The arterial response function: A new concept demonstrated in a simulation study investigating the influence of the injection rate on the quantification of plasma flow

Michael Ingrisch[1], Steven Sourbron[2], Felix Schwab[1], Mike Notohamiprodjo[3], Maximilian F Reiser[3], Michael Peller[1], and Olaf Dietrich[1]

[1]*Josef Lissner Laboratory for Biomedical Imaging, Institute for Clinical Radiology, Ludwig-Maximilians-University Hospital Munich, München, Germany,* [2]*Division of Medical Physics, University of Leeds, Leeds, United Kingdom,* [3]*Institute for Clinical Radiology, Ludwig-Maximilians-University Hospital Munich, München, Germany*

Target audience Clinicians and physicists interested in perfusion quantification

Purpose To study the influence of the contrast agent (CA) injection on the quantification of perfusion, it is necessary to link the injection scheme with the form of the resulting arterial input function (AIF). In a previous study, this has been accomplished by modeling the human vasculature [1] for brain tissue with an intact blood-brain barrier. In this study, we propose a model-free approach by introducing 'arterial response functions' (ARF), which allow for the generation of realistic AIFs for arbitrary contrast agent (CA) injections.

We use this approach in a simulation study that investigates the influence of CA injection rate on the quantification of plasma flow in tumor tissue. The hypothesis is that, for the quantification of plasma flow, fast injections are required in tissues with short plasma transit times, whereas in tissues with long transit times slower injections suffice.

Theory The AIF can be seen as the response of the arterial system to the CA injection which can be described as a boxcar function with amplitude "CA amount per time". Since, within certain limits, the body can be assumed to be a linear and stationary system, the AIF can be written as the convolution of the injection with a yet unknown ARF: $AIF = Injection \otimes ARF$. The ARF describes the arterial response to an infinitely fast injection of a unit amount of CA and as such has the unit ml^{-1}. It can be determined from a measured AIF by means of numerical inversion of the convolution. When the ARF is known, arterial input functions and ensuing tissue curves can easily be calculated for arbitrary CA injection schemes: Convolution of the ARF with an injection yields the AIF, which can then be used for the calculation of tissue curves with a pharmacokinetic tissue model.

Methods A single AIF was measured in the descending aorta after injection of 7ml of CA (Gd-DTPA) with an injection flow of 4ml/s and a temporal resolution TR of 1.0s [2]. The ARF was obtained by deconvolving this AIF (interpolated to TR=0.2s) with a boxcar function describing the injection (amplitude c_{CA}=2mmol/s and duration of 1.75s) using truncated singular value decomposition with a regularization parameter of 0.2. Synthetic injection functions with the same CA volume and injection rates of 3.0, 2.0, 1.0, 0.5 and 0.3 ml/s were convolved with this ARF to generate artificial AIFs.

For the simulation study, four synthetic tissue curves with parameters typical for strongly vascularized tumors [2] were generated from these AIFs with a two-compartment exchange (2CX) model [3] with plasma flows F_p=[10,40,90,130]ml/100ml/min, v_p=4.8%, plasma transit times of [28.8, 7.2, 3.2, 2.2] seconds, permeability-surface area product PS=2.9ml/100ml/min and interstitial volume v_e=9.7%. Monte Carlo simulations with fixed noise standard deviation of max(original AIF)/400, TR=1.0s and 1000 repetitions were used to assess the relative errors ($F_{p,est}$–$F_{p,true}$/ $F_{p,true}$) of plasma flow estimates resulting from fitting a 2CX-model to these tissue curves.

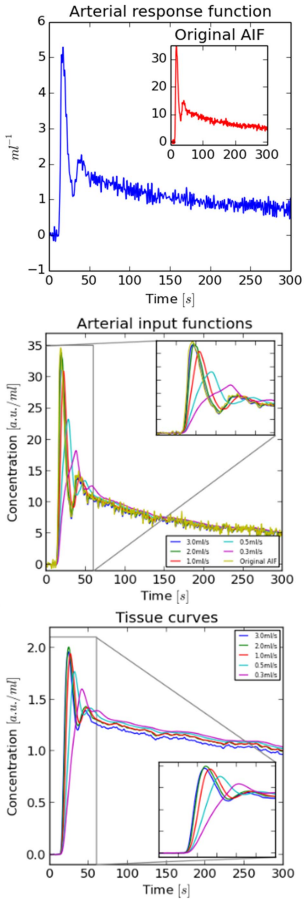

Figure 1: Arterial response function (top), synthetic AIFs for several injection flows (center) and synthetic tissue curves for F_p=90 ml/100ml/min (bottom)

Results Measured AIF and ARF are displayed in Fig. 1 (top). Fig. 1 (center) displays synthetic AIFS for injections with different rates, FWHM of the AIFs are 9.0, 9.4, 10.4, 17 and 84 seconds. Slower injections yield lower peak heights, longer duration of the first pass and flatter slope than the original AIF. This behavior can also be observed in the generated tissue curves (see Fig. 1 bottom for F_p=90 ml/100ml/min). Boxplots in Fig. 2 display the relative error of plasma flow estimates for all simulated injection flows and plasma flows: In tissue with low plasma flow, all injection schemes yield similar bias and variance; for higher plasma flows, the variance is notably smaller if a faster injection is used.

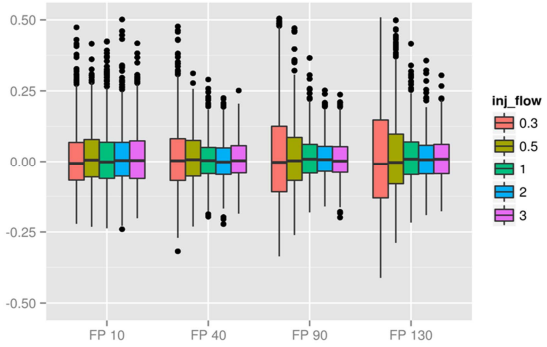

Figure 2: Relative error of F_p estimates for all simulated injection rates (color coded) and plasma flows (grouped)

Discussion The ARF and the original AIF have very similar appearance – presumably since a rapid injection has been used for the measurement of the AIF. The ARF also accounts for CA recirculation, in that a second pass is clearly visible, as well as for CA washout on a longer time scale. This illustrates that, unlike in previous studies for the simulation of AIFs [1], no modeling or additional assumptions are required for the generation of artificial AIFS as in Fig. 1. For the validation of the ARF approach, volunteer measurements with several different CA injections would be very useful.

Simulation results confirm the intuition that the bolus width has to be shorter than tissue transit time in order to quantify the plasma flow: in the low-flow tissue with 44s transit time, all five injections yield estimates with similar variance, whereas in the tissues with high flow short transit times of 3.2s and 2.2s the slow injections result in considerably larger variance and lower precision of F_p-estimates (see Fig.2). This is in accordance with a previous simulation study [4] in which similar observations were made for the dependence of K^{trans} on the injection rate – although the results cannot be directly compared, since a different model was used.

Conclusion The formalism of arterial response functions, to the best of our knowledge not reported previously, allows for straightforward simulation of different CA injection schemes. Potential applications of the ARF approach include the simulation of multi-bolus injection schemes as well as the reconstruction of arterial input functions from pre-bolus measurements – in fact, the ARF approach can be seen as a generalization of established pre-bolus techniques [5].

References 1.van Osch MJ et al. Magn Res Med. 2003;50:614 **2.Notohamiprodjo M** et al. J Magn Res Imaging. 2010;31:490 **3.Ingrisch M** et al. J Pharmacokinet Pharmacodyn. 2013;40:281 **4. Aerts HJ** Magn Res Med. 2008;59:1111. **5. Kostler H** et al.. Magn Res Med. 2004;52:296