24.5 Bulk Flow Versus Perfusion

In this and the last chapter, we have shown that flowing spins can be imaged with minimum artifacts due to motion during data acquisition, and important morphological information such as vessel lumen can be obtained to, say, evaluate a stenosis (vessel wall narrowing) in a vessel. Once a vessel is visualized, it is then possible to quantify the bulk flow, F, through a vessel by calculating its area A and the speed of the blood v at each pixel via

$$F = Av \tag{24.29}$$

This approach is practical when the vessel is large enough to be resolved, so that both the cross-sectional area of the lumen and the speed of the blood at every pixel within it can be measured, the latter with, for example, the velocity encoding methods discussed above. The total flow is then found by summing the contributions from all the pixels within the lumen.

It is instructive to rewrite (24.29) in a form which does not depend explicitly on either the area or the speed. Consider a segment of the vessel of length d. The volume of blood contained in this segment is $V = Ad$, and the time taken for blood moving with speed v to pass from one end of the segment to the other, the transit time, is $t_0 = d/v$. The bulk flow can then be written as

$$F = \frac{V}{t_0} \tag{24.30}$$

That is, the flow through a region is given by the volume of blood in that region divided by the time it takes the blood to pass through it. For a single straight vessel, (24.30) is identical to (24.29). It is, however, of much more general use, since it requires only a knowledge of the volume of blood in the region being considered (the transit region) and of the time taken for the blood to cross it. Strictly, for a distribution of transit times, t_0 must be replaced by the flow-weighted mean transit time.

This distinction becomes critical when the vessels are too small to be seen. As the arteries branch into arterioles and, finally, into capillaries, the vessel diameters decrease to less than ten microns and the blood speeds fall to the order of a millimeter per second. A single imaging voxel then contains a very large number of vessels with many different orientations, lengths and speeds, and neither A nor v can be found for any one of them. The delivery of blood to the tissue through this capillary network is referred to as perfusion. Since it is at this level that oxygen and nutrients are exchanged with the tissue, perfusion is of considerable physiological and clinical interest. It is usually quoted not as a flow through a given vessel but as the volume of blood delivered per unit time to a given mass of tissue.

In this section, the concepts needed to estimate flow at this level are introduced. The key change from the bulk flow picture is that there is no longer a single transit time through the region of interest. Blood entering the region may follow many different pathways, each with its own length and speed and, hence, there will be a distribution of transit times. The question then arises as to which time should be used in place of t_0 in (24.30). The following problem addresses this question for the simple geometry of a set of parallel tubes.

Problem 24.19

a) Show for a parallel set of n identical tubes, each of length d, each with a blood speed v in the same direction, that the total flow over all tubes is given by

$$F_{\text{total}} = V_{\text{total}}/t_0 \tag{24.31}$$

b) Show, for the general case of varying speeds v_l that

$$F_{\text{total}} = \frac{1}{n} V_{\text{total}} \sum_{l=1}^{n} \left(\frac{1}{t_l}\right) \tag{24.32}$$

where t_l is the transit time through tube l. Only if $t_l = t_0$ for all l does this expression reduce to (24.31).

Based on the result in (24.32), it is clear that for such a bulk flow geometry, only $V_{\text{total}}\overline{\left(\frac{1}{t}\right)}$ yields the average flow rate of material across the tubes. Instead, if the expression $\frac{V_{\text{total}}}{\bar{t}}$ is used, where the mean transit time, $\bar{t}$, replaces t_0 in (24.30), $\frac{V}{\bar{t}}$ can be used as a measure of the flow. *Since the distribution of transit times (and $\bar{t}$) contains information about the different path lengths in the transit region, this effective flow estimate characterizes the geometry.*

24.5.1 Example calculations of effective flow

As described above, the effective flow is calculated by taking the ratio of the volume of blood in the region of calculation (in imaging terms, the voxel, in which case we denote this volume as V_{blood}) to the average value of the time taken to transit the region-of-interest (called the mean transit time or MTT, denoted by $\bar{t}$). Therefore, the computation of an effective blood flow involves determining the local blood volume and the MTT. The measurement of local blood volume is the topic of discussion in Sec. 24.5.4. In this subsection, two simple examples will be presented for calculating $\bar{t}$ in simple geometries and different temporally constant flow regimes.

One-dimensional plug flow

First, let us consider the case of region of transit, AB, for a material flowing through this region with a constant velocity. Suppose that an elemental volume V of the flowing material enters point A at time $t = 0$. Assume that the arrival of this same volume of material can be detected at point B. Because of the plug flow example considered here, this volume V will arrive at point B without any redistribution and all at the same time. Let this time of arrival be t_0, which is also the MTT. Then, the (effective) flow $\bar{F}$ is given by

$$\bar{F} = \frac{V}{\bar{t}} = \frac{V}{t_0} \tag{24.33}$$

To get a physical picture of this example, consider a long cylinder containing material flowing inside it with a plug flow, constant-velocity pattern. Let A and B be two spatially separated points where the presence of a dye that has been injected into this cylinder somewhere upstream (see Fig. 24.25a) is measured. Assume that a volume V of the dye was injected quickly enough that the spatial spread of the

dye volume in the direction of motion is elemental. Such a dye injection, which approaches the limit of an impulse (of volume), is referred to as an 'impulse bolus' injection.[9] Suppose that the two dye detectors placed at A and B are capable of measuring the instantaneous volume of the dye crossing the two points, respectively. The time traces of the volumes measured per unit time at these two points, $r_A(t)$ and $r_B(t)$, respectively, are as shown in Fig. 24.25b. For the plug flow case

$$r_B(t) = r_A(t - t_0) \tag{24.34}$$

and this temporal shift in $r_B(t)$ relative to $r_A(t)$ yields the MTT value, t_0.

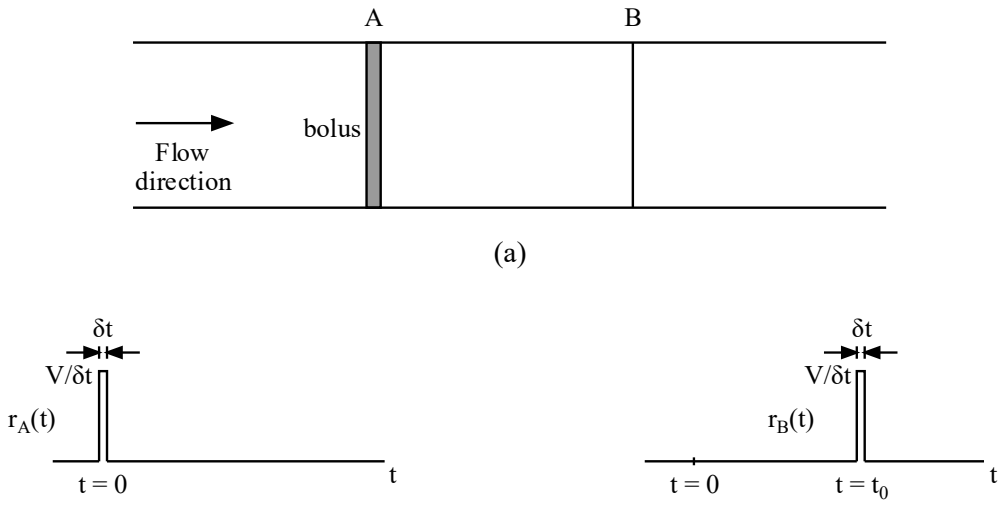


Fig. 24.25: Effective flow computation in a 'plug flow in a cylinder' case. (a) As shown here, an impulse bolus of volume V is injected upstream from the observation points A and B. (b) Volume of dye measured instantaneously at A and B, is given by $r_A(t)$ and $r_B(t)$, respectively. As shown here, the difference in dye bolus arrival times, t_0, is the mean transit time.

One-dimensional laminar flow in a cylinder

With laminar flow through the cylinder, the same bulk analysis of effective flow can be performed. Now, $r_B(t)$ will measure the presence of different parts of the bolus arriving at different times depending on their flow velocity. That is, $r_B(t)$ reflects the distribution of arrival times since it measures the fractional volume arriving at the point B. Since each time-point is in fractions of V, normalizing $r_B(t)$ to V then gives the probability density of transit times across the region AB. If $h(t)$ is this density function,

$$h(t) \equiv \frac{r_B(t)}{V} \tag{24.35}$$

where $V = \int_0^\infty d\,t\, r_B(t)$. Then the MTT is given by

$$\bar{t} = \int dt\, t \cdot h(t) \tag{24.36}$$

[9] A 'bolus' is an unmixed ball of dye or contrast agent.

In the above analysis, the MTT value is obtained by using a bulk measurement at the input port (point A) and then looking at one measurement at the output port (point B). The mean transit time reflects the multiple pathways taken by the blood and in this sense characterizes the geometry of the vessels.

The same measurement could have been performed by splitting the cylindrical cross-section at point B into a grid of dye-volume detectors, each sampling an infinitesimal part of the cross-sectional area such as shown in Fig. 24.26.[10] In this case, each of the N detectors will record a different transit time, say t_i, where $i \in \{1,2,\cdots N\}$ (the time-traces for two such detectors are shown in the insets in Fig. 24.26). Now

$$\bar{t} = \frac{1}{N}\sum_i t_i \tag{24.37}$$

assuming each detector receives the same amount of dye, otherwise a weighted average must be used. With such a grid of detectors, sampling an infinitesimal part of the cross-sectional area at the output port (or with a small voxel imaging setup), it is possible to determine the amount of material flowing through different pathways over localized volumes, each having different flow properties.

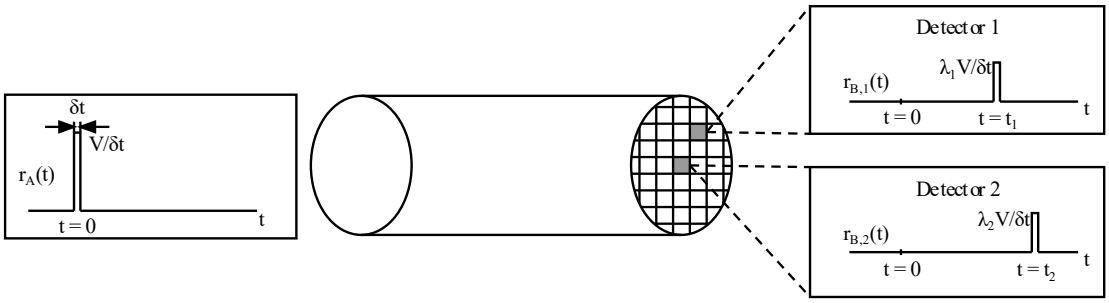


Fig. 24.26: Effective flow computation in the laminar flow case. Computation can be either done with a single bulk measurement of $r_B(t)$ or with a grid of detectors at B, in which case, the inset shows the output response obtained at two such detectors labeled 1 and 2. With such a setup, $h(t)$ can be measured.

Extension to MR imaging

Perfusion measurements were first performed using radionuclides by injecting a radioactive bolus in a major artery feeding the organ of interest (for example, the internal carotid artery for measuring perfusion to each hemisphere of the brain). Then, a radioactivity detector was placed in a major vein draining all the blood out of the organ of interest. Using this method, it was possible to obtain a bulk measure of perfusion to the whole brain. So, the whole brain can be thought of as a single large voxel.

In an imaging situation, it is possible to measure only an effective flow across each voxel. Since different parts of the brain are fed by different arteries and blood drains out through different venous structures, the blood from the internal carotid artery supplies different parts of the brain through different watersheds. In short, the goal in this section is to discuss the measurement of the mean transit time across a voxel, $\bar{t}_{\text{voxel}}$, and the local blood volume in the voxel, V_{blood}, and use the results to estimate a conventional flow in terms of volume per unit time via

[10] Although this might not be possible to use in the dye detection setup without disturbing the flow, let us continue this discussion, given that from a noninvasive imaging perspective, such an arrangement of small imaging voxels is possible. Such a set of small voxels is required in any case when the primary bolus is distributed into several parallel pathways, each having its own flow properties.

$$F_{\text{voxel}} = \frac{V_{\text{blood}}}{\bar{t}_{\text{voxel}}} \tag{24.38}$$

To accomplish this, the signal from the blood itself must be observable and distinguished from the surrounding tissue. To better differentiate blood from surrounding tissue, an intravascular contrast agent is introduced locally into the blood to significantly increase (using a T1 reducing contrast agent) or decrease (using an iron based contrast agent) signal from the blood (see Sec. 24.4). Although the amount of contrast agent injected is known, there still remains the question of determining how much contrast agent is in the blood at a given time; this quantity is denoted as $q(t)$ and can be represented in units of moles, for example. If the concentration, $c_{\text{blood}}(t)$, in the blood contained in the voxel of interest can be determined, then for a given voxel

$$q(t) = c_{\text{blood}}(t)V_{\text{blood}} \tag{24.39}$$

The units of $c_{\text{blood}}(t)$ are moles/m^3. *Once $q(t)$ is known for an impulse input, the mean transit time can be calculated. In this limit, $q(t)$ is written as $q_I(t)$.* Finally, experimental examples of finding $q(t)$ and V_{blood} will be presented to create an estimate of local flow.

The mathematical analysis of $q(t)$ to obtain $h(t)$ differs depending on which of two situations occurs: a 'large voxel limit' or a 'small voxel limit.' In either case, the estimation of MTT requires relating $q(t)$ in the impulse input case to $h(t)$ and computing an effective value therefrom. As will be shown in sections 24.5.2 and 24.5.3, a normalized zeroth moment of $q_{\text{voxel}}(t)$ is used in the large voxel limit to find the mean transit time while a normalized first moment of $q_{\text{voxel}}(t)$ must be used in the small voxel limit. The $q(t)$ that should be used in either case is the dose response of the voxel in the impulse bolus input case, $q_I(t)$. If the bolus is any arbitrary time function, a convolution with the bolus shape blurs this distribution, and the convolution theorem needs to be invoked to obtain the correct, unblurred distribution, $q_I(t)$.

Although bulk flow models will be used to generate the necessary formula for calculating the effective flow, the results are general and can equally well be used for estimating perfusion. Hence, flow and perfusion are indistinguishable in this sense and the MR experiment is insensitive to the actual mechanisms propagating the blood through a voxel. Finally, it should be noted that it is the signal from the blood itself which is critical, hence the use of an intravascular contrast agent. This allows the use of simple mass conservation rules, for example, in later discussions. For convenience, we will focus on the brain as a region where perfusion is measured. Other organs of interest include the heart and kidneys. The methods discussed herein are applicable to any of these areas as long as an intravascular contrast agent is used.

24.5.2 Inflow/Outflow Mechanics and the Large Voxel Limit

The type of MR imaging experiment which is used to visualize blood flow and find $q(t)$ after injection of a contrast agent involves rapid acquisition of the data, roughly a 2D image every second. Images are collected prior to the injection of a contrast agent and then continuously collected during and after the injection, lasting for a few minutes. The signal in each voxel, $\hat{\rho}(\vec{r},t)$, is monitored, and the goal is to relate the changes in $\hat{\rho}(\vec{r},t)$ during the first pass of the bolus to blood flow and blood volume. Generally, the voxel signal is a function of $q(t)$; so, for the following discussion, we will assume that $\hat{\rho}(\vec{r},t)$ has already been converted to $q(t)$ and we will return to how $q(\vec{r},t)$ is extracted from $\hat{\rho}(\vec{r},t)$ in Sec. 24.5.4.[11] For the remaining discussion, the spatial dependence will be understood and $q(t)$ will be used instead.

[11] The term 'first pass' refers to the first time that blood flows through the organ of interest before blood containing the contrast agent is recirculated through the heart and sent back to the organ again (the second pass).

An impulse input function

The simplest approach to take in quantifying perfusion is to consider an intravascular contrast agent with an input function $r_{in}(t)$, a tissue response $q(t)$, and an output function $r_{out}(t)$, all measurable quantities, in principle. This concept is represented by Fig. 24.27, where a bolus of contrast-enhanced blood enters the voxel or 'transit region.' The injected bolus may not simply flow through the voxel unperturbed but may follow tortuous pathways that lead to $r_{out}(t)$ being very different in shape than $r_{in}(t)$. If no change in shape took place then $r_{out}(t)$ would equal a translated version of $r_{in}(t)$, i.e., $r_{out}(t) = r_{in}(t - t_0)$ where t_0 would represent the transit time across the voxel. When $r_{in}(t)$ is an impulse

$$r_{in}(t) = q_0\delta(t) \tag{24.40}$$

then

$$\int dt\, r_{in}(t) = q_0 \tag{24.41}$$

The rate of outflow follows from conservation, dq/dt = r_in − r_out; for t > 0, after the impulse has entered, $r_{in} = 0$ and $r_{out}(t) = -dq/dt$. This can be viewed as the amount of material flowing out of the voxel per unit time, $r_{out}(t)$, being given by the difference between $q(t + dt)$ and $q(t)$ which implies

$$r_{out}(t) = -\frac{dq(t)}{dt} \tag{24.42}$$

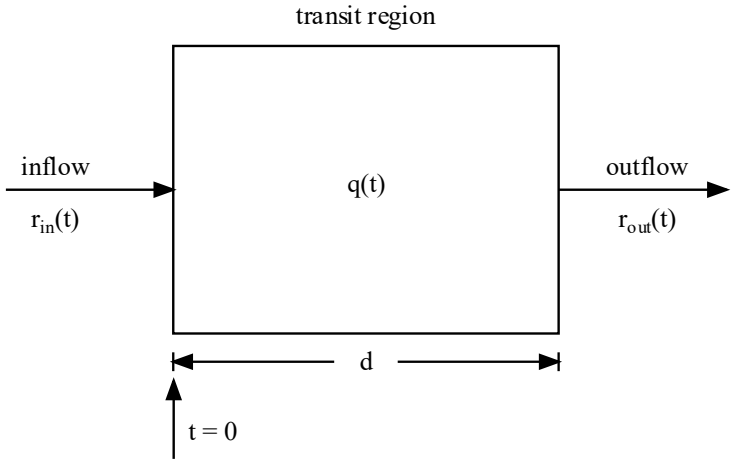


Fig. 24.27: A simple model of blood flow in tissue. The amount of the contrast agent in the pixel (transit region) is indicated by $q(t)$. The blood is assumed to occupy only a fraction of the voxel volume. In MR, the function $q(t)$ is indirectly measured by changes in signal following a bolus of contrast agent.

Problem 24.20

Find an expression for $r_{in}(t)$ in terms of $q(t)$ for the single velocity case.

Therefore, assuming that there is only one input and one output to the voxel, a measure of $q(t)$ is tantamount to measuring $r_{out}(t)$. However, some care needs to be taken here, as it is implicitly assumed that the bolus is short compared to the transit time of the voxel, otherwise (24.42) is not valid.[12]

Consider a bolus of contrast agent injected instantaneously at the edge of the voxel as illustrated in Fig. 24.28a. The time for the bolus to traverse the voxel is found from $t = d/v$. If the bolus moves through the voxel undispersed with speed v_0, then the measured signal in the voxel and hence, $q(t)$, is constant for $0 < t < d/v_0$. If there are multiple pathways with transit times distributed uniformly between $t_0 = d/v_0$ and $t_1 = d/v_1$, then the arrival at the output of the dispersed bolus varies uniformly from $t_0 = d/v_0$ to $t_1 = d/v_1$ as shown by the dashed line in Fig. 24.28b. Physiologically, the distribution of velocities tends to lead empirically to a decay of the tail of $q(t)$ after t_0. The decay of $q(t)$, the amount of contrast agent in the voxel, is governed by the velocity or equivalently, flow distribution within the voxel.

A number of issues have been taken for granted. For example, the contrast agent is assumed to be a non-diffusible intravascular tracer.[13] The flow is assumed to be constant over time, as is the blood volume. Also, blood is assumed to have no stagnant pools or sinks in which it is lost. When a contrast agent is used, the analysis used to find $q(t)$ and blood volume generally assumes there is no recirculation of blood containing contrast agent from the first pass. Hence, either a first pass analysis or complete steady state analysis is usually done.

Mean transit time

To find the mean transit time (MTT), the amount of tracer distributed over each velocity must be found. From mass conservation principles, the integrated output of $r_{out}(t)$ must be the same as the integrated input for the voxel (assuming no leakage of contrast agent into the tissue). Let the probability density function describing the fraction of the input tracer that reaches the output point at time t be represented by $h(t)$. It is the probability density of all possible transit times through the transit region (the voxel), i.e.,

$$\int_0^\infty d\, t\, h(t) = 1 \tag{24.43}$$

where $h(t)$ has units of inverse time. The mean transit time of the tracer is then

$$\bar{t} = \int_0^\infty d\, t\, t\, h(t) \tag{24.44}$$

The value determined for $\bar{t}$ using (24.44) is dependent on the time chosen as $t = 0$. It is typical to use the time when the leading edge of the bolus arrives at the input port to be the time origin. From an MRI perspective, $h(t)$ represents the distribution of spin isochromats with different speeds arriving at the output.

[12] In the case of a typical brain voxel in MRI, the input bolus is clearly a broadened time function because it has transited a large region from the site of, say, an intravenous injection in the arm. Compared to the transit time across the voxel, this function has a much larger time-spread.

[13] This type of contrast agent is often referred to as a blood-pool agent since it remains in the blood and does not diffuse out of the vessels.

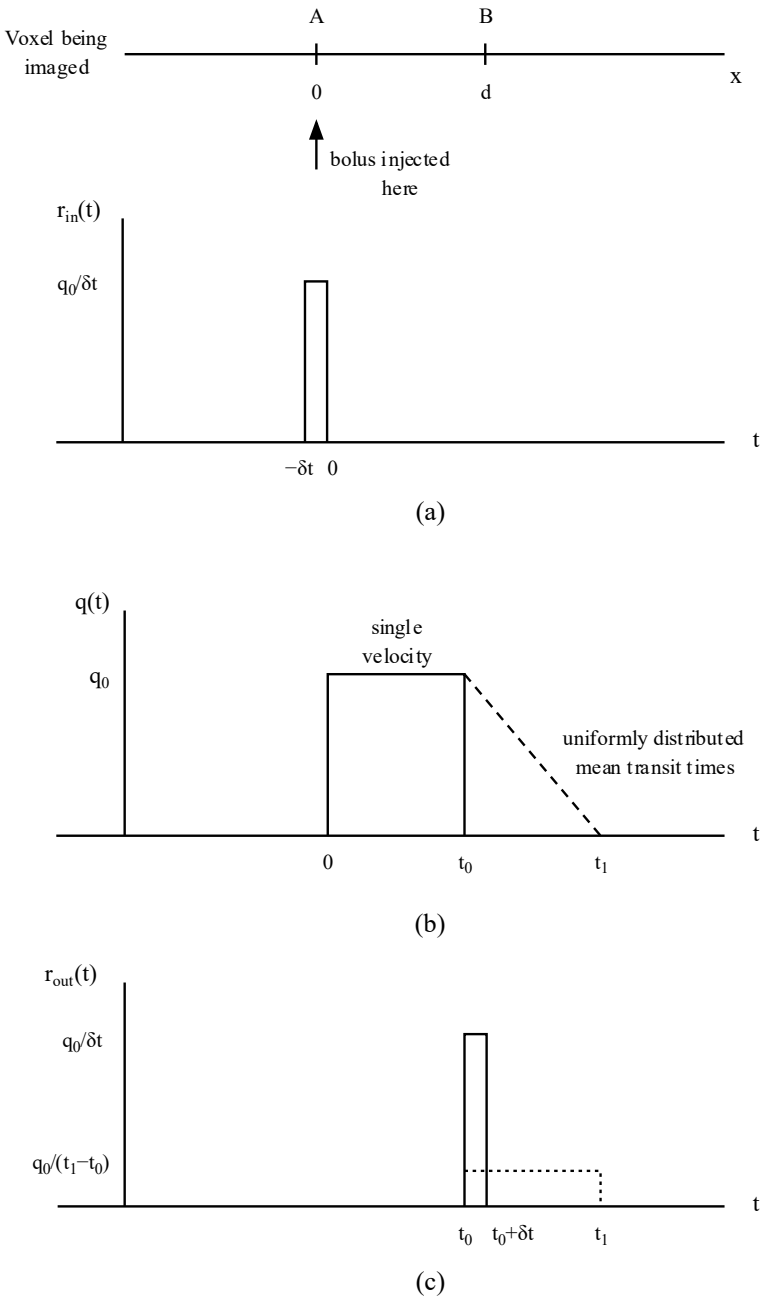


Fig. 24.28: (a) Illustration of the injection of a bolus of contrast agent (whose time-trace is also shown) into the edge of a pixel of length d. (b) Amount of the contrast agent in the voxel as a function of time for a straight tube through the voxel (solid line) for the input shown in the previous figure. A spread occurs with the bolus waveform if there are multiple pathways for the contrast agent to reach the output from the input port (dashed line). (c) Output dose rate as a function of time. Since $r_{out}(t)$ is proportional to $h(t)$, then $h(t)$ is seen to represent an equal amount of contrast agent exiting per unit time. [The figure label 'uniformly distributed mean transit times' in Fig. 24.28b should read 'uniformly distributed transit times'.]

An expression can be found for $h(t)$ in terms of flow and the amount of contrast agent. Since the amount of tracer leaving the system between times $(t,\ t+dt)$ is the product of blood outflow times the concentration, then

$$q_0 h(t)dt = r_{out}(t)dt = F(t)c_{out}(t)dt \tag{24.45}$$

or

$$h(t) = F(t)c_{out}(t)/q_0 \tag{24.46}$$

where q_0 is the total amount of tracer injected into the voxel, $c_{out}(t) = r_{out}(t)/F(t)_{\text{blood}}$ and $F(t)$ is the flow which, in physiological situations, is usually a function of time. However, for the moment, assuming $F(t)$ is constant, say F_0, and using

$$q_0 = \int_0^\infty d\,t\,F(t)c_{out}(t) = F_0 \int_0^\infty d\,t\,c_{out}(t) \tag{24.47}$$

then $h(t)$ can be rewritten as

$$h(t) = \frac{c_{out}(t)}{\int dt\,c_{out}(t)} \tag{24.48}$$

$$= \frac{r_{out}(t)}{\int dt\,r_{out}(t)} \tag{24.49}$$

The MTT is then given by

$$\bar{t} = \frac{\int dt\,t\,r_{out}(t)}{\int dt\,r_{out}(t)} \tag{24.50}$$

The challenge therefore lies in isolating either $h(t)$ or $r_{out}(t)$ by an appropriate experimental design.

Large voxel limit

As it is often not possible to measure $c_{out}(t)$ or $r_{out}(t)$ directly, an alternate means of accessing $h(t)$ through a measurement of $q(t)$ is sought with the idea of determining $\bar{t}$ later. *In this process, $q(t)$ is defined in terms of the probability function $h(t)$ in a way which assumes at some time that all the contrast agent lies within a voxel. That is, the voxel is assumed to be large enough to contain all the contrast agent.*

The amount of contrast agent which appears in the transit region prior to the output measurement is then defined as $q_I(t)$ and can be rewritten as an integral over $r_{out}(t)$. Hence

$$\begin{aligned} q_I(t) &= q_0 - \int_0^t d\,t'\,r_{out}(t') \\ &= q_0\left(1 - \int_0^t d\,t'\,h(t')\right) \\ &= q_0\big(1 - H(t)\big) \qquad t \geq 0 \end{aligned} \tag{24.51}$$

where $H(t)$ is, by definition, the cumulative distribution function of $h(t)$.[14] At $t = 0$, $q(t) = q_0$ and the 'large' voxel contains all the contrast agent as shown in Fig. 24.28b. For $t > 0$, particles are leaving the voxel at the output, but no new particles are entering the voxel anymore. Hence, (24.51) is valid for the case shown in Fig. 24.28.

That is, this expression is strictly valid only for a bolus input function $r_{in}(t)$ starting at $t = 0$ (see Fig. 24.28). If the fastest spin has a speed v_0, then the minimum time for $H(t)$ to become nonzero is d/v_0. Clearly, $q_I(t)$ remains constant until $t > t_0 = d/v_0$ when it drops to zero in the simplest case described by the solid lines in Fig. 24.28b. In this particular example, $h(t)$ is zero prior to $t = t_0$. If all the contrast agent is in the pixel by this time, then (24.51) is valid. That is, the shortest transit time t_0 must be greater than the input pulse width, t_b, for the large voxel limit to be valid. Again, large voxel simply means that the entire bolus lies within the voxel prior to any contrast agent escaping.

Problem 24.21

Show that

$$\int_0^\infty d\,t\,\big(1 - H(t)\big) = \int_0^\infty d\,t\,t\,h(t) = \bar{t} \tag{24.52}$$

by using integration by parts. Note that $\bar{t}$ as evaluated using $\int_0^\infty d\,t\,\big(1 - H(t)\big)$ is a definite integral since $H(\infty) \equiv \int_0^\infty d\,t\,h(t) = 1$. Clearly, $\bar{t}$ depends on the time origin. Note that the function (1 -H(t)) is referred to as the residue function and is equal to $q_I(t)/q_0$.

The result derived in Prob. 24.21 makes it possible to achieve the goal of finding the MTT from $q_I(t)$. Using the results of (24.52), the integral of $q_I(t)$ becomes

$$\int_0^\infty d\,t\,q_I(t) = q_0\bar{t} \tag{24.53}$$

The MTT is then given by

$$\bar{t} = \frac{1}{q_0}\int_0^\infty d\,t\,q_I(t) \tag{24.54}$$

where $t = 0$ corresponds to the time of arrival of the leading edge of the bolus time function at point A in Fig. 24.28a. For the impulse input and boxcar response for $q_I(t)$, this translates into

$$\bar{t} = \frac{\text{area of } q_I(t)}{\text{peak value of } q_I(t)} \tag{24.55}$$

As shown in Prob. 24.22, this approximation is not always valid. *The estimate of mean transit time for the large voxel limit is seen to be proportional to the zeroth moment of* $q_I(t)$.

[14] Written in this way, $q(t)$ is sometimes referred to as the residue function since it contains what has not yet left through the output port.

Problem 24.22

In this example, the integral of $q(t)$, divided by the peak value of $q(t)$ is a measure, $\hat{t}$, of $\bar{t}$.

a) Show for an impulse bolus through a straight tube with plug flow that

$$\hat{t} = \frac{\text{area under } q(t)}{\text{peak value of } q(t)} \tag{24.56}$$

if $q(t)$ is given by the solid line in Fig. 24.28b.

b) Assume that there are two pathways for the contrast agent to enter and leave the voxel. Take the velocity of each pathway to be v_1 and v_2, respectively. Calculate the mean transit time in terms of F_1 and F_2, the corresponding volume flow rates in the two pathways.

c) Show that $\hat{t} = \mathrm{e}\bar{t}$ if $q(t) = q_0 e^{-t/\bar{t}} \cdot t/\bar{t}$ and hence demonstrate that not all $q(t)$ obey (24.56).

In practice, the injected bolus is not a δ-function and the contrast agent dose gets broadened before it reaches the region of interest. This broadening occurs even for an arterial injection close to a region of interest where perfusion is to be measured because the blood flow is not plug flow and different parts of the blood travel at different speeds such as in laminar flow.

Problem 24.23

For an instantaneous injection in the carotid artery of diameter 1 cm, how long will it take the fastest blood isochromat to get to a point 20 cm away? Assume the blood flow is along a straight tube with a peak velocity of 20 cm/sec. What would the distribution $h(t)$ look like if the flow in the vessel is broken into four annular rings of equal area and the mean flow in each ring is used to estimate arrival time? Assume a parabolic laminar flow. Should h(t) be weighted by flow or area? Evaluate both.

The conditions of the large voxel limit are only easily met in MRI if the entire brain is used as a voxel. This is because the contrast agent is injected intravenously and the input function is quite long (usually on the order of many seconds). *Guaranteeing that all the bolus is in the voxel is very difficult otherwise. Hence, an alternate solution is needed to deal with the fact that voxels in MR are very small and mean transit times will be accordingly short compared to the temporal width of the bolus.*

A practical example of MTT in tissue

Other modalities have measured flow rates in brain parenchyma ranging from 20 ml/min/100 gm of tissue for white matter to 80 ml/min/100 gm of tissue for gray matter. If one assumes a blood volume fraction of

$$\lambda \equiv \frac{V_{\text{blood}}}{V_0} \tag{24.57}$$

where V_0 is the voxel volume. Then this implies

$$P = \bar{F}/\text{mass of tissue} = \text{volume of blood passing through a given mass of tissue per minute}$$
$$= \text{flow per pixel} \times \text{number of pixels per unit mass of tissue}$$
$$= F_{pixel}/\rho V_0$$
$$= \lambda/\rho\bar{t} \tag{24.58}$$

where V_0 is the volume of a voxel. With $\lambda = 0.05$, $\rho = 1.08$ gm/cc, and $P = 80$ ml/min/100gm = 1.33 ml/sec/100 gm

$$\bar{t} = \frac{\lambda}{\rho P} = 3.5 \text{ sec} \tag{24.59}$$

The actual velocity this corresponds to depends on the geometry of the voxels. For example, if they are arranged as a grid 10 cm × 10 cm then the area is 100 cm^2 and the speed through this area is 0.8 cm/min. If the voxels are aligned in a line of cross-section 1 cm^2 then the velocity is 4/3 cm/sec, much faster. Both perfuse the tissue with the same volume per unit time. Recall 100gm tissue equals 93 cc.

24.5.3 General Relation Between Arterial Input Function and Impulse Response Function and the Small Voxel Limit

In the previous discussion, $q_I(t)$ was the response to an impulse input and represented the transfer function of the voxel from input to output (not the measurement voxel). In the small voxel imaging limit, it will not be possible to measure at the input of a voxel, and the output of a voxel; all that is measured in MRI is the dose response of the voxel. This dose response $q(t)$ $(= q_{\text{voxel}}(t))$ is a measure of all that has happened to the part of the injected bolus before it has reached the voxel of interest, and from a systems perspective, the dose response of the voxel to an impulse input, $q_I(t)$, can be thought of as the voxel dosage transfer function. Ideally, we would like to have $r_{in}(t) = q_0\delta(t)$. Practically, this is very difficult to achieve. For example, injecting a very small bolus into the carotid artery of a pig is essentially a δ-function input. But by the time the contrast agent gets to the brain, the bolus is dispersed. The spreading out of the arrival times creates a $q(t)$ which is a function of both the properties of flow in the voxel (the transfer function) as well as the input function shape itself.[15] In this subsection, $q(t)$ will be found in terms of these two functions, the input function, $r_{in}(t)$, and the transfer function, $q_I(t)$. Following that discussion, the actual value of $q(t)$ when the large voxel limit is not valid will be examined. The voxel sizes in MRI are so small, only several mm^3, that transit times are closer to several hundred milliseconds and difficult to measure. An alternate approach to finding MTT is presented. The discussion ends with the open question as to whether perfusion is even feasible to measure under these circumstances except, perhaps, for the entire brain itself. Note that voxel MTT (a few s) is not $\ll$ bolus width (≈10–15 s for an IV injection). This is why deconvolution, rather than the pure small-voxel limit, is used in practice.

[15] Note the usage of the term 'arrival time' rather than 'transit time' here. In the small voxel case, the mean value computed using the normalized voxel dose response does not signify the transit time across the voxel. Since $q_{\text{voxel}}(t)$ is a measure of the distribution of bolus arrival times, the computed time is a mean arrival time, not MTT. The MTT is then obtained by subtracting the arrival times of neighboring voxels belonging to the same watershed.

$q(t)$ as a convolution of $r_{in}(t)$ and $q_I(t)$

Relating $q(t)$ to $r_{in}(t)$ and the transfer function $q_I(t)$ can be understood by building up the signal for $q(t)$ one impulse at a time. Consider a second bolus as shown in Fig. 24.28 arriving at a time dt later containing ${q_0}'$ of contrast agent. A similar pattern to that in Fig. 24.28b will result, but it will be delayed by a time dt so that the dose response $q_2(t)$ for the second bolus is simply a translation of that from the first bolus ($q_1(t)$), i.e., for $t \geq dt$,

$$q_2(t) = q_1(t - dt) = \left(\frac{{q_0}'}{q_0}\right) q_I(t - dt) \tag{24.60}$$

where ${q_0}'$ is the amount of contrast agent injected for the second bolus. The total dose response of the voxel, $q(t)$, can be taken to be the sum over all contributions from the pixel at a given time, i.e.,

$$q(t) = q_I(t) + \frac{{q_0}'}{q_0}\, q_I(t - dt)\, \Theta(t - dt) \tag{24.61}$$

where $\Theta(t)$ is the Heaviside function, i.e., it is zero for $t < 0$ and 1 for $t \geq 0$. Multiplication by the Heaviside function $\Theta(t - dt)$ signifies that although the second impulse response appears at a later time dt, it does not contribute until t ≥ dt.

The generalization of this retarded effect is the convolution of the arbitrary arterial input function, $r_{in}(t)$, with the impulse response of the voxel, $q_I(t)$, to yield the pixel dose $q(t)$

$$\begin{aligned} q(t) &= q_I(t) * r_{in}(t)/\mathrm{q_o} \\ &= \int_{-\infty}^{\infty} d\,\tau\, q_I(t - \tau)\, r_{in}(\tau)/\mathrm{q_o} \end{aligned} \tag{24.62}$$

Problem 24.24

a) Find the mean transit time from $q(t)$ using (24.56) and (24.62) if $q_I(t) = ate^{-bt}$ and $r_{in}(t) = cte^{-dt}$, respectively, for $t \geq 0$.

b) Comment on this transit time compared to that of each individual function computed by replacing $q(t)$ in (24.56) with $q_I(t)$ and $r_{in}(t)$, respectively.

The function which needs to be used to extract flow information in a voxel is $q_I(t)$ not $q(t)$. The value of $q_I(t)$ can be found from $q(t)$ by applying the convolution theorem (see Ch. 11) to (24.62) if $r_{in}(t)$ is known. This convolution requires that both $q(t)$ and $r_{in}(t)$ be measurable. If the whole brain is used as the 'voxel,' then the above assumptions are reasonable and the input function $r_{in}(t)$ can be found directly from the blood signal in a major artery feeding the region-of-interest. Practically, measuring the arterial input near a small voxel in the brain is very difficult.

Problem 24.25

Why may extracting $q_I(t)$ mathematically from the convolution theorem prove difficult in practice?

Small voxel limit

Consider a small voxel such that the transit time across the voxel of the fastest flowing material (t_0) is much less than the input bolus width, t_b. If $h(t)$ is the probability density of arrival times at the voxel input (or the density of transit times over the large voxel from the site of bolus injection to the imaging voxel of interest), then $r_{out}(t)$ of the large voxel including all pathways the blood traversed to reach the voxel input is the voxel input function, i.e.,

$$r_{in}(t)|_{sv} = r_{out}(t)|_{lv} = q_0{}'h(t) \tag{24.63}$$

where the subscript 'sv' is used to signify small voxel and the subscript 'lv' a large voxel where $q_0{}'$ is the amount of contrast delivered along the pathways leading to the voxel under question. Next, given that $t_0 \ll t_b$, $q_I(t)$ of the voxel acts like a sampling function of $r_{in}(t)|_{sv}$ as shown in Fig. 24.29. Hence,

$$q(t)|_{sv} \simeq \frac{1}{2}\, q_0{}'h(t)(t_0 + t_1) \tag{24.64}$$

i.e., $r_{out}(t)|_{lv}$ is being measured by the voxel response function. *Since $q(t)$ is now proportional to $r_{out}(t)$, $\bar{t}$ is then computed using (24.50) with $r_{out}(t)$ in (24.50) replaced with the $q(t)$ measured in the voxel:*

$$\bar{t} = \frac{\int dt\, tq(t)}{\int dt\, q(t)} \tag{24.65}$$

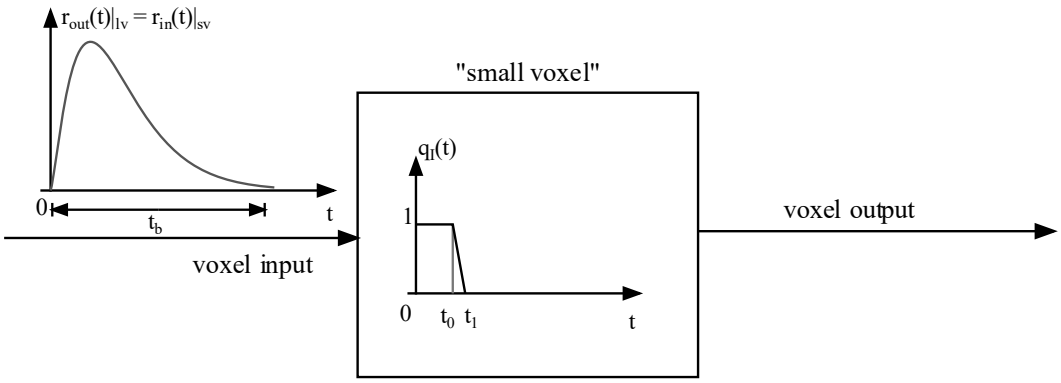


Fig. 24.29: Small voxel input dose function and transfer function time-traces. As shown, compared to the time width of $r_{in}(t)|_{sv}$, t_b, $q_I{}'(t)$ is a sampling function. Note the label in the figure should be $q_I{}'(t)$.

It now makes little sense to talk about $\bar{t}_{\text{voxel}}$ since $q_I(t)$ is effectively a δ function or, more realistically, a sampling function. Voxel sizes in MRI are so small that even for a slow flow of 1 cm/s through a voxel 2 mm across, the transit time is 200 ms. This is much shorter than bolus times of several seconds. Hence, it would appear that MRI data fits in the small voxel limit category. However, the mean transit time calculated from these small voxels represents $\bar{t}$ from all that has passed earlier in the voxel AC in Fig. 24.30, i.e., the calculated value of $\bar{t}$ includes both the mean arrival time as well as the MTT across the voxel-of-interest. An estimate of the mean transit time between two voxels can then be had by subtracting the mean transit times for each voxel.

Approximate calculation of $\bar{t}$ for an arbitrary input function for any arbitrary transit region

After having focused on $q_I(t)$ as the critical function to calculate mean transit time, in some circumstances it will be seen that $q(t)$ is acceptable to use to find the MTT between two MR imaging voxels. Consider two small imaging voxels A and C such as shown in Fig. 24.30. Assume that they both belong to the same perfusion watershed. The goal is to calculate the MTT across the transit region AC. Here, the dose response of voxel 1 (at position A) serves as the input function for the transit region AC, while the dose response of voxel n (at position C) serves as the output function. A $\bar{t}$ value can be calculated for both these functions as well as for $q_I(t)$ of the transit region AC. Let these be $\bar{t}_{in} \equiv \bar{t}_A$, $\bar{t} \equiv \bar{t}_{AC}$ and $\bar{t}_{out} \equiv \bar{t}_C$. It can then be shown that

$$\bar{t}_C \simeq \bar{t}_A + \bar{t}_{AC} \tag{24.66}$$

for voxel C in Fig. 24.30 independent of the size of the transit region AC. This relation is exact for first moments; Prob. 24.26 verifies it for Gaussian and exponential examples. The expression on the right-hand side of (24.66) is only an approximation for $\bar{t}_C$ because of the result obtained in the following problem which shows that (24.66) is valid in the case when both $r_{in}(t)$ and $q_I(t)$ are Gaussian in the small voxel case and exponential in the large voxel case.

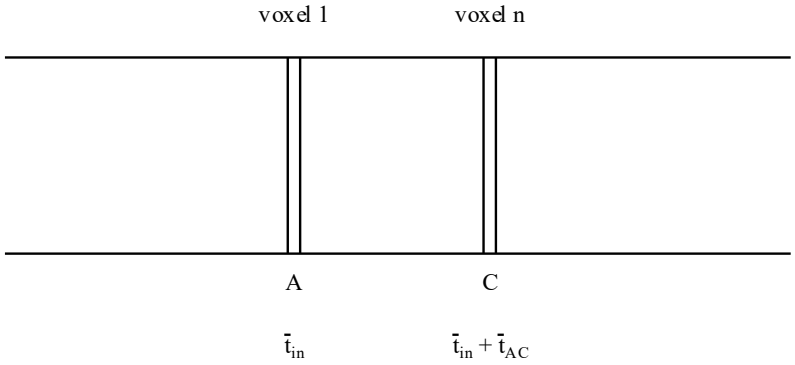


Fig. 24.30: Approximate computation of the transit time across the region AC. If $\bar{t}_{in}$ is the value of $\bar{t}$ computed using $r_A(t)$ and $\bar{t}_{out}$ is the value of $\bar{t}$ computed using $r_C(t)$, it can be shown that $\bar{t}_{out} \simeq \bar{t}_{in} + \bar{t}_{AC}$ where $\bar{t}_{AC}$ is the value of $\bar{t}$ obtained using $q_I(t)$ corresponding to the region AC. Each of these 'transit times' is more like an arrival time in practice. The time $\bar{t}_{AC}$ is closest to an MTT.

Problem 24.26

small voxel case

a) If $r_{in}(t) \propto e^{-at^2}$ and $q_I(t) \propto e^{-bt^2}$, show using (24.62) and

$$\bar{t}_{\text{total}} = \frac{\int dt\, t\, q(t)}{\int dt\, q(t)} \tag{24.67}$$

that

$$\bar{t}_{\text{total}} = \bar{t}_{in} + \bar{t} \tag{24.68}$$

Now try shifted Gaussians: $r_{in} \propto e^{-a(t-\bar{t}in)^2}$ and $q_I'(t) \propto e^{-a(t-\bar{t}in)^2}$.

Hint: Show that the convolution of these two Gaussian functions is proportional to $e^{-ab(t-\bar{t}in-\bar{t})^2/(a+b)}$.

large voxel case

b) If $r_{in}(t) \propto e^{-at}$ and $q_I(t) \propto e^{-bt}$ for $t \geq 0$, show using

$$\bar{t}_{\text{total}} = \frac{1}{q_0} \int dt\, q(t) \tag{24.69}$$

that (24.68) holds for the large voxel case as well.

Actually, with $r_{in}(t) \propto e^{-at}$ and $q_I(t) \propto e^{-bt}$, the voxel content gives $\frac{1}{q_0} \int dt\, q(t)$ = 1/b = $\bar{t}$ alone, independent of the input. (This is a useful general property of the zeroth moment.) (24.68) holds only if q(t) is the residue of the combined upstream-plus-voxel region, giving (1/a + 1/b). It also holds for the first moment of the voxel content.

Exact computation of $\bar{t}$ in the presence of an arbitrary input dose function

Having $q(t)$ from two pixels makes it possible to calculate the mean transit time between them. That is, $q_1(t)$ (the dose response of the first pixel) can be considered the input function $r_{in}(t)$, and $q_2(t)$ (the dose response of the second pixel) as the dose response function $q(t)$ of the region between the two voxels. Using (24.62), $q_I(t)$ can then be found and then $\bar{t}$ computed (for the small voxel region between the two pixels under consideration) from

$$\bar{t} = \frac{\int dt\, t q_I(t)}{\int dt\, q_I(t)} \tag{24.70}$$

If $q_2(t) = q_1(t - t_0)$ then the transit time is simply t_0.

A caution should be noted in applying these formulas to *in vivo* studies. It is necessary to ensure that the two voxels being considered are, in fact, part of the same watershed. For example, in the brain, blood in one area can be fed by a different major vessel than blood in another adjacent area. Hence, taking a voxel too far away may lead to two unconnected measures of $q_I(t)$. This may be a significant clinical problem in estimating flow since several major vessels often feed one organ. *In summary, after all this effort to estimate MTT, its value may lie only in local differences where there is some assurance that flow is progressing from voxel to voxel.* Otherwise, MTT will simply be a map of arrival times to the tissue and will not represent local flow at the voxel level.

Problem 24.27

The total volume of particles with a given transit time t can be found from the rate at which the flowing spins leave the system times the time t, i.e.,

$$dV_b = F(t)h(t)dt \cdot t \tag{24.71}$$

Find the total volume through which the spins have traversed following injection and show that (similar to the discussion after (24.32) where $\bar{t}$ is the tracer (flow-weighted) MTT)

$$V_b = \bar{F}\bar{t} \tag{24.72}$$

Consider cross-referencing it from the discussion after (24.32), since it shows V/$\bar{t}$ is the true flow when $\bar{t}$ is the tracer (flow-weighted) MTT.

Problem 24.28

This problem addresses the differences between a zeroth moment calculation of mean transit time for the large voxel and a first moment calculation of MTT in the small voxel approximations, respectively.

If $q(t) = q_0 \frac{t}{\tau} e^{-at/\tau}$, show

a) $\bar{t}_{lv} \equiv 1/q_0 \int dt\, q(t) = \tau/a^2$

b) $\bar{t}_{sv} \equiv \int dt\, t\, q(t) / \int dt\, q(t) = 2\tau/a$

c) Find $\bar{t}_{sv}/\bar{t}_{lv}$ and comment on why the ratio is either less than or greater than unity.

24.5.4 Extracting Blood Volume and $q(t)$ from Dynamic MR Imaging

Once the mean transit time has been found, the blood volume within a voxel is required to find the flow from (24.38). There are two approaches. The first is a calculation of relative cerebral blood volume (rCBV). The second is an absolute determination of CBV. These approaches can be used in either a steady-state or dynamic first-pass mode depending on the contrast agent used. However, due to the nature and dose of currently used contrast agents, they are naturally separated into two categories. The initial dose of contrast agent has a very high concentration and, in practice, a very high R_2^*. This makes it ideal to use for dynamic measurements since the signal from the surrounding tissue can be reduced to zero despite the fact that the blood volume fraction, λ, in a tissue is small (roughly 5 to 10%) by subtracting a pre-contrast images from each of the post-contrast images. Although T_1 is reduced dramatically as well, the potential increase in signal is overwhelmed by the loss of signal from a reduced T_2^* value at these initially high blood concentration levels (see Ch. 21). On the other hand, when steady state is reached, the remaining effect on T_2^* is negligible and only a T_1 effect remains as the blood concentration level reaches a much lower steady-state value.

T_2^* measurements for relative blood volume quantification

During the first-pass injection of 10 cc of contrast agent intravenously, the bolus is somewhat reduced in concentration but not so much that T_2^* effects vanish. The intravenous injection leads to a dispersion of the bolus in time roughly on the order of 15 to 60 seconds. The signal loss associated from T_2^* comes not just from the blood itself but also from signal dephasing outside the blood vessels. However, there is no guarantee here that the concentration as a function of time is the same from voxel to voxel or even closely related to its neighbor during a bolus injection. However, if the same distribution of contrast agent in the

blood exists, then a ratio of integrals over $q(t)$ will give relative values for cerebral blood volume at two positions $\vec{r}$ and $\vec{r}\,'$, i.e.,

$$\lambda(\vec{r}\,')/\lambda(\vec{r}\,) = \frac{\int dt\, q(\vec{r}\,', t)}{\int dt\, q(\vec{r}, t)} \tag{24.73}$$

Problem 24.29

How does the calculation of $\lambda(\vec{r}\,')$ change if both T_1 and T_2 changes are significant?

Although it is not possible to get an absolute blood volume without knowing the concentration in the blood directly, taking the natural logarithm of the signal normalized to the data prior to injection of the contrast agent gives a function $\tilde{q}(t)$ which is directly proportional to $q(t)$ since $R_2{}'$ (the relaxation rate induced by the presence of the contrast agent) is directly proportional to $q(t)$, the amount of contrast agent present:

$$\begin{aligned} \tilde{q}(t) &= -\ln(\text{signal post-contrast}/\text{signal pre-contrast}) \\ &= \left(R'_{2_{\text{post}}}(t) - R'_{2_{\text{pre}}}\right) T_E \\ &= \kappa c(t) T_E \end{aligned} \tag{24.74}$$

where κ is related to the magnetization, ΔM_{ca} of the contrast agent (it also depends on the agent's susceptibility, vessel size and geometry, B0 and the sequence type (GE vs SE)), the geometry of the blood vessel distribution and the blood's T_1 and T_2 signal dependence on ΔM_{ca} and c(t) is the voxel-averaged concentration $q(t)/V_0$.

One reason for using a T_2^* reducing agent to measure rCBV dynamically is that the signal loss can be quite substantial so the signal-to-noise ratio should be very good for this calculation. An example set of images in a human brain are shown in Fig. 24.31. The examples in Figs. 24.31a and b showing a pre- and post-contrast image give an idea of the relative CBV. For example, the gray matter seems to have been most darkened by the delivery of contrast agent and must have the highest CBV.

Problem 24.30

a) Assume that $q(t)$ and V_{blood} and hence, the concentration, $c(t)$, have been found for each pixel. If all vessels have the same concentration-time curves, $c_v(t)$, is it reasonable to assume that the blood volume fraction, λ, in the tissue is

$$\lambda = \frac{c(t)}{c_v(t)} \tag{24.75}$$

for all pixels?

b) Is it appropriate to use the form $\lambda = \frac{\int dt\, c(t)}{\int dt\, c_v(t)}$ in this situation too? If so, why?

Use of T_1-based contrast agents

For T_1-reducing agents, the signal from blood will be enhanced because of the shorter T_1. Subtracting the pre-contrast from post-contrast steady state data will eliminate the background tissue occupying the same voxel as the blood. Hence,

$$\begin{aligned}\Delta\hat{\rho}_{\text{voxel}} &= \left((1-\lambda)\hat{\rho}_{\text{tissue}} + \lambda\hat{\rho}'_{\text{blood}}\right) - \left((1-\lambda)\hat{\rho}_{\text{tissue}} + \lambda\hat{\rho}_{\text{blood}}\right) \\ &= \lambda\Delta\hat{\rho}_{\text{blood}} \\ &= \lambda\rho_{\text{blood}}\sin\theta\left\{\frac{(1-E_1')}{1-E_1'\cos\theta} - \frac{(1-E_1)}{1-E_1\cos\theta}\right\}\end{aligned} \tag{24.76}$$

where $\hat{\rho}_{\text{blood}}$ is the blood signal post-contrast, and E_1 and E_1' are the values of $E_1 = e^{-T_R/T_1}$ pre- and post-contrast, respectively, and T2* effects have been ignored. Although it is possible to extract ρ_{blood} knowing T_1 of blood and θ, accuracy is compromised by errors in T_1 and θ. To avoid these difficulties, a normalized solution is sought which cancels all these dependencies. The solution is to be found by using the signal from a voxel which is completely blood.

By normalizing the signal differences pre- and post-contrast injection, the blood volume estimate can be found from

$$\lambda = \frac{\hat{\rho}_{\text{brain,post}} - \hat{\rho}_{\text{brain,pre}}}{\hat{\rho}_{\text{blood,post}} - \hat{\rho}_{\text{brain,pre}}} \tag{24.77}$$

since the denominator is simply $\Delta\rho_{\text{blood}}$. The signals for gray matter and blood are obtained from a 3D, T_1-weighted, sagittal or coronal coverage of the entire brain. This assures that the blood is saturated so that significant changes occur pre- and post-contrast injection. Actually, some practical problems may exist. Since rf coils are not perfectly uniform in their response and arterial flow can be very fast, some of the relevant assumptions made are violated. In practice, it may be possible to correct for signal variations due to rf variability, and a saturation band can be applied caudally (toward the feet) to keep blood signal properly saturated.

Problem 24.31

a) If the blood were not saturated, and inflow refreshed the blood flow significantly, why would (24.77) fail?

b) If inflow is still a problem near the base of the brain, how could the blood be saturated in this region?

The ability to determine the blood volume hinges on changes in signal pre- and post-injection of a contrast agent from the blood itself. In the steady state, the contrast agent is so diluted that R_2^* is effectively $R_{2_0}^*$, but R_1 is still significantly different than $R_{1,0}$. Most contrast agents obey the relations

$$R_1 = R_{1_0} + \alpha[c] \tag{24.78}$$

and

$$R_2^* = R_{2_0}^* + \beta[c] \tag{24.79}$$

where $[c]$ is the concentration of the contrast agent. With current contrast agents, $\alpha \simeq 4.0$ /mM/s and $\beta \simeq 5.0$ /mM/s. Usual doses of contrast agent are 0.1 mmol/kg of body weight. For a 50 kg person, this implies a dose of 10 cc when the contrast agent formulation is 0.5M. The blood volume in the body is roughly 5 liters, hence the concentration is reduced by a factor of 500 in the steady state.

Problem 24.32

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a) For the given values of α and β, find the changes in R_1 and R_2 for $[c] = 1.0$ mM.

b) Discuss why little signal loss occurs due to T_2^* dephasing if $T_{2_0}^* = 100$ ms and the imaging sequence uses a T_E of 5 ms.

c) Practically, small amounts of the agent can escape the vasculature so that the effective volume of dispersement is 10 liters. If an intravascular contrast agent has a relaxivity of 4 /mM/sec, what is the T_1 value of blood after equilibrium is reached?

Measured results using this method reveal a normal GM blood volume of roughly 5% and WM blood volume of 2%. The errors are roughly 10% per voxel for voxel sizes of about 4 mm^3. The numbers quoted for blood volume in GM and WM were obtained over large regions of interest to increase the statistical confidence of these estimates.