Computational Methods for Molecular Imaging

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Abstract Molecular imaging is a new research discipline enabling the visualization, characterization and quantification of biologic processes taking place at the cellular and subcellular levels within intact living subjects. Applications of molecular imaging techniques will benefit various clinical practices including classification and tracking of chemotherapy and treatment planning of radiotherapy, as well as drug discovery and development. Molecular imaging typically includes two or three dimensional imaging with quantification over time, and is often applied on molecular imaging modalities, such as Positron Emission Tomography (PET), and Single Photon Emission Computed Tomography (SPECT). Computational methods serve as an essential part in molecular imaging. Various computational methods are developed to accelerate image processing, identify underlying diseases hidden in the image volumes, evaluate the effectiveness of drug and radiotherapy etc. Computational methods for molecular imaging are in a fast growing field and full of potentials and challenges, and related topics have attracted many researchers from both academia and industry. This book covers the selected topics in computational methods for molecular imaging. As the start, this review provides a brief introduction to the current status of computational methods for molecular imaging and their applications.

Keywords Computational methods · Molecular imaging · Positron emission tomography (PET) · Clinical applications

1 Introduction to Molecular Imaging

Molecular imaging provides the images of molecular and cellular level activities inside the body. Molecular imaging enables doctors to measure the biological processes quantitatively and reflects the functionality of organs and tissues inside

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patients. According to the definition from the Society of Nuclear Medicine and Molecular Imaging (SNMMI), molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems [52]. Molecular imaging is a noninvasive procedure and can be used to study and diagnose cancer, brain diseases and disorders, cardiology, and various disorders in different organs and tissues. Major molecular imaging modalities are Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), furthermore, hybrid modalities, i.e. hybrid PET/CT [73], PET/MRI [64], PET/SPECT/CT [50] significantly enrich the ability of molecular imaging.

PET as a biomedical research technique and clinical diagnostic procedure is one of the most important part in nuclear medical imaging devices. In the past three decades, there have been significant advancements in PET scanners and image processing methods [4, 75, 77]. Currently, PET scans are most commonly used to detect cancer, heart problems, brain disorders and other central nervous system disorders. PET scan can be used to track the spread of disease inside body and patient response to drugs and therapies, which help to determine the more effective treatment plans for individual patient. PET scans can also be used to follow-up and manage ongoing cares. Quantitative dynamic PET imaging also offers good promise for personalized drug treatment by accurate pharmacokinetic analysis and will enable medicine to be tailored to each person's needs, and improve the safety, quality and effectiveness of healthcare for every patient.

PET scans rely on the injected radiotracers which circulate inside the body. Different radiotracers will reveal different diseases. Besides ^{18}F-FDG, which is widely used for cancer diagnosis, cardiology, neurology, there are many other radiotracers used in research and clinical applications, for example, ^{18}F-FLT (3′-fluoro-3′-deoxy-l-thymidine) is developed to image tumor cell proliferation [12], ^{11}C-acetate is developed to localize prostate cancer [57], ^{13}N-ammonia is developed to quantify the myocardial blood flow [46], ^{11}C-dihydrotetrabenazine (DTBZ) is developed for brain imaging, which can be used for differentiating Alzheimer's disease from dementia and Parkinson's disease [45]. Labeling drugs with various biomarkers is always a hot topic for pharmaceutical studies, where critical quantitative information can be generated by using dynamic PET imaging.

SPECT scan uses a gamma camera that rotates around the patient to detect the radiotracer inside body. SPECT will also produce a set of 3D images but generally have a lower resolution. The radiotracers commonly used for SPECT scan include ^{99m}Tc [54], ^{188}Re [39], ^{68}Ga [84], ^{82}Rb [24], etc. Electrocardiography (ECG)-Gated ^{82}Rb can also be used for myocardial perfusion PET [6]. Hybrid SPECT/CT is also designed to provide more accurate anatomical and functional information [71]. SPECT scan differs from PET scan in that the tracer stays in your blood stream rather than being absorbed by surrounding tissues, therefore, SPECT scan can show how blood flows to the heart and brain are effective or not. SPECT scan is cheaper and more readily available than higher resolution PET scan. Tests have shown that SPECT scan might be more sensitive to brain injury than either MRI or CT scanning because it can

detect reduced blood flow to injured sites. SPECT scan is also useful for presurgical evaluation of medically uncontrolled seizures and diagnosing stress fractures in the spine (spondylolysis), blood deprived (ischemic) areas of brain following a stroke, and tumors [5, 9].

2 Computational Methods for Molecular Imaging

Computational methods play a critical role in the development of molecular imaging, from image synthesis to data analysis and from clinical diagnosis to therapy individualization. They continuously deepen the visualization depth, enhance the imaging resolution, extend the molecular scope and improve the precision. The applications of computational methods can be in both generating images and understanding images, with the aim to improve the accuracy and efficiency. This section will provide a brief introduction to computational methods for molecular imaging within our topic coverage.

2.1 Data Correction and Image Reconstruction

The first step of all processing is to generate the image from raw data, which includes but not limit to data correction, system modeling and image reconstruction. The computational methods are designed to either improve the quantification accuracy or accelerate the processing. The challenges in PET data analysis come from the change of statistical properties of measurement data after various data corrections. The quality of results from all image reconstruction algorithms depends on the accuracy of statistical models in each data correction and image reconstruction. However, due to the complexity of PET scan, it is nearly impossible to propose a perfect model. Furthermore, a complicated model will apparently slow down the whole image reconstruction process. The modeling and processing in data correction includes scatter correction [37, 43, 80], attenuation correction [38, 68], partial volume effect correction [23, 67], etc. The image reconstruction includes analytical reconstruction and model-based reconstruction [2, 26]. In the studies involving a large amount of images from different patients, normalizing these images is also critical to the quantification of the studies [28].

2.2 Dynamic PET Imaging and Pharmacokinetic Analysis

Dynamic PET imaging is a combination of short interval PET scans and reflects the dynamic metabolism of injected radiotracers. Dynamic PET brings more challenges to PET imaging due to the poorer statistical property and low SNR from the low count

PET data. The series of acquisitions can be used to estimate the kinetic parameters which represent the metabolism of radiotracers in vivo.

In order to obtain the kinetic parameters, a traditional approach is first to reconstruct the activity distributions from the dynamic PET data, and then to fit the calculated time activity curve (TAC) to a predefined kinetic model. The accuracy of this kind of approaches relies on the reconstructed activity distributions. The complicated statistical noise properties, especially in the low-count dynamic PET imaging, and the uncertainties introduced by various PET data corrections will affect the activity reconstruction and lead to a suboptimal estimation of kinetic parameters [31]. There are also many efforts that try to estimate the kinetic parameters from PET projection data directly and achieve better bias and variance including both linear and nonlinear models [56, 74, 83]. The optimization algorithms are generally very complicated. Kamasak et al. applied the coordinate descent algorithm for optimization but it is still limited to specific kinetic models [41]. Wang et al. applied a generalized algorithm for reconstruction of parametric images [79], however, estimating individual kinetic parameter is still a challenging issue, which will be critical to clinical research, drug discovery and drug development [14, 27, 75].

In drug discovery and development, quantitative pharmacokinetic analysis with dynamic PET imaging now plays a promising role as determinants of in vivo drug action to help select drug candidate. Fast and accurate pharmacokinetic analysis with rapid information feedback in the early stage of drug discovery and development is critical to obtain the in vitro and in vivo drug properties [13, 81].

2.3 Mathematical and Statistical Modeling

Mathematical and statistical models have long been used in molecular imaging [47]. For static reconstruction, researchers unitized various system probability models [3], statistical models for data acquisition [86] and prior models [1]. For dynamic studies, compartment models are used in many fields including pharmacokinetics, biology, engineering etc. Compartment models are the type of mathematical models to describe the way materials (radiotracers and their metabolite in PET and SPECT scan) are transmitted among the compartments (different organs and tissues). Inside each compartment, the concentration of radiotracers is assumed to be uniformly equal. Due to their simplicity and plausibility, compartment models are widely used in the dynamic PET scans to describe the tracer/drug kinetics. Drug kinetic models include simple drug transport model, which generally contains equal or less than three compartments and can be solved directly, and complicated biological models, which can contain up to twenty compartments and generally require prior knowledge to solve [32, 33]. Most of the complicated models with many compartments can usually be decomposed into a combination of simple models with less than four compartments. The most basic compartment models include two compartment blood flow model, standard two tissue three compartment Phelps 4 K model with reversible target tissue and Sokoloff 3 K model with irreversible target tissue, three tissue five

parameter bertoldo model, standard three tissue four compartment model. More complicated models with more compartments and parallel model with multiple injection can be extended from aforementioned standard models [25, 42].

2.4 Feature Selection

Feature selection is widely used in computer aided diagnosis. Correctly selected features from a large set of clinical data can be used to improve the diagnosis accuracy of various diseases and provide a guidance for future clinical trials. The most commonly used method is Principal Component Analysis (PCA), which is a statistical procedure to convert a set of observation of possibly correlated variables to a set of linearly uncorrelated variables, i.e. principal components. These principle components can then be used as the feature for following studies, for example, comparing the functional connectivities in human brain studies [62, 70]. Machine learning and data mining techniques have also been applied to molecular imaging by various researchers. Researchers extract features to analyze cancer treatment outcome [20], utilize FDG-PET scan in lymphoma by WHO classification [21], classify the tissue in PET/MR scan with the potential for attenuation correction [53]. For clinical applications, support vector machine can also be used to identify imaging biomarkers of neurological and psychiatric diseases [59], and in therapy decision [58]. The application of machine learning is also very active in cancer prediction and prognosis [16].

2.5 Disease Specific Analysis and Image Quantification

In molecular imaging, the high activity concentrations (hot spots) are identified and analyzed as Region of Interest (ROI). In some clinical studies, different diseases may show similar activity concentrations inside the same organ tissue, then disease specific dynamic analysis become a superior tool to differentiate these different diseases [18, 27]. Disease specific dynamic analysis utilizes predefined disease models and the time activity curves from molecular imaging to classify the studies into proper disease categories. However, the accuracy of quantitative dynamic PET studies depends on various factors including kinetic models, quantitative methods and the approximation of arterial input function from blood sampling. The most general kinetic models used are compartment model with assumptions that physiological process and molecular interactions are not influenced by injected radioligand. Current clinical adopted quantitative methods are actually semi-quantitative methods, which include methods using reference regions or calculating Standard Uptake Value (SUV) [8]. Methods using reference regions are easy to implement but have several drawbacks, e.g. the reference tissue is hard to define and has low SNR due to the low resolution of PET and SPECT scans, and the uptake of the reference tissue may

change after the radiotherapy. SUV now is included in every clinical study, which is calculated as a ratio of tissue radioactivity concentration and injected dose divided by body weight, the advantage of SUV in clinical study is that the blood sampling is not required. However, the full quantitative analysis requires both dynamic PET scans and tracer concentration in the arterial blood plasma. The gold standard of blood sampling is serial arterial sampling of a superficial artery, and clinical alternative methods include venous blood sampling, image derived input function and population based input function [34, 48]. The drawback of the full quantitative method is only one FOV/bed position can be taken into consideration at one time. For metastasized disease, not all lesions can be quantified simultaneously [69, 76].

2.6 Other Conventional Image Processing Applications

1. Image Segmentation. Image segmentation is the process of partitioning an image into multiple different segments (group of pixels). Especially in molecular imaging, the image segmentation is used to simplify the representation of an image and extract Region of Interest (ROI) that is more meaningful and followed by image analysis. Image segmentation is also important to find the boundaries of different regions and organs by applying different labels. Image segmentation can also be applied to 3D image stacks to help 3D image reconstruction [17, 87]. Computational methods for image segmentation including basic thresholding methods [19, 22, 40], cluster based methods, which are multivariate data analysis methods using predefined criteria to partition a large number of objects into a smaller number of clusters [82], gradient based methods, which are to find the boundary of an object of interest with the gradient intensity observed in the images [29], level set based methods [51, 60], 3D level set methods [85], and kinetic model guided segmentation methods, which assume different ROIs have different tracer kinetic properties to separate different functional regions [11].
2. Image Registration. Image registration is the process to transform different sets of data into one coordinate system. Image registration is widely used in molecular imaging, e.g. patient radiotherapy follow-up by transforming PET images from a series of studies, diagnosis by images from multiple imaging modalities [15, 35, 36, 65]. Major computational methods include intense based methods, which compare intensity patterns in multiple images and register the reference image and target image by defining correlation metrics [44], feature-based image registration, which extract common features from the anatomical information of organs and tissues as references [63], this method can also be used for multiple imaging modalities [30, 49, 55]. The image registration can be improved by different patient preparation and pre-positioning [7], respiratory gating [10], various tracking devices, etc. [66].

3. Image Fusion. Image fusion is the combination of relevant information from two or more images into one single image. The fused image will provide more information than any single input image. Accurate image fusion from combined PET, CT, MRI scans can significantly improve the diagnosis and provide better understandings of diseases. Image fusion generally works together and shares similar technologies with image registration [61, 72, 78].

3 Future Directions

Molecular imaging is a relatively new but fast-growing area for both research and clinical applications. Although with some technical limitations, molecular imaging modalities show the superior ability to quantitatively measure the biologic processes in a functional way at the cellular and subcellular level within living subjects, and this significantly improved our understanding of various diseases and greatly benefited the clinical diagnosis. The emerging new scanner systems with new detectors will further enhance their abilities, and bring new challenges in data correction and image analysis at the same time.

Computational methods play a critical role in processing the images, from data processing based on the physical natures of the molecular imaging modalities to image reconstruction, analysis and understanding. The data processing algorithms need to be adjusted with the properties of new system design, and new features in detector system correspondingly. Monte Carlo simulation is a faithful way to study the new design and provide references for validation of new methods. Application-specific statistical models will greatly improve the image qualities of certain disease compared with generic models, and new techniques like machine learning have shown promising prospects in classifying diseases, generating atlas based models etc. The image post-processing including image analysis and understanding must also adopt related changes. Researchers are actively using computing methods to guide applicable pathological studies from a series of patient studies using dynamic analysis, this has the great potential to apply to personalized treatment. Pharmaceutical companies are also interested in the accurate quantitative pharmacokinetic analysis using PET to study the metabolism of new drugs, which has the potentials to shorten the drug development cycle and save tons of money for the industry and patients. With the evolution of both image pre-processing and post-processing methods, molecular imaging is believed to be able to study more complicated diseases currently in the unknown area, and computational methods for molecular imaging will help us to mine the potentials buried in the data and images.

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