Modeling and Simulation of 4D PET-CT and PET-MR Images

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INTRODUCTION
The growing success of radiologic imaging has led to the evolution of new molecular imaging modalities that assist in improving diagnosis and staging of diseases. A successful commercial molecular imaging device is the PET scanner combined with computerized tomography (CT)1 or more recently with MR imaging scanners.2–4 The new PET-CT/MR imaging systems are among the most elegant devices available in the clinic. This article provides a critical discussion on the current advances achieved in modeling and simulation of four-dimensional PET-CT/MR images from the PET perspective. In addition, it provides a vision on how recent advances in biomechanics, biophysics, and biochemistry may help improve the realism and accuracy towards personalized four-dimensional PET modeling and simulation.

The improvement in PET image quality depends on the development of scanners with better

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KEY POINTS
- Digital phantoms used for simulation in hybrid PET imaging are usually developed from segmented CT scans or MR images.
- MR or CT dynamic images can be used for realistic three-dimensional motion simulation of human body motion in PET imaging.
- Data simulation and PET modeling software tools are necessary for the simulation of physical processes and data acquisition, which are based on either Monte Carlo or analytical methods.
- Future computational four-dimensional PET-CT/MR imaging simulations may include multiscale and multiphysics mathematical modeling derived from physiologic measurements of organs.
- Statistical iterative reconstruction techniques include physics models, statistics, and potentially tracer kinetics of the PET acquisition to make the inverse problem more consistent.

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hardware and software capabilities. Several factors may cause degradation of image quality and accuracy. For example, the subject’s motion and the potentially fast tracer kinetics may generate images with poor quantification information. The estimation of their effects can be examined using realistic four-dimensional simulations. Furthermore, accurate and realistic simulations of the four-dimensional PET acquisition can help beyond the validation and evaluation performance of hardware and software. PET statistical iterative reconstruction approximates the measurement with modeling of physics (eg, scatter, detector response), patient motion and anatomy, statistics, and potentially tracer kinetics, which helps to make the inverse problem less ill-posed and obtain more consistent results. An improved acquisition model will increase the accuracy and precision of the estimated physiologic parameters of interest. Therefore, computational simulations offer a pathway to the characterization of the acquisition process from the injection of the tracer to the detection of the photons to derive physiologic information.

During the early days of emission tomography research, four-dimensional simulations were not practical because of the highly demanding computational power requirements. However, with the development of modern computers possessing large processing capabilities four-dimensional simulations have become feasible. For the successful generation of these simulations, realistic information is necessary. The first aspect is the four-dimensional computational phantom, which usually consists of a (realistic) three-dimensional numerical phantom; realistic three-dimensional motion fields; and pharmacokinetic/physiologic properties for different tissues. The second aspect is the data simulation software that includes the scanner geometry and physical characteristics. This article discusses these aspects in detail.

**FOUR-DIMENSIONAL COMPUTATIONAL PHANTOMS**

**Realistic Three-Dimensional Numerical Phantoms**

Numerical phantoms have been used since the 1960s and have evolved alongside the revolution of computed medical imaging. Undoubtedly, the computational phantoms have been very useful in emission tomography. They offer the convenience of virtually evaluating different scenarios of human anatomy and physiology, enabling the most optimal design of acquisition protocols, image reconstruction, and processing methods to be developed. An example of this kind of phantom is the VIP-Man model, which includes several organs. The standard approach to designing a realistic computational phantom is the segmentation and combination of multiple high-resolution MR or CT images. For example, Zubal and coworkers designed the Voxelman, one of the most widely used numerical phantoms in emission tomography. However, voxelized phantoms have some limitations, especially in cases where walled organs have been segmented or body tissues have been altered. Mesh phantoms have been recommended as the next generation of advanced computational phantoms that can avoid these limitations.

An example of the most widely used mathematical phantom is the cardiac torso MCAT and its evolution the XCAT (also known as NCAT) and PCAT. The MCAT is based on geometric primitives. XCAT allows much more realistic modeling of cardiac anatomy than MCAT and expands its applications beyond nuclear medicine. PCAT is a four-dimensional perfusion cardiac-torso phantom designed for dynamic perfusion nuclear medicine simulation studies. This family of phantoms belongs to a new generation, the so-called hybrid phantoms, where the organs are described using volumetric measurements and mathematical models. For example, in the case of the most recent version of this phantom, the XCAT, the human body is based on a very high-resolution anatomic datasets, the Visible Male and Female from the National Library of Medicine (http://www.nlm.nih.gov/research/visible/visible_human.html) as shown in Fig. 1. The mathematical model that describes the phantom is the nonuniform rational B-splines. These are mathematical models used in computer graphics for the generation and representation of curves and surfaces. Their advantage is that they offer great flexibility and precision for handling analytic and freeform shapes and they have been used by several research groups for the development of hybrid patient-dependent phantoms (Fig. 2). In particular, the XCAT phantom represents more than 9000 regions of the human body in detail. In addition, one version has been expanded such that it includes the anatomies of 30 organs of the grown child until the age of 16 months. The flexibility in fitting the XCAT phantom to existing patient anatomic data offers new opportunities for exploiting four-dimensional simulations with realistic anatomic variability. The high-resolution detail of the phantom allows for the simulation of CT acquisitions, as shown in Fig. 3. Furthermore, Fig. 4 illustrates an example of a dynamic PET cardiac image based on the...
PCAT phantom. Finally, Segars and his colleagues\textsuperscript{25} extended their methodology to support the development of small animal imaging research and developed the dynamic rodent phantom called MOBY, which includes respiratory and cardiac motion based on a mouse.

Another type of hybrid computational phantom is illustrated in Fig. 5.\textsuperscript{26} These phantoms model overweight and underweight individuals and they can be used to optimize four-dimensional PET acquisition protocols by simulating with higher complexity multiple patients or longitudinal PET imaging sessions that may be subject to functional and anatomic variability. Similarly, another series of hybrid-voxel phantoms with variable age (eg, newborn, 1, 5, 10, and 15 year old, and adult male and female) has been developed by Bolch at the University of Florida and Lee at the National Cancer Institute.\textsuperscript{27} Currently, these phantoms do not necessarily include respiratory or cardiac motion, but this could potentially be adapted in the future.

Fig. 1. Human anatomy of the extended NCAT or XCAT phantoms. Such details as circulatory system, organs, glands, skeleton, muscles, and respiratory motion are illustrated (top). Respiratory positions at end-expiration and end-inspiration of the enhanced four-dimensional XCAT are illustrated (bottom left and bottom right, respectively). (From Segars WP, Tsui BM. MCAT to XCAT: the evolution of 4-D computerized phantoms for imaging research. Proc IEEE 2009;97(12):1960–3, http://dx.doi.org/10.1109/JPROC.2009.2022417; with permission.)
One of the main disadvantages of most three-dimensional numerical phantoms is that they do not include a realistic representation of the patient’s variable function and anatomy caused by disease. Usually, these phantoms are designed from healthy volunteers or from single patients. The development of representative anatomic and functional disease models is an open research area in modeling and simulation of whole-body PET images.

**Realistic Motion**

Realistic simulation of the human body motion that occurs during acquisition is highly complicated. The motion of each point of the human body can be approximated by a normal periodic pattern with potential variation in respiration and cardiac cycle, combined with body repositioning (ie, bulk movement). Additional types of motion exist, such as peristalsis, prostate, and bladder motion.
but these considerations are beyond the scope of this article. Any kind of motion that is of the same order as PET resolution can affect accuracy and potentially create a fundamental problem in count-limited acquisitions. The number of counts that correspond to the same position strongly depends on the changes of periodic motion magnitude, frequency, and other types of movement. To satisfactorily eliminate the motion artifacts, measurement of motion at least as accurate as the actual imaging system resolution is necessary.

Many researchers extract respiratory motion with sufficient temporal and spatial resolution from MR imaging or CT acquisitions and use them for simulations of four-dimensional single-photon emission computed tomography (SPECT) and PET (Fig. 6). These acquisitions are often combined with mathematical tools (eg, image registration) to estimate the voxel displacements caused by motion of the subject. For example, Pollari and colleagues used a method to simulate PET respiratory motion of thorax by measuring it with nonrigid registrations between different positions of the respiratory cycle. In the case of the state-of-the-art XCAT phantom (Fig. 7), dynamic information was obtained from multidetector CT scanners for the motion of the heart and several sets of respiratory-gated CT images for the approximation of the respiratory cycle. This phantom includes more than 100 time frames over the cardiac cycle and 20 time frames over the respiratory cycle. Compared with the previous version of the phantom, this has been a substantial improvement for simulation of respiratory motion because it has higher resolution and can include variable respiration signal modifiable to match real breathing pattern that can also be irregular. This is particularly complicated when imaging with PET because a few patients’ respiratory traces have relatively small quiescent period fractions, which can yield results with large motion artifacts.

Another problem especially in cardiac studies is the diaphragm motion: it can generate severe attenuation correction artifacts. As suggested by McQuaid and colleagues, modeling motion of the diaphragm could help gate the CT images, which reduces the errors in the reconstructed PET images. A similar approach was followed in $[^{13}N]$-NH$_3$ PET-CT studies by Schleyer and colleagues, who modeled the motion in CT using motion information from gated PET. Finally, little work has been performed for motion correction of preclinical PET imaging partly because the motion of rodents is not particularly large and it can be easily gated because of low variability.
Pharmacokinetic and Physiologic Modeling of Different Tissues

In addition to the standard respiratory and cardiac gated simulations, integration of pharmacokinetics is the next step that will increase the realism of PET simulations. This is particularly interesting for development of new tracers. However, the level of complexity in modeling the biochemical aspects of a PET acquisition is much higher than physical and anatomic modeling. In practice, the radiotracer molecules follow the biochemical laws within the entire physiologic system being imaged. Therefore, the tracer and the tissue properties of the entire body might need to be included in the model. Simulation of the biochemical interactions could be theoretically described by quantum chemistry and require detailed understanding of the radiotracer chemical properties and their binding/interaction sites. A common molecular modeling software used in chemistry and drug development for this purpose is Gaussian v0.9 (http://www.gaussian.com/).

Fig. 4. Generated phantom (left) and simulated PET image sequence of a dynamic PCAT simulation with $^{82}$Rb PET tracer. (From Fung G, Higuchi T, Park M, et al. Development of a four-dimensional digital phantom for tracer kinetic modeling and analysis of dynamic perfusion PET and SPECT simulation studies. In: 2011 IEEE Nuclear Science Symposium and Medical Imaging Conference. 2011. p. 4195, http://dx.doi.org/10.1109/NSSMIC.2011.6153803; with permission.)
chemical research and help to study and predict the properties of molecules and reactions under a wide range of conditions.”

Recently, an analytic biomathematical modeling approach to predict the in vivo performance of radioligands in the biologic system based on prior information from in vitro and in silico measurements has been suggested. Nevertheless, the parent radiotracer is chemically active and can generate inside the body daughter radiotracer molecules, known also as the metabolites. Apart from augmenting the PET signal, these can also act as competitors of the parent tracer biochemical interactions. Therefore, in a few occasions the behavior of these molecules needs to be encapsulated within the pharmacokinetic simulation of a PET study.

In addition to the traditional radiotracer investigations, there has been emerging interest in dual bimodal agents where more complex biomolecules, such as proteins, peptides, and antibodies, can be labeled by a positron (or photon) emitter and imaged with PET (or SPECT) and CT–MR imaging. These multimodal agents have large size, and thus exhibit significantly slower kinetic behavior than standard PET tracers. Consequently, imaging requires long half-life radiotracers and potentially multiple acquisition sessions over hours or even days. Accurate longitudinal four-dimensional simulation of such studies would help to simplify the complicated imaging protocols needed for that type of investigation.

Finally, beyond dynamic PET simulations that include pharmacokinetic modeling, biomechanical tissue properties could be included in the next generation of dynamic phantoms as envisaged by Zaidi and Xu. For example, the biomechanical properties of tumors, blood flow, the main arteries (illustrated in Fig. 8), and the cardiac cavities (Figs. 9 and 10). The latter may become relevant in future hybrid four-dimensional PET simulations that could include multiscale and multiphysics mathematical modeling derived from physiologic measurements of the heart, lungs,
Fig. 6. Simulated PET-MR imaging acquisitions at inspiration and expiration phases of multiple volunteers with different respiration style. All images displayed in a fused style with the same color scale for PET and grayscale for MR imaging. (From Tsoumpas C, Buerger C, King AP, et al. Fast generation of four-dimensional PET-MR data from real dynamic MR acquisitions. Phys Med Biol 2011;56(20):6610, http://dx.doi.org/10.1088/0031-9155/56/20/005; with permission.)

Fig. 7. Enhanced cardiac model of the four-dimensional XCAT based on multidetector CT. This model has been developed for males and females. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (From Segars WP, Tsui BMW. MCAT to XCAT: the evolution of 4-D computerized phantoms for imaging research. Proc IEEE 2009;97(12):1962, http://dx.doi.org/10.1109/JPROC.2009.2022417; with permission.)
and other organs and specific disease-type tumors. Furthermore, as CT systems evolve, they may provide additional information in modeling blood flow properties and lung tissue function as recently demonstrated with a CT radiographic velocimetry technique (http://rsif.royalsocietypublishing.org/content/9/74/2213/suppl/DC1).53

**DATA SIMULATION SOFTWARE**

**Monte Carlo Simulators**

The most common approach to simulate physical processes of PET or SPECT acquisition is based on Monte Carlo (MC) simulation. Several MC packages exist in medical imaging and they vary accordingly in precision, accuracy, and computational demand. Among these, GATE,54 an open source software package (www.opengatecollaboration.org), is the most used. It can accommodate different scanner geometries and has been validated for numerous PET and SPECT scanners.55–57 Although GATE has the additional advantage of allowing modeling of time-dependent phenomena under realistic acquisition conditions, its main limitation is the extremely high computational demands for simulations without compromising statistical accuracy. Other packages that have supported PET research are SimSET58 (http://depts.washington.edu/simset/html/user_guide/simset_asim_usergroup.html), PET-SORTEO59 (Simulation of Realistic Tridimensional Emitting Objects; http://sorteo.cermep.fr/home.php), PeneloPET60 (http://nuclear.fis.ucm.es/penelopet), Eidolon,61 and GAMOS62 (http://fismed.ciemat.es/GAMOS/). SimSET is based on MC simulations and aims to model the physical processes in emission tomography. It has a modular structure that allows one to speed up the simulation by reducing accuracy of the...
physical modeling. Moreover, the current version includes time-of-flight modeling and random coincidences. PET-SORTEO generates PET data from voxelized descriptions of tracer distributions taking into consideration the scanner’s geometry, noise sources, and physical properties. Its output is normally in sinogram format but it has recently been extended into List-Mode. Eidolon MC has been designed to simulate fully three-dimensional cylindrical PET scanners on parallel computing. The software simulates the photon path length and the interaction processes within the phantoms and detectors. GAMOS is another recently developed simulation package, which like GATE is based on GEANT4 for medical imaging applications and has been designed with the aim to provide a flexible and well-validated toolkit.

Generally, the MC packages can become faster at the expense of modeling accuracy and precision. Sometimes computational speed-up is achieved by the use of variance reduction techniques that may predict the correct physical response of the scanner, but without necessarily preserving the statistical properties of a real acquisition. Additionally, even if several investigations have shown very good agreement with the acquired data, to the best of our knowledge none to date has investigated thoroughly their noise distribution and properties because of the extreme computational demand.

MC techniques are often used together with realistic numerical phantoms for several investigations. For example, they can be used to simulate numerous studies to develop a database (OncoPET_DB; https://www.creatis.insa-lyon.fr/oncoPET_DB) of clinical cases in whole-body PET. An extension to this concept has been recently performed by Le Maitre and colleagues who incorporated patient four-dimensional anatomic and functional variability of realistic whole-body FDG studies. The specific simulation was based on PET-SORTEO using the XCAT phantom, which was modified to fit actual CT scans of PET-CT patients. In addition, the phantom included inhomogeneous tumors and the effect of respiratory motion. In this way the simulations provide data with an extended spectrum of realism and they can be used as gold standard for future investigations. The objective of most of these simulations is the generation of realistic PET databases that would minimize computational cost. An example of the simulated dataset...
was compared with the corresponding real PET-CT image, it is illustrated in Fig. 11. This offers
the advantage to researchers to optimize their methodologies. However, the computational
burden to repeat multiple realizations of a simulation can still be very high (ie, 70 hours for one real-
ization of a static scan). A completely realistic and statistically accurate four-dimensional study for
whole-body imaging that includes physiologic and anatomic variability is computationally
demanding. Thus, there is still need for development of faster simulation toolkits.

Analytic Simulators

An attempt to address the need for computational speed is the development of fast analytic simulation
packages. A rigorous approach has first been implemented by Ma and colleagues,15,69 who has shown
realistic simulations of brain PET data derived from MR imaging measurements. In these investigations
analytic approaches to simulate different physical effects have been developed. In particular they
demonstrated a simulation of real measurements including such effects as attenuation, scatter,
random coincidences, detector variability and detector gaps, and statistical noise, showing that it
is possible to satisfactorily simulate PET data with analytic techniques.

Another example of an analytic simulator is Analytic SIMulator70 (ASIM; http://depts.washington.
edu/asimuw/Info.html), an open-source software specifically designed for PET. ASIM provides
several options, such as the simulation of emission data in two-dimensional or three-dimensional
mode, attenuation correction, random and scatter events, detector blurring, normalization, and noise
propagation. It has been used in various studies (eg, lesion detectability in response to various
parameters).71 An example of PET image simulation based on ASIM is illustrated in Fig. 12. In this
computational experiment ASIM generated multiple noisy realizations of a three-dimensional sinogram
for whole-body datasets that would be virtually impossible to achieve with MC methods. ASIM
is being developed further to provide an integrated environment72 with the open-source reconstruction
package Software for Tomographic Image Reconstruction (STIR),73 which will enable more efficient
four-dimensional simulations and reconstructions of realistic PET data (http://stir.sf.net).

Finally, another demonstration of the powerful
capabilities of analytic methods has been recently
presented by Tsoumpas and coworkers.32 This
method is used to simulate dynamic PET data
based on anatomic and dynamic information
from real MR images. After dynamic MR imaging
acquisition, fluorodeoxyglucose (FDG) distribu-
tions are produced by segmenting four-
dimensional MR images and assigning FDG
uptake values or, alternatively, using a high-
resolution three-dimensional segmented MR

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Fig. 11. PET images. (A) Clinical image. (B) PET-SORTEO simulated image of a healthy patient. (C) PET-SORTEO
simulated pathologic image containing three lesions (black arrows). (From Tomei S, Reilhac A, Visvikis D, et al.
OncoPET_DB: a freely distributed database of realistic simulated whole body 18F-FDG PET images for oncology.
image and three-dimensional motion fields from the dynamic MR image. The dynamic FDG distribution is the input to this fast analytic simulation technique (FAST) and raw PET data are created. FAST is performed with a proper combination of STIR utility programs and the simulated projection data include the effects of respiratory motion of the emission and attenuation maps, photon attenuation, and scatter and statistical (Poisson) noise. Realistic four-dimensional simulated datasets are freely available to other investigators (http://www.isd.kcl.ac.uk/pet-mri/simulated-data). An example is illustrated in Fig. 13 and the supplementary animations. An extension of this

![Fig. 12](image-url) (A–C) Several simulated scans using ASIM software corresponding to three different acquisition protocols. The arrows show simulated targets. (From Lartizien C, Kinahan PE, Comtat C. A lesion detection observer study comparing 2-dimensional versus fully 3-dimensional whole-body PET imaging protocols. J Nucl Med 2004;45(4):714–23, Fig. 3; with permission.)

![Fig. 13](image-url) Fig. 13. One plane from expiration (top row) and one from inspiration (bottom row) positions of the dynamic MR images, and the corresponding derived segmented image; FDG PET distribution; and attenuation image (see also animations). (From Buerger C, Tsoumpas C, Aitken A, et al. Investigation of MR-based attenuation correction and motion compensation for hybrid PET/MR. IEEE Trans Nucl Sci http://dx.doi.org/10.1109/TNS.2012.2209127; with permission.)
approach combined real respiratory signal derived from PET-CT images with motion modeling formed from MR imaging acquisitions and used FAST to create almost real-time (100 millisecond) four-dimensional PET simulations. The study investigated the impact of motion blurring on lesion detectability as a function of lesion size, location, and tracer uptake with variable breathing pattern.76

FUTURE PERSPECTIVES

Four-dimensional simulations of respiratory and cardiac gated PET acquisitions have made significant progress in the last decade. The availability of multimodal imaging has brought together experts from different radiologic imaging areas and MR imaging and CT data have been used to generate four-dimensional PET data. Although the simulation packages have evolved, more technologic advancements are necessary. There is a need to expand the current simulation toolkits toward a framework that includes irregular respiration patterns and cardiac cycles and bulk motion, peristalsis, and bladder expansion, paving the way toward realistic real-time motion simulations,77,78 tracer kinetics, and physiologically related motion combined with high-resolution computational phantoms and biologically relevant heterogeneities. These seem to be the future challenges, which once met, will allow more accurate simulation and, consequently, planning and design of PET scanning to the level of complex multicenter clinical trials to improve early diagnosis and therapeutic success.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.cpet.2012.10.003.

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