Generalized Central Volume Principle for Recirculation with Contrast Elimination

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Purpose: To respond to the challenge of tracer recirculation in perfusion measurements, a problem acknowledged since the early days of the method (cf. Ref. 1 and references therein), by creating a framework for analytical modeling of circulation in the whole organism. In particular, the key features of a bolus passage (Fig. 1), which are (i) multiple recirculation boluses, and (ii) a decaying long-time tail, are related to characteristics of global circulation. We analytically solve three global circulation models of increasing complexity (Fig. 2), and select the most adequate one. We also derive exact expressions for the long time tail, generalizing the central volume principle1 (CVP) to recirculation with contrast elimination.

Target Audience: Quantitative DSC, DCE and CT scientists and clinicians.

Methods: We represent global circulatory system, Fig. 2a, by a few impulse response functions (IRFs) \( h_i(t) \) normalized to \( \int h_i(t) dt = 1 \) to enforce contrast mass conservation. The system is stationary and linear. It is convenient to consider the problem in the frequency domain, \( h_i(\omega) \to H_i(\omega) \), such that convolutions become products, the delays \( t_i \) are accounted for by the factors \( e^{-\omega t_i} \), and the problem maps onto that of linear electric circuits with the currents obeying Kirchhoff laws and governed by the complex-valued admittances \( h_i(\omega) \).

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To derive the overall contrast decay, we note that, since an IRF has a mean transit time probability distribution, its frequency expansion near \( \omega=0 \) has the following form: \( h_i(\omega) \to 1 + i \omega \tau_i + \text{[terms higher-order in } \omega] \), where \( \tau_i \) is the corresponding mean transit time. Plugging this expansion in Eqs. (1) and (2) yields the Lorentzians whose inverse Fourier transforms correspond to \( x^{(i)}(t) \), the asymptotically exact long-time behavior of \( x(t) \) for the two exemplary models, Fig. 2b and 2c [3C model not shown for brevity]:

1C:

\[
x^{(1)}(t) = c_0 e^{i(\omega t_1)} x^{(1)}(\tau_1 + t_1),
\]

\[
\tau_1 = \tau(1 + t_1) ;
\]

2C:

\[
x^{(2)}(t) = c_0 e^{i(\omega t_1)} x^{(2)}(\tau_1 + t_1) + \text{[terms higher-order in } \omega] \]

We observe that, in contrast to the plateau \( x(t) \to \text{const} \) representing the classical CVP, the presence of elimination in at least one contour leads to the overall exponential decay with the time constant \( \tau_c \), which is the essence of the generalized CVP, one of our main results. The classical CVP is obtained by setting the elimination rate \( 1/\tau_c = 0 \). We emphasize that Eqs. (3) and (4) are model-independent: they are valid for any \( h_i(t) \), and are only determined by the global topology of the circulation contours, since we only used the universal low-frequency behavior of the IRFs. To further analyze the DSC MRI data, we use the gamma-variate function for \( h_i(t) \), approximate the infinite series in Eqs. (1) and (2) by the first four bolus passes, and substitute \( x^{(i)}(t) \) from Eqs. (3) and (4) for the rest of them.

MRI: Informed consent was obtained from a glioma patient. GE EPIs of Gd-DTPA administered at a dose of 0.1mmol/kg and rate of 5mL/s were acquired 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 8ch phased array head coil. Parameters: TR=1000ms, TE=32ms, 10 contiguous 3mm thick axial slices, matrix 128x128, FOV=220x220mm2, FA=30°, BW=1396Hz/pixel, in-plane resolution 1.7x1.7mm2.

Results: All models capture the recirculation boluses as in Fig. 1, but the 1C model cannot explain the fast loss of coherence between oscillations. The heart-pulmonary block \( h_1 \) in the 3C model does not improve fit quality much compared to 2C. As shown in Fig. 3, the 2C and 3C residuals comply with our iid normal noise assumption, while 1C does not. Residual correlations are mostly random for 2C and 3C, but correlation at 1s lag is about 40% for 1C. Further, 2C and 3C performances are similar according to corrected Akaike Information Criterion (cAIC) scores for over 600 voxels (Fig. 3).

Discussion: From our analysis and overall fit quality, the simplistic 1C model cannot explain the data well. Between 2C and 3C, the less complex 2C was chosen as the candidate model, since the added complexity of 3C does not affect model performance and parameter estimation.

Conclusions: We formulated the first framework in which the contrast recirculation in a given organ (here in the brain) is linked to the topology and quantitative parameters of circulation in the whole organism. In particular, these global features determine the degradation of subsequent boluses and the exponentially decaying tail, thereby generalizing the classical central volume principle onto any recirculation topology and contrast elimination rate. This framework lays the theoretical basis for quantitative perfusion studies using DCE, DSC and CT techniques.