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Some Thoughts on a Joint PET/MR model for Pharmokinetic Analysis.

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Arterial and Voxel Input Functions.

We are interested in understanding the mechanism for delivery of blood to perfusing tissues in the brain. One way of quantifying the process is via DCE MRI. The accepted model for describing this data contains terms including arterial input function, bolus dispersion distribution, and voxel residence distribution. We need to understand the expected significance of each of these in the generation of data. We start with a simple three part convolution model based on Gaussian functions. We will then show that, given the circumstances of data acquisition, typical values seen in the literature and measurement accuracy, various prediction of this model would be expected to hold. In particular, the final contrast time curve seen in many tissue locations for MRI data are in fact almost indistinguishable from the voxel input function at the level of expected errors. I then suggest a method for local modelling of the AIF based upon measurements in the carotid artery and superior saggital sinus.

We define;

- the "arterial input function" (AIF) as the distribution of contrast arrival time in the large vessel of the brain.
- the "bolus dispersion distribution" (BDD) as the distribution of arrival times of contrast molecules prior to a specific location in the brain, defined relative to their arrival in large blood vessels.
- the "voxel residence distribution" (VRD) as the distribution of times for which contrast molecules arriving in voxel remain within it (and are therefore available to modify observed MR signal within that voxel).
- the "voxel input function" (VIF) is the true distribution for arrival of contrast at a voxel, and the distribution we should be using in order to compute flow (see below).

We will avoid definitions such as mean tissue transit time (MTT), or bolus arrival time (BAT), until later due to their non specific nature.

A Simple Gaussian Convolution Model

We will write the convolution of two distribution $d_a(t)$ and $d_b(t)$ can be written as

$$d_{ab}(t) \;=\; d_a(t) \otimes d_b(t)$$

the convolution of three distributions is given by

$$d_{abc}(t) \;=\; d_a(t) \otimes d_b(t) \otimes d_c(t) \tag{1}$$

For purely Gaussian distributions we can write

$$d_{abc}(\sigma_{abc}, \delta_{abc}, t) \;=\; g_a(\sigma_a, \delta_a, t) \otimes g_b(\sigma_b, \delta_b, t) \otimes g_c(\sigma_c, \delta_c, t) \tag{2}$$

where σ is the usual Gaussian width parameter (standard deviation) and δ is the mean temporal offset. For purposes of understanding the perfusion process we are not very interested in δ_{abc}, however, σ_{abc} can be written as

$$\sigma_{abc} \;=\; \sqrt{\sigma_a^2 \;+\; \sigma_b^2 \;+\; \sigma_c^2} \tag{3}$$

i.e. the width of the resulting distribution is given by the quadrature addition of widths. Using this relationship we can use the final distribution to estimate any one of these components given knowledge of the other two. For example,

$$\sigma_c \;=\; \sqrt{\sigma_{abc}^2 \;-\; \sigma_a^2 \;-\; \sigma_b^2} \tag{4}$$

It is a well known property of this calculation, when applied to imperfectly measured (noisy) estimates of these terms that estimated values can be highly unstable. A corollary to this is that during quadrature addition, slight imbalances between the relative magnitudes of terms leads to domination by the larger ones. As a rule of thumb, if $\sigma_c \;\leq\; \sigma_{ab}/4$ then $\sigma_{abc} \;\approx \sigma_{ab}$ within a few percent. For example $\sigma_a \;=\; 4$, $\sigma_b \;=\; 3$ and $\sigma_c \;=\; 1$ then $\sigma_{ab} \;=\; 5$ and $\sigma_{abc} \;=\; 5.1$. Clearly, our ability to then estimate σ_c using equation 4 then crucially depends upon our ability

to observe differences between values of 5 and 5.1. If these values have a few percent error then the resulting value is effectively random noise.

As the behaviour of the Gaussian solution is a statistical argument which derives from the quality of input data it is largely independent of the numerical approach used for the deconvoltution (e.g. PCA, Fourier or quadrature subtraction). We could continue this argument further and apply error propagation [Tina memo 2001-003], but this is unnecessary for what follows.

Back of the Envelope Calculations for DCE-MRI data

We now make the association that DCE-MRI time curves can be thought of as a convolution such as equation (1). With the observed contrast concentration time curve being generated in a voxel according to

$$C(t) \;=\; AIF(t) \otimes BDD(t) \otimes VRD(t)$$

Clearly, given $C(t)$, the AIF and BDD (the effective VIF), then $VRD(t)$ can be estimated via a process of deconvolution as a precursor to estimation of perfusion flow.

The point to be made here is that although we expect the various distributions to vary [1], to a good approximation the process of deconvolution must have the same stability properties as our Gaussian model approach for the estimation of σ_c. i.e. if we can't get a good estimate using equation 4 due to the noise on data then we would not expect to do better with slightly differently shaped distributions.

The mathematical consistency of any deconvolution based algorithm such as that proposed by [Ostegaard] is not challenged here. However, the stability and suitability of calculations for such data now depends crucially upon the relative importance of these three distributions during the formation of data and this is reflected in the corresponding values of σ.

We know from the established literature that although MTT is often estimated as 4 seconds, the time that contrast is expected to remain in a capillary (and a voxel) is nearer to 1 second (± 0.5) [Scott]. Also, when using a deconvolution approach to estimate flow the presence of bolus dispersion can introduce a systematic error in the estimate of flow of a factor of 2-3 (say 2.5) [Calamante]. By making the following associations,

$$C(t) \;=\; d_{abc}, \quad AIF \;=\; d_a \quad BDD \;=\; d_b \quad and \quad VRD \;=\; d_c$$

we can interpret these observations as constraints on the typical widths of distribution used in the Gaussian model. MTT estimated via deconvolution of C(t) with AIF can be associated with

$$\sigma_{bc} \;=\; 4$$

For the voxel residence of the contrast we might assume

$$\sigma_c \;=\; 1$$

Alternatively, by associating the underestimate of flow with the methodological error of using MTT (i.e. $BDD \otimes VRD$) rather than VRD

$$\sigma_{bc}/\sigma_c \;=\; 2.5$$

i.e. rather than 4. However, the two estimates are consistent within the expected uncertainties and we expect $\sigma_b \approx 3\sigma_c$.

Taking the value of $\sigma_{bc} \;=\; 4$ this relationship can now be used to estimate

$$\sigma_c \;=\; 1.33$$

and

$$\sigma_b \;=\; 3.77$$

To compute flow we need a valid (per voxel) VRD (σ_c in the Gaussian model), as this is the term which relates to the velocity of molecules in a voxel and therefore the flow. Clearly, what is really needed to calculate VRD is then a valid (per voxel) estimate of the VIF (σ_{ab} in the Gaussian model). Recent publications which attempt to estimate such a local "AIF", by selecting time curves with large RCBV, fail to generate distributions with a

[1] AIF is often assumed to be a Gamma-variate, and[Calamante] assumed that the BDD distribution was exponential, though such an asymmetrical distribution is biologically unrealistic.

sufficient variation in "VIF" to account for the required corrections to flow estimates [Ref]. The likely explanation is that even though the new AIFs are spatially closer to the location of voxel analysis, they still do not reflect the true VIF.

Taking a typical value for AIF of $\sigma_a = 4$, we now have all of the required parameters for our model and can see that the calculation of VRD follows the previous numerical example. i.e. it requires us to be able to perform a quadrature subtraction of two numbers of approximately 5.5 and 5.6. In fact, given the noise on typical $C(t)$ data is of the order of 10% we must predict flow to be uncomputable [Tina memo 2001-003] even for a perfect estimate of VIF.

Consequences for Flow Estimation in MR

Of course we are free to change these numbers and investigate the possible consequences of various combinations. The bottom line is that we need to believe that $\sigma_b \leq \sigma_c/2$ if we wish systematic errors on flow to be better than 50% when deconvolving with an AIF. With 10% measurement error we also need $\sigma_{ab} \leq 4\sigma_c$ to obtain a statistical error better than 50%.

I finish this analysis with a statement I have made for the last 10 years; **de-convolution based estimates of flow using DCE-MRI data generate results which correlate with true flow due to physical properties other than those the theory accounts for**. In particular, use of a direct estimate of AIF and not VIF for deconvolution makes flow estimates susceptible to the variations in time taken for blood to reach a voxel, rather than the velocity of blood through it. Although this estimate of MTT will scale with average flow, and therefore lead to the expected correlations with ground truth (e.g.PET), given the magnitude of the processes involved in the calculation, it is not a justifiable estimate of true flow. Consequently, estimated values cannot be reliable compared between different subjects or even between different areas of the same brain. Unfortunately for those who have an interest in this technique, this conclusion conflicts with many of the intended clinical uses of perfusion based analysis. These conclusions follow not from a criticism of the concept of deconvolution per-se, but from consideration of the characteristics (widths) of typical distributions involved.

We can see that for these values of typical parameters the observed distribution $C(t)$ is actually an estimate of $VIF(t)$. i.e. for small VRD values what we see in the voxel is effectively the arrival time distribution. The smaller we make our voxels the more accurate this approximation and therefore also the poorer the approximation to the standard de-convolution approach. Even large voxels however, will not make deconvolution with AIF generate valid estimates.

Deriving the extended Tofts Model

Determining the contrast conncentration of the extravascular space $C_e(t)$ requires the solution of

$$\frac{\partial C_e(t)}{\partial t} \; + \; \alpha_2 \; C_e(t) \; = \; \alpha_1 \; C_p(t)$$

where $C_p(t)$ is the concentration in plasma.

This is a specific form of a forced first order system

$$\frac{\partial y(t)}{\partial t} \; + \; g(t) y(t) \; = \; x(t)$$

the standard solution of which involves using an integrating factor in order to rewrite the L.H.S. to be of the form

$$I(t) \; \left[\frac{\partial y(t)}{\partial t} \; + \; g(t) \; y(t) \right] \; = \; \frac{\partial (I(t) y(t))}{\partial t} \; = \; I(t) \frac{\partial y}{\partial t} \; + \; y(t) \frac{\partial I(t)}{\partial t}$$

so that by associating terms

$$I(t) g(t) \; = \; \frac{\partial I(t)}{\partial t}$$

rewriting gives

$$g(t) \; = \; \frac{1}{I(t)} \frac{\partial I(t)}{\partial t}$$

therefore

$$ln(I(t)) \;=\; \int g(t)\; dt$$

i.e.

$$I(t) \;=\; exp(\int g(t)\; dt)$$

for the Tofts model the $g(t) \;=\; \alpha_2$ so that $I(t) \;=\; exp(\alpha_2 t)$ and we have

$$\frac{\partial(exp(\alpha_2 t)\; C_e(t))}{\partial t} \;=\; \alpha_1 exp(\alpha_2 t) C_p(t)$$

$$exp(\alpha_2 t\; C_e(t)) \;=\; \int_0^t \alpha_1\; exp(\alpha_2 \tau) C_p(\tau)\; d\tau$$

so that

$$C_e(t) \;=\; \frac{\int_0^t \alpha_1\; exp(\alpha_2 \tau) C_p(\tau)\; d\tau}{exp(\alpha_2 t)}$$

$$=\; \int_0^t \alpha_1\; exp(-\alpha_2(t-\tau)) C_p(\tau)\; d\tau$$

The contrast seen in a voxel will be the volume weighted extravascular and vascular contrast concentration

$$C(t) \;=\; \beta_1 C_p(t) \;+\; \beta_2 \int_0^t \alpha_1\; exp(-\alpha_2(t-\tau)) C_p(\tau)\; d\tau$$

this is the standard form of the Tofts model, although the exact definition of paramters will depend upon how the αs and βs are defined. Strictly they are all independant parameters whereas the Tofts model

$$C(t) \;=\; v_p C_p(t) \;+\; k_{trans} \int_0^t exp(-k_{trans}(t-\tau)/V_e) C_p(\tau)\; d\tau$$

has several less.

$$v_p \;=\; \beta_1 \;\;,\;\; k_{trans} \;=\; \beta_2 \alpha_1 \quad and \quad V_e \;=\; \beta_2 \alpha_1 / \alpha_2$$

Making the forward and backward leakage rates equal $\alpha_1 \;=\; \alpha_2$ simplifies things. We can then say that V_e is the volume of extra vasular contrast within the hypothetical boundaries of the voxel, and k_{trans} is the rate of contrast volume leaked into that volume.

Interpolation of Arterial Input Functions

The above assumes a Gaussian convolution as an approximation for the effects of bolus broadening. However, an estimate of the true broadening process can be made as follows.

The sagital sinus (SS) and internal carotid artery (ICA) have different apparent AIF's ($ss(t) \in \mathbf{ss}$ and $ica(t) \in \mathbf{ica}$), **ss** being broader. If we assume that this change is due to successive application of some fixed perturbation process, described by a convolution, then

$$\mathbf{ss} \;=\; \mathbf{ica} \otimes \mathbf{r}$$

adopting an upper case notation for the Fourier transform,

$$SS(\omega) = F_\omega(\mathbf{ss}) \quad and \quad ICA(\omega) \;=\; F_\omega(\mathbf{ica})$$

we can write the complex frequency terms of the perturbation as

$$R(\omega) \;=\; SS(\omega)/ICA(\omega)$$

for a repeated convlution, the possible set of allowable convolutions is described by the power law[2]

$$R(\omega)^x$$

the complex Fourier terms of any allowable voxel input function can be interpolated using

$$AIF_x(\omega) \;=\; ICA(\omega) R(\omega)^x$$

[2]It must be remembered, it is convenient to represent $R(\omega)$ as $A_\omega exp(-i\theta_\omega)$ in order to interpret $R(\omega)^x$.

and

$$aif_x(t) \;=\; (F^{-1})_t(\mathbf{AIF}_x)$$

such that $aif_0(t) \;=\; ica(t)$ and $aif_1(t) \;=\; ss(t)$

This is a purely mathematical relationship, practical numerical calculation would need something which takes appropriate account of measurement errors, e.g. the Wiener Filter.

If we wished to be really clever we could try to use all voxels with $k \equiv 0$ as a sample of the allowed input functions and perform some form of joint analysis. Ideally, the interpolation function would be chosen to best approximate these samples.

MRI Perfusuion / Permiability Summary

By now the literature survey of pharmokinetic modelling should be making things clear that many models used for the analysis of MRI data do not have biological validity. We are approaching a time when we will have to define our own model, base upon what we believe to be logically possible. This is my view regarding the key constraints we must consider.

To recap; Perfusion data (particularly in the brain) shows us directly the complexity of the process of blood plasma and contrast delivery in biological tissue. The first thing to appreciate is that (unlike PET) observed signal due to passage of contrast is not proportional to nutrient delivery at capillaries. Due to the linearity of the measurement of contrast, it is an indication of all blood passing through any sized vessel.

While a relative blood volume and mean time of arrival can be meaningfully defined and measured, blood flow cannot. This is because, for a deconvolution based flow estimate to be correct, AIF estimates need to be local estimates of voxel input[3]. While we can say that any voxel input function is probably the result of the AIF convolved with something like a Gaussian, we do not know what the characteristic width of this is. We do know from our own Perfusion data that the width is expected to grow approximately linearly with mean arrival time (Figure 1), consistent with Sourbrons field theory model (voxel input distributions must monotonically increase their width over time), but this may not be immediately useful to us in pathology. The key point to be made here is that what is seen in MRI perfusion data is effectively the voxel input function, this is an insight we can exploit.

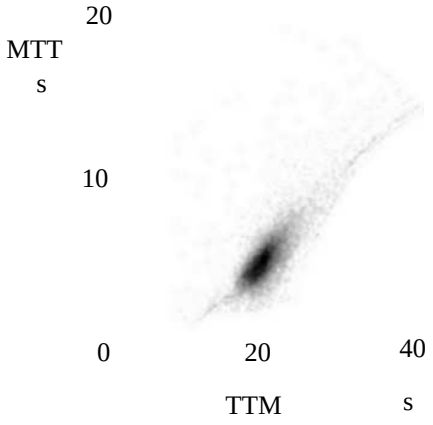

Figure 1: Distribution of first pass bolus standard deviation (MTT) plotted against time of arrival (TTM) for normal brain tissue.

Turning now to pharmokinetic Permiability data, the same biological arguments apply. We do not know the true AIF with which to construct compartmental models. However, applying our understanding of Perfusion data we can say that a model of contrast delivery can be constructed as the measured AIF convolved with a broadening function of unknown width at any given location. Also the compartmental delivery model (for whatever number of components) can be constructed assuming this "first pass" term. It should therefore be possible to analyse time course Permiability data using an AIF and time course as input and estimating the time shift along with **broadening of the voxel input function** and the total contrast volume, while simultaneously extracting the other parameters of the compartmental kinematic model. As the effective numbers of compartments is unknown,

[3]However, as per S. Sourbron's paper, there is a process which operates between observation of an AIF in an artery and the voxel input which must be expected to dominate the effects of voxel transit time in the generation concentration time curve (calculations above).

it would be necessary to perform model selection, and this in turn requires a good appreciation of the measurement accuracy of time course data. As always any Likelihood analysis needs to be appropriately constructed.

We can confirm the behaviour of our parameter estimations by plotting fitted convolution width against time of arrival. As for perfusion data (Figure 1) there should be a strong correlation in normal tissue. In addition, for normal tissue with an intact blood brain barrier, any fitted permiability term (k_{trans}) should be zero (to the accuracy we can measure it). This is also true for large veins such as the sagital sinus.

While this model is similar to many pharmokinetic models, in detail I believe that it differs, particularly with respect to interpretation of the origins of first pass bolus width, the recirculation effects and the appreciation of statistical properties of measurement. It would be very different if we were to incorporate a local field theory by applying a smoothness constraint to local arrival time and broadening.

Turning now to synergies with PET data, there are more parameters in this model than could be reliably estimated with MRI data alone, so a fusion with PET data might be useful in local selection of the order of compartmental model whilst also constraining the total contrast volume. Direct estimation of local flow is not possible without considering the variation in transit time between neighbouring voxels. However, the ability to normalise the volume of the first pass uptake curve and constrain recirculation effects would probably be useful, as permiability parameters are expected to correlate strongly. PET will need its own arterial input function obtained in an equivalent artery. The delay and dispersion parameters en-route to a voxel (or region) and all recirculation processes can then be assumed to be equivalent as in MRI data (metabolism would be different I expect). We must remember there must be an additional local scaling parameter which relates observed volumes to that which is available for perfusion. This parameter is structural in nature but plays exactly the same role as the haematocrit. We also need to be able to register PET/MR data and also assume that pharmokinetic factors and blood delivery are identical between acquisitions.

I suggest we now attempt to construct a mathematical model within this framework, and then try to assess its practical (goodness of fit) and statistical viability (parameter MVB's) using a carefully defined Likelihood.