values are shown below:

```
DISPLY T,QI,C4,C0,INT4,INT0,FM4,FM0
T= 100.000000      QI= 0.25000000      C4=2.3838E-09
C0=4.5492E-07      INT4=0.00247582     INT0=0.0024711
FM4=100.97700      FM0=101.166000
```

Here the relatively small final values of C0 and C4 indicate that apparently our choice of TF = 100.0 is an adequate integration time. However, the estimates of cardiac output, FM0 and FM4, are about 1 percent off; this results because the concentration integrals INT0 and INT4, which should equal $Q_I/F = 0.0025$, are about 1 percent off.

To determine cardiac output in a living subject the recirculation "tail" of the concentration must be eliminated. One way of doing this is to fit a decaying exponential to the falling concentration curve just before recirculation appears, and to use this in place of the continuing tail of the complete curve. Two points on the concentration curve will serve to define an exponential as to initial value and time constant.

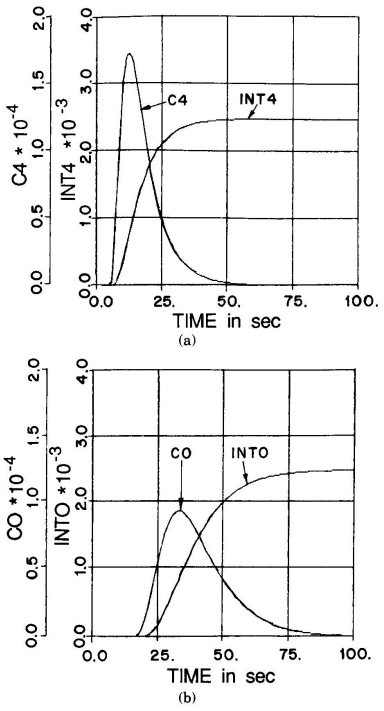


Figure 3.4.6. (a) Concentration γ_4 (C4 in ACSL) and its integral, INT4. (b) Concentration C0 and INTO.

Some other interesting and important quantities may be determined from indicator-concentration curves; these include average transit times between any two compartments and blood volume for any compartment or sequence of compartments. These quantities are most conveniently determined using the transport function, defined as

$$h_n(t) = F*\gamma_n(t)/Q_I \tag{3.4.13}$$

This function contains the instantaneous flow of solute $F*\gamma_n$, which, when divided by the total input of solute Q_I, gives the fraction of solute arriving at the output of compartment n per unit of time. The equations for this transport function in ACSL form for compartments 4 and 0 are

```
H4 = F*C4/QI
H0 = F*C0/QI
```
(3.4.14)

If the input FD is a true impulse, and if recirculation is somehow removed, then any $h_n(t)$ for the resultant open-loop case is the unit impulse response at the output of compartment n. Plots of H4 at the end of four compartments and H0 at the end of all eight compartments for the near impulse input used in IND-DIL4 are shown in Fig. 3.4.7a.

The average time of transit from compartment 0 to any compartment, n, may be determined by using the transport function in the integral

$$t_n = \int_0^t t*h_n\ t)\ dt \tag{3.4.15}$$

or, in ACSL notation, for compartment 4

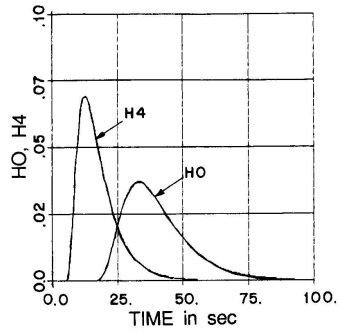
```
TA4 = INTEG(T*H4, 0.0)
```

If (3.4.14) and (3.4.15) are included in the Derivative section of IND-DIL2, the final values of the average transit times TA4F and TA0F may be determined by calling for the values of TA4 and TA0 using the DISPLY command after the run is completed. (Here their values will be found to be TA4F = 17.7423 and TA0F = 39.9598; note how close the latter is to the sum of all the time constants in the model.)

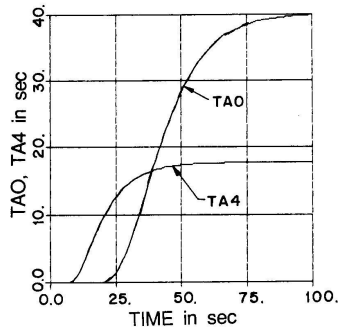
The volume of blood in the system may be determined by using the command

```
V = FM0*TA0
```
(3.4.16)

which is the product of estimated average flow and average transit time. Use of DISPLY will then show that the total volume V is 4042.57, which is close to the exact value for Fig. 3.4.2 of 4000 ml. For the first four compartments, calculation of volume using V4 = FM4*TA4 will give 1791.55, which is close to the calculated model volume V1 + V2 + VP + V3 + V4 = 1750 ml.



(a)



(b)

Figure 3.4.7. (a) Plots of transport functions γ_4 and γ_0 (H4 and H0). (b) Plots of transport times TA4 and TA0.

PROBLEMS

3.3. **(a)** Run ACSL program IND-DIL1 for indicator transport in a complete cardiovascular loop (Fig. 3.4.2, Section 3.4), for the case of no VSD. Check the concentration curves against those shown in Fig. 3.4.3.

(b) Note that the indicator concentration curves in Fig. 3.4.3 all converge to the value $0.6*10^{-4}$. Explain and verify this value.

(c) Repeat (a) using the improved program IND-DIL2 for FVSD = 0.0 (Section 3.4) with F = 100., and F = 60. Explain the changes in the concentration curves when F is reduced.

(d) Run IND-DIL2 for the case of a VSD (use F = 100., FVSD = 10.) and check results against Fig. 3.4.4(c) and (d). Repeat for F = 60.

3.4. **(a)** Run the parameter-sweep (of FVSD) program IND-DIL3, and check results against Fig. 3.4.5.

(b) Rewrite program IND-DIL3 for the system of Fig. 3.4.3 with an atrial septal defect (ASD) between compartments M2 and M7); plot and explain results for concentration curves if FASD = 10.

(c) Repeat (b) for a patent ductus arteriosus (PDA) existing between ascending aorta and the pulmonary artery (between M4 and M1 in Fig. 3.4.1).

3.5. Program IND-DIL4 is the same as IND-DIL2 with commands (3.4.11) and (3.4.12) included. Set up IND-DIL4 and study the determination of cardiac output and total blood volume using TF = 200.