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INSTRUMENTATION AND QUANTITATIVE
METHODS OF EVALUATION

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PROGRAM OVERVIEW

This document reports progress made during Year 2 of the current three-year cycle of DOE funding under Grant No. DE-FG02-86ER60418 entitled "Instrumentation and Quantitative Methods of Evaluation," with R. Beck as Principal Investigator and M. Cooper as Co-Principal Investigator. The research program under this grant is very closely integrated with that funded under DOE Grant No. DE-FG02-86ER60438 entitled "Quantitative Studies in Radiopharmaceutical Science," with M. Cooper as Principal Investigator and R. Beck as Co-Principal Investigator. Together, they constitute the Program of Nuclear Medicine and Quantitative Imaging Research within The Franklin McLean Memorial Research Institute (FMI).

This program and the facilities of FMI provide the basis for collaborative research not only with the Department of Radiology Section of Clinical Nuclear Medicine (Director: M. Cooper), but also with a network of multidisciplinary faculty/investigators who bring expertise (and separate funding) from the Departments of Radiation Oncology, Pharmacology and Physiology, Medicine (Cardiology and Endocrinology), Obstetrics and Gynecology, Surgery, Psychiatry, Neurology, Biopsychology as well as the Committees on Molecular Genetics and Cell Biology, Structural Biology, and Argonne National Laboratory (ANL).

In addition, this program relates closely with other programs within the Department of Radiology Section of Radiological Sciences (Director: R. Beck), which include the Digital Radiography Research Program (Director: K. Doi, Ph.D.) and the NMR/MRI Research Program (Director: D. Levin, M.D., Ph.D.), which are funded separately, as well as the Graduate Program in Medical Physics (Director: K. Doi).

Thus, the FMI and its Program of Nuclear Medicine and Quantitative Imaging Research play a critically important role in fostering multidepartmental, multidisciplinary imaging research at The University of Chicago. In addition, under separate funding, the FMI Administrative/Editorial Offices serve the needs of the newly formed Center for Imaging Science (Director: R. Beck) which is designed to promote research and education in this rapidly emerging field, and which encompasses activities related to imaging science on campus and at ANL.

During the past year, we have acquired new equipment for electronic circuit design (under separate funding) and have initiated a number of new projects and collaborations, some of which have already proven to be productive. In this connection, we call your attention to the following items. Specifically, we have:

- collaborated in the development of a new and powerful method for integrating PET images with CT or MRI images of the same slices. (See Project II.)
- designed and have under construction a miniature, hand-held scintillation camera which we believe will have many applications in nuclear medicine. (See Project III.)
- designed a new detector module for high resolution, multi-slice PET imaging. (See Project III.)
- designed and built three prototype devices to reduce radiation exposure to staff. (See Project IV.)

We look forward to the years ahead with enthusiasm and confidence.

I. PHYSICAL ASPECTS OF RADIONUCLIDE IMAGING

D.L. Gunter and R.N. Beck

Introduction

The field of nuclear medicine is based on the fact that important biomedical information can be derived from knowledge of the distributions of certain radiolabeled materials measured *in vivo*. Quantitative radionuclide imaging procedures provide the means for making these measurements.

Our concern in this project is with the *physical factors* that affect the accuracy, reproducibility, and spatial localization of these measured distributions. (Other factors related to the biological/biochemical issues, as well as the dynamics of uptake mechanisms and issues of radiation absorbed dose, are dealt with in the companion grant covering radiopharmaceutical research.) These physical factors include the gamma ray energy, the attenuation and scattering of gamma rays within the patient (and thus the emergent spectrum), the transport of radiation through the collimator (and, again, the emergent spectrum entering the scintillation detector), the resultant pulse amplitude spectrum, and, finally, the means for utilizing this output spectrum to form an image of the distribution *in vivo*.

The number of parameters involved in such procedures obviates an empirical approach that would, in principle, provide answers to such questions as:

- For a given distribution, how does the choice of gamma ray energy affect accuracy, reproducibility, spatial localization, etc., and what is the optimum energy for a given imaging procedure?
- What is the optimum trade-off between sensitivity, resolution, septal penetration, and image contrast, i.e., the optimum collimator design for monoenergetic emitters, or for multi-energy emitters?
- What is the optimum trade-off between sensitivity and spatial resolution of the scintillation camera, i.e., the optimum crystal thickness?
- What is the optimum way of using the entire output pulse amplitude spectrum to maximize accuracy of quantitation in three (spatial) dimensions?
- How do these various optimizations depend upon the object, i.e., on the size and shape of structures within which the activity is to be measured?
- What is an appropriate criterion for the optimization of such parameters; e.g., maximum signal-to-noise ratio, or maximum correspondence between object and image, or maximum likelihood that an observer will interpret the image correctly, or maximum accuracy in the measurement of object features, etc.?

Recognizing the impracticality of an empirical approach, we have undertaken the development of quite general computer codes to simulate the major physical processes involved in imaging with a scintillation camera; thus,

SCATII is a Monte Carlo code that simulates the emission of gamma-rays and the transport of radiation through tissue (taking account of attenuation and scattering), and computes the energy and direction of the radiation spectrum that emerges at each point on the surface of the patient.

RAYTRC is a code which simulates the geometrical and septal penetration components of collimator response for any given input radiation and set of collimator parameters.

COLSCAT incorporates RAYTRC and computes, in addition, the effects of scatter and fluorescence within the collimator, thus yielding the spectrum of radiation entering the crystal.

3-D RECON is a code for reconstruction of the 3-D distribution of activity from a *single* view, utilizing the entire output pulse amplitude spectrum. [Ultimately, sets of such reconstructions (obtained from multiple views) will be combined to produce a single, more accurate 3-D reconstruction of the activity distribution in the SPECT mode.]

The ultimate goal of this project is the integration of these programs to enable the simulation of images of given object distributions of activity, and the optimization of parameters of system design for SPECT imaging. During the past year, our research has continued on the two major aspects of this project. First, we are continuing our development of computer simulations for the optimal design of collimators for gamma ray cameras used in nuclear medicine. Second, we are attempting to utilize scattered radiation for three-dimensional imaging without moving the camera. Considerable progress was made on both of these projects during the last year. Details are provided below.

1. Collimator Design

We have extended the development of two major packages of computer programs used for the design of collimators used in nuclear medicine. The two packages are called RAYTRC and COLSCAT, and serve complimentary purposes. The RAYTRC package is a collection of programs for collimator design with high-energy gamma rays in which septal penetration may be a significant design problem. The RAYTRC package is intended for rapid evaluation of numerous designs (all having the same geometric proportions), and is ideal in searching for good design parameters. The COLSCAT package is a Monte Carlo simulation of collimator imaging properties which includes scattering and fluorescence effects within the collimator. Because the Monte Carlo simulation technique is inherently slow, the COLSCAT package is intended for in-depth analysis of a collimator *after* the RAYTRC package has produced an "optimal" design based on geometrical and penetration effects.

The RAYTRC programs are well tested; written over three years ago, RAYTRC has been compared frequently with experiment and proven to give reliable results. Subsequently, we started an extensive project of collimator design using RAYTRC to search for "optimal" collimator design. Over 560 hours of computer CPU time have been used to compile extensive tables of collimator sensitivities, resolutions, hole pattern and star pattern parameters, and penetration fractions for various collimator designs. So far, our work has concentrated on collimators for the most popular isotope--Tc-99m. In the coming year, we intend to shift to other isotopes which produce higher energy gamma rays and which consequently pose more difficulties in collimator design (due to penetration). Our close scrutiny of collimators for Tc-99m has allowed us to focus our attention on the fundamental research question "What constitutes an "optimal" design for a collimator in nuclear medicine?"

Traditionally, collimator design has been viewed as a trade-off between sensitivity and resolution, with the choice based upon the requirements of a particular application. For high-energy gamma rays (>150 keV), the situation is complicated by numerous secondary effects associated with penetration of radiation through the collimator septa. Long penetration "tails" on the point spread function can significantly degrade the contrast of the images produced. Assymmetric penetration can lead to "star patterns" in the images. Thick collimators designed to prevent penetration can lead to hole pattern in the image. We have developed criteria to detect each of these problems when they arise in a collimator design. Perhaps the most delicate problem is the estimation of an acceptable level of penetration through the collimator. The most commonly quoted

measure of penetration is the "penetration fraction"--the fraction of radiation entering the collimator after penetrating one or more septa. Our research indicates that successful collimators often have large penetration fractions--much larger than previously considered acceptable (up to 20% or more!). The crucial point is not the penetration fraction, but where the penetration goes. Successful collimators can have large penetration fractions so long as that penetration occurs within the region of normal "geometric" resolution of the camera. Indeed such penetration enhances images with greater sensitivities and suppressed hole pattern. Penetration *does* degrade images significantly when it occurs far from the region of "geometric" resolution (the so-called penetration tail). This suggests that the definition of penetration fraction should be modified to include only radiation outside the "geometric" region. Our researchers are continuing in this area.

The COLSCAT package represents our other major area of research in collimator design. While RAYTRC can successfully predict the effects of septal penetration in a collimator, the COLSCAT program is designed to simulate the scatter and fluorescence from the collimator material. The existence of fluorescence peaks in the spectra produced by gamma ray cameras has long been observed. With the development of commercially available WAM systems which use multiple windows covering the entire pulse amplitude spectrum, rather than a single energy window, the importance of the scatter and fluorescence has grown. The COLSCAT package produces the complete response of the camera-collimator system from a point source including the PSRF as a function of detected photon energy. During the last year, major programming was completed to implement variance reduction techniques to speed the execution time of the Monte Carlo simulation. We have just begun testing the COLSCAT package for comparison with experimental data.

2. Three-Dimensional Imaging Utilizing Scattered Radiation

Conventional PET and SPECT image reconstruction utilizes projection data from many directions without any depth information. It has been demonstrated that, with even modest depth resolution (FWHM of 8 cm) obtained by time-of-flight techniques, the signal-to-noise ratio (SNR) in TOFPET images is a factor of 3 to 7 higher than in conventional PET images. We would expect a similar increase in SNR in SPECT images, if similar depth resolution could be obtained in projection images from each direction. This expectation provided the basis for the investigation of 3-D imaging utilizing scattered radiation.

In a 1983 invention disclosure, we proposed a method of producing three-dimensional images from a multichannel gamma ray camera with images taken from a *single* direction. The fundamental idea relies upon the scattering of radiation within a patient's body. With each scattering process, the radiation loses energy. A source located deep within the body will result in more scattering before the radiation emerges than a source located near the surface of the body. As the source depth increases, the result is not only a significant change in the emergent energy spectrum, but also a significant change in the images. Deeper sources produce wider point source response and more counts in the low-energy region of the spectrum (with a corresponding decrease in the counts detected in the emission peak due to the attenuation). Originally, the scatter component in images was considered to be a nuisance, and energy windows were set to exclude the "background" of scattered radiation in images. More recently, "scatter subtraction" and "weighted acquisition" were introduced as more sophisticated methods of enhancing the two-dimensional images by making some use of the scattered radiation to sharpen edges and increase contrast.

Our proposal is intended to make the greatest possible use of the data provided by the scattered radiation. Images are taken from many energy windows over the entire observable spectrum. These images can be interpreted as intensities in a three-dimension space: the two spatial dimensions of the image, and the energy of the observation. The algorithm, which we have developed, transforms these three-dimensional intensities into three-dimensional source distribution functions within the body.

Significant progress toward implementing the 3-D scatter reconstruction algorithm has been made since its proposal in 1983. First, experimental data was collected during 1984. A special camera with the required energy discrimination was made available by Siemens Gammasonics Incorporated and used to measure point source response functions as a function of detected energy and source depth. Then conventional two-dimension phantom images were acquired in numerous (<46) different energy windows for use in the three-dimensional reconstruction. During 1985, the computer algorithms needed for image reconstruction were written and tested using the acquired data. The initial results were discouraging. The algorithm enhanced the noise and most of the images proved unacceptably noisy. During 1986, we tested modifications of the algorithm which filtered the images to prevent the enhancement of noise. In particular, the Singular Value Decomposition (SVD) algorithm was used to implement Tikhonov regularization in the reconstruction. This successfully surpassed the noise, but also prevented the reconstruction of source distributions deep within the scattering medium. During the past year, we made considerable progress by introducing a new method of filtering, which we have called backprojective regularization. The results are very promising, but require the selection of numerous parameters for each spatial frequency of the image. We are in the process of determining (by both experimental and theoretical means) an optimal set of filter parameters for the reconstruction.

II. IMAGE RECONSTRUCTION AND QUANTITATIVE EVALUATION

C.-T. Chen, C.E. Metz and R.N. Beck

"Image-space" reconstruction algorithms for TOFPET, conventional PET, and SPECT have been developed and tested. (These algorithms operate iteratively on the back-projected image, using probability density functions.) Much effort has been directed toward the investigation of various methods for calculating probability density functions (PDFs) that relate all pixels in the image matrix. These PDFs depend on the geometric relationship between the image matrix and the projection data set, as well as the physical and statistical processes involved in the image formation (the latter will be discussed separately in the following section). The geometric configuration dictates the forward- and back-projection operations in the reconstruction. Various techniques that calculate weighting factors representing the combination of forward- and back-projection operations have been studied. For TOFPET, image-space reconstruction algorithms can save some computation time and provide better image quality. Better computational efficiency can be realized for conventional PET and SPECT only in those cases which have fewer projection bins than pixels. Noise properties and quantitative uncertainties resulting from these forward- and back-projection operations have been studied also.

More general EM algorithms that incorporate the effects of physical and statistical factors involved in the image formation processes have been developed. Focus has been placed on the inclusion of the effect of scattered radiation in conventional PET and the effect of photon attenuation for TOFPET and SPECT. Three general categories of strategies for implementation have been examined: (1) methods that employ pre-processing steps that compensate approximately for scattered radiation or photon attenuation; (2) methods that use PDFs which include the effects of these factors; and (3) methods that incorporate a binomial model representing the statistical nature of these factors. In all cases studied, the second category appears to be the most effective approach in terms of computation time and image quality. Evaluation of various models for describing the characteristics of scattered radiation and their associated computing methods are in progress.

Additional acceleration methods for speeding up the rate of convergence to the maximum likelihood in the EM algorithms have been developed. Focus has been placed on the following three areas: (1) development of methods for selecting parameter values to ensure an optimal step size at each iteration; (2) design of remedies for preserving properties of non-negativity and self-normalization, and study of the resulting convergence properties; and (3) development of methods for determining the stopping rules. Similarities between these acceleration schemes used in the EM algorithms and those strategies employed in other optimization methods, e.g., steepest descent, conjugate gradient, etc., are being examined and compared.

Applications of the EM algorithms in digital image processing in general have been studied. EM algorithms, and their associated developments originally designed for tomographic image reconstruction, are equally applicable in image processing. They can be used as iterative methods for image restoration and enhancement. Statistical models have been built based on the EM approach for image processing. Preliminary studies using radionuclide images show that image contrast can be enhanced by the EM algorithms. Applications to digital radiography and other imaging modalities are in progress.

Investigation of the applicability of other general methods for estimation, e.g., the least-squares and Bayesian approaches, to image reconstruction is in progress. An attempt to incorporate some prior information in the statistical model has been initiated. The idea is to utilize readily available characteristics or information related to the image under study (e.g., continuity of neighboring pixels, physical configuration of the object, etc.) in modeling the physical and statistical processes of image formation. For example, a penalty function that characterizes the smoothness of the image can be defined in combination with the EM algorithms to produce reconstructed images with better noise properties. Implementation of such approaches and

evaluation of their performance are in progress. Development of more general models for incorporating additional prior information will be initiated also.

Development of quantitative methodology for evaluating imaging systems and image quality has concentrated on the methods for characterizing quantitative accuracy. In general, quantitative accuracy can be defined either for the average value within a well-defined region-of-interest (ROI), or for a point-to-point comparison between the estimated image and the supposedly "true" image (or an ensemble average image). The spatial resolution of the imaging system dictates the resulting quantitative accuracy, especially if small ROIs are of interest. Parameters representing the partial volume effect and remedies by which quantitative accuracy can be improved are being developed. Also, an improved quality assurance program for our existing PETT VI system has been developed in accordance with these quantitative methods for evaluation.

Quantitative analysis of PET images would be greatly facilitated by the superposition of CT or MRI images (which show tissue structures in great detail) upon PET images of the same slices. In collaboration with colleagues in Radiation Oncology (G. Chen and C. Pelizzari) and MRI (D. Levin), we have made a significant advance toward achieving this goal. Specifically, we have developed a new computer program that incorporates components of software previously developed by colleagues at Berkeley, Brigham Young University, and Massachusetts General Hospital, plus a unique iterative algorithm for surface fitting, which we have devised. This program is very powerful in that it does not require the use of fiducial marks or attention to patient positioning. Typical results are shown in Figures 1 and 2.

Figure 1. Fifteen-Year-Old Patient with Non-Responding Fungal Abscess of Brain (Aspergilloma)
PET and CT Studies

The positron emission tomogram (top left) shows a large region of reduced metabolism and a focal zone of non-metabolising tissue in the left frontal lobe.

The x-ray computed tomogram (top right), through the identical plane, shows a region of increased attenuation from contrast material and an adjacent hypolucent area, also in the left frontal lobe.

The integrated PET/CT images are shown as the single combined tomogram (lower left).

The combined images show that the infected frontal lobe of the brain has a breakdown in the blood-brain barrier and structural damage which coincides with reduced metabolic function and an adjacent area of tissue which may be assumed necrotic.

Figure 2. Fifteen-Year-Old Patient with Non-Responding Fungal Abscess of Brain (Aspergilloma)
PET and MRI Studies

The same positron emission tomogram as in Fig. 1 is shown (top left) with an MRI tomogram through the identical plane (top right), and the integrated images (lower left).

The lesion by MRI (T₂ weighted) appears much more extensive than the metabolic deficiency shown in PET. This indicates that the abscess shown on CT and PET is associated with increased tissue water content, edema, and swelling of surrounding brain which is viable and metabolising.

The combination of the PET, CT, and MRI images using correlated integrated images as shown reveals pathological and functional information about the abscess and its extent in the brain which is not revealed by any of the imaging techniques alone.

III. PET-RELATED INSTRUMENTATION FOR IMPROVED QUANTITATION AND NEW INITIATIVES

N.J. Yasillo

1. PETT VI

The PETT VI Tomograph has functioned reliably during the last year. Repairs have been limited to replacement of a servo-motor controller damaged by an external power surge and routine replacement of nine CsF detector assemblies. All CsF detectors replaced were from the original complement purchased in 1981 and were replaced because of slow deterioration in performance. Since mid-1985, we have been using an improved detector design. No replacement detector of this improved design has failed to date.

Support electronics for PETT VI, including the fast coincidence circuits, CAMAC pre-processor/buffer memory modules, and the motion control interface, have remained totally reliable since modifications made during 1985-1986 were completed.

We do not anticipate making any major modifications of PETT VI during the next year, but do expect to continue with the routine replacement of small numbers of detector assemblies. In addition, some replacement of mechanical components will be required due to wear.

2. ^{18}F FDG Synthesis

While continuing production of ^{18}F FDG using our manual synthesis system, we have constructed a second generation parallel system which is fully remote-controlled. All chemical transport through the process is accomplished using small electrically operated solenoid valves for liquid and vacuum switching.

In addition to remote operation, the experimental system incorporates various sensors with support electronics capable of measurement and recording of important process parameters. These include reaction temperature, drying gas flow rate, and moisture content of the system exhaust gas.

We believe that by carefully monitoring these system parameters, we will be able to take any corrective steps necessary to insure a highly reliable radiopharmaceutical yield during the process.

Recent testing indicates that the fully remote controlled system will be capable of high yield FDG production very soon.

3. ^{15}O Production

Recent improvements in the ^{15}O cyclotron target and gas handling hardware have resulted in increases in the yield of H_2^{15}O for PET studies. We can now reliably produce H_2^{15}O at a rate of up to 200 mCi every 10 minutes. In addition, we are continuing to improve the efficiency of our $\text{C}^{15}\text{O}/\text{C}^{15}\text{O}_2$ gas production systems.

Since we expect increased usage of ^{15}O in our PET Center in the near future, it is imperative that dedicated dose monitoring and quality assurance equipment is installed. This should include an additional dose monitor and a gas chromatograph in the ^{15}O production area.

Recent measurements also indicate that some additional radiation shielding will be required around the ^{15}O production system and the delivery lines. We expect to construct and install this shielding as necessary.

4. Prototype Miniature Gamma Camera

Design of the basic prototype miniature gamma camera is essentially complete. (See Figures 3 and 4.)

We have placed orders for all of the commercially supplied components with outside vendors and have recently accepted delivery of two position-sensitive photomultiplier tubes. Several small camera plate NaI scintillation crystals have also just been delivered for use in our initial experimental configuration of the camera.

Although we have not yet received components such as the support electronics modules and the tungsten alloy shield material, we do expect to be able to begin initial development of this device very soon.

If initial tests of the prototype device are successful, we would propose the construction of several additional complete units for clinical testing beginning sometime in 1988.

Since we believe it is important to demonstrate the capability of the prototype camera as soon as possible, we will be using a substantial amount of commercial support electronics systems. It is likely that the camera's ultimate performance could be improved as well as its cost lowered by developing an optimized, dedicated electronics support package. If the prototype development proceeds as planned, it is possible that we could be in a position to begin design and development of this package sometime next year.

5. High Resolution Multi-Slice PET

We believe that recent developments in component technology now make possible the construction of a multi-slice positron tomograph having spatial resolution equal to that of the highest resolution single-slice device constructed to date. We have designed a four-ring, seven-slice detector module and propose to develop several of these modules to evaluate this design.

FIGURE 3.

MINIATURE GAMMA CAMERA
FULL SIZE SCALE = 1:1

TOTAL WEIGHT = 3.035 Kg

SPATIAL RESOLUTION $\approx$ 2MM @ 140KeV

11/21/86 N.J.Y.

FIGURE 4.

IV. THE FMI CYCLOTRON AND NEW DEVICES FOR REDUCING RADIATION EXPOSURE AND/OR IMPROVING IMAGE QUALITY

D.B. Charleston

In addition to fulfilling maintenance responsibilities for the CS-15 cyclotron (used for production of radioactive materials for radiopharmaceutical research and for neutron therapy), the FMI Electronics Development Laboratory and the Machine Shop have undertaken a number of new initiatives in response to the need for new devices that would reduce radiation exposure to patients or staff, and/or improve image quality. Support for these projects has come largely from a combination of non-DOE grants, State of Illinois (through the Technology Commercialization Center), corporations, and gift funds; thus, they fall into the category of "Work for Others," which has been performed on a recharge basis.

The projects most relevant to the DOE mission include the following:

1. Remote-Controlled Semiautomated Processing System for Radiolabeling Monoclonal Antibodies

D.B. Charleston, W. Geiger, S.J. Heimsath, P.S. Prieto, B.J. Steranka and J.C. Wood

In collaboration with members of the Department of Surgery, we have designed and built a shielded remote-controlled, semiautomated processing system for radiolabeling and purifying monoclonal antibodies. The system fits within a negative-pressure hood that exhausts low levels of radon produced by the radium-224/bismuth-212 generator (which is prepared in multi-millicurie levels at Argonne National Laboratory and shipped to The University of Chicago on a biweekly schedule).

The bismuth-212 is generated as needed by eluting the cation-exchange column with hydriodic acid and collecting the solution in a shielded test tube.

Several steps are necessary in the processing procedure, which require that a number of shielded test tubes be positioned, one at a time as needed, directly under the generator elution tubing. A rotating disc ("carousel") contains 18 test tubes held in lead-shield pots, each of which is advanced by remote control to the position required for each step of the process. Accurate indexing of the 18 shielded test tubes is accomplished by means of a solid-state infrared optical-interrupter that is activated by 18 precisely located slots in the carousel rim.

There are three stations around the edge of the carousel that require precise positioning of the test tubes as they are rotated into position. The first is the elution position beneath the generator. The second position is an activity-level measuring detector that views only the solution in the test tube through a narrow collimator in the shield. The third position requires that the test tube be positioned directly under a teflon insert plug for capping. The insert plug holds two lines of teflon tubing that are lowered to the bottom of the test tube by means of a remote-controlled elevator arm. One line is connected to a remote syringe for adding the buffers, the antibody, and air for mixing. The second line is connected to a high-pressure liquid chromatography (HPLC) valve. The labeled antibody is then introduced, via the valve and a remote syringe, to an HPLC column for purification.

The entire carousel is kept at a temperature of 37° C ($\pm .10$) by means of six heaters and six temperature sensors embedded in the carousel plate. Each of the six heating zones is accurately controlled by means of a precision thermistor bridge and an integrated circuit voltage comparator. Power is applied from an external source to the heaters and comparator circuits on the rotating table by means of a center-mounted slip-ring system. Six zones of control were selected because of the nonuniform airflow around the carousel within the negative-pressure hood.

Use of this system greatly reduces the radiation exposure to staff who carry out this procedure.

2. Automated Syringe Drive System

D.B. Charleston, B.J. Steranka, R. Mintzer and A. Kittler

We have designed and built a portable, shielded, automated syringe drive system with programmable digital control for precise injection and/or aspiration of radioactive solutions.

Although there are a number of syringe drive systems on the market, there remains a need for a convenient portable, shielded system which will allow for filling a syringe at one location (where radiopharmaceuticals are prepared, for example) to be transported to another location where the radioactive solution can be administered by accurately controlled injection.

The system incorporates an operator-friendly, digital control device that is programmable by means of rotary, digitally-encoded thumb wheel switches which determine the increment of solution to be aspirated or injected. High-density sintered tungsten is used for shielding to reduce operator exposure.

The syringe, with shield, can be disengaged from the drive mechanism for easy transport to another location where it can be re-inserted into the same drive unit or into another separate drive unit at the remote station. This eliminates the need for handling the unshielded syringe, thus minimizing personnel exposure to radiation.

The unit incorporates an operator-controlled means to advance the syringe until the syringe needle or extension tubing with needle are cleared of air. This operation does not influence the preset volume selected for injection. Once cleared of air, a foot-switch signal advances the plunger a preselected amount for each injection, allowing both hands of the operator to be free to inject a mouse, for example.

The system holds standard sterile disposable syringes eliminating the need for sterilization between procedures. The syringes can be filled to a predetermined volume either by digitally controlled aspiration drive or by external pressure (from a high pressure liquid chromatograph, for example) to the preset volume required. The syringe shield is designed to hold either a 10 cc, 5 cc, or 1 cc hypodermic syringe with a 2 mm aluminum beta particle/Bremsstrahlung shield adjacent to the syringe.

An invention disclosure has been filed on this device.

3. Automated Micropipetting System

D.B. Charleston, B.J. Steranka, J. Wood and S. Heimsath

In collaboration with members of the Department of Surgery, we have designed and built a system for automated micropipetting of solutions into microwell plates with precision and rapidity.

Micropipetting is a very labor-intensive, time-consuming, manual, and tedious process involving considerable hand-eye coordination and great care to achieve accuracy. Most microwell plates contain 96 wells. Laboratory research may require thousands of wells to be filled for a single study.

The system design incorporates a digital microprocessor-controlled system which allows for automated, precise filling of wells in microwell plates. A high-contrast two line, forty character liquid crystal display (LCD) is used to assist the operator in presetting variable pipetting operation parameters by means of keyboard entry.

For example, the required parameters which would be typed in for a standard 96-well microwell plate are listed as follows: Spacing between wells in millimeters = 7; number of wells in the X direction = 8; number of wells in the Y direction = 12; size of syringe in cc = 20; volume to be injected into each well in microliters (from 10 to 400 γ) = 200 γ ; end point (total number of wells) = 96.

Once these data are entered, an initiate code is typed and the unit "homes" to the Number 1 well and automatically dispenses 200 microliters into each of the 96 wells. When finished, it returns to the Number 1 well position. The display indicates whether or not the syringe is empty. If the syringe is empty, the operator is instructed to turn a three-way valve to allow automatic aspiration from a reservoir of solution. When the syringe is full, the display instructs the operator to turn the valve to normal position, insert a new microwell plate, and initiate a restart of the cycle.

With this system, a 96-well microwell plate can be filled in less than two minutes.

The system holds sterile, disposable syringes as large as 20 cc and also will hold smaller sizes down to 1 cc with the appropriate adapters.

When used for dispensing radioactive solutions (for example, when dispensing radioisotope-tagged cells), the radiation exposure to the operator is greatly reduced.

An invention disclosure has been filed on this device.

4. Film-Cassette Support Arm for Portable X-Ray System
N.J. Yasillo, H. MacMahon and D.B. Charleston

In collaboration with members of the Department of Radiology, we have designed and built a prototype collapsible arm (attached to a portable x-ray machine) which supports the film cassette with grid in alignment with the focal spot of the x-ray tube. With this system, images of the highest quality can be obtained routinely, thus eliminating the need for repeated exposures to the patient.

A second system has been designed and is now under construction. It features an arm that can be folded for ease of transport to the patients' bedside, with electromechanical locking joints for patient safety and for ease of operation by a single technologist.

An invention disclosure has been filed on this device.

5. High-Speed Interface for Myocardial Sonicated Echocontrast Studies
S. Powsner, J. Wood, P. Prieto, D. Charleston and S. Feinstein

Quantitative measurement of regional myocardial perfusion would be invaluable for detecting and monitoring the treatment of ischemic heart disease. Sonication of albumin produces microbubbles that are smaller than red blood cells, and more stable than sonicated Renographin-76, the contrast agent commonly used in x-ray studies. We have designed and built a real-time, high-speed interface for computer acquisition of echocardiogram data from sonicated albumin. This system enables us to capture the digitized RF envelope signal *before* video processing, and is capable of operating at burst rates up to 8 MB/s. This is an essential step toward quantitation of perfusion. Manufacturers of medical imaging systems have expressed great interest in this device.

6. Positioning System for Multiple-Slit Array in Digital Radiography
P. Prieto, J. C. Wood, D.B. Charleston, Y. Kume and K. Doi

In collaboration with colleagues in Radiology (Kume and Doi), we have designed and built a device for accurately moving a multiple-slit collimator assembly (MSA), which reduces the effects of scatter in the patient as well as veiling glare in the image intensifier-TV system used in digital radiography. The MSA is driven a preset distance (0.1 to 2 mm in 100 msec.) by a stepper motor under microprocessor control. Accuracy of movement is kept within $\pm 10 \mu\text{m}$ with the aid of a shaft encoder, which eliminates line artifacts. By reducing the effects of scatter and veiling glare, image contrast is improved significantly.

7. New Acquisitions

With separate funding, we have acquired an IBM/AT compatible Houston Instruments MP51 Plotter and ALTERA Erasable Programmable Logic Device (EPLD) for use by the Electronics Development Laboratory personnel. These tools enable us to design electronics hardware from a top-down approach, using state-machine design entry or Boolean equation entry. The system verifies and minimizes the design hardware, then programs an EPROM-like I.C. with the finalized design. This I.C. supplants many MSI- and TTL-level chips, making hardware implementations efficient by the large reduction in design time, as well as chip-count reductions. The plotter is used to produce schematic documentation of the designed hardware, as well as to produce camera-ready artwork for printed circuit layout boards. Thus, this system will enable us to undertake more complex circuit designs, utilizing state-of-the-art components.

V. METHODOLOGY FOR QUANTITATIVE EVALUATION OF DIAGNOSTIC PERFORMANCE

C.E. Metz

Four of our computer programs (ROCFIT, INDROC, CORROC, and ROCPWR) are now well-known among investigators who employ ROC analysis in medical applications. During the past year, we mailed out copies of these programs and our new LABROC1 program (described below) on magnetic tape--together with printed examples of output--in response to requests from investigators at 18 institutions. The first four of these programs had been sent to 35 other institutions during the four preceeding years.

Also during the past year, we completed modification of our ROCFIT program, which employs maximum-likelihood estimation to fit a binormal ROC curve to *categorical* confidence-rating data, so that it can be used with the *continuously-distributed* data that are generated by inherently quantitative diagnostic tests. The new program, which we call "LABROC1," is not theoretically optimal for continuously-distributed data, but it represents our initial step toward providing a reliable and practically useful approach to the problem of evaluating the performance of inherently quantitative diagnostic tests in terms of ROC analysis. We have evaluated LABROC1 by applying it to computer-simulated input data (for which the true parameter values are known) and found it to be highly reliable and accurate.

In addition, we have nearly completed the development and testing of two other new programs. One, called "LABROC4," addresses the same task as LABROC1 but takes a more sophisticated approach that avoids categorization of the continuously-distributed data; instead, LABROC4 works directly with the ranks of the individual results. Preliminary evaluation of LABROC4 with computer-simulated input data (for which the true parameter values of the two ROCs are known) has shown it to be highly reliable and accurate. The other new program, called "CLABROC," is a generalization of LABROC1 that estimates the *correlation* between the results of continuously-distributed tests and then determines the statistical significance of apparent differences between the two tests' ROC curves. Evaluation of CLABROC with computer-simulated input data is currently underway.

In collateral efforts, we contributed methodology developed in this project to several clinical projects that received their primary support from other sources; we published in Investigative Radiology a major tutorial review article on ROC analysis in medical imaging; and we presented six invited lectures on ROC analysis at various universities and national meetings.

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