

# Automatic extraction of an AIF using a novel blood-tissue equilibrium approach

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**Introduction:** Methods to determine the arterial input function (AIF) usually require manual blood sampling or assume that blood/tissue exchange rate ( $K^{\text{Trans}}$ ) and/or extracellular/extravascular volume ( $v_e$ ) are known in one or more reference tissues. In addition, arterial blood AIF may not accurately represent the AIF inside capillaries, and  $K^{\text{Trans}}$  can vary due to several physiologic parameters. However, the variation of  $v_e$  is expected to be limited – except perhaps in the presence of oedema during inflammation. We developed a new method that exploits the existence of blood/tissue equilibrium (BTE) points in DCE-MRI to automatically extract the shape of the AIF from the tissue concentration ( $C_T$ ) maps. Then, using the average  $v_e$  spectrum of a population, the method could accurately determine the absolute plasma concentration of Gd-DTPA ( $C_P$ ).

**Theory:** The two compartment model describing the exchange of a contrast agent between the blood compartment ( $C_P$ ) and the tissue compartment ( $C_T$ ) can be expressed as eq. [1]. Using eq. [1] and a known  $C_P$ ,  $C_T$  curves were calculated with different values of  $K^{\text{Trans}}$  and  $v_e$  (Fig. 1, blue curves [ $K^{\text{Trans}} = 0.14 \text{ min}^{-1}$ ,  $v_e = 0.6, 0.1, 0.14, 0.2, 0.3, 0.4$ ] and red curves [ $v_e = 0.14$ ,  $K^{\text{Trans}} = 0.6, 0.1, 0.14, 0.2, 0.3, 0.4 \text{ min}^{-1}$ ]). Inspection of Fig. 1A and Eq. 1 reveals the existence of two equilibrium points between tissue and blood, where  $dC_T/dt = 0$ . The first is located at the maxima of  $C_T$  (MCT), and the second at the end of the kinetic (END). These equilibrium points are described by eq. [2] and [3]. Substituting [2] in [3], equation [4] is obtained and can be used to recover  $C_P$  relative to  $C_{P, \text{END}}$ , yielding a **relative AIF** ( $\text{AIF}_{\text{BTE}}$ ). This is clearly apparent in Fig. 1B and 1C, where the maxima (x) are superimposed on the relative AIF (black line). As can be seen, the approximation is better for tissues where the maximum concentration (high  $K^{\text{Trans}}/v_e$  ratios) is reached quickly. In the tail region (END), most curves superimpose on the relative AIF (red dots), as a result of the pseudo steady-state described in eq. [3].

$\frac{dC_T}{dt} = K^{\text{Trans}} \left( C_P - \frac{C_T}{v_e} \right)$ [1]	$C_{P, \text{MCT}} = \frac{C_{T, \text{MCT}}}{v_e}$ [2]	$C_{P, \text{END}} \sim \frac{C_{T, \text{END}}}{v_e}$ [3]	$\frac{C_{P, \text{MCT}}}{C_{P, \text{END}}} \sim \frac{C_{T, \text{MCT}}}{C_{T, \text{END}}}$ [4]
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**Method:** Ten Fisher rats were anesthetised and prepared for DCE-MRI in a 7T animal scanner. After the acquisition of a pre-contrast  $T_1$  map (multiple flip angle approach),  $T_1$ -weighted images were acquired at high temporal resolution (4 s) and high spatial resolution ( $0.273 \times 0.273 \times 1.5 \text{ mm}^3$ ) before and during a caudal injection of Gd-DTPA. Thirty minutes later, the same animals were injected identically, and the blood AIF was sampled ( $\text{AIF}_S$ ) via the caudal artery. Gadolinium was dosed by inductively coupled plasma mass spectrometry (ICP-MS). The BTE algorithm was coded in Matlab.

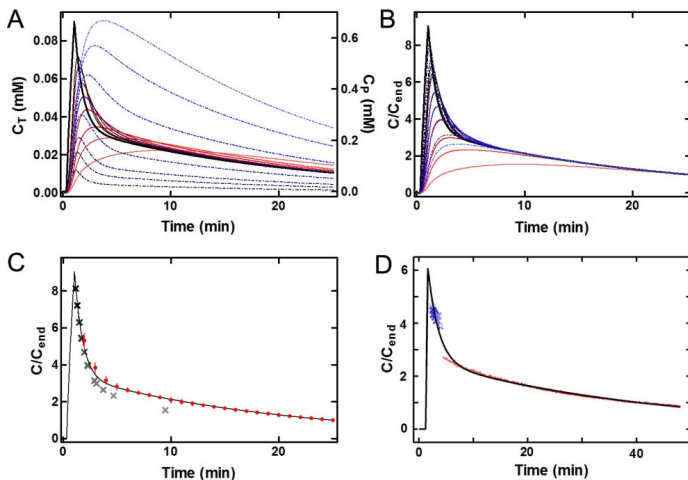
## Results:

**Data preparation:**  $C_T$  maps were calculated from the  $T_1$ -weighted images and  $T_1$  maps. Noisy voxels were filtered out, and all voxels with the proper characteristics (e.g., high  $C_{T, \text{MCT}}/C_{T, \text{END}}$  ratio) were automatically selected to calculate the  $\text{AIF}_{\text{BTE}}$ .

**BTE algorithm:** Concentration maps relative to the steady-state concentration were calculated ( $C_{T, R} = C_T/C_{T, \text{END}}$ ). The method uses both eq. [3] and [4] to determine the shape of the tail and peak region of the AIF. Fig. 1D shows a representative experimental example of this. An AIF (i.e., a commonly used bi-exponential decay convoluted to a box input) is fitted to these data points, yielding the  $\text{AIF}_{\text{BTE}}$ .

**Calibration using  $v_e$  distributions:** The sampled AIF ( $\text{AIF}_S$ ) were used to fit  $K^{\text{Trans}}$  and  $v_e$ . The relative distribution (spectrum) of  $v_e$  from all animals was determined, and the average distribution served as a reference (ADR). Then, the  $\text{AIF}_{\text{BTE}}$  were used to fit  $K^{\text{Trans}}$  and  $v_e$ .  $v_e$  values were corrected to obtain a distribution overlapping the ADR. The residuals ( $C_{T, \text{Fitted}} - C_T$ ) from fits using  $\text{AIF}_{\text{BTE}}$  were lower than when using  $\text{AIF}_S$ , suggesting that the  $\text{AIF}_{\text{BTE}}$  may be more accurate.

**Discussion and conclusion:** The BTE method allows for the automated AIF extraction from tissues. This method (1) is non invasive, (2) does not assume  $K^{\text{Trans}}$  or  $v_e$  in a specific tissue are known, (3) is automated (no user input/ROI tracing) and (4) corresponds to the average AIF as “perceived” by the voxels inside the volume of interest. The method requires initial  $v_e$  measurements in a reference population and it is assumed that the distribution of  $v_e$  does not vary significantly between animals under the same experimental condition. We proposed a novel blood/tissue equilibrium approach for the extraction of an AIF from a tissue. The method is simple, automatic and does not depend on the measurement of the blood contrast agent concentration or on the assumption that the dynamic parameter  $K^{\text{Trans}}$  is known in a reference tissue. Instead, the method only assumes that the distribution of  $v_e$  values is comparable between animals.



**Figure 1.**

(A)  $C_T$  curves with varying  $K^{\text{Trans}}$  (red) and  $v_e$  (blue) and the corresponding  $C_P$  (AIF, black line).

(B) Same curves as in (A), but relative to their final concentration ( $C_T/C_{T, \text{END}}$  and  $C_P/C_{P, \text{END}}$ ).

(C) As can be seen in (B), the maxima superimpose to the  $C_P$  curve in the peak region (x). The tail of most  $C_T/C_{T, \text{END}}$  curves superimposes on  $C_P/C_{P, \text{END}}$  (red dots in (C)), as predicted by eq. [3]. Both superimpositions correspond to time points at which  $C_P = C_T/v_e$  (blood/tissue equilibrium).

(D) Example of the BTE method to extract the AIF from real  $C_T$  data. The MCT region (blue x) and END region (red dots) are used to fit the  $\text{AIF}_{\text{BTE}}$  (black line).