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# "NEW TECHNIQUES FOR POSITRON EMISSON TOMOGRAPHY IN THE STUDY OF HUMAN NEUROLOGICAL DISORDERS"

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## Part 1 - Physics (Robert Koeppe, Ph.D., Project Leader)

### Abstract

The general goals of the physics and kinetic modeling projects are to: 1) improve the quantitative information extractable from PET images, and 2) develop, implement and optimize tracer kinetic models for new PET neurotransmitter/receptor ligands aided by computer simulations.

Work towards improving PET quantification has included projects evaluating: 1) iterative reconstruction algorithms using supplemental boundary information, 2) automated registration of dynamic PET emission and transmission data using sinogram edge detection, and 3) automated registration of multiple subjects to a common coordinate system, including the use of non-linear warping methods.

Simulation routines have been developed providing more accurate representation of data generated from neurotransmitter/receptor studies. Routines consider data generated from complex compartmental models, high or low specific activity administrations, non-specific binding, pre- or post-injection of cold or competing ligands, temporal resolution of the data, and radiolabeled metabolites. Computer simulations and human PET studies have been performed to optimize kinetic models for four new neurotransmitter/receptor ligands, [$^{11}$C]TRB (muscarinic), [$^{11}$C]flumazenil (benzodiazepine), [$^{18}$F]GBR12909, (dopamine ), and [$^{11}$C]NMPB (muscarinic).

Future efforts will continue to focus on improving quantification in areas such as 3-D PET acquisition and reconstruction, and on optimizing kinetic modeling and parameter estimation techniques through the use of computer simulations.

## Part 2 - Chemistry (G. Keith Mulholland, Ph.D., Project Leader)

### Abstract

The project aims have been to improve isotope production and handling methods for clinical PET applications using solid phase approaches, and to develop new $^{11}$C and $^{18}$F labeling strategies. We have developed high yield direct in-target production of [$^{15}$O]water and [$^{13}$N]ammonia which enables rapid repeat deliveries of these tracers for brain and heart studies. We have worked on approaches to simplify and make more reliable fluorodeoxyglucose production. Practical solutions for insuring highly reactive purified [$^{18}$F]fluoride ion, and recovery and purification of used [$^{18}$O]target water by photochemical combustion have been developed. In view of current shortages in commercial supplies of O-18 water, these techniques are likely to have immediate use in the field. The resin supported synthesis of FDG, successfully implemented during the previous period of this grant, is now of interest to several manufacturers of PET systems. Our search for improved ion exchange materials for resin based labeling has led to graphitized carbon anion exchange materials and the development of phosphazenium functionalized polystryrene resins which are stable to strong bases and high temperatures. Other developments have been "dry" radiofluorination by ion exchange formation and decomposition of aryl-$Me_3^+$ $^{18}F^-$ salts and rapid $^{11}$C-methylation of tBoc-activated anilines. These new chemistries were applied to cholinergic tracers MABV and fluorobenzyl vesamicol as well as new agents under study.

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# NEW TECHNIQUES FOR POSITRON EMISSION TOMOGRAPHY IN THE STUDY OF HUMAN NEUROLOGICAL DISORDERS
## PROFESS REPORT FOR THE PROJECT YEAR BEGINNING 14 JUNE 1991

**Principal Investigator: David E. Kuhl, M.D.**

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## Introduction

We continue our focus to develop more simple and less expensive , yet at the same time more powerful, means for acquiring and interpreting quantitative data, and to develop cost - effective and efficient means for producing new functionally specific tracers for positron emission tomography (PET). These improved processes are required for the future growth of PET as a sophisticated research tool and for the transfer of this technology to clinical use.

The overall project is divided into two subprojects, one concerning physical principles , and the other concerning chemical principles. This progress is summarized below.

## Subproject 1

### Methodological Developments for Improved Extraction of Quantitative Information from PET

Robert A Koeppe, Ph.D., Subproject Leader
Gary D. Hutchins, Ph.D., Co-investigator
Jeffrey Fessler, Ph.D., Co-investigator
Satoshi Minoshima, M.D., Co-investigator

### I. Goals

One major objective of this project is to develop methods which optimize the extraction of information from PET image data. This includes (1) consideration of the methods used to measure the PET data, (2) image reconstruction algorithms, and (3) region-of-interest techniques for the efficient extraction of data from PET images. Due to the difficulty of evaluating the influence of factors such as the distribution of radionuclides within organs of the human body, scatter and attenuation from the 3-D structure and orientation of the human body relative to the imaging device, and the complex 3-D detection characteristics of PET tomographs, the relationship of the PET measurements to reality is often difficult to assess. One of the primary objectives of this project is to develop simulation tools to assist with the evaluation of quantitative PET methods. These simulation tools also enable the efficient development of new data analysis methods by providing rapid feedback with regard to bias and variance characteristics of these methods. Statistical approaches to iterative image reconstruction which incorporate anatomical information (such as is obtainable from high-resolution MR or CT images) into the reconstruction procedure are being investigated to address problems of partial volume and limited resolution.

A second major objective of this project is to develop optimized tracer kinetic models for better extraction of quantitative information from PET data. Specific objectives to be

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accomplished include: (1) the development of a sophisticated set of computer simulation routines to examine how accurately PET techniques can be used to estimate parameters of interest in PET neurotransmitter/receptor studies; (2) the development of a set of criteria or guidelines that the radiochemistry research personnel can use to direct choices in the development of potential new PET radioligands; and (3) the development of simplified tracer kinetic models to be used with new PET neurotransmitter/receptor ligands, when more realistic compartmental models are too complex to yield reliable measures of neurotransmitter function or receptor density.

A final major objective of this project is the development of improved methodology for performing blood flow activation studies with the goals of increasing signal-to-noise and improving the statistical analyses used to test for significant change in the activation studies. Areas of investigation include: 1) the use of iterative reconstruction algorithms or constrained least-squares filtering as an alternative to filtered back projection, 2) automatic registration of the emission data with the transmission data used for attenuation correction, 3) improving registration of data from CBF scans both within subject and between subjects using AC-PC standardization in conjunction with either linear or non-linear warping routines, and 4) development of more appropriate statistical tests for assessing changes between activation and control tasks.

## II. Accomplishments

During the period from June 15,1991 to March 15, 1992, several developments have taken place. We have been involved in the migration of many of our existing software simulation and analysis tools into a UNIX environment so that we can take advantage of the dramatically improved computational speeds that RISC based computer systems offer. These new simulation tools have been developed using the software package "Application Visualization System" (AVS) originally developed by Stardent Computer Inc. This system enables design of modular software which can be reconfigured using a simple user interface. Software tools which have been developed include the following: 1) digital phantoms of the brain and heart for generating realistic radionuclide distributions for both static and dynamic PET studies, 2) digital phantoms of the attenuation and scatter maps associated with the radionuclide distribution phantoms for examining the influence of photon interaction with matter upon PET studies, 3) tomograph simulator for generating sinograms of the radionuclide distributions, 4) standard filtered backprojection and iterative maximum likelihood algorithms for reconstructing image data, and 5) image display interface for mapping the results from the parameter estimation routines to standardized surface displays of the object being studied.

Several dozen software modules using AVS have been implemented that perform fundamental tasks associated with image reconstruction. These tools are used perform computer simulations of PET emission image reconstruction using an iterative penalized-likelihood approach that, through the use of a weighted penalty function, can easily accommodate side-information from MR or CT. The effects of imperfect registration or imperfect correspondence between anatomical and functional boundaries were investigated though computer simulations. AVS tools have also been used in collaboration with another independently funded project for investigation of a joint emission/transmission estimation method that accounts for the statistical uncertainty in PET transmission scans.

Extension of these tools, originally developed for examining PET brain methods, have been developed for the evaluation of cardiac PET applications, resulting in new techniques for the measurement of myocardial blood flow. In addition, these tools have been used to examine the effects of attenuation, scatter, image count densities, and kinetic characteristics of radiotracers upon the ability to quantitatively evaluate physiology using PET.

Simulation routines were developed that provided a more accurate representation of the actual data generated from neurotransmitter/receptor PET scans. The routines generate simulated data taking into account complex compartmental models, high or low specific

activity injections, non-specific binding, pre-injections of cold or competing ligand, post-injection administrations of cold or competing ligands, effects of the temporal resolution that the data is acquired at, and effects of radiolabeled metabolites in the plasma or brain. Over the past year, problems and difficulties directly related to the scanning instrument have been incorporated into the simulation routines. These additions include accounting for the effects of spatial resolution, scattered coincidence events, and attenuation correction effects.

Computer simulations and human PET studies were performed to analyze the quantitative potential of one new neurotransmitter/receptor ligand, [$^{11}$C]N-methyl piperidyl benzilate (NMPB), a muscarinic cholinergic antagonist, and one existing ligand, the central benzodiazepine antagonist, [$^{11}$C]flumazenil (FMZ). Currently, computer simulations following results from animal have been performed for a second new radioligand, [$^{11}$C]tetrabenazine (TBZ), a tracer for pre-synaptic vesicular storage of dopamine. Simulations have indicated that parameter sensitivity when performing kinetic analysis using a three-compartment model yields estimates with a high degree a variability for each of these three PET agents. Results from the human studies, described in the following paragraphs, further indicate the difficulty in employing this complex a model. Thus, potential simplifications in the kinetic model have been investigated. Appropriate simplifications appear promising for the muscarinic agent, NMPB. A 2-parameter 2-compartment simplification has been implemented for the benzodiazepine ligand, FMZ, and a similar model appears to be suitable for TBZ based on simulation and preliminary animal data.

[$^{11}$C]-NMPB studies were carried out in seven young normal volunteers during the past six months. Kinetic data was acquired for 110 minutes, and arterial blood samples were obtained and corrected for radiolabeled metabolites. Data are being analyzed by a variety of kinetic approaches with a range of complexities in order to be able to develop an analysis technique with an optimal degree of model complexity, balancing the levels of variability and bias in the parameter estimates. Analysis schemes range in complexity from a simple single scan or a graphical approach to a more complex 3-compartment, 3-parameter estimation of the ligand's transport rate, free plus non-specific distribution volume, and the combined forward rate constant representing the product for the ligand-receptor association rate and the receptor density. Preliminary results have indicated that this new agent can yield better estimates of receptor density than previous muscarinic ligands developed at our facility, [$^{11}$C]-TRB and [$^{11}$C]scopolamine. TRB and scopolamine have previously been shown to be only partially successful ligands due to varying degrees of flow limitation. Simulations indicate that this should not be nearly as great a problem for NMPB due to the 2.0-2.5 fold increase in ligand transport observed in the first 7 human studies (~60% first pass extraction). Initial modeling efforts on the human data seem to support the conclusions derived for simulation studies.

[$^{11}$C]-FMZ studies have now been carried out in over 30 normal volunteers and a 2-compartment, 2-parameter model has been routinely implemented (estimating ligand transport and distribution volume). Studies in 4 patient groups) epilepsy, olivopontocerebellar atrophy, Huntington's disease, and Alzheimer's disease) have been initiated with kinetic analysis using this simplified model. Currently, additional normal controls are being studied to examine the difference in performance between the current bolus injection acquisition/2-compartment 2-parameter analysis approach and a direct equilibrium approach for estimating the distribution volume using a continuous infusion of the radioligand.

Poor results from previous work (reported last year) with the [$^{18}$F]GBR compound has prompted the new efforts with [$^{11}$C]TBZ. Preliminary studies in rats and monkeys show a rapid clearance of activity from the brain and rapid equilibration between bound and unbound states, indicating that a 2-parameter 2-compartment model will probably fit the human data well . Human studies of this agent should be initiated very shortly. Similar kinetic approaches to those used for the initial analysis of FMZ data will be employed with TBZ.

During the past year we have focused on techniques for inter-subject comparison of functional brain PET images, such as from CBF activation studies. To compare PET images

from different subjects, localization of the functional signals in a common spatial system is required. One solution is to use anatomical images (i.e., X-ray CT, MRI) as a reference to localize the signals. However, anatomical images are not necessarily obtained from each subject in clinical situations as well as some research situations. Our strategy is to put PET images into a standard coordinate system using only the PET images themselves. We found that the intercommissural (AC-PC) line could be estimated accurately using internal landmarks of the brain in a PET image set. Then the PET image set can be reoriented into the standard stereotactic coordinate system according to the estimated AC-PC line, allowing anatomical localization of functional signals without anatomical reference images. To avoid inter-observer differences and increase reproducibility in estimating the AC-PC line, internal landmarks are detected by a completely automated program. Accuracy of the estimated AC-PC line has been validated in FDG and O-15 water PET studies.

After PET image sets are reorientated into the stereotactic space, conventional region-of-interest (ROI) analysis can be performed by referring to the stereotactic coordinates of specific structures in the brain. Alternatively, we have developed image standardization techniques to correct individual anatomical differences in the stereotactic space, enabling pixel-by-pixel comparison among subjects. This technique is useful especially for summation analysis of O-15 water activation studies and for group comparison between averaged normal function and pathological states. Our preliminary method using automated two-dimensional linear stretching showed precise standardization of cortical areas in the brain. Applying the method to the O-15 water activation studies, we could delineate activation foci clearly in the summation image of five subjects, and in addition, the method allows pixel-by-pixel statistical analysis. We have also created a standard metabolic atlas by standardizing and averaging fifteen normal FDG-PET studies. The atlas has been used to demonstrate pathological areas of the brain in Alzheimer's disease patients in terms of the number of standard deviations from normal values on pixel-by-pixel basis.

Another algorithm has been developed and tested for the realignment of image data in dynamic imaging sequences. This algorithm finds edges in emission sinogram data and fits an ellipsoid to this surface for the purpose of determining the 3-D orientation of the head. The image data is then corrected for motion based upon the orientation differences observed in fits to individual sinograms. This particular approach may also be useful for accurate registration of a measured transmission data set (for attenuation correction) with emission data sets.

During this reporting period, Raymond R.Raylman completed his Ph.D. dissertation entitled " Reduction of Positron Range Effects by the Application of a Magnetic Field: For Use With Positron Emission Tomography". The project was directed by Dr. Hutchins and was funded by this DOE grant.

**III. Future Plans**

During the next year of this project, we will focus in three major areas. One major area is the continued development of the PET simulation tools for testing methods designed to improve our ability to quantitatively extract information from PET data, and in addition, the continued migration of these routines and methods to the AVS/Unix environment. Our computer simulations have shown that iterative reconstruction methods, particularly with the fusion of MR or CT information, offer significant quantitative benefits for certain tasks, such as estimating uptake in small structures surrounded by regions of higher activity. The conventional filtered back-projection method produces biased estimates in these cases due to spill-over from neighboring regions. We have recently implemented an AVS module that allows us to read CTI-format sinogram files, and have acquired line-source response data from our scanner to use for calibrating and verifying the system model. With these in hand, we have recently produced the first PET image reconstructed by iterative techniques at this institution, complementing our extensive experience with SPECT iterative reconstruction. Having demonstrated the potential of our methods via simulations, we will now proceed with phantom studies to verify that the models are robust to the imperfections inevitably associated with real

PET systems. Within the next few months, we will begin to validate the methods on clinical applications. We will also begin work in assessing the performance of 3-D PET applications using tomographs without interplane septa. Our group will have a Siemens ECAT EXACT tomograph installed by late summer 1992. This scanner has 47 slices and retractable septa for 3-D acquisition. These systems have dramatically increased detection sensitivities over current scanners, however, this increased sensitivity is accompanied by higher levels of noise (scatter, randoms, deadtime). The relative merit of removing the interplane septa under various scanning conditions (i.e. for a variety of radiotracers, static vs. dynamic imaging, etc.) will be examined.

A second major area we will focus on is kinetic modeling for PET neurotransmitter/receptor studies. We will continue to development, implement, and optimize kinetic models for potential new ligands, with goals of aiding the radiochemists in selecting the best compounds when more than one alternative is available and the pursuit of simplified models that can be validated and implemented for use on a routine basis. We will also begin a study comparing the quantitative properties of image reconstruction algorithms (filtered backprojection, maximum likelihood methods, and the constrained least squares method) from the standpoint of estimating tracer kinetic model parameters, and evaluating the influence of attenuation and scatter correction errors on the determination of kinetic parameters for cerebral studies of neurotransmitter/receptor systems,

A third major area of focus will be the new work started this past year on cerebral blood flow activation studies. In addition, we will extend the use of the registration and alignment techniques to other types of PET studies. In devising new standardization techniques for brain images, we will apply a non-linear three-dimensional stretching technique to PET studies, which will improve standardization accuracy of subcortical structures. We also will develop intra-subject comparison techniques, which are crucial for longitudinal studies and neuronal activation studies of PET. Finally, statistical analysis which is suitable for image analysis on pixel-by-pixel basis will be combined with those intra- and inter-subject comparison techniques to delineate different states of brain function objectively.

## Subproject 2

## New Labeling Strategies for Short-Lived Positron Emitting Nuclides

G. Keith Mulholland, Ph.D., Subproject Leader
Douglas M. Jewett, Ph.D., Co-Investigator

### I. Goals.

The goals have been to improve production and handling of isotopes and labeled compounds of biological interest for clinical PET applications and to develop new labeling strategies for shortlived positron emitting isotopes using solid phase approaches and novel chemistry.

### II. Accomplishments.

Nucleophilic radiofluorination has been a major theme during this period. Convenient and practical methods for recovering highly reactive [$^{18}$F]fluoride ion and purification of used $^{18}$O-target water by photochemical combustion have been developed. These techniques are likely to have immediate applications in view of present shortages of commercial supplies of O-18 water, and the lack of reliability seen in with reuse of $^{18}$O-target water. The resin supported synthesis of FDG, and direct in-target [$^{13}$N]ammonia production

method which were successfully implemented during the previous period of this grant are now being developed commercially by manufacturers of PET systems.

The search for improved ion exchange materials for heterogeneous nucleophilic radiolabeling has led exploration of mechanically rigid graphitized carbon anion exchange materials and the development of phosphazenium functionalized polystryrene resins which are stable to strong bases and high reaction temperatures. Other developments have been "dry" radiofluorination by ion exchange formation and decomposition of aryl-$Me_3^+$ $^{18}F^-$ salts , rapid $^{11}C$-methylation of tBoc-activated anilines, and production of [$^{11}C$]methyl triflate as an extremely reactive reagent for [$^{11}C$]methylations.

Chemistry efforts supported by this grant have been applied to the primary development and continuing delivery of a host of agents under preclinical and clinical study, including cholinergic tracers MABV , fluorobenzyl- and fluoroethoxy-benzovesamicol, a variety of muscarinic tracers including TRB, MTRB, MQNB, and NMPB, and GABA tracers flumazenil and $^{18}F$-labeled chloride channel blockers.

III. Future Plans.

-Continuation of work with nucleophilic fluorine-18. Applications to CNS drugs .

-Explorations of "no-carrier -added" [$^{13}N$]$NO_x$ chemistry for radiolabeling applications.

-Exploration of heat stable phosphazenium ion exchange resins with faster kinetics.

Applications of [$^{11}C$]cyanide in resin-based labeling of compounds of biological interest.

-Development of efficient production methods for [$^{13}N$]nitrogen oxides and other small molecules labeled with positron emitters, and examination of their potential as tracers in animals.

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