Applications of the Lagged Normal Density Curve as a Model for Arterial Dilution Curves

By James B. Bassingthwaighte, M.D., Ph.D., Francis H. Ackerman, and Earl H. Wood, M.D., Ph.D.

The dispersion of an indicator in a flowing liquid increases with time and with the distance travelled. The form of the dispersion and its rate of increase have only recently come to the attention of investigators. Poiseuille's model, parabolic flow, has been used as an approximate description of flow in the vascular system in spite of the fact that there are priori reasons for expecting it to be unsuitable. The observations by Griffiths, Hull and Kent, and G. Taylor were that spatial dispersion of indicator in fluids flowing through rigid tubes was symmetric and nearly Gaussian. Sheppard had arrived independently at the hypothesis that this might also be true for the vascular system and had begun a series of experiments using the random walk equation as a model.

In the present study on normal men, the lagged normal density curve was used to describe the primary portion of recorded curves. From the resultant concise descriptions of the data, further analyses of flow characteristics and dispersion were made, which led to the inescapable, yet far from new, conclusion that, in the arterial system, the flow profile is not parabolic but is blunter and is probably always somewhat turbulent.

The nomenclature of this study is intended to be in accordance with that standardized by Wood.

The Model

The random dispersion occurring with turbulence and pulsatile flow suggests the use of the equation for a normal density curve (fig. 1):

\[ h_1(t) = \frac{1}{\sigma \sqrt{2\pi}} e^{-1/2((t-t_c)/\sigma)^2} \]

for \( t \geq 0 \) and (1)

\[ h_1(t) = 0 \]

for \( t < 0 \).

\( h_1(t) \) is a frequency function of unit area, representing a symmetric random distribution of transit times of the indicator about a central time, \( t_c \) (seconds), with standard deviation, \( \sigma \). This is a Gaussian curve; it is often colloquially called a normal distribution curve, but this name refers more properly to its sigmoid-shaped integral, the cumulative frequency distribution curve.

The occurrence of mixing in cardiac chambers, in the aorta during diastole, and in eddy currents at points of vessel branching, as well as the observation that dye curves are always skewed, suggests that a first-order exponential process may also be involved:

\[ h_2(t) = \frac{1}{\tau} e^{-t/\tau} \]

for \( t \geq 0 \) and (2)

\[ h_2(t) = 0 \]

for \( t < 0 \).

\( \tau \) is the time constant and \( h_2(t) \) has unit area. (Flow through a hypothetical mixing chamber washes out indicator at a rate such that the concentration at the end of an interval of duration, \( \tau \), is \( 1/e \) (= 1/2.718 = 0.37) of its initial value).

The convolution of these two equations, representing the sequential or simultaneous effect of one process on the distribution produced by the other may be described by the differential equation:

\[ h_3(t) = \frac{1}{\sigma \sqrt{2\pi}} e^{-1/2((t-t_c)/\sigma)^2} e^{-t/\tau} \]

\[ -\tau \frac{dh_3(t)}{dt} \]

which also has unit area. The three parameters, \( \sigma \), \( \tau \), and \( t_c \), provide a complete description of the curve's shape and position in time. The mean transit time, \( \bar{t} \), of the model is \( t_c + \tau \), the vari-
CIRCULATORY DILUTION MODEL

\[
\begin{align*}
    h_1(t) &= \frac{1}{\sqrt{\pi}} e^{-t^2} \\
    h_2(t) &= \frac{1}{\tau} e^{-t/\tau} \\
    h_3(t) &= \frac{1}{\sqrt{\pi}} e^{-t^2/\tau^2} - \frac{1}{\tau} e^{-t/\tau^2} \cdot \frac{d}{dt} h_3(t)
\end{align*}
\]

FIGURE 1

Model for indicator dilution curves. Left panel: normal density curve. Middle panel: single exponential. Right panel: lagged normal density curve.

\begin{itemize}
    \item \( h_3(t) \) is the dummy variable of integration and increases from zero to \( t \) during the integration. In applying this equation to concentration-time curves in the circulation,
    \[ C(t) = \frac{m_i}{Q} \cdot h_3(t) \]

\end{itemize}

METHODS

Five men, 25 to 33 years of age, served as subjects. They were given 100 mg of secobarbital as premedication. During the experiment they rested supine on a padded fluoroscopic table. For two periods of 30 to 50 minutes during each experiment, adenosine triphosphate (ATP), 1.0 mg/ml in Ringer’s solution, was infused into the right common iliac artery at the level of the inguinal ligament, was advanced a distance equal to 5 cm less than the distance from the groin to the third intercostal space at the sternal border, for injection of dye into the lower thoracic aorta.

2. An 80-cm Afford catheter (internal diameter, 0.5 mm; external diameter, 0.8 mm), introduced into the left femoral artery at the level of the inguinal ligament, was advanced a distance equal to 5 cm less than the distance from the groin to the third intercostal space at the sternal border, for injection of dye into the lower thoracic aorta.

3. A no. 20 thin-walled needle was inserted into the right dorsalis pedis artery on the dorsum of the foot, for sampling.

4. A special assembly for combined dye injection and blood sampling was used at the right femoral artery. A no. 17 thin-walled needle was introduced into the artery and through it a 40-cm thick-walled Afford catheter (internal diameter, 0.25 mm; external diameter, 0.8 mm) was introduced and advanced 8 to 9 cm beyond the needle tip. This assembly was used for injection of dye via the Afford catheter and for continuous sampling of blood through the needle around the catheter via the side arm leading to the densitometer.

5. A no. 19 thin-walled needle was introduced into the right femoral artery and a 40-cm thin-walled Afford catheter (internal diameter, 0.50 mm; external diameter, 0.8 mm) and was advanced 8 to 10 cm beyond the tip of the needle. This was used for the infusion of ATP.

NEEDLE AND CATHETER POSITIONS

The following were introduced by percutaneous needle puncture:

1. A 70-cm Lehman no. 5 catheter, inserted via the right medial antecubital vein, was advanced into the superior vena cava just above the right atrium, for injection of dye.

2. An 80-cm Afford catheter (internal diameter, 0.5 mm; external diameter, 0.8 mm), introduced into the left femoral artery at the level of the inguinal ligament, was advanced a distance equal to 5 cm less than the distance from the groin to the third intercostal space at the sternal border, for injection of dye into the lower thoracic aorta.

3. A no. 20 thin-walled needle was inserted into the right dorsalis pedis artery on the dorsum of the foot, for sampling.

DYE INJECTION

Indocyanine green, at a concentration of

* A radiopaque polyvinyl catheter made by Mr. A. E. Afford, 340 Marne Avenue, Haddonfield, New Jersey.

† Cardio-Green, Hynson, Westcott and Dunning, Inc., Baltimore, Maryland.
2.5 mg/ml, was used as indicator. For each experiment, 200 mg of the dye were dissolved in 10 ml of water, 4 ml of 20% human serum albumin were added to stabilize the indocyanine green solution, and isotonic Ringer’s solution was added to make a final volume of 80 ml. The same solution was used for making up the calibration dilutions for the densitometers.

Dye solution was injected by means of a pneumatically driven syringe and the duration of the injection was regulated with an electrically operated solenoid valve. The syringe movement was recorded via a linear potentiometer mechanically in parallel to it. The amount of dye injected, \( m_i \), was calculated from the equation, \( m_i = C_d (V/D) \), in which \( C \) is concentration of the dye solution (mg/ml), \( d \) is deflection (cm) produced by the syringe movement, and \( D \) is the deflection (cm) recorded when the syringe was emptied of a known volume, \( V \) (ml). The injections were accomplished in 0.6 to 1.0 second; the time at which the syringe was at the midpoint of its movement was used as zero time for the indicator dilution curves.

**SAMPLING SYSTEMS**

Blood was withdrawn from the femoral and dorsalis pedis arteries with a Harvard constant-rate sampling device at a constant rate of 9.8 to 10.0 ml/min. The differences in rates were due to differences in diameters of the barrels of the 30-ml glass syringes used; therefore, each rate was checked by timed withdrawal of water from a graduated cylinder.

The dynamic response of each sampling system was determined, with blood, by recording the response to a step change in indicator concentration at the tip of the needle, as described by Fox and co-workers. The volumes of the two systems (at femoral and dorsalis pedis arteries) were adjusted so that their dynamic responses were similar (Fig. 2). The femoral system consisted of needle (with Afford catheter filling part of the lumen), right-angled adapter, 10 cm of nylon tubing (internal diameter, 1.0 mm; external diameter, 1.8 mm), three-way stopcock, and densitometer. The stopcocks allowed thorough flushing of the sampling system without introducing large quantities of saline into the subject. The total volumes of the sampling systems from needle tip to densitometer lumen were 0.5 to 0.6 ml and, therefore, caused significant distortion of the indicator dilution curves. However, the magnitude of this distortion was not great and was similar at the two sampling sites. The data presented in this paper are from the uncorrected curves.

**DENSITOMETRY**

The densitometers selected have their greatest sensitivity at 800 m/μ, the absorption maximum of the dye. The light sensor is a photoconductive cell which forms one limb of a Wheatstone bridge; the output voltage from a properly adjusted instrument is linearly related to dye concentration over the range of 0 to 40 mg/liter.

The dynamic response of the photocell, circuitry, and galvanometer for each densitometer was tested by recording the output when a wire was rapidly withdrawn from the lumen of the densitometer (this produces a step change in incident light intensity). The 90 and 98% response times of both instruments were 0.09 and 0.15 second, respectively.

For calibration of the densitometers (Fig. 3), dilutions were made up by the addition of 0.01, 0.02, 0.03, 0.04, and 0.05 ml of a solution of dye (2.5 mg/ml) to 10.0 ml of whole blood. Blood was drawn through the densitometers in tandem at a constant rate of 10 ml/min. The deflection produced by the densitometer was set to a base line when undyed blood was flowing through the lumen (sensitivity potentiometer setting, \( P_a \)). With blood containing dye at 2.5 mg/liter flowing through the lumen, the deflection was recorded and the galvanometer beam was reset to the base line by adjusting the sen-

*Harvard Apparatus Company, Dover, Massachusetts.

*XC250A made by Waters Company, Rochester, Minnesota.
CIRCULATORY DILUTION MODEL

Femoral Artery
(XC250H2)

Dorsalis Pedis Artery
(XC250H2)

Calibration of two densitometers for indocyanine green in whole blood. Calibration was done on blood containing no background dye (lines passing through the origin) and on blood having background dye levels of 2.5 or 5.0 mg/liter (lines intercepting the abscissa at 2.5 and 5.0). The increase in calibration constant (decrease in slope) with higher background dye levels indicates a loss in sensitivity.

RECORDING SYSTEMS

Two recording systems were used in parallel. The photokymographic assembly described by Wood18 was used to record: output of densitometer II (femoral artery), output of densitometer I (dorsalis pedis artery), respiration, aortic pressure, femoral artery pressure, femoral injection syringe travel, aortic injection syringe travel, superior vena cava pressure, electrocardiogram, binary marking signal for coordinating this record with the analog tape record, and injection signal for superior vena caval injections. Selected data were recorded on 7-channel Ampex analog tape at three and three-fourths inches per second with carrier frequency of 3,400 cycles per second. These were: output of the densitometer at the femoral artery, output of the densitimeter at the dorsalis pedis artery, aortic pressure, aortic injection syringe position, electrocardiogram, and audio and binary tape-marker signals used for search and synchronization during subsequent analog-to-digital conversion. The analog tape was used for analog computer analysis1 and, for the
purposes of this study, was converted into taped digital information by means of an analog-to-digital converter assembly described previously. Conversion rates for the dye curves and for the syringe travel were 139 and 23 samples per second, respectively.

**Methods of Analysis**

**PREPARATION OF DATA**

From the digital tape, the recorded dye curves were converted into concentration-time curves, with the midpoint of the injection (to the nearest 1/23 second) taken as the zero time. The slow sampling rate for the syringe travel was used in order to keep within the memory limits for the IBM 1620 digital computer used for the data reduction and analysis.

The dye calibration factors for each densitometer were calculated from the digitized tape record of the calibration dilutions. For each dye curve, the base line value was ascertained and subtracted from the total curve. The curves were smoothed by means of a 7- or 9-point moving average to reduce the artifact introduced by pulsatile flow, to which these densitometers are sensitive. The smoothed data were converted to terms of milligrams per liter and preserved on punched cards at 0.25-second intervals (each to the nearest 1/139 second). The punched cards were used as the data source throughout the remainder of the analysis. The appearance time, \( t_a \), was chosen to be the time at which the concentration first equalled or exceeded 1.5\% of the peak concentration, \( C_p \).

**GENERATION OF THE MODEL IN THE COMPUTER**

The lagged normal density curve was generated from the differential equation by Simpson's method, expressed numerically at 0.25-second intervals, and truncated when its ordinate value decreased to less than 1.5\% of the peak value.

**CURVE-FITTING PROCEDURE**

Fitting of the recorded curves with the model was accomplished on the computer by a method adapted from that of Hazelrig and co-workers. Programming was in Fortran II. The number of variable parameters for the trial adjustments could be reduced to two because the mean transit time of the recorded wave equals \( \tau + t_c \) and the peak height of the model was adjusted to fit the peak of the dye curve.

The best \( \sigma \) and \( \tau \) were obtained by a systematic search in the \( \sigma, \tau \) plane. Trial parameters were initially assigned, and then the computer generated the curve having these parameters and also generated eight other curves having \( \sigma \) and \( \tau \) values located at the corners and midpoints of the sides of a square surrounding the original trial point. The width of the square was set at 0.6 second or less. The pair of parameters forming a curve having the smallest coefficient of variation from the recorded curve was used as the center of the next trial square. The coefficients of variation for points previously tested were retained and not recalculated. When the center of the square was the best answer, the square size was reduced to 31\% of the original width and the search was repeated until the central coordinates provided the best parameters.
and the square size was reduced again. When the center of this small square (9.6% of the original) was found to give the smallest coefficient of variation, the search was complete. Thus, $\sigma$ and $\tau$ were obtained, at the worst, to the nearest 0.03 second.

The coefficient of variation, labelled "coeff" in figures 4, 5, and 6, is given by:

$$\left[ \sum_{i=1}^{n} (F_i - C_i)^2 \right]^{1/2} \left[ \sum_{i=1}^{n} F_i \right] \cdot \frac{n}{n-1}$$

in which $F_i$ and $C_i$ are the ordinate values at time, $i$, for the recorded and computed curves, respectively. The recorded and computed curves were plotted by the computer by means of an incremental x-y plotter.*

**CALCULATION OF MOMENTS**

Moments of the curve may be calculated from the recorded curve if the downslope is approximated in some fashion to exclude recirculation. The Hamilton extrapolation or some model, such as the lagged normal density curve, may be used (the difference is real, but slight).

The first moment is the mean transit time:

$$t = \int_{0}^{\infty} t \cdot C(t) \, dt$$

(5)

The higher moments are calculated by using $t$ as the centroid:

$$\frac{1}{A} \int_{0}^{\infty} (t - t)^n \cdot C(t) \, dt = \pi_n = \text{variance}$$

(6)

The general equation for the $n^{th}$ moment is:

$$\frac{1}{A} \int_{0}^{\infty} (t - t)^n \cdot C(t) \, dt = \pi_n = (\pi_t)^{n/2} \beta_{n-2}$$

(7)

in which $A$ is the area, $\int_{0}^{\infty} C(t) \, dt$, of the curve, and $\beta_{n-2}$ is a family of parameters expressing the shape of the distribution curve ($\beta_1$ measures the skewness and $\beta_2$, the flatness or kurtosis). For a normal density curve, $\beta_1$ is zero and $\beta_2$ is 3.0.

**Results**

Wide variation in the spread of recorded dilution curves was obtained by injecting at sites distant (superior vena cava) and close (aorta) to the sampling sites and by infusing ATP to produce large changes in flow in the leg and, secondarily, moderate changes in cardiac output. The result was that the curves used for analysis in this paper represented mean transit times from injection site to recording site ranging from 3 to 34 seconds. The difference between the mean transit times of paired femoral and dorsalis pedis curves is

---

*Calcomp model 565 made by California Computer Products, Downey, California.
the average time for the indicator to travel between these sites. On the basis that the volume of the arterial system in the leg is little affected by flow rate, the range of mean transit time differences, from 2.1 to 16.4 seconds, indicates that the fastest flow rate was eight times the slowest. When there was no ATP infusion, the average mean transit time difference was 10 to 12 seconds, while external iliac artery flow rates obtained at these times (by a method using constant-rate dye injection into the external iliac artery via the catheter numbered 4 under Methods) were 350 to 500 ml/min. The highest external iliac artery flow rates obtained during ATP infusion were greater than 3,000 ml/min.

**MODEL FITTED TO RECORDED CURVES**

One hundred eighteen dilution curves recorded from five subjects were fitted with the lagged normal density curve. On each of the recorded curves, the appearance time, $t_a$; the time constant of the downslope, $T_d$; and the first and second moments, $I_1$ and $I_2$, were calculated. The model was found to fit not only the broad dye curves produced by injection into the superior vena cava but also the sharply peaked curves produced by aortic injection. Because there were no significant differences, data from the five subjects were combined for consideration.

Figure 4 illustrates the relationship between representative curves recorded after injection of dye into the superior vena cava and the matching model. The average coefficient of variation for 60 curves was 0.043 (standard error of mean = 0.002).

Figure 5 shows the model fitted to curves recorded after dye injection into the aorta. The match was poorer in most instances (co-
coefficients of variation averaged $0.069 \pm 0.004$), the model often departing from the recorded curve at the end of the downslope and particularly with the curves recorded from the femoral artery. These curves, which usually return to the base line before recirculation appears, are very short and are especially sensitive to the influences of dispersion at the injection site and of slurring by the sampling system.

When two slugs of dye are injected a few seconds apart into the thoracic aorta, the curve recorded at the femoral artery always reveals two distinct peaks while at the dorsalis pedis the two peaks may or may not be slurred together. The model is still applicable (fig. 6). To fit such a curve, the model is generated twice, the amplitude of the components being in proportion to the amount of dye in each injection, and with values of $t_c$ differing by the time between injections, the two similarly shaped components (having the same $\sigma$ and $\tau$) are summed. The application of the model to these curves involves the same assumptions regarding constancy and stationarity of flow as does application to the simpler curves and, therefore, provides a more critical test of the model and of the stability of the physiologic state of the subject.

**RELATIONSHIPS BETWEEN PARAMETERS OF THE MODEL AND THE MEAN TRANSIT TIME**

The data indicate that the spread of the dye curves is linearly related to mean transit time ($t$) and also that the shape of the curves is almost constant; if $t$ is known, $\sigma$ and $\tau$ may be estimated approximately. Figure 7 shows $\sigma$ and $\tau$ to be related linearly to $t$. The right panel shows the relationship between $\sigma$ and $\tau$ (average $\sigma/\tau = 0.44$), indicating the curve shape to be nearly constant. This and the fact that the square root of the variance, $(\sigma^2 + \tau^2)^{1/2}$ or $\sigma \tau$, was proportional to $t$ (fig. 8) provide the

![Figure 7](http://circres.ahajournals.org/)

**FIGURE 7**

Parameters of the model simulating recorded dye curves. Left and center panels: the linear relationships (see table 1) between $\sigma$ or $\tau$ and the mean transit time show that the temporal dispersion of indicator is inversely proportional to the average velocity of the blood between the injection and sampling sites. Right panel: the correlation of $\sigma$ and $\tau$ indicates that the shape of the curves is fairly constant. In the left and middle panels the points for curves following SVC injection (open triangles for curves sampled at the femoral arteries, closed triangles for those from the dorsalis pedis arteries) are higher than those for aortic injections (plus signs for curves sampled at the femoral arteries, X's for those from the dorsalis pedis arteries) but the slopes of the regression equations (table 1) for the two groups are not significantly different. The positive intercepts indicate that dispersion in the central circulation is greater than in a peripheral artery. In these and subsequent graphs the length of the vertical line through the average point is two standard deviations. The correlation coefficient is $r$. 

*Circulation Research, Vol. XVIII, April 1966*
basis for the linear relationships of $\sigma$ and $\tau$ with $t$.

The regression lines for $\sigma$ and $\tau$ with $t$ do not pass through the origin but have positive ordinate intercepts. The regression lines calculated for the data concerning each injection site (table 1) show $\sigma$ and $\tau$ to be greater for curves recorded after injection into the superior vena cava than for those following aortic injection. The regression lines were approximately parallel but the intercepts differed. Since the magnitude of the intercepts is dependent on the dispersion occurring upstream from the femoral sampling site, and the magnitude of the slope is proportional to the dispersion occurring between the two sampling sites, two inferences may be drawn.

1. Since the intercepts are larger for curves recorded after injection into the superior vena cava than for those recorded after injection into the aorta, it follows that dispersion is proportionately greater during passage through the heart and lungs than through the aorta. 2. Since the slopes are not statistically different for the two injection sites, it may be concluded that either the injections cause no reactive error in the arterial system of the leg or whatever reactive error exists is the same for the two injection sites. These inferences cannot be based on the ratios $\sigma/t$ or $\tau/t$ (table 2) but the fact that $\sigma/t$ and $\tau/t$ are smaller for curves from the dorsalis pedis artery than for curves from the femoral artery does indicate that
CIRCULATORY DILUTION MODEL

**TABLE 1**

<table>
<thead>
<tr>
<th>Injection into superior vena cava*</th>
<th>Injection into aorta†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation</td>
<td>Equation</td>
</tr>
<tr>
<td>( \sigma = 0.44 + 0.0695t )</td>
<td>( \sigma = 0.10 + 0.0703t )</td>
</tr>
<tr>
<td>SD</td>
<td>0.23</td>
</tr>
<tr>
<td>( \tau = 1.03 + 0.141t )</td>
<td>( \tau = 0.48 + 0.151t )</td>
</tr>
<tr>
<td>SD</td>
<td>0.51</td>
</tr>
<tr>
<td>( \tau^2 = 0.37 + 0.185t )</td>
<td>( \tau^2 = 0.36 + 0.177t )</td>
</tr>
<tr>
<td>SD</td>
<td>0.84</td>
</tr>
<tr>
<td>( (\hat{t} - \hat{t}_a) = 1.77 + 0.290t )</td>
<td>( (\hat{t} - \hat{t}_a) = 1.04 + 0.263t )</td>
</tr>
<tr>
<td>SD</td>
<td>0.98</td>
</tr>
<tr>
<td>( t_a = -3.26 + 0.777t )</td>
<td>( t_a = -1.25 + 0.759t )</td>
</tr>
<tr>
<td>SD</td>
<td>0.98</td>
</tr>
<tr>
<td>( t_a = 0.23 )</td>
<td>( t_a = 0.13 )</td>
</tr>
<tr>
<td>SD</td>
<td>0.51</td>
</tr>
<tr>
<td>( \tau^2 = 0.84 )</td>
<td>( \tau^2 = 0.36 )</td>
</tr>
<tr>
<td>SD</td>
<td>0.65</td>
</tr>
<tr>
<td>( (\hat{t} - \hat{t}_a) = 1.77 + 0.290t )</td>
<td>( (\hat{t} - \hat{t}_a) = 1.04 + 0.263t )</td>
</tr>
<tr>
<td>SD</td>
<td>0.98</td>
</tr>
<tr>
<td>( t_a = -3.26 + 0.777t )</td>
<td>( t_a = -1.25 + 0.759t )</td>
</tr>
<tr>
<td>SD</td>
<td>0.98</td>
</tr>
</tbody>
</table>

*Except for \( \tau \), equations are based on 60 points.
†Equations are based on 58 points.
‡\( \tau \) is the coefficient of correlation.

Peripheral arterial dispersion is less than the sum of dispersion at the injection site and dispersion in the central circulation.

**RELATIONSHIPS BETWEEN NONPARAMETRIC MEASURES OF THE SPREAD AND MEAN TRANSIT TIME**

Further evidence for the linear increase of spread with \( t \) is given in figure 8. The appearance time, \( t_a \), and the appearance time—mean transit time difference, \( t-t_a \), are different ways of expressing the same simple measures of the spread. Their linear relationship with \( t \) is in part dependent on the approximate constancy of shape of the curves. The variance, \( \sigma^2 \), is a calculation independent of shape. Its square root, \( \sigma \), is the standard deviation of the curve and is seen to be linearly related to \( t \). That the dispersion or spread is greater following injection into the superior vena cava than into the aorta is seen in the relationships of \( t_a \), \( t-t_a \), and \( \sigma^2 \) to \( t \) in this figure and in table 1 where the regression lines for each injection site are given. The more negative the intercept in the plot of \( t_a \) against \( t \), the greater the dispersion of indicator in the circulation proximal to the femoral sampling site. The linear relationship between \( t-t_a \) and \( \sigma^2 \) indicates again the constancy of shape of the curves.

**RELATIONSHIPS BETWEEN MODEL PARAMETERS AND VALUES OBTAINED FROM THE RECORDED CURVES**

Figure 9 provides more information on the close relationships between the parameters of the spread of the lagged normal density curve, \( \sigma \) and \( \tau \), and the spread of the recorded curves as given by \( t-t_a \) and \( \sigma^2 \). The linear relationships are expected from the data of figures 7 and 8. Because of the close correlations and the fact that \( \sigma \) and \( \tau \) provide a complete description of the shape of the curve, it is apparent that \( \sigma \) and \( \tau \) can be more useful in describing the data than \( t-t_a \) and \( \sigma^2 \), which provide only a partial description.

Figure 10 relates parameters of the model to standard measurements made on the recorded curves. The model almost always had a slightly earlier appearance time and first portion of the upslope than did the recorded curve (figs. 4, 5, and 6). The ratios of theoretical to recorded appearance times averaged 0.94 ± 0.005. \( T_D \) is the time constant of an exponential curve fitted to that portion of the downslope between 70 and 30% of the peak concentration, \( C_p \); the ratio of \( T \) to \( T_D \) was 0.98. Thus, \( \sigma \) had very little influence on the downslope in this region. The lagged normal density curve decreases to zero slightly faster than does the Hamilton extrapolation.

The relationship between the mean transit time of the model, \( \tau + t_a \), and the calculated (see equation 5) mean transit time, \( \hat{t} \), showed good agreement; the relationship between the square root of the variance of the model, \( (\sigma^2 + \tau^2)^{1/2} \), and the square root of the variance, \( \sigma \), calculated (see equation 6) from the recorded curve would fall on the line of identity if the model fitted the curves exactly. However, the moments of the model are greater than the
The experiments of Allen and Taylor on dispersion in water mains, of Taylor on dispersion in smooth and rough pipes, and of Hull and Kent on dispersion in oil pipe lines indicate that it is appropriate to consider indicator dispersion in flowing fluids as a probability distribution of transit times. The most straightforward approach is to examine the dilution curve itself as Stephenson, Meier and Zierler, Korner, and others have done. The information obtainable may be phrased in terms of the area, of the time of certain points of the curve (the appearance time, $t_a$, and the peak, $t_p$), and of the first few moments (mean transit time, variance, skewness, kurtosis). Fruitful attempts have been made to reduce the number of parameters to a minimum by the use of specific mathematical models which can be fitted to the recorded curve. The random walk, the log normal curve, a gamma variate equation, a triple exponential model, a simple velocity probability model, and a variable path-length probability model have been considered. Any such model may be criticized on the basis that it does not completely represent the physical situation, and, when the components of a model have extrapolated too far, both theoretical objections and experimentally documented contradicting evidence have appeared.

Another approach has been to consider various laminar flow models. Only the generalized approach of González-Fernández and extensions of detailed and mathematically difficult approaches such as those of McDonald and Streeter et al. seem appropriate to circulatory studies.

**Discussion**

The lagged normal density curve is a description of recorded dye curves.
probability model. It has the virtue of relative simplicity but is certainly not unique. Its particular virtue in this study is one common to any useful model: it provides a brief and fairly accurate description of recorded dye dilution curves of widely varying shape. In using it, high-frequency information concerning the details of the flow during each cardiac cycle is lost. The model is appropriate only when the cardiac cycle is short compared to (1) the mean transit time between the injection and sampling sites and (2) the passage time of the bolus of dye past a sampling site. These same limitations apply to the classical methods of estimating flow from a dye curve. The shape of the model is expressed completely by \( \sigma \) and \( \tau \); the area, by its amplitude factor, \( m/Q \); the mean transit time, by \( \tau + t_0 \); and the variance, by \( \sigma^2 + \tau^2 \). Thus, it is probably easier to relate this model to terms with which most workers are already familiar than to so relate models such as the random walk,\(^5\) the log normal curve,\(^20\) or the mixing chamber model.\(^20\)

The choice of the model was based in part on physical analogy (which is not completely appropriate for blood flowing in the vascular system) and in part because this model describes transfer functions in the arterial system.\(^7\) But the lagged normal density curve does not represent a physical system; such representation would require a much more complex model. The dispersion defined by \( \sigma \) and \( \tau \) defines intra-arterial plus catheter dispersion when the injection is made into the aorta; this might be defined more realistically by serial combinations of different random walk equations if flow were turbulent. However, the model also describes the distribution of transit times when the indicator passes through the pulmonary capillary bed. There is no apparent physiologic reason for there being any particular distribution of path lengths through the lung. The distribution could be multipeaked or skewed to the

---

*Circulation Research, Vol. XVIII, April 1966*
FIGURE 10

Relationships between recorded curves and the model. Left upper panel: the appearance time for the models fitted to the curves (t_a, Model) were less than the recorded ones, t_a, indicating that the earliest recognized indicator had a lower velocity than the equation implied. Right upper panel: the values of r were only slightly smaller than the time constants, T, showing that r had little effect on the decay slope. Left lower panel: the values of T were only slightly smaller than the time constants, T, showing that r had little effect on the decay slope. Right lower panel: The square roots of the second moments of models, (a^2 + r^2)^1/2, were almost 2% larger than those of the recorded curves, (a^2 + r^2)^1/2.

It is apparent from the ratios of t_a/t and from the shapes of the curves that, in the arteries, the velocity profile is very blunt compared to a parabola. It appears also that this flow profile and the rate of spatial dispersion of indicator did not vary significantly over the several-fold range of flows observed in the external iliac artery, because the relationships of the various parameters to t were linear (table 1 and figs. 7 and 8). The lack of any transition from laminar to turbulent flow is in accord with McDonald’s concept that blood flow is “disturbed flow,” neither laminar nor turbulent.

The variation in curve shape obtainable with the lagged normal density curve can be obtained with the random walk and the log normal models only if considerable adjustments in time origin, time-scale factors, and randomizing factors are made. Because
of the necessity for such artifices the theoretical basis for these equations is invalidated, and they must be classed with the lagged normal density curve and the gamma variate as equations that merely describe the shape of the curve.

The excellence of the lagged normal density curve as a description of recorded curves is expressed not only by the coefficients of variation but also by the relationships shown in figure 10 (these are close to the line of identity). However, this also suggests that one should consider describing the dye curve in terms of its first few moments rather than by using a parametric model. This would be quite useful if moments higher than the third or fourth conveyed so little information that they could be ignored.

**Dispersion in Specific Segments of the Circulation**

The data of figures 8 and 9 and of table 1 are concerned primarily with the dispersion between the two sampling sites. This is expressed in the slopes of the relationships, which are very similar to those for the transfer functions between the femoral and dorsalis pedis arteries.44

Less precise, but still useful, information concerning the dispersion between the injection site and the femoral artery is given by the intercept values. The greater the intercept values for \( \sigma, \tau, f - t_0, \) or \( \pi_c \) plotted against \( f \) and the smaller the intercept for \( t_s \) versus \( f \), the greater the dispersion occurring in this segment (see figs. 8 and 9 and table 1). A similar type of information is given by the ratios to \( f \) for curves sampled at the femoral artery (first and third columns of data in table 2). Both the intercept values and the ratios are functions of the dispersion due to three types of events: (1) dispersion at the injection site due to the energy of the injection and the disturbance in flow at the injection site, (2) dispersion within the sampling system, and (3) dispersion in the circulation.

A sudden injection of dye solution through an end- or side-holed catheter results in immediate dispersion of dye some distance in all directions. The spread of this bolus is also dependent on the duration of injection because, during a 0.5-second injection, aortic blood may flow more than 10 cm. If the flow pattern is laminated and is undisturbed by the injection, dye movement will not likely represent blood movement. Even with a forceful injection which causes mixing, the labelling at the injection site is likely to be neither cross sectional nor flow tagging as defined by González-Fernández.48 The labelling is probably not uniform (with respect to flow or volume) until there has been significant downstream movement of the bolus. The aortic injection probably produced more dispersion: the energy of injection was \( 1 \times 10^6 \) g cm\(^2\) sec\(^{-2}\) and injection was at high velocity through a small catheter pointed upstream against the rapidly flowing aortic blood. The superior vena caval injection was at low velocity through a larger catheter pointed in a downstream direction in slowly flowing blood.

The dispersion due to the sampling system consists of a delay time plus a slurring of the concentration-time curve as it passes through the sampling apparatus. This may be characterized fairly well12, 45, 46 and a correction can be made for the distortion by a variety of methods.40-49 Certain of the curves recorded during these experiments have been corrected either by using a method similar to that of González-Fernández and co-workers47 (by using the inverse of the convolution integral) or by using exponential lead circuits in an analog computer.7 The same model, the lagged normal density curve, has been found to fit the corrected curves even though they are more sharply peaked and less slurred out.7 Although the femoral sampling system was more complex, its dynamic response to a step input was only slightly slower than that for the dorsalis pedis sampling system (fig. 2). The difference between the mean transit times of the sampling systems was 0.25 second and was considered to be small enough to be ignored in the analysis.

The dispersion in the segment of the cir-
calculation between the sampling sites from which the paired curves are recorded is indicated by the slopes of the regression lines of table 1. The values of the slopes should not be affected by the dispersion at the injection site but would be influenced by any significant difference between the sampling systems.

The intercept values are probably little influenced by the sampling system, for the degree of dispersion in the tubing is similar to that produced by the vascular system, and the mean transit time of the sampling system is a significant proportion of \( t \) of the recorded curves only for those recorded at the femoral artery after aortic injections. The appearance time:mean transit time ratios found by Cheesman\(^4\) for catheter sampling systems were very similar to those usually observed in the human or the canine circulation and to those found in this study (table 2).

The ratios shown in table 2 may therefore be considered primarily as functions of dispersion at the injection site plus dispersion in the circulation between injection and sampling sites. The dispersion upstream to the femoral artery is always greater than that downstream to it because the ratios \((\sigma/t, \tau/t, \pi/\pi^t/t\) and \([t-t_a]/t\) are all less for curves recorded at the dorsalis pedis artery than for those recorded at the femoral artery.

The dispersion subsequent to superior vena caval injections is greater than that after aortic injections. The evidence is that the intercept values are higher (regression lines of table 1) for aortic injections. The positive intercept for aortic injections indicates that dispersion at injection site plus dispersion in the aorta due to the turbulent flow, especially at the bifurcation,\(^4\) is greater than dispersion in the arteries of the leg.

In their figure 7, Edwards and Korner\(^2\) plotted variance against mean transit time for curves recorded from the femoral artery of dogs after injection of dye into either the inferior vena cava at the renal veins or into the pulmonary artery. Their data showed the ratio, \( \pi/\pi^t \), to be 0.2 to 0.3. In general their data indicate \( \pi/\pi^t \) to be greater and \( t_a/t \) to be smaller for curves recorded after pulmonary artery injection than for curves recorded after inferior vena caval injection. This suggests that the dispersion occurring during the traversal of the inferior vena cava is less, relative to the mean transit time, than the dispersion occurring in the heart, lungs, and aorta. In other circumstances this may not be so, for the streamlining of flow that occurs in the inferior vena cava produces a wide range of transit times through the segment. For example, radiopaque indicators have been observed to take nearly a minute to be washed out of the inferior vena cava below the diaphragm in anesthetized dogs.

Korner,\(^2\) in his table 5, gave the regression equation:

\[
\log \pi = 3.699 - 2.432 \log \text{flow (ml/min)} + 2.020 \log \text{volume (ml)}
\]

This equation can be rewritten:

\[
\log \pi = 3.699 - 0.412 \log \text{flow} + 2.020 \log \text{volume (ml)}
\]

in which \( \pi \) is in units of minutes. At an average value for flow of 2,000 ml/min, the relationship reduces to \( \pi = 0.26 \ t \) (sec) which is quite comparable to the ratio, \( \pi/\pi^t = 0.233 \), shown in table 2 of this paper for curves recorded at the femoral artery after superior vena caval injection.

The most effective mechanism for circulatory dispersion occurs with the great diversity of path lengths and flow rates through the capillary and venous beds of the peripheral organs and tissues. It is clear from this study that there is no great difference in the dispersion of a bolus of material in the central circulation or peripheral arteries. The ratio of dispersion to transit time was largest following superior vena caval injection probably because of the diversity of path lengths and flows in the various segments of the lung and because of the mixing-chamber effects of the left atrium and left ventricle.
reason that dispersion in the aorta is greater than in the peripheral artery is not that it is more turbulent (for this would probably mean less dispersion) but that there is greater longitudinal mixing due both to the greater pulsation of flow and to eddy formation at major branches.

ASYMMETRY OF THE CONCENTRATION-TIME CURVE

If the spatial distribution of indicator particles in the bloodstream were symmetric, concentration-time curves recorded at any site must be skewed to the right (the tail prolonged) if the indicator is being dispersed during its transit.

Taylor and Hull and Kent observed that indicator concentration-time curves become more symmetric as the number of events increases the distribution tends toward normality. Therefore, with an increase in $t$, the theorem would predict a decrease in skew, kurtosis, and the ratio of $\tau$ to $\sigma$. The last relationship is $\tau/\sigma = 3.8 - 0.093 t$ ($sd = 5.1; r = 0.47$). Similar evidence is seen in figure 7 (right panel) and in the relationships of $\sigma$ and $\tau$ to $\pi^{2/6}$ (fig. 9). These data indicate the tendency for $\tau$ to form a smaller portion of the spread of the broader curves. Korner observed that the asymmetry of curves recorded at the femoral artery of dogs decreased as the injection site was changed from pulmonary artery to right ventricle to superior vena cava, i.e., as the distance travelled was increased.

Dow found the greatest asymmetry in curves recorded at the femoral artery after left ventricular injection. The reason for this may be that not only is the path length short but ventricular mixing is poor and dye may be sequestered to some extent in the apex. With complete ventricular mixing, the concentration-time curve in the ventricle would be a single exponential in step form which is highly skewed and leptokurtotic. It is probable that the ascending aortic arch has a similar effect since there is no forward flow there during diastole. Edwards and Korner observed a similar phenomenon. Curves recorded at the femoral artery were more asymmetric after right atrial injection than after caval injection. They interpreted this as due to nonuniformity of clearance from blood near the wall of the atrium.

Summary

1. Indicator dilution curves (concentration versus time) were recorded from the femoral and dorsalis pedis arteries of normal men after injections of indocyanine green into the superior vena cava or thoracic aorta. A four-parameter mathematical model, the lagged normal density curve, adequately described the form of the portion of these curves representing indicator passing by the sampling site for the first time.

2. The curves were observed to be of constant shape, the spread of the curve being approximately linearly related to the mean transit time $t$. The spread was dependent on the injection site; dispersion was shown to be greatest in the central circulation, less in the aorta, and still less in the arteries of the leg. For the latter segment, the mean transit time $t$. The spread was dependent $0.3 t$, the square root of the variance was $0.18 t$, and the parameters of the lagged normal density curve, $\sigma$ and $\tau$, were $0.09 t$ and $0.16 t$, respectively.

3. The linear relationships between parameters of the recorded curves and the mean transit times indicate that the effect of rate of flow, over a range from resting values to four to six times above resting values, has almost no influence on the dispersion. This suggests that the flow characteristics are essentially unchanged over this range. Such linear relationships always occur with laminar flow but cannot prove its existence because turbulent flow can also produce this result. The similarity of the linear relationships at low flow rates to those at high flow rates, where turbulence almost certainly is present, suggests that arterial flow is usually turbulent. Turbulence may be expected at relatively low flow rates in nonhomogeneous fluids.
driven by a pulsatile head of pressure through elastic, branched, tapering, curved tubes.

Acknowledgment

The help of Dr. Homer Warner, Department of Biophysics and Bio-engineering, Latter-Day Saints Hospital, University of Utah, Salt Lake City, was essential in the analog computer programming which led to the choosing of the circulatory model. The authors express their appreciation to their colleagues who were subjects and to those who were a part of the experimental team, Dr. H. W. Marshall, W. F. Sutterer, Lucille Cronin, Donald Hegland, Julius Zarins, and Irene Donovan. The personnel of the Mayo Clinic computer facility helped in carrying out the voluminous data analysis, and Mrs. Jean Frank and her co-workers prepared the illustrations.

References


Circulation Research, Vol. XVIII, April 1966
CIRCULATORY DILUTION MODEL


Applications of the Lagged Normal Density Curve as a Model for Arterial Dilution Curves
James B. Bassingthwaighte, Francis H. Ackerman and Earl H. Wood

Circ Res. 1966;18:398-415
doi: 10.1161/01.RES.18.4.398

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1966 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/18/4/398