Tissue Mean Transit Time from Dynamic Computed Tomography by a Simple Deconvolution Technique

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In order to calculate the mean transit time of tissue, such as brain, from dynamic computed tomography performed after a bolus injection of intravenous contrast material, the time dependence of the input of contrast material to the tissue must be "deconvolved" from the observed time course of the tissue contrast enhancement. If the approximate shape of the curve of the response of the tissue to an instantaneous injection of contrast material is assumed, the width of this curve that gives the best fit to the observed tissue response can be used to find a value for the tissue mean transit time. Applying this technique to dynamic CT scans of two normal volunteers yielded values comparable to those in the literature by other techniques. The method has the advantages of being simple to implement, relatively insensitive to noise and the details of the assumed curve shape, and not requiring any curve fitting to correct for recirculation.

Key words: cerebral blood flow, computed tomography, contrast enhancement, dynamic computed tomography, deconvolution, mean transit time.

DYNAMIC, or rapid sequence, computed tomography (CT) performed after a bolus intravenous injection of intravascular contrast material allows the observation of the appearance of the bolus of contrast material in organs such as the brain, its wash-out from the organ, and its reappearance due to recirculation. The recirculation will usually be superimposed on the later portion of the wash-out phase. The time course of the concentration of contrast material will depend both on the time course the tissue concentration would have after a hypothetical instantaneous input of contrast material to the tissue and on the actual time course of the contrast concentration in the arterial input to the tissue (Fig. 1). Specifically, the resulting tissue concentrations will be given by a mathematical relationship called the convolution of these two time functions,[1] as is discussed further below. Since the change in CT number is proportional to the concentration of contrast, the time course of contrast concentration in selected regions of the tissue can be found from the sequence of images by suitable analysis programs. If branches of the artery supplying the tissue are also imaged on the scans, a measure of the time course of the contrast input to the tissue can also be found. Then, in principle, the effect of the input could be separated from the observed contrast time course by the process of deconvolution, so as to find the impulse response of the tissue, that is, the time course of concentration that an instantaneous input of contrast material would have yielded. This could then be used to calculate the mean transit time (MTT) of the tissue, which is equal to the ratio of the blood volume of the tissue to the blood flow through the tissue. The MTT can be calculated from the impulse response by dividing the area beneath the curve of contrast concentration as a function of time by its initial (maximum) value.[2]

Deconvolution techniques have been applied to similar problems in indicator-dilution analysis,[3–7] but they generally have the disadvantage of being very sensitive to noise from the data[8]; the results tend to yield unrealistic oscillations in the computed impulse reponse unless restrictive assumptions about the nature of the impulse response are made. If we are only interested in computing the impulse in order to find the MTT, a measure of its width, the details of its shape are unimportant. If we could assume a certain family of shapes for the impulse response curves, an alternative approach would be to try "convolving" the ob-

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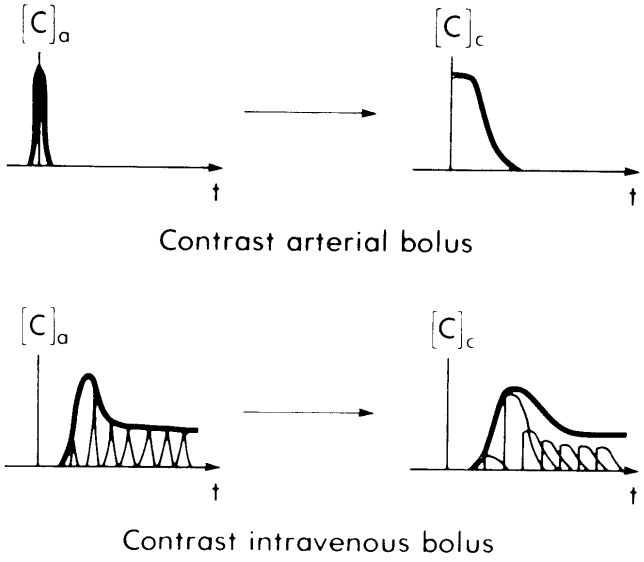


Fig. 1. Schematic demonstration of how time course of contrast concentration in capillaries, $[c]_c$, is related to contrast concentration in arteries supplying tissue, $[c]_a$. The capillary response to a hypothetical instantaneous arterial input is the "impulse response." If an actual, prolonged, arterial input is considered as a series of instantaneous inputs, the resulting capillary concentrations can be found from the superposition of the corresponding impulse responses.

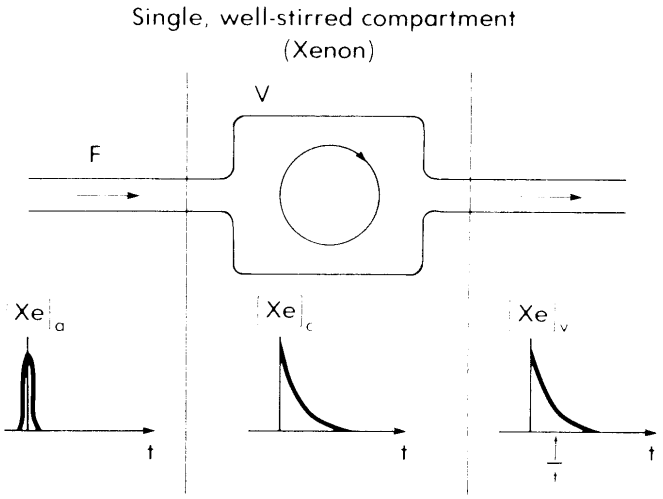


Fig. 2. Schematic model of the transit of an arterial instantaneous bolus of diffusible contrast material, such as xenon, through tissue. For a single mixing volume V and flow F, the tissue and capillary impulse response will be given by a falling exponential, with constant equal to the mean transit time, t = V/F. $(Xe)_a$ is the concentration of contrast material in the artery, and $(Xe)_c$ and $(Xe)_v$ are the concentrations in the capillaries and draining veins, respectively.

served arterial input contrast concentration-time data with assumed impulse responses of different widths. The resulting convolution could be compared with the actually observed tissue contrast concentration-time data. For a given family of impulse response curve shapes, the curve width yielding the best fit to the observed tissue values could then be used to give an estimate of the MTT.

The advantage of such a simplified approach to the deconvolution is that it is relatively insensitive to the noise of the data, compared with a direct deconvolution of the arterial input and tissue concentration-time curves. In comparison with another approximate deconvolution method previously proposed,[9-11] which fits the observed curves with smooth (gamma variate) curves and then computes the first moment (center of gravity) of the impulse response, this approach does not require any direct curve fitting of the data. The shape to be assumed for the impulse response curve depends on the nature of the clearance of contrast material from the tissue. In all cases, after an initial maximum value, the concentration will decrease continuously to zero (assuming all the contrast eventually exits from the tissue). In one idealized case, the tissue might act as a single, well-stirred compartment (as for diffusible contrast agents such as xenon); the contrast concentration of the tissue will then decrease as a simple exponential function of time (Fig. 2). In another idealized case, the tissue might act as a set of tubes of uniform length (as for nondiffusible contrast agents confined to an idealized vascular network); in this case, the contrast concentration in the tissue will remain constant, while the contrast bolus traverses the vessel lengths, then it will drop abruptly as the bolus exits the ends of the tubes. If there is a range of lengths

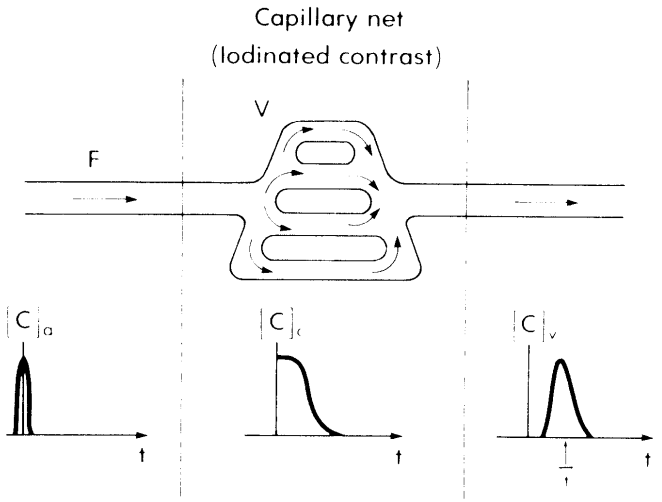


Fig. 3. Schematic model of the transit of an arterial instantaneous bolus of intravascular contrast material, such as iodinated contrast in the brain, through tissue. The bolus travels as a plug through the capillaries and exits essentially intact from their ends. If the capillaries are of equal length, the plug flow yields a square-shaped tissue impulse curve.

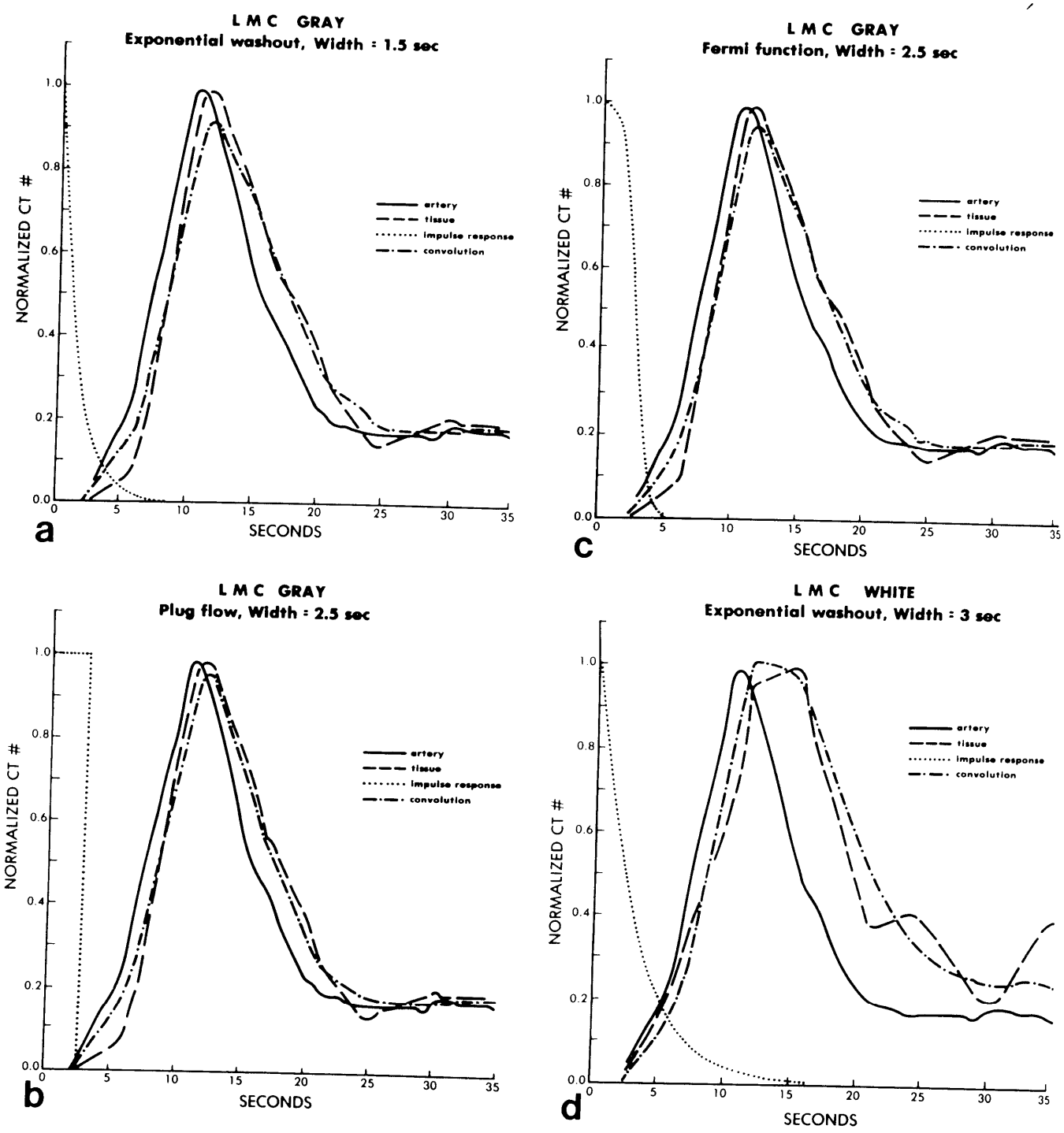
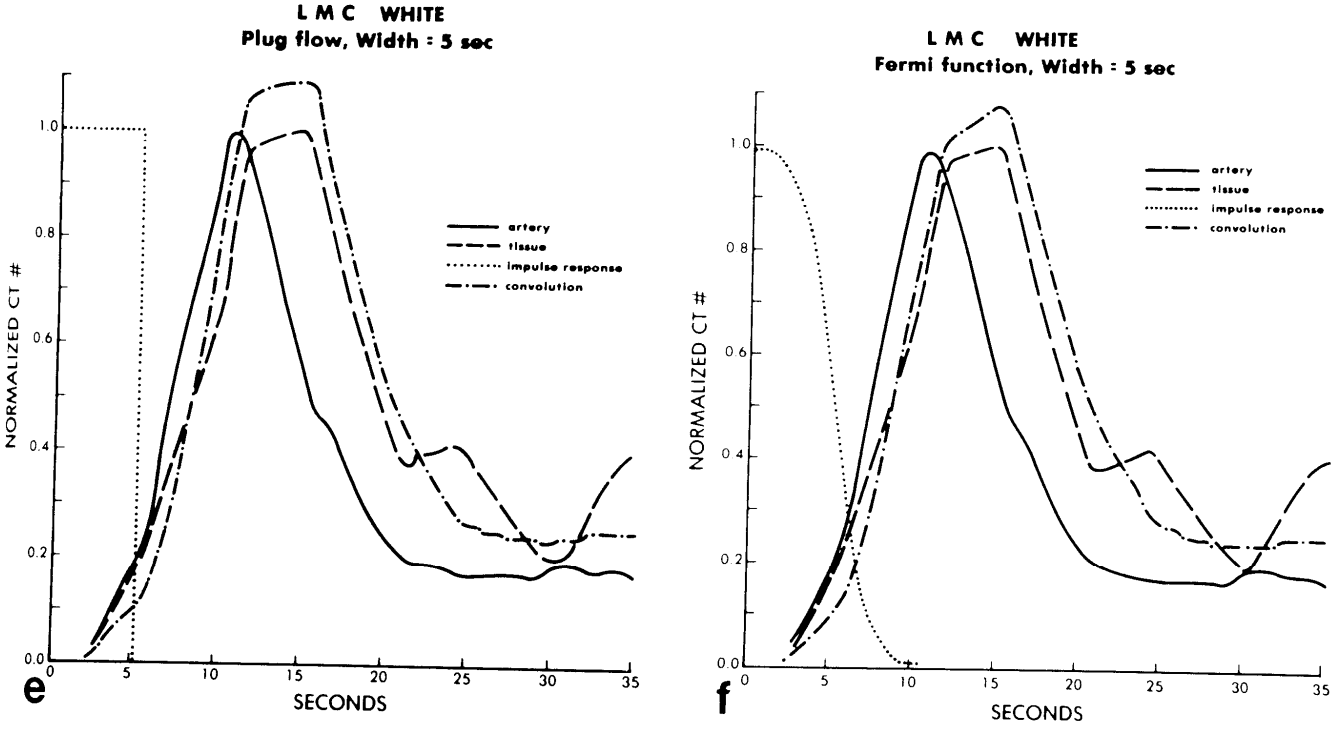


Fig. 4. Comparison of normalized CT numbers of branches of left middle cerebral artery (solid line) and tissue in corresponding region of distribution (broken line) with best fit calculated convolution (dot–dash line) for gray matter (a, b, and c) and white matter (d, e, and f) of arterial input with assumed tissue impulse responses (dotted line) of exponential (single compartment) (a, d), square (plug flow) (b, e), and intermediate (Fermi function) (c, f) shapes. The Fermi function shown yields approximately the same mean transit time as the square impulse response. (The bump in the tail of the white matter curve is due to noise.)

of the tubes, the drop will be less abrupt (Fig. 3). Particularly in the brain, iodinated contrast material is largely confined to the intravascular space, especially during the first pass through the tissue,[12] and these latter models of the impulse reponse ("plug flow") would be more likely to hold. In this study, a computer program was written to implement an iterative approach to deconvolution of contrast concentration-



time curves, seeking to find what duration of impulse response for a curve of a given shape would best fit the data, and its usefulness was tested on dynamic CT brain scans of normal subjects.

Methods

The concept of a convolution, as expressed in Fig. 1, can be defined more formally. For an impulse response function (the tissue contrast concentrations after an instantaneous input), f(t), the tissue response to an abitrary input function, g(t), will be given by the convolution of the impulse response and the input function, f*g, defined by

$$f(t) * g(t) = \int_0^t f(\tau)\, g(t - \tau)\, d\tau = \int_0^t f(t - \tau)\, g(\tau)\, d\tau \quad (1)$$

For finite time steps Δt, this can be approximated by a sum

$$f * g_k = \sum_{i=1}^{k} f(t_k - t_i)\, g(t_i)\Delta t \quad (2)$$

In the situations sketched in Figs 2 and 3, the capillary concentration after an instantaneous arterial injection would correspond to an exponential or a square curve; this would be f(t). For an actual prolonged arterial input, g(t), the resulting capillary concentration for a given f(t) (the impulse response), can be calculated from equations 1 or 2 (the convolution of f and g); Fig. 1 is a graphic demonstration of the meaning of this calculation.

A Fortran computer program was written to accept the sequential CT values of the branches of desired arterial vessels and selected tissue regions supplied by those arteries. Initial values were taken as a baseline and subtracted from subsequent values. The values of the change in CT number as a function of time were normalized by dividing by the areas beneath the curves for the duration of the scans. Different impulse response curve shapes (with unit area) were tried, consisting of a falling exponential function, a square function, and a Fermi function (which is essentially a square-type function, with rounded corners, which approaches either a square function or a falling exponential-type function, depending on the choice of a single parameter). The width of the impulse response was increased in half-second steps from 0.5 to a maximum of 6 to 10 seconds. For each width of the assumed impulse response function, the (normalized) arterial input was "convolved" with the impulse response function (using linearly interpolated values of the input), using equation 2, and the sum of the mean square differences between the resulting convolution and the (normalized) actual tissue response curves was calculated. The width of the impulse response curve yielding the minimum mean square deviation was used to calculate the corresponding best estimate of the mean transit time for a hypothetical impulse response curve of the given assumed shape. The actual and computed curves were also displayed graphically.

Two normal volunteers were studied at the level of the cerebral basal ganglia and Sylvian fissure with a modified GE 7800 CT scanner (13) designed for rapid sequence scanning. Sequential 3.5-second overscans (525°) were reconstructed into two overlapping 2.4-second full scans (360°); there was a 1.2-second pause between consecutive scan pairs. Slice thickness was 1 cm. Thirty-five ml of Conray-400® (Na iothalamate 66.8%, Mallinckrodt) was injected rapidly (in less than 5 seconds) into an antecubital vein at the start of a sequence of eight of the above-described CT scans. The resulting scans were analyzed with histogram-selectable

region-of-interest programs,[11] and the sequence of CT numbers was found for branches of the right and left middle cerebral arteries in the sylvian fissure and for gray and white matter (identified on early enhanced images by the CT number values of the pixels) in a roughly 2-cm elliptical region centered in their distribution regions. The use of histogram-based pixel selection for analysis minimizes problems of volume averaging with these small and irregular regions. This is important to avoid mixing gray and white matter curves and to get the best arterial curves. These data were used with the program described above to calculate the mean transit time for different assumed shapes of the tissue impulse response. For comparison, the data were also fit with gamma variate curves, and the fitted curves were used to calculate the first moments ("center of gravity") of the input and tissue curves and thus the first moment of the impulse response.[9] The first moment of the impulse response should be equal to the MTT for an exponential impulse response function, equal to ½ the MTT for a square function, and equal to an intermediate value for an intermediate shape.

Results

Typical experimental and computed curves for the region of the left middle cerebral artery distribution of one subject are shown in Fig. 4. The curves were quite similar for the other subject and for the right side of this subject. Because there was less contrast enhancement during passage of the bolus, the curves for white matter are more affected by noise than the curves for gray matter. The bump in the tail of the white matter curve in Fig. 4 is due to noise; the data were too noisy to permit a determination of the MTT of the white matter in the right middle cerebral artery distribution of one subject. As expected, the MTTs computed for a hypothetical square impulse response were approximately twice the values computed for an exponential. The MTT values computed for the intermediate Fermi function impulse response were fairly insensitive to shape; even quite rounded corners yielded values of the MTT very close to those computed for a square function. The fits were generally somewhat better with the square and Fermi function impulse response, as measured by the squared deviation of the convolutions from the tissue curves, but the difference was not significant for this small series. The mean values for both subjects of the MTT for right and left middle cerebral artery distribution gray matter were 2.6 seconds for a square impulse response and 1.2 seconds for an exponential impulse response, with standard deviations of 0.25 and 0.29, respectively. The mean MTT values of corresponding white matter were 5.6 seconds (SD 0.76) and 4.0 seconds (SD 0.50) for square and exponential impulse responses, respectively. If blood volumes are estimated as 5% for gray matter and 3% for white matter, these MTTs are equivalent to 115 and 250 ml/minute per 100 cc of gray matter for assumed square and exponential impulse responses, respectively, and 32 and 45 ml/minute per 100 cc of white matter for square and exponential impulse responses, respectively. Lower values for the blood volumes would correspond to lower values for the blood flows.

The values computed from the gamma variate curve fitting routine for the first moment of the impulse response were quite comparable with those computed for the MTT for a hypothetical exponential impulse response: 1.4 seconds for gray matter and 3.4 seconds for white matter. There seemed to be slightly more scatter in the values computed using the gamma variate curve fitting, but the difference is probably not significant.

Discussion

Deconvolution techniques have been applied to tracer studies in organs such as the lungs and heart, usually in order to compute the full distribution of transit times. If we only need the mean transit time (which in conjuction with the blood volume yields blood flow), and if a reasonable assumption can be made about the shape of the impulse response of the tissue, the technique described above provides a stable method to estimate the width of the impulse response and thus the MTT. For the normal brain, iodinated contrast material acts like an intravascular tracer. For most organs, the impulse response for intravascular tracers (equal to 1 minus the integral of the distribution of transit times[2]) is close to a square function with rounded corners. Although comparable data for brain gray and white matter are not available, a similar shape is likely. We have found that a squared shape for the impulse response yields values for the mean transit time that are closer to those expected from other techniques than do exponential-type impulse responses. The values computed for blood flow in the gray matter are still somewhat higher than those usually found with external counting of xenon-133 wash-out from the brain (generally on the order of 80 ml/minute/100 g of brain); the discrepancy may be slightly greater since the red cell flow velocity is slightly faster than the plasma flow.[14] The reason for this overestimation of flow is uncertain, but it may simply be a consequence of the relatively long scanning times employed; as faster CT scanners are developed, this will become clearer.

The method was quite insensitive to the precise shape assumed for the impulse response: as long as it approached a square curve, even with appreciable rounding of the corners, the calculated MTT was similar. This suggests that the calculation of the convolution can be quite efficient, as the convolution with a square impulse response becomes simply a linear

average of the values of the input over a duration equal to the width of the assumed impulse response.

The major limitation of this technique, as in any method that seeks to find the tissue mean transit time, is that the time course of the input of the tracer (here, contrast material) must be well characterized. In order to derive these data from the CT scans themselves, we must be able to identify the images of arteries and assign them to corresponding regions of distribution. For axial slices through the Sylvian fissure, as in this study, the branches of the middle cerebral arteries in the Sylvian fissure can usually be seen well and much of the corresponding regions of distribution confidently identified. The anterior cerebral arteries also usually are seen well at this level. Difficulty can be found in identifying the posterior cerebral arteries and in defining the precise boundaries between vascular distributions, which are subject to some individual variation. At other levels in the brain, the arteries are smaller and less advantageously oriented, making identification more difficult. Even though the lumen of the arteries cannot be separately imaged, the use of histogram-based pixel analysis minimizes problems of volume averaging, particularly at the level of the Sylvian fissure, where many branch arterial vessels pass through axial slices at nearly right angles. The ambiguity in defining the precise boundaries between vascular distributions will limit the applicability of this method to the creation of functional images of MTT. Although a slowly changing arterial input could be difficult to "deconvolve" in practice, in principle, this iterative technique should work regardless of the particular shape of the arterial input.

A great advantage of this approach is that it is quite stable in the presence of noise, in comparison to most explicit deconvolution techniques, such as those involving transform methods.[8] No curve fits are necessary to correct for recirculation in this technique, since the recirculation is automatically included in the input. However, the curve fitting techniques may still be necessary in order to find a value for the blood volume of the tissue for the calculation of blood flow. Since CT scanning involves ionizing radiation, it is likely that future scanners will remain somewhat noise-limited in order to minimize radiation-doses to patients; thus, relatively noise-insensitive deconvolutions will remain important. This approach to MTT determinations already allows a fairly reliable measurement of times not much greater than the time between scans; faster scanners with more rapid scan sequences should improve the reliability of the determination of MTT.

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