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Modern Quantitative Techniques for PET/CT/MR Hybrid Imaging

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1. Introduction

The relentless progress that is being made in tomographic imaging modalities is inexorably expanding the application of positron emission tomography (PET) in the clinical field. Some of the most noteworthy advances involve innovations in quantitative techniques for hybrid imaging modalities such as PET/Computed Tomography (CT) and PET/Magnetic Resonance Imaging (MRI), which have greatly improved the ability to segment and analyze functional images produced with radiotracers such as (^{18}F) Fluorodeoxyglucose (FDG). With continued technological progress, quantitative approaches can supplant the more subjective qualitative and semi-quantitative techniques that currently dominate the clinical use of PET.

Although it does not meet the rigorous standards for objectivity in medical research, the qualitative method of visual assessment continues to be very prevalent in the clinical field. The benefits of this technique's simplicity are offset by its immense subjectivity and the consequent lack of reproducibility and pervasiveness of inter-reader variability. These limitations are mitigated in the somewhat more consistent semi-quantitative technique of standardized uptake value (SUV), but concerns about reproducibility still linger. The manual delineation of the regions of interest (ROIs) within an image maintains a degree of subjectivity that hinders the reproducibility of the analysis. Therefore, while these methodologies may be less demanding, they open the door to the possibility of variability.

Using structural and functional imaging, namely PET/CT and PET/MRI, and combining structural information with functional data by various quantitative techniques provide a far more objective method of image analysis, but also carry their own set of inherent difficulties. This method of quantification is far more technically demanding and requires complex mathematical computations[1,2].

Despite its limitations, it appears likely that quantitative analysis of hybrid imaging will become the method of choice in the future. Recent developments in tomographic imaging have improved the ability of PET to accurately assess global function in addition to the more conventional ROI analysis. Global assessment, which combines data on the activity of a lesion measured by PET and its segmented volume defined by CT, has wide-reaching applications in a diverse range of medical fields. The viability of this alternative method

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depends on the accuracy of segmentation and quantification, as well as the alleviation of some of the inherent obstacles of hybrid imaging.

2. Classifications of PET data analysis

The techniques employed for the analysis of functional images can be subdivided into three categories: qualitative, semi-quantitative, and quantitative. The first of these three is by far the most subjective, and entails the visual interpretation of data by human observers. The second utilizes indices such as SUV and lesion-to-background ratio to measure activity in assigned regions of interest. Lastly, the third employs more complex mathematical and technical processes, such as non-linear regression and Patlak-Gjedde graphical analysis. Despite the superior reproducibility and objectivity it provides, this final technique is arguably rendered impractical for clinical use by its technical rigors. On the other hand, the other two techniques are far more susceptible to both inter-reader and intra-reader variability, but are widely employed due to their simplicity.

3. Models for quantifying absolute glucose metabolic rate

The metabolic rate of glucose is estimated with the aid of FDG, an analog of glucose that is currently the most widely used PET radiotracer[3,4,5]. The metabolism of FDG is in turn measured through kinetic modeling of the data[6]. This process reveals a series of rate constants that shed light not only on the absolute metabolic rate, but also the steps within glucose metabolism.

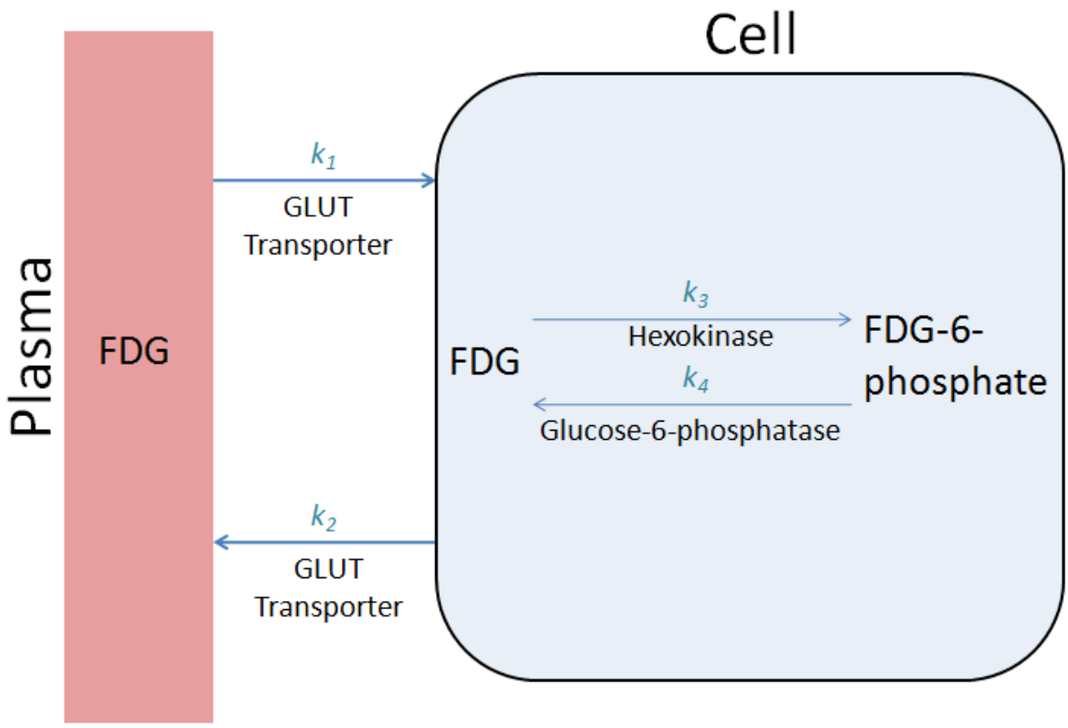

Fig. 1. The three-compartment model involves the transport of FDG from the plasma to the cell, as well as the phosphorylation and dephosphorylation of FDG within the cell. Simpler models ignore the dephosphorylation of FDG, thereby eliminating the k_4 rate constant.

When dealing with FDG, the tracer kinetic model comprises three compartments that encompass the processes of transportation and phosphorylation. More specifically, these compartments demarcate the FDG in the blood plasma, the FDG in the cell, and the FDG-6-phosphate in the cell (**Fig. 1**). The first compartment (C1) is assumed to be open, with free exchange with other tissues in the body. It is for this reason that the input function of this compartment (i.e., FDG levels in the plasma) cannot be calculated and must be measured by arterial sampling. The second compartment (C2) refers to FDG that is in the tissue and not in the vasculature. These pools of FDG in the cell are available for phosphorylation by hexokinase. Once FDG is in its phosphorylated form, it occupies the third compartment (C3).

If a kinetic model accounts for the dephosphorylation of FDG-6-phosphate by glucose-6-phosphatase in addition to transportation and phosphorylation, it is termed "reversible."[7] However, this three-compartment model is far from the only one in use; more simplified "irreversible" models often ignore the dephosphorylation of FDG on the assumption that the incorporation of fewer parameters will lower variance.[1] These methods include non-linear regression analysis, which estimates a single rate constant K_i in the place of k_1, k_2, and k_3, and Patlak-Gjedde graphical analysis, which calculates activity as a function of the concentration, distribution volume, and net rate of influx of FDG.[8]

By applying this simplified irreversible model to dynamic PET data, non-linear regression analysis can estimate the net rate of FDG influx. The advantages of this method of quantification include its lack of dependence on the length of time over which uptake occurs and its ability to provide insight into the rate constants behind glucose metabolism. But on the other hand, the technical complexity of the method makes it demanding and time-consuming, with the required arterial sampling only exacerbating these issues.

In comparison to non-linear regression, the method of Patlak-Gjedde graphical analysis is more robust due to a simpler scanning protocol that is less susceptible to noise. This technique, which also has the ability to produce parametric images, is modeled by the following equation:

$$c(t) = \lambda \cdot c_p(t) + K_i \int_0^t c_p(\tau) d\tau$$

where

$c(t)$ = activity in the tissue as measured by the PET scanner at time t,

$c_p(t)$ = concentration of FDG in the plasma,

λ = distribution volume of FDG,

K_i = net rate of FDG influx into the tissue, and

τ is a dummy integration variable

Unlike non-linear regression, Patlak-Gjedde graphical analysis cannot calculate individual rate constants for the metabolism of glucose. But similar to non-linear regression, it requires dynamic scanning, which carries with it a host of limitations.

Dynamic scanning, which is crucial to both non-linear regression and Patlak-Gjedde graphical analysis, entails an extended sequence of acquisitions that are subsequently reconstructed. The high availability of dynamic data, which is comparatively less dependent on imaging time, works to the advantage of these quantitative techniques. On the other hand, the rigors of the procedure make it technically demanding and time-consuming. Moreover, since only one bed position can be assumed per scan, each lesion may have to be acquired separately. The need to quantify FDG concentration in the plasma also necessitates arterial blood sampling at several points during the scan.

The arterial sampling performed during dynamic scans allows for the extrapolation of time-vs.-activity curves, which can yield rate constants through non-linear least squares approximation. This approach to quantifying FDG activity is certainly more objective than more popular alternatives such as SUV and visual assessment, but is far from immune to error. First and foremost, the assumption that FDG-6-phosphate is not dephosphorylated once it is inside the cell is overly simplistic and can lead to inaccurate estimates. Variance due to imaging noise and partial-volume effects further limit these methods of quantification.

In addition to non-linear regression and Patlak-Gjedde graphical analysis, there exist other, more simplified kinetic methods for quantifying the rate of glucose metabolism. This is done using only a single static scan, albeit with somewhat lower accuracy. An autoradiographic method developed by Sokoloff *et al.* is one such single-scan method, but is still limited by the need of arterial sampling to determine FDG concentration[9,10]. A similar technique devised by Hunter *et al.* is able to quantify metabolic rates with the aid of limited venous blood sampling[11].

4. Quantification of activity through SUV

Standardized uptake value (SUV)—also known as differential absorption ratio (DAR), differential uptake ratio (DUR), and standardized uptake ratio (SUR)—is currently the most common semi-quantitative index employed in the clinical field. It has the ability to measure FDG metabolism through tracer concentration in the tissue. It is calculated according to the following formula:

$$SUV = \frac{Mean\,ROI\,concentration(MBq/ml)}{Injected\,dose(MBq)/Body\,weight(g)} \times \frac{1}{decay\ factor\ of\ ^{18}F}$$

The advantages of SUV lie in its ease of use; when compared to the aforementioned kinetic models, SUV is far less technically demanding and computationally complex. The fact that its values are automatically estimated by software makes the SUV method highly expedient for clinical use. The lack of dependency on arterial sampling and the comparatively short scanning time also work in its favor. In spite of these shortcuts, kinetic modeling reveals a strong correlation between SUV and glucose metabolic rate. However, that is not to say that SUV measurements are not just as—if not more—prone to error than kinetic modeling (**Table 1**).

Currently, PET scanners are most often normalized to the body weight of the patient. This causes the systematic overestimation of SUV in obese patients, since adipose tissue

demonstrates comparatively low FDG uptake because of its dampened metabolic activity. Studies that employed the parameters of lean body mass and body surface area instead of body weight were found to be more accurate[12,13,14].

a. Patient-Related Factors

Factor	Effects	Corrective measures
Body size and habitus (3.3)	SUV in obese patients overestimates FDG uptake relative to normal patients	Use of lean body mass (SUV_{LBM}) or body surface area (SUV_{BSA})
Serum glucose levels (3.4)	Reduced FDG uptake in target tissues with increasing blood glucose levels	Control of blood glucose before administering FDG and applying correction factor for glucose level
Organ and lesion motion	Reduction of SUV	Respiratory gating or 4D reconstruction

b. Technical Factors

Factor	Effects	Corrective measures
Duration of uptake period (3.5)	Increase in SUV with increasing time in malignant lesions	Standardization of time of image acquisition
Attenuation correction and reconstruction methods (spatial filter kernel, image resolution, number of iterations)	Underestimation of SUV with highly smoothed reconstruction	Standardize acquisition and reconstruction algorithms
Partial-volume effects (4.1, 4.2)	Underestimation of SUV in lesions with diameters smaller than 2-3 × spatial resolution	Adopt an optimal partial volume correction factor
Size of the ROI and non-uniformity of tracer distribution in the lesion	Low SUV_{mean} for large ROIs and high random errors in smaller ROIs	Standard size ROIs placed reproducibly in the same location, SUV_{max} preferable to SUV_{mean}.
Organ and lesion motion	Mismatch between EM and CT data	Respiratory gating or 4D reconstruction

Table 1. Factors influencing standardized uptake value (SUV) determination for FDG at intended regions of interest, their undesirable effects, and associated required corrective measures. (Based on Basu *et al.* [95] with permission from Elsevier Inc.).

5. Effect of respiratory motion on SUV

The accuracy of quantification through PET/CT imaging is affected by several factors. Historically, one of the most problematic factors—especially in the scanning of thoracic lesions or non-small cell cancers—has been respiratory motion, which impacts diagnostic and staging accuracy. Misregistration due to respiratory motion in the thorax and abdomen between data acquired through PET and CT was reported soon after commercial introduction of PET/CT and has been one of the most challenging research topics in the field.

Fast gantry rotation of less than one second per revolution and sizeable detector coverage of over 2 cm enable CT systems to scan over 100 cm in the cranial-caudal direction in 20 seconds. By comparison, PET typically requires 2 to 5 minutes to scan 15 cm. The temporal resolutions of CT and PET are also disparate: less than 1 second for CT and about one respiratory cycle for PET. This discrepancy in temporal resolution may lead to a misalignment of the tumor position between the CT and PET data, and may compromise the quantification process.

These issues with misregistration due to motion can be remedied by respiratory gating. 4D-PET can also be performed on this PET/CT for RT, but its application has been limited due to the total acquisition time of approximately 40 minutes. Most patients cannot hold their arms over their heads for such a long period of time, and the inevitable motion that results compromises the PET data. Moreover, the splitting of coincident events into multiple bins or phases and the low spatial resolution of 5 to 10 mm further hinder the applicability of 4D-PET. When combined with respiratory gating, this technique of 4D-PET yields higher SUVs and more consistent tumor volumes between PET and CT.

6. Factors affecting SUV measurements

The SUVs of malignant lesion are heavily dependent on glycemic status. Hyperinsulinemia causes enhanced glycolysis in adipose tissue and muscles, leading to comparatively low SUVs elsewhere. For this reason, the glucose level of patients undergoing PET is normally capped at 150 to 200 mg/dl. Studies have shown the elevated blood glucose levels (up to 250 mg/dl) do not affect SUV in inflammatory or benign lesions.

Most centers measure SUV at a single time point by assigning ROIs. Variation in the time interval between tracer injection and image acquisition, which have a significant effect on SUV, is unavoidable to some extent. The confounding effect can be minimized by standardizing protocols outlining the time and direction of the scan. The SUV of tumors continues to rise for several hours after injection, whereas that of the surrounding non-malignant tissue can actually fall. As a result, delayed PET scans often demonstrate better contrast than early PET scans because of an increased lesion-to-background ratio.

The overlap between inflammatory and malignant lesions precludes SUV from being able to distinguish between them. Dual-time point imaging has been used instead to assess malignancies in the head, neck, lungs, breast, cervix, gallbladder, and CNS. The lack of glucose-6-phosphatase in the tumor cells relative to normal cells slows the dephosphorylation of FDG. This leads to increased contrast between tumor and normal cells over time. This also provides a means of differentiating between benign and malignant lesions.

In many studies of various malignancies, dual-time point imaging improved the sensitivity and specificity of PET. The higher specificity is due to the increasing difference in FDG uptake over time between malignant and benign lesions. On the other hand, the higher sensitivity is due to increased lesion-to-background ratio that results from increased uptake in malignancies and the clearance of FDG in other tissues.

7. Future Implications for SUV

It has been suggested that SUV is not optimal for classifying tumors. Dual-time point imaging and delayed PET imaging may be embraced as a more accurate method in the

future. As structural and functional imaging become increasingly fused, it is likely that PET/CTs and PET/MRIs will be integral in the assessment of pathophysiological processes.

8. Correcting for Partial-Volume Effects

The partial-volume effect (PVE) affects objects that are less than 2 to 3 times the spatial resolution of the PET scanner. PVE causes the systematic underestimation of SUVs yielded from PET data. Physiological and patient motion also cause the degradation of spatial resolution and exacerbate PVE. These difficulties can be compensated for with 4D respiratory gated PET/CT. Studies have shown that using anatomic imaging (namely CT) to measure the true size of lesions also causes substantial increases in the accuracy of PET data.

The best resolution that can be achieved by modern clinical whole-body scanners is 4 mm. In the field, spatial resolution is normally worse by a significant margin. Structures that are less than 2 to 3 times the spatial resolution of the system, as measured by the full-width at half-maximum, are subject to PVE. Contrast between a lesion and the background decreases the smaller the region is. There are three broadly-defined approaches to minimizing PVE:

1. Correcting for the loss of resolution after reconstruction;
2. Incorporating PVE modeling into the reconstruction process;
3. Using the size of a lesion as determined by anatomic imaging to correct for PVE.

Correction of PVE was broached as early as the 1980s when CT and PET were used to examine patients with AD and other CNS disorders that cause cerebral atrophy. High resolution MR imaging has since led to accurate segmentation and measurement in the gray matter, white matter, and cerebrospinal fluid (CSF).

9. Factors affecting recovery coefficients

The recovery coefficient (RC) is the ratio of observed activity to true activity in PET. It is affected by lesion-to-background ratio, matrix size, etc. RC is usually measured in a static condition, but is subsequently applied in the field to scans with physiological and patient motion. A study carried out by Hickeson *et al.* reported an increase from 58% to 89% in the accuracy of metabolic activity measurements in lung nodues smaller than 2 cm when partial-volume effects were corrected for and a threshold SUV of 2.5 was used to differentiate between malignant and benign lesions[15].

10. Assessing global metabolic activity

Global metabolic activity is calculated by multiplying partial-volume corrected SUV and the volume of the organ of interest, as determined by CT or MRI. The ability to segment images into organs and even subcomponents of organs will no doubt have enormous value in the field of oncology. The therapeutic efficacy of treatment on multiple malignancies can be better measured in this manner.

The assessment of disease through global metabolic activity is particularly useful in neuropsychiatric disorders, where the measurement of glucose metabolism in the entire brain can be a more reliable indicator of disease than that of a single region of interest. Atrophy-corrected whole brain metabolism shows a high degree of sensitivity to and correlates well with cognitive function, as measured by mini-mental status examinations[16].

$$\text{Atrophy corrected average CMRGlc} = \frac{\text{Mean CMRGlc}}{\text{percentage of brain tissue in the intracranial volume}}$$

Global metabolic activity was first measured in studies of AD by Alavi *et al.*[1]. It was calculated by multiplying segmented brain volumes—as determined by MR—by the mean metabolic rate for glucose to yield metabolic volumetric product (MVP). Volume has to be measured accurately by algorithms on computers, while metabolic rate has to be corrected for partial-volume effects to be on target. Quantitative approaches that employ either structural or functional imaging are prone to more inaccuracy and variability than those utilizing both modalities.

The extent of athereosclerosis in the aorta can also be quantified by multiplying SUV in the aortic wall with volumetric data of the aortic wall, as determined by CT. The resulting MVP value is representative of the atheroscleoritc burden in each segment of the aorta[17]. The same principles can be applied to the diffuse hepatic steatosis; hepatic MVP can be calculated by multiplying the mean hepatic SUV by the liver volume measured by MRI[18].

Perhaps one of the most valuable applications of global metabolic activity is in the field of oncology. This technique of analysis can determine the metabolic burden of individual lesions. Metabolic burden (MB) is calculated by multiplying the partial-volume corrected SUV by the volume of the lesion measured by CT and dividing the product by the recovery coefficient.

$$MB = SUV_{meanCT}\left(V_{CT}\right)/RC$$

Metabolic burden is a promising method of assessing total body tumor burden, but there are other techniques that also draw from the concept of global metabolic activity. The measure of Total Lesion Glycolysis (TLG) multiplies SUV by lesion volume without accounting for the recovery coefficient.

11. Image segmentation in quantitative PET imaging

Segmentation, a crucial step in analyzing structural images, groups voxels into sets of distinct classes. Despite its technical complexity, the process of segmentation has breached the clinical field. Through segmentation, organ and tumor volume can be accurately measured, target treatment volumes can be defined, attenuation maps can be generated, and voxel-based anthropomorphic phantoms can be constructed from high resolution anatomical images. Approaches to segmentation are myriad, and include:

- Thresholding
- Region growing
- Classifiers
- Clustering
- Edge detection
- Markov random field models
- Artificial neutral networks
- Deformable models
- Atlas guidance

The process of segmenting CT images of regions such as the lungs is normally preceded by inhomogeneity correction and intensity standardization, and can be accomplished through thresholding and the construction of masks. Subtracting masks from one another allows for the segmentation of smaller structures. Lesion detectability is enhanced by similarity measures (e.g., cross-ψ_B-energy operator), while the reliability of the algorithms behind partial-volume correction is dependent on the accuracy of segmentation and coregistration. Errors in segmentation only affect the partial-volume correction of the mis-segmented region[19]. It is believed that errors in segmentation carry greater weight in measuring the true tracer concentration of a region in comparison to errors in coregistration.

12. Novel approaches to segmentation

Image segmentation is necessary for the quantification of tumor activity, assessment of tumor response to treatment, and definition of target volumes for treatment[20,21]. Demarcating target regions in noisy functional images is one of the most challenging aspects of the oncological applications of PET. Delineating target volumes is normally operator-dependent in the clinical setting. Since this methodology opens the door to high inter-reader variability, moving towards automated techniques would reduce subjectivity.

A method for automated segmentation involving Expectation Maximization-based mixture modeling using k-means clustering has been proposed. A multiscale Markov model can refine segmentation by modeling spatial correlations between neighboring image voxels[22]. Anthropomorphic phantom experiments evaluated the proposed segmentation algorithm. Segmentation using the Markov Random Field Model was shown to reduce relative error.

13. Conclusions

The incorporation of functional imaging such as MR and CT into PET analysis has expended and strengthened its applications in the medical field. Measures of global metabolic activity that can be made with PET/CT and PET/MRI may be superior to those of SUV_{max}, especially in oncology. Further refinements might prove invaluable for the optimal utilization of this powerful imaging technology.

14. View to the future

We believe that the future of imaging is going to shift rapidly from a single modality approach to hybrid imaging with heavy emphasis on PET-CT and possibly PET-MRI. Clearly, the impact of PET-CT has been substantial in many domains. In particular, this approach has revolutionized the practice of oncology and other disciplines with regard to monitoring the effects of various interventions. In particular, PET-CT has been critical in the preoperative assessment of the staging of disease and optimal characterization of the structural abnormalities noted before surgery. Similarly, the field of radiation oncology has rapidly adopted PET-CT imaging for effective control of a variety of cancers, in particular, those that originate in the lungs and the head/neck regions. The role of contrast enhanced CT can be expected to decline if PET data indicates that this extra step may be redundant and will not substantially alter the results generated from PET alone. The role of PET-MRI is unclear at this time. However, its applications in the brain will obviate the need for PET-CT for this anatomic site. This is mainly due to the fact that information provided by CT for

central nervous disorders is suboptimal and therefore combined PET-MRI will provide superior data in the brain. It is possible that orthopedic applications of PET may substantially improve by combining PET and MRI, particularly in the structures of the feet and the knees. It is unclear whether PET-MRI will be as successful in assessing disease activity in the chest and abdomen. This is primarily due to the fact that attenuation correction in these anatomic sites is complex and may not be feasible with MR approaches alone. Efforts are on the way to estimate the degree of attenuation at these sites but we are uncertain that this will lead to overcoming the difficulties that exist in this particular domain. Finally, the use of hybrid imaging has substantially improved our ability to optimally quantify PET data. This will further enhance the role of functional imaging for accurate characterization of lesions and response to therapy.

15. Summary

The information provided in this chapter reveals a paradigm shift in medical imaging and has described in detail the need for hybrid imaging with an emphasis on PET-CT as major modality for the future in medicine. Therefore, practitioners of medicine must make every effort to amiliarize themselves with the capabilities of these modalities in order to optimize treatments and care for their patients.

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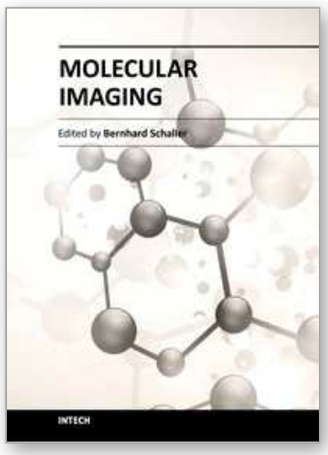

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The present book gives an exceptional overview of molecular imaging. Practical approach represents the red thread through the whole book, covering at the same time detailed background information that goes very deep into molecular as well as cellular level. Ideas how molecular imaging will develop in the near future present a special delicacy. This should be of special interest as the contributors are members of leading research groups from all over the world.

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