Information Technology Applications in Biomedical Functional Imaging

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***Abstract*—In parallel with rapid advances in computer technology, biomedical functional imaging is having an ever-increasing impact on healthcare. Functional imaging allows us to see dynamic processes quantitatively in the living human body. However, as we need to deal with four-dimensional time-varying images, space requirements and computational complexity are extremely high. This makes information management, processing, and communication difficult. Using the minimum amount of data to represent the required information, developing fast algorithms to process the data, organizing the data in such a way as to facilitate information management, and extracting the maximum amount of useful information from the recorded data have become important research tasks in biomedical information technology. For the last ten years, the Biomedical and Multimedia Information Technology (BMIT) Group and, recently, the Center for Multimedia Signal Processing have conducted systematic studies on these topics. Some of the results relating to functional imaging data acquisition, compression, storage, management, processing, modeling, and simulation are briefly reported in this paper.**

***Index Terms*— Biomedical functional imaging, information technology.**

I. Introduction

BIOMEDICAL functional images obtained from positron emission tomography (PET) and other nuclear medicine imaging modalities play an important role in modern biomedical research and clinical diagnosis, providing a window to internal human biochemistry that was not previously available. For example, parametric images of the local cerebral metabolic rate of glucose derived from PET provide image-wide quantification of physiological and biochemical processes within the human brain and visualization of their distributions in relation to anatomical structures when MRI data are available and coregistered with the PET images. In order to estimate physiological parameters using PET tracer kinetic modeling to form physiological functional images, a sequence of dynamic images needs to be recorded. Counts are recorded continuously and stored according to a predesigned sampling schedule. Conventionally, an empirical image sampling schedule is used, which requires the taking of a large number of images, and may not provide maximum information for the study. For a routine dynamic study with PET, it is easy to acquire nearly 500 images for just one patient in one study. Such a large number of images imposes a considerable burden on the computer image storage space and data processing. Therefore, techniques to minimize the amount of data recorded, to facilitate the data management, to improve the quality of visualization, to improve the accuracy of physiological parameter estimation, and to minimize the computational complexity in data processing, are of great interest. For the last ten years, the Biomedical and Multimedia Information Technology (BMIT) Group and, recently, the Center for Multimedia Signal Processing have conducted systematic studies on information management and processing in biomedical functional imaging, particularly in the areas of functional imaging data acquisition, compression, storage, management, modeling, simulation, analysis, processing, registration, visualization, and communication, which are represented by the blocks in Fig. 1. Some of our results and related research by other investigators are discussed in the following sections.

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II. Data Acquisition

A. Image Sampling Schedule—A Critical Issue

Great attention has been paid to the design of PET image frame sampling or data acquisition schedules. Hawkins [16] studied the effects of temporal sampling on the glucose model using tracer 18-fluoro-deoxy-D-glucose (FDG). In the same year, Mazoyer [29] proposed a general method for estimating the precision of parameters resulting from the use of various rates of tomographic data collection. Delforge [6] applied the experimental design-optimization framework and various criteria to the estimation of receptor-ligand reaction model parameters with dynamic PET data. At the same time, Jovkar [21] addressed the general problem of finding an optimal scan schedule in PET dynamic studies to minimize parameter-estimation errors. The influence of scan intervals in PET on the accuracy of estimation of the rate constants was investigated. They found that for realistic noise levels there is a monotonic improvement in the index of parameter accuracy with increasing sampling frequency, particularly over the initial minutes after the tracer injection. Most of the previous studies suggested that a higher sampling frequency, particularly in the early stage, should be used. This conclusion, however, imposes a considerable burden on the computer image storage space and data processing.

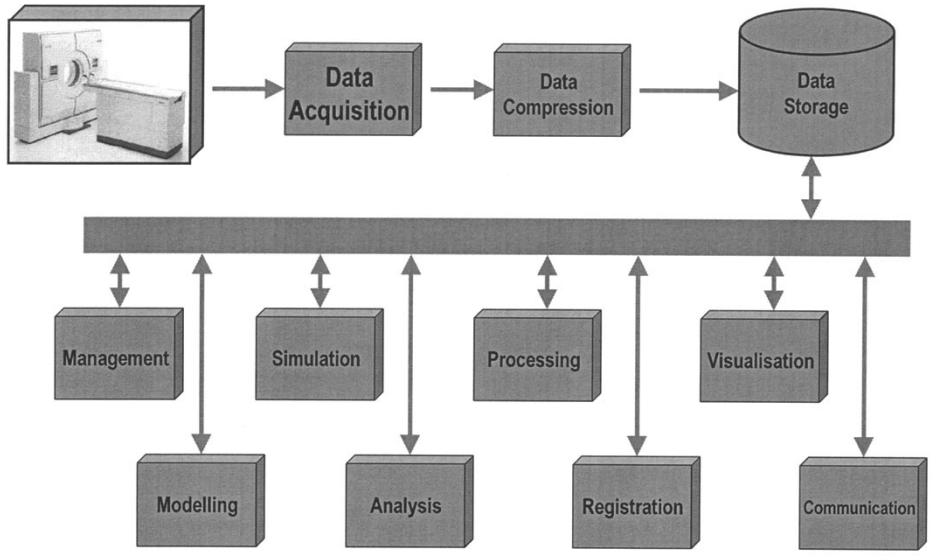

Fig. 1. Biomedical functional imaging research focuses on the research of the BMIT Group and the Center of Digital Signal Processing for Multimedia Applications.

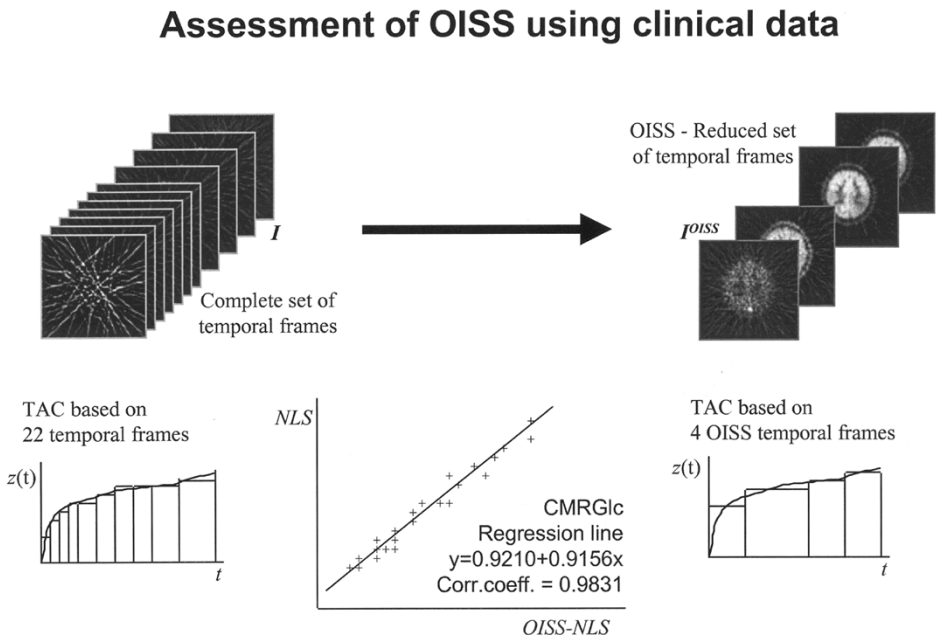

Fig. 2. Clinical data were used to show that the estimation accuracy of cerebral metabolic rate of glucose (CMRGlc) using only four image frames based on the OISS is comparable to that using 22 image frames based on the conventional sampling schedule. In this diagram, $z(t)$ is the FDG tracer time-activity curve in tissue.

B. Optimal Image Sampling Schedule

We have reinvestigated this issue, i.e., an optimal sampling schedule design for PET image data acquisition [14]. We found that if a different cost function for parameter estimation is used, which depends only on the direct PET measurement, rather than the instantaneous measurement, the accuracy of parameter estimation can remain almost unchanged when two neighboring image frames are combined into one [27]. We have further proven that the minimum number of image frames needed to be recorded is equal to the number of parameters to be estimated, and, under certain conditions, the combination of several neighboring image frames will not change the parameter estimation quality. We proposed the optimal image sampling schedule (OISS) design and used computer simulation [26] and clinical data [18] to show that the estimation accuracy of metabolic rate of glucose (when a four-parameter model is used) using only four image frames based on the OISS is comparable to that using 22 image frames based on the conventional sampling schedule, as shown in Fig. 2. The OISS idea has been extended to data acquisition for whole body PET dynamic studies [19]. The results of our study have permitted the data recorded in the data acquisition stage to be greatly reduced. Furthermore, we have extended

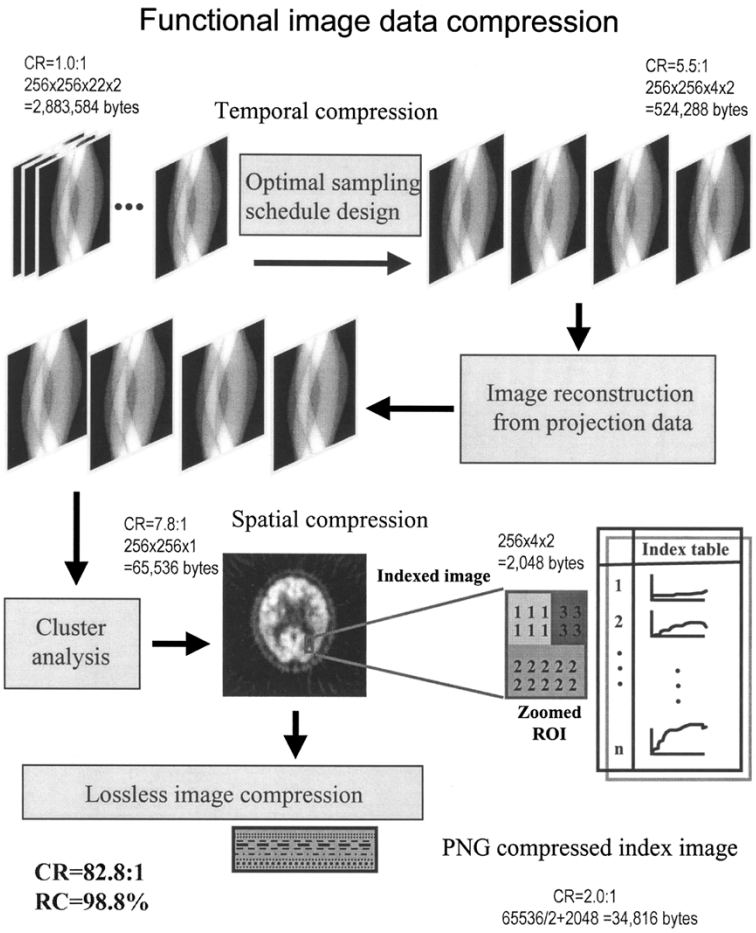

Fig. 3. The three stages for dynamic image data compression.

the idea to perform quantitative studies with dynamic image data recorded from rotating camera systems, such as single photon emission computed tomography (SPECT) [24] and to study the minimum dynamic SPECT image acquisition time required for T1-201 tracer kinetic modeling [23].

III. Data Compression, Storage, and Management

Conventional image compression algorithms can be divided into two main categories, lossless and lossy compression algorithms. Lossless compression algorithms allow for perfect reconstruction of the original images from compressed data. These algorithms yield modest compression ratios, typically between 1.7 : 1 to 2.1 : 1 for medical image data. On the other hand, lossy compression can achieve higher compression ratios. However, the original images can only be reconstructed approximately from compressed data, though the differences may not be distinguishable by the human visual system [5], [25], [31], [32]. The challenge in the development of a practical image compression scheme for dynamic medical images is the development of compression algorithms that are lossless for diagnostic purposes, i.e., make no difference to doctors, qualitative and quantitative assessment, yet attain high compression ratios to reduce storage, transmission, and processing burdens. It should be noted that in the clinical situation a slight loss of precision in a derived parameter may be undetectable visually and may be quite insignificant relative to the measurement error. The conventional compression algorithms mentioned above are not specifically tailored for the diagnostic use of dynamic medical image data. Therefore, new algorithms have to be developed to fully exploit spatial and temporal redundancies in these data.

A. Dynamic Image Data Compression

We have recently proposed a three-stage technique for dynamic image data compression [17], as described in Fig. 3. In Stage 1, the proposed OISS is first used to remove temporal redundancies and reduce the number of frames to a minimum. Even data sets obtained using conventional sampling schedules can be reorganized using the procedures described in Stage 1 to remove the temporal redundancies. Then, in Stage 2, compression in the spatial domain exploits spatial redundancies in the data. Using cluster analysis, the reduced set of temporal frames can be further compressed to a single indexed image. However, as our functional image data are multidimensional, clustering algorithms suitable for grouping vectors, rather than just pixel values, have been developed. Cluster analysis involves grouping and classifying pixel-wise time-activity curves (TAC's) by natural association according to self-similarity (or dissimilarity) characteristics. As expected, TAC's with high degrees of natural association belong to the

same cluster groups, and, conversely, TAC's with low degrees belong to different groups. The indexed image maps each pixel into a particular cluster. The respective temporal information for each cluster group is contained in an index table. This table is sequentially indexed by the cluster group and each index contains the mean TAC cluster values for that group. In Stage 3, we compress and store the indexed image obtained from cluster analysis using the portable network graphics (PNG) file format. The coding technique presently defined and implemented for PNG is based on deflate/inflate compression with a 32-kB sliding window. Deflate compression is based on an LZ-77 derivate and encoded using fixed or custom Huffman codes. The PNG file format was chosen over other lossless image compression file formats due to its portability, flexibility, and being legally unencumbered. Furthermore, PNG supports a variety of features, such as indexed color images, greyscale images up to 16 bit per pixel, true color images up to 48 bit per pixel, transparency, gamma information, progressive display, and file integrity checking. Stages 1–3 in combination can reduce storage requirements by more than 95%.

B. Image Database Management Systems

Conventional database management systems (DBMS) do not lend themselves to efficient storage, flexible retrieval or manipulation of image data. The image retrieval (IR) problem is principally concerned with retrieving images that are relevant to users' requests from a large collection of images, referred to as the *image database*. There is a multitude of application areas that consider image retrieval as a principal activity. Tamura and Yokoya provided a survey of image database systems that are in practical use [34]. More recently, the work in [15] provided a comprehensive survey and relative assessment of a picture retrieval system. We recently proposed a signature for content-based image retrieval using a geometrical transform [35]. Since the application areas are extremely diverse, there seems to be no consensus as to what an image database system really is. Consequently, the characteristics of existing image database systems have essentially derived from domain-specific considerations. Image databases for the storage of dynamic image data have not yet been developed because dynamic images are a relatively new phenomenon and, at the same time, are complex and space-demanding. Due to the success of functional image data compression, it is possible to design a model for the record and content-based dynamic image database.

C. Content-Based Image Retrieval

Normally, because of their large storage space requirements, PET dynamic image sequences are recorded and archived to off-line storage media. Retrieval is therefore time-consuming and labor-intensive. One of the principal advantages of the image database system, based on the compressed data using the above developed three-stage technique, is its ability to rapidly recover images almost identical to the original dynamically acquired images, for direct visual interpretation or recalculation of functional parameters. Because of the high compression ratio, it will be possible to maintain the data of a large number of patient investigations on-line for immediate availability to the physician, and to perform content-based retrievals based on image characteristics.

Content-based retrieval of dynamic data will open up important new opportunities for research. As our data are compressed in such a way that features, in terms of the similarity in medical functions, are grouped in the same clusters and their features are stored in the index table. Features from each region can be easily extracted for indexing and retrieval, which will make it possible to readily identify and study, from patient data stored in the database, tissue regions that exhibit similar physiological behavior. For example, tumors of a particular type and grade should have a characteristic pattern of kinetic behavior. This characteristic will be a useful research tool for increasing our understanding of physiological processes in normal tissue and a range of disease states. The knowledge gained will hopefully lead to improved specificity in diagnosing disease. At the moment, the development of a content-based functional image database is actively conducted in the BMIT Group and the Center for Multimedia Signal Processing.

IV. Data Processing, Modeling, and Simulation

A. Processing of Compressed Data

Raw and parametric images can be recovered much more rapidly from the compressed data produced by our compression scheme than by conventional methods, because parameters need only be estimated for each cluster rather than pixel-by-pixel. The steps involved in generating images from the compressed data are as follows.

- *Step 1:* *Decompression of Indexed Image*: Since lossless compression is used for compressing the indexed image, a perfect reconstruction of the image is possible.
- *Step 2:* *Tracer Kinetic Modeling and Parameter Estimation*: Using the cluster TAC's defined in the index table, parameter estimates for the tracer kinetic model are obtained by fitting the cluster TAC's to the model parameters. Subsequently, the physiological parameters of interest are calculated using the obtained estimates. The required input function can be prestored or derived directly from the compressed images.
- *Step 3:* *Pixel-Wise Mapping*: Map the obtained estimates and calculated physiological parameters for each cluster TAC to their respective pixel locations by referencing the indexed image. The resultant images are the required parametric images. The overall speed for generating parametric images would be more than 10 000 times faster than the conventional approaches.

B. Fast Algorithms for Parametric Imaging

In addition to fast algorithms for processing the compressed data, it is also important to develop fast algorithms for the generation of parametric images based on the conventional

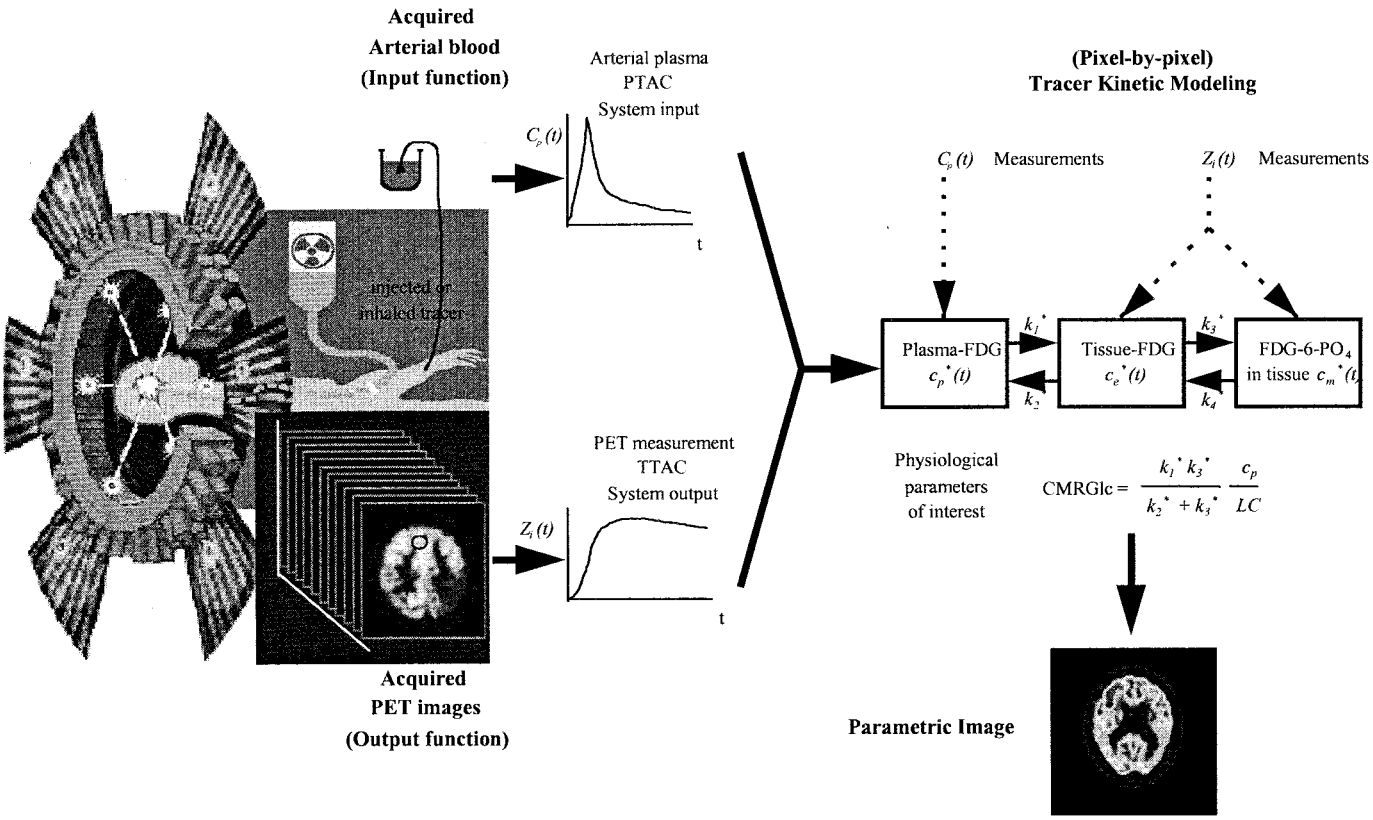

Fig. 4. Generation of parametric images based on pixel-by-pixel FDG tracer kinetic modeling.

uncompressed data sets, i.e., based on the pixel-by-pixel tracer kinetic modeling as shown in Fig. 4. Medical parametric imaging, which requires the estimation of parameters for certain biosystems at the pixel-by-pixel level, is an important technique providing image-wide quantification of physiological and biochemical functions and visualization of the distribution of these functions corresponding to anatomic structures. With the recent development of high spatial and temporal resolution PET, a variety of parametric imaging techniques have been developed. The steady-state method [33] employs a constant input of tracer allowing the radioactivity concentrations in blood and tissue to reach constant levels. The autoradiographic method [22] allows for the uptake and clearance of tracer after a bolus injection and uses one tissue concentration measurement in conjunction with a fully sampled arterial input function to estimate usually one parameter. In both the steady-state and autoradiographic methods, estimation is based on many assumptions which will reduce the estimation accuracy. In the dynamic protocols, more than one unknown parameter can be estimated from a single input/single output (SISO) experiment. The classic *nonlinear* least squares (NLS) method can provide parameter estimates of optimum statistical accuracy. However, this NLS method requires considerable computation time and good initial parameter values (without a good initial guess, NLS will not converge). It is, therefore, impractical for estimation of image-wide parameter estimates. Several alternative rapid parameter estimation schemes for certain specific dynamic PET data or model types have been proposed. For example, the well-known integrated projection method can simultaneously estimate cerebral blood flow and distribution volume from the decay uncorrected and corrected PET data in a very efficient way [20]. The famous Patlak graphical approach (PGA) can estimate the combination of the model rate constants, which allows for the determination of cerebral metabolic rate of glucose, when a unidirectional transfer process is dominant during the experimental period, i.e., the returning rate constant for the model used must be assumed to be zero [30]. Among these schemes, the weighted integration method (WIM) is more generally applicable [1]. However, to increase the estimation reliability by predetermining the optimal sets of weighting functions for every pixel in the functional image is not practical. A generalized linear least squares (GLLS) algorithm for parameter estimation of nonuniformly sampled biomedical systems is therefore proposed by our research team [11]. This algorithm: 1) can estimate continuous model parameters directly; 2) does not require the initial parameter values; 3) is generally applicable to a variety of models with different structures; 4) can estimate individual model parameters as well as physiological parameters; 5) requires very little computing time; and 6) can produce unbiased estimation. Therefore, the GLLS algorithm has been widely used for generating parametric images, such as for myocardial blood flow images with N-13 Ammonia [3], for local cerebral blood flow images with ^{15}O water [8], and for local cerebral metabolic rates of glucose images [10]. Fig. 5 shows the parametric image of cerebral metabolic rates

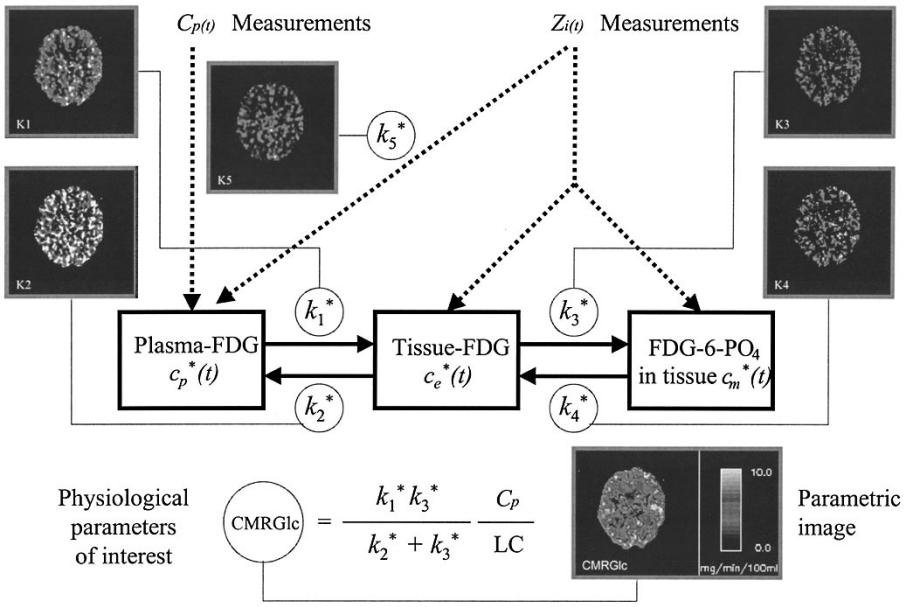

Fig. 5. The parametric image of cerebral metabolic rates of glucose (CMRGlc) and parametric images of individual rate constant k values of the five-parameter glucose model generated by using the GLLS algorithm. In this diagram, K_5^* is the spillover constant parameter from plasma ($C_P^*(t)$) to the measurement $Z_i(t)$.

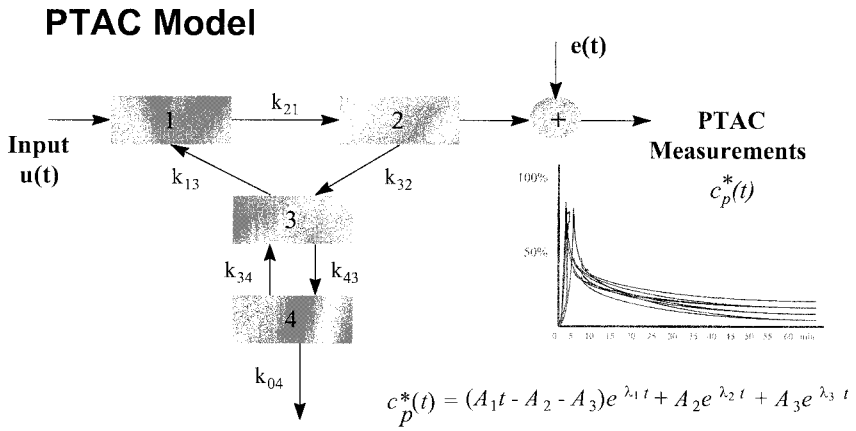

Fig. 6. A four exponential curve with a pair of repeated eigenvalues has been validated by clinical data [responses of FDG bolus injections, $u(t)$] to be the most suitable PTAC model.

of glucose as well as the parametric images of individual rate constant k values of the five-parameter glucose model, generated by using the GLLS algorithm.

C. Novel Modeling and Simulation Approaches

In PET tracer kinetic modeling, the directly measured (piecewise linear approximation) plasma time-activity curve (PTAC) of tracer is often used as the input function to estimate regional physiological parameters. However, no explicit general model has been available for PTAC itself, which limits the further study of the effects of PTAC, such as PTAC measurement noise or PTAC sampling schedules, on the physiological parameter estimates. A PTAC model has been proposed by our research team [7] based on clinical data (responses to FDG bolus injections). A four-exponential curve with a pair of repeated eigenvalues has been validated by the clinical data to be the most suitable PTAC model as depicted in Fig. 6. Multiple experimental data sets were used to test the models and several statistical criteria were used to validate their adequacy. This model has been found very useful for generating realistic PTAC curves in computer simulation studies of other tracers and their kinetic modeling characteristics. Applications of the model to study the effects of input function measurement noise in PET data modeling [7], to study the effects of input function sampling schedules [9], and to study the spillover effects and corrections [12], [28] were conducted. This PTAC model has been found particularly useful in noninvasive quantification of brain function [13] which will be discussed in detail in Section IV-D.

D. Extracting Maximum Information from Data

PET is an important tool for enabling quantification of human brain functions. However, quantitative studies using tracer kinetic modeling require the measurement of the tracer

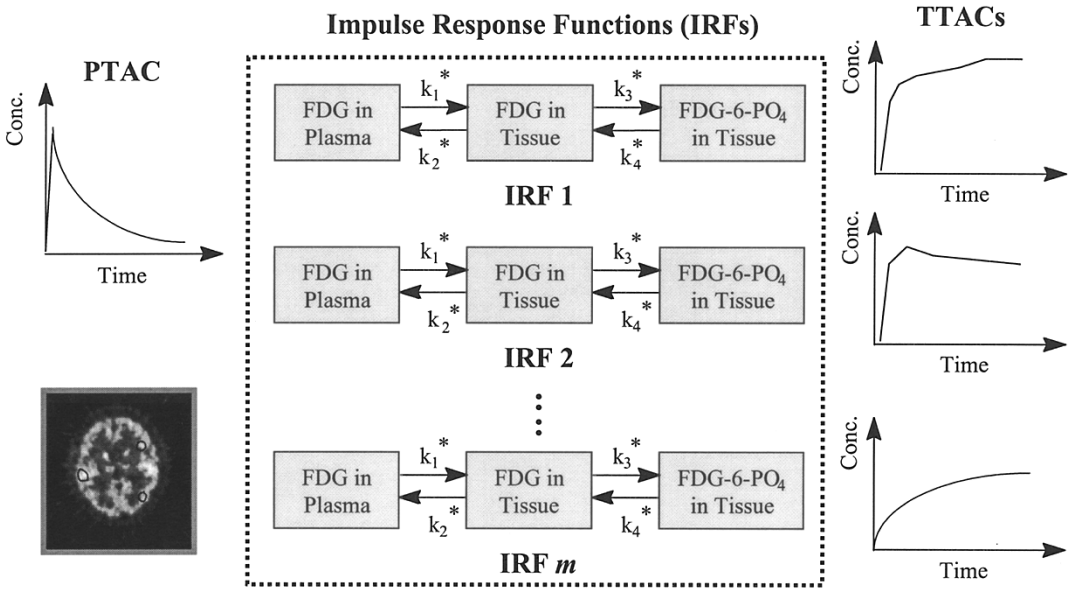

Fig. 7. A cascaded modeling approach to extract the input function together with the physiological parameters from the brain dynamic images alone.

PTAC as the model input function. It is widely believed that the insertion of arterial lines and the subsequent collection and processing of the biomedical signal sampled from the arterial blood are not compatible with the practice of clinical PET, as it is invasive and exposes personnel to the risks associated with the handling of patient blood and radiation dose. Therefore, it is of interest to develop practical noninvasive measurement techniques for tracer kinetic modeling with PET.

Watabe *et al.* recently presented a method for the pixel-by-pixel quantification of regional cerebral blood flow (CBF) using oxygen-15 labeled water [36]. They defined two regions as gray matter and whole brain, respectively. Two equations representing two regions derived from the CBF model were utilized for eliminating blood terms. The method can accurately detect relative changes in CBF which is mainly restricted to brain activation studies. Carson *et al.* presented a method for absolute CBF determination also using oxygen-15 water and PET [2]. They treated the unmeasured M discrete blood samples as the M unknown parameters to be estimated during the modeling process, together with the N pixel blood flow parameters. In other words, $N + M$ parameters would be estimated from the M scan frames with the total number of measurements being $N \times M$. If the number of scan frames is large, the computational complexity is very high. Moreover, this method is difficult to be extended to the tracer for glucose metabolism or other general higher order systems, as many discrete PTAC sample values are involved.

Based on the PTAC model [7], we have recently proposed a cascaded modeling approach to extract the input function together with the physiological parameters from the brain dynamic images alone [13]. The main idea (refer to Fig. 7) is that, for a given output curve of a linear time-invariant system, if the system transfer function is known, we can use deconvolution techniques to obtain the input function, or, if the input function is known, we can estimate the transfer function.

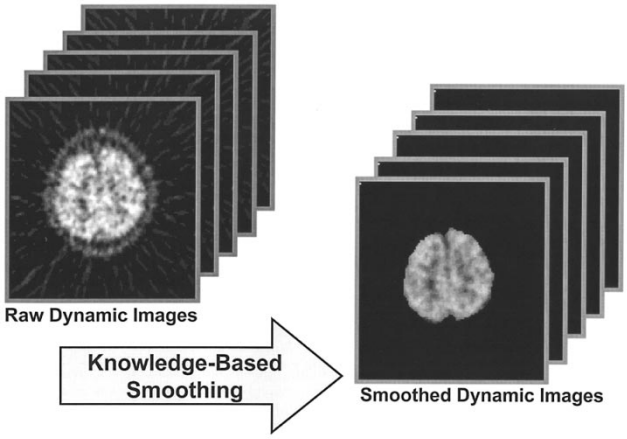

Fig. 8. Knowledge-based image smoothing technique which combines the image processing technique and physiological information to smooth the dynamic images can successfully remove the noise and greatly improve the quality of the dynamic images.

Nevertheless, we cannot obtain both the input function and system transfer function simultaneously from the SISO system. However, in PET dynamic studies, multiple output functions can be obtained from different regions of interest (ROI's). These output functions or measurements are the convolution of the physiological impulse-response functions corresponding to the local regions with the same input function (PTAC). In other words, we are dealing with multiple systems with a single input and multiple outputs. Each of the outputs is associated with a SISO system. Thus, the PTAC and physiological parameters can be estimated simultaneously from two or more output curves (TTAC's) sampled from various regions in the dynamic images as discussed in [13]. The identifiability of this method is tested rigorously using the Monte Carlo simulation. The results show that the proposed method is able to quantify all the required parameters by using the information obtained

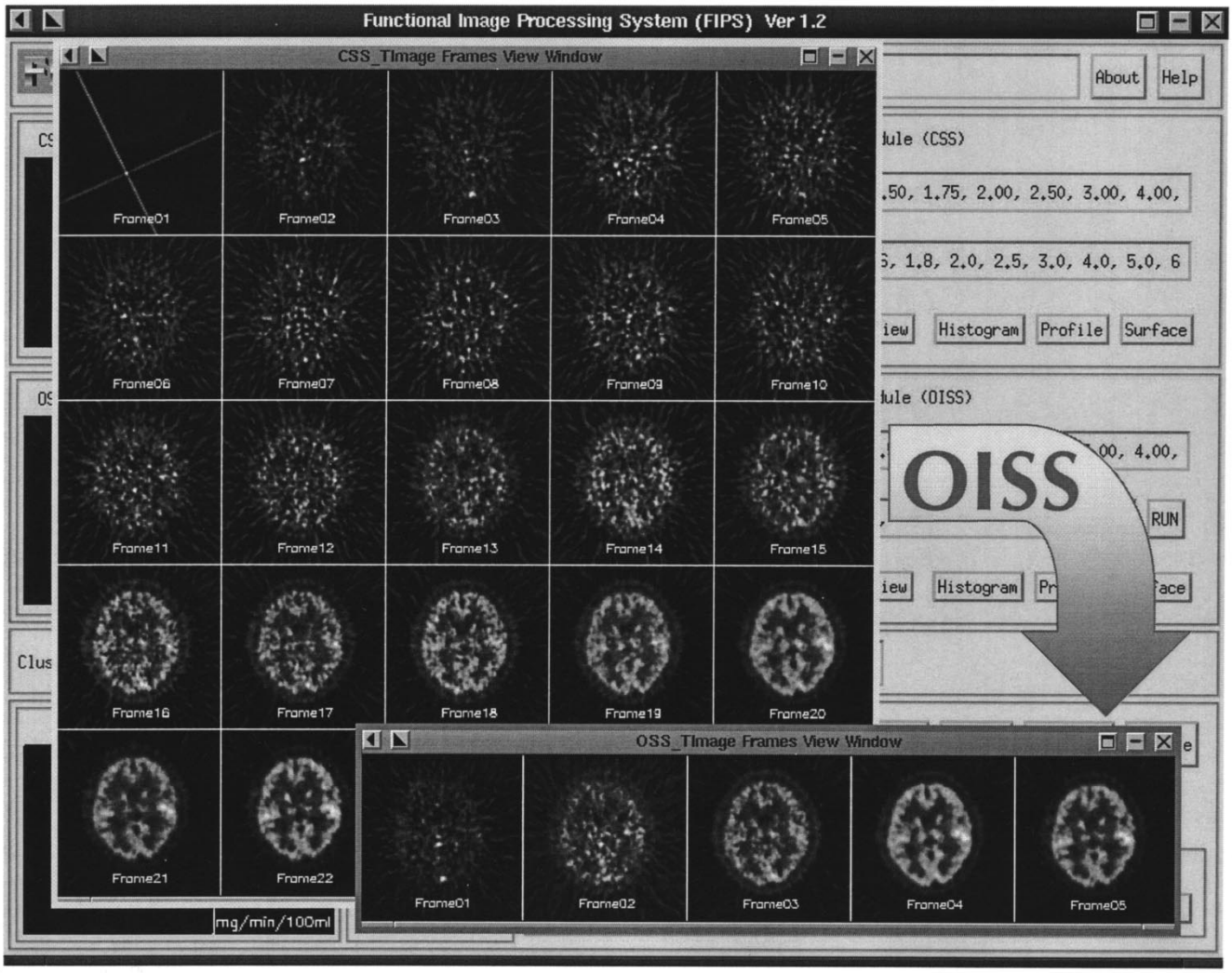

Fig. 9. The process of converting 22 PET image frames obtained from the traditional sampling schedule into five frames based on the optimal image sampling schedule design for a five-parameter glucose model using FIPS.

from two or more ROI's with very different dynamics in the PET dynamic images. This method has further been validated by and applied to clinical data as described in [37]. The results demonstrated that the cascaded modeling approach is able to extract the input function, i.e., the tracer PTAC, noninvasively from the brain images reasonably well. Moreover, we also developed a different approach to extract PTAC from the brain image carotid arteries (CA's) [4] to maximize the useful information for noninvasive quantitative studies.

E. Knowledge-Based Image Smoothing Techniques

Due to the small amount of tracer used in nuclear medicine imaging, the dynamic images are often very noisy. Although there are many existing smoothing algorithms available, they have not utilized the information and knowledge related to the living systems under investigation, or not quite object-orientated and knowledge-based, for example, to assign a value to a pixel by averaging the values of a block of pixels around this pixel in the image, according to certain weighting. However, the physiological structures and properties corresponding to the pixel and its neighboring pixels may be very different, such as the brain tissues and blood vessels. Therefore, we have recently proposed a knowledge-based image smoothing technique to combine the image processing techniques and physiological information to smooth the dynamic images, which can successfully remove the noise and greatly improve the quality of the dynamic images as shown in Fig. 8. Details will be reported separately.

V. Software Development

The above mentioned new techniques have been integrated into a software system called the functional image processing system (FIPS). Fig. 9 shows the process of converting 22 PET image frames obtained from the traditional sampling schedule into five frames based on the optimal image sampling schedule design for a five-parameter glucose model using FIPS. Fig. 10 shows the output of a three-dimensional (3-D) MRI volume image and a 3-D parametric image of cerebral metabolic rates of glucose generated by FIPS using the GLLS algorithm. A more comprehensive description of the overall structure,

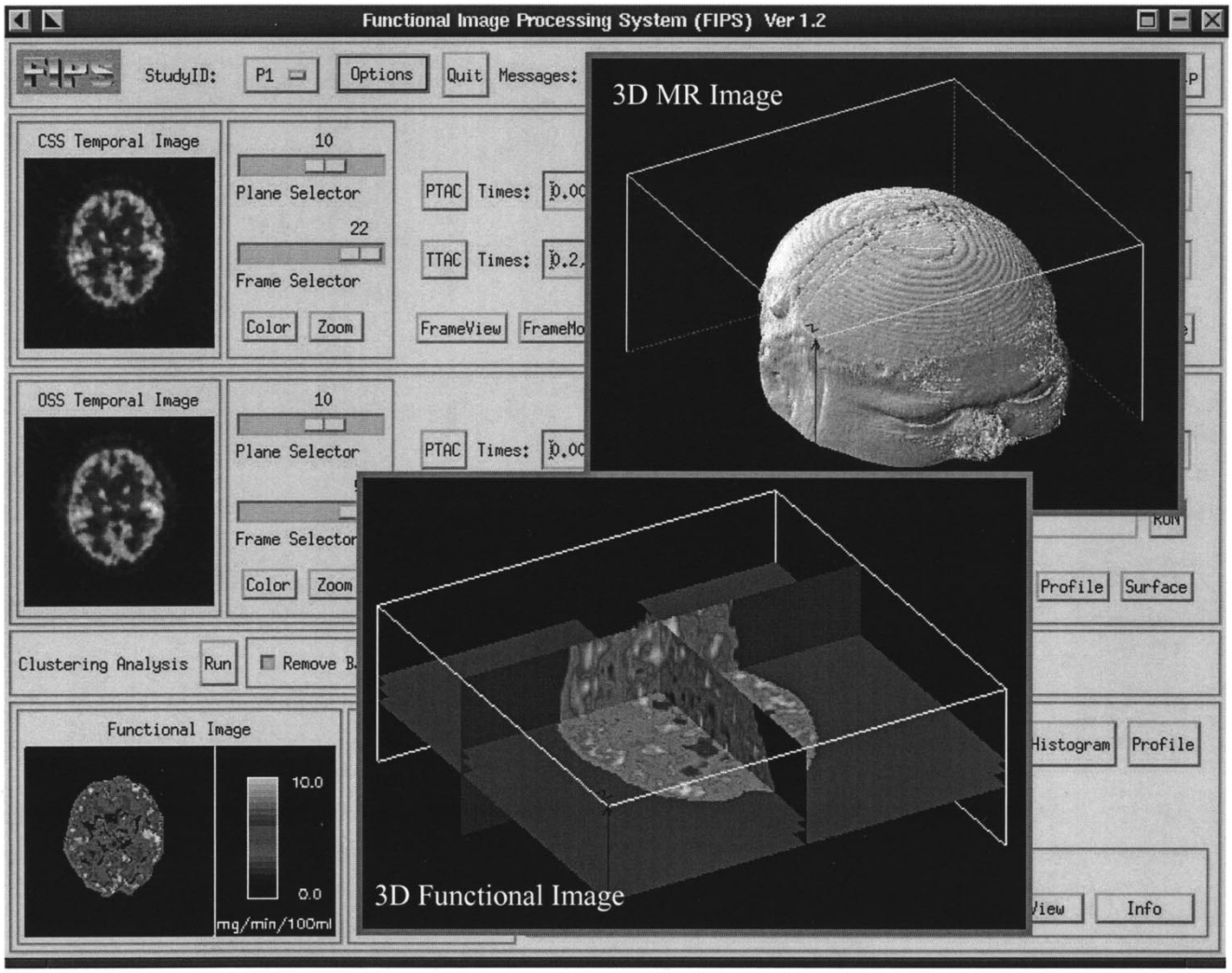

Fig. 10. The output of a 3-D MRI volume image and a 3-D parametric image of cerebral metabolic rates of glucose generated by FIPS using the GLLS algorithm.

various functions, and novel applications of this software system will be reported separately.

VI. Conclusion

Reducing space and computational complexity and facilitating information management and communication are of vital importance to the success of applications of biomedical functional imaging and the modernization of the healthcare system. This paper has given a brief summary of work related to the information technology in biomedical functional imaging in the context of data acquisition, compression, storage, management, processing, modeling, and simulation, which has been done by others and by us at the Biomedical and Multimedia Information Technology Group and the Center for Multimedia Signal Processing.

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