Intrarenal Distribution of Blood Flow in Man

A New Analytical Method for Dye-Dilution Curves

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SUMMARY
To measure blood flow through fast and slow pathways of the kidney separately, a new method of analyzing dye-dilution curves was devised. Twenty-five patients with hypertension or renal disease were selected for study. Indocyanine green was injected into one renal artery and dye-dilution curves were recorded in blood from the ipsilateral renal vein, using a densitometer. Recirculation effect was eliminated by the curve obtained from the contralateral renal vein. For analyzing the dye-dilution curves, a new mathematical model and an iterative least squares method of fitting the curve using a digital computer were employed. Basic assumption for the model was that the transit time of each molecule of the dye through fast and slow pathways was a random variable and followed a log-normal distribution. The fast flow measured by the new method was significantly decreased in 11 patients with azotemia compared with that in 14 without azotemia, while changes in slow flow were not significant. Consequently, the ratio of the slow flow to the total flow was increased in renal failure.

Additional Indexing Words:
Blood flow of kidney Recirculation curve Log-normal distribution
Curve fitting Least squares method Azotemia

INDICATOR dye-dilution methods have been used to measure cardiac output for many years. In recent years, several studies of the renal circulation have used this technic. To investigate the intrarenal circulation, Kramer,1 2 Reubi,3 4 Nakamura,5 Ueda,6 and their co-workers attempted to measure renal cortical (or fast) and medullary (or slow) blood flows separately. Kramer and his associates measured renal cortical and medullary flows directly in dogs, while the others analyzed dye-dilution curves by the graphical method developed by Reubi’s group3 4 and estimated fast and slow blood flows indirectly. However, there have been uncertainties concerning the interpretation of the two components obtained from a dye-dilution curve by the graphical method, as suggested by Gomez and his co-workers7 and others8 9.

In the present paper, we have devised a new analytical method that uses dye-dilution curves for the separate measurement of blood flow through fast and slow pathways in the kidney. In addition, intrarenal distribution of blood flow in patients with normal and impaired renal function was estimated by the new analytical method.

Methods
Dye-dilution curves were recorded from 37 patients with hypertension or renal disease. Patients received 100 mg of pentobarbital intramuscularly and 30 mg of diphenhydramine (Benadryl) subcutaneously as premedication. After local anesthesia with lidocaine (Xylocaine),
a Kifa* green catheter of 67.4 cm and 0.90 ml in volume was inserted into a renal artery through the transfemoral route by Seldinger's technique10 under fluoroscopic guidance and a Kifa red catheter (62.0 cm in length and 0.80 ml in volume) was also inserted into the corresponding renal vein. The tip of the arterial catheter was placed in the middle portion of the renal artery, as confirmed by injections of a small amount of contrast medium through the arterial catheter. No regurgitation of contrast medium from the renal artery to the aorta was seen. An instant injection of 1.1 to 1.8 ml of 0.1% indocyanine green into

\[
F(t) = \frac{c_1}{\sqrt{2\pi} \sigma_1} e^{-\frac{1}{2} \sigma_1^2 (\log (t - t_1) - \frac{t-t_1}{\sigma_1})^2}
\]

the renal artery without flushing was carried out, and a dye-dilution curve was recorded by withdrawing blood at a constant rate of 24 ml/min from the ipsilateral renal vein through an Erma cuvette densitometer which has the linearity between recorder's deflection and changes in the concentration up to the range of the indocyanine-green concentration of 30 mg/L of blood. A few curves were recorded in each case. Then, the venous catheter was placed in the contralateral renal vein and a recirculation curve was recorded following the injection into the original renal artery of the same amount of dye.

After the recording of the dye-dilution curve, renal arteriography was performed to reconfirm the position of the catheter tip and to visualize the branching of the renal artery. The densitometer was calibrated by adding a known amount of dye to the patient's blood. To eliminate catheter delay,11,12 the transit time from the tip of the venous catheter to the cuvette was measured and the appearance time (AT) was corrected by 2.4 sec and mean transit time (MTT) by 3.9 sec.

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Clearance of paramino-hippurate (C<sub>PAH</sub>) and thiosulfate (C<sub>chlosoulfate</sub>) were measured by a single injection method,13 and maximal concentrating ability of the kidney was measured according to Fishberg's method, using Fiske's osmometer. Total renal blood flow measured by PAH clearance method was calculated from \(C_{PAH}\) and hematocrit. The total renal blood flow (RBF) measured by PAH clearance method, and the glomerular filtration rate (GFR) by (C<sub>chlosoulfate</sub>) were expressed as one half of the values for both kidneys. RBF, measured by the dye-dilution and PAH clearance methods, and GFR, measured by C<sub>chlosoulfate</sub>, were corrected to the standard body surface area of Japanese (1.48 m²).

For analyzing the dye-dilution curve, we introduced a new mathematical model. Basic assumption underlying the model was that the transit time of each molecule of the dye through the fast as well as the slow pathways was a random variable and followed a log-normal distribution, respectively. A recorded dye-dilution curve was, therefore, assumed to be a sum of two (fast and slow) log-normal curves. The expression of the curve was:

\[
F(t) = X_1 e^{-\frac{(t-\mu_1)^2}{2\sigma_1^2}} + X_2 e^{-\frac{(t-\mu_2)^2}{2\sigma_2^2}}
\]

where

\[
c_1 = c_2 e^{\sigma_1^2/2}, \\
X_1 = \frac{c_1}{\sqrt{2\pi} \sigma_1} e^{-\frac{(t-\mu_1)^2}{2\sigma_1^2}}, \\
X_2 = \frac{c_2}{\sqrt{2\pi} \sigma_2} e^{-\frac{(t-\mu_2)^2}{2\sigma_2^2}}, \\
X_3 = (\mu_2 - \mu_1)e^{\sigma_1^2/2}, \\
X_4 = t_1, \\
X_5 = t_2
\]

X1 and X5 represent maximal concentration of dye; X3 and X7, time lapse from appearance of dye to the maximal concentration; and X4 and X6, appearance time of each curve.

The concentration of the dye with respect to a dye-dilution curve at every one-third second after injection was recorded. A set of digital data thus obtained from a curve was entered on punch cards. To obtain the least squares estimates of the

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* "Kifa" Radiopaque catheter, Odman-Ledin, Sweden.
† Model EN-6, Erma Optical Works, Ltd., Tokyo, Japan.
parameters, \( X_1, X_2, \ldots \), and \( X_n \) \((c_1, c_2, \sigma_1, \sigma_2, t_1, t_2, \mu_1, \text{and} \ \mu_2)\) by an iterative method, a computer program written in FORTRAN IV computer language was prepared. A high-speed electronic computer named TOSBAC 3400-model 41* was used for the calculation. The flow diagram of our program is given in the "Appendix." It should be noted that, in our program, the AT of the slow pathway was assumed to appear after the peak concentration of the fast component. Using the estimates of the parameters and the injected dose, renal fast flow \((RFF)\), renal slow flow \((RSF)\), and total renal blood flow \((RBF)\) were calculated. MTT, and MTT\(_2\) corrected for catheter distortion,\(^{11}\) and \(VV_1\) and \(VV_2\) were also determined.

Following relationships\(^4,16\) were used for the calculation:

\[
F = \frac{1}{S_1 + S_2}, \quad F_i = \frac{S_i}{S_1 + S_2} \times F, \\
MTT_1 = (\mu_1 - t_1) e^{-\frac{x}{2}} + t_1, \\
VV_i = MTT_1 \times F_i \quad (i = 1, 2)
\]

where \(F\), \(F_i\), and \(F_2\) denote RBF, RFF, and RSF, respectively; \(I\) denotes amount of dye injected; \(S_1\) and \(S_2\), are of fast and slow components; MTT\(_1\) and MTT\(_2\), MTT of fast and slow components; and \(VV_1\) and \(VV_2\), vascular volume of fast and slow components, respectively.

**Results**

Curves obtained from nine of the 37 patients were discarded because of the inappropriate position of the catheter. Fifteen of the remaining 28 patients were nonazotemic (blood urea nitrogen \([\text{BUN}]\) less than 25 \(\text{mg}\%)\) and 13 were azotemic \((\text{BUN} \text{more than 30 mg}\%)\). Among the 15 nonazotemic subjects were nine with essential hypertension, three with chronic glomerulonephritis, two with diabetes mellitus, and one with mitral stenosis. The 13 azotemic patients included nine with chronic glomerulonephritis, two with hypertensive nephrosclerosis, one with subacute glomerulonephritis, and one with collagen disease. Curves from 25 of the 28 patients could be separated into two blood flow components by our analytical method. Separate measurements of renal blood flow failed in three cases from unknown cause.

Figure 1 shows an observed curve and the recirculation wave. The recirculation wave was subtracted from the original curve and the part of the curve from which recirculation was eliminated was figured in dotted curve. The late part of the downslope of this curve partially showed a slightly slow slope. The amounts of injected dye into a renal artery less than 0.2 to 0.3 ml did not make any recirculation wave in our cases.

Examples of normal and azotemic dye-dilution curves fitted by our method are shown in figure 2. Excellent fits were obtained for each curve. The width of the dye-dilution curves of azotemics \((\text{fig. 2B})\) was broader than that of nonazotemic patients \((\text{fig. 2A})\), and the area of the slow components of the former was larger than that of the latter. The estimated values of each of 25 cases are shown in tables 1 and 2.

The mean total renal blood flow \((RBF)\) in patients without azotemia was 375 ± 95

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*Tokyo Shibaura Electric Company, Ltd., Tokyo, Japan.

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F(t)  
mglL

recorded curve  
fast and slow components  
combined curve

Figure 2

Dye-dilution curves analyzed by our method. (A) Curve obtained from nonazotemic patient. (B) Curve from azotemic patient. In each curve, first large curve shown in bold solid line indicates fast component and second small one indicates slow component. Combined curve (dotted line) of fast and slow components calculated by our method is equal to observed curve (fine solid line).

(mean ± sd) ml/min (for one kidney) and that of azotemic patients was 214 ± 66 ml/min. The mean RFF in nonazotemias was 304 ± 89 ml/min and 158 ± 46 ml/min in the azotemias indicating a significant decrease of RFF in the latter (P < 0.01). The mean RSF was 71 ± 19 ml/min in nonazotemias and 56 ± 24 ml/min in azotemias with no statistical difference between the two groups (tables 1 and 2). These results suggest that the decrease of RBF in azotemias was mainly due to a decrease of the fast flow component, without a corresponding decrease of the slow flow component. Therefore, the ratio of the slow flow to the total flow in azotemias was higher than that in nonazotemias (19.5 ± 5.2% in nonazotemias and 25.5 ± 4.7% in azotemias). The difference between the two groups was significant (P < 0.01).

MTT through the slow pathway was significantly delayed (P < 0.05) in azotemias, while the change of MTT through the fast pathway between two groups was statistically insignificant. The total vascular volume (VV) was 45 ± 10 ml in nonazotemias and 38 ± 14 ml in azotemias. Vascular volume of fast flow component (VV1) was reduced in azotemias (P < 0.05), but the difference of vascular volume of slow flow component (VV2) was insignificant between the two groups. The percentage of vascular volume of slow component to the total one was higher in azotemias (P < 0.05).

A comparison of the values for RBF as measured by dye-dilution method and PAH clearance technic is shown in figure 3, and a good correlation was obtained in the two methods. A positive correlation between RFF by
### Table 1

Intrarenal Hemodynamics in 14 Nonazotemias

| Patient | Diagnosis | Total (ml/min) | Fast (ml/min) | Slow (ml/min) | Ratio of slow to total (%) | Fast (sec) | Slow (sec) | MTT Fast (sec) | MTT Slow (sec) | Total Vascular Volume (ml) | Slow Vascular Volume (ml) | Ratio of slow to total (%) |
|---------|-----------|----------------|---------------|---------------|-----------------------------|============|------------|---------------|---------------|-----------------------------|---------------------------|---------------------------|
| H.I.    | EHT       | 256            | 187           | 69            | 27.0                        | 0.24       | 6.59       | 3.56          | 19.01         | 33                          | 22                        | 66.7                      |
| T.Y.    | CGN       | 302            | 241           | 61            | 20.2                        | 2.27       | 7.34       | 4.63          | 30.53         | 48                          | 29                        | 60.4                      |
| S.K.    | DM        | 597            | 526           | 71            | 11.9                        | 2.25       | 8.30       | 4.64          | 11.89         | 55                          | 14                        | 25.5                      |
| Y.H.    | MS        | 224            | 198           | 26            | 11.6                        | 4.25       | 12.88      | 7.66          | 24.21         | 35                          | 10                        | 28.6                      |
| M.M.    | EHT       | 266            | 197           | 69            | 25.9                        | 1.53       | 7.04       | 4.18          | 24.15         | 41                          | 27                        | 65.9                      |
| K.H.    | DM        | 399            | 316           | 83            | 20.8                        | 1.40       | 5.86       | 3.56          | 17.40         | 41                          | 22                        | 53.7                      |
| T.K.    | EHT       | 396            | 308           | 88            | 22.2                        | 2.06       | 6.97       | 4.11          | 13.35         | 40                          | 19                        | 47.5                      |
| A.N.    | EHT       | 384            | 314           | 70            | 18.2                        | 1.40       | 6.28       | 3.88          | 16.47         | 39                          | 19                        | 48.7                      |
| K.T.    | EHT       | 437            | 385           | 52            | 11.9                        | 2.93       | 8.30       | 5.18          | 17.09         | 48                          | 15                        | 31.3                      |
| N.Z.    | EHT       | 408            | 354           | 54            | 13.2                        | 2.91       | 7.72       | 5.02          | 14.48         | 43                          | 13                        | 30.2                      |
| Y.S.    | EHT       | 298            | 221           | 77            | 25.8                        | 1.32       | 5.16       | 2.84          | 16.02         | 31                          | 21                        | 67.7                      |
| M.S.    | EHT       | 457            | 353           | 104           | 22.8                        | 1.98       | 7.09       | 5.36          | 14.82         | 58                          | 26                        | 44.8                      |
| M.H.    | CGN       | 386            | 300           | 86            | 22.3                        | 2.08       | 7.69       | 4.56          | 16.50         | 45                          | 22                        | 48.9                      |
| N.S.    | CGN       | 442            | 355           | 87            | 19.7                        | 4.59       | 9.43       | 7.73          | 15.22         | 68                          | 22                        | 32.4                      |
| Mean    |           | 375            | 304           | 71            | 19.5                        | 2.23       | 7.62       | 4.78          | 17.94         | 45                          | 20                        | 46.6                      |

Abbreviations: EHT = essential hypertension; CGN = chronic glomerulonephritis; DM = diabetes mellitus; MS = mitral stenosis.
Intrarenal Hemodynamics in 11 Azotemics

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| Mean    |           | 214           | 158          | 56           | 25.5                     | 2.87           | 8.94| 6.01           | 26.36 | 38  | 23  | 58.7       |

| ±SD     | ±SD       | ±SD           | ±SD          | ±SD          | ±SD                      | ±SD            | ±SD | ±SD           | ±SD   |
|---------|----------|---------------|--------------|-------------|-------------------------|----------------|-----|----------------|
| 66      | 46       | 24            | 4.7          | 1.29        | 2.32                    | 1.87           | 9.45| 14            | 11     |

Abbreviations: HNS = hypertensive nephrosclerosis; CGN = chronic glomerulonephritis; SGN = subacute glomerulonephritis; CD = collagen disease.

Discussion

To measure cortical and medullary blood flows separately by the dye-dilution method, it is essential to record cortical and medullary outflow curves separately but simultaneously. However, it is impossible to obtain such curves because of the anatomic basis of the renal vasculature. Therefore, Reith and associates' used a logarithmic extrapolation of the Stewart-Hamilton principle to determine the ratio of the slow flow to the total flow ( = 0.54, P < 0.05, fig. 5).

Our method and CFR measured by sodium thiosulfate clearance were also established (fig. 4). Significant reverse correlation was observed between the maximal urinary osmolality and the ratio of the slow flow to the total flow.

Fig. 3

Comparison of total renal blood flow (one kidney) determined by our dye-dilution method and by the PAH clearance method. A good correlation is shown.

Fig. 4

PAH Clearance Method

Our dye-dilution Method

Table 2

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Figure 4
Correlation between renal fast flow (RFF) analyzed by our method and glomerular filtration rate (GFR) measured by cysteine sulfinic acid.

\[ r = 0.77 \quad (p < 0.01) \]

Figure 5
Comparison of maximal urinary osmolality and the ratio of the slow flow (RSF) to the total blood flow. Significant reverse correlation was observed between two.

\[ r = -0.54 \quad (p < 0.05) \]

Figure 6
Comparison of the medullary curve (indicated by the solid line) from the experiment by Meier and associates, and the curve fitted for a log-normal (indicated by the dotted line), using the method of least squares. This illustrates that an excellent fit can be obtained by the least squares method. (Ordinate calibration was made by us arbitrarily.) The same excellent fitting was obtained in the cortical curve. (Figure omitted.)

only one part of the slow flow might be calculated as the total slow flow. Reubi's method for eliminating recirculation might be improper theoretically, as he did not record the isolated recirculation wave. The dye-dilution curve seen in azotemics was broader, since the entire curve included the upper slope and the downslope, than that of nonazotemics and the changes of renal hemodynamics under various conditions might be seen through the whole part of the dye-dilution curve. Therefore, a new analytical method was desired by which the downslope of a dye-dilution curve and also the ascending slope could be evaluated for the analysis of two flows.

Our analytical method was devised from the assumptions that the transit time of each molecule of the dye through the fast as well as the slow pathways was a random variable and followed a log-normal distribution and that the appearance time of the slow component appeared after the peak concentration of the fast component. The reasons that the log-
normal distribution was taken for the mathematical model were as follows: (1) Wise\(^\text{14}\) described that some of the dye-dilution curves which Deetjen\(^\text{2}\) and Meier\(^\text{19}\) and their associates recorded directly in the cortex and the medulla appeared to be log-normal. (2) An excellent fit was obtained by us for the medullary and cortical curves recorded by Meier and associates\(^\text{19}\) to one log-normal distribution (fig. 6). (3) It was a reasonable possibility that natural phenomenon such as a dye-dilution curve would have a log-normal distribution.\(^\text{14}\) Medullary MTT was longer than cortical MTT,\(^\text{1, 20}\) but the medullary flow directly recorded in some positions of medulla might start from the nearly equal time of cortical AT, according to Meier and co-workers\(^\text{19}\) experiments. Even if the medullary flow should start at nearly the same time as the cortical AT, the earlier part of the medullary flow might be too small to be detected when compared with that of cortical. We, therefore, assumed that the blood flow through the slow pathway started after the peak concentration of the dye-dilution curve.

The merits of our new analytical method are as follows: (1) All parts (up and down slope) of the dye-dilution curve are estimated mathematically for analysis. (2) Recirculation waves which are recorded separately are subtracted from original dye-dilution curves. This technic is valid when both kidneys have equal transit times. The need for a computer is the main disadvantage of our method.

Reubi claimed that the failure of separate measurements of RBF was due to the ascending part of the slow component falling within the main peak. (Personal communication from F. C. Reubi.) Reubi’s method can analyze the separate blood flows when the AT of the slow component appears at a late part of descending slope, but our method can analyze them even though the AT of the slow component appears at the early part of descending slope.

The reproducibility of our method was 7.6 ± 6.5% in RBF, 7.6 ± 6.6% in RFF, and 17.3 ± 12.9% in RSF. These values might mean that flows were changing about 20% time as reported by Effros and associates.\(^\text{21}\)

Close linear correlation existed between RBFs measured by the dye-dilution method and those measured by the PAH clearance technic; this correlation indicates the validity of the measurement of RBF by the dye-dilution method. The RBFs obtained by the dye-dilution method were higher than those obtained by the PAH clearance method by 70 ml/min according to the regression curve. Since PAH is not entirely extracted from the kidney, this difference appeared to represent blood flow through the nonfunctional part of the kidney. This means that RBF obtained by dye-dilution method shows the true renal blood flow. A good correlation between GFR obtained by thiosulfate clearance and RFF measured by our dye-dilution method was established. Since most of the cortical blood flow goes through cortical glomeruli (85% of all glomeruli), the data presented above seem to indicate that the fast component estimated by our method represents, or is very closely related to, the cortical component. The slow component likely represents the medullary component.

Fast blood flow (one kidney) estimated by this new method ranged from 187 to 526 ml/min and averaged 304 ± 89 ml/min in nonazotemias, and slow blood flow ranged from 26 to 104 ml/min and averaged 71 ± 19 ml/min. The ratio of mean slow flow to mean total flow was 19.5 ± 5.2%, which was nearly equal to the 19 to 25% obtained with the thermal dilution method by Sadler and Tuttle.\(^\text{22}\) Our values were larger than those of Reubi’s group,\(^\text{4}\) probably for the above-mentioned reasons and because the areas of fast and slow components were calculated as the integration of the log-normal equation from AT to infinity by our method.

The ratio of slow to total blood flow was 25.5 ± 4.7% in azotemias, a significant increase compared with that of nonazotemias (19.5 ± 5.2%; \(P < 0.01\)). Reubi and co-workers\(^\text{4}\) found that the flow ratio of slow to fast component was not altered significantly in chronic renal disease, but Nakamura and associates,\(^\text{5}\) using an ascorbic acid-dilution method, found an
increased ratio. Our results in this study confirm those of Nakamura's group. Bruchhausen calculated a cortex to medulla quotient based on separate determinations of the weight of the renal cortex and medulla of healthy and vascular sclerotic kidneys, and this quotient in vascular sclerotic kidneys was smaller than that from healthy man. Takeuchi reported from a study of renal vasculature that in nephrosclerosis and contracted kidney due to chronic glomerulonephritis, relatively well-preserved medullary vessels with increased vasa rectae were observed, in spite of extensive involvement in the cortical vasculature. These reports are consistent with the increased ratio of the slow flow to the total flow in azotemics. In renal failure, maximal urinary osmolality decreased as the ratio of slow flow to total flow increased. This supports the view that the impaired concentrating ability of the kidney in renal failure is due partially to the excessive washout of solutes from the medulla by the relatively increased blood flow through the countercurrent exchanger system.

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Appendix

Flow Diagram of Analysis of Dye-Dilution Curves

This flow diagram shows an iterative least squares procedure for the analysis of a dye-dilution curve. The expression of the curve is:

\[
F(T) = X(1)e^{X(3)} - X(2)\left(\frac{\log\frac{T - X(4)}{X(3)}}{X(6)}\right)^2 + X(5)e^{X(7)}\left(\frac{\log\frac{T - X(8)}{X(7)}}{X(8)}\right)^2.
\]

In this flow diagram subscripts have the following ranges: \( J_1 = 1, 2, \ldots, 8 \), \( J_2 = 1, 2, \ldots, 8 \), \( K = 1, 2, \ldots, N \), \( J = 1, 2, \ldots, 8 \), \( J_I = 1, 2, \ldots, 8 \).

Input: Read MAM where MAM is the total number of sets of input data.

Set \( II = 1 \) for initialization. (\( II = 1, 2, \ldots, \) MAM)

Input: Read NDATA, N, Y(K) and TSTAT, where NDATA is the file number of the case, N: total number of measurements in a set of data, Y(K): K-th measurement of dye concentration and TSTAT = 3* (actual time (T(1)) of the first measurement) - 1.

Set \( LI = 5 \). (\( LI = 5, 6, 7 \))
Set LMI = 1. (LMI = 1, 2, 3)

Set NITR = 0 where NITR is no. of iterative adjustment for least squares.

Set NH Alf = 0, where NH Alf is no. of "half."

Subroutine: Call subroutine SUB4, which determines the initial values (nine cases are considered) for 8 parameters X(1), · · · , X(8) of two Stow’s equations in order to obtain the least squares estimates of them by an iterative adjustment.

\[
X(1) = \max_K \{Y(K)\} \quad (K = 1, 2, \ldots, N)
\]

\[
X(3) = \text{TH} - X(4) \quad \text{TH: time indicating the peak concentration of } Y(K).
\]

\[
X(2) = [\log \left(\frac{X(1)}{H1}\right)] / [\log \left(\frac{(T1 - X(4))/X(3)}{X(3)}\right)^2]
\]

where T1 = TH + 5 (sec) and H1 = (the concentration at time T1) * (LI/10).

\[
X(5) = \max_K \{Y(K) - T1F(K)\} \quad (K = K_0 + 1, K_0 + 2, \ldots, N - 1)
\]

\[
X(7) = \text{THH} - X(8) \quad \text{THH: time indicating max } \{Y(K) - T1F(K)\}.
\]

\[
X(6) = [\log \left(\frac{X(5)}{H2}\right)] / [\log \left(\frac{(T2 - X(8))/X(7))}{X(7)}\right]^2]
\]

where T2 = T(N) and H2 = [Y(N) - T1F(N)].
Is $X(J) + B303B(J) > 0$?  
Yes: $X(J) = X(J) + B303B(J)$  
No: Reduce all corrections to half.  
$B303B(JJ) = B303B(JJ) \times 0.5$  
$NHALF = NHALF + 1$

Is $X6LO \leq X(6) + B303B(6) \leq X6UP$?  
where in the case $NITR \leq 10$,  
$X6LO = X(6) \times (1 - NITR/20)$  
and $X6UP = X(6) \times (1 + NITR/20)$  
and in the case $NITR > 10$,  
$X6LO = X(6) \times 0.7$ and $X6UP = X(6) \times 1.4$

Yes: $B303B(JJ) = B303B(JJ) \times 0.5$  
$NHALF = NHALF + 1$

Is $TH - 1/3 < X(8) + B303B(8) \leq 20$?  
Yes:  
No: $B303B(JJ) = B303B(JJ) \times 0.5$  
$NHALF = NHALF + 1$

Is $NHALF \leq 30$?  
Yes:  
No:  
Is $NHALF = 0$?  
No: Is $NITR = 40$?  
No: $NITR = NITR + 1$

Yes:  
Yes:  
Yes:  
Yes:
\[ \text{RAT}(J) = \left| \frac{B3033(J)}{X(J)} \right| : \text{relative magnitude to be corrected.} \]

Is RAT(J) \leq 0.001? 

Yes

\[
\begin{align*}
C_1 &= \sqrt{\pi/X(2)} \cdot X(1) \cdot X(3) \cdot \exp \left[ \frac{1}{4 \cdot X(2)} \right] \\
C_2 &= \sqrt{\pi/X(6)} \cdot X(5) \cdot X(7) \cdot \exp \left[ \frac{1}{4 \cdot X(6)} \right] \\
U_1 &= X(4) + X(3) \cdot \exp \left[ \frac{1}{2 \cdot X(2)} \right] \\
U_2 &= X(8) + X(7) \cdot \exp \left[ \frac{1}{2 \cdot X(6)} \right] \\
S_1 &= \frac{1}{\sqrt{2 \cdot X(2)}} \\
S_2 &= \frac{1}{\sqrt{2 \cdot X(6)}} \\
XMTT_1 &= X(4) + X(3) \cdot \exp \left[ \frac{3}{4 \cdot X(2)} \right] \\
XMTT_2 &= X(8) + X(7) \cdot \exp \left[ \frac{3}{4 \cdot X(6)} \right] \\
RCC &= \frac{C_2}{C_1 + C_2} \cdot 100
\end{align*}
\]

No

\[
\begin{align*}
T_1F(K) &= X(1) \cdot \exp \left[-X(2) \cdot \left( \log \frac{T(K) - X(4)}{X(3)} \right)^2 \right] \\
T_2F(K) &= X(5) \cdot \exp \left[-X(6) \cdot \left( \log \frac{T(K) - X(8)}{X(7)} \right)^2 \right] \\
FT(K) &= T_1F(K) + T_2F(K)
\end{align*}
\]

Output: Print NDATA, X(1), X(2), \cdots, X(8), C1, C2, U1, U2, X1, S2, XMTT1, XMTT2, RCC, Y(K), T(K), T1F(K), T2F(K) and FT(K).

Where C1(C2) is the area of fast (slow) component, U1(U2): median \((\mu_1, \mu_2)\) of fast (slow) one, S1(S2): standard deviation \((\sigma_1, \sigma_2)\) of fast (slow) one,

XMTT1 (XMTT2): fast (slow) MTT without correction for distortion and RCC: ratio of slow flow to total flow.
References


15. STOW RW, HETZEL PS: An empirical formula for
Basic Versus Applied Research
Two and a Half Centuries Ago

It is stranger that we are not able to inculcate into the minds of many men, the necessity of that distinction of my Lord Bacon's, that there ought to be Experiments of Light, as well as of Fruit. It is their usual word, What solid good will come from thence? They are indeed to be commended for being so severe Exactors of goodness. And it were to be wished, that they would not only exercise this vigour, about Experiments, but on their own lives, and actions: that they would still question with themselves, in all that they do; what solid good will come from thence? But they are to know, that in so large, and so various an Art as this of Experiments, there are many degrees of usefulness: some may serve for real, and plain benefit, without much delight; some for teaching without apparent profit; some for light now, and for use hereafter; some only for ornament, and curiosity. If they will persist in condemning all Experiments, except those which bring with them immediate gain, and a present harvest; they may as well cavil at the Providence of God, that he has not made all the seasons of the year, to be times of mowing, reaping, and vintage.—From SPARAT, THOMAS: History of the Royal Society, ed 3, 1722. Quoted by BENNETT I Jr: Trans Ass Amer Physicians 80: 57, 1967.
Intrarenal Distribution of Blood Flow in Man: A New Analytical Method for Dye-Dilution Curves
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