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Parameter estimation of perfusion models in dynamic contrast-enhanced imaging: a unified framework for model comparison

Blandine Romain[a,c,e,*], Laurence Rouet[e], Daniel Ohayon[a], Olivier Lucidarme[d], Florence d'Alché-Buc[b,c], Véronique Letort[a]

[a] Laboratory of Mathematics in Interaction with Computer Science, CentraleSupélec, Chatenay Malabry
[b] INRIA-Saclay, LRI CNRS 8632, Orsay
[c] IBISC, University of Evry, Evry, France
[d] Hospital La Pitié-Salpétrière , AP-HP, Paris
[e] Philips Research Medisys, France

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ABSTRACT

Patients follow-up in oncology is generally performed through the acquisition of dynamic sequences of contrast-enhanced images. Estimating parameters of appropriate models of contrast intake diffusion through tissues should help characterizing the tumour physiology. However, several models have been developed and no consensus exists on their clinical use. In this paper, we propose a unified framework to analyse models of perfusion and estimate their parameters in order to obtain reliable and relevant parametric images. After defining the biological context and the general form of perfusion models, we propose a methodological framework for model assessment in the context of parameter estimation from dynamic imaging data: global sensitivity analysis, structural and practical identifiability analysis, parameter estimation and model comparison. Then, we apply our methodology to five of the most widely used compartment models (Tofts model, extended Tofts model, two-compartment model, tissue-homogeneity model and distributed-parameters model) and illustrate the results by analysing the behaviour of these models when applied to data acquired on five patients with abdominal tumours.

1. Introduction

Providing earlier assessment of drugs efficiency is a major challenge for the improvement of patient care in oncology. Follow-up of patients presenting tumours is traditionally performed through various morphological measurements (number of tumours, size of tumours,...) (Shanbhogue et al., 2010). However, such measurements are known to reflect only partially the disease progression. Indeed, morphological assessment may be insensitive to or provide markedly delayed indications of the tumour response to treatment even when the therapeutic effect is substantial. It has been shown that the physiological response to a given therapy often precedes the evolution of its morphological descriptors (Li and Padhani, 2012). In this context, dynamic contrast-enhanced (DCE) imaging is a promising tool for the assessment of tissue differentiation based on its intrinsic nature (normal, tumour, necrotic...). The technique, based on the temporal analysis of the contrast intake curve extracted from the images after bolus injection of a contrast agent, aims at characterising tissue microcirculation and microvascularisation.

Functional imaging of the microcirculation, using either magnetic resonance imaging (MRI) (Sourbron and Buckley, 2012), computed tomography (CT) (Miles et al., 2012; Ingrisch and Sourbron, 2013), ultrasound (Lassau et al., 2010), positron-emission tomography (Keiding, 2012) or single-photon emission CT (Zhang et al., 2012), is based on dynamic contrast imaging, although the diffusion kinetics depends on the type of contrast agent. In this paper, we focus on DCE-MRI and DCE-CT. In such cases, contrast agents are small inert molecules that propagate in extracellular spaces. The kinetics of contrast agent diffusion are similar for both modalities.

From contrast intake curves, simple parameters, such as time to peak or mean transit time (Našel et al., 2000), may be extracted to describe the change of contrast agent concentration and compute parametric images. However, more informative approaches exist, that aim to provide physiologically-based parameters. By

* Corresponding author.
E-mail address: blandine.romain@gmail.com (B. Romain).

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associating the temporal variation of contrast intake to physiological parameters, the analysis of contrast intake curves provides a way to characterize the pharmacokinetics of the contrast agent. These parameters can be derived using the tracer kinetic theory (Brix et al., 2010). In this theory, two different concepts have been highlighted. The first one, the indicator dilution theory, is based on a convolution approach and does not rely on any assumption about the diffusion process (Meier and Zierler, 1954). The second approach, which will be considered in this paper, is based on pharmacokinetic compartment models, usually formulated as systems of coupled differential equations. They rely on the assumption that tissues can be represented as a set of interacting subcompartments within which an administered tracer can circulate with different dynamics that depend on each compartment properties. Compartment models are likely to provide a better biological insight, relying on several physiological parameters such as the local vascular permeability, blood flow, intravascular and extracellular volumes (Ingrisch and Sourbron, 2013). These parameters can be extracted from contrast intake curves in a given tissue region through model parameter estimation. However, several models have been developed in the literature and no consensus exists on their clinical use. Each type of model has long been confined to specific applicative domains and only recently efforts have been undertaken to review the full range of existing models (Sourbron and Buckley, 2012; Ingrisch and Sourbron, 2013; Brix et al., 2010). For instance, Sourbron and Buckley (2012) and Ingrisch and Sourbron (2013) present a classification that provides clearer insight into the links between the different models. Ingrisch and Sourbron (2013) discuss the difficult problem of model selection: they argue that, while the classical goodness-of-fit criteria such as the χ^2 value are the most widely used, they are inappropriate to compare models with different numbers of free parameters and should be replaced in that case by penalized criteria such as the Akaike information criterion (AIC). Some mathematical aspects of model analysis, and their systematic applications to a whole group of models, are nevertheless still lacking. Indeed, to obtain reliable and relevant estimates of parameters, one must ensure that the chosen model meets a certain number of requirements: plausibility of the underlying hypotheses and parameters biological meaning, parameter sensitivity and identifiability, solvability of the optimization problem associated to the estimation process, robustness to noise. With a few exceptions (Orton et al., 2007), these conditions are hardly examined; most studies focus on direct applications of the models without questioning their validity.

Therefore, complementary to other review papers that present and classify the models, the objectives of this paper are (i) to define the biological context and general form of perfusion models, (ii) to propose a generic framework for parametric estimation problem of perfusion models in the context of DCE-MRI or DCE-CT imaging through the definition of a unified mathematical framework providing tools to perform robust parameter estimation, sensitivity and identifiability analysis, (iii) to apply the framework to the most widely used compartment models, and finally (iv) to illustrate the results on abdominal DCE-CT images.

2. Data acquisition and general modelling framework

2.1. Data

DCE imaging consists in the acquisition of temporal sequences of 3D images. Several acquisition protocols can be selected, depending on the modality (CT or MRI) (Kambadakone and Sahani, 2009; Sourbron, 2010) and on the values of the temporal resolution (time delay between consecutive acquisitions) and the duration of acquisition. In this work, the parameters of reconstruction (the spatial resolution and the smoothing filter) were set following the recommendations of Romain et al. (2012). From these images, signal variations can be registered before, during and after the injection of the contrast agent in a given region of interest (ROI). These signal-time series $S^i(t)$, measured at each voxel i from the acquired image volume, are converted into the time-series of contrast agent concentration y^i according to Eq. (1):

$$\forall i \in \Omega\,,\ \forall t \in \Omega_T\,,\quad y^i(t) = f_c\left(S^i(t) - S_0^i\right), \tag{1}$$

where $\Omega = \{1, \dots N\}$ refers to the set of voxels and $\Omega_T = \{t_1, \dots t_T\}$ is the sequence of acquisition times. S_0^i is the precontrast signal (before injection) at voxel i and f_c a conversion function of the measured signal intensity to contrast agent concentration.

In DCE-CT, there is a proportional relationship between contrast agent concentration and signal enhancement: $f_c = Id$ is assumed. In DCE-MRI, this assumption is not valid since the signal is non-linear with respect to concentration: f_c is then a more complex function that may be estimated through phantom calibration; a possibility is to quantify the T1 relaxation time of each voxel and relate this change in T1 to the change in contrast agent concentration. For a given imaging modality, f_c is supposed to be known and $(y^i)_{i\,\in\,\Omega}$ is hence considered hereafter as our observed data.

Perfusion models also require a time series of agent concentration in the feeding artery of the considered tissue, $(y^a(t))_{t\in\Omega_T}$, where a denotes a ROI delineated in this feeding artery.

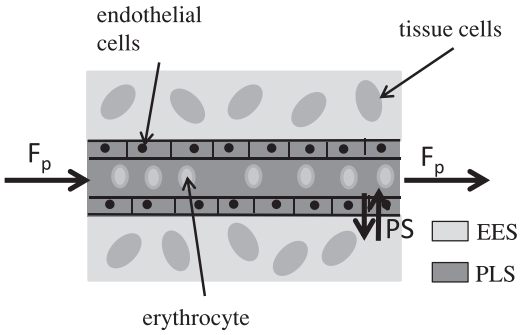

Fig. 1. Schematic drawing of a capillary bed. Blood plasma and erythrocytes are pushed through the capillaries by the plasma flow F_p. The flux of molecules between tissue and blood is controlled by the permeability-surface area product of the barrier *PS*.

2.2. General form of perfusion models

Perfusion models describe the biological behaviour of tissue microcirculation in the body. As illustrated in Fig. 1, an exchange of molecules between tissue and blood occurs within the capillary bed. Nutrients and oxygen are supplied to the cells via capillaries which are composed of erythrocytes, blood plasma (PLS) and a single layer of endothelial cells. Their barriers are semi-permeable to small molecules. Tissue is composed of cells separated by a frost of protein fibers called interstitium, assimilated to the extravascular extracellular space (EES). The relative volumes per unit of tissue volume of the EES and the PLS are respectively denoted v_e and v_p ($\mathrm{mL.mL^{-1}}$). Blood plasma and erythrocytes are pushed through the capillaries by the plasma flow F_p, defined as the volume of plasma that enters a unit of tissue volume per unit of time ($\mathrm{mL.mL^{-1}.min^{-1}}$). The flux of molecules between tissue and blood is controlled by the permeability P per unit area of the barrier, assumed to be isodirectionnal and invariant with respect to time and space, for the considered molecule. The permeability-surface area product PS is defined as the number of contrast agent molecules that cross the barrier per unit of plasma concentration per unit of