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ProstateAtlasSimDCE: A simulation tool for dynamic contrast enhanced imaging of prostate

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Abstract

T1-weighted Dynamic Contrast Enhanced (DCE) MR imaging is emerging as a method with the potential of predicting pharmacodynamic response of biomarkers for cancer. It is becoming an important tool for the detection, staging, and monitoring of highly vascularized tumors. Pixel-wise model-based methods are used for analysis purposes through the computation of quantitative parameters maps. These methods are multi-steps algorithms and their technical and clinical implementations remain difficult. In this study, we describe a dedicated simulation tool to create dynamic images of prostate. Ground truths of the pharmacokinetics parameters maps are well known allowing an effective platform for the validation.

Keywords: Dynamic imaging, Pixel-wise analysis, Toft model, simulation.

1 Introduction

T1-weighted Dynamic Contrast Enhanced (DCE) MR imaging is emerging as a method with the potential of predicting pharmaco-dynamic response of biomarkers for cancer. It is becoming an important tool in both preclinical and clinical research for the detection, staging, and monitoring of highly vascularized tumours. The obtained images could be analysed in three different ways. The first is a simple visual assessment of the contrast agent (CA) uptake, the second is a semi-automatic approach allowing to quantify CA kinetics as the wash in, the peak and the wash out while the last way groups the quantitative methods that compute different pharmacokinetics parameters maps. Nevertheless, implementation of this modality in routine clinical practice remains limited due to the lack of standardization in acquisitions protocols, analysis and interpretation of the data. In order to address these challenges, phantoms construction was investigated. The phantoms implement semi-permeable hollow fibres, found in hemo-dialysis cartridges, to simulate permeable vasculature ([1], [2]). However, these physical phantoms remain constrained by the technical limitations of the materials.

From another side, computational and numerical simulation could allow a complete modelling framework. It is increasingly used in this application to optimize acquisition and processing strategies ([3], [4]). In this study, we describe a dedicated simulation tool to create dynamic images of prostate. A reverse path is used. Indeed, starting from a defined pharmacokinetics parameters map, a set of transformations from the Tofts Model, is applied to obtain temporal signals. Then, the computed signals are merged with 3D images to form 4D data.

In the following sections, we provide a background on compartmental modelling and CA kinetics (next section), then we describe the use of this model in our simulation tool (section 3). Section 4 describes the implementation while the last section concludes the study.

2 Compartmental modelling and tracer kinetics

Compartmental modelling remains the most applied model to analyse the CA distribution with DCE-MRI. The simplest model considers two compartments: a blood plasma compartment and the extracellular-extra vascular (EES) compartment. It enables modelling of the exchange between the capillary and the adjacent spaces. The model consists in defining the exchange flows based on four parameters: k_{trans} (the permeability surface area product per unit volume of tissue, also called transfer coefficient expressed in min^{-1}), k_{ep} (the efflux rate

constant expressed min⁻¹), v_e (extravascular extracellular space volume per unit volume of tissue) and v_p (plasma volume).

Time-course changes in tissue CA concentration are modelled as a result of first-order exchange between compartments and described by the following equations:

$$V_p \frac{dC_p}{dt} = K_1(C_e - C_p) - K_2 C_p \quad (1)$$

$$V_e \frac{dC_e}{dt} = K_1(C_p - C_e) \quad (2)$$

$$V_t \frac{dC_t}{dt} = k_{trans} (C_p - C_t) \quad (3)$$

Where:

K_1 and K_2 are constants describing the flow rate per unit concentration difference,

V_p is the plasma volume,

V_e is the volume of the extracellular space,

V_t is the volume of the tissue,

C_e is the concentration in the extracellular space,

C_p is the concentration in the plasma space,

C_t is the concentration in the tissue space,

These equations are used to obtain the equation modelling the plasma concentration $C_p(t)$ of Weinmann[5]:

$$C_p(t) = D(a_1 e^{-m_1 t} + a_2 e^{-m_2 t}) \quad (4)$$

where D is the contrast agent dose (expressed in mM/kg patient).

While the total tissue concentration $C_t(t)$ is described as:

$$C_t(t) = D \cdot k_{trans} \sum_{i=1}^2 \frac{a_i}{k_{ep} - m_i} (e^{-m_i t} - e^{-k_{ep} t}) \quad (5)$$

Where k_{ep} is related to k_{trans} and v_e through: $k_{ep} = \frac{k_{trans}}{v_e}$

3 Methods

The initial Toft model [6] and the extended Toft model [7] were the first solutions proposed to solve the first order differential equations exposed above. In this solution, C_p is modelled as a bi-exponential decay. Later, other models were introduced ([8], [9]). However in 2012, the Quantitative Imaging Biomarkers Alliance (QIBA) DCE–MRI Technical Committee from the Radiological Society of North America (RSNA) published recommendations to define basic standards for DCE–MRI measurements and quality control with the goal of promoting consistent and reliable results across platforms, clinical sites, and time ([10]). Also, in regard to analysis, the QIBA DCE–MRI recommended the use of Toft’s model. Thus, in this study we adopted this modelling.

3.1 Time-intensity simulation

The simulation allows different curve behaviours and mimicking realistic situations as the fact that the bolus does not appear immediately. The curves are in concentration of contrast agent by time. For each voxel, the evolution of the concentration is modelled using the equation (5)

We have fixed D to 0,1mM/Kg. Arterial Input Function parameters a_1 , a_2 , m_1 and m_2 are fixed as described by Weinmann *et al.*[5] ($a_1 = 3.99$, $a_2 = 4.78$, $m_1 = 0.144$ et $m_2 = 0.011$). These parameters were obtained by studying the plasmatic concentration variation of gadolinium (DTPA-Gd) in twenty healthy volunteers.

For prostate imaging, the following values were reported in literature for k_{trans} and k_{ep} ([11], [12]): $k_{trans} = 0.05 \text{ minute}^{-1}$ and $k_{ep} = 0.1 \text{ minute}^{-1}$ for prostate healthy tissues and $k_{trans} = 0.4 \text{ minute}^{-1}$ and $k_{ep} = 1.4 \text{ minute}^{-1}$ for lesion tissues. These values are proposed as default value but can be changed in order to have different behaviour schemes depending on the tissue nature, different pharmacokinetic parameters k_{trans} and k_{ep} were chosen.

Lastly, a Gaussian noise with kernel $\sigma^2 = 0.2$ is added to the curves to obtain perturbed signals.

The obtained curves represent the time concentration evolution for each voxel j . In real DCE-MR data, the signal represents the time intensity variations. Thus, conversion is needed. The conversion is done using equation 6:

$$S_j(t) = m(t) * \sin(\alpha) \frac{1 - e^{-\left(\frac{TR}{T_{10}} + R_1 C_j(t) TR\right)}}{1 - \cos(\alpha) * e^{-\left(\frac{TR}{T_{10}} + R_1 C_j(t) TR\right)}} \quad (6)$$

$$\text{Where } m(t) = m(0) * e^{-R_2 C_j(t) TE} \quad (7)$$

With:

$m(0) = 6000$,

α is the flip angle (17°),

TR is the Repetition time (8.9 ms),

TE is the Echo time (4,2 ms),

R_1 ($4,5 \text{ s}^{-1} \text{ mM}^{-1}$) and R_2 ($5,5 \text{ s}^{-1} \text{ mM}^{-1}$) are the longitudinal and transverse tissue contrast agent relaxivities respectively.

T_{10} is the longitudinal relaxation time (1000 ms).

The above values are proposed as default values as reported in literature. They could be changed to allow personalised tissue modelling.

3.2 Spatial simulation

As DCE MR images are 4D data, representing the time-intensity evolution of each voxel. The obtained 1D curves are combined with a 3D model of prostate: ProstateAtlas([13], [14]) to obtain 4D images.

The data are immersed in an environment with iliac and obturator arteries. Figure 1 depicts an example of the generated data.

Figure 1. Top: Time-intensity curves for the Artery (blue), healthy (green) and cancer (red) tissues. Bottom: Combination of the 1D curves with 3D images from the ProstateAtlas images. The image depicts the prostate, a tumour region inside the prostate gland, the iliac and obturator arteries.

4 Implementation

The above described equations were implemented using Matlab® version 2008 (MathWorks, Massachusetts, USA). Graphical User interfaces (GUI) (figure 2) allow convivial interaction to tune the different features parameters. Starting from the Atlas image, the user can define different specific areas inside the gland as tumoral regions with different sets of parameters. Each cancerous tissue could be set up by defining its location inside the prostate gland, its form, its volume and its specific pharmacokinetics parameters. After generation of the corresponding time-intensity curves, they are merged and applied on the images. The final images are recorded in DICOM standard format and exported with the adequate temporal positions to be used by any analysis tool.

(a)

(b)

(c)

Figure 2. Graphical User Interface of SimDCE Module tool. (a) Main interface of the software. (b) Arterial Input Function (AIF) parameters and T1 weighted Magnetic resonance signal parameters definition. (c) Tumours areas definition and associated pharmacokinetics parameters tunings.

Images samples and the Matlabcode of the platform are available for free download from the following URL: <http://www.medataweb.u703.net>.

5 Discussion - Conclusion

The construction and the use of digital phantoms present the benefit to provide ground truth to optimize, control or validate different image based procedures. In, this study, we have presented an open source platform containing a dedicated tool to simulate dynamic contrast enhanced MR images of prostate. It combines temporal and spatial simulation to generate 4D images, usable by pharmacokinetic analysis tools. The platform contains also image samples with the corresponding parameters maps.

As recommended by the QIBA-RSNA technical group, the temporal simulator implements the Toft model. However, as an open source platform, additional models could be included. Moreover, other tissue models could be added to allow specific tissue modelling as cysts or different grade tumours.

The time-intensity signals generated are placed in a 3D frame representing an atlas of the prostate to obtain temporal images. We are aware, that the images do not exhibit signal distributions similar to those observed on real MR images, however they could be used to perform a validation of the mutli-steps process of pharmacokinetics maps estimation[15]. As future evolution, the signals could be merged and combined with a real MR simulator.

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