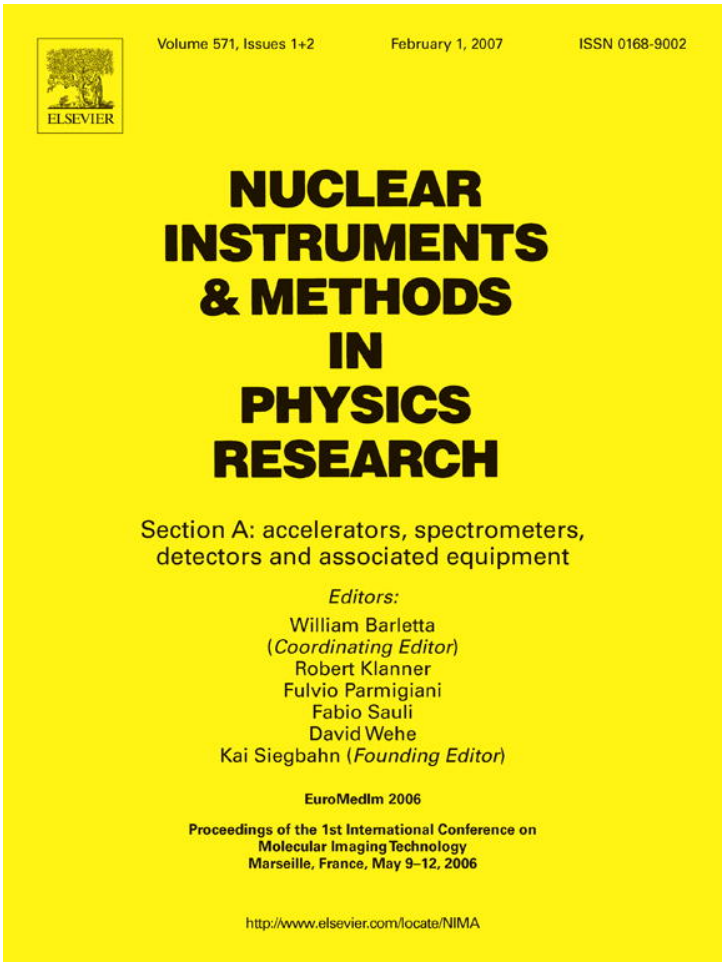

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Quantification in emission tomography: Challenges, solutions, and performance

Irène Buvat

U678 INSERM – Université Pierre et Marie Curie, CHU Pitié Salpêtrière, 75634 Paris Cedex, France

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Abstract

Emission tomography (single photon emission tomography—SPECT—and positron emission tomography—PET) offers a great potential for the quantitative characterization of functional and molecular processes in vivo. Indeed, voxel values in the reconstructed SPECT and PET images can theoretically be translated into a well-understood physical quantity, namely radiotracer concentration, from which all kinds of parameters characterizing molecular processes can be derived using appropriate modeling. Such quantitative interpretation of SPECT and PET images is often referred to as "quantification". The objective of this short review is to examine how far we are in this quest for quantification by presenting the different problems that have to be addressed, the methods that have been developed to solve these problems, and the current performance of these methods.

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1. Introduction

Emission tomography, including single photon emission computed tomography (SPECT) and positron emission tomography (PET), makes it possible to estimate parameters characterizing physiological and molecular processes, such as ejection fraction for characterizing the cardiac function, glucose metabolic rate (GMR) for assessing myocardial viability or staging tumors, or dopaminergic transporter density for brain disease diagnosis. This process of extracting parameters from SPECT or PET images, often called "quantification", actually includes two steps. The first step consists in converting pixel values into radiotracer concentrations, as the radiotracer—a biologically active compound combined with a radioisotope—is what reveals the targeted physiological process. Given the radiotracer concentration in different regions of the physiological system under study, the second step consists in solving a physiological model describing this system, to deduce the physiological parameters of interest.

This quantification process is extremely appealing for many applications, as it results in much richer information than the only visual interpretation of images. This is especially true for differential diagnosis, when comparing a parameter value with a certain threshold can help determine the proper diagnosis, for prognosis, as the value of a physiological parameter can help stage the patient, for therapeutic management, and probably even more important, for therapeutic followup and radiotherapy. The possible use of emission tomography for monitoring the patients in the course of therapy is extremely promising, as the first signals revealing the response or lack of response to therapy are at the molecular level, which is the level emission tomography can probe. In radiotherapy, the motivation for quantification is clear: treatment planning has to be based on objective, hence quantitative criteria. If these criteria have concerned the anatomy of the tumors so far, it is anticipated that criteria relating to the biochemical processes in progress within the tumor would be more relevant. Quantification is therefore one of the greatest

E-mail address: irene.buvat@imed.jussieu.fr.

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challenges of emission tomography—and actually medical imaging in general—for the near future.

2. From pixel values to radiotracer concentration

To derive physiological parameters from SPECT or PET images, a required step is to determine the relationship between the pixel values and the radiotracer concentrations. A number of phenomena introduced by the imaging process make this relationship highly nonlinear. However, the physics of emission tomography being well understood, these phenomena are now identified. The most important to be aware of are patient or organ motion, photon attenuation and scatter, limited spatial resolution of the tomograph, sampling, tomographic reconstruction, and measurement procedure. In PET, random coincidences also have to be accounted for. The impact of most of these phenomena and how they can be dealt with are now briefly reviewed.

2.1. Patient motion

Patient and organ motions have become of great concern only recently, mostly because quantification is getting accurate enough for motion to appear as a disturbing effect while before, the impact of motion could be neglected with respect to other disturbing phenomena.

Motion can actually introduce large biases, for instance tracer uptake underestimation greater than 50% in lung tumor [1]. Two strategies are currently developed to reduce or compensate the biases due to motion. First, companies try to reduce the scanning time, by increasing the sensitivity of the detector, so that spurious motion is less likely. Second, much research is dedicated to cardiac and/or respiratory gating. A first level is to get an image corresponding to only one "gate", i.e., a small fraction of the cardiac or respiratory cycle, thus removing temporal blurring, but also losing a lot of signal. More advanced approaches consist in combining all gates in some way to remove motion blur while keeping sensitivity identical. This type of approach show promise, but is not available in routine yet [2].

2.2. Photon attenuation

Photons are attenuated when they travel through tissue, yielding underestimation in radiotracer concentration often greater than 70% [3] together with image artefacts.

Attenuation compensation requires a measurement of tissue density and composition, which directly affect the magnitude of attenuation. Such measurement is now most often performed using CT scanners associated with PET and SPECT tomographs. Then, attenuation compensation can be performed before or after tomographic reconstruction or even better, during tomographic reconstruction, by accounting for attenuation in the system matrix to be iteratively inverted [3]. Attenuation correction is currently very efficient, and in a fine-tuning stage to account for additional effects like motion or the presence of contrast medium in the patient.

2.3. Scatter correction

Photon scattering in the patient or in the detector are detected at a wrong location, hence mostly decrease contrast. Depending on the type of SPECT or PET scan, the percentage of detected photons that have scattered varies from about 20% to more than 50%. Scatter photons can be just removed, at the expense of sensitivity. More appealing are the methods aiming at relocating scattered photons at the right position in the images. Such methods have the great advantage of not decreasing sensitivity, but are difficult to implement. Indeed, scatter occurs in 3D, and the system matrix used for reconstruction, which contains many zero if scatter is ignored, becomes more difficult to invert when scatter is introduced. Also, scatter due to out-of-the-field-of-view activity is difficult to account for in this latter approach [4].

2.4. Spatial resolution of the tomograph

In both SPECT and PET, spatial resolution varies in space, for instance with the source-to-collimator distance in SPECT. Limited spatial resolution introduces partial volume effect (PVE), which in turn introduces severe activity underestimation in small structures, typically less than three times the full-width at half-maximum characterizing the spatial resolution. To compensate PVE, the simplest approach consists in multiplying measured values by recovery coefficients, which depend on the size of the structure of interest and on the spatial resolution [5]. A more sophisticated approach consists in estimating the cross-contamination between regions in the images (i.e. which percentage of activity coming from a specific region is actually detected within this region and within adjacent regions), and calculating the true values in each region given the measured values and the cross-contamination values [6]. These two approaches definitely improve quantification, but both have the considerable drawback of assuming that the contours of the functional regions (needed to apply the corrections) are identical to those of the anatomical compartments, derived from magnetic resonance imaging or CT for instance. Other PVE correction strategies that would not require such an assumption are still needed.

2.5. Tomographic reconstruction

The relationship between pixel value and radiotracer concentration indirectly depends on the reconstruction method, because the reconstruction algorithm directly affects spatial resolution, which in turn determines the importance of PVE and the noise level [7]. Two algorithms leading to the same tradeoff in terms of spatial resolution and noise would yield similar quantitative accuracy. It is

therefore very important to report the spatial resolution and noise level achieved by the reconstruction algorithm used to produce the images, as these partly determine the quantitative accuracy that can be reached, especially when no PVE correction is performed.

2.6. Measurement procedure

Finally, quantitative accuracy also depends on the very measurement procedure, and mostly on the drawing of regions of interest (ROI) [8]. For instance, tumor uptake is currently measured either using the average value in a manually drawn ROI, or the maximum value in that ROI, or the average value within a region determined using a pixel intensity threshold. The sensitivity/specificity tradeoff for detecting tumor response actually depends on the measurement procedure [9]. There is therefore a need for optimization and standardization of measurement procedures. The way functional regions should be defined is a very challenging issue that now needs to be addressed.

In summary, all the phenomena mentioned above have to be properly dealt with to achieve an almost linear relationship between radiotracer concentration and pixel values. A calibration procedure can then be used to determine the unique coefficient of this relationship. Several studies have shown that in well-controlled protocols, in the absence of motion, applying corrections for all other perturbing effects yield to activity concentrations that are accurate within 15%, for instance in neurotransmission SPECT imaging [10]. The three effects that are not yet properly accounted for in the clinics are motion, PVE and measurement method. Developments regarding these three effects are ongoing, which make accurate estimation of radiotracer concentration within reach.

3. From radiotracer concentrations to physiological parameters

3.1. Comprehensive approach

The most appropriate approach to derive physiological parameters in emission tomography involves four steps: (1) measurement of radiotracer distribution in the physiological system of interest over time, by acquiring a time series of images; (2) measurement of the amount of radiotracer that has been made available to the organs of interest, using arterial blood sampling over time to get what is called the arterial input function (AIF); (3) modeling of the physiological system of interest using a small number of "compartments" linked using unknown physiological parameters that describe the exchanges between compartments; (4) fitting the AIF and the radiotracer concentrations measured in different regions (compartments) to the kinetic model, to estimate the physiological parameters of the model.

Acquiring time series of images takes time and arterial blood sampling is invasive. This is why in most applications, a simplified quantification procedure is used, often at the expense of quantitative accuracy.

3.2. Simplified kinetic analysis

A good example that illustrates the different levels of complexity that can be used for deriving physiological parameters in emission tomography concerns the estimation of the glucose GMR in F18-fluorodeoxyglucose (FDG) PET. The simplest method to roughly estimate the GMR consists in calculating a standardized uptake value (SUV), using only a static acquisition (no time series) and no AIF. This is actually the most common method used to estimate GMR, despite the over-simplification it is based on. Indeed, when calculating an SUV, unmetabolized glucose is neglected, the FDG available to the tumor is assumed to be equal to the total FDG activity injected to the patient divided by the patient volume, which is considered to be equal to the patient weight (or derived quantities, like lean body mass). Finally, the time dependency is neglected, assuming acquisition is performed at equilibrium. Several studies have demonstrated that SUV is a poor estimate of GMR in some instances [11]. Other simplified kinetic analysis have been proposed to estimate the GMR, without involving all the complexity required when performing a full kinetic analysis, but which are more accurate than a simplistic SUV [12,13].

Most often, increased model complexity goes with greater accuracy in physiological parameter estimates. There is still quite a lot of room for improvement in finding the best tradeoff between the feasibility of an acquisition and processing protocol and the accuracy of the resulting physiological parameter estimates.

4. Discussion and conclusion

To sum up what is currently a huge domain of research in emission tomography, recent results have shown that accurate quantification (within 10–15%) is feasible in specific PET and SPECT applications. However, it still takes a lot of efforts, as quantification is a complicated process, requiring tissue density map, perfectly controlled acquisition and processing protocols, high resolution anatomical information, and accurate kinetic modeling, this latter part being often neglected. Accurate quantification is easier in PET than in SPECT, mostly because attenuation correction is more accessible (more PET scanners are PET/CT than SPECT scanners are SPECT/CT), and mostly because spatial resolution is better, hence PVE is less of a problem. The hybrid SPECT/CT and PET/CT scanners could make quantification a clinical reality in a near future, by facilitating the use of motion and PVE corrections, and by assisting in the region-drawing step when necessary. Partial volume effect, motion, and drawing functional regions are currently the most difficult issues to deal with.

Given that all corrections are often not performed, quantification accuracy currently depends highly on the acquisition and processing protocols [14]. For a given protocol, quantitative accuracy should absolutely be characterized using phantom experiments. Meta-analyses are often impossible—or meaningless—given the variety and lack of information regarding acquisition and processing in the clinical literature. Comparing quantitative values (e.g., for therapeutic followup, malignancy indices) requires highly controlled protocols to ensure constant acquisition and processing conditions.

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