The Physiological Significance of the Tmax Parameter in Bolus Tracking MRI

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Background: Tracer kinetic analysis of bolus tracking MRI studies provides insight into the regional hemodynamics of brain tissue. Physiological parameters often derived are CBF, MTT and CBV, but recently the Tmax parameter has proved a promising penumbra pseudo marker in several studies [1, 2]. However to the best of our knowledge, no interpretation of the underlying physio-/pathological phenomena that Tmax reflects has been made. Tmax is the time to peak of the impulse response and theoretically it reflects bolus arrival time delay from the site of AIF selection to the tissue (time to travel – TTT), provided that no downstream dispersion is taking place. However, due to the properties of the deconvolution algorithm using SVD, Tmax is not a simple TTT measure even in the absence of dispersion.

Aim: We performed simulations to investigate the influence of the fundamental hemodynamic parameters CBF, MTT, CBV and TTT on Tmax and analyzed cases with hemodynamic disturbances to accompany the simulation results.

Methods: Simulation: We simulated perfusion data with MTT and TTT ranges/increments of 4-16s/2 s and 0-10 s/0.5 s respectively. Simulations were repeated for 3 different types of residue functions: exponential, linear and boxcar. Convolution was performed analytically to avoid discretization errors. Signal simulation and AIF parameters was performed as in [3], with parameters: TR=1.5, SNR=50; k values were set to reflect a gradient echo sequence with AIF signal drop of 80 % and a 40 % signal drop gray matter. These parameters are consistent with our clinical data. The number of runs was 500 for each combination of parameters. We calculated MTT=CBV/CBF and thus simulated over a range of 8 CBF values for each combination of CBV, TTT and MTT.

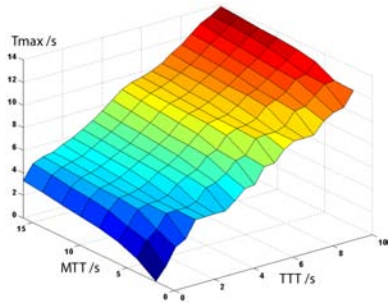

Figure 1: Depicts how Tmax can be described as a linear combination of TTT and MTT. The example is an exponential r(t) with CBV=0.04. Colormap is Tmax values.

Cases: We examined two acute stroke patients and use the results of the simulations to make inferences about the hemodynamic disturbance of the patients. Scan protocol was TR=1.5 s, TE=45 ms. Time to scan from onset and NIHSS was 4h:55m /NIHSS=19 and 1h:45m /NIHSS=10 for patient 1 and 2 respectively. We produced Tmax maps using the standard SVD algorithm and MTT maps using the circular SVD method [3] in order to get an MTT estimate that is unbiased by delay. No blurring of the raw data was done in order keep the SNR in line with the simulations and to maintain spatial resolution.

Results: Simulation: Figure 1 shows Tmax as a function of TTT and MTT for a CBV of 4% and 2% respectively. We found that the Tmax parameter was described well as a linear combination of TTT and MTT in the simulation domain as a whole; the results of the linear regression are seen in Table 1. TTT influence Tmax invariably across r(t) and CBV, but the dependency of MTT as well as the static offset varies across different residue functions (the coefficients were significantly different at p=0.05).

	CBV	Exponential r(t)	Boxcar r(t)	Linear r(t)
1	2%	0.2M+1.0T+1.3, R=0.99*	0.5M+1.0T-0.1, R=0.99*	0.4M+1.0T+2.7, R=0.98*
2	4%	0.1M+1.0T+1.6, R=0.99*	0.5M+1.0T-0.2, R=0.99*	0.4M+1.0T+2.9, R=0.98*

Table 1: Shows the linear dependency on Tmax of MTT (M) and TTT (T). R: The correlation coefficient. *: p-value for the linear model is<0.01.

Cases: In patient 1 (figure 2) the area of prolonged MTT roughly corresponds to the area of prolonged delay. In patient 2 the delay prolongation is accompanied by a very modest MTT prolongation.

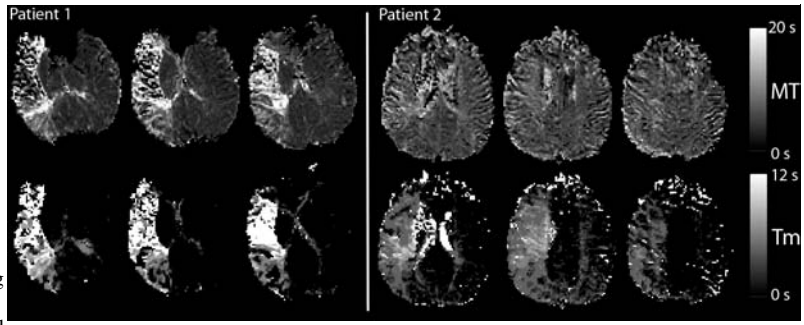

Figure 2: Shows MTT (upper row) and Tmax (lower row) maps for 2 patients. Same colormap scalings are used for both patients.

Discussion: Simulations: Tmax maps appears to be reflecting mainly TTT and to a lesser degree MTT. The MTT dependency is theoretically unexpected but we hypothesize that it is introduced by the filtering properties of the SVD algorithm acting as an adaptive filter being influenced by MTT. MTT is a property of the microvasculature whereas TTT is the delay from the AIF selection site to the microvasculature. As such, it is conceivable that TTT will be sensitive to phenomena affecting the macrovasculature e.g. unlysed thrombi or occlusions of other origin. The MTT map as calculated by the circular SVD is delay insensitive and therefore more sensitive to the microvascular hemodynamics [3, 4].

Cases: Patient 1 has similar volumes of tissue with prolongation of MTT and Tmax. Keeping the results of the simulations in mind, we recognize that an MTT lesion will always affect Tmax, although with a modest weight (table 1). The very high Tmax values indicate that MTT in combination with TTT are responsible for the hyperintensities. Interestingly patient 2 seems to have a delay abnormality but with a very modest MTT abnormality. We speculate that this represents a case where sufficient collateral supply exists (although the supply is delayed) to maintain microvascular integrity, i.e. the Tmax abnormality reflects almost only TTT prolongation and not MTT prolongation. Three clinically useful features make the Tmax parameter attractive: *1)* it can be determined from a limited number of sampling points at the beginning of the bolus, so that studies that are corrupted by severe motion half way into the bolus passage are thus still usable. *2)* As seen in patient 1, areas of very low perfusion will have very low CBV (dark spots on MTT) and often CBV will be biased due to limited sampling time. Tmax is independent of CBV and resistant to CBV introduced bias; with just a minimal amount of tracer it will still yield an estimate of Tmax. [2] *3)* It is expected to be uniform across gray and white matter, a useful property when thresholding for various purposes. Disadvantages include the sensitivity to macrovascular delay in general and not just acute occlusions; sufficient collateral supply can be delayed and will show up on Tmax maps, but will not necessarily indicate an acute hemodynamic disturbance (e.g. a ICA stenosis contralateral to the site of AIF selection), a problem well described on conventional MTT maps as well [5, 6]. Tmax can only be directly quantized in multiples of the sampling time (here TR=1.5 s) this limits its ability to describe in detail the heterogeneity of an acute infarction, but faster bolus tracking techniques might address this issue [7]. Being sensitive to delays, Tmax is also sensitive to the timing differences of slices during acquisition, these can affect Tmax by up to one unit sampling time and these timing differences should be appropriately accounted for.

Conclusion: Tmax is a parameter with several attractive properties for clinical use. It reflects a combination of Time To Travel from the site of AIF selection to the tissue and to a lesser degree MTT, it is therefore mainly a measure of macrovascular delay. Used in conjunction with a delay insensitive MTT map it provides additional information on the hemodynamic status. Slice acquisition timing will confound the Tmax estimates and should be corrected for before post-processing.

References: 1: Ludy C. Shih et al. Stroke 2003; 34. **2:** K.S. Butcher et al. Stroke 2005; 36. **3:** O. Wu et al. MRM 2003; 50. **4:** L. Ostergaard et al. MRM 1996; 36. **5:** F. Calamante et al. MRM 2000;44. **6:** O. Wu et al. MRM 2003; 50. **7:** M. Pedersen. JMRI 2004; 20.