Scopes and Utilization of Tomographic Images in Drug Development, Issues and Challenges: A Short Review

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Abstract

To assess the mathematical and statistical issues related with acquired images, and to make inferences in diagnostic detection based on general linear models (GLM) for each and every pixel/voxel of the tomograms, in addition multiple comparison as well as sample size and power issues will be outlined. The steps involved range from tomographics image reconstruction to statistical inferences:

A. Image Data Acquisition: X-Ray CT, SPECT, PET, MRI and combined modalities such as: PET-CT, PET-MRI, etc.,

B. Image Segmentation: Automation, Validation and Reproducibility

C. Feature Extraction: Automatic Extraction, Reproducibility and Low Redundancy and

D. Mathematical and Statistical Analysis and Database: Clinical and Research PACS System, Storage and Sharing of Reports and Annotations, Integration and of Clinical, Genomics and Imaging Database, Analysis. The overall drug development process is shown in figure 1.

Keywords

Medical imaging, Imaging modalities, Tomographics, Statistical interfaces, Drug development

Introduction

As after one of the greatest discoveries of X-ray in human history by German physicist Wilhelm Conrad Roentgen in 1895, and after a long gap of almost eight decades the other revolutionary work was done by the physicist Allan MacLeod Cormack and Godfrey Newbold Hounsfield as an electronic engineer had developed the computed tomography, subsequently there were other imaging modalities were discovered and saw a great leap and bound in medical sciences for the last few decades of the 21st century.

Whereas the greatest surprise in the healthcare and pharmaceutical industry came with the fusion of anatomical (computed tomography: CT) with other functional imaging modalities such as positron emission tomography (PET), single photon emission tomography, and etc., and the first prototype PET/CT scanner was built in 1998 by David Townsend et al. [1]. This development had made the clinical physicians to make a better diagnosis and treatment and had ensured a longer and better life for the patients.

An overall development in medical modalities such as: computed tomography (CT), ultrasound imaging, nuclear imaging and magnetic resonance imaging
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(MRI) had advanced the clinical research with greater accuracy with micron level information in the diagnosis or prognosis of the numerous fatal diseases. And, the advent of high-speed computers with high resolution imaging tools have made it possible to view the images in three dimensions to deduce vital clinical information from the raw images.

Medical imaging plays a vital role in development of new medical instruments and products. The imaging industry is in a constant state of flux - due to increased investment in companies, as well as mergers and acquisitions - adoption of novel imaging technologies to support clinical trials for the pharma, biotech, and medical device industries continues to increase. In fact, “centralized” imaging data is now used as a primary endpoint in many clinical research studies.

Imaging modalities: Currently, there are multitude of imaging modalities available from manufacturers, and the images produced from them are focal point of scientific research in many areas such as: from nondestructive testing in aerospace to the molecular biology. In this section some of the scanning modalities will be outlined as follows, broadly categorized as:

Anatomical modalities: X-ray radiography, Ultrasound, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), and they help to study the anatomical morphology. Whereas there are other modalities as derivative of these also available and they are: Magnetic Resonance Angiography (MRA), Digital Subtraction Angiography (DSA), computed tomography angiography, etc.

Functional modalities: Single Photon Emission Tomography, Positron Emission Tomography, and functional Magnetic Resonance Imaging, etc. They are commonly used in the study related with the diagnosis of the disease for the heart, the neuroimaging, etc.

X-ray Projection Imaging

The X-ray projection imaging may be one of the most frequently recommended by clinician in order to examine any kind of injury, fracture of a limb, clinical diagnosis, etc., although there is great stride of sophisticated and advanced devices, but it is still widely used. X-ray projection imaging is due to a German Scientist Roentgen et al [2] discovered in 1895, a non-invasive procedure and gave the birth of a new discipline known as radiography, and in 1901 he got the Nobel Prize.

X-Ray Computed Tomography (X-ray CT)

The X-ray Computed Tomography, commonly known as CT scanner was the first non-invasive device. Moreover, it is based on transmission of monochromatic X-rays from a source that passed through any object such as patient’s body, and the transmitted rays are collated at the detector end. Since there are different contrast (densities) in the human’s tissue due to the differential attenuation of X-rays in the body, and can be described as follows

\[ I = I_0 e^{-\mu r} \quad \text{(1)} \]

where \( I \) is the x-ray intensity, and the \( I_0 \) is the initial intensity without the object, whereas the attenuation of x-rays could be given as

\[ I_0 = I e^{\int_{\mu(z)} dx} \quad \text{(2)} \]

In CT scanners the x-ray attenuation according to the above equation is measured along a variety of lines within a plane perpendicular to the long axis of the patient with the goal of reconstructing a map of the attenuation coefficients for the plane.

Nuclear Medicine Techniques: SPECT and PET

In emission tomography there are basically two modalities such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) are the main non-invasive tools to be utilized in the diagnosis of disease as well as understanding of the physiological processes inside the body at a molecular level. The mathematical algorithms are identical and similar such as in X-ray CT; and their wide utilization are into understanding of the physiological process, for example: glucose consumption, blood flow, oxidative metabolism, neurotransmission, and many others [3].

Ultrasound Tomography

This imaging modality is also a noninvasive and utilized in many clinical areas. Moreover, this modality is based on the diffraction of sound waves (scattering theory), whereas from the diffracted images, the reconstruction algorithms are used to reconstruct the image. It is very safe imaging modality as there is no radiation and highly applied in the detection of the soft tissues, for example in the assessment of fetal health, intra-abdominal imaging of the liver, kidney, and the detection of compromised blood flow in veins and arteries. But there are disadvantages such as difficult to distinguish the noises, as well as to detect the small features like cysts in breast imagery.

The ultrasound tomography is based upon the Helmholtz’s partial differential equation and given as below
\[ \nabla^2 \varphi(r) + k^2(r) \varphi(r) = -f(r) \]

where \((r)\) is the total acoustic field, \(k(r) = \omega/c(r)\) is the wavenumber associated with angular frequency \(\omega\) and sound speed \(c(r)\) is the source function. Assuming \(k(r) = k\), a uniform background medium, the solution \(g(r, r')\) to the above equation for a point source \(f(r) = \delta(r - r')\) is defined as free space Green's function, and for 2-D space is given by \(g(r, r') = (j/4)H_1^0(k|r - r'|)\), a complete description about the Green's function and transforming into Lippmann-Schwinger Integral equation interested reader's are referred to the Chew et al., and Mathias et al., [4, 5]. Moreover, images obtained from ultrasound tomographic devices are having high resolution and there is no radiation with operating frequencies between 1 and 10 MHz. They produce images via the backscattering of mechanical energy from interfaces between tissues and small structures within tissue.

**Magnetic Resonance Imaging (MRI)**

This non-invasive imaging is based on the exposition of high frequency energy in the presence of magnetic field and that exploits the hydrogen atoms of water molecules, as the patient undergoes for the scanning. And this puts the atoms in excited or charged state and from these images are created from the differences in relaxation rates in different tissues. In early stage of development this modality was also known as nuclear magnetic resonance (NMR), but now it's known as magnetic resonance imaging (MRI).

The principles of magnetic resonance imaging (MRI) is based upon Bloch equations as below:

\[ \frac{dM}{dt} = \gamma M * H - \frac{M_{eq} - M_0}{T_1} - \frac{M_0}{T_2} \]

where is the gyromagnetic ratio1, \(H\) the effective field, \(M_0\) the equilibrium magnetization and \(T_1\) and \(T_2\) the relaxation times. \(T_1\) is the characteristic relaxation time for longitudinal magnetization to align with the magnetic field, notation adopted from Mathematics and Physics of Emerging Biomedical Imaging [6]. Moreover, there is no closed-form solution for the above equation and could be solved by approximation of the equation by numerical methods. Application of MRI is very promising especially in the study of functional neuroimaging and blood flow imaging and quantification, for a good exposition on this topic could be found in Morris et al., [7]. This modality is safe and produces highly resolution of images.

**Computed Tomography: Reconstruction Algorithms**

Though around 1900, the mathematician Johann Radon had put forward the foundation of mathematics behind the principle of computed tomography by introducing the projection integral or Radon transform but after a big gap of almost 70 years later Cormack, and Hounsefield (1970) worked independently had provided a sigh of relief from unwanted invasive medical procedures by induction of the first computed tomographic machine to obtain images for medical diagnosis in a non-invasive fashion, a great breakthrough in the field of radiology; both Cormack and Hounsefield were jointly awarded Nobel Prize in 1984. The word tomography is derived from the Greek word 'tomo' means slice and 'graphy' means to write. Thus, tomography is the science drawing slices by stacking slices to obtain 2D or 3D objects. Moreover, in medical imaging the object is reconstructed without dissecting or cutting the object, the reconstruction is done through indirect measurement as some function of interest. So, what needs to be recorded and how it is reconstructed solely based upon the physical process involved, and it's kind of an 'Inverse-Problem'.

In the following sections: Radon transform, Filtered Back projection Algorithm, and Iterative Algorithms will be discussed. Commonly used in the medical imaging a phantom or a “Mathematical Phantom” simulated by Shepp et al. and Shepp et al. [3, 8]. This head phantom consists of several ellipses with different intensities (attenuation), whereas prior to their work it usually was done by creating real physical models and they were prone to error measurement. The Shepp-Logan phantom using MATLAB from MathWorks a simulated object is shown in figure 2.

**Analytical Based Reconstruction Algorithms**

The most widely used methods of image reconstruction are direct analytical methods, moreover very first such a practical algorithm was published by Shepp et al [8], known as Filtered Backprojection Algorithm (FBP) and images were reconstructed with faster and better scan time, but there some problems associated with these reconstructed images, as they tend to be 'streaky' and display interference between regions of low and high tracer concentration.

The FBP reconstruction algorithm has the following steps:

- Acquire 1D projections: Radon transform
- Convert 1D projections to Fourier Transforms
- Buildup Fourier Transforms into 2D image
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- Reconstruct 2D real space image from 2D Fourier Transform image

Moreover, in the following subsections: Radon transform, Fourier Slice Theorem, Filtered Back projection Algorithm have been explained, notations have been adopted from Khan et al. [9].

Radon transform

The Radon transform [11] of the density function \( f(x, y) \) in two dimensional space (\( \mathbb{R}^2 \)) is a line integral of \( f \) over the line \( L = x \cos \theta + y \sin \theta - \rho \) in the \( x-y \) plane for all possible directions. The assumed \((\rho, \theta)\) coordinate system is shown in figure 3, where \( \theta \) is the perpendicular distance on the ray \( AB \) from the origin \( O \) and \( \theta \) is the projection angle subtended with the \( X \)-axis.

The Radon transform \( p(\rho, \theta) \) of the function \( f(x, y) \) can be written as

\[
p(\rho, \theta) = \int_{-\infty}^{\infty} f(x, y) \delta(x \cos \theta + y \sin \theta - \rho) \, dx \, dy
\]

where \( s \) is the dummy variable for the line AB. This can be written also using the Dirac function.

\[
p(\rho, \theta) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x, y) \delta(x \cos \theta + y \sin \theta - \rho) \, dx \, dy
\]

Fourier slice theorem and inversion algorithm

There are several ways to find the inversion of Radon transform. Among all the inversion algorithms the filtered back projection Algorithm is most popular. Since, filtered back projection algorithm is easy to implement and also it is fast computationally. This algorithm consists of merely two steps, namely filter and back projection.

\[
F(k_x, k_y) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x, y) e^{-2\pi i (k_x x + k_y y)} \, dx \, dy
\]

and the inverse Fourier transform is

\[
f(x, y) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} F(k_x, k_y) e^{2\pi i (k_x x + k_y y)} \, dk_x \, dk_y
\]

In the polar form the equation can be written as

\[
F(v \cos(\theta), v(\sin(\theta))) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x, y) e^{-2\pi i (v \cos(\theta) x + v \sin(\theta) y)} \, dx \, dy\]

\[
= \int_{-\infty}^{\infty} \left[ \int_{-\infty}^{\infty} f(x, y) e^{-2\pi i (\rho - x \cos \theta - y \sin \theta)} \, dx \right] d\rho
\]

Hence,

\[
F(v \cos(\theta), v(\sin(\theta))) = \int_{-\infty}^{\infty} p(\rho, \theta) e^{-2\pi i v \rho} \, d\rho
\]

(3)

This above equation (3) is a well-known Fourier Slice theorem. The term \( p(\rho, \theta) \) is the Radon transform of the density function \( f(x, y) \) for parallel beam data.

The reconstructed images from analytical methods are having advantages such as fast, simple, predictable, linear behavior, but there are some disadvantages too and are: not very flexible, sub-optimal, noise and having resolution issues.

Materials and Methods

In general, tomographic’s reconstruction algorithms are very similar both in emission and X-ray based tomography. Lately, the hybrid modalities such as: PET-CT, PET-MRI, etc., are used to understand the physiological processes, e.g.: glucose consumption, blood flow, oxidative metabolism, neurotransmission, and many others. In drug development applications are gaining momentum as it’s cost effective and save time. Moreover, the reconstruction algorithm commonly known as ‘Filtered Back projection (FBP)’ and it’s variant have mainly 4 steps:

1. Acquire 1D projections: Radon transform
2. Convert 1D projections to Fourier Transforms
3. Building Fourier Transforms into 2D image
4. Reconstruct 2D real space image from 2D Fourier Transform image

The Radon transform is the ‘Work-Horse’ of the reconstruction algorithm along with the ‘Fourier Slice Theorem’. This approach has several advantages such as: speed, simplicity, predictable, and linear behavior. However, there are some disadvantages too including: not very flexible, sub-optimal, noise and resolution issues. Moreover, to make inferences from these images (pixel/voxel) is an uphill task. For example: an element \( H_{ij} \) of the system model \( H \) as it’s representing the image space with the probability that emitted rays or photons from pixel/voxel \( j \) is detected in projection \( i \), and could be given as:

\[
P_i = \sum_{i=1}^{N} H_{ij} f_j
\]

\( i=1 \) \( H_{ij} \) \( f_j \) where \( pi \) is the mean of the \( i \)th projection and \( f_j \) is the activity in voxel \( j \) and shown below in figure 4.

The main task is to elaborate the complexities involved in these tomographic images, they are highly correlated therefore to make inferences in each voxel using classical theory is almost not feasible. Hence, to understand every bit of information

Figure 3: Parallel-Beam Geometry.
requires some form understanding of advanced mathematics and there is a need to rely on some advance tools such as utilizing ‘Random Field theory’ and focusing more towards differential manifolds. Even the use of Benjamin-Hochberg multiple comparison yields numerous false positive results.

Results

Using simulated phantom available in MATLAB, the true phantom, sinogram, un-filtered, and filtered images are shown figure 5. And the figure 6 shows to quantification of a collection of stroke lesion images in diffusion weighted images (DWI), [10]. The statistical significance of the equality of the proportions of stroke lesions between the two groups were applied.

In the figure 7 the Random Field Theory was applied to infer the statistical significance of the equality of the proportions of stroke lesions between the two groups after Gaussian kernel smoothing with 10 pixel wide FWHM (Full Width at Half Maximum) were used.

Conclusions

The above simulated results show that these medical imaging modalities are playing a pivotal role in diagnostic detection, and drug development processes thereby assisting clinical decision making. They may also be applied in clinical trials studies, since detection and diagnosis of lesions, evaluations of lesion severity, therapeutic monitoring has tremendous potential in drug safety evaluations and reducing the need of surgical procedures. Furthermore, it seems that sophisticated mathematical and statistical algorithms are extremely important and would rely upon experienced and skilled computational scientists to play an important role in deducing scientific information, clinical decisions making. Some of the key pivotal areas are use include:

- Pharmacokinetic and pharmacodynamic processes that requires the use of short-lived isotopes, to determine the inter and intra tumoral distribution within the body. The combo
application of PET and CT could be used to assess such tumoral distribution.

• FDG-PET are currently used to assess the 'Tumor Response', since this approach is helpful in assessment of whether the drugs have cytostatic rather than a cytotoxic effect due to changes in tumor metabolism. The changes can be visualized using tomograms rather than relying on physical tumor shrinkage. Such an application could introduce a new era for ‘Anti-Cancer Drug Development’.

• As there are positive responses with the use of PET in neurology since the use PET is not being utilized in oncology as there is a key issue in oncology to assess the response for inter-patient variation in tumor drug uptake.

• Currently there are many (mathematically and statistical) challenges regarding these acquired images, since these are highly correlated, and the classical approaches do not suffice to explain such as scaling factors, the curse of dimensionalities, etc. in human anatomy.

Therefore, to analyze tomographic images requires in understanding as well as development of mathematical topology since these images are based on geometrical features, hence there is need apply Riemannian Geometry.

Future Research

Combo modalities can have used us as a primary research tool to visualize and understand the underlying molecular mechanism associated with disease. These multiplexed imaging methods could help in identifying the characterization of a therapeutic intervention through visualization and measurement of the biodistribution of both the drug and drug target, the drug target interaction, the activation of signal transduction pathways, and finally the morphological and physiological consequences of these molecular events.

Acknowledgments

I gratefully acknowledge to be thankful and grateful to: Dr. Mohammed A. Hussein (Chairman of the Department), Dr. Barak Al Somaie (Director of Operation), Dr. Ahamad Al Askar (Executive Director of the KAIMRC) for their help and support.

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