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A vascular transport operator

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Abstract

A pulse or a sharp front in concentration of a tracer or a substrate in the blood within a vessel becomes dispersed while being transported along a vessel. Cross-stream mixing and pulsations in flow with the heartbeat cause the dispersion to be less than would occur with a parabolic velocity profile (Newtonian flow). These characteristics allow intravascular mass transport to be described well by a simple two-parameter differential operator, which is a one-dimensional representation of the rather complex real situation. The operator consists of two components in series, a pure delay and a fourth-order linear differential operator. The latter is merely two underdamped second-order operators in series, with fixed relationships between the natural frequencies and damping coefficients. The operator is useful because it provides a transport function with skewness and kurtosis suitable to intravascular transport where the mean velocity profile is blunter than in Newtonian parabolic flow. The parameters of the operator are its mean transit time, t , and its relative dispersion, RD, which is the standard deviation of the response impulse divided by t . The operator transport function describes blood transport through the human leg arterial system, where the RD values are ~ 15-20%.

Keywords

vascular transport delay; velocity profile in blood; human femoral artery; dorsalis pedis artery; indocyanine green dye; indicator dilution

There is a need for a simple mathematical function that describes the delay and dispersion of material being transported within the blood. Ideally it should describe fully the impulse response (or transport function) and the probability density function of transit times, $h(t)$, through a pipe or an artery. It would be advantageous if it could be used as an operator, that is, could function by accepting an input of general form continuously and providing the output response continuously, for by doing so a convolution integration can be avoided. This is critically important for modeling recirculating systems. Such an operator would be useful in models of organ systems and in closed loop models of the whole body. In the case of organs, the operator could be used to model the arteries, arterioles, venules, and veins,

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The computer code is available from nsr.bioeng.washington.edu or as a model #296 at: <http://nsr.bioeng.washington.edu/jsim/models/webmodel/NSR/VascularOperator/> where it can be run over the web or downloaded to run on one's own computer under JSim, also available for free download at the same site for Linux, MacOSX and Windows.

whereas some other operator is used to model the tissue-capillary units. Separately modeling both the arterial and venous trees is especially important in the case of externally detected tracer residues (e.g., positron emission tomography) where the tracer in the arteries and veins contribute directly to the signal.

The principle of using low-order differential operators to describe transport along a flowing stream came from Paynter (11), who used such an approach in studies of flood control on the Charles River through Boston. Various low-pass filters were described in detail by Hansen (8); whereas standard texts on network analysis give good insight into the general ideas (e.g., Ref. 9), Hansen goes well beyond the standard texts in giving the power spectral analysis for a variety of filters, showing that the Paynter lines (of various orders) have the special characteristic of giving phase lags that match a Gaussian filter at regular frequency spacings.

Transport of material in the blood through the vascular system is like the passage of an electrical current through a passive electrical network of resistors and capacitors, except that the system must be overdamped: concentrations at the outflow cannot be higher than at the inflow, and there can be no negative concentrations. A type of function that fulfills these criteria is an $h(t)$ that has no negative components, e.g., a Gaussian or exponential distribution. These two are not particularly useful for vascular transport, since they do not provide suitable shapes; vascular impulse responses are always right skewed (1), eliminating the Gaussian operator from consideration, but not so skewed or dispersed as the single lag operator, the exponential. Other more suitable dispersing functions that have been used are the random walk with a first traversal (12), the gamma variate function (14), and the singly lagged normal density curve (LNDC; Ref. 3), which is a convolution of a Gaussian distribution with a single exponential. All of these require convolving the input function with the transport function of the vascular segment to estimate the output function. Because convolution is slow, requiring n^2 computations, where n is the number of evenly spaced intervals covering the duration of the impulse response, it is not suitable for incorporation into closed-loop systems such as a recirculating vascular system because the computation would soon be overwhelming. Nor is the use of finite Fourier series transformations suitable, since the data cannot be well described by such transformations when the curves do not return to the baseline (7), and the use of transformations is not suitable for running real time solutions to compare with data. Instead, we seek an operator of a differential form that can accept a time-varying input continuously, forever, without expanding the time for computation per unit step in time. Such an operator can serve as a descriptor for indicator dilution studies in the circulation and therefore as a component of more comprehensive models for vascular transport in pharmacokinetics and blood-tissue exchange processes. Having vascular transport operators as a part of whole organ models is also the key to accounting for the larger vessel contributions to externally detected signals from radiotracers, as in positron tomographic imaging, and single photon emission-computed tomography, or from contrast agents as in magnetic resonance imaging and X-ray-computed tomography.

DEFINITION OF THE MODEL

Vascular transport

In formulating multicapillary models for tracer exchanges within an organ, one might use a single operator to represent a common “large” vessel pathway as in Fig. 1. The intravascular transport through a single vessel can be described mathematically by convolution of the input function with $h(t)$ for the organ

$$C_{\text{out}}(t) = C_{\text{in}}(t) * h(t) \quad (1)$$

where $C_{\text{in}}(t)$ and $C_{\text{out}}(t)$ represent the concentration-time curves at inflow and outflow, respectively, and the asterisk denotes the process of convolution. The mean transit time through the vessel, $\bar{t}$, is the first moment of $h(t)$, and $\bar{t} = V/F$, the system volume divided by the flow. The relative dispersion (RD) of $h(t)$ is calculated from the variance, the second moment around the mean, $\bar{t}$, and is its square root, the standard deviation (SD), divided by $\bar{t}$. Thus $RD = SD/\bar{t}$.

The same type of operator can be used for both the large and small vessels and tubes. Our presentation will focus on intravascular transport along a single path, showing applications of the model to experimental studies on the human leg arterial system.

Configuration of vascular transport operator

The vascular transport operator has two components: a pure delay, t_d , and a fourth-order differential operator giving a dispersive delay with mean t_p and a fixed $RD_p = 0.48$ [subscript “p” denotes the fourth-order Paynter operator (8,11); see Fig. 2]. This approach reduces computation time and allows a continuous range of values for the dispersiveness of the operator, up to a maximum RD of 0.48. The moments of the impulse response for the vascular operator can be calculated from those of the component operators, as given in APPENDIX B. The $\bar{t}$ is the first moment, and the higher moments (defined in APPENDIX B, *Moments of impulse responses*) define the variance or dispersion (second moment), the skewness (from the third moment), and the kurtosis (from the fourth moment). For the delay and the dispersive components of the operator the t values are

$$\bar{t} = \bar{t}_{\text{vasc}} = t_d + \bar{t}_p = \text{system } V/F \quad (2)$$

where $\bar{t}_{\text{vasc}}$ is mean transit time of total vascular operator. Because the delay line is nondispersive, the SD for $h(t)$ is determined solely by the dispersiveness of the Paynter operator, RD_p , which is fixed at 0.48

$$SD = RD_p \cdot \bar{t}_p \quad (3)$$

Therefore

$$RD = \frac{RD_p \cdot \bar{t}_p}{\bar{t}} \quad (4)$$

where $\bar{t}$, $\bar{t}_d$, and $\bar{t}_p$ are the mean transit times for the overall vascular operator and for its two components. The Paynter operator provides a phase lag similar to that produced by a Gaussian dispersion of the operator's impulse. The parameters of the various orders of Paynter operators described by Hansen (8) were chosen to provide a match to a linear change in phase (lag) vs. frequency at each 3-dB diminution in the power spectrum. It is composed of two underdamped second-order operators in series and actually has a minor negative component to the tail, too small to be seen on plots of $h(t)$. RD and $\bar{t}$ are the parameters that define the vascular operator completely. For this to be so, the fourth-order Paynter operator is of invariant form relative to its mean, having internal parameters at fixed values, and one can vary only its mean transit time, $\bar{t}_p$

$$\bar{t}_p = \frac{RD}{0.48} \cdot \bar{t} \quad (5)$$

from which t_d is defined

$$t_d = \bar{t} - \bar{t}_p = \bar{t} (1 - RD/RD_p) \quad (6)$$

Because the Paynter operator is composed of two second-order operators, as in Fig. 3, the intravascular transport operator is represented by three equations, representing a delay line and two second-order differential operators. None of the individual components of the vascular operator are physically realistic analogues for mass transport in blood vessels, but put together they describe both the effects of a blunt intravascular velocity profile and the appropriate dispersiveness. If one assumes cylindrical symmetry in a single tube with viscous flow, then the impulse response of the model can be translated directly into a velocity profile within the tube that is in accord with observations in human arteries (1) and in dog aortas (2), and by other investigators (e.g., see Ref. 10). The ratio of mean velocity to peak velocity is ~0.65-0.7, not the 0.5 of Newtonian flow, and is seen in the impulse response as the ratio of appearance time, t_a , to $\bar{t}$ (e.g., as shown by the regression line in Fig. 6 of Ref. 1, $t_a = 0.70 \bar{t}$ over a range of $\bar{t}$ from 2 to 16 s). The vascular operator may therefore be regarded as providing a description of a blunted velocity profile representing the average profile over a few cardiac cycles, but it should be primarily regarded as providing a stochastic description of the $h(t)$ values between two observation points.

Delay operator

The t_d operator is

$$C_1(t) = \begin{cases} C_{in}(t - t_d) & \text{for } t \geq t_d \\ 0 & \text{for } t < t_d \end{cases} \quad (7)$$

where C_{in} is the input and C_1 is the output of the delay operator. The algorithm is described in APPENDIX A, where pseudocode for a program is also given. A delay line is completely defined by its first moment, $t = t_d$. A t_d does not change the absolute dispersion but does reduce the relative dispersion, as described in APPENDIX B, *Moments of the delay operator*. Because the input signal is read at the input at each time step only, without interpolation, the numerical method may be looked on as an Euler integration. The

advantage is that the form of the input is exactly preserved at the output but delayed by an integer number of time steps, N_d . The disadvantage is that $N_d \bar{t}$ may not be exactly what is wanted, so that the strategy of usage was to use $N_d \bar{t} \simeq t_d$ and to adjust $\bar{t}_p$, so that $\bar{t}_p$ is then redefined

$$\bar{t}_p = \bar{t} - N_d \Delta t \quad (8)$$

which results in an exactly correct overall $\bar{t}$ but changes the dispersion ever so slightly.

Dispersive operator

The fourth-order dispersive operator, shown in Fig. 2, is composed of two second-order operators in series, following the approach of Bassingthwaight et al. (5). The input is $C_1(t)$, the output of the first second-order operator is $C_2(t)$, and the final output is $C_{out}(t)$

$$\frac{d^2 C_2}{dt^2} + 2\zeta_1 \omega_1 \frac{dC_2}{dt} + \omega_1^2 C_2 = \omega_1^2 C_1 \quad (9)$$

$$\frac{d^2 C_{out}}{dt^2} + 2\zeta_2 \omega_2 \frac{dC_{out}}{dt} + \omega_2^2 C_{out} = \omega_2^2 C_2 \quad (10)$$

where ω is the natural frequency in radians per second, and ζ is the dimensionless damping coefficient.

The analytical solution for the lower moments of a second-order operator are given in APPENDIX B, *Moments of a second-order operator*. The method for calculating the moments of any two operators in series is in APPENDIX B, Calculating moments of the impulse response for two operators in series, and the analytic form of the moments for the general fourth-order operator is provided in APPENDIX B, Moments of a fourth-order operator composed of two second-order operators in series.

From this latter section of APPENDIX B, $\bar{t}_p = 2(\zeta_1/\omega_1 + \zeta_2/\omega_2)$, and given that certain parameter values are fixed ($\zeta_1 = 0.95$, $\zeta_2 = 0.8$, and the ratio $b = \omega_2/\omega_1 = 1.82$), then ω_1 can be calculated directly from the governing parameter $\bar{t}_p$

$$\omega_1 = \frac{2}{\bar{t}_p} \cdot \left(\zeta_1 + \frac{\zeta_2}{\omega_2/\omega_1} \right) = \frac{2.7791}{\bar{t}_p} \quad (11)$$

The relative dispersion is calculable from the parameters, as derived in APPENDIX B, Moments of a fourth-order operator composed of two second-order operators in series

$$RD_p = \frac{[b^2 (\zeta_1^2 - \frac{1}{2}) + (\zeta_2^2 - \frac{1}{2})]^{1/2}}{b\zeta_1 + \zeta_2} = 0.4799 \quad (12)$$

Because RD_p is fixed at 48%, the apportionment between the delay line and the Paynter line can be chosen to give the desired overall RD for the intravascular transport model as is

shown in Fig. 4 and Eq. 8, but the overall RD cannot exceed 0.48. Because RD values for intra-arterial transport range from 16 to 20% (1), this is not a problem, but it should be noted that even with RD = 0.48 this operator is less dispersive than is Newtonian parabolic flow. With RD = 0.48 the vascular operator uses only the Paynter filter. With RD = 0, only the delay line is used.

RESULTS

Behavior of vascular model

Representative responses to a 2-s pulse input are shown in Fig. 5 for various levels of RD. Figure 5B shows the responses with the same $h(t)$ values, using an input function of a form commonly produced experimentally by a pulse injection, an LNDC (1).

Comparisons of the impulse response form can be made with a Gaussian dispersive delay line, Fig. 6A or with Poisson operators composed of equal-sized stirred tanks in series (N_{tanks} ; Fig. 6B). The RD of the Poisson operators is fixed at $N_{\text{tanks}}^{-1/2}$, so that the smallest number that can be compared is $N_{\text{tanks}} = 5$, giving an RD of 0.447. With N_{tank} large, the Poisson operator has a virtually Gaussian impulse response.

Applications of experimental data

Application of the vascular operator to situations in which one has both the input and output functions serves as a strong test of the model's general capabilities.

In Fig. 7 are shown a pair of ^{51}Cr -labeled red blood cell concentration-time curves obtained simultaneously with identical flow-through γ -detectors separated by a tubing volume of 3.98 ml (75 cm length). Nonrecirculating blood (20% hematocrit) flow through the system was at a rate of 22.8 ml/min (Gilson pump), giving a t of 10.5 s. The signal obtained by the first detector was used as an input to the vascular operator, and its RD was adjusted as the only free parameter. Figure 7A presents the best fit of the model to the data, obtained by manual optimization giving an RD of 0.32 and resulting in a coefficient of variation of somewhat <2% between the model solution and the measured outflow-dilution curve.

In a further modeling exercise, the RD and the tubing volume (normalized by flow) were treated as free parameters. Solutions were obtained for a range of RD values and volumes, and the coefficient of variation was calculated for each solution. These results are shown in Fig. 7B in the form of a contour plot of coefficient of variation vs. RD and $t, \bar{V}/F$, where F was held constant. Each contour line represents a set of equally good-fitting results with different RD values and V/F ratios. The centermost contour on the plot ranges over RD values between 0.29 and 0.34 and V/F ratios between 10.5 and 11.0 s. The vertical elongation of the contour lines reflects the higher sensitivity of the model solutions to changes in V/F ratio than to the RD.

Another application is to the inflow-outflow relationship for the human leg artery. Transport functions applicable to the human leg were originally described in terms of an LNDC (1), but a gamma variate function (14) or a random walk with first traversal (12) could also be used. To use these probability density functions, however, it is necessary to convolute the

input curve with the model function and adjust parameters of the model function to fit the output curve. The deconvolution must be repeated for each trial. Using the vascular operator avoids the deconvolution and makes it possible to analyze a data set that is as long as one chooses to record.

An example of this application is shown in Fig. 8. The data are taken from experiments in which the input dye dilution curve was sampled from the femoral artery of an awake human and the outflow curve from the dorsalis pedis artery on the arch of the foot. The input and output curves were measured with small volume sampling systems having almost identical impulse responses. The data curves were typical of those in a closed circulatory system in which the presence of recirculated indicator prolongs the tail of the curves. A model of a recirculating system was used to fit not only the C_{in} -to- C_{out} transformation but also the recirculation. The model, shown Fig. 8A, is composed of a series-parallel arrangement of vascular operators; each box of the diagram was modeled by a separate vascular operator. The injection upstream of *artery 1* was assumed to have the shape of lagged normal density curve (LNDC). The steps used to fit the model to the data were as follows.

First, the initial operator parameters were set. Dispersions were chosen based on previous measurements of dispersions typical for arteries (12%), veins (30%), and whole organs (40%). Volumes of the arterial operators were set to 50 ml each, and the venous operators were set to 75 ml each. The volumes of the flow pathways were based on known estimates of anatomic regions: head, 500 ml; central, 1,000 ml; high flow (renal circulation), 150 ml; medium flow (splanchnic circulation), 600 ml; and slow flow (remainder of body), 1,500 ml. Total vascular volume was 4,050 ml.

Second, the LNDC parameters to fit the peak of the *artery 3* input curve to the peak of the observed femoral artery curve (C_{in}) were adjusted. An LNDC has four shaping parameters: area, mean, relative dispersion, and skewness. The area was set by the amount of tracer injected, and an automated parameter optimizer adjusted the other three parameters to obtain the best fit to the C_{in} curve up to 15 s. For these data, this gave a mean of 4.5 s, an RD of 43%, and a skewness of 1.9.

Third, the volume of *artery 3* to fit the peak of the *artery 3* outflow curve to the observed dorsalis pedis artery curve (C_{out}) was adjusted. The parameter optimizer was used again to obtain the best fit to the C_{out} curve up to 25 s. This gave a volume of 109 ml ($\bar{t} = 5.2$ s).

Fourth, we adjusted the volume and dispersion of the central circulation and the dispersion of the high flow path to fit the recirculation peak of the observed femoral artery curve. Manual parameter of parameters was used for this final step to obtain the best fit to the C_{in} curve from 15 to 37 s. The central circulation volume was decreased to 825 ml ($\bar{t} = 9.9$ s) to give the correct peak, and the dispersions of the central and high-flow paths were decreased to 30 and 15%, respectively, to give the correct shape of the recirculation tail of the femoral curve. This also gave the best fit of the model to the recirculation peak of the dorsalis pedis curve.

In fitting these data, a total of seven parameters were adjusted. However, no more than three parameters were adjusted to fit any specific part of the data, and only one parameter, the

volume or $\bar{t}$, was adjusted to characterize the transfer function of *artery 3*. In regard to the recirculation peak, this solution may not be unique (i.e., there may be other combinations of parameters for the veins and flow pathways that would produce a similar solution). The specific goal of the experiment was to characterize the arterial circulation of the leg. Tracer dilution curves for other observation sites in the whole body circulation would be required to characterize the other operators with any degree of confidence.

As a test of the conservation of mass in the recirculation model the clearance of indicator was set to zero and the solution allowed to run for 10,000 s. The expected equilibrium concentration is the mass injected divided by the total system volume, in this case 938 $\mu\text{g/l}$. The model solutions settled at 936 $\mu\text{g/l}$ by 300 s and were unchanged at 10,000 s. We conclude that with single precision 32-bit words the model composed of 10 vascular operators (10 delay lines and 20 second-order operators) conserved mass to within 0.2%.

The sensitivity of the system to nonstationarity in similar experiments is demonstrated by the input-output curves obtained after a single injection or a pair of brief pulse injections of dye into the external iliac artery, shown in Fig. 9.

The results using the two-parameter vascular operator are quite good in terms of providing an overall fit to the curves. Where the fit is not so good reveals something interesting about the physiology, namely that the system is not stationary for either experiment. These two data sets were collected ~2-3 min apart in a 30-year-old man lying supine and unsexed. Figure 9A shows that the vascular operator, assuming a constant flow and t_{vasc} , gave an output, G_{out} , that matched the observed dorsalis pedis curve well enough on the upslope and first half of the downslope. However, for times after $t = 16$ s the model solution is too late. It appears that the flow increased during the period of 15-20 s. On refitting the dorsalis pedis curve so that the recirculation peak was fitted, the transit time t_{vasc} was reduced to 5.6 s instead of 6.6 s, indicating a flow increase of 15%. This raises the question of whether the increase in flow was a spontaneous fluctuation, as is normally found in limb arteries (6), or possibly induced by the injectate solution.

With the double injection, the fit shown was chosen to be a compromise between fitting the primary (double) response and the recirculation curve at 30-37 s. An input waveform of this type poses an exacting test for any model function. It appears again that flow must be slowly fluctuating, hindering obtaining a good fit, for the upslope of the model $C_{\text{out}}(t)$ is too late and too steep, whereas the downslope after the double peak is too early and not steep enough. Again the model recirculation peak is too late, indicating that flow in the artery was faster 30 s after the injection than it was when the first indicator reached the distal sampling site. Additional evidence of nonstationarity is seen in the change in $\bar{t}$ and RD from the single-pulse experiment (Fig. 9A) to the double-pulse experiment (Fig. 9B). (It should be said that these effects are not due to sampling system variation, because the blood sampling used constant flow through carefully matched densitometer-catheter systems of 0.5 ml total volume.)

DISCUSSION

This vascular operator has only two parameters, $\bar{t}$ and RD. It is therefore not as flexible as the lagged normal density function, the gamma variate function, and the random walk with a first traversal, which all have three free parameters. These other models allow one to define not only the means $\pm$ SD of the transport function but also the skewness. The fact that the fits are as good as they are with our simple vascular operator gives credence to the idea that the skewness (β_1) of ~ 1.0 and the kurtosis (β_2) nearing 4.0 inherent to the simple fourth-order operator are more or less suitable for intravascular transport. These approximate values, $\beta_1 = 0.8-1.0$, and $\beta_2 \approx 3.8$, can be calculated from the analyses presented by Bassingthwaighe and co-workers (1-3). The result is an operator that is easy to work with, having only two parameters, both of which are easy to understand, namely the mean delay and the degree of dispersiveness.

The calculations for skewness and kurtosis are given in APPENDIX B, *Moments of the vascular operator*. Knowing these one can calculate the moments of the output function given any input function whose moments can be defined. However, in using this particular vascular operator model to characterize a system from known inputs, only the first two moments are worth calculating, and all higher moments are redundant. For the LNDC, a parameter transport descriptor, the fourth moment (giving kurtosis) was redundant. The same applies to the random walk and the gamma variate functions. Now we have simplified the situation a little further, since this vascular transport operator gives approximately the appropriate skewness and kurtosis for transport in flowing blood. This is not fortuitous; Paynter (11) chose parameters that give phase lags that match Gaussian operators at particular relative frequencies, and so it is expected that the approximation to all three of these standard probability density functions is fairly close.

For less skewness, two or more Paynter operators may be used in series, as was done by Bassingthwaighe et al. (5). With adjustments to skewness, the nearly Gaussian responses of oil pipelines modeled by Taylor (13) can be well modeled. Likewise, the dispersion of tracer in flow along a neuronal axon should be equally well susceptible to the use of this model, even though the time scale for axonal transport is days to weeks rather than seconds.

This type of vascular operator has been found to describe the input-output relationship for transport through the vascular system when the flow is constant. Bassingthwaighe et al. (5) dealt with the problem of unsteady flow by using a twelfth-order operator composed of three of the fourth-order operators in series to match a dilution curve recorded with a high dynamic response system from the root of the aorta after an injection of indocyanine green dye into the pulmonary artery. By driving the model function for the flow from the recorded flowmeter waveform, and using no free parameters except for the $\bar{t}$ of the operator in the steady flow state, the model solution gave a very close fit to the recorded aortic curve in the unsteady flow situation. They used a twelfth-order operator to obtain a narrow dispersion approximating that observed in nature. We have here achieved the same objective with greater computational efficiency by using a delay plus a fourth-order operator instead. Their code for the twelfth-order operator allowed flow to be continuously varying, something not allowed in the code given in APPENDIX A. Continuously changing the natural frequency

and the delay can be accomplished but is more complicated and can be regarded as a useful future effort. A model with continuously variable t can be expected to give a better fit to the data of Fig. 9 and might even be used to estimate the variation in flow.

For certain experimental preparations and conditions (e.g., isolated organs), the assumption of steady flow is valid. For others, such as that shown in Fig. 9, the assumption is not strictly correct. Even in these cases, however, it is possible that the vascular operator may be used without introducing significant error. The magnitude and frequency of the flow variation over the duration of the experiment and the frequency and accuracy of the data collected must all be considered in deciding whether or not a model using the vascular operator can be used to analyze a specific set of data.

The vascular operator is useful in interpreting the time sequences of images from studies using positron emission tomography and other techniques in which the residual content of an indicator is recorded with a region of interest. The regions of interest contain indicator in arteries and veins as well as in the blood-tissue exchange units. When the processes are nonlinear, for example the transformation of ^{15}O -oxygen by tissue metabolism to ^{15}O -water, the metabolic product, then the transport through (and content within) arteries must be accounted for separately from that in the veins. A simple yet useful model for analyzing such data might contain a single artery that feeds a set of parallel pathways that drain into a single vein. Each pathway could be comprised of an arteriole, a blood-tissue exchange unit, and a venule in series in which the artery, arterioles, venules, and vein could be modeled by a set of vascular operators.

In some cases it will be possible to use the vascular operator, perhaps in conjunction with other operators, to model the specific geometry of a given experiment. Consider, for example, positron emission imaging of the thigh after intravenous injection of tracer. In addition to a signal from the tracer passing through the thigh muscles being imaged, there will also be a signal from tracer that flows through the imaged volume to the lower leg and then reenters the imaged volume in the venous circulation. Because, after intravenous injection, the tracer bolus will be quite dispersed by the time it reaches the thigh, the signals from the thigh muscles and the venous return will greatly overlap. With the use of vascular operators, a model could be constructed that included both the thigh muscles and the venous return in the volume of interest.

Conclusion

A two-parameter Paynter-type delay operator provides good descriptions for intravascular mass transport. The model is a reduced form of a five-parameter model composed of a delay line and two second-order operators in series. By use of an operator rather than a probability density function, convolution is avoided. Computationally efficient algorithms are used for the component operators, a delay operator, and a fourth-order differential operator. The result is a simple, fast, and useful operator for transport by flow along a pipelike system, including the human leg arterial system.

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APPENDIX A

Numerical Methods

The delay line

This is set up as an integer number of the delay of t , where $t_{\text{delay}} = N_{\text{delay}} \Delta t$, and Δt is the time step for the computer solution. The idea of the algorithm is that the value of $C_{\text{in}}(t)$ is put into the first location of a one-dimensional array at time t and then moved along the array one location for each time step. Then after N_{delay} time steps, this value is in the (N_{delay}) th location and is read out as $C_1(t - N_{\text{delay}} \Delta t)$. The function $C_{\text{in}}(t)$ emerges undeformed but delayed. This is akin to an Euler integration in style but introduces no error so long as the desired delay is an exact integer number of steps.

To save computation time, two simple devices are used: 1) the points of $C_{\text{in}}(t)$ are not moved along the array, but instead a pointer is indexed to designate the location from which to read out; and 2) the same pointer is used to index the location in which to place the input. The array is therefore configured to be a circular array of N_{delay} points: the N th point is read out, the value of $C_{\text{in}}(t)$ is put into that same location, and the pointer is moved clockwise by one location in preparation for the next time step (Fig. 10).

The array is loaded during the initial condition portion of the program, either with zeroes or a constant. (In principle, it could be loaded with any designated waveform, but zeroes are usually appropriate.) In pseudocode this can be written as in Table 1.

The second-order operator

The operator, op2, provides the solution for Eq. 9 of the text in which the input is of general form $C_1(t)$ and the output is $C_2(t)$. A solution is obtained, as suggested in the pseudocode in Table 2, by putting the two first-order components of Eq. 9 in state variable form, solving the homogeneous solution by matrix inversion. The solution for each time step provides the elements of an “updating matrix” that is applied during each time step. Two of these are used for the fourth-order Paynter operator, given in the form of a fourth-order operator, op4, in Table 3. More can be used for higher-order operators.

The vascular transport operator

With the use of the subroutines delay and op4 described above, the code for the vascular transport operator is constructed as in Table 4.

APPENDIX B

Moments of Vascular Operator

Moments of impulse responses

A linear system (Fig. 11) composed of several components in series can be characterized in a general way through the moments of its impulse response. The impulse response is the output of the system, $h(t)$, when the input is a unit impulse, $\delta(t)$. The notation and terminology used in defining input-output relationships follows accepted international usage (4). The impulse function, $\delta(t)$, or Dirac delta function, is an infinitely narrow spike of unity area at time zero. (It can be regarded, for example, as a Gaussian or normal density function centered at $t = 0$ and with SD diminished to the limit of zero. To preserve area at unity this infinitely narrow pulse has an infinite height. Although such an idealized $\delta(t)$ cannot be achieved physically, it is a useful approximation for any situation in which the input function is very narrow compared with the response at the output.)

The most familiar moments of an $h(t)$ are the $\bar{t}$ and the variance, μ_2 . They differ conceptually. The mean, or $\bar{t}$, is the first moment around $t = 0$, whereas the variance is the second moment around the mean. Moments around zero are denoted by α ; moments around the mean are denoted by μ . Therefore for $h(t)$, the units of which are fraction per second, the moments around zero are

$$\alpha_n = \int_0^\infty t^n \cdot h(t) \, dt \quad \text{for } n=0 \text{ to } \infty \quad (\text{B1})$$

The transport function or impulse response, $h(t)$, is defined as the response to an infinitely narrow pulse with unity area. The response has also an area of unity, that is $\alpha_0 = 1.0$. When an unscaled concentration-time curve $C(t)$ is used for the moments, the calculation must take this into account by normalizing with respect to its area

$$\alpha_n = \frac{\int_0^\infty t^n C(t) \, dt}{\int_0^\infty C(t) \, dt} \quad (\text{B2})$$

The zeroth and first moments of a probability density function are its area (A) and its mean

$$A = \int_0^\infty C(t) \, dt \quad (\text{B3})$$

so that when the input is an impulse function of A , then $h(t) = C(t)/A$. The mean, $\bar{t}$, is obtained with $n = 1$ in Eq. B1

$$\bar{t} = \int_0^\infty t \cdot h(t) \, dt \quad (\text{B4})$$

or for the unnormalized impulse response

$$\bar{t} = \frac{\int_0^\infty t \cdot C(t) \, dt}{\int_0^\infty C(t) \, dt} \quad (\text{B5})$$

The central moments, the moments around the mean, are denoted μ_n ,

$$\mu_n = \int_0^\infty \left(t - \bar{t}\right)^n \cdot h(t) dt \quad \text{for } n=2 \text{ to } \infty \quad (\text{B6})$$

The units of μ_n are those of t to the n th power. These give rise to the shaping factors of the distribution, its spread, asymmetry, and peakedness. The variance is the moment of inertia, μ_2

$$\mu_2 = \text{variance} = \int_0^\infty \left(t - \bar{t}\right)^2 h(t) dt \quad (\text{B7})$$

or when starting with an unnormalized impulse response $C(t)$,

$$\mu_2 = \frac{\int_0^\infty \left(t - \bar{t}\right)^2 C(t) dt}{\int_0^\infty C(t) dt} \quad (\text{B8})$$

The units of variance are time squared. These shaping factors are most universally expressed in dimensionless terms. The square root of the variance is the SD; to generalize its meaning it is divided by the mean to obtain the coefficient of variation, CV, or the RD

$$RD = \frac{SD}{\bar{t}} = \frac{\sqrt{\text{variance}}}{\bar{t}} = \frac{\mu_2^{1/2}}{\alpha_1} \quad (\text{B9})$$

(Because $\mu_2 = \alpha_2 - \alpha_1^2$, the relative dispersion can also be written $RD = (\alpha_2 - \alpha_1^2)^{1/2} / \alpha_1$, which is a common expression for the coefficient of variation.)

The higher-order shaping factors, β_n , are normalized relative to the spread or dispersion. The literature is mixed on the definitions, but the most common is to use the SD as the reference, thus

$$\beta_{n-2} = \frac{\mu_n}{SD^n} = \frac{\mu_n}{\mu_2^{n/2}} \quad (\text{B10})$$

The most useful shaping factors are the skewness, β_1 and the kurtosis or peakedness, β_2 . For a symmetric function such as a Gaussian, $\beta_1 = 0$. A density function with a long tail at times less than the mean is left skewed with a negative β_1 . Right-skewed functions have positive values of β_1 .

Kurtosis is considered as peakedness relative to a Gaussian distribution whose $\beta_2 = 3.0$. Thus high peakedness or leptokurtosis indicates density functions with higher narrower peaks than a Gaussian distribution with the same RD, and $\beta_2 > 3$. The corollary is that leptokurtic curves must have long tails to have the same RD. Stubby, relatively square, or flat-topped density functions are platykurtic, i.e., exhibit platykurtosis by having $\beta_2 < 3$, and have tails smaller than a Gaussian distribution.

Moments of delay operator

The moments of the delay are all trivial, and equal to zero, except the mean. With a t_d as in Fig. 12

$$\bar{t} = t_d \quad (\text{B11})$$

The response to another input is an output with a later mean time

$$\bar{t}_{\text{out}} = \bar{t}_{\text{in}} + t_d \quad (\text{B12})$$

The variance is zero, so the variance of C_{out} is identical to that of C_{in} . Likewise, skewness and kurtosis are unaffected. However, the relative dispersion of G_{out} is changed from that of C_{in} .

$$RD_{\text{out}} = \frac{\sqrt{\text{variance}}}{\bar{t}_{\text{out}}} = \frac{RD_{\text{in}} \cdot \bar{t}_{\text{in}}}{\bar{t}_{\text{in}} + t_d} \quad (\text{B13})$$

Consequently, a delay without dispersion diminishes relative dispersion.

Moments of a second-order operator

For a second-order operator the moments may be calculated directly from the parameters for the homogeneous form of the differential equation, $d^2y/dt^2 + 2\zeta\omega dy/dt + \omega^2y = 0$, where ω is the natural frequency in radians per second, and ζ is the dimensionless damping coefficient. The first moment of the second-order operator, α_1 , is its mean transit time, t_{op2}

$$\bar{t}_{\text{op2}} = \alpha_1 = \frac{2\zeta}{\omega} \quad (\text{B14})$$

For the second-order operator, the variance is

$$\mu_2 = \frac{4\zeta^2 - 2}{\omega^2} \quad (\text{B15})$$

and the RD is the SD divided by the mean

$$RD = \frac{\mu_2^{1/2}}{\alpha_1} = \frac{(4\zeta^2 - 2)^{1/2}}{2\zeta} = \left(1 - \frac{1}{2\zeta^2}\right)^{1/2} \quad (\text{B16})$$

Values of $\zeta < 2^{-1/2}$ give meaningless estimates of RD.

The shaping factors, skewness (β_1), and kurtosis (β_2) are

$$\beta_1 = \frac{2\zeta(\zeta^2 - \frac{3}{4})}{(\zeta^2 - \frac{1}{2})^{3/2}} \quad (\text{B17})$$

and

$$\beta_2 = \frac{3(6\zeta^4 - 6\zeta^2 + 1)}{2(\zeta^2 - \frac{1}{2})^2} \quad (\text{B18})$$

Because the second-order operator has only two parameters, ζ and ω , both β_1 and β_2 are redundant parameters, in the sense that they do not further define the impulse response, but they do tell us about the shape. The normalization by the dispersion removes any influence of the natural frequency ω on the shaping parameters.

Calculating moments of impulse response for two operators in series

In a linear, stationary system, the combined response $h_C(t)$ of two operators in series is given by the convolution of their individual responses (15)(Fig. 13). The convolution integral is

$$h_C(t) = \int_0^t h_A(t) \cdot h_B(t - \lambda) \, d\lambda \quad (\text{B19})$$

or expressed in informal notation

$$h_C(t) = h_A(t) * h_B(t) \quad (\text{B20})$$

where h_A , h_B , and h_C are transport functions.

The means and the second and third moments are additive

$$\bar{t}_C = \bar{t}_A + \bar{t}_B \quad (\text{B21})$$

$$\mu_{2C} = \mu_{2A} + \mu_{2B} \quad (\text{B22})$$

and

$$\mu_{3C} = \mu_{3A} + \mu_{3B} \quad (\text{B23})$$

The relative dispersion of h_C is its SD divided by its mean

$$RD_C = \frac{(\mu_{2A} + \mu_{2B})^{1/2}}{\bar{t}_A + \bar{t}_B} \quad (\text{B24})$$

The skewness, β_1 , is calculated similarly

$$\beta_{1C} = \frac{\mu_{3A} + \mu_{3B}}{(\mu_{2A} + \mu_{2B})^{3/2}} \quad (\text{B25})$$

By applying these formulas, virtually any combination of operators in series can be characterized in analytic terms so long as the moments of each individual function are calculable.

For the fourth moments, the product of variances contributes

$$\mu_{4C} = \mu_{4A} + \mu_{4B} + 6\mu_{2A} \cdot \mu_{2B} \quad (B26)$$

so that the kurtosis can be expressed from the moments of the components

$$\beta_{2C} = \frac{\mu_{4C}}{\mu_{2C}^2} = \frac{\mu_{4A} + \mu_{4B} + 6\mu_{2A} \cdot \mu_{2B}}{(\mu_{2A} + \mu_{2B})^2} \quad (B27)$$

Moments of a fourth-order operator composed of two second-order operators in series

From Eqs. B21 -B27 one can obtain in analytic form the moments for any two second-order operators in series. The $\bar{t}$ is

$$\bar{t} = \frac{2\zeta_A}{\omega_A} + \frac{2\zeta_B}{\omega_B} \quad (B28)$$

or with $b = \omega_B/\omega_A$

$$\bar{t} = \frac{2}{\omega_A} \left(\zeta_A + \frac{\zeta_B}{b} \right) \quad (B29)$$

The variance μ_2 is

$$\mu_2 = 4 \left(\frac{\zeta_A^2 - \frac{1}{2}}{\omega_A^2} + \frac{\zeta_B^2 - \frac{1}{2}}{\omega_B^2} \right) \quad (B30)$$

and the RD, using $b = \omega_B/\omega_A$

$$RD = \frac{\left[b^2 \left(\zeta_A^2 - \frac{1}{2} \right) + \left(\zeta_B^2 - \frac{1}{2} \right) \right]^{1/2}}{b\zeta_A + \zeta_B} \quad (B31)$$

The skewness and kurtosis are

$$\beta_1 = \frac{\frac{16\zeta_A^3 - 12\zeta_A}{\omega_A^3} + \frac{16\zeta_B^3 - 12\zeta_B}{\omega_B^3}}{\left[\left(4\zeta_A^2 - 2 \right) / \omega_A^2 + \left(4\zeta_B^2 - 2 \right) / \omega_B^2 \right]^{3/2}} \quad (B32)$$

and

$$\beta_2 = 6 \frac{\left[\frac{6\zeta_A^4 - 6\zeta_A^2 + 1}{\omega_A^4} + \frac{6\zeta_B^4 - 6\zeta_B^2 + 1}{\omega_B^4} + \frac{(2\zeta_A^2 - 1)(2\zeta_B^2 - 1)}{\omega_A^2 \omega_B^2} \right]}{\left[(2\zeta_A^2 - 1) / \omega_A^2 + (2\zeta_B^2 - 1) / \omega_B^2 \right]^2} \quad (\text{B33})$$

For the general fourth-order operator, there are four independent parameters, ω_A , ζ_A , ζ_B , and either ω_B or b , so the first four moments are all independent.

Moments of Paynter fourth-order operator

When fixed ratios of values are used, the Paynter operator becomes a one-parameter function. With $b = \omega_B / \omega_A = 1.82$, $\zeta_A = 0.95$, and $\zeta_B = 0.8$, the only remaining parameter is ω_A . This is calculable from the t for the operator, t_p , using Eq. B29

$$\omega_A = \frac{2}{t_p} \left(\zeta_A + \frac{\zeta_B}{b} \right) \quad (\text{B34})$$

$$= \frac{2(0.95 + 0.8/1.82)}{t_p} = \frac{2.7791}{t_p} \quad (\text{B35})$$

The higher moments are now fixed. Their values are calculated from Eqs. B31 -B33

$$RD = 0.4799 \quad \beta_1 = 0.8784 \quad \beta_2 = 3.8311 \quad (\text{B36})$$

Values for t , RD , β_1 , and β_2 were computed from computer solutions from the code described in APPENDIX A, using the general equations for the moments given in Eqs. B1 and B6. The calculated values were the same as the theoretical values above to four significant digits using single precision on a 32-bit word workstation (SUN Sparcstation 2).

Moments of the vascular operator, the combination of the delay, and Paynter operators

After the formulas for combining operators in series, APPENDIX B, Calculating moments of the impulse response for two operators in series Eqs. B21-B23 and B26, again, for the vascular operator or Paynter-delay operator we have only to add together the t values and adjust the RD . The variance for the t_d is zero, so the overall variance, etc., is that of the Paynter operator

$$\bar{t} = t_d + \bar{t}_p \quad (\text{B37})$$

$$RD = \left(\bar{t}_p / \bar{t} \right) \cdot RD_p \quad (\text{B38})$$

$$\beta_1 = 0.8784 \quad (\text{B39})$$

$$\beta_2=3.8311 \quad (\text{B40})$$

From the physiologist's viewpoint, the governing parameters are $\bar{t}$, or V/F , and the relative dispersion, RD . Given these, and the fixed $RD_p = 0.48$, the unknown model parameters are t_d and t_p , with the constraint that values of RD are <0.48

$$\bar{t}_p = \frac{RD \cdot \bar{t}}{0.48} \quad (\text{B41})$$

and

$$t_d = \bar{t} \left(1 - \frac{RD}{0.48} \right) \quad (\text{B42})$$

REFERENCES

1. Bassingthwaite JB. Plasma indicator dispersion in arteries of the human leg. *Circ. Res.* 1966; 19:332–346. [PubMed: 5330717]
2. Bassingthwaite JB, Ackerman FH. Mathematical linearity of circulatory transport. *J. Appl. Physiol.* 1967; 22:879–888. [PubMed: 5337940]
3. Bassingthwaite JB, Ackerman FH, Wood EH. Applications of the lagged normal density curve as a model for arterial dilution curves. *Circ. Res.* 1966; 18:398–415. [PubMed: 4952948]
4. Bassingthwaite JB, Chinard FP, Crone C, Goresky CA, Lassen NA, Reneman RS, Zierler KL. Terminology for mass transport and exchange. *Am. J. Physiol.* 1986; 250:H539–H545. *Heart Circ. Physiol.* 19. [PubMed: 3963211]
5. Bassingthwaite JB, Knopp TJ, Anderson DU. Flow estimation by indicator dilution (bolus injection): reduction of errors due to time-averaged sampling during unsteady flow. *Circ. Res.* 1970; 27:277–291. [PubMed: 4917088]
6. Burton AC, Yamada S. Relation between blood pressure and flow in the human forearm. *J. Appl. Physiol.* 1951; 4:329–339. [PubMed: 14938261]
7. Coulam CM, Warner HR, Wood EH, Bassingthwaite JB. A transfer function analysis of coronary and renal circulation calculated from upstream and downstream indicator-dilution curves. *Circ. Res.* 1966; 19:879–890. [PubMed: 5333498]
8. Hansen PD. New approaches to the design of active filters, Part One. *Lightning Empiricist.* 1965; 13:3–16.
9. Kuo, FF. *Network Analysis and Synthesis.* Wiley; New York: 1962.
10. MacDonald, D. *Blood Flow in Arteries.* Arnold; London: 1960.
11. Paynter HM. Methods and results from M.I.T. studies in unsteady flow. *Boston Soc. Civil Eng. J.* 1952; 39:120–124.
12. Sheppard, CW. *Basic Principles of the Tracer Method.* Wiley; New York: 1962.
13. Taylor G. The dispersion of matter in turbulent flow through a pipe. *Proc. R. Soc. Lond. A.* 1954; 223:446–468.
14. Thompson HK, Starmer CF, Whalen RE, McIntosh HD. Indicator transit time considered as a gamma variate. *Circ. Res.* 1964; 14:502–515. [PubMed: 14169969]
15. Zierler, KL. *Handbook of Physiology. Circulation. Vol. I.* Am. Physiol. Soc.; Washington, D.C.: 1962. Circulation times and the theory of indicator-dilution methods for determining blood flow and volume.; p. 585-615.sect. 2chapt. 18

Fig. 1.

Diagram of vascular transport operator with input (C_{in}) and output (C_{out}). Only 2 parameters are mean transit time ($\bar{t}$) and relative dispersion (RD) of impulse response [$h(t)$].

Fig. 2.

Diagram of vascular operator. Components are pure delay with transit time (t_d) and a 4th-order Paynter operator with mean transit time (t_p).

Fig. 3.

Diagram of 4th-order dispersive operator of Paynter type. Both of the 2nd-order operators are slightly underdamped. ω , natural frequency (in rad/s); ζ , dimensionless damping coefficient.

Fig. 4.
RD of overall vascular transport operator as a function of fraction of transit time, which is provided by dispersive (Paynter) component of the operator.

Fig. 5.

Responses of vascular transport operator (at 5 different RD values) to 2 different inputs. *A*: responses to a 2-s pulse input. With RD = 0, input is delayed by 1 transit time and is not deformed. RD values of 0.12-0.48 lower peak of response and spread the curves. An RD of 0.15-0.30 is suitable for most arteries. *B*: responses of same 5 vascular transport operators to a lagged normal density curve input with $t = 5.0$ s, RD = 0.3, skewness = 1.0.

Fig. 6.

Comparisons of vascular operator outputs (solid lines) with Gaussian responses (dashed lines, *A*) and with Poisson operator, serial stirred tanks (dashed lines, *B*) having same means and RD values. Vascular operator solution is skewed less than Poisson output of order 5 or less but is more skewed than Gaussian or higher-order Poisson operators. N_{tanks} , no. of serial stirred tanks.

Fig. 7. Fitting of ^{51}Cr -labeled red blood cell concentration-time curve recorded in a tube perfusion experiment. *A*: model curves fitted to outflow concentration-time curve using inflow concentration-time curve to generate input. Open squares, measured input curve; filled circles, measured outflow curve. Lines are the model solutions. *B*: contour plot of coefficient of variation for model fit to outflow concentration-time curve shown in *A*. Each line represents a series of model solutions having an identical coefficient of variation. Value adjacent to each contour line gives coefficient of variation in percent. V/F , volume per flow.

Fig. 8.

Fitting dye dilution curves in a human leg artery with a recirculating model composed of vascular operators. *A*: schematic arrangement of recirculating model. All flow pathways are modeled by vascular operators. Injection site and sampling sites for input curve (C_{in}) and output curve (C_{out}) are shown. *B*: model curves (solid lines) fitted to dye concentration-time curves recorded from the femoral artery, C_{in} (open squares), and dorsalis pedis artery, C_{out} (filled circles), after a bolus injection of indocyanine green dye into descending aorta. Parameters for artery 3 were $RD = 12\%$ and $t = 5.2$ s. [Data are from subject H. D. in the studies by Bassingthwaite et al. (3)].

Fig. 9.

Plasma indicator dispersion in human leg fitted with vascular transport operator. *A*: single slug injection of indocyanine green dye into internal iliac artery, sampling femoral and dorsalis pedis arteries. Parameters of vascular operator: $t_{\text{vasc}} = 6.6$ s and $\text{RD} = 14\%$. *B*: double pulse injections ~4 s apart at same site, ~2 min after experiment in *A*. Parameters were $t_{\text{vasc}} = 7.85$ s and $\text{RD} = 15.8\%$. Change in parameter values is consistent with nonstationarity of system.

Fig. 10. Circular integer delay line. Pointer designates N th location. When value there is read out, new input value is read in, and pointer moves 1 location clockwise.

Fig. 11.

Transport function $h(t)$ is response to an impulse input but is scaled by area (A) when input is a Dirac delta function (δ) scaled by A .

Fig. 12.

Response of delay operator is a delayed, underformed copy of input function. t_0 , zero time.

Fig. 13.

Response of 2 operators in series to an impulse input is convolution of their individual impulse responses. Asterisk denotes convolution process. h_A , h_B , and h_C are transport functions.

Table 1

Pseudocode for delay operator

Algorithm	init_delay(C0, Cin, ndelay) eval_delay(Cin)
Title	Delay line with an integer number of steps.
Comments	Gives the solution to the equation: $C_{out}(t) = C_{in}(t - t_{delay})$. init_delay is called at t_0 and initializes the operator. eval_delay is called at each time step. Delay is nondispersive.
Parameters	C0 The initial concentration. (Type: real). Cin The present concentration of the input to the vascular operator. (Type: real). ndelay The number of time steps to delay the input. (Type: integer).
Globals	C[] The concentration array. (Type: real vector. Size: ndelay). idelay Pointer into C[]. (Type: integer).
Variables	i The loop index. (Type: integer). Cout The returned output concentration. (Type: real).
BEGIN	init_delay idelay = 1 FOR i = 2 TO i = ndelay DO C[i] = C0 END FOR Cout = C0 C[idelay] = Cin RETURN Cout
END	
BEGIN	eval_delay IF idelay < ndelay THEN idelay = idelay + 1 ELSE idelay = 1 END IF Cout = C[idelay] C[idelay] = Cin RETURN Cout
END	

Table 2**Pseudocode for second-order operator**

Algorithm	init_op2(ufreq, zeta, C0, dC0, dt) eval_op2(Cin)	
Title	2nd-order linear differential operator with constant coefficients.	
Comments	Each operator gives a numerical solution to the equations	
	$\frac{d^2 C_{out}}{dt^2} + 2\zeta \cdot \omega \cdot \frac{dC_{out}}{dt} + \omega^2 \cdot C_{out} = \omega^2 \cdot C_{in} \quad (T2.1)$	
	$C_{out}(0) = C0, \quad \text{and} \quad \frac{dC_{out}(0)}{dt} = dC0 \quad (T2.2)$	
	where zeta = ζ , the dimensionless damping coefficient; ufreq = ω , the undamped natural frequency (rad/s). Init_op2 is called at t_0 to initialize the operator. Eval_op2 is called at each time step.	
Parameters	ufreq	The undamped natural frequency (in rad/s). (Type: real. Range: ufreq > 0.0).
	zeta	The damping coefficient. (Type: real. Range: zeta ≥ 0.0).
	C0	The initial concentration. (Type: real).
	dC0	The initial condition of the derivative of the output with respect to time. (Type: real).
	dt	The time step to be used in the solution, in seconds. (Type: real).
	Cin	The present concentration of the input to the 4th-order operator. (Type: real).
Globals	Cout	The return output concentration of the 2nd-order operator. (Type: real).
	dC	The current time derivative, dC_{out}/dt . (Type: real).
	z11, z12, z21, z22	The matrix exponential of the coefficient matrix.
Variables	w0, w1, w2, w3, w4, Ctmp	Temporary storage. (Type: real).
BEGIN	init_op2	
	IF zeta > 1 THEN	
	w0 = SQRT(zeta*zeta - 1.0)	
	w1 = EXP(-dt*ufreq*(zeta-w0))	
	w2 = EXP(-dt*ufreq*(zeta+w0))	
	w3 = 0.5*(w2+w1)	
	w4 = -0.5*(w2-w1)/w0	
	ELSE IF zeta < 1 THEN	
	w0 = SQRT(1.0 - zeta*zeta)	
	w1 = EXP(-dt*ufreq*zeta)	
	w3 = w1*COS(dt*ufreq*w0)	
	w4 = w1*SIN(dt*ufreq*w0)/w0	
	ELSE	
	w3 = EXP(-dt*ufreq)	
	w4 = dt*ufreq*w3	
	END IF	
	z11 = w4*zeta + w3	

```
z12 = w4/ufreq
z21 = -w4*ufreq
z22 = -w4*zeta + w3
Cout = C0
dC = dC0
RETURN Cout
END
BEGIN eval_op2
  Ctmp = Cout - Cin
  Cout = Cin + z11 * Ctmp + z12 * dC
  dC = z21 * Ctmp + z22 * dC
  RETURN Cout
END
```

Table 3**Pseudocode for fourth-order operator**

Algorithm	init_op4(tmean, wratio, zeta1, zeta2, C0, dt) eval_op4(Cin)	
Title	4th-order linear differential operator with constant coefficients.	
Comments	Each operator gives a numerical solution to the equations.	
	$\frac{d^2 C_{\text{mid}}}{dt^2} + 2\zeta_1 \cdot \omega_1 \cdot \frac{dC_{\text{mid}}}{dt} + \omega_1^2 \cdot C_{\text{mid}} = \omega_1^2 \cdot C_{\text{in}} \quad (\text{T3.1})$	
	$C_{\text{mid}}(0) = 0.0 \quad \text{and} \quad \frac{dC_{\text{mid}}(0)}{dt} = 0.0 \quad (\text{T3.2})$	
	$\frac{d^2 C_{\text{out}}}{dt^2} + 2\zeta_2 \cdot \omega_2 \cdot \frac{dC_{\text{out}}}{dt} + \omega_2^2 \cdot C_{\text{out}} = \omega_2^2 \cdot C_{\text{mid}} \quad (\text{T3.3})$	
	$C_{\text{out}}(0) = 0.0 \quad \text{and} \quad \frac{dC_{\text{out}}(0)}{dt} = 0.0 \quad (\text{T3.4})$	
	where zeta1 = ζ_1 and zeta2 = ζ_2 are dimensionless damping coefficients; ω_1 and ω_2 are the frequencies, and wratio = ω_2/ω_1 . This program uses two separate op2 codes, designated, op2a and op2b; op2a solves equation c.1 and op2b solves equation c.2. Init_op4 is called at t_0 and initializes the operator. Eval_op4 is called at each time step.	
Parameters	tmean	Transit time of the operator in seconds. (Type: real).
	wratio	The ratio of the frequency of the second 2nd-order operator to the first 2nd-order operator. wratio = ω_2/ω_1 .
	zeta1	The damping coefficient of the first 2nd-order operator. (Type: real).
	zeta2	The damping coefficient of the second 2nd-order operator. (Type: real).
	C0	The initial concentration. (Type: real).
	dt	The time step to be used in the solution, in seconds. (Type: real).
	Cin	The present concentration of the input to the 4th-order operator. (Type: real).
Variables	Cout	The return output concentration of the 4th-order operator. (Type: real).
	ufreq2	The frequency of the second 2nd-order operator. (Type: real).
	ufreq1	The frequency of the first 2nd-order operator. (Type: real).
	Cmid	The output of the first 2nd-order operator. (Type: real).
BEGIN	init_op4 ufreq_1 = 2.(zeta_1 + zeta_2/wratio) / tmean ufreq_2 = ufreq_1/wratio Cmid = init_op2a (ufreq1, zeta1, C0, 0.0, dt) Cout = init_op2b (ufreq2, zeta2, C0, 0.0, dt) RETURN Cout	
END		
BEGIN	eval_op4 Cmid = eval_op2a (Cin)	

```
Cout = eval_op2b (Cmid)
```

```
RETURN Cout
```

```
END
```

Table 4**Pseudocode for vascular transport operator**

Algorithm	init_vasop(C0, tdelay, rd, dt) eval_vasop(Cin)	
Title	Vascular operator specified by transit time delay and relative dispersion.	
Comments	The vascular operator is a combination of a pure delay operator and op4, a 4th-order differential operator. During initialization, the routine calls NINT to calculate the nearest integer number of steps, init_delay to initialize the delay line, and init_op4 to initialize the 4th-order differential operator with the parameters to make it a Paynter operator. During evaluation, the routine calls eval_delay to evaluate the delay line and eval_op4 to evaluate the 4th-order operator. Init_vasop is called at t_0 and initializes the operator. eval_vasop is called at each time step.	
Parameters	C0	The initial concentration. (Type: real).
	tdelay	The total transit time required, in seconds. (Type: real).
	rd	The relative dispersion of the system. (Type: real. Range: 0.0 rd 0.48)
	dt	The time step to be used in the solution, in seconds. (Type: real).
	Cin	The present concentration of the input to the vascular operator. (Type: real).
Variables	Cout	The return output concentration of the operator. (Type: real).
	ndelay	The number of delay steps for the delay operator. (Type: integer).
	top4	The transit time of the 4th-order operator, in seconds. (Type: real).
	Cdelay	The concentration output of the delay operator. (Type: real).
	wratio	The ratio of the frequency of the second 2nd-order operator to the frequency of the first 2nd-order operator. It is set to 1.82 for the Paynter operator. (Type: real).
	zeta1	The damping of the first 2nd-order operator used by op4. It is set to 0.95 for the Paynter operator. (Type: real).
	zeta2	The damping of the second 2nd-order operator used by op4. It is set to 0.80 for the Paynter operator. (Type: real).
BEGIN	init_vasop ndelay = NINT ((1 - rd / 0.48) * tdelay / dt) Cdelay = init_delay (C0, 0.0, ndelay) top4 = tdelay - ndelay*dt wratio = 1.82 zeta1 = 0.95 zeta2 = 0.80 Cout = init_op4 (top4, wratio, zeta1, zeta2, C0, dt) RETURN Cout	
END		
BEGIN	eval_vasop Cdelay = eval_delay (Cin) Cout = eval_op4 (Cdelay) RETURN Cout	
END		