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A 5D computational phantom for pharmacokinetic simulation studies in dynamic emission tomography

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ABSTRACT

Introduction: Dynamic image acquisition protocols are increasingly used in emission tomography for drug development and clinical research. As such, there is a need for computational phantoms to accurately describe both the spatial and temporal distribution of radiotracers, also accounting for periodic and non-periodic physiological processes occurring during data acquisition.
Methods: A new 5D anthropomorphic digital phantom was developed based on a generic simulation platform, for accurate parametric imaging simulation studies in emission tomography. The phantom is based on high spatial and temporal information derived from real 4D MR data and a detailed multi-compartmental pharmacokinetic modelling simulator.
Results: The proposed phantom is comprised of three spatial and two temporal dimensions, including periodic physiological processes due to respiratory motion and non-periodic functional processes due to tracer kinetics. Example applications are shown in parametric [^{18}F]FDG and [^{15}O]H_2O PET imaging, successfully generating realistic macro- and micro-parametric maps.
Conclusions: The envisaged applications of this digital phantom include the development and evaluation of motion correction and 4D image reconstruction algorithms in PET and SPECT, development of protocols and methods for tracer and drug development as well as new pharmacokinetic parameter estimation algorithms, amongst others. Although the simulation platform is primarily developed for generating dynamic phantoms for emission tomography studies, it can easily be extended to accommodate dynamic MR and CT imaging simulation protocols.

1. Introduction

The continuous development of anthropomorphic and small animal computational phantoms during the last few decades has led to their ever increasing use in clinical and preclinical research [1]. The improved level of their realism and flexibility compared to physical phantoms has led to their widespread use and adoption in emission tomography. The ability to perform simulation studies using these computational phantoms allows a number of methods and techniques used in the field of medical imaging and more specifically emission tomography to be developed, evaluated and validated under controlled and known conditions.

Three-dimensional computational phantoms fall into three categories based on their design principle: mathematical stylized phantoms, voxelized phantoms and hybrid equation-voxel phantoms. Mathematical phantoms use mathematical equations to approximate the surface of simple and complex body structures. A number of such designs exist in the literature, such as the Shepp–Logan [2] and the mathematical cardiac-torso (MCAT) phantoms [3]. Such designs are useful, but their inability to model complex structures limits their application, especially since there is need for more realistic simulation studies [4].

On the other hand, voxelized phantoms are based on using segmented anatomical information from high resolution tomographic

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data (CT or MRI). A number of voxelized phantoms exist, covering anatomical variants (age, sex, body weight, height etc) [5–9]. Their main advantage is the level of realism compared to stylized approaches; however, it fails to provide the level of flexibility offered by mathematical phantoms.

The need to combine the detailed anatomical information provided by voxelized phantoms with the flexibility offered by the mathematical phantoms, has led to the development of hybrid phantoms [10]. These models enable the combination of flexibility and realism within a single anatomical phantom representation. The most popular is the non-uniform rational B-splines (NURBS)-based cardiac-torso (NCAT) phantom [11,12].

All these three-dimensional (3D) computational phantoms offer a relatively simple and practical simulation platform, but fail to take into account time-dependent physiological processes occurring during the course of the imaging process. Consequently, this has led to the development of four-dimensional (4D) phantoms incorporating time-dependent processes, such as cardiac and respiratory motion. The NCAT phantom and the latest generation in this family of phantoms, the extended cardiac-torso phantom (XCAT) [13] were generated from multi-detector respiratory-gated CT data, to model cardiac and respiratory motion. Similarly, dynamic MRI has also been used to derive the motion information, which is then used in a four-dimensional (4D) simulation framework [14,15].

Although such 4D phantoms combine accurate anatomical information with models of temporally periodic physiological processes, they do not take into account the variable and temporally non-periodic functional processes occurring during the course of the study, constraining the level of realism and thus their potential application in dynamic studies. However, the need for more accurate quantification both in clinical research and drug development has lead to the increasing use of dynamic imaging protocols [16]. Moreover, pharmacokinetic analysis of the time course of the activity distribution enables more targeted physiological parameters, such as blood flow, metabolism and receptor occupancy, to be derived. In many studies, such parameters are more informative compared to standardized uptake value (SUV) index, which remains the most widely adopted metric in static whole-body PET imaging [17]. Consequently, the development of realistic digital phantoms for multi-compartmental tracer kinetic studies in dynamic PET and SPECT is of interest. Although a number of studies in the field of image reconstruction and kinetic modelling have used in-house developed parametric phantoms, they often feature roughly approximated anatomical structures with simple geometrical shapes, while lacking the anatomical and physiological variability caused by temporally periodic phenomena such as respiratory motion [18–22]. Recently a variant of the XCAT phantom was developed, named the perfusion cardiac-torso phantom (PCAT), but its scope was limited to dynamic perfusion studies in cardiac imaging [23].

In this work, using high resolution anatomical and temporal information from real MR data, we develop a five-dimensional (5D) computational anthropomorphic phantom, incorporating temporal gating from respiratory induced body motion and compartmental modelling tracer kinetic capabilities for parametric imaging simulation studies in dynamic emission tomography. This new voxelized phantom, allows respiratory gated and non-gated datasets to be simulated along with any tracer-specific compartmental model representing the temporal distribution of the activity concentration during dynamic imaging protocols in PET and SPECT. Rather than being region and application specific, kinetic parameters are freely assigned in the entire field-of-view (FOV), generating voxel-wise parametric maps based on the tracer of interest.

2. Methods

This section describes the generic methodology used by the simulation platform for generating 5D parametric imaging simulation phantoms using MR information for discerning anatomy and motion along with a kinetic modelling simulator and a virtual tomograph.

2.1. The KCL–HUG series 5D phantom

2.1.1. 3D anatomical phantom

Anatomical information are obtained from a high resolution 3D MRI scan and different organ structures are segmented in order to generate the anatomical regions comprising the phantom, as described in Tsoumpas et al. [24] and Buerger et al. [25]. Segmentation of the major structures is performed using a semi-automatic algorithm with local thresholding [25]. This allows fast generation of 3D anatomical phantoms, facilitating personalized patient-specific anatomical phantom designs, derived from a real MR scan. Apart from template organ structures segmented from the MRI data, tumours of varying characteristics (e.g. size and tracer uptake) can be manually inserted in different phantom regions. However, since these tumours represent additional patient-specific structural variants, they can easily be manipulated. Other anatomical variants can also be included depending on the required anatomy and simulation conditions. Tumours or other anatomical variants can be manually delineated/drawn on the 3D anatomical phantom and the tumour ROI mask can be saved and given a separate value, different to the region it is embedded within. The complete anatomical phantom is a superposition of separate regions segmented from the MRI data.

2.1.2. 4D dynamic phantom for 1- and 2-tissue models

To describe the temporal distribution of a given tracer and simulate time–activity curves (TACs), custom-made software capable of providing multi-compartmental modelling for 1- and 2-tissue models was developed. Given an input function, a temporal sampling protocol and known tracer-specific pharmacokinetic parameters (constant rates) controlling the bi-direction flux of the tracer between the blood and tissue compartments (for each organ structure in the anatomical phantom), TACs are generated. Typical input functions derived from arterial sampling can be used, along with user defined ones, based on a parameterized model. For the sampling protocol, any number of frames and frame durations can be accommodated within the typical scan times used for dynamic studies in emission tomography. A blood volume component can also be included to generate the simulated TACs, since typically both tissue and blood components are sampled at the voxel level in clinical acquisitions. The same principles apply for the different kinetic parameters used, with separate constant rates for the different organs and values obtained from the literature, if a generic activity distribution is to be realized. Alternatively, if a dynamic emission scan is available from a patient, personalized patient-specific pharmacokinetic parameters can be used based on mean organ parameters. Although individual micro-parameters are the endpoint parameters of interest, in some applications certain macro-parameters, such as the volume of distribution (V_T) and the tracer's net uptake rate into the irreversibly bound compartment (K_i) are often more relevant and provide a more complete picture of the underlying patho-physiology. These macro-parameters are combinations of micro-parameters and can easily be adjusted to reflect specific conditions. Generic schematic diagrams for a single-tissue and a two-tissue compartment model, used to generate the dynamic phantom image sequence, are shown in Fig. 1. The time-dependent activity concentration in the tissue C_T, can be described as a convolution of the impulse response function (IRF),