FACTOR ANALYSIS
Delineation of Organ Structures and Automatic Generation of In- and Output Functions in PET Studies of Prostate Cancer

Christiaan Schiepers, Carl K. Hoh [*], Johan Nuyts [#], *Member, IEEE*, Christine HM Wu, Marc S. Seltzer, Michael E. Phelps, and Magnus Dahlbom, *Senior Member, IEEE*

***Abstract*--: Factor Analysis (FA) is used for extracting the properties of dynamic sets. *Objective*: FA was applied to dynamic PET studies to create factor images, from which ROIs were derived and input and output functions generated. These functions were subsequently used for kinetic modeling. This non-invasive, automated, and image based analysis should permit routine application of quantitative PET in cancer patients. *Methods*: In men with prostate cancer, dynamic PET studies were acquired on an ECAT HR+ system. After administration of 250-300 MBq of C-11 labeled acetate, data were acquired during 20 min. Framing rate was 12x10, 9x20, 5x60, 2x300 sec with a total of 28 frames. The images were reconstructed with iterative algorithms, a MAP for transmission, and OS-MLEM for emission scans. The body contour was determined with a 40% threshold on the transmission images. This threshold assured exclusion of the bed. All voxels included in the body contour were used for further processing. FA then extracted the shape of the pure time activity curves (TACs) of vascular input and tumor output functions. The factors were used to create functional images, from which ROIs could be generated with thresholding techniques. The ROIs were used to create image based TACs. *Results:* The automated procedure generated reliable curves in all patients. Since the magnitude of the factors is normalized, TACs have to be adjusted using a scale factor. Two methods were utilized: 1) reversed normalization, 2) image based parameters. In principle, the factors generated by FA have no spillover and are pure vascular curves. The method is operator independent and reproducible. Processing time was 7 min/patient on an UltraSPARC5. *Conclusion:* FA can non-invasively generate input and output functions from dynamic PET data. The automated procedure generated curves corresponding to vessels and tumors, and had a success rate of about 80%. This processing tool facilitates PET as a reproducible quantification method in routine oncological applications.**

Manuscript received November 8, 2001.

Christiaan Schiepers, is with UCLA School of Medicine, Los Angeles, CA 90095 USA (telephone 310-825-8892, e-mail: cschiepers@mednet.ucla.edu). Christine Wu, Marc Seltzer, Michael Phelps and Magnus Dahlbom are also at UCLA School of Medicine.

Carl Hoh[*] is with UCSD School of Medicine, San Diego, California USA (telephone: 619-543-6681, e-mail: ckhoh@ucsd.edu).

Johan Nuyts [#] is at the Catholic University, Leuven, Belgium (telephone: +32-16-3715, e-mail: johan.nuyts@med.kuleuven.ac.be).

I. INTRODUCTION

The unique feature of Positron Emission Tomography (PET) is quantification of metabolic processes in-vivo. This requires the measurement of a so-called input function, i.e. clearance of injected tracer from the blood, and an output function, i.e. uptake in the organ or structure of interest. The input function can be derived from images if a large vascular structure is in the field of view. Otherwise, invasive methods have to be used, e.g. blood sampling from an artery, a labor intensive procedure with a small risk of complications. A non-invasive, automated, image based method of generating input and output functions would be patient friendly, efficient, and would allow quantitative PET to be applied routinely.

Factor analysis (FA) has been used to distinguish functional parameters in dynamic image sets. FA has been proposed some time ago [1], but the perceived mathematical difficulty [2] has limited its use [3]. Initially, computing time was long, but current computer speed permits FA to be performed in a few minutes. An implementation of our method has been reported earlier [4]. We have presented data in osteoporosis [5], and were able to derive input functions that provided accurate values of bone flow and fluoride influx rate. Also data on breast and prostate cancer with FDG as tracer were reported [6].

Here we describe the implementation of a fully automated procedure, without operator intervention during the processing steps. This system produces an input function, describing the disappearance of tracer from the vascular pool, and an output function, describing tracer uptake in the prostate cancer. These functions serve as input for the kinetic modeling program, which calculates the diffusion constants between compartments with non-linear regression. In addition, factor images are created, a parametric representation of the contribution of each factor in the final set of dynamic images.

II. METHODS

Population: Five men with primary prostate cancer and three with prostate cancer relapse were studied. They fasted at least 4 hrs before the study. After positioning of the pelvis in the scanner with the prostate gland in the approximate center field of view, 13.5 mCi of C-11 labeled acetate was injected and PET imaging started simultaneously.

Acquisition: All studies were performed with an ECAT HR+ scanner (Siemens/CTI, Knoxville, TN). A dynamic emission scan was acquired over 20 min. and consisted of 28 frames of 12x10, 9x20, 5x60, 2x300 sec duration. A transmission scan of 20 min was acquired to correct for attenuation effects. The images were reconstructed with iterative algorithms. For the transmission scan a MAP scaled gradient ascent was used, accelerated with ordered subsets (OS-MAPTR). The emission scan was reconstructed with a maximum likelihood expectation maximization (OS-MLEM) algorithm, with transmission weighted attenuation correction. Here too, ordered subsets were used as acceleration technique. The reconstructed image matrix was 128x128 with zoom 1.5 and pixel size 3.4 mm.

Processing: The body contour was derived from the transmission images by applying a 40% threshold. This resulted in exclusion of the bed, and sometimes air pockets within the bowel, which was corrected for. All voxels within the body contour were included. After rebinning of the data (to speed up processing) the algorithm generated time-activity-curves (TACs) for each individual pixel. Such a TAC was formerly called a dixel (dynamic pixel) in 2D [1,2], and can be represented as a vector. For our system implementation, the zooming, rebinning and summation of planes produced voxels of 6.8 x 6.8 x 7.3 mm3. TACs were generated for all voxels within the body contour, and comprised the complete vector set for the patient. Optionally, the magnitude of voxel TACs for further processing can be selected, e.g. between 50 and 100% of the maximum. Such 'histogram windowing' or 'thresholding' removes voxel TACS with a relatively constant pattern or small magnitude (noise). After smoothing with a temporal 1-2-1 kernel and normalization, principal component analysis (PCA) was performed. Using a non-orthogonal transformation, the principal components were rotated to obtain axes that have the maximum explained variance in the selected vector set. Thus, curves were produced that have the shape of the 'pure factors', but have incorrect magnitude due to the initial normalization step. Subsequently, the pure factors are transformed back to the image space, yielding factor images for each plane. The magnitude of the factor curves and factor images need adjustment to undo the initial normalization step. Scaling of the factors was done with two methods: 1) *reversed normalization*: multiplication by the initially used scalars that produced the normalized vectors (i.e. voxel TACs), 2) *image derived constants*: the pure factor images were used as masks for the delineation of an ROI with thresholding techniques. With this ROI and the original reconstructed PET images, an image based TAC was generated for the vessels and tumor. The image TAC was used to normalized the pure factor curve by using: 1) peak of the curve, 2) full area under the curve (AUC), 3) first half AUC, 4) second half AUC, 5) FWHM, or 6) FWTM of the initial peak.

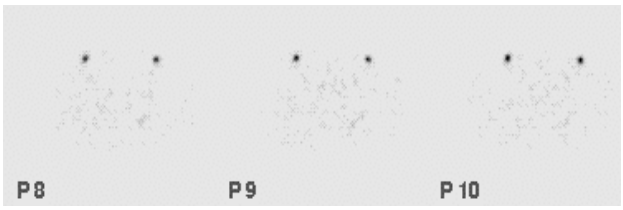

Fig 1. Three transverse planes during the early phase of the acquisition. Note the high tracer uptake in both iliac arteries during bolus passage and the low background.

In this way, 'pure' input and output curves are created which can be used for kinetic modeling. The standard UCLA three compartment model was utilized to calculate the micro parameters (k1-k4) and macro parameter (K) of the acetate uptake in the prostate cancer. The image interface, PCA, FA, and curve and image processing were written in IDL-5™. The kinetic modeling was done with non-linear regression routines and were also written in IDL-5™. Processing of a typical study took 10-15 minutes on an UltraSPARC-5, and 5-8 min on an Ultra-60 workstation.

III. RESULTS

By using 2 principal components three factors are generated with FA, i.e. a vascular factor (iliac vessels in the pelvis), a tumor factor (prostate cancer) and a residual. In Fig. 1 factor images are shown of the iliac arteries in three adjacent planes. The vessels can be delineated with thresholding techniques, and the ROIs subsequently be used to generate an input function. The iliac vessels have a lumen of 3-6 mm and suffer from partial volume effects in the reconstructed images. The same procedure to derive a tumor ROI and generate an output function, can be followed for the prostate tumor.

In Fig 2, an example is given of the input curves of the blood vessels in the pelvis (left), and output curves of the prostate tumor (right). The factor curves are generally smoother than the image based TACs. The 'pure' vascular factor curve or input function was normalized (scaled) using the FWHM of the peaks. The tumor TAC was generated with a mask obtained by thresholding the tumor factor image. The tumor ROI was comprised of those voxels within the tumor mask that contain 75% or more of the 'pure' tumor factor. The tumor factor curve was then scaled by using the integral (total area under the curve) of the image based tumor TAC.

Reliable factor curves were obtained in 5/6 primary and 3/3 recurrent prostate cancer patients, yielding a success rate of 8/9 or 89% for automatic processing. The failure was related to bladder uptake, highly unusual for this tracer. The contribution of bladder activity was removed by manual masking, which resulted in more realistic input and output functions.

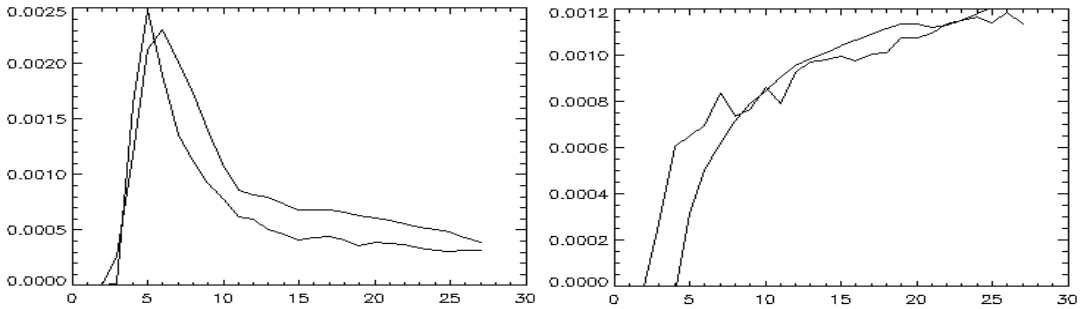

Figure 2 Input function or vascular curve (left panel) and out put function or tumor curve (right panel. In general, the factor curves are smoother and 'less noisier' than the image derived curves.

Fig 3 shows a summed image (top) at the end of acquisition and the tumor factor image (bottom). Comparison shows the bilobular prostate gland in the summed images (top row, Fig 3). The factor images reveal the cancer inside the right prostate lobe (bottom row, Fig 3), because of the different behavior in time of normal and cancer tissue.

With the standard 3-compartment model, the micro and macro parameters, i.e. diffusion rates between compartments, were estimated. k1 reflects the flow to the tumor in the prostate and K the metabolic rate of acetate. Three situations of input and output functions were used: 1) both generated with FA, 2) input FA and output image derived, and 3) both image derived. The results of these 3 conditions were compared to those obtained with semi-automatically drawn ROIs and corresponding image based TACs. Table 1 gives the average values and results of the linear regression analyses for the primary cancer group of 6 patients.

TABLE I

Input	**Output**	**k1**	**K**	**r^2**	**slope**
Primary Cancer		*N = 6*			
FA	FA	0.54	0.092	0.52	0.34
FA	Image	0.57	0.073	0.55	0.56
Image	Image	0.71	0.125	0.57	0.68
Semi	*Semi*	*0.72*	*0.115*	*1.00*	*1.00*
Recurrent Cancer		*N = 3*			
FA	FA	0.63	0.057	N/A	N/A
FA	Image	0.53	0.039		
Image	Image	0.59	0.129		
Semi	*Semi*	*0.58*	*0.136*		

The correlation between estimated parameters with factor curves, i.e. input and output functions, and imaged-based TACs was 0.75 for macro K in primary cancer. Linear regression supplied a slope significantly different from unity (Table I). A 5 parameter modeling program was also attempted, i.e. a correction for the blood volume inside the tumor was introduced. However, this kinetic model yielded less favorable fits and parameter estimates. Therefore, only results of the standard 3 compartment model with 4 parameters are shown.

IV. DISCUSSION

An automated procedure for the generation of a vascular input function and tumor output function, based on factor analysis of dynamic sets, was devised, written and successfully implemented on a standard workstation. Reliable factor curves were obtained in 8/9 prostate cancer patients, a success of 89%. In one patient, there was uptake in the bladder, unexpected for C-11 acetate. Filling of the bladder is a major temporal change, readily picked up by FA. After masking the bladder by manual intervention, adequate input and output curves were obtained. This case example prompted the addition of modules to mask undesirable structures in the image set.

Fig 3 reveals a potential application of clinical significance. FA could distinguish tumor from normal prostate tissue in this patient. The presence of tumor in the right lobe and absence in the left was confirmed by pathology in the surgical resection specimen. Analogously, FA may reveal tissue inhomogeneity and differentiation within the tumor. In other words, specific tumor components may be distinguished based on temporal patterns of tracer uptake.

The success rate of kinetic modeling was mixed in the present set of data. In 4/9 patients, the final fit appeared not adequate. This suggests that the 3 compartment model is not optimal for the acetate kinetics of prostate cancer. There is no validated model described for humans in the literature. More research into the kinetics of cancer is necessary to elucidate the appropriate model.

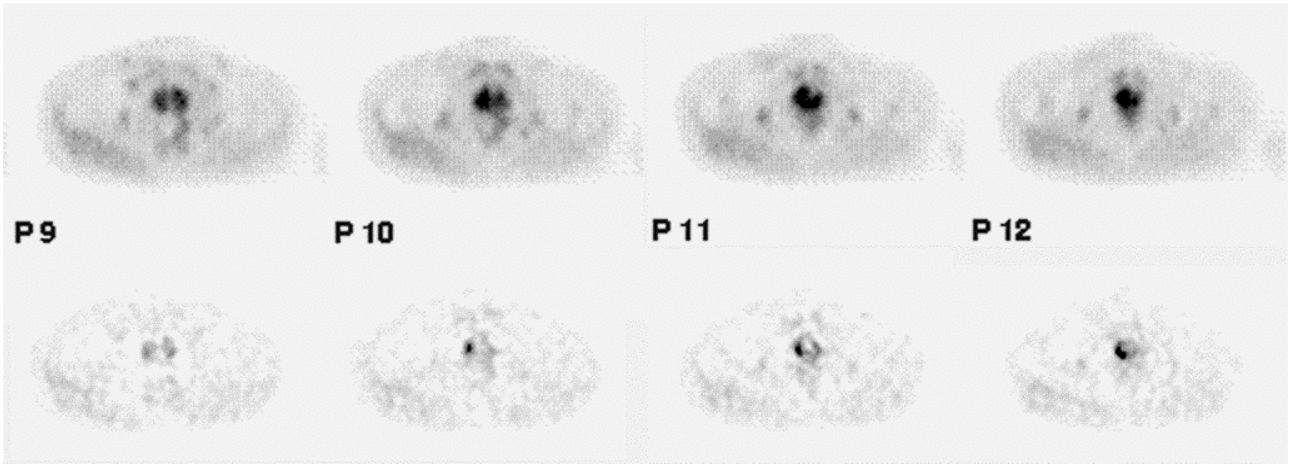

Figure 4 Top: summation of the last 10 min of the dynamic dataset. Note the bilobular prostate gland. Bottom: corresponding factor images. Note the tumor in the right lobe. The central photopenia on plane p11 bottom, is the urethra.

V. Conclusions

In dynamic PET studies, an accurate input and output function can be obtained with Factor Analysis. The input and output functions generated with FA appeared similar to those calculated with ROIs on the images. Kinetic Modeling with input from Factor Analysis or TACs generated with functional ROIs supplied parameters that revealed high correlations in this limited population. Factor curves permit reliable parameter estimation, an important finding for the evaluation of sequential studies such as therapy monitoring in cancer. Our FA implementation provides a standardized method for evaluating quantitative PET images, applicable to studies across institutions and therapeutic regimens.

VI. References

[1] Barber DC. "The use of principal components in the quantitative analysis of gamma camera dynamic studies" *Phys Med Biol,* **25**: 283-292, 1980

[2] Di Paola, R, Bazin JP, Aubry F, Aurengo A, Cavailloles F, Herry JY, Kahn E. "Handling of dynamic sequences in nuclear medicine". *IEEE Trans Nucl Sci*, **4**: 1310-1321, 1982

[3] Barber D, Martel A. "Factor Analysis revisited". *Eur J Nucl Med*, **19**: 467-468, 1992

[4] Wu HM, Hoh CK, Choi Y, Schelbert HR, Hawkins RA, Phelps ME, Huang SC. "Factor Analysis for extraction of blood time activity curves in dynamic FDG-PET studies". *J Nucl Med*, **36**: 1714-1722, 1995

[5] Schiepers C, Wu HM, Nuyts J, Dahlbom M, Hoh CK, Huang SC, Phelps ME. "Fluoride PET: is non-invasive quantitation feasible with factor analysis ?" *J Nucl Med,* **38**: 93P, 1997

[6] Schiepers C, Hoh CK, Dahlbom M, Wu HM, Phelps ME. "Factor analysis for delineation of organ structures, creation of in- and output functions, and standardization of multicenter kinetic modeling" *Proceedings SPIE* **3661**: 1343-1350, 1999