Absolute CBV and AIF from Global Recirculation Approach

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Target Audience: Clinicians and researchers in quantitative perfusion MRI, CT and PET.

Purpose: **To estimate absolute cerebral blood volume (CBV) and arterial input function (AIF) without the need for direct measurement.** CBV provides valuable diagnostic contrast. However, so far only *relative* CBV (rCBV) has been estimated. The practically important parameter, CBV, relies on the fundamental quantity, the AIF, whose direct measurement is challenging [1,2]. So far, AIF estimation has relied on the first bolus passage, which is inaccurate, as the first pass and subsequent recirculation boluses overlap. **Here we design the global recirculation framework for determining AIF which includes all recirculation boluses, and which further allows us to redefine CBV.** We highlight the potential clinical relevance of our new biomarker, absolute CBV, in a glioma patient.

Methods: AIF estimation is a century-old problem, which technically requires modeling *recirculation* as opposed to a single pass of contrast through an organ. To resolve this problem, we consider the *global circulatory system*, Fig.1a, and model blood flow by three appropriately delayed impulse response functions (IRFs) $h_i(\omega)$ as in Fig.1b. IRFs are presented in the Fourier domain as convolutions turn into products:

$$j_{\text{out}}(\omega) = h_1(\omega)\, j_{\text{in}}(\omega) \quad , \quad j_{\text{in}}(\omega) = \lambda\, h_3(\omega)\,[\,I(\omega) + j_{\text{out}}(\omega) + j_2(\omega)\,] \qquad (1)$$

$$j_2(\omega) = (\,1-\lambda\,)\, h_2(\omega)\, h_3(\omega)\,[\,I(\omega) + j_{\text{out}}(\omega) + j_2(\omega)\,]$$

for any injection profile $I(\omega)$, usually a rectangular pulse in accordance with MR contrast injection protocols. The coupling between IRFs from different parts of the body enables adequate description of recirculation. We solve Eqs (1) exactly and obtain $j_{\text{in}}(\omega)$, contrast influx to the brain. Our next step is to tie $j_{\text{in}}(\omega)$ to the brain MRI measurement. To do that, we relate it to the *total contrast amount* $M(\omega) = j_{\text{in}}(\omega)\, R_1(\omega)$ via the brain residue function $R_1(\omega) = [\,1 - h_1(\omega)\,]/(-i\omega)$. The exact time domain expression, $M(t)$, is derived using methods of complex integration with IRFs as gamma distributions. The key now is to realize that $M(t)$ is contained in the DSC MRI signal $S(t)$, and that *it has exceptionally low noise* (Fig.1c) as it is averaged over N~10^5 voxels. Effectively, $M(t)$ is the average of ln $S(t)$ over the brain:

$$S_n(t) = S_{0,n} e^{-\Delta R^*_{2,n}(t)\, T_E} \quad , \quad \sum_{n=1}^{N} \Delta R^*_{2,n}(t) = \Omega \sum_{n=1}^{N} \zeta_n\, c_n(t) = \Omega \frac{M(t)}{V_v} \qquad (2)$$

Here $S_{0,n}$ is the pre-bolus signal and T_E is echo time. The transverse relaxation rate in the nth voxel $\Delta R^*_{2,n}(t)$ is expressed in terms of the blood concentration $c_n(t) = m_n(t)/v_n$ of contrast agent and the volume fraction $\zeta_n = v_n/V_v$ of blood in that voxel, or the CBV [3]. The voxel volume, V_v, and the proportionality constant, $\Omega = \chi\gamma B_0/3$, are known. Using the estimated IRF parameters, AIF is obtained as $c_{\text{in}}(\omega) = j_{\text{in}}(\omega)/F_{\text{in}}$, and subsequently transformed into time domain using methods of complex integration. The blood inflow into the brain, $F_{\text{in}} = \lambda F_c$, is the fraction λ of cardiac output $F_c = 8 \cdot 10^{-5}\,\text{m}^3/\text{s}$ which we presume known.

We are now **defining the CBV as the ratio of the two diverging integrals**:

$$\zeta_n = \lim_{T\to\infty} \int_0^T c_{v,n}(t)\,dt \Big/ \int_0^T c_{\text{in}}(t)\,dt. \qquad (3)$$

Both numerator and denominator of Eq (3) diverge due to recirculation, but their ratio *converges*, Fig.2d. This definition resolves the common issue of having to isolate the first bolus. Our ability to correctly define CBV relies on the global AIF, $c_{\text{in}}(t)$, compensating the divergency in the numerator of (3). This provides the desired connection between the fundamental problem of recirculation and the clinically valuable contrast.

MRI: Informed consent was obtained from a glioma patient. Gradient echo images were acquired during Gd-DTPA administration (0.1mM/kg, 5mL/s) at 1s intervals for first 60s, and at 5s intervals for next 300s totaling 120 samples. Imaging was performed on a 3T Siemens whole body scanner with an 8-channel phased array head coil. Parameters: TR=1000ms, TE=32ms, 10 contiguous 3mm thick axial slices, matrix 128×128, FOV=220×220mm^2, FA=30°, BW=1396Hz/pixel, in-plane resolution 1.7×1.7mm^2.

Results: Compared to the relative CBV (rCBV), Fig.1e, our approach provides the absolute measure of CBV. Small fraction of voxels with a diverging ratio in Eq (3) (Fig.3) correspond to imaging artifacts, regions of high blood volume and tracer leakage at tumor edge, where relation (2) between signal and CBV breaks down.

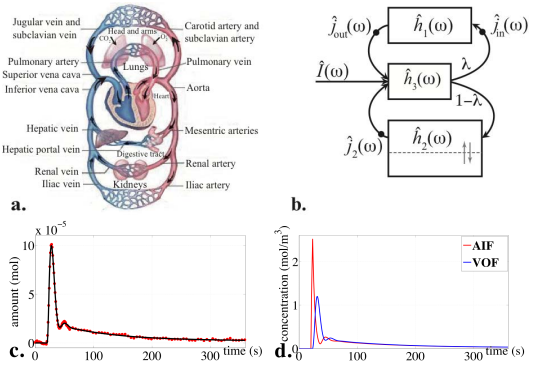

Fig.1: Three IRFs: h_1 represents the brain, h_2 the rest of the body (kidney, muscles, etc.), and h_3 represents the heart/lungs. Arrows in h_2 represent exchange between intravascular and interstitial spaces. Mass fraction λ of the contrast enters the carotid artery towards brain. **c.** The black line is the fit to $M(t)$ (red dots, data). **d.** The estimated AIF and VOF. **e.** Flair and post-contrast T_1 images of a glioma patient along with CBV and the conventional rCBV are shown from left to right. The red WM ROI is used to normalize rCBV. While rCBV is confounded by different angio-architectures and not diagnostically useful here, measures of absolute CBV may prove useful for early detection of clinically significant changes in tumor perfusion in gray matter structures.

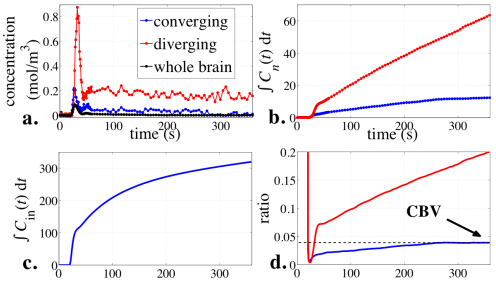

Fig. 2: **a.** Contrast concentration in two voxels (blue and red) and the whole brain (black). **b,c.** Integrals of AIF and voxel concentrations diverge. **d.** Ratio of Eq(3) converges to CBV for the blue voxel whereas it diverges for the red voxel.

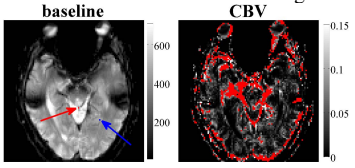

Fig. 3: Left: Fig. 2 voxels are marked. Right: all diverging voxels, mostly artifacts, are marked with red.

Discussion: We formulated the first framework in which the contrast dynamics in a given organ (here, in the brain) is linked to the topology and quantitative parameters of recirculation in the whole body. This approach generalizes the formula for the regional blood volume to incorporate the whole tracer concentration time course thus releasing the current restriction to its first pass. Our theory is applied in a technically feasible DSC MRI study for a glioma patient. Our global framework lays the theoretical basis for quantitative perfusion studies using MRI, PET and CT techniques.

References: **[1]** Kellner E. MRM 2013. **[2]** Kellner E. MRM 2013. **[3]** Yablonskiy D. MRM 1994. **[4]** Zierler K. Ann Biomed Eng. 2000.