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I am submitting herewith a dissertation written by Jonathan Paul Dyke entitled "Dosimetry and Stability Studies of the Boron Neutron Capture Therapy Agent F-BPA-Fr Using PET and MRI." I have examined the final copy of the dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Engineering Science.

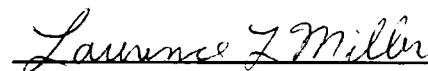


Gary T. Smith, M.D., Major Professor

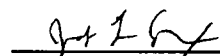
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Dosimetry and Stability Studies of the Boron Neutron Capture Therapy Agent F-BPA-Fr Using PET and MRI

A Dissertation
Presented for the
Degree of Doctor of Philosophy
The University of Tennessee, Knoxville

Jonathan Paul Dyke
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First and foremost, I give credit to God for giving me the ability and opportunity to reach this goal and for instilling in me the hope and desire to succeed.

Gary Smith sat down with me one afternoon soon after I had passed my candidacy exams and was looking ahead to my research. He said that he wanted me to follow the path of Albert Einstein and to know the joy of discovery, the victory of solving a problem and to treat this portion of my career as an opportunity to "push the envelope". It is this attitude that I have strived to maintain, and hope to have met in some small degree. For this I am grateful.

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ABSTRACT

The treatment of deep seated brain tumors such as Glioblastoma Multiforme has been unsuccessful for many patients. Surgical debulking, chemotherapy and standard radiotherapy have met with limited success. Boron Neutron Capture Therapy offers a binary mode brachytherapy based on the following capture reaction that may provide an innovative alternative to standard forms of treatment:



Boron is chemically attached to a tumor binding compound creating a non-toxic neutron absorber. A dose of epithermal neutrons provides the catalyst to produce the Lithium and alpha particles which destroy any tissue within a length of one cell diameter from the boron compound.

This dissertation uses ^{19}F -MRI and ^{18}F -PET to provide answers to the localization and biodistribution questions that arise in such a treatment modality. Practical patient dosimetry and actual treatment planning using the PET data is also examined. Finally, theoretical work done in the areas of compartmental modelling dealing with pharmacokinetic uptake of the PET radiotracer and dose analysis in microdosimetry is also presented.

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Chapter I

Introduction

Problem Definition

Boron neutron capture therapy is based on the delivery of ^{10}B to individual tumor cells followed by a single or fractionated exposure to a neutron source. Boron has a high nuclear cross section for absorption of low energy neutrons. A fission reaction takes place as the boron compound captures a neutron which then forms ^{11}B . This unstable isotope then decays into a lithium ion (^7Li) and an alpha particle or helium nucleus (^4He). These decay products carry a total energy of 2.79 MeV between the two particles as shown in Figure 1 below.

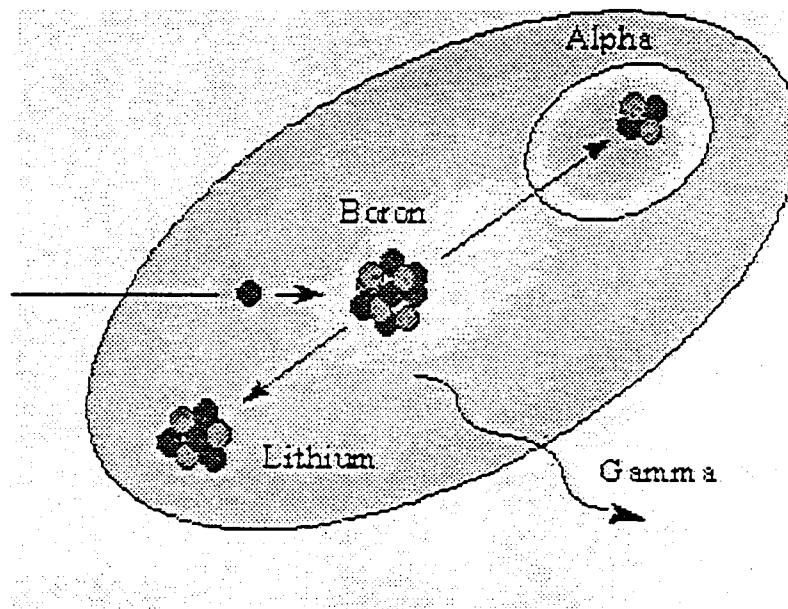


Figure 1. Boron Neutron Capture Therapy Nuclear Reaction

It is this energy that is deposited in the tissue and hopefully at the nucleus of the tumor cell. The ions travel approximately 10 microns or one cell diameter from the point of neutron capture. Given the high mass and energy of the ions, they primarily travel in a linear fashion causing highly ionizing events at closely spaced intervals along their track. This reaction may then break the DNA in the tumor cell nucleus preventing further proliferation of the cell.

The two main difficulties encountered in the 1954 BNCT clinical trials were lack of neutron beam purity and an inability to localize the boron compound at the tumor site [21]. The beam from a nuclear reactor is composed of gamma rays, fast, epithermal and thermal neutrons. High energy, fast neutrons induce tissue damage, due to direct collisions and interactions. Fast neutrons also do not become captured by the boron at the tumor site given the boron reaction cross section in BNCT is inversely proportional to the velocity of the neutron. A flux of epithermal neutrons is then needed to increase capture reactions and reduce surface irradiation. Epithermal neutrons are attenuated rapidly by diffuse interaction in the tissue. In order to allow an adequate fluence of epithermal neutrons to pass through the cranium and into the tumor, which may be as deep as 6 cm as permitted by the current BNL protocol, a nuclear reactor must currently be used to produce the neutrons as shown in Figure 2 in a cross section of the Brookhaven Medical Research Reactor.

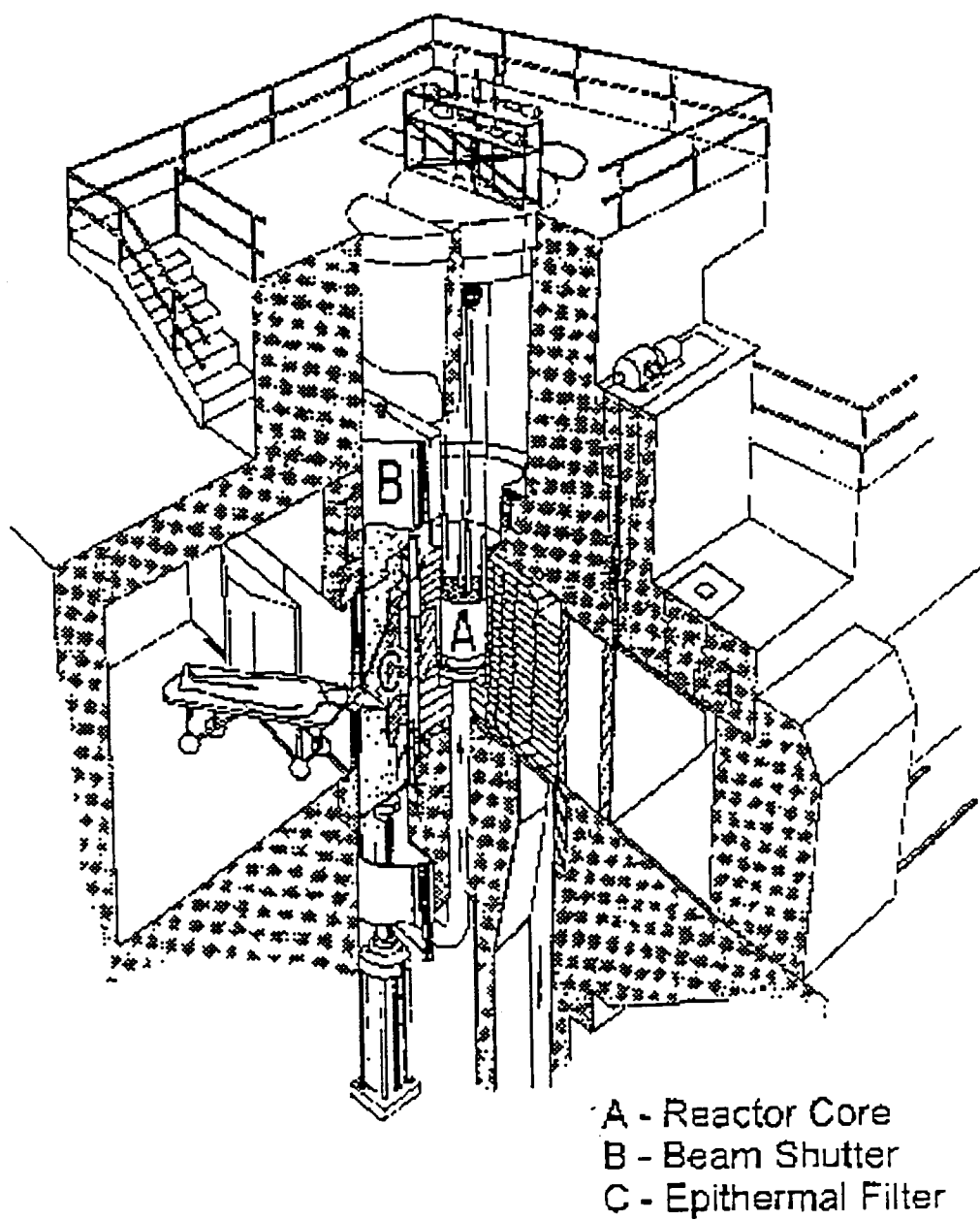


Figure 2. Brookhaven Medical Research Reactor, Upton, NY.

Filters placed between the patient and the reactor allow primarily only epithermal neutrons of energies at 10keV to pass through as shown in Figure 2. Currently, beam purity and energy distribution of the neutron flux that is used in BNCT at BNL is of very high quality. Unlike earlier studies, fast neutron irradiation is minimized and slow neutron irradiation is maximized.

Another area of concern arises from the fact that capture reactions can occur with other elements that naturally occur in the body. Although the boron reaction has the highest cross section in a BNCT therapy situation, the concentration of nitrogen and hydrogen in the body is very high. Figure 3 contains a summary of other possible reactions that might occur within the body [46].

Expected Reactions Caused by Thermal Neutrons in Tissue					
Element	Natural Abundance (%)	Reaction	Thermal neutron cross section		Released energy per reaction (MeV)
			Microscopic σ (barn) ^a	Macroscopic Σ (cm ⁻¹) ^b	
¹ H	99.985	¹ H(n, γ) ² H	0.332	1.99×10^{-2}	2.22
² H	0.0145	² H(n, γ) ³ H	0.0005	4.34×10^{-9}	6.25
¹² C	98.892	¹² C(n, γ) ¹³ C	0.0034	2.52×10^{-3}	4.95
¹³ C	1.11	¹³ C(n, γ) ¹⁴ C	0.0009	7.43×10^{-4}	3.15
¹⁴ N	99.635	¹⁴ N(n,p) ¹⁴ C	1.81	2.70×10^{-3}	0.63
¹⁵ N	0.365	¹⁵ N(n, γ) ¹⁶ N	0.000024	1.31×10^{-10}	2.48
¹⁶ O	99.759	¹⁶ O(n, γ) ¹⁷ O	0.00013	4.34×10^{-4}	4.14
¹⁷ O	0.037	¹⁷ O(n, α) ¹⁴ C	0.24	2.39×10^{-4}	1.82
¹⁸ O	0.204	¹⁸ O(n, γ) ¹⁹ O	0.00021	1.15×10^{-4}	3.95
¹⁰ B	19.61		3837		2.79
		¹⁰ B(n, α) ⁷ Li [*]	(93.7%) ^c	4.33×10^{-3}	($\gamma = 0.473$)
		¹⁰ B(n, α) ⁷ Li	(6.3%)	2.91×10^{-4}	(no γ)

Figure 3. Expected Reactions Caused by Thermal Neutrons in Tissue

Although the neutron beam itself is no longer a factor in patient safety, tumor specificity of the ^{10}B carrier continues to present difficulties. Given the binary products of the neutron capture reaction by the boron compound travel approximately one cell diameter from the capture point, effective localization is extremely important. This was the primary difficulty encountered in the initial BNCT studies where non-specific boron compounds were injected into patients. The resulting ratio of boron in tumor to that of boron in healthy tissue was very close to unity. Given the non-preferential uptake of boron throughout the body, healthy tissue was destroyed. After the failure of the initial trials, research in this area was abandoned for years. Dr. T. Hatanaka and others slowly began to utilize a sulfhydryl borane reagent, sodium borocaptate. At the present time, the compound of choice is L-borono-phenylalanine-fructose which gives an approximate tumor to brain ratio of 3:1 and it is used in clinical trials around the world. The search for other boronated compounds that will provide higher tumor specificity is being conducted in the Department of Chemistry at UTK by Dr. George Kabalka and at institutions throughout the world [40-43]. A number of compounds show promise in providing a BNCT agent that might yield a 10:1 ratio thereby increasing the overall effectiveness of treatment.

Current research in the area of dosimetry and patient specific radiation treatment planning as well as confirmation of boron localization in-vivo then become the focus of this dissertation. The process that takes a new BNCT agent into the

clinical setting is an arduous one. Initially, many animal studies must be carried out in order to determine levels of toxicity, solubility and localization. Standard practice is to sacrifice the animals at specified intervals after administration of the ^{10}B in order to determine an accurate concentration in the tissue. This then gives a time activity curve in the mouse or rat that may or may not directly translate to human studies due to differences in the blood brain barrier and pharmacokinetic uptake of the drug on a much larger scale. In the current BNL clinical trials during debulking surgery, tissue samples are taken in minute amounts at possibly two time points. These samples are then analyzed using direct atomic emission spectroscopy to provide the quantitative concentration levels. Measurements of boron concentration in the blood are easily taken and an accurate time activity curve, TAC, is provided using direct venous samples.

The amount of information known on each patient is then solely derived from two closely spaced time points gained from invasive tissue samples of the deep seated brain tumor itself. This procedure is extremely invasive and provides a very minimal amount of data in exchange for the risks associated with intra-cranial biopsy such as infection and non-uniform sampling. The need for more accurate estimation of boron concentration in both the spatial and time domains is imperative to accurate and predictive treatment planning.

Standard radiotherapy involves determining the location of the tumor including the

shape and volume in-vivo. Boron neutron capture therapy is dependent on this information as well as knowledge of the specific concentration of the boron compound. To be effective, it has been estimated that at least 10^9 boron atoms must concentrate at each tumor cell. Assumptions made using biopsy data include the presumption that the distribution of boron throughout the entire tumor region is homogeneous. This is known not to be true based on data in numerous pathology articles describing the composition and heterogeneity of cells found in typical glioblastoma multiform tumors [8,54]. With existing code, this assumption thus leads to inaccurate dose contours for treatment planning in BNCT. The amount of boron typically found in a tumor, between 30-40 ppm, does not provide a significant thermal flux depression of the neutron beam. An inhomogeneous amount of boron can significantly affect that component of dose specifically from the boron capture reaction. It is this inhomogeneity, that truly cannot be known by a single tissue biopsy and significantly affects the candidacy, treatment planning and efficacy of BNCT. It is this specific problem of compound localization as it applies specifically to fluoro-borono-phenylalanine-fructose that this dissertation addresses.

Methods

Two problems must now be addressed: that of in-vivo localization of the boron agent, and accurate dosimetry planning assuming inhomogeneous boron distribution. In general, the solution to the first problem may be found in the field

of medical imaging. A brief introduction to Magnetic Resonance Imaging, MRI, and Positron Emission Tomography, PET, will be given. Each of these modalities offers distinct tools that will be useful in solving the localization problem. The dosimetry problem can be addressed using a statistical approach called the Monte Carlo method.

The Monte Carlo method had a very interesting early application in the 18th century that will explain its usefulness. A French historian and mathematician by the name of Georges Louis Leclerc Comte de Buffon in 1768 performed an experiment in his house. He would take stick loaves of French bread of length L , throw them over his shoulder and see if they crossed the lines on his tile floor which had a spacing of D . For L less than or equal D , he obtained that the probability the loaf intersects the tile is given by:

$$P = 2 L / (\pi D)$$

If we drop the loaf N times and count R intersections we obtain:

$$P = R / N; \pi = 2 L N / (R D)$$

thereby obtaining an estimate for π through statistical methods.

In general, this method was developed for standard scientific use around 1944 named after the city in Monaco because of the association between the method and the roulette gambling wheel. This method uses random number generation to provide approximate solutions to problems through statistical sampling. The key

asset of this method is the fact that the absolute error of the estimate decreases as $N^{-1/2}$, where N is the number of samples taken. Basically, if you throw enough loaves of bread over your shoulder, you can estimate π !

The real use of the Monte Carlo method relating to neutrons came in 1948 out of experiments on the atomic bomb during the second world war. Fermi, Metropolis and Ulam obtained a solution of the Schroedinger equation using this method. With an increasing number of random samples, the solution to a variety of mathematical problems, such as neutron transport and dosimetry may be solved with statistical accuracy and convergence. The Monte Carlo method is employed in both the macrodosimetry and microdosimetry simulations. The macrodosimetry code uses the method to simulate the flux of neutrons incident on the patient, thereby yielding energy deposition per pixel. The microdosimetry code uses the method to simulate a neutron flux incident on a cell structure of specific design. This method provides a mathematical tool that may then be applied in a specific manner to the current research areas in BNCT. Monte Carlo history may be obtained at: <http://www.geocities.com/CollegePark/Quad/2435/>.

The problem of in-vivo localization is also not trivial and must be examined using current technology in medical imaging. One modality that provides a possible solution to localization is Magnetic Resonance Imaging. Nuclear Magnetic Resonance was developed in 1946 by Bloch and Purcell which allowed the

reception of resonant frequencies of specific chemical shifts as governed by the equations in Figure 4.

These equations predict the exact behavior of the magnetic dipole while in the presence of a magnetic field. Knowing this, the received signal intensity may be related to the inherent relaxation times of the nuclei and to a specific frequency shift. Fourier transformation of the received frequency spectrum as emitted from the dipole and received in the coil was then performed. This allowed identification of a chemical compound as well as an estimate of the relative concentration. 1954 brought about the introduction of the spin echo pulse sequence by Carr and Purcell. This was the forerunner of all modern day imaging pulse sequences as shown in Figure 5.

This sequence allowed a maximum amount of signal to be acquired at the "echo time". This point occurred when the dipoles were "in phase" in the transverse plane and combined each of their signals to produce a single echo. It was this sequence that also allowed "weighting" of images towards either T_1 or T_2 relaxation.

It was not until 1973, when Lauterbur implemented gradients, that the concept of producing an image became a reality. The gradients produced a linearly increasing magnetic field in a specific direction during the acquisition. The

- $dM/dt = \gamma M \times B$
- $M_x = \gamma M_y B_0 + \gamma M_z B_1 \sin \omega t - M_x/T_2$
- $M_y = -\gamma M_x B_0 + \gamma M_z B_1 \cos \omega t - M_y/T_2$
- $M_z = -\gamma M_x B_1 \sin \omega t - \gamma M_y B_1 \cos \omega t - (M_z - M_0)/T_1$

B_0 = Main Magnetic Field along z-axis

B_1 = Applied RF

T_1 = Spin-Lattice Relaxation Time - Longitudinal

T_2 = Spin-Spin Relaxation Time - Transverse

Figure 4. MRI Bloch Equations Giving Magnetization over Time

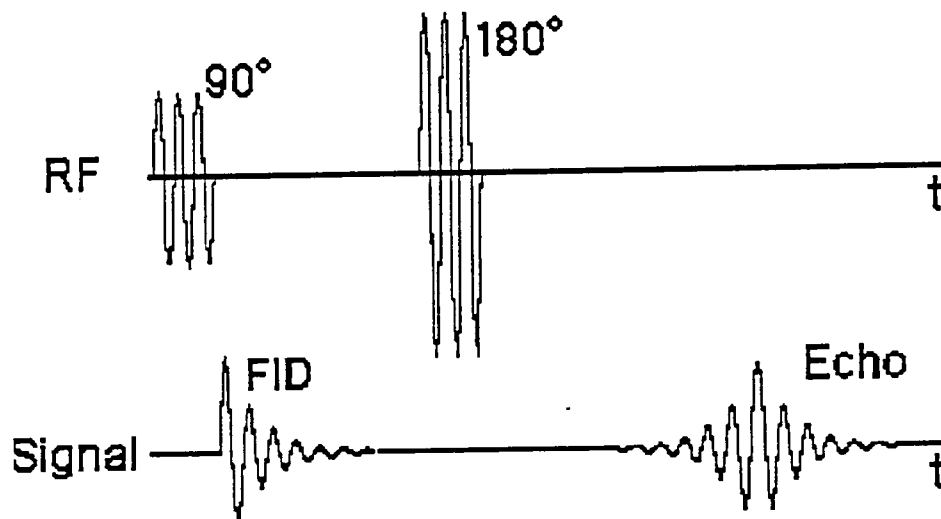


Figure 5. Carr-Purcell Spin Echo Sequence - 1954

magnetic dipoles precessed in accordance with the Larmor equation:

$$\omega = \gamma B$$

where the precessional frequency of the magnetic dipole is directly related to the strength of the magnetic field. Therefore, when Lauterbur applied a linearly increasing field, atoms in different positions along that field emitted signals at slightly different frequencies. This was the missing step needed to determine spatial positioning within a volume. The signal received by Bloch and Purcell in 1946 came from the entire sample volume. Soon after in 1977, Damadian produced the first clinical MRI image. The first application of MRI to boron neutron capture therapy was the development of boron-11 MRI by Kabalka and his co-workers in 1988 [40]. It is with MRI that in-vivo localization of the F-BPA-Fr will become possible. Use of imaging and spectroscopy will provide valuable localization of specific nuclei within the BNCT compound.

The next modality that will be used as a tool to confirm localization in-vivo is Positron Emission Tomography, PET. The first non-invasive technique to image the body came from Wilhelm Roentgen in 1896. Through his discovery of x-rays he was able to produce a negative photograph showing structures inside the body. The discovery of the positron in 1929 by Dirac was the theoretical foundation for the positron emitters used as radiotracers in PET today. That same year, Lawrence invented the cyclotron which became the forerunner of those used in hospitals today for the production of radioisotopes. Experimental evidence in

a cloud chamber of the positron by Anderson in 1931 proved that "anti-matter" did exist. It was also known that when a positron came in contact with an electron that annihilation occurred producing two 511 keV photons emitted at 180 degrees to each other. This is depicted below in Figure 6. from UCLA's "Let's Play PET" (copyright 1992,1993). Given photons are massless, the combination of matter with antimatter produced pure energy. These photons may then be detected by a ring of coincidence detectors composed of a scintillation crystal and photomultiplier tubes. The data that is obtained, allows the position of the annihilation to be limited to the path of the photons in one dimension.

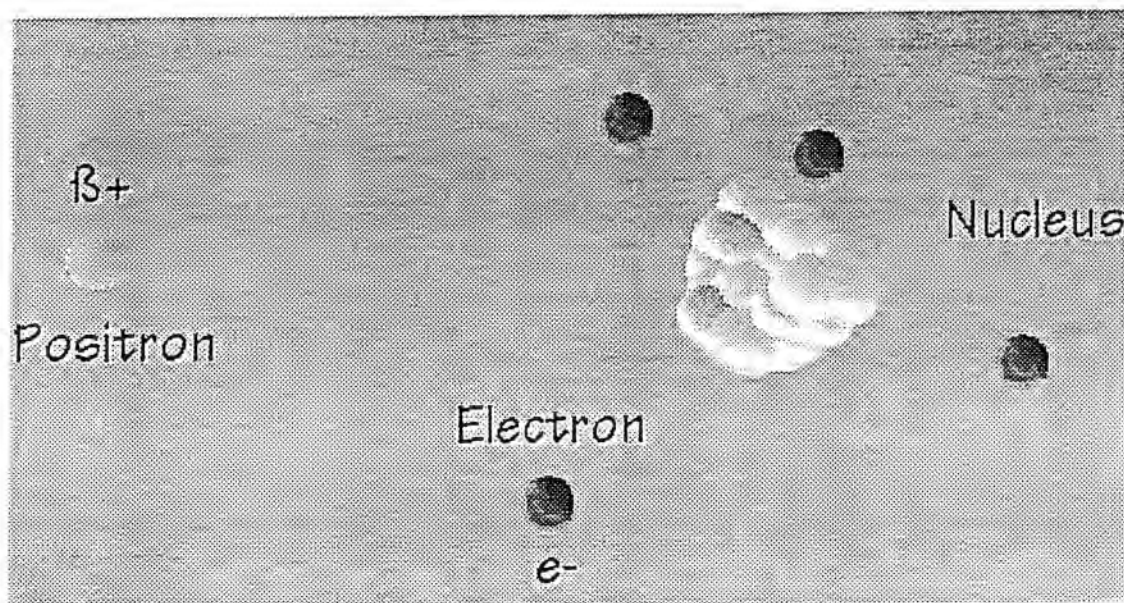


Figure 6. Depiction of Atomic Structure Prior to Annihilation

The creation of an image from a large number of coincidences is called "back-projection" and was derived in 1917 by Radon. The process involves normalization, back projection, decay correction, scatter correction, and filtering to actually produce a standard PET image. It is this same method that is employed in producing an image from a CT scanner as well. Each coincidence detection in a PET scan comes from a pair of detectors at a specific angle. A spectrum is received at each angle and is then sequentially added across a grid to produce an image according to the equation in Figure 7.

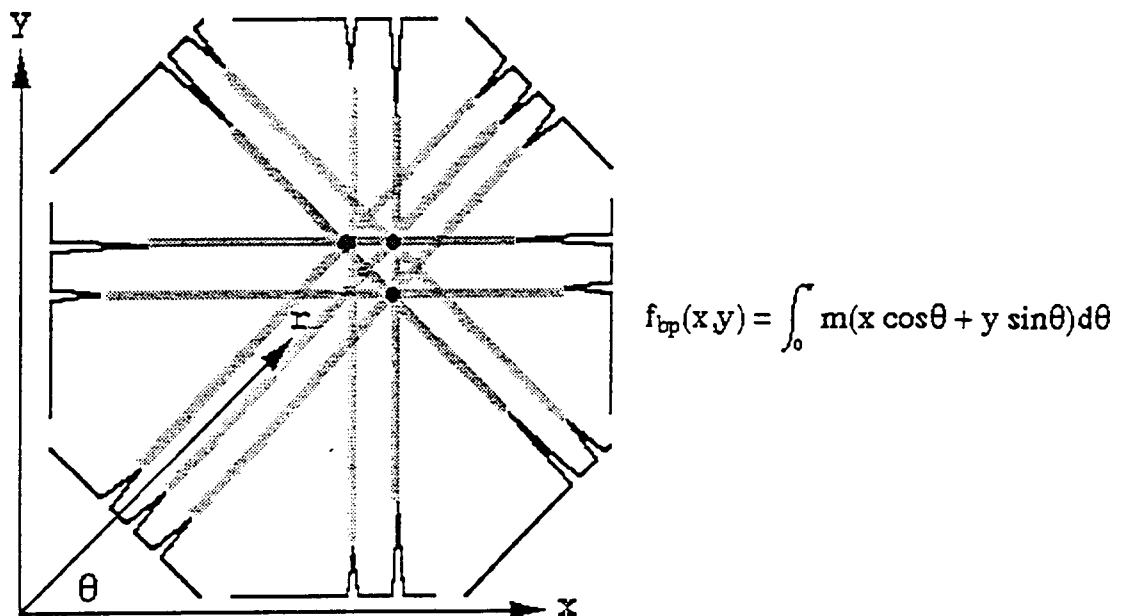


Figure 7. Back-Projection Governing Equation and Process Description

Using this technology, the first clinical PET scanner was produced in 1975 with the name of PET III (EG&G Ortec, Oak Ridge,TN.) which was a precursor to our current ECAT 931 scanner developed in 1985. The images obtained are directly related to the distribution of radiotracer in the object. Given the organ specificity of the radioactive tracer that is administered, the image is also a measure of the metabolic uptake of that tracer in that specific region. Relating the number of disintegrations per second to the number of tracer atoms, allows a calculation of concentration in the region at a specific time point. This is directly applicable to the problem in BNCT where a specific concentration of boron is to be determined at a specific time point. A time activity curve or TAC may then be produced which will allow the physicist or clinician to view the uptake kinetics in a specific region over time. PET was first applied to BNCT by the Japanese and in the US by Kabalka and his colleagues [33,42].

The field of compartmental modelling will also be used as a general methodology to gain quantitative information on biochemical parameters from the PET scan itself. Knowing that each pixel in the final image represents a TAC, this information can be fit with a specific defined physiological model. The tracer itself, in order to be accurately modelled, must fulfill certain requirements. It must be metabolized in a manner identical to the compound it is attached to and should not alter the process being studied. Having a high activity and a primary branching ratio are also requirements for accurate modelling to occur. Distribution volumes

can then be defined that simulate compartments in the body itself whether on a cellular level or on a much larger scale.

Results

The macrodosimetry was accomplished using Bnct_Rtpe, the Boron Neutron Capture Therapy Radiation Treatment Planning Environment developed by INEEL/MSU [62]. This software package allows input of raw image data from any modality, but generally from MRI scans. Utilizing our PET data using ^{18}F -BPA-Fr as a tracer allowed us to accurately describe the nonhomogeneous distribution of the compound. This permitted the actual metabolic uptake of the tumor itself to be used to define the physical boundaries needed for the Monte Carlo neutron transport calculation. A much more accurate region of interest, ROI, is defined on the tumor allowing more accurate treatment planning to be accomplished using identical software to that at BNL.

Not only is boundary definition improved but the amount of boron at each pixel is now known. The assumption of homogeneous distribution throughout the tumor and actually through the whole image can now be abandoned. Each pixel gives a specific concentration of boron that is then used to compute the boron dose contours. These contours show lines of similar dose from the boron capture reaction specifically. No assumptions are made as to the boron distribution and each pixel provides accurate levels that alter the contours. The result is that better

defined contours are placed on actual areas of metabolic uptake. The dose to the tumor is also more accurately displayed given the contours, provided by the PET scan, are focused on the center of metabolic uptake and not the anatomical center as defined in an MRI or CT scan. This is a significant result and gives striking dose contours in comparison with standard curves gained through MR scans. Voxel based concentration and density definition is being pursued at INEEL as a next phase software step to the Bnct_rtp package.

The microdosimetry simulations were performed using the BCT, Boron Capture Therapy code written by David Charlton at Concordia University [13]. This code has yielded results on a cellular level that, within statistical deviance, are identical to those on a macroscopic scale as reported by Brookhaven in their clinical trials. The program uses a Monte Carlo simulation to randomly choose neutrons of a specific velocity and angle to traverse a defined geometrical system. This system has been simulated using spheres and ellipses to model actual cell colonies of Glioblastoma Multiforme. Continuing research described in the pathology literature has shed light on the actual growth patterns of the tumor yielding accurate estimates of cell and nuclear size as well as approximate spacing and absorbed boron concentrations. This code also allows for survival curves to be estimated based on the packing of cells in the volume and the amount of boron present in each of the cellular compartments. Survival curves obtained are similar to those in the literature and are a good first estimate to use for expected experimental

results [14,63].

The area of microdosimetry analysis is one that has much potential for new research. Areas of interest include more accurate cell structure simulations, as well as more random placements of "quiescent" or non-metabolically active tumor cells. Little has been done to describe the accurate distribution of healthy cells, that take up the boron to a lesser degree as compared to that among the proliferating tumor cells. It has been shown in the pathology literature that it is these quiescent cells that often cause regrowth at a tumor site given they are resistant to standard radiotherapy , surgery and even BNCT to some degree. Assignment of specific boron concentrations to different cells based on nuclear volume fraction is an area of research that has been explored. The assumption, as on a macroscopic level, that the boron distribution is homogeneous is definitely false. Correction of this assumption will lead to more accurate microdosimetric studies that will provide confirmatory results on toxicity experiments as well as macroscopic trials.

The area of medical imaging as it relates to MRI was pursued in the region of ^{19}F imaging and spectroscopy. Given the fact that BPA can be fluorinated, both boron and fluorine can be used for imaging studies. Boron is inherently difficult to image due to the extremely short transverse relaxation time in-vivo as well as the quadrupole moment of the nuclei which causes broadening of the signal itself.

Fluorine was chosen because of a sensitivity and resonant frequency similar to hydrogen as well as the opportunity to provide similar results to those gained in PET using the ^{18}F analog of the BPA-Fr compound. A spectroscopy system was developed that yields good results in-vivo. Localization of the compound through imaging is still being pursued as the signal to noise ratio of the system improves.

Images have been produced at concentrations higher to those found in-vivo and pulse sequences have been modified to help correct this difficulty. Overall, the possibility of providing ^{19}F scans to corroborate those of the PET scans will prove to be extremely useful. Images could be taken rapidly to simulate a time activity curve although accurate concentration levels of the fluorine in-vivo would be difficult due to inherent relations between not only signal intensity and concentration but also that of relaxation times. The ability to use MRI would also enable overlay of the standard proton scans to confirm anatomical location which is unavailable in standard PET scans.

PET scans were performed using ^{18}F -BPA-Fr on patients prior to debulking surgery, prior to BNCT and post-BNCT. Scans were used as input for the macrodosimetry code as well as to compartmental models and even as estimates to microdosimetry calculations. Knowing the activity in each scan prior to and post-BNCT allowed region of interest comparison of tumor uptake. Ratios were taken and normalized to the area of the ROI in order to provide an estimate of a kill ratio for that region. This is a process by which PET may provide useful non-

invasive efficacy calculations to the clinician following patient treatment. PET scans, as stated before, were also used to input the heterogeneity factor of boron concentration on a macroscopic level to the treatment planning code.

Compartmental modelling was done on data obtained from the tissue and blood time activity curves. Using graphical, analytical and computational means the theoretical compartmental data was fit to that of the true activity as measured in the PET scan. Actual biochemical flow rates were computed between the intracellular and extracellular compartments in the tissue. Models were explored that also allowed the blood pool to be divided into diffusible and non-diffusible regions identical to those of plasma vs. proteins and red blood cells. Data was confirmed by actual well counter measurements on venous samples from our latest BPA patient. Compartmental modelling also provided a predictive tool to be used for candidacy concerns in patient admittance to the BNCT protocol. A ratio of time activity curves from the tumor to that of normal brain yielded a relative concentration plot. The point on this plot where a peak or plateau was reached is the point of optimal irradiation time after infusion. If no appreciable peak or level were found, this might also be a factor in exclusion of the patient from the trial prior to actual neutron irradiation.

One final result from the compartmental modelling relates the dose volume given in the PET scan to that given at BNL. The PET reagent is contained in a bolus

dose of 5-10 ml. BNL utilizes 250 mg/kg in order to provide sufficient concentration at the tumor while eliminating toxicity effects. The conversion of PET data to that produced during BNCT is accomplished through the technique of convolution integrals. Effectively, a series of bolus injections administered to the length of the infusion time, typically on the order of 2 hours, is summed to produce an expected activity curve based upon a continuous infusion input function. In this manner the low concentration of boron administered during the PET scan may be mathematically translated to the dose actually expected during treatment. This mathematical simulation corresponds well with the actual blood data taken during and after treatment.

Conclusions

Results obtained using various software packages allow simulations of the macro and microdosimetry of the BNCT problem and produce results yielding information on the resulting treatment planning assuming inhomogeneity in boron distribution. This new treatment planning will provide more accurate results when applied to actual patient administrations. Combined with the qualitative information from the PET scans showing general distribution of the compound in-vivo, a more accurate clinical tool has been produced. The quantitative data obtained from the PET scans through compartmental modelling have provided a research tool that yields biochemical transfer rates and uptake curves. The data are also useful as a predictive tool to the clinician to evaluate efficacy of treatment on a per patient

basis. Other research within this area will allow for construction of parametric images showing uptake in specific compartments of the model such as the intracellular or nuclear space.

Chapter II

^{19}F Magnetic Resonance Imaging

Introduction

The technique of nuclear magnetic resonance was conceived independently by Bloch and Purcell in 1946 for which they shared the Nobel Prize in Physics. Their discovery of 1D NMR allowed the elucidation of chemical structures and measurements of concentrations in vitro. In 1954, Carr and Purcell announced the formulation of the spin echo pulse sequence. This sequence is the father of all MRI protocols and opened the door for imaging to occur. One final piece of the puzzle was missing in order to allow an image to appear from a 1D spectrum. The discovery of gradients by Lauterbur in 1974 produced the ability to assign a spatial position to a specific NMR frequency. Soon after, in 1977, Damadian performed the first wide bore clinical proton density image on a patient.

Prior to 1981, only proton density images had been taken. In the field of chemistry, a 1D spectrum of ^{13}C , ^{31}P , ^{19}F , ^{11}B or a myriad of other nuclei was common. There are three inherent reasons that non-proton nuclei had limited use in clinical applications. All nuclei are less sensitive than hydrogen in an NMR

experiment which makes them more difficult to detect. To be successfully imaged, nuclei other than hydrogen require a stronger magnetic field as well as increased limits of detection. Quadrupole moments of various nuclei broaden the width of the primary signal, which also limits resolution. Lastly, the ability to perform chemical shift imaging on a single resonance, to allow metabolite studies, was hindered due to artifacts and blurring from other peaks.

Although the first clinical ^1H scan of a patient came in 1973, it was not until 1981 that the first ^{31}P clinical image of a patient was produced [75]. The ATP levels in the brain were measured in-vivo in a non-invasive manner by Ross. Fluorine imaging followed soon after with the scanning of chemotherapy patients using 5-Fluoro-Uracil, a chemotherapy agent, in 1984 by Stevens. Nakada, in 1987, produced the first animal studies of ^{19}F -Fluoro-Deoxy-Glucose [57-61].

Problem Definition

The treatment of deep seated tumors has been unsuccessful for many patients. 7000 new patients each year develop a Glioblastoma Multiforme which cannot be eradicated by chemotherapy, radiation or surgery [20]. Deep seated tumors that have metastasized often cannot be treated by surgery. Normal brain tissue has a very high tolerance to the levels of radiation used in treatment therapy but cognitive affects have been found. Patients who are diagnosed with a malignant glioma (WHO III/IV) have an average survival time of approximately 12 months.

BNCT is a treatment modality that works upon the following nuclear reaction:



Boron is chemically attached to a tumor binding compound creating a non-toxic neutron absorber. A 40-50 minute dose of epithermal neutrons is then applied to the patient. The boron-10 capture reaction generates the lethal products which kill all tissue within 10um of the atom [20]. Since the neutrons pass through healthy tissue, only the cancerous region that contains the boron agent is destroyed. 4-Borono-2-fluoro-L-phenylalanine-fructose, developed at UTK, it is the primary imaging agent in this study.

Detection of the Borono-Phenylalanine-Fructose at UTMCK may be achieved using two separate imaging frequencies. The GE Signa scanner is fitted with a ^{11}B imaging system. The standard dose of BPA given at BNL is 250 mg/kg body weight in a 2 hour i.v. infusion. Toxicity studies must be done on rats that have implanted tumors from BNL in order to increase this level of dosage for BPA-F. Boron has only 16.5% the sensitivity of proton density images. A difficulty inherently related to boron is the extremely short T_2 relaxation time that is less than 100 ms. This implies, that if the scans are not taken very rapidly, the signal will undergo spin diffusion and will be lost prior to detection. More averages, offline reconstruction methods, as well as faster pulse sequences have been explored to overcome this.

Fluorine has a sensitivity second only to proton at 83% which is 5 times that of ^{11}B . Resolution for a standard proton scan is on the order of 1mm and is dependent on the FOV, sweep width, matrix size and other factors. Similar resolution may be expected with ^{19}F imaging due to its high sensitivity. At present, our ^{19}F imaging system has a minimum limit of detection for spectroscopy below 40ppm and below 250mM for imaging.

MRI scans could also provide chemical shift imaging which would lead to enhanced pharmacokinetic information and would provide answers about possible dissociation of the compound in-vivo. This data would also lead to a better knowledge about metabolic uptake as provided by our compartmental models.

^{19}F -BPA-Fr will be the primary compound imaged in this dissertation due to the following reasons. The ^{18}F analog is a new imaging agent developed by the UT Department of Chemistry. Few studies have been performed on ^{19}F -BPA-Fr using MRI. Secondly, a protocol for human studies has been developed for PET using this agent and funded by DOE. MRI on this compound will begin with animal studies that will be needed to provide a base for LD37 toxicity studies. Such studies would lend themselves to obtaining a small animal protocol for beginning a colony. The applications for research on F-BPA-Fr are real and available and may provide a viable source of successful cancer treatment options.

Once the ^{19}F imaging system is perfected, other imaging agents with an extremely wide range of applications may also be explored. The following four compounds will be mentioned briefly and will hopefully be explored as the opportunities arise.

Perfluorocarbons, PFC's, have been used as accepted blood substitutes for over a decade [18,36,49,52,53,55,66,68,]. Their high level of oxygen solubility has allowed them to deliver O_2 to patients with respiratory difficulties. They contain no hydrogen atoms and are completely inert and non-toxic in even the large amounts needed for MRI imaging (14.7g/kg LD50). Their excretion from the body is accomplished primarily through expiration from the lungs and may remain in-vivo for days and even weeks. Using a calibration curve based on T_1 measurements from an ROI, the actual oxygen concentration in-vivo for various organs may be determined as well as determination of tumor hypoxia [37,55]. The long intravasculature persistence also allows for arterial imaging needed in patients of infarction, stroke or tumors [75]. This class of imaging agents has been approved for human use and provides a possibility for another immediate application of ^{19}F imaging.

5-Fluoro-Uracil has been used from the inception of fluorine imaging to provide a patient specific method of dose prescription for chemotherapy treatment. Administration of 5FU is a difficult procedure in chemotherapy due to a number of unknown factors. Presently, no compartmental models have been proposed for

the metabolic uptake of this drug in-vivo but chemical shift imaging on its metabolic products has been done [6,27]. Tumor response varies widely to 5FU and as yet, cannot be predicted. A minimum dose must be given and then increased if needed. A standard dose used in MRI is 20 mg/kg body weight [6,27]. Assessment of 5FU modulation due to administration of other chemotherapy drugs is also unknown. ^{19}F imaging has been able to provide answers to the above questions. UTMCK provides 5FU chemotherapy and therefore has the patient base to begin a clinical study using this imaging agent.

Imaging of 2-Fluoro-Deoxy-Glucose and 3-FDG with MRI has been limited to animal studies due to questions of toxicity. FDA approval has been given for ^{18}F -FDG administration in certain PET studies. LD50 values in rats for 2-FDG and 3-FDG respectively are 300 mg/kg, 5 g/kg [57-61]. Animal studies will allow further confirmation of a minimum level of detection and an LD50. Goals of such studies would be similar to those in standard PET scans. Metabolic uptake of FDG in tumors would be accomplished as well as the opportunity for chemical shift imaging [58,61]. The human body has three known pathways for sugar metabolism. Shifting the resonance frequency and using a saturation pulse has been successful in providing images of a specific metabolic product. This factor as well as increased tumor localization with coregistered proton scans provides this imaging agent with many future possibilities in MRI.

A problem in modern psychotherapy arises in administration of psychotropic drugs needed to treat the symptoms of mental illnesses such as depression or schizophrenia. Similar to 5FU, patient response to various drugs is not well defined and must currently be estimated. Fluphenazine, and Fluoxetine (Prozac) are two drugs that are beginning to be studied using ^{19}F imaging [5,81]. Similar studies have been done in PET and provided in-vivo localization of the specific drug. Saturation of the brain receptor may be determined by using either an image ROI or a 1D spectroscopic integration and a phantom calibration. The effect of additional drugs such as caffeine and other psychotropic drugs on the primary imaging agent could also be determined. This area of study would provide a non-invasive in-vivo determination of drug localization that would be patient specific.

Methods

Epic 5.5 PSD Modifications

Following a PSD modifications supplement by Glenn Reynolds of GE Medical Systems (Milwaukee, WI.) I was able to modify both the standard csmemp, spin echo pulse sequence, and the 2dfast, gradient echo sequence to work at the ^{19}F frequency. The following general changes were made to both pulse sequences.

The CV **specnuc**, which sets the default nuclei being scanned was changed to 19 in order to allow the prescan to define a default frequency of 60.087831 MHz.

The gyromagnetic ratio, **GAM**, must be input for the specific nuclei being scanned according to:

$$\gamma = \frac{\omega}{B}$$

where the frequency is 60.08×10^6 Hz and the magnetic field strength is 1.5×10^4 Gauss yielding a ratio of 4005.8 Hz/Gauss. The correct low pass filter on the output of the broadband RF amplifier must be selected by the software for the correct frequency range. These filters allow the central frequency to pass and the higher harmonics to be trapped. The three filters are connected as shown in Table 1 using Epic 5.5 software.

Table 1. GE Signa Filter/Relay Connections

Cable Connections	pibbandfilt CV	Nuclei
J1 Filter<->J5 Relay J2 Filter<->J7 Relay	0	^1H
J3 Filter<->J4 Relay J4 Filter<->J8 Relay	1	^{31}P , ^{11}B
J5 Filter<->J3 Relay J6 Filter<->J6 Relay	2	^{19}F

For ^{19}F imaging, we have found that although the base frequency is only 4% lower than that of proton it used the mid-range filter, 0-24MHz, set by pibbandfilt=2. In order to compensate for this, we find it necessary to change cable connections in the Broadband Spectroscopy RF Cabinet. Disconnect the J3 cable from the relay

and connect it to J5 on the relay block. Disconnect the J6 cable from the relay and connect it to J7 on the relay block. What this accomplishes is to allow the 64 MHz filter to run through the 24 MHz relay for software switching purposes.

The CV pibbandfilt allows software switching of the relays that connect to the filter box in the spectroscopy cabinet. As stated in the previous table, pibbandfilt=2 for ^{19}F which must be set either in the auto-prescan menu if imaging or in the spectroscopy menu manually if doing 1D.

Once the above changes were implemented in the structured C code of the GE pulse sequence, a variety of tools must be applied by the programmer to test the PSD prior to getting machine time. Figure 8 illustrates the main menu of the WTools.x package provided by GE for pulse sequence development.

Options are given to the user to compile or "make" the sequence in one of two modes. The first is the "simulation" mode which allows the user to vary CV's or control variables within WTools.x and actually determine the real time effects. Once completely finished with off-line testing, a "hardware" version is compiled that may then be FTP'd directly out to the /usr/g/genesis directory to be run on the MRI. The "Lockoff" option should be engaged on the Maketool window in order that successive compilations will be displayed in the same window. As a note, there is also a command line compiler that may be used directly from the MR

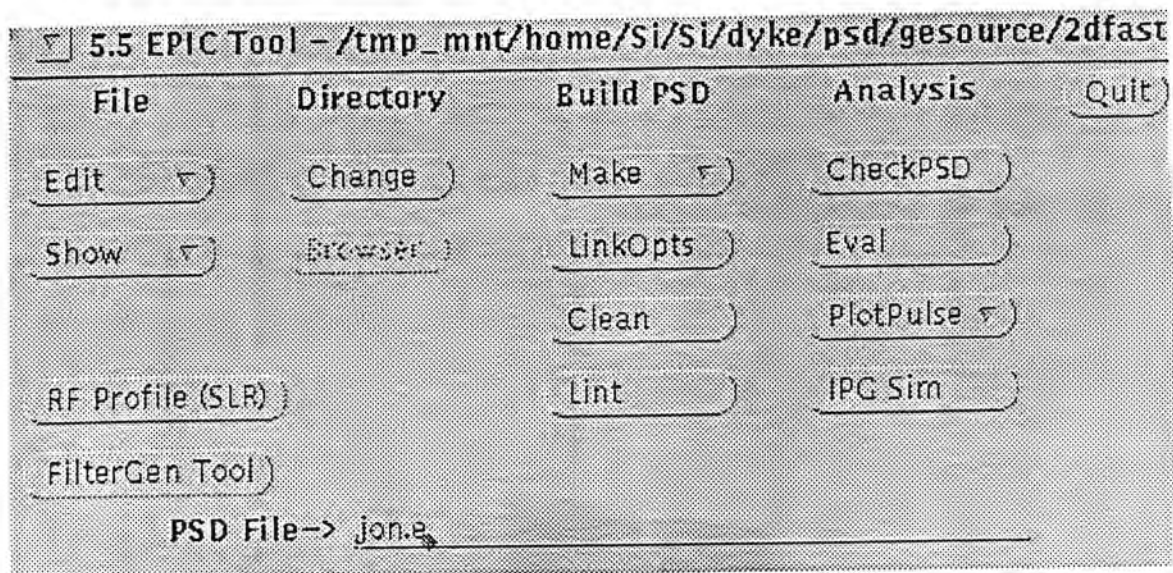


Figure 8. GE Signa Epic 5.5 WTools Command Window

scanner from a unix shell window (MRTTools->GShell). The file "Makefile.gen" must be modified to ensure the correct PSDFILE variable is in place. To compile the ^{19}F 2DFAST sequence offline the following commands should be used:

```
%cd /uhd/Si/dyke/psd/gesource/2dfast
%make -f Makefile.gen &
```

Note that inside the makefile, the variable PSDFILE= 2dfast must be set to correspond to the source code file name of 2dfast.e.

The next step would be to perform a "CheckPSD" on the compiled PSD. This actually simulated the following processes encountered on the MR: cvinit, cveval, cvcheck, predownload and a range check. This may also be done on the command line by typing: **checkpsd 2dfast.host** for the above example.

A successful completion produces the following message in the TTY window or WTools.x display:

**Running checkpsd on 2dfast.host
to create cv file 2dfast.host.sav.
Starting Process.
start a PSD, pid = 7697
checkpsd successful**

The CV evaluation tool may now be opened in order to check the values and ranges of different variables in the PSD under the conditions imposed with checkpsd as shown in Figure 9. For example, variables may be changed and fixed such as **opte** or **optr** prior to running. This allows the user to check that the range of the variable is correct, and the default value is initialized properly.

PSD is connected

PSD name: <u>jon.host</u>		<u>quit</u> <u>save</u>	
PSD pid: _____		<u>header</u> <u>display cv</u> <u>unfix</u>	
Eval Mode:	Eval Routines:	Debug:	
☐ Automatic	☒ Full Eval	☒ OFF	
☒ Manual	☐ Partial Eval	☐ ON	
	☐ User-specified		
		<u>rangecheck</u>	
		<u>load cvs</u> <u>store cvs</u>	
		<u>eval</u>	
Name: <u>opte</u>	Value: <u>25000</u>	exist: ☐ no	fixed: ☐ no
Name: <u>optr</u>	Value: <u>400000</u>	exist: ☐ no	fixed: ☐ no

Figure 9. WTools CV Evaluation Tool Command Window

The sequence may now be examined using the PlotPulse menu to display a static output of the gradients, rf pulses and angles as given in Figure 10.

Figure 11 shows a sample plot of the 2dfast sequence with the x,y and z gradients as well as the rf pulse time progression. A number of analysis tools are also provided in Plotpulse such as: BlochSim, GradHeat, RFHeat and TimeHist. These provide simulations of the Bloch Equations, Gradient and RF Heating considerations as well as a step by step instruction list for the PSD over time.

PlotPulse Options

Section to plot: 1

Start time in msec: 0

End time in msec: 50

Choose generators to plot:

☒ xgrad ☒ ygrad ☒ zgrad ☐ ssp

☒ rho1 ☐ rho2 ☐ theta ☐ omega

Screen Option: ☐ New page setup.

Figure 10. WTools PlotPulse Options Menu

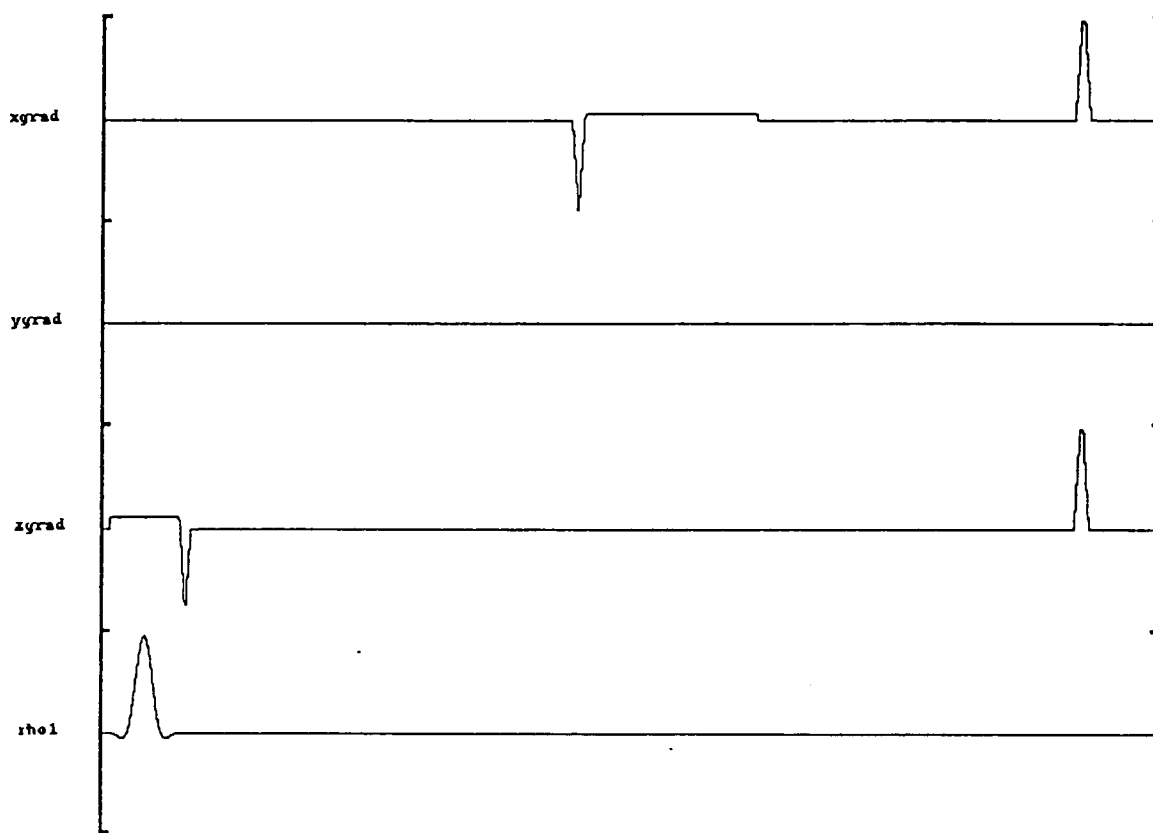


Figure 11. Epic 5.5 2dfast Pulse Sequence Display

The BlochSim tool will allow the user to view the signal strength, flip angle (theta) and phase angle(phi) using the following equations:

$$Signal = \sqrt{M_x^2 + M_y^2}, \theta = \sin^{-1}(Signal/M_z), \phi = \tan^{-1}(M_y/M_x)$$

One last tool in PlotPulse that is very useful is the GNU Db function. This tool allows one to save the various amplitude vs. time plots that are displayed in PlotPulse as separate test files with tab delimited columns which may be read into any standard spreadsheet or MATLAB for further analysis.

A final tool that may be utilized prior to testing on the GE is the IPG or Integrated Pulse Generation Tool. This produces a real time animation of the variables plotted in PlotPulse as the sequence progresses in time. An RF Profile (SLR) tool is provided that allows the user to design and load various RF pulses, such as a sinc pulse in the frequency domain. The pulse may also be viewed in the time domain and the M_z may be viewed as well. Spin-echo, Inversion and small-tip pulses are just a few of the options this tool provides.

Figure 12 shows an image taken using the broadband modified 2dfast pulse sequence of a 5M TFA phantom placed in a 5mm NMR tube. The parameters used were a 20 degree flip angle, a 10 ms TE and a 500 ms TR. The image was taken March 7, 1997 and reflects changes made in the T/R design up to that point in time. The 2dfast sequence was used given the fast T_2 of the sample in-vivo required a quicker recovery than that provided by the spin-echo sequence.



Figure 12. 5M TriFluoroAcetic Acid ^{19}F Image

SAGE/IDL Spectroscopic Analysis

Once the spectrum is taken and stored on the machine it must then be processed and analyzed. This is accomplished through the SAGE/IDL package version 0.2 (August 22, 1994) provided by GE Medical Systems. The data is first read in through the **FILE-->LOAD** button. The data may either be retrieved from a local disk or transferred directly from the MRI and saved in the directory structure given in Figure 13. A raw Free Induction Decay plot or FID as shown in Figure 14.

The screenshot shows a graphical user interface window titled "SAGE/IDL Input Menu". At the top, there are four buttons: "Load Data", "Reset", "Help", and "Dismiss". Below these buttons are six input fields, each with a label and a text box. The fields are: "Database:" with the value "/mri/dyke/sdbm/", "Site:" with the value "mr01-0c0", "Patient:" with the value "early_19F", "Study:" with the value "5155", "Series:" with the value "2", and "File:" with the value "G00113". At the bottom of the window, there is a "List:" label followed by a series of dropdown menus for "Site", "Patient", "Study", "Series", and "File". The "File" dropdown menu is currently expanded, showing a list of files.

Figure 13. SAGE/IDL Input Menu Showing Directory Structure

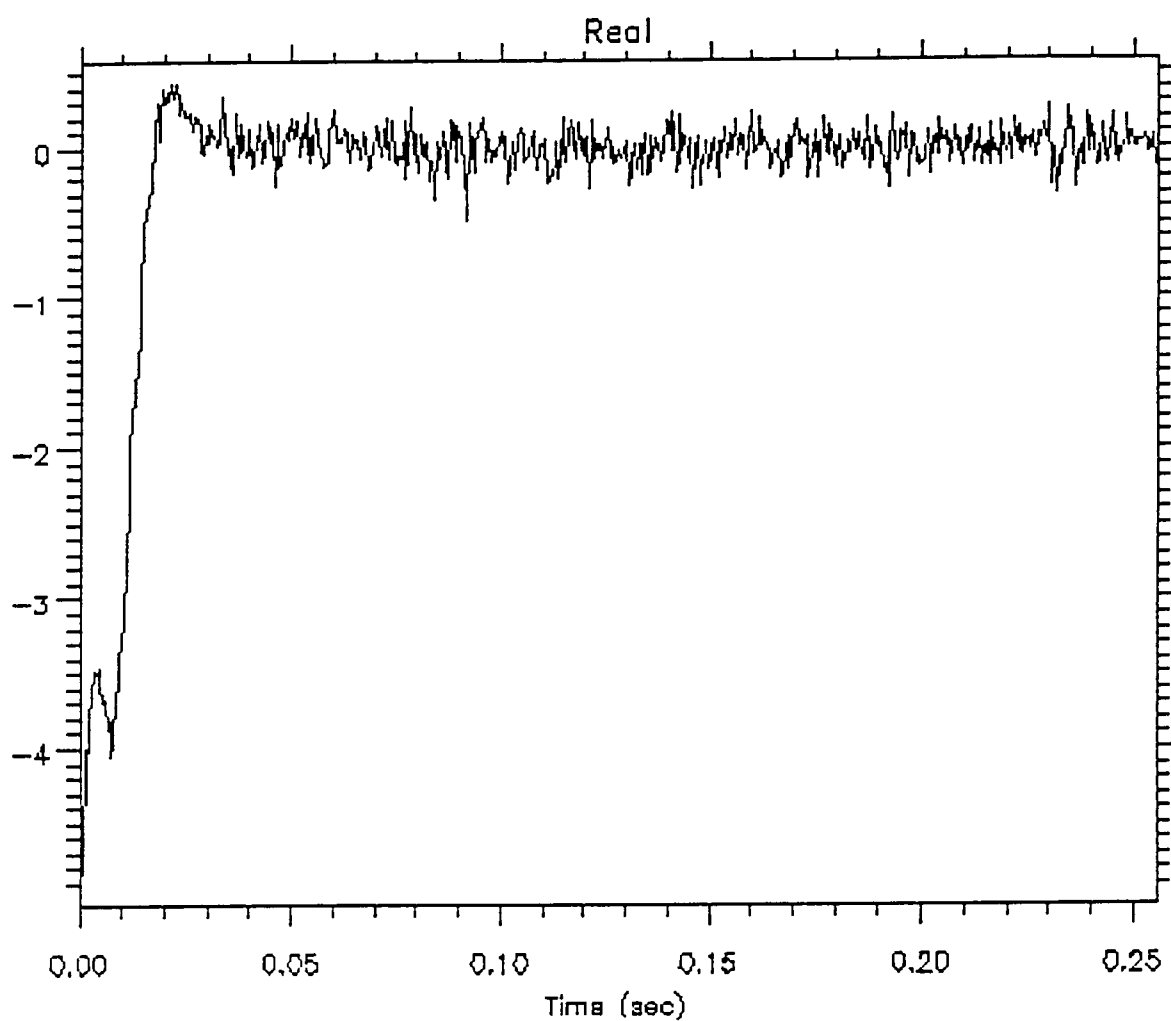


Figure 14. Free Induction Decay Signal Prior to Fourier Transformation of a 36ppm Phantom of F-BPA-Fr

This plot displays the signal strength versus time in the frequency domain. This is the raw data received by the coil from the sample over the time defined by the read gradient in the pulse sequence. One key item to notice on this plot is that many NMR machines do not automatically adjust the base frequency to the central resonance peak. The GE Signa unit does, but from this plot, it can be seen that the central proton frequency is slightly off resonance. If the FID displays a damped resonance or does not appear "flat", then the field is not completely on resonance. From Figure 14 an approximate estimate of the T_2 , transverse relaxation time, of the sample according to the following formula:

$$T_2 = t_{0.50s}$$

where $t_{0.50s}$ indicates the time at which half of the signal strength is reached. The above FID yields a T_2 of approximately 12.1 ms for the in-vitro phantom of F-BPA-Fr at 36 ppm in a volume of 9 ml.

Figure 15 represents the data taken from a 300 g rat bearing a human GBM tumor that was administered 25 mg/kg body weight of F-BPA-Fr and then euthanized. Note the T_2 is much shorter in-vivo and allows the user to set the TE appropriately.

The next step, as shown in figure 1.16, is to fourier transform the raw data from the frequency domain, k-space, into the spatial domain. The algorithm used is a Fast Fourier Transform which is common in image processing.

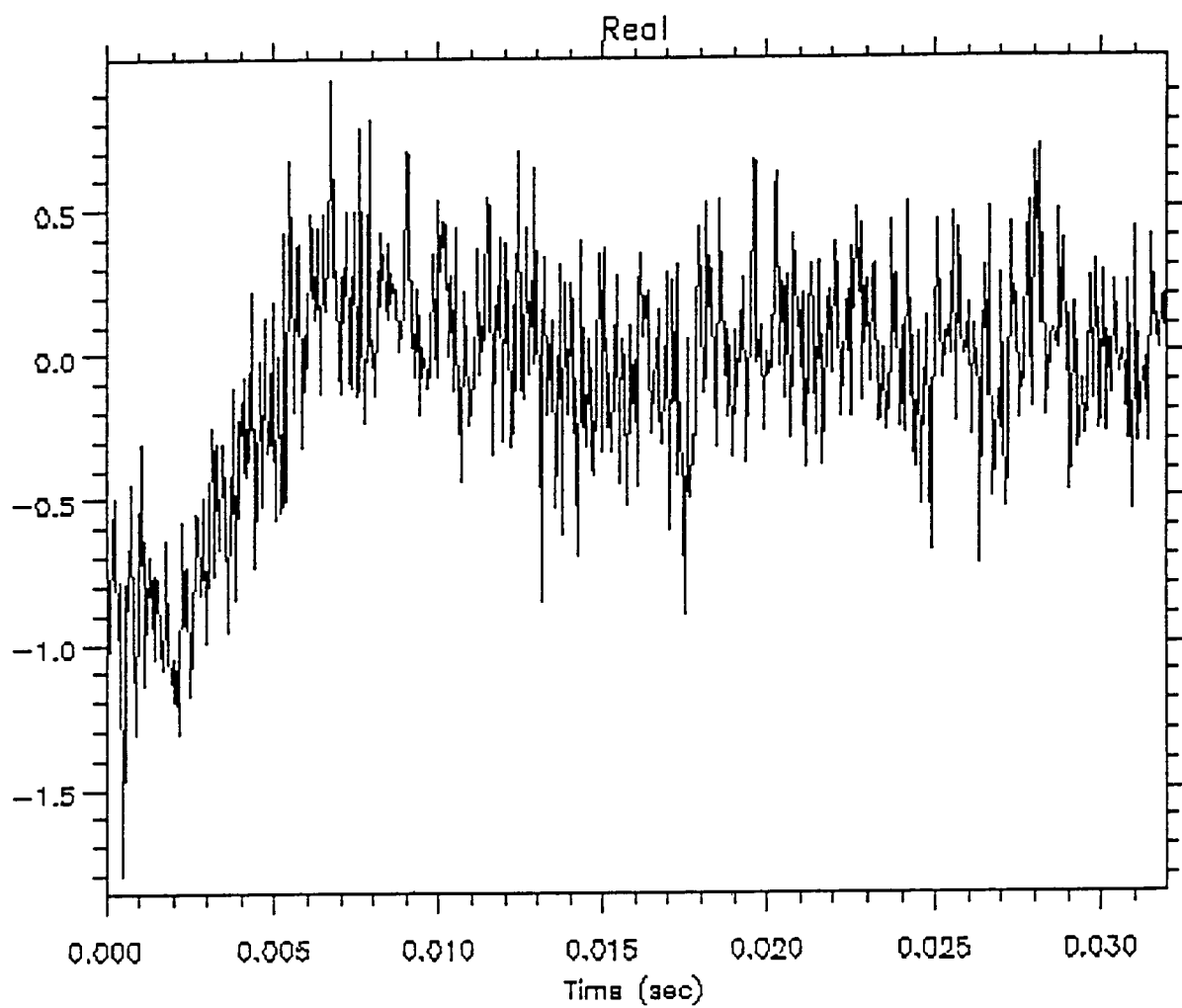


Figure 15. Free Induction Decay Signal Prior to Fourier Transformation of a Rat Injected with F-BPA-Fr

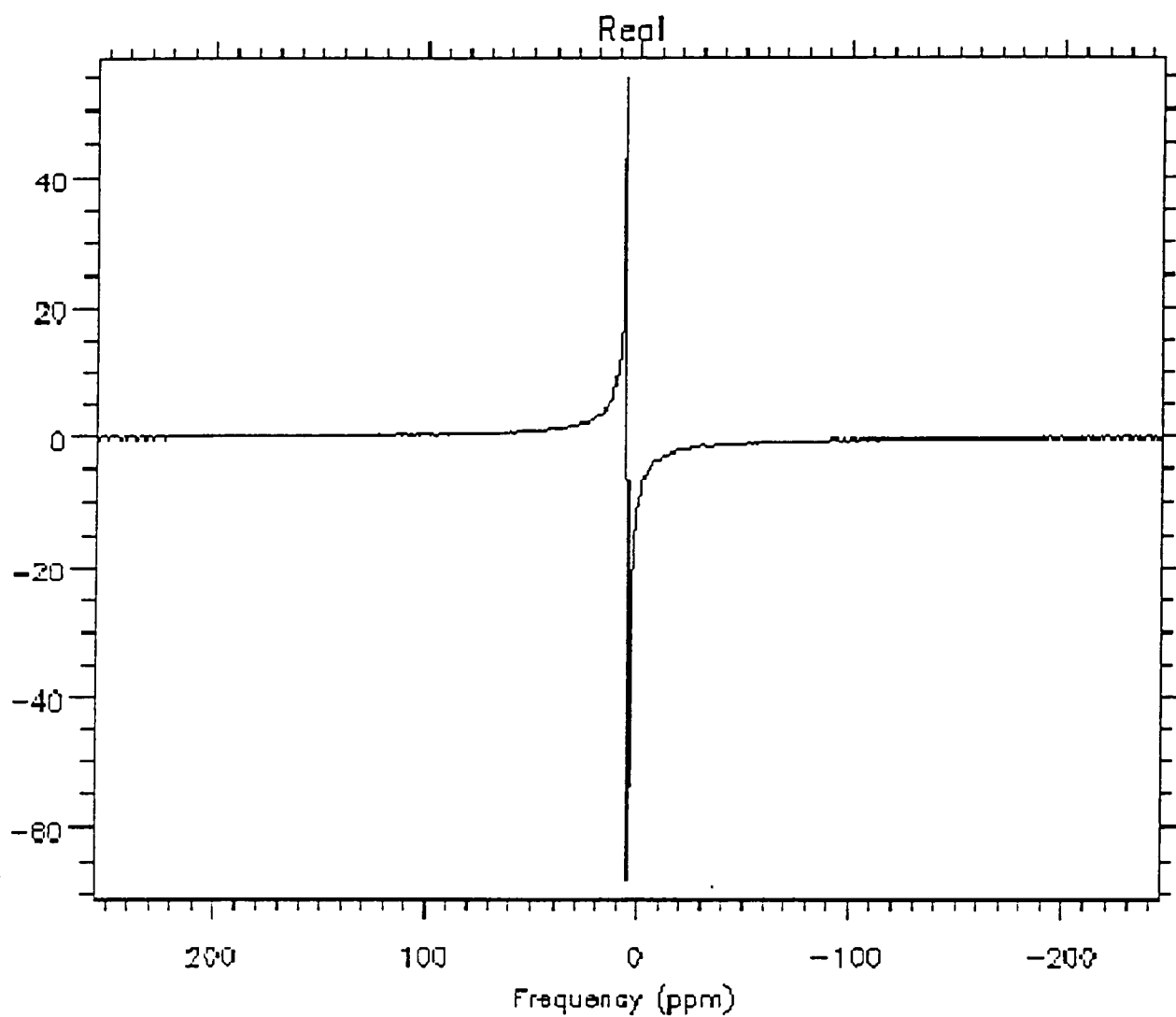


Figure 16. Fast Fourier Transform of Free Induction Decay Signal

The last step to basic processing is to phase the spectrum. GE advises that one should manually set the first order phase as close as possible, apply a baseline correction and then do the zero order autophase. As a side note, the autophase routine performs a simplex optimization algorithm to minimize the sum of the absolute values of the real values.

Sage/IDL may now be used to compute some quantitative parameters from each individual 1D set. Once the 1D set is processed, a peak table may now be created that will yield peak locations, noise standard deviation, FWHM and other parameters. The analysis menu has an option to create a peak table. This menu then allows the peak to be chosen in one of two manners. The first allows automatic peak determination based on a threshold level set by the user. For example, the default threshold is 25% and then any peak 25% above the baseline would be placed in the table for further analysis. Secondly, a manual mode allows the user to individually click on each peak desired with the mouse. The following is an excerpt from the peak table that may be viewed under the edit menu.

```

* noise standard deviation 0.0669190
#      Amp      Freq      Width      Phase      Area
#-----
      3.9435      2687.5      62.500      -1.0438      206.44

```

From this table, the signal to noise ratio for this single peak may now be determined. Assuming NEX averages, the following formula may be used to calculate signal to noise assuming identical sweep widths.

$$\frac{S}{N} = \frac{\sqrt{2} AMP}{2 SD} \frac{1}{\sqrt{NEX}}$$

This allows a normalized value for comparison between scans. If the sweep widths do vary, this may be accounted for by multiplying by a factor of $\text{Sqrt}(\text{sweep width})^{-1}$ for each measurement..

¹⁹F Transmit/Receive System Description

The beginning of construction on the ¹⁹F imaging hardware began February 15, 1996 after Dr. Cecil Charles, Director, Center for Advanced MR Development at Duke University Medical Center gave a training seminar here at UTMCK on Multinuclear MRI/MRS. His suggestion was to use a basic T/R design based on 1/4 wavelength cables and a third party pre-amplifier as shown in Figure 17. All the CAD drawings were created using Tgif, an Xlib based 2-D drawing facility under X11 by William Chia-Wei Cheng, Copyright (C) 1990-1996. Figure 18 illustrates the basic modules of the transmit/receive system in a block diagram format.

The RF theories governing Figures 1.17 and 1.18 are identical. The simplicity is still apparent, but each component of the original diagram has now been improved and placed in separate non-magnetic boxes with only exposed male BNC connectors on the outside to minimize RF noise.

The basic circuit theory may be understood in two components. The transmit

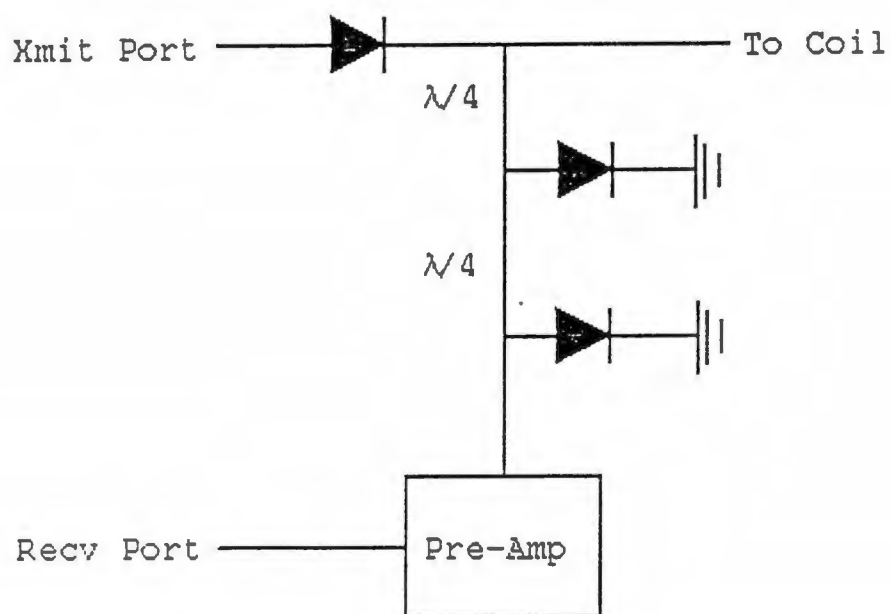


Figure 17. Initial Theoretical Transmit/Receive Design

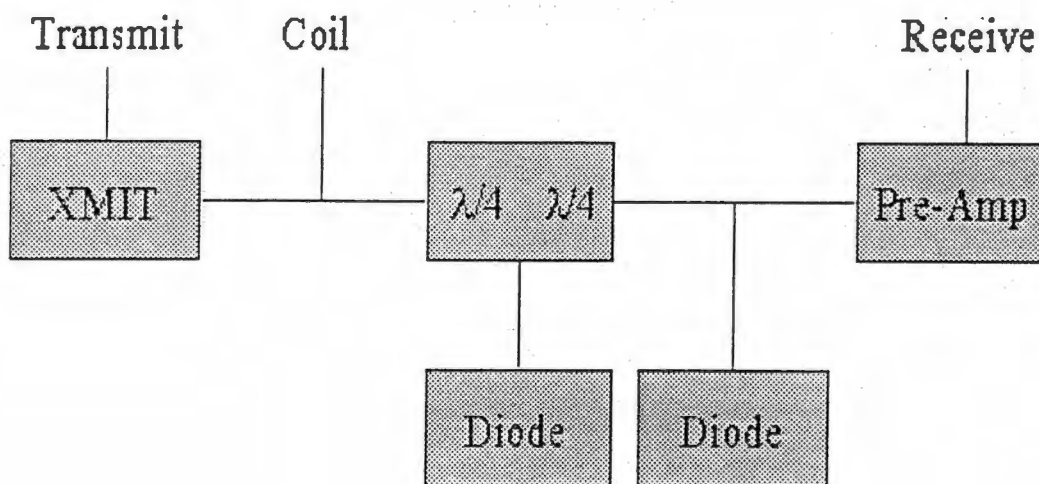


Figure 18. Modular Design of Transmit/Receive ^{19}F System

cycle, as shown in Figure 19, and the receive cycle, Figure 20, have different paths through the circuit given the difference in voltage bias. During RF transmission, a positive bias voltage of 15 V is applied to the above circuit. This results in the signal passing through the transmit box and directly out to the coil as seen in the figure below. If the 15 V bias and the RF signal were to reach the pre-amp, the Germanium Arsenic Field Effect Transistor that actually amplifies the signal, would be instantly destroyed. In order to avert this situation, the diode boxes are biased on and the resulting signal goes directly to ground once past the coil.

During the receive cycle, a negative 15 V bias is applied to the circuit. This does not bias the diode boxes and they remain open in the circuit. The resulting RF and voltage received from the coil pass directly through the 1/4 wavelength boxes into the pre-amp as shown in Figure 20. The method by which this occurs and the safeguards that have been implemented in each component of the system will be explained later in further detail.

Pre-Amplifier Testing

The pre-amplifier itself had to maintain a comparable noise figure and gain factor with that provided by GE. Advanced Receiver Research of Burlington, CT. manufactures a tuned pre-amp in the range of 60-66 MHz with a noise figure of 0.5 and a gain of 24 dB. GE supplies a pre-amp with a noise figure of 0.5 and

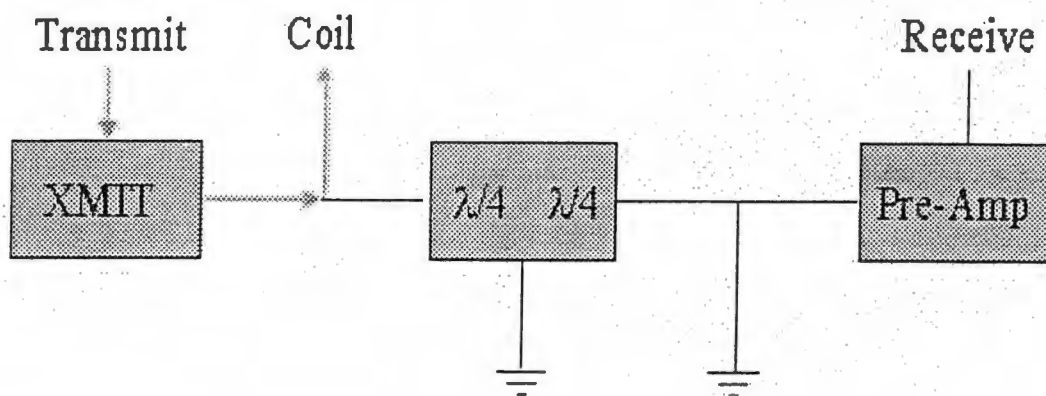


Figure 19. Transmission Circuit Path in ^{19}F System

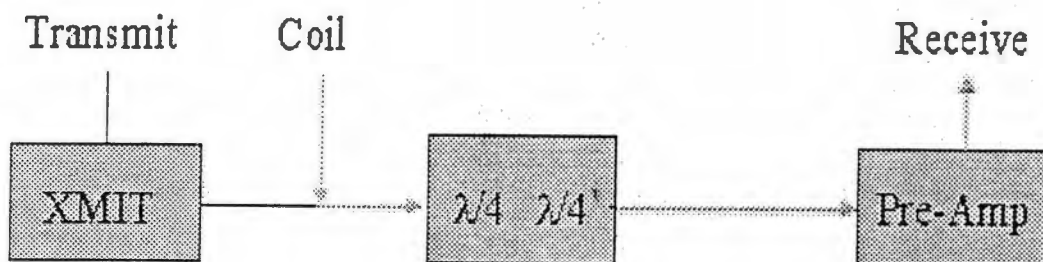


Figure 20. Receive Circuit Path in ^{19}F System

a gain of 20 dB with its manufactured T/R units. The units from AR² are shielded in a custom aluminum enclosure and have been modified to receive the bias voltage through the BNC connectors. Figure 14 shows the circuit diagram and is actually quite simplified in comparison with the pre-amp supplied by GE.

A separate gain test on the pre-amplifiers purchased from AR² as shown in Figure 21. The frequency generator was used as an input to the pre-amp and the spectrum analyzer was connected to the output. Given the pre-amp receives the first unamplified raw signal from the MR sample, a starting level of -80 dB increasing by steps of +5 dB until reaching the saturation point was used. This was done using a single pre-amp as well as with 2 pre-amps connected in series in the hopes of improving the signal to noise ratio. Performing a linear regression on both curves yielded the gain for the single pre-amp at 26.733 dB and for the pair 41.585 dB. This may also be read approximately off the graph as the point of crossing the 0dB output mark. Notice that as the second pre-amp is driven by the first that a point of saturation occurs resulting in a gain of less than the expected 52 dB.

Transmit Module Theory

The transmit box, as shown in Figure 22, has two primary functions in the T/R circuit. The first is to "decouple" the frequency component of the signal from the

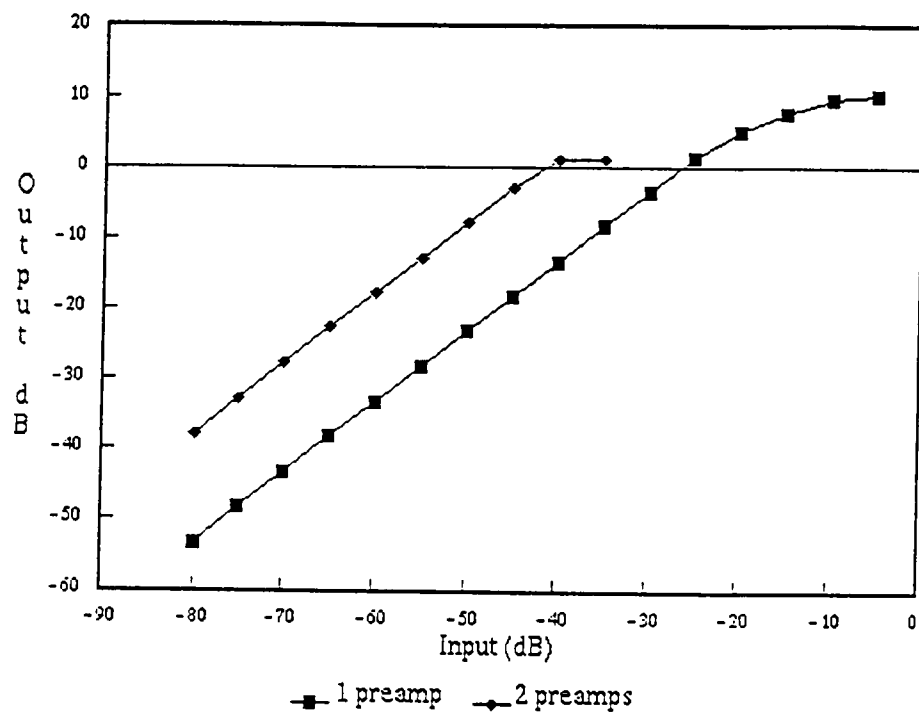


Figure 21. AR² Pre-amplifier Response Curves

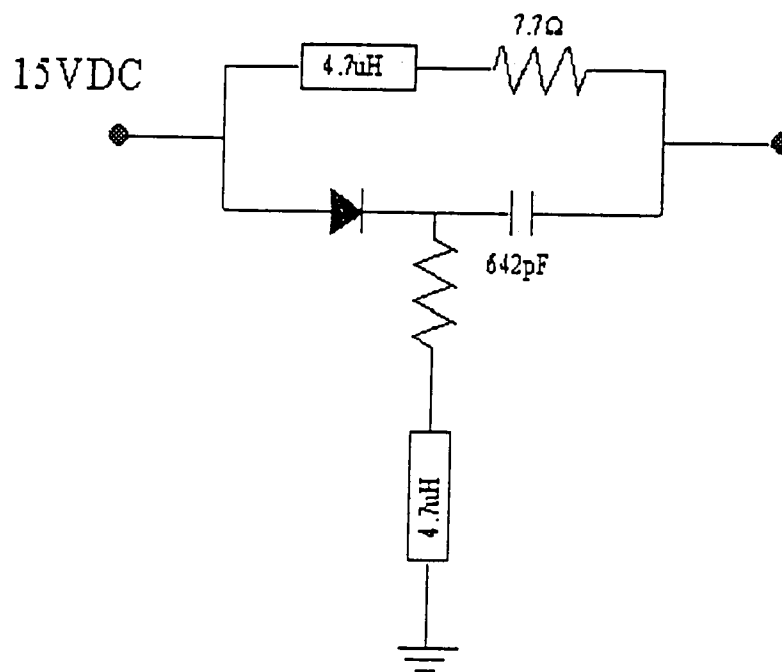


Figure 22. Transmit Module Internal Schematic

voltage component. Each of these components are dealt with differently and in different parts of the circuit.

In RF theory, a "choke" or coil of high value creates a high impedance being defined below:

$$Z = \sqrt{(X_L - X_C)^2 + R^2}; X_C = 1/C\omega; X_L = \omega L;$$

where the capacitance is assumed 0.0 for a coil and the frequency is given by

$$\omega = 2\pi \nu; \nu = 60.08 \text{ MHz};$$

Therefore, if the capacitance of the circuit is low, the impedance is dominated by the inductance of the coil. For example, for the top branch of the transmit box, the impedance would be calculated to be 29.3 ohms including just the coil and the resistor. The lower branch calculates to be 5.1 ohms for the capacitor. The RF will then take the path of lowest impedance and cross through the diode and the capacitor out to the solenoidal coil to excite the sample. At this point it has now been separated from the DC voltage component of the signal. Voltage cannot pass through the capacitor but will readily pass through the upper branch where it goes to ground through the diode boxes to be explained later. The resistor/coil pair on the lower branch of the circuit is in place to provide a DC path to operate the diode and block the transmitted RF from leaving to ground on the lower path.

A final purpose of the transmit box is to isolate the received signal from the sample

from leaving down towards the transmitter. The choke on the top path will block the RF component of the received signal from the transmitter circuit. The diode is reversed biased during receive and will therefore not allow any signal to pass beyond it. In addition, the voltage received by the coil from the sample is much less than the 0.7 V needed to bias a diode even in forward mode. The diode itself is a PIN diode used for switching applications having low capacitance and low noise considerations.

RF Coil Construction

The next portion of the circuit involves as much pure art as theoretical RF design. The construction of the transmit receive coil, shown in Figure 23 , must not only fulfill low noise requirements but must also be perfectly tuned and matched at the resonant frequency as well as have identical impedance as that of the MR [39,70] This initial coil is constructed on a solenoidal form of plexiglass. The inner diameter, or largest allowable sample size, is 50 mm and was chosen primarily for animal studies of mice and rats. The outer diameter is 58 mm upon which the coil is actually wound. 6 mm copper tape with adhesive on one side is used as the coil conductor. 3 turns are then wrapped around the form at a spacing of 6 mm.

The values of the capacitors in Figure 23 are by no means fixed and must be "tuned and matched" to center the maximum absorption peak on the spectral frequency. They must be varied for each sample that is placed in the coil.

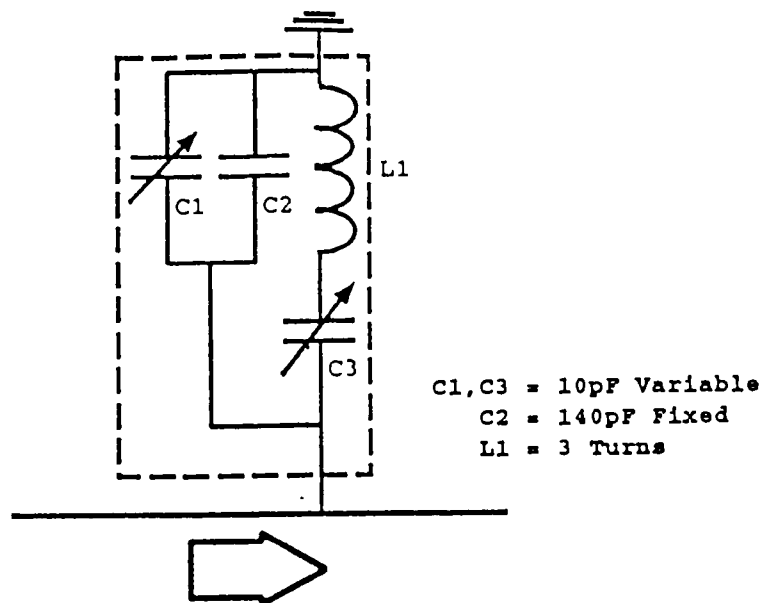


Figure 23. Transmit/Receive Coil Schematic Diagram

Different samples "load" the coil in various ways shifting and decreasing the absorption peak off resonance. For normal operation, the 10pF variable capacitors may be used to "tune" the coil, or place it at the central frequency and "match" the coil, or achieve the maximum gain in the absorption peak. Upon optimizing the capacitance of the coil, the impedance of the coil system must then be checked. A HP8753A Network Analyzer in conjunction with a HP85046A S-Parameter Test Set are used to determine the magnitude of the peak in dB and its resonance in MHz. A sample plot of the coil with a TFA phantom inside is shown in Figure 24. On Figure 24, the impedance is given as 45.924 ohms on the lower Smith plot. The closer this value is to exactly 50 ohms, the greater the power transfer between

those two components in the system becomes and a lesser loss due to noise is incurred.

One last point dealing with coil construction concerns the quality factor of a coil. The "Q", as it is commonly referred to, is determined by the following equation:

$$Q = (\text{Central Frequency}) / (\text{Full Width Half Maximum of Peak})$$

For the above coil, we have obtained a Q of 60.112 MHz/4.524 MHz = 13.294. This is a combined unitless measure of the sharpness of the absorption peak normalized to the central frequency. The higher this number is, the better signal reception the coil will produce. Another measure called the "fill" factor employs a ratio of:

$$F = Q_{\text{unloaded}} / Q_{\text{loaded}}$$

where a high fill factor indicates good "loading" of the coil [24]. A full schematic diagram of the complete T/R circuit and its various components is given in Figure 25 and will be referred back to in future discussions.

1/4 Wavelength Circuit Design

The quarter wavelength box is the next component the signal reaches after being

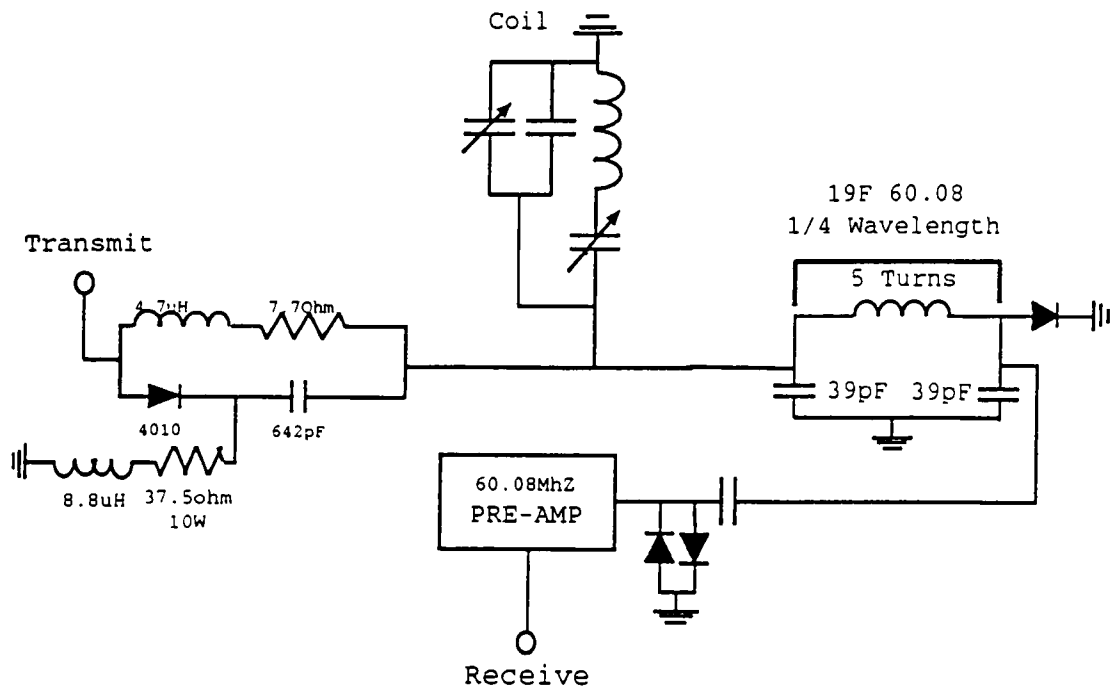


Figure 25. Complete Transmit/Receive Component Schematic

received by the sample with the coil. The primary function of this circuit is to isolate the pre-amplifier from the circuit during transmit. The quarter wavelength cable is governed by the following equation:

$$Z_i Z_o = |Z|^2$$

where Z_i represents the input impedance and Z_o the output impedance. If one end of a quarter wavelength cable is shorted, then the input impedance is 0 ohms. This implies that the output impedance for the cable impedance, Z , of a 50 ohm system will be 50 ohms/ 0 ohms or infinite! This is exactly what happens in our circuit as the diode on the output side of the quarter wavelength box is biased on

during transmit. The RF then sees theoretically an infinite impedance block and travels only to the coil and not the pre-amp.

The construction of a quarter wavelength box came in three stages for my system. The first step was to actually use a length of cable given by the relation:

$$\lambda = \frac{c}{v}$$

This would imply that a cable of length $(3.0 \times 10^8 \text{ m/s})/4(60.08 \text{ MHz}) = 1.25 \text{ m}$ would need to be utilized. This would be correct in a theoretically perfect cable with no loss. Typical coaxial cables such as RG-223/U have a signal loss of about 40% yielding a cable of 0.75 m. A simple conversion factor to remember would be $45/v$ yields the length in meters given the frequency in MHz [24]. In reality, a length of cable is hooked up to the network analyzer and adjustments are made in the length until the resonant absorption peak is obtained. This is actually done for the ^{31}P GE surface coil as a standard practice. The surface coil has long cables from the coil to the T/R box. This method of switching has the advantages of reliability, large power capabilities and simplicity. Disadvantages are the inherent lengths of the cable, the monochromatic frequency application and the strict impedance matching requirements.

The next step in quarter wavelength development is a "lumped" element. A standard "pi" circuit, Figure 26, has been utilized since the birth of NMR [38].

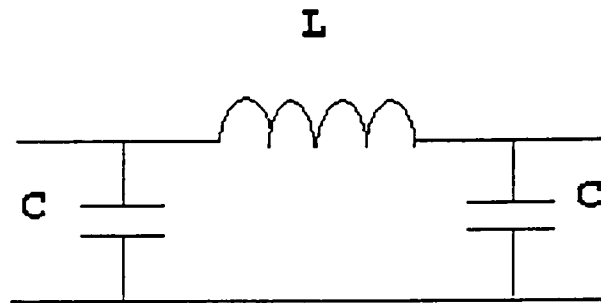


Figure 26. Theoretical "Pi" Circuit Simulating 1/4 Wavelength

The formulas governing the values of the components are derived using Kirchoff's Law and reduce to the following simple solutions:

$$Z^2 = \omega^2 L^2; Z^2 = 1/(\omega^2 C^2);$$

Knowing the internal impedance of the GE is 50 ohms, one calculates that a pi circuit with capacitors of 53pF and an inductor of 0.13uH would not only be tuned to the resonant frequency but would also be matched to the system impedance.

I chose to follow GE's approach initially and use capacitors at a value of 39pF and then hand wind a 5 turn coil and adjust the spacing to achieve the correct inductance and matching. The testing procedure is accomplished by placing the pi circuit on the network analyzer and displaying a phase plot. The quarter wavelength system should produce exactly a 90 degree phase shift between a

short and a 50 ohm load. The short is accomplished, as described earlier when the transmit bias turns on the diodes and completes the path to ground. The 50 ohm load simulates the coil and impedance of the system.

The next step in this progression was to implement the calculated quarter wavelength system described initially to improve matching and reduce noise if possible. Although the hand wound coil seems a crude approach, this is also taken by GE and has produced a 47 ohm impedance and a 91 degree phase shift at the ^{19}F frequency which is very acceptable. A noise figure analysis of each block component will be discussed later in detail.

Receive Circuit Theory

After the quarter wavelength circuit, a branch containing a coil and diode lead to ground. The PIN diode and coil are used to provide a DC path for the voltage to ground, to provide the short on the quarter wavelength during transmit. The diode itself is used primarily as a switch and has low capacitance and a moderate level of noise. If this noise reaches the pre-amp it will degrade the quality of the incoming signal from the sample. The coil placed in series between the diode and the receiver provides RF noise isolation to insure that this does not occur.

The impedance of the coil in series with the diode is calculated to be 1774 ohms which is actually the inductive reactance of the branch assuming the capacitance

is negligible. This high level of impedance is in place during receive mode and will therefore block the acquired signal from "leaking" out to ground.

Working our way towards the pre-amplifier, we notice a PIN diode that is reverse biased along the main signal path. This is due to the inherent negative bias on the GE machine that occurs during receive. Although a positive 15 V bias is applied during each transmit pulse, it is the negative voltage on receive that allows this diode to act as a switch. This in conjunction with the 1000 pF capacitor in series prior to the pre-amp serves as a final bastion protecting the pre-amp against transmit voltages. Even stray voltage spikes will be multiplied in the pre-amp to produce devastating results. The coil going to ground between the reverse biased diode and the capacitor provides a current path for the DC to ground. It also prevents any of the RF received from the sample from leaking out along the DC current path.

The last main component in the circuit consists of a pair of cross coupled diodes. These diodes are high capacitance Motorola 514 or MBD701 diodes that are very low noise. The low noise factor is a key issue to these diodes as any continuous production of noise by the diodes will be fed directly into the pre-amplifier. This could be a cause of a higher noise baseline in all subsequent signal acquisitions. The purpose of these diodes is to completely shunt any signal greater than the 0.7 V to ground preventing saturation of the pre-amplifier. The actual signal emitted

from the sample will be orders of magnitude less and will not inhibit the passage of acquired data. This also provides protection to the MR circuitry in the machine itself from any voltage spikes. A noise figure study should be done of all the block components in the circuit.

Final Testing Procedures

Physically, we chose to modularize each basic circuit component into separate shielded cases with external BNC type connectors as shown in the Figure 27.

Using the signal generator, a sine wave of resonant frequency equal to that of ^{19}F , was fed in to the circuit at a fixed level of -50 dB. Prior to placing any experimental circuit on the MR, it must be thoroughly bench tested. In order to accomplish this, a -50 dB wave is placed on the input of the pre-amplifier directly. In order to get power to the pre-amp, a small test circuit having a 0.1 μF capacitor was placed in line with the positive bias. This will provide power to the output side of the pre-amplifier and yet isolate the spectrum analyzer from the incoming voltage. This above setup yielded an output of -29.53 dB given an input of -50.0 dB or a gain of 20.47 dB. The gain figure of the pre-amp is listed at 24 dB but may be attenuated due to the test circuitry.

Once the pre-amp was checked, components were added in the receive path, eventually ending up where the coil connects. Upon adding Block D, containing the cross coupled diodes and in-line capacitor, the output was -29.75 dB or only

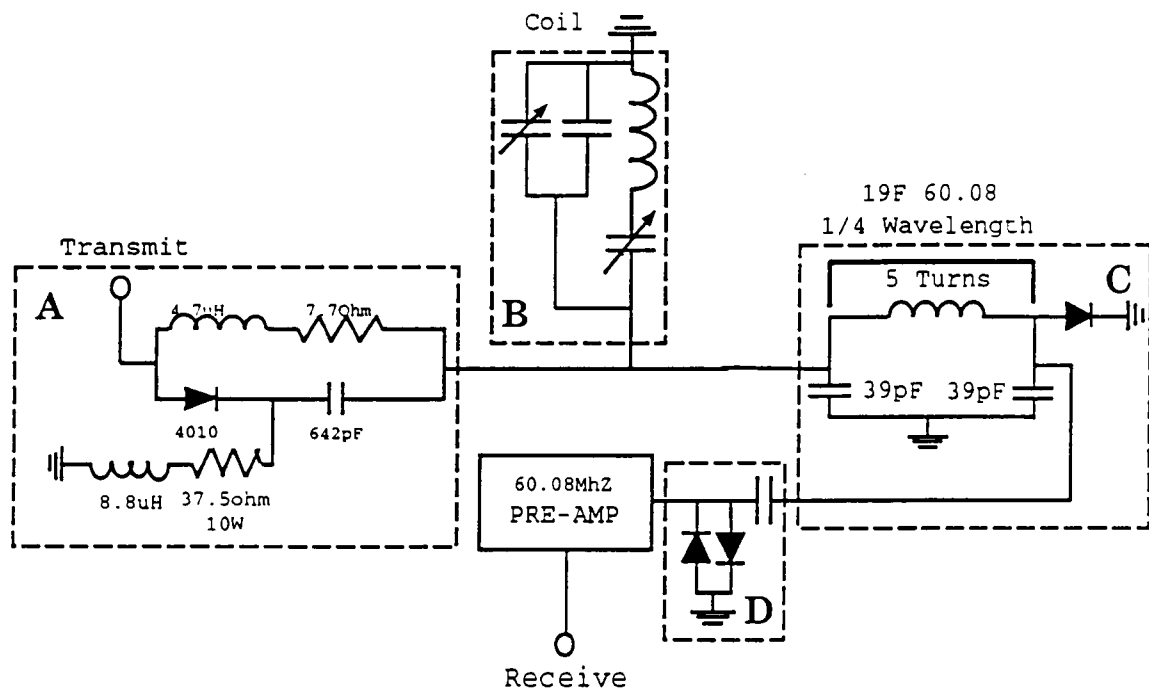


Figure 27. Modified Component Schematic of the ^{19}F T/R System

a loss of 0.22dB. This module has very little noise and does not impede the signal at all and yet isolates the pre-amp input from DC. The quarter wavelength circuit and the diode branch of Block C pushed the output to -29.60dB. Again, the loss caused by this module has remained negligible. The primary factor to note from this result would be that the quarter wavelength circuit did not impede the RF flow in receive mode.

It is at this point that we reach the input of the coil and may actually simulate the path occurring in receive mode on the MR. Using another bias test circuit, a +15V was applied at the coil input to allow biasing of the diodes. It is now that we may

short one end of the quarter wavelength circuit to ground and see what effect it has on RF impedance. The result was an output of -62.0 dB with the positive bias applied. The shorted quarter wavelength effectively produces the infinite impedance block allowing none of the -50.0 dB input signal to pass through during transmit. The circuit works well in receive mode with a negligible amount of noise.

We must now test the circuit in transmit mode to be sure that signal is getting out to the coil. Passing through the transmit box, Block A, with no applied voltage yields an output of -74.57 dB. During transmit however, the bias voltage will be applied which then yields an output of -53.7 dB. There is then about a 4 dB loss in signal strength upon passing through the decoupling circuitry in this module. This may be a point of refinement to increase signal to noise ratios.

The circuit is not correctly simulated without the addition of the actual coil used for transmission. This coil was matched at approximately 45-47 ohms depending on the sample. Passage beyond the coil, with voltage applied, yielded an output of -58.05 dB or another 4 dB loss. Better matching of the coil to limit the signal loss will also improve this result. Note that all of the components pass approximately -76.0 dB during transmit if no bias voltage is applied. This assures us that the receive signal is not flowing backwards towards the transmitter. Overall, the bench test was successful and has shown that our circuit is ready to test and has also shown modules in the circuit that may be better tuned to decrease noise.

Results

Phantom Spectroscopy Runs

Figure 28 was generated from our first data run, located in Appendix B, on May 24, 1996 using a 5 Molar trifluoroacetic acid phantom. Fixing the flip angle at 90 degrees for the fidcsi sequence and varying the Transmit Gain yielded Figure 28. As in 1D NMR experiments, the optimal flip angle may be determined by varying the power of the RF pulse across its range. On the GE system, a TG of 0 does not imply 0 dB but a minimum value. Increments of TG are allowed from 0-200 where each step indicates a variance of 0.10 dB. The plot shows that for this sample, a peak occurs at a TG of 60 and then begins to taper off, implying the 90 has been passed. Other runs to optimize signal to noise have been taken on other samples of various concentrations.

Figure 29 was generated by fixing the Transmit Gain at 0 and varying the flip angle. One would expect the maximum signal to be obtained at or around 90 degrees. This plot indicates that a peak occurs at a flip angle of 100 degrees for this specific sample. The value of 90 degrees is determined in the auto pre-scan and may need to be manually adjusted if the pre-scan fails due to low signal. The circuit used for this run had two quarter wavelength modules and a reversed biased diode prior to the preamp.

The next set of data, given in Appendix C, was taken November 13, 1996 with a

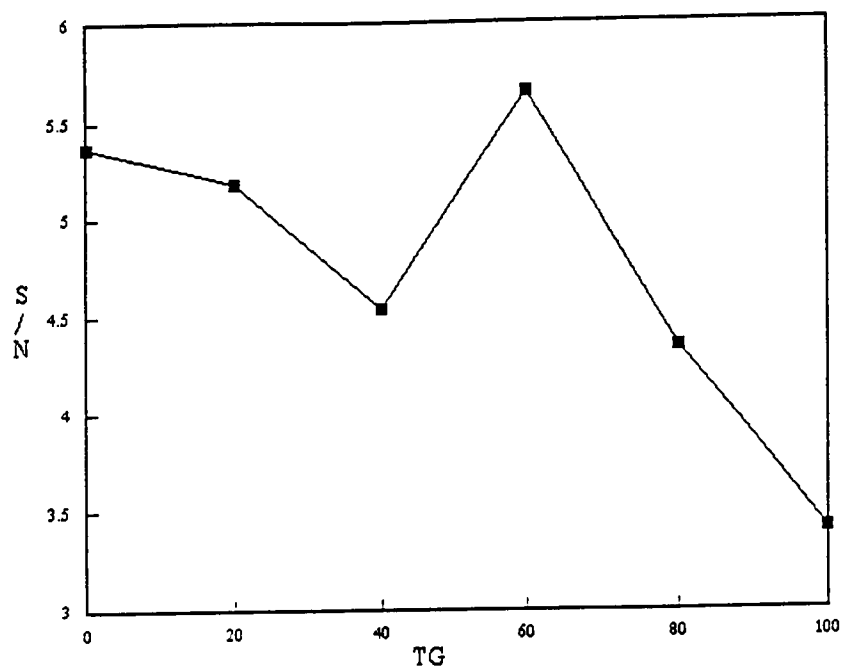


Figure 28. Transmit Gain Optimization Plot - 5M TFA

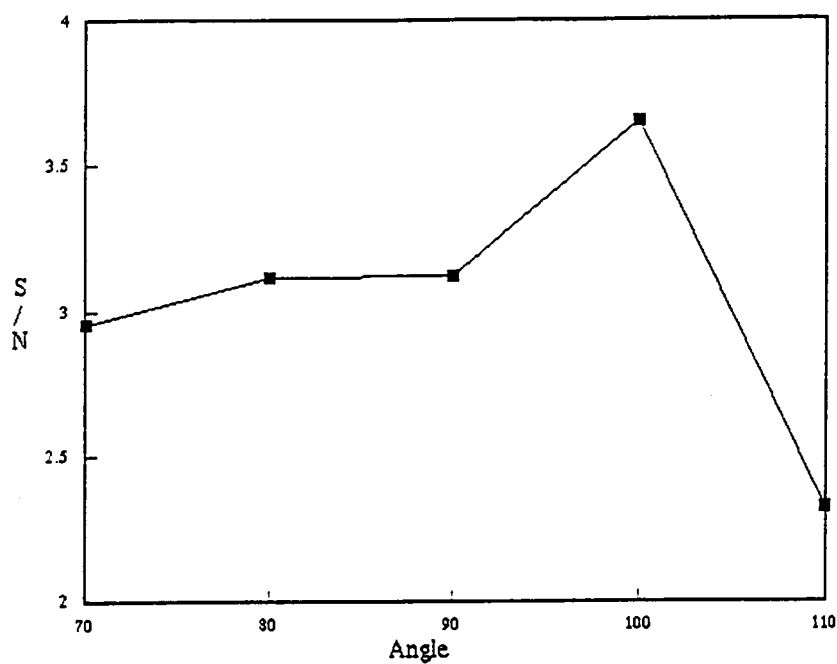


Figure 29. Flip Angle Optimization Plot - 5M TFA

250mM TFA phantom using a circuit very similar to that of Figure 25. It can be seen from Figure 30 that an optimal value of TG has been reached at 25. Obtaining good signal to noise ratios we then proceed to lower the sample concentration to determine our limits of detection in Figure 30.

A run with 100mM of TFA produces an interesting change in signal to noise from file 98 to 99 as the TG was returned to 20 from 15. File99 was taken as a single spectrum and no averaging was done and yet has a signal to noise ratio of 36.8 whereas file 98 has a S/N of 7.17. The final data runs continue downward in

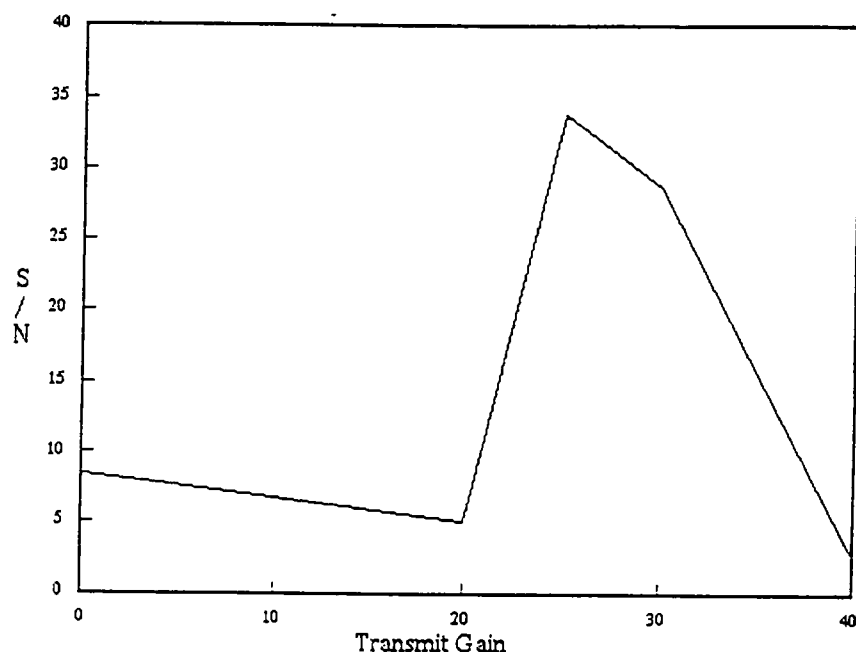


Figure 30. Transmit Gain Optimization Plot - 250mM TFA

concentration with previously made TFA samples that have a volume of 65 ml. Concentrations of 50 mM and 10 mM in ^{19}F produce data given in Appendix C.

In-Vivo F-BPA-Fr Rat Studies

In preparation for submission of an abstract on this work to the ISMRM conference, in Appendix D, we utilized a phantom of Fluoro-BPA-Fructose at a concentration of 36 ppm in a volume of 9 ml. These parameters were chosen to be similar to those in the 300 g tumor bearing rat from BNL. As a note, the F-BPA-Fr phantom calculations for the above run were taken from a prior mouse study and found to be calculated incorrectly. The actual concentration is then:

$$\frac{(327.4 \text{ mg F-BPA})}{(10 \text{ ml H}_2\text{O})} \frac{(1 \text{ mol F-BPA})}{(226 \times 10^3 \text{ mg F-BPA})} \frac{(10.8 \text{ g B})}{(1 \text{ mol})} \frac{(1 \times 10^6 \text{ ug})}{(1 \text{ g})} = 1565 \text{ ppm}$$

Listed below are the corrected phantom calculations for successive runs:

$$\frac{(\text{ml TFA}) (1.493 \text{ g TFA}) (1 \text{ mol TFA}) (3 \text{ mol } ^{19}\text{F}) (19 \text{ g } ^{19}\text{F}) (1 \times 10^6 \text{ ug})}{(10 \text{ g H}_2\text{O}) (1 \text{ ml TFA}) (114.023 \text{ g TFA}) (1 \text{ mol TFA}) (1 \text{ mol } ^{19}\text{F}) (1 \text{ g})} = \text{ppm}$$

Using the 250 mMol phantom already created I would need 0.164 ml in 10 ml of water to produce a 10 ppm phantom according to :

$$M_1 V_1 = M_2 V_2$$

where M represents molarity and V represents volume.

If a concentration of 36 ppm is chosen, assuming a 10 ml vial of water, a 0.48 uL amount of TFA would be needed. Obviously, a larger amount would need to be

produced to insure accurate measurement of the TFA. This also translates into a concentration of 4.1mMol for TFA. For F-BPA the calculation becomes:

$$\frac{(x \text{ ml F-BPA}) (r \text{ g F-BPA}) (1 \text{ mol F-BPA}) (3 \text{ mol } ^{19}\text{F}) (19\text{g } ^{19}\text{F}) (1 \times 10^6 \text{ ug})}{(10 \text{ g H}_2\text{O}) (1 \text{ ml}) (226.0\text{g F-BPA}) (1 \text{ mol F-BPA}) (1 \text{ mol } ^{19}\text{F}) (1\text{g})} = y \text{ ppm}$$

For the in-vivo experiment, an absorption peak or "match" in the coil of 40 dB was achieved. A TR of 500 ms was used which when confirmed with later sequences was too short. Although the number of averages in a specific amount of time increases with a lower TR and therefore a shorter acquisition time, it also does not collect all of the signal. If the T_1 of the system in-vivo is longer than 500 ms, then the acquired echo will only contain a portion of the emitted signal. Later ^{19}F runs show that a 2 s TR produces better signal to noise than a 500 ms TR on TFA/F-BPA phantoms.

The other drawback of this experiment, as seen in hindsight, is that the T_2 in-vivo appears as 4.2 ms. As stated in the abstract, this may be too fast for the spin echo sequence to acquire the signal. The next step is to employ a gradient echo pulse sequence to acquire the signal in a more rapid manner.

Imaging Studies

Figure 31 gives an image taken using the 2dfast sequence modified for ^{19}F . This was taken with a 100 ms TR, a 10ms TE and a 24x24x10 cm field of view. A 256x160 matrix was used and 4 averages were taken in an experiment time of

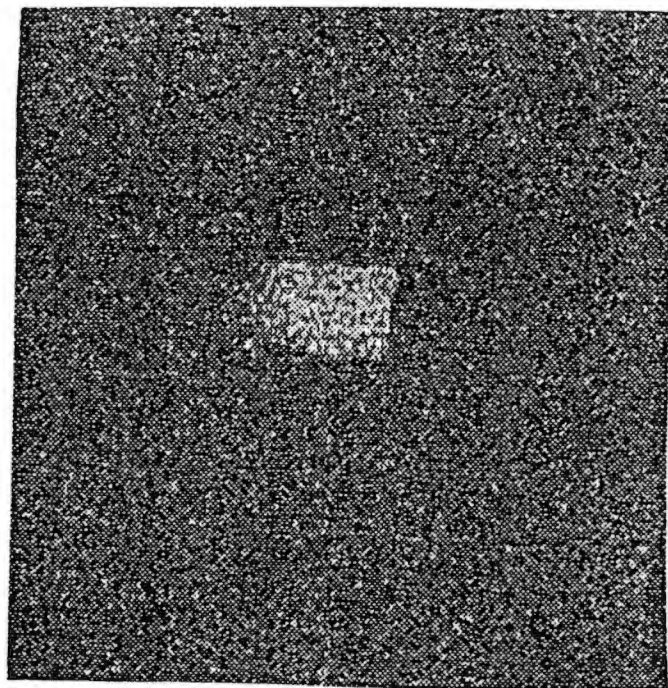


Figure 31. 250mM TFA Image Using 2dFast Broadband Sequence

about 1 minute. Normalizing to the number of averages, the signal to noise ratio was calculated to be 0.64, although the image quality is definitely reasonable.

36ppm Spectroscopic Studies

The results in Appendix F represent spectroscopic runs using a 36ppm TFA phantom. Optimization was done on not only the fine receiver gain, R2, but also the TR to some extent. Runs 130 through 134 represent expected good results for the 250mMol sample. Runs 169 through 170 represent initial runs using an actual 36ppm TFA phantom. Signal to noise starts out poor using a transmit gain of 0 and a R2 of 15, even with an increasing number of averages. The runs from 172

through 173 show an improved signal by increasing the transmit gain from 0 to 12 and fixing the sweep width at 32 kHz. Finally, fixing TG and R1 we vary R2 over a wide range in order to achieve a reasonable amount of signal in runs 174 through 185. It can be seen in Figure 32, that as expected, the signal/noise ratio remains constant. It can also be seen that increasing the R2 by 1 unit doubles the signal as well as the noise on the GE scanner.

The final set of runs from 186 through 188 exhibit a change in TR from the 500 ms used in the previous runs to a longer 3s TR. If the TR is much shorter than the inherent T_1 of the sample, less of the signal will be received. A greater danger lies in the fact that the next RF pulse will flip the dipoles 90 degrees even if they are not fully relaxed. This will lead very quickly to "saturation" of the signal and the dipoles will remain aligned with the magnetic field and will produce no signal.

Conclusions

Beginning the experiment in the phase of hardware and coil construction allowed me to gain a greater understanding of the operation of the MRI itself as well as the underlying physics. Continuing on to phantom composition, spectroscopic analysis and finally imaging has allowed me to gain a broader and fuller understanding of this problem as well as concepts in MRI/MRS that were purely theoretical prior to this experiment.

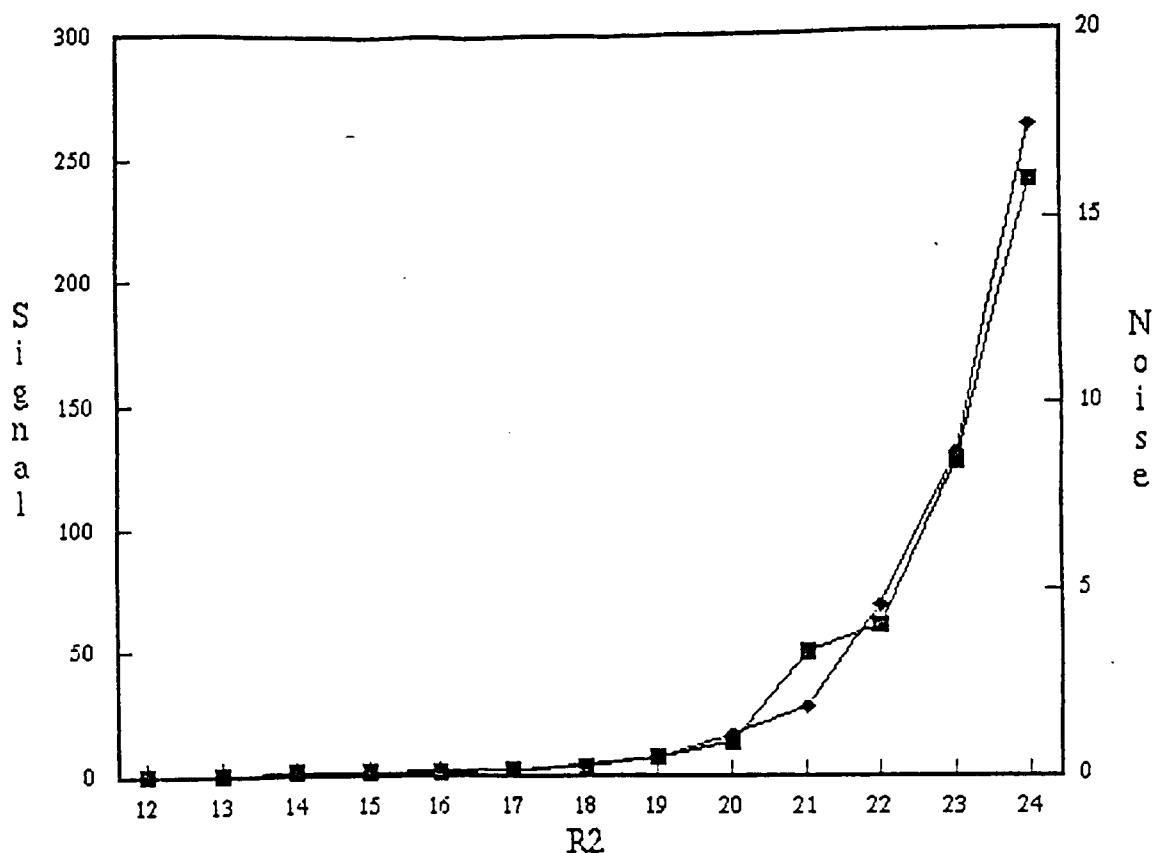


Figure 32. R2,TR Optimization Plot - 36ppm TFA

It has then been shown that ^{19}F MRI/MRS provides a method by which the in-vivo distribution and localization of the BNCT agent F-BPA-Fr may be examined. Future studies will serve to improve image quality through software development and hardware modification. Correlative images with those in PET as well as co-registered proton MR images will provide more accurate determination of tumor location and uptake information. Volume selective spectroscopy may also prove to be a useful tool in defining Fluorine localization. Further work in this area will prove to be a useful tool to researchers in BNCT.

Chapter III

Microdosimetry

Introduction

At first glance, the microdosimetry of the BNCT compound would appear to have little direct effect on the individualized treatment planning of each patient. The macrodosimetry allows the specific dose contours to be drawn on individual patient scans of different modalities. These contours, in conjunction with the PET studies at UTMCK show that ^{18}F -BPA-Fr is taken up selectively by the tumor in-vivo. Initially, it would appear that the distribution and pharmacokinetics problems are solved. In reality, there are now fundamental questions to be answered to determine effectiveness of treatment prior to actual irradiation at BNL.

Problem Definition

Questions as to whether the Boron compound is localized in the intra or extracellular regions or on the surface of the cell must be addressed to evaluate various drug delivery methods. Is the localization sufficient to allow the ^7Li ion and the ^4He particle to travel 10um into the tissue and actually kill the tumor cell? What sort of cell survival curves or kill ratios, may be predicted for a given dose of BPA-Fr at a specific beam exposure? Do the PET compartmental models provide any insight into biodistribution at a cellular level? These are questions that cannot be answered by looking at a standard diagnostic image. Parametric PET images formed by solutions of mathematical models that simulate physiological

compartments will provide insight into some of these questions. Monte Carlo simulations of particle trajectories striking various geometric constructs will also allow us to model response at the cellular level. The combination of these and other analytical tools will allow us to probe for answers and formulate theories that will answer these questions on a more basic level.

Methods

Input Parameters

The primary tool that is being used for microdosimetry analysis is a published program by Dr. David Charlton of the Department of Physics at Concordia University in Montreal, Canada [13-15]. The program is entitled BCT2, Boron Capture Therapy 2, and contains two separate sections of code. The first section allows the cells to be modelled in various geometric constructs and allows definition of ^{10}B and ^{14}N concentration levels. The second section actually performs a Monte Carlo analysis whereby a known neutron flux passes into the defined volume and the energy deposition by the reaction products are recorded. The geometrical placing of the cells in a volume is accomplished through the use of an input file to the program as displayed below:

0.25	:fractional filling
10	:number of sections (integer)
80	:Number of migration steps
2.0 2.0 2.0	:% of ^{14}N in nucleus,cytoplasm,external (g/100g)
20.0 20.0 20.0	:ppm boron in nucleus, cytoplasm, external
3.7E12	:neutron fluence (n/cm ²)
10	:number of times section is cycled

Each of these input parameters will be dealt with individually and must be set as close to physiologically correct as possible, based on current literature as well as experimental data and theoretical simulations. Assumptions must be grounded in all three areas to insure global accuracy and to not propagate errors throughout the calculations.

A fixed volume to be studied is defined and then the percent filling of this volume by cells is placed in the input file. The number of cells actually placed in the volume depends primarily on the size of the cells to be studied, but also on the number of migration steps. The program then begins by assigning cells to the center of the defined volume as shown in Figure 33.

Migratory Steps

It then concurrently checks for overlap with previously defined cell locations as well as boundary conditions. Once the cell is fixed within the volume, the migration subroutine is then called. The number of migration steps is defined in the input file and will be the number of 1% incremental steps that the cell takes towards the center of the volume. After each step, the overlap of the cell in relation to other cells and boundaries is again checked. This process continues until an intersection with another object is reached or the number of migration steps has been exceeded. This routine allows for either a very "loose" packing or a "tight" packing depending on the number of migratory steps. Knowing that the cell

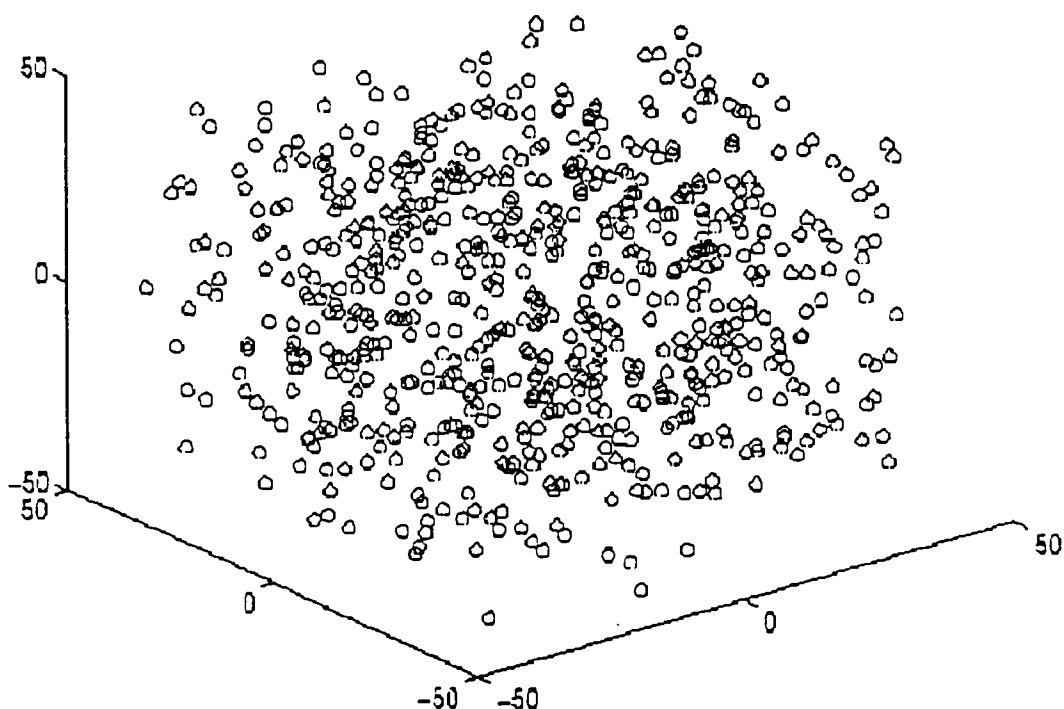


Figure 33. 3D Scatter Plot of Cell Filling 100uL³

placements are completely random in nature, the whole volume will be filled in time with zero migration steps. Given that a fractional filling level is also given as an input function, the amount of extracellular space is then in direct proportion to the number of migrations. For example, knowing 25% of the volume is to be filled, a value of zero migration steps would provide the maximum allowable extracellular space. This will affect the calculations due to the fact that if the boron becomes concentrated in the extracellular space, the binary products of the capture reaction will then have a longer distance to reach the nucleus. This could then increase the survival fraction throughout the entire volume. Conversely if the agent to be modelled is linked to a monoclonal antibody that remains on the surface of the cell, than a large extracellular space may accommodate this to a greater extent.

The opposite choice of migratory steps would allow a large number of steps to be simulated. This would then "compact" all of the cells towards the center of the volume, thereby decreasing the amount of extracellular or interstitial space between the cells. Given the ratio between extra and intracellular boron levels, this could dramatically increase the kill ratios and decrease the survival fractions. The products of BNCT would have a much shorter distance to travel to deliver a lethal dose. A lethal dose in this case would be assigned based on a number of criteria. The passage of the ^7Li ion or the alpha particle must pass through the nucleus itself. Physiologically, the particle could pass through the nucleus and not break the chain of DNA. If this occurs, then the cell could continue to replicate and remain intact. This assumption though is not the only factor that must be fulfilled in order to determine a cell kill. The energy of the particle left at the end of the track must be sufficient to provide damage to the cell. The energy is related to the dose delivered by the RBE or relative biological effectiveness factor. This allows calculation of the dose delivered on an average to each region of the cell as modelled by the program.

Cellular Pathology Research

One major assumption that has been overlooked and which would be an interesting future research topic would deal with "quiescent" cells. It is known that quiescent cells or "Q" cells are non-proliferating tumor cells that have a different level of oxygenation than standard tumor cells. Another key characteristic of these

"Q" tumor cells is the fact that they are metabolically inactive as well as non-proliferating [63]. These cells would have a different intracellular uptake of BPA than other tumor cells. Realistically, if these cells are not metabolically active, the level of BPA taken up would be no different than normal cells. Ono,et.al., feels that these cells may be the primary reason for tumor regrowth after BNCT [63].

Tumor heterogeneity among cell types presents a challenge to standard microdosimetry modelling. This package assumes uniform cell sizes and types with a homogeneous distribution of boron throughout all regions. Current literature in pathology stands in stark contrast to this simplifying assumption. Burger, et.al, describes a number of untreated GBM cases on a cellular level [8]. His drawing as shown below is a tracing of a histologically stained section that outlines various cell types and locations. The key to the Figure 34 defines the various symbols assigned to different cell types within the same tumor.

It can be seen that due to the diversity of the cell types and locations in the tumor region that extreme care must be taken in interpreting data from a needle biopsy. Burger states that if the needle misses a target point by only a few millimeters than a non-representative sample could be taken that might be used to determine a diagnosis of anaplastic astrocytoma but not actual tumor composition [8]. Scarpelli also comes to this conclusion in examining nuclear structures in various tumor types [71].

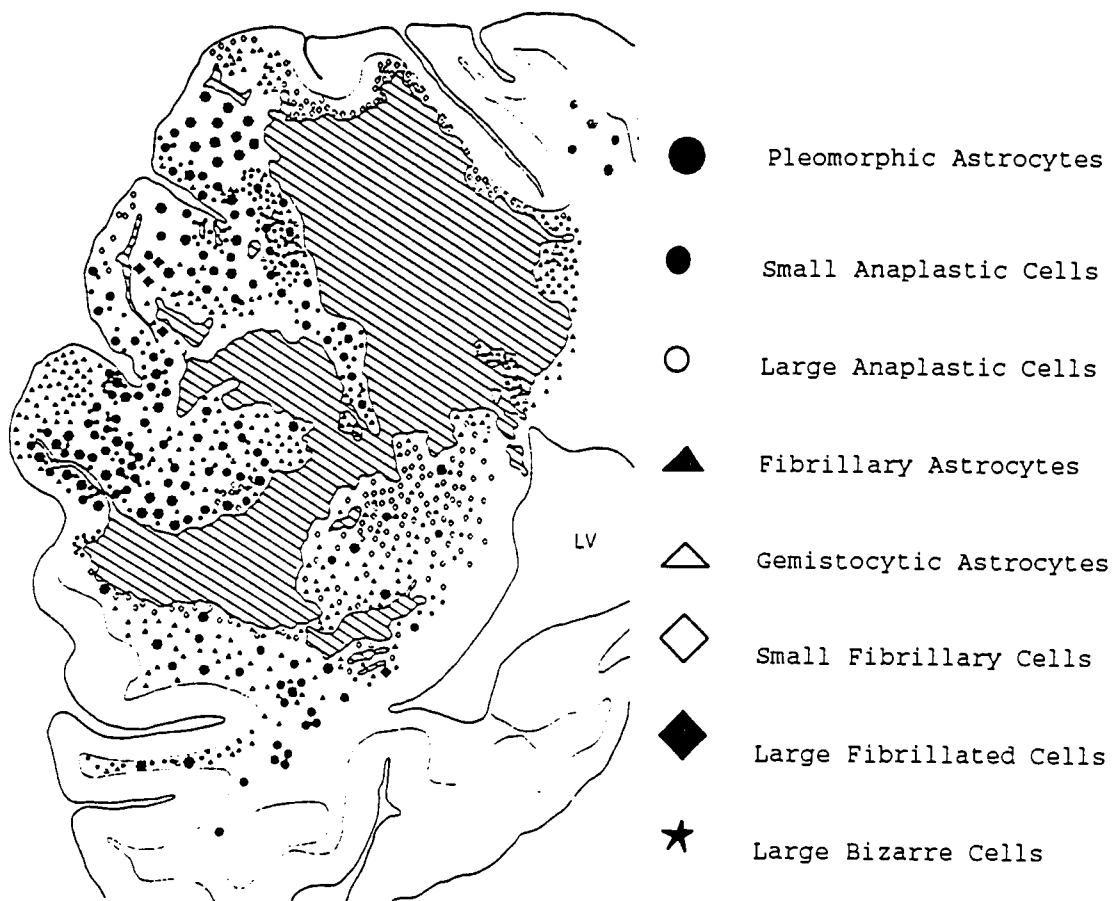


Figure 34. Glioblastoma Multiforme Histology Tracing

Factors such as fractional filling must then strive to take into account the diversity caused by interleaved healthy cells and non-malignant groups. This will also affect the boron distribution within the geometrical construct given different cell types will take up the BNCT agent in different concentrations.

Cell Size and Shape

In the original program, the cell sizes were computed on a random basis out of a choice of 4 variations as shown in Appendix G. This subroutine assigns RADC as the radius of the cell itself and RADN as the radius of the nuclei, which is placed automatically at the center of the cell. A random number generator is used to pick cell sizes from among 4 variations. If cell sizes could be correlated to those defined by Burger above, a more accurate picture of tumor histology would be portrayed throughout the simulation.

Scarpelli, et.al., examined glioblastoma multiforme tumors specifically and studied the cell structures and morphology of the nucleus [71]. The results are summarized for GBM of which 8 cases were studied:

MaximumNuclearDiameter:13.44±4.67 μ m

MinimumNuclearDiameter:8.77±2.86 μ m

The study also differentiated between those cells having one or more nucleoli per cell. I am not convinced that this factor would have any direct bearing on this

microdosimetry simulation given the fact that the nucleoli do not carry any replicating information.

Another factor that might be taken into account to improve physiological accuracy concerns the vasculature of the tumor itself. A simulation done at the Petten BNCT facility in the Netherlands takes this factor into account [83,84]. Wesseling, et.al. states that microvascular proliferation is very prominent in GBM [85]. There was a significant increase in the mean number, area and perimeter of blood vessels in the tumor region in comparison with that of normal brain. He also states that the heterogeneity is vast and the standard deviation within a tumor for these parameters is much higher than that of normal brain. This may be difficult to model but could provide an interesting study that would more closely resemble actual tissue in-vivo.

McKeever, et.al. provides the best study found in the literature concerning specific cell sizes and variations for GBM [54]. His study focuses on human GBM cells that have a higher level of Fibronectin, FN, and a lower level of Glial Fibrillary Acidic Protein, GFAP. He compares these cells with those of a continuous glioma line, LM, and those of normal Fibroblasts. The other striking result of this study is the nuclear to cytoplasmic ratio. As shown in Figure 35, these values are calculated by taking the area of the nucleus or sum of the nuclei in a cell divided by the area of the cytoplasm.

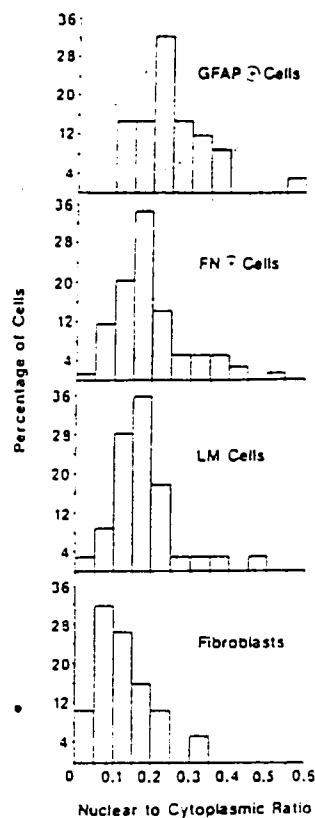


Figure 35. Nuclear to Cytoplasmic Cell Histogram Ratios

These factors as well all other measurements were obtained as an average to minimize the effects from single abnormal cells in a population. The data from this study will be used as direct input to the microdosimetry package to simulate sizes of both the nucleus and cell itself. The volume ratio of the nucleus to the cell is fixed at 0.75 for all cases in the BCT2 program. This value differs by almost a factor of 5 from that in McKeever's study [54]. The BCT2 program was not written specifically for GBM cells but was used later to model V79 Hamster Cells [14].

A personal communication with Dr. Subhash Chandra of the Ion Microscopy Lab in the Department of Chemistry at Cornell University has provided another approximate volume fraction for gliomas. Dr. Chandra states that for the glioblastoma cell line of T98G, the volume fractions of nucleus versus cytoplasm would be between 0.35 to 0.65 which corresponds more closely to the values used in BCT2 [12,78].

An actual photo of a typical Glioblastoma Multiforme, in Figure 36, is taken from the online tumor database at:

<http://www.tumorboard.com>

The photo shows the inhomogeneity of various cell shapes, sizes and orientations. Such variance is also examined and an excellent summary on cell size and shape variance from McKeever's study is also given in Figure 37.

The shape was originally modelled as an ellipsoid but was changed to a sphere. The choice of an ellipsoid was pursued given that nearly all astrocytomas possess cells with cigar-shaped nuclei [8,54]. This was also verified by examining the shape factors in the tables on the previous page. Dr. David Charlton has used the BCT2 program to run simulations of cells in suspension and monolayer. The suspension cells were of radii 4x4x4um and the monolayer cells of dimensions 7.43x6.05x1.42um. His results for survival curves simulating V79 hamster cells and alpha particle irradiation indicate almost no difference in the survival curve

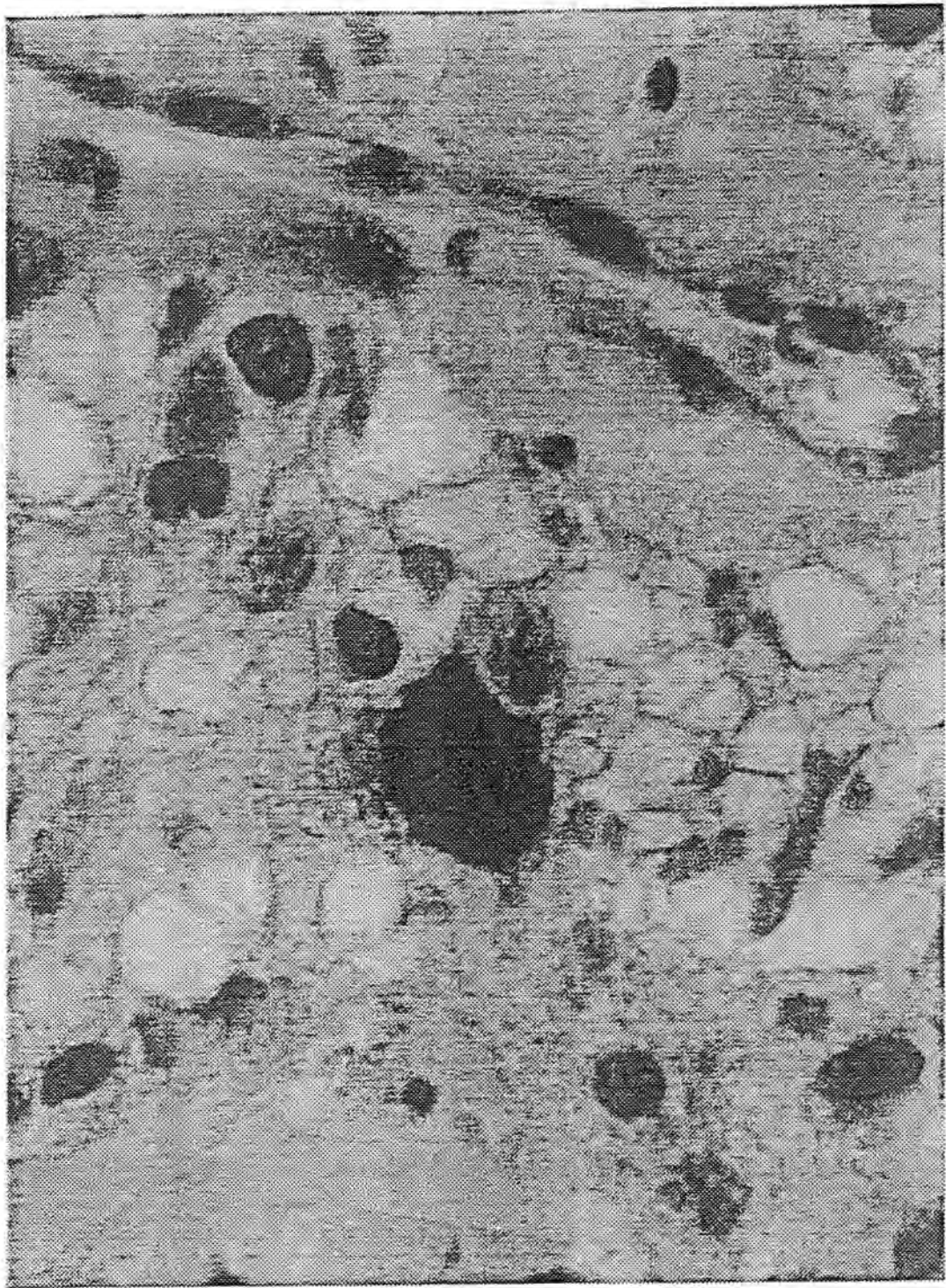


Figure 36. Glioblastoma Multiforme Photographic Image

TABLE 1.—Areas of glioma cell types and controls^a

	Nuclear area		Cytoplasmic area		Nuclear-to-cytoplasmic ratio	
	Mean ± SD, μm^2	Significantly different means ^c	Mean ± SD, μm^2	Significantly different means ^c	Mean ± SD	Significantly different means ^c
FN ^b	1,252 ± 1867	GFAP ⁺ , LM	8,376 ± 7422	GFAP ⁺ , LM, Fb	0.192 ± 0.091	GFAP ⁺ , Fb
GFAP ⁺	289 ± 234	FN ⁺ , LM, Fb	1,350 ± 817	FN ⁺ , LM, Fb	0.245 ± 0.091	FN ⁺ , LM, Fb
LM	803 ± 365	FN ⁺ , GFAP ⁺ , Fb	5,737 ± 3,124	FN ⁺ , GFAP ⁺ , Fb	0.176 ± 0.083	GFAP ⁺ , Fb
Fb	1,290 ± 450	GFAP ⁺ , LM	12,902 ± 10,136	FN ⁺ , GFAP ⁺ , LM	0.131 ± 0.074	FN ⁺ , GFAP ⁺ , LM

^a Fb = fibroblast.^b For multinucleated cells, each nucleus was counted separately in calculating mean nuclear area. Each nuclear area of a single multinucleated cell was then added to obtain a total nuclear area and divided by the total cytoplasmic area in calculating the nuclear-to-cytoplasmic ratio.^c Each of the 4 groups of cells was compared by analysis of variance (ANOVA) with direct comparisons between experimental groups as well as with fibroblasts. Abbreviated names of cell groups with significantly different means ($P < .05$) are recorded directly to the right of the mean with which they were compared. Rank sum results were comparable to ANOVA.TABLE 2.—Perimeters and shape factors of glioma cell types and controls^a

Cells	Nucleus			Cytoplasm		
	Perimeter	Significantly different means ^c	Shape factor ^b	Perimeter	Significantly different means ^c	Shape factor
	Mean ± SD, μm		Mean ± SD	Mean ± SD, μm		Mean ± SD
FN ^b	134 ± 45	GFAP ⁺ , LM	0.802 ± 0.116	459 ± 284	GFAP ⁺ , Fb	0.562 ± 0.209
GFAP ⁺	63 ± 23	FN ⁺ , LM, Fb	0.836 ± 0.134	257 ± 169	FN ⁺ , LM, Fb	0.384 ± 0.260
LM	108 ± 31	FN ⁺ , GFAP ⁺ , Fb	0.823 ± 0.133	389 ± 125	GFAP ⁺ , Fb	0.463 ± 0.148
Fb	145 ± 33	GFAP ⁺ , LM	0.761 ± 0.133	838 ± 241	FN ⁺ , GFAP ⁺ , LM	0.239 ± 0.127

^a Fb = fibroblast.^b The shape factor is calculated by the formula: $4\pi \times \text{area}/(\text{perimeter})^2$. A circle has a shape factor of 1, and a line has a shape factor of 0.^c Each of the 4 groups of cells was compared by analysis of variance (ANOVA) with direct comparisons between experimental groups as well as with fibroblasts. Abbreviated names of cell groups with significantly different means ($P < .05$) appear directly to the right of the mean with which they were compared. Rank sums were comparable to ANOVA.TABLE 3.—Variation in measurements of individual cells compared with entire cell populations^a

Cells	Nuclear perimeter		Cytoplasmic perimeter		Nuclear-to-cytoplasmic ratio	
	Individual cells ^b	Population ^c	Individual cells ^b	Population ^c	Individual cells ^b	Population
FN ^b	0.15	0.34	0.07	0.62	0.20	0.48
GFAP ⁺	0.13	0.37	0.11	0.65	0.15	0.37
LM	0.18	0.29	0.03	0.32	0.19	0.47
Fibroblast	0.07	0.23	0.04	0.29	0.12	0.57

^a All numbers are calculated by the formula: SD/mean = CV.^b The number of measurements on a cell was 8 for all individual cells.^c The number of cells measured was 79 for FN⁺, 31 for GFAP⁺, 68 for LM, and 19 for fibroblast populations.

Figure 37. Cellular Size and Shape Parameters for GBM and Fibroblasts

slopes [14]. He states that this would then indicate that cell survival is dependent upon DNA damage principally given the nuclei are large with respect to the range of the ions. I chose to alter the sizes of the nuclei to determine what sort of affect this would have upon dose as stated in the results section.

Cellular Concentration Levels

The next variable to be studied as input to the Monte Carlo program concerns the concentration and localization of the nitrogen and boron *in-vivo*. Starting with the nitrogen statistics, a concentration of 2.0 g/100g is chosen as an average value for tumor cells. This is based upon a value of 1.71 g/100g for brain tissue as quoted by Charlton [13]. The only point of concern in this estimation arises *in-vitro* with cellular level studies. The nitrogen reactions outside the cellular boundaries contribute to 23% of the total dose. The program estimates the concentration in the cytoplasm, the nucleus and exterior to the cell. Standard growth medium have a concentration of 0.1 g/100g which would drastically change the dose given to the nucleus from the nitrogen reaction [13]. Dr. Tom Byrne's growth media, Ham's F-12 Media, contains 20 amino acids of which all contain nitrogen. *In-vivo*, it is assumed that the concentrations of nitrogen in the three regions are identical, but further research and studies need to be done to confirm this assumption.

The boron concentration *in-vivo* depends on the individual compound, experiment,

modality and treatment facility. One factor written into the BCT2 program allows for delivery of the boron to the cell by monoclonal antibodies. This is done by defining the fraction of atoms that move from the surface into the cytoplasm or nucleus of the cell and thereby increase the concentrations in the respective regions.

Chandra, et.al. shows in Figure 38 that using ion microscopy, the concentration of boron in the nuclei and cytoplasm show subtle differences [12,78]. This would imply the boron that is distributed to the cells reaches an equilibrium across the cellular membrane, and therefore, equal concentrations intra/extracellular are reasonable. A fact that may also need to be accounted for is that disruption of the blood brain barrier might allow a higher concentration of boron in the extracellular spaces.

The amount of boron that is taken up by the tumor has also been studied by Chandra, in Figure 39, to reveal a difference in concentration based upon whether the cells are in the main tumor mass or are clusters of neoplastic cells [78]. At the site of the main tumor mass, the cells take up BPA-F at 99 ± 36 ppm compared to 27 ± 12 ppm in normal brain. In clusters of neoplastic cells the concentrations are 47 ± 15 ppm vs. 16 ± 8 ppm in normal brain.

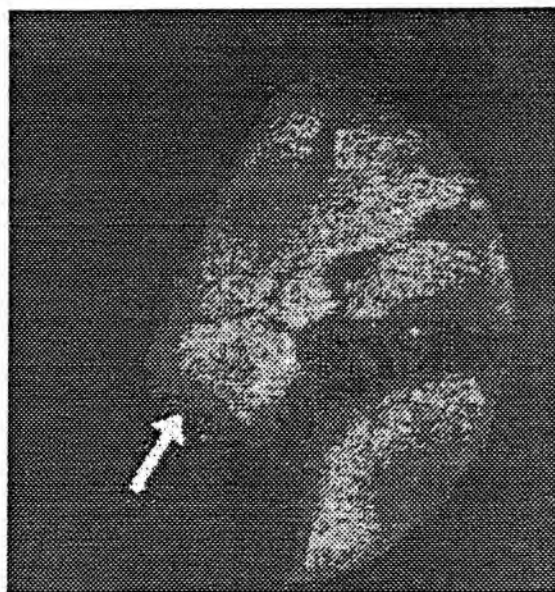


Figure 38. BPA-F Ion Microscopy Cellular Boron Distributions

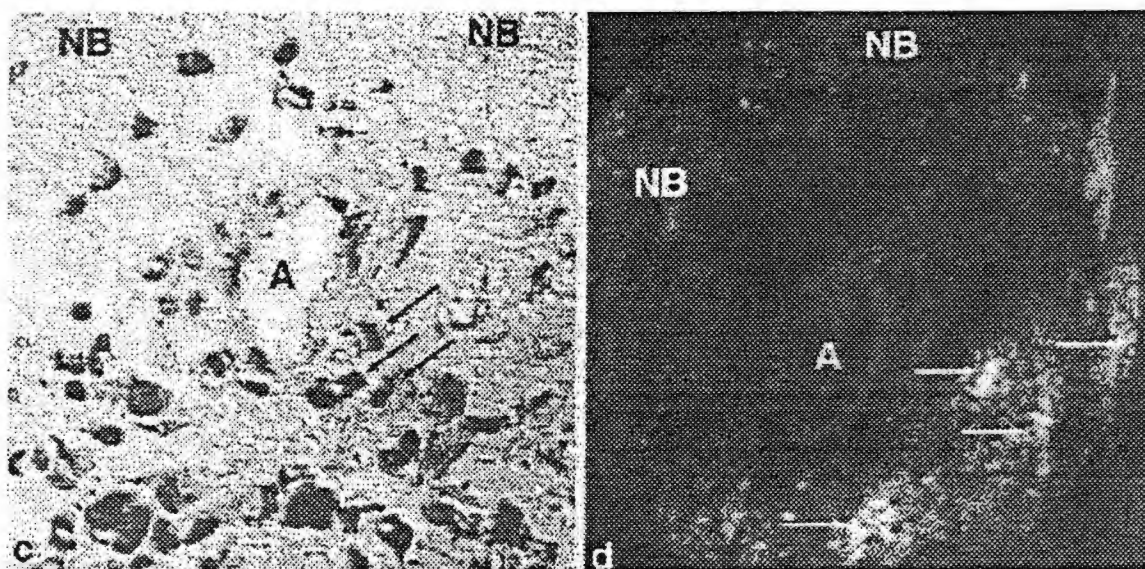


Figure 39. Pathology/Microscopy View of BPA-F Uptake in Neoplastic Cell Clusters

Monte Carlo Microdosimetry Analysis BCT Program

Now that the user variables have been placed in the input file, the program sets up the geometrical volume taking into account migration steps, cell size and shape and boundary conditions as discussed earlier. The second program reads in the distance and energy data for the products of the capture reaction as well as the stopping powers for protons. The location of the nuclear reaction is chosen at random and the resulting ions are generated opposite each other at an angle defined by a random direction cosine. These particles are then tracked and linear energy deposition is calculated once the nuclear boundary is crossed. The energy deposition as a function of distance was evaluated numerically at intervals of 0.1 μ m in the program. The average number of reactions that occurs is based on a Poisson distribution if less than 100 and on a Gaussian distribution if greater than 100 reactions occur.

Points of discussion on the output from BCT, given in Appendix H, include the area specific doses, dose fractions and dose spectrum. The output represents the BNL BNCT Trials using 33.6ppm of boron evenly distributed through all three cellular regions. The doses are then calculated for the nuclei, cytoplasm and external areas. The number of interactions in each region is dependent on the cell dimensions and concentrations. The surface dose is zero as it was not incorporated into the input file but, as described earlier, could play a prominent part as shown by Charlton if antibody studies were to be simulated [15].

The fractional filling of volume statistics also represent an interesting result that translates directly into the fractional dose results. Notice that, in this particular run, the external cellular space takes up 52.8% of the defined cell volume within the region of study. This is the highest volume fraction and directly translates into receiving the highest dose in both boron and nitrogen given the equal distributions. The primary dose component would be the dose to the nucleus of the cell given the probability for a cell kill is highest due to the proximity of the reaction point to the DNA itself.

Nuclear Volume Fraction

In conjunction with the volume fraction studies of the microdosimetry program, BNL has placed an interesting plot in their #4 Clinical Protocol Description activated on May 10, 1996 with Dr. A.D. Chanana as the principal investigator. Figure 40 shows ^{10}B concentration as a function of nuclear volume fraction, NVF, assuming spherical nuclei:

$$\text{NVF} = r_{\text{nucleus}}^3 / r_{\text{cytoplasm}}^3$$

Figure 40 gives the expected concentration of boron in the tissue as a function of nuclear size. This information is invaluable as an input to the microdosimetry program. Knowing the NVF, one can now give an estimate of the amount of boron to place in that specific nucleus. At present, the concentrations of boron in the different cell regions are homogeneous and independent of NVF. Knowing the slope of the linear regression fit to the data, one may then calculate on a per cell

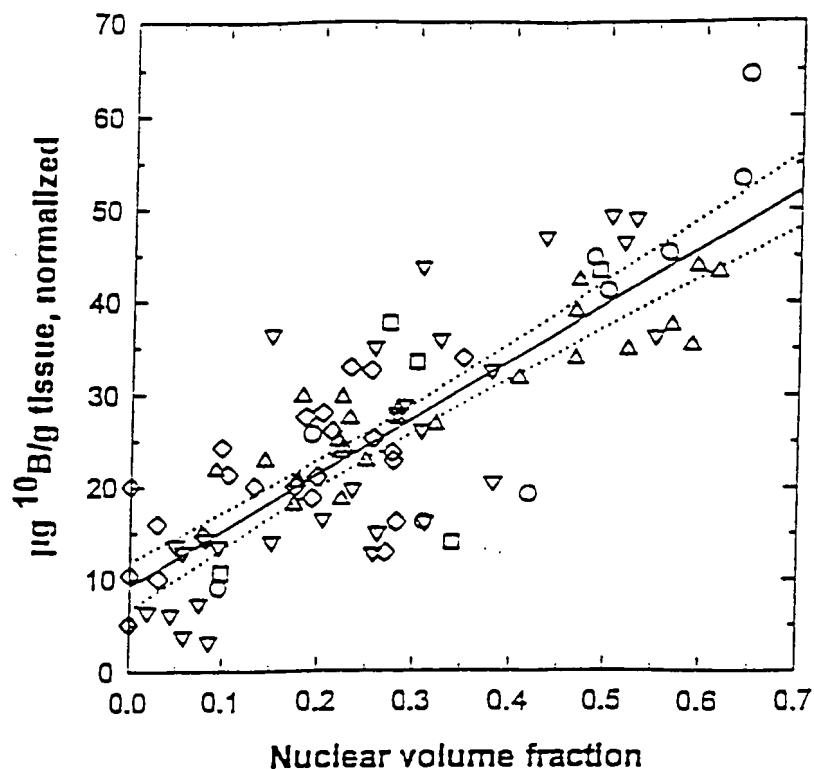


Figure 40. Nuclear Volume Fraction vs. Cellular ^{10}B Concentration

basis the concentrations of boron based on the random assignment of NVF. This could provide a much more accurate distribution pattern of boron throughout the tumor region. This would also correlate with the pathology studies done claiming heterogeneity of tumor cell size and shape within a single tumor mass.

If one could input the sizes and shapes of cells inherent to a specific tumor cell line, the appropriate amount of boron at that cell could be approximated. This would provide a much more accurate distribution of dose on a cellular level than has ever before been published. In the future, one could even foresee taking a

tissue sample from a patient during debulking surgery as a basis for cellular type distribution. Using pattern recognition software, one could read in cell shapes and sizes, from a set table of known cell types. A patient specific table could be produced that would create a geometrical template for microdosimetry analysis using position and size information from the tissue sample. This is truly an open field that I feel would provide the next leap in patient studies for BNCT.

Another point of interest in the output results is that of dose as distributed among the source particles. The proton dose or "recoil" dose, including the carbon in the nucleus, is the lowest component of total dose. Again, note that the gamma and fast components of dose are not simulated in this model and would need to be approximated to provide an accurate dose picture. This will be dealt with in the results section as output from the microdosimetry package is compared with the actual BNL protocol results. The lithium and alpha doses are treated equally given there is very little data on lithium. The stopping powers were assumed to be identical in the input file. Both particles are high linear energy transfer particles at these energies and the trajectories follow straight paths through the tissue. The ranges of each of these particles are on the order of one cell diameter and important deviations from the average energy deposited in this track length were not expected. Current experimental data for ^7Li ions and alpha particles as well as cross section data may be found at the Nuclear Energy Agency in France. They serve as a repository for experimental and reference nuclear data on many

reactions and can be reached via the WWW at <http://www.nea.fr> and the databases may be searched using a login of **dyke** and a password of **manxje**.

One interesting note that sets this program apart from many dosimetry packages is the output of a microdosimetric dose spectrum. Many authors determine the dose for a specified area and divide by the number of cells to obtain a mean cellular dose. The microdosimetry dose spectrum is plotted as a function of dose in Figure 41 using equally spaced 10 rad bins. The results are plotted for a fluence of $3.7 \times 10^{12} \text{ n/cm}^2$ and also $5.0 \times 10^{12} \text{ n/cm}^2$ which would correspond to either a higher flux or a longer time of irradiation. Notice the higher fluence gives a broader spectrum and a slightly greater maximum dose as expected. The one drawback of this package is that a user definable neutron spectrum cannot be used as an input for initial neutron energies into the Monte Carlo routine. In a recent communication with Dr. David Charlton, he said that this could be implemented into the program if the energy dependent cross sections for the reactions were known.

Energy Dependent Cross Sections

I have received the energy dependent cross sections for the B-10(n,alpha) reaction from the Nuclear Energy Agency database in France using the following search criteria in the EXFOR database:

z=b; a=10; particle=n; process=a; parameter=sig

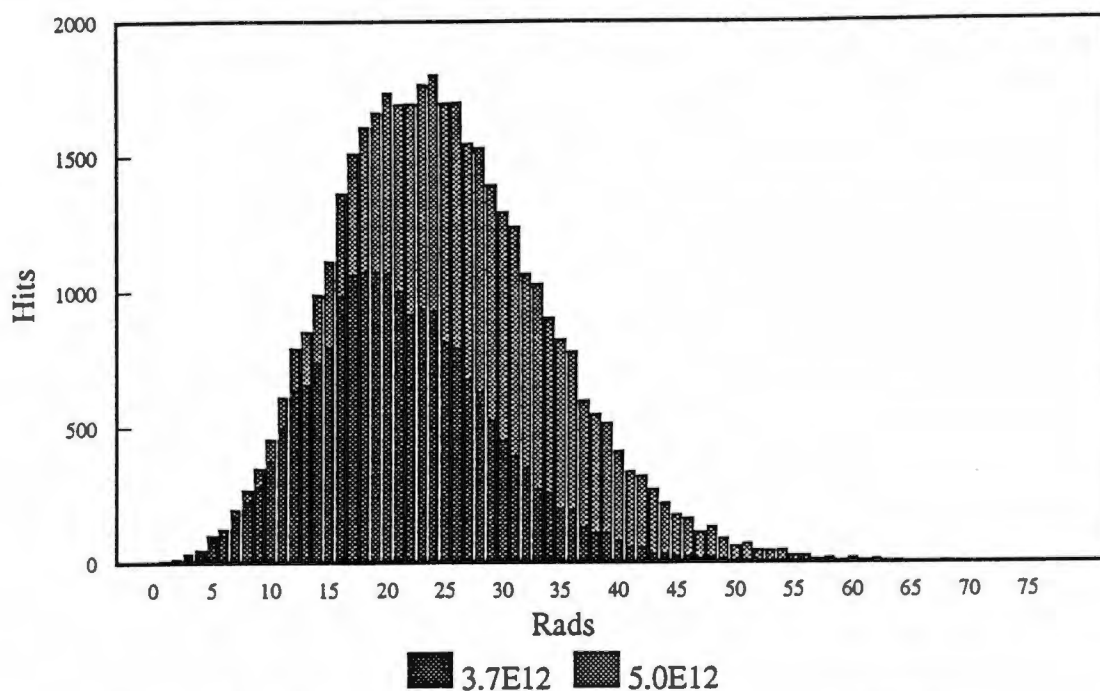


Figure 41. Microdosimetry Dose Spectrum from BCT Program

with the assistance of Dr. Marek Konieczny in Nuclear Data Services at NEA. This data could be used to determine the dose in the following sample calculation:

$$(3877 \times 10^{-24} \text{ cm}^2/\text{atom})(20 \times 10^{-6} \text{ g boron/g tissue})(6.023 \times 10^{23}/10 \text{ boron atoms/g}) \\ (2.34 \times 10^6 \text{ eV alpha energy})(1.6 \times 10^{-19} \text{ J/eV})(10^{13} \text{ neutrons/cm}^2)(10^3 \text{ g/kg}) = 17.49 \text{ Gy}$$

Where the first factor is the cross section for the boron reaction at a fixed thermal neutron energy of about 10keV [13]. The assumption is that 20ppm of boron is distributed through the cell structure. A reactor flux of 10^{13} n/cm^2 is assumed where the BMRR reactor at BNL is approximately half this value. This also assumes on a macroscopic level that all of the energy of the alpha particle is deposited within the volume of study. On the cellular level this value is replaced by the sum of energy depositions within that particular region.

A sample entry from a thermal neutron experiment is given in Appendix I that gives energy dependent data from the NEA database. Notice that the cross section is given in barns with its standard deviation as well as an energy range of approximately 100 eV. This experimental data may now be compared with data obtained from Oak Ridge National Laboratory from Dr. Dan Ingersoll and Dr. Charles Slater for various reactions at different energies. The defined energy levels in the following data are in "free-field FIDO format" from the BUGLE96 cross-section package in 47 neutron-group boundaries. Data are given for ^{10}B (5010), ^{11}B (5011), ^{12}C (6012), ^1H (1001), ^2H (1002), ^{14}N (7014), ^{15}N (7015), ^{16}O (8016), and ^{17}O (8017). The data was obtained, by Dr. Charles Slater, from the VITAMIN-B6 fine-group (199 neutron groups) cross-section library and were collapsed to the 47-group structure using a spectrum obtained from a 1-D calculation of the MIT homogeneous leg model. When the cross sections are folded with the fluxes and the energy deposition per event, then eV/cc-s is obtained as a measure of dose that can be converted to Gy with the appropriate RBE. A look at the data, given in Appendix J, in the lower energy range definitely shows that the cross section does vary with energy and would be a factor to include to provide more accurate results.

The plots of the energy dependent cross section data from the NEA server as well as ORNL show in a definitive sense that a fixed value should not be used. Note that the NEA data is a macro cross section and the ORNL is a micro cross

section. The conversion is given by the following where capital/lower case sigma

$$\Sigma = \sigma \rho N_e/A$$

represent the macro/microscopic cross sections respectively.

A full scale comparison plot, as shown in Figure 42, from 0 to 1500KeV allows one to see the exponential behavior of the cross section as the neutron energy increases. This could be fit to allow cross section calculation within the program without a need for table look up [46].

A closer view of Figure 42 is allowed by decreasing the energy range to 0 to 35KeV. This allows the epithermal neutron range to be viewed more accurately. It can be seen in Figure 43, that there is an order of magnitude change in the cross section from low KeV neutrons to those near the 10KeV mark. The following section will describe the Tower Shielding Facilities beam purity and flux spectrum. Note that these plots are correlated in energy to the cross section plots for direct comparison.

Tower Shielding Facility Dose Spectra

As stated above, once the energy dependent cross sections are known, one then needs to examine the actual spectra from the specific facility to be simulated. For the Tower Shielding Facility in Oak Ridge, the dose spectrum has been obtained.

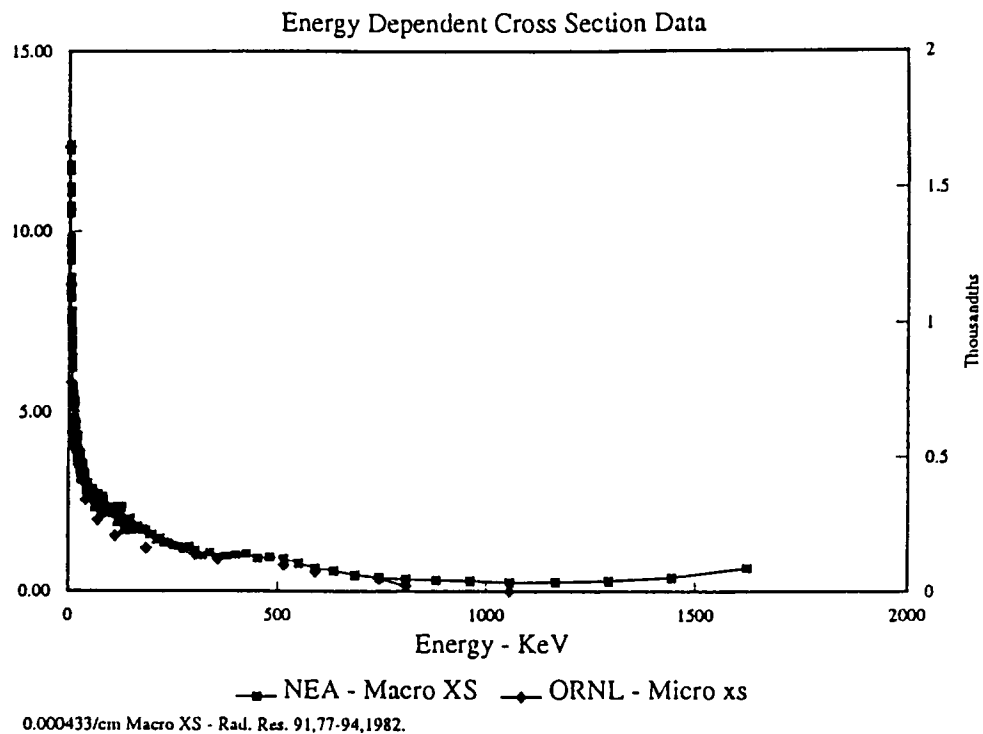


Figure 42. Full Spectrum Energy Dependent Cross Section Comparison

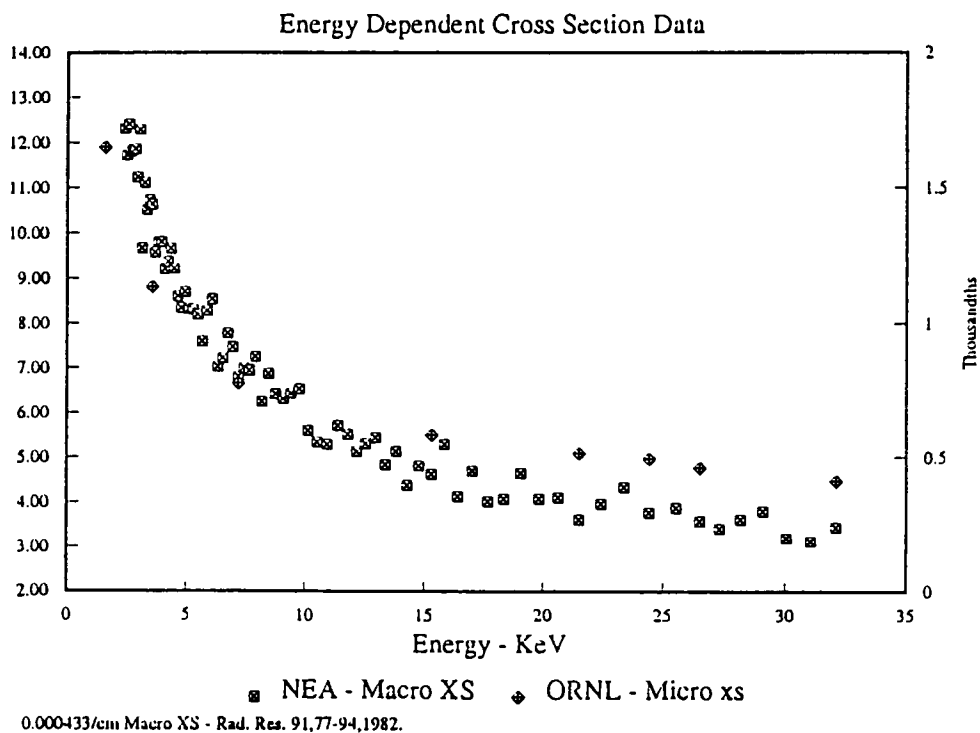


Figure 43. Epithermal Energy Dependent Cross Section Data

The results have been plotted for two different scales. Figure 44 gives the full energy spectrum up to 1.5MeV. This allows one to estimate the "purity" of the beam and to determine a fraction of the beam that is contributing to the higher energy dose components. Noting the difference between the raw unfiltered beam and that of the filtered beam, the contribution from the high end of the energy spectrum is minimized. The obvious trade-off with using the filter is although beam purity increases, the flux decreases as can be seen in Figure 44.

Beam purity on a large energy scale is easy to recognize. On a clinical scale the epithermal neutrons which are less than 10KeV must also be constant in production and not vary over the desired range in flux and energy level. It can be seen in Figure 45 that the TSF provides a constant source of epithermal neutrons that was untouched by the filter. The 10KeV component of the beam can be compared with the cross section plots shown previously.

TNC6 Microdosimetry Package

A separate program written by Dr. David Charlton allows calculation of survival curve data in addition to the functions given in BCT [13-15]. This package allows ellipsoidal modelling of cells instead of spheres and places them in either a monolayer or a suspension. This methodology allows accurate comparison with in-vitro cell irradiating studies. The third radii of the ellipsoid becomes the thickness of the monolayer in the simulation. This program also includes the

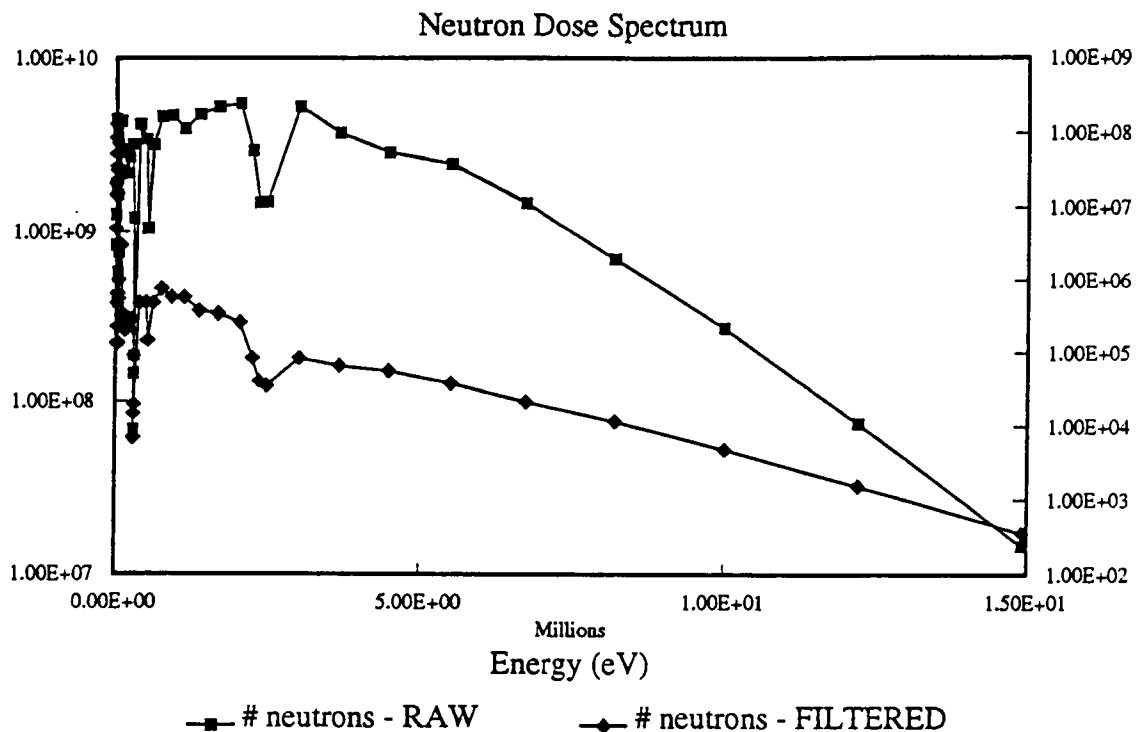


Figure 44. Full Energy Neutron Spectrum of Tower Shielding Facility

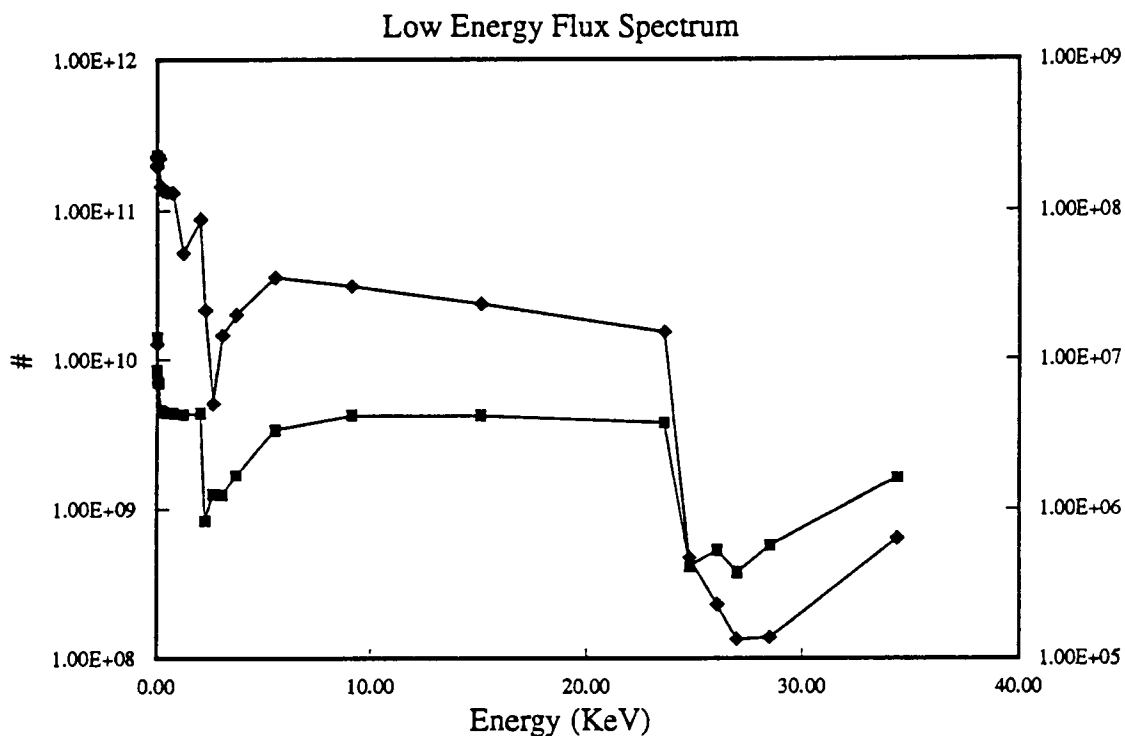


Figure 45. Low Energy Neutron Spectrum of Tower Shielding Facility

migration of cells from the surface to the nucleus and cytoplasm. Monoclonal antibodies may then be simulated as carriers of the BNCT agent in this manner. Dose spectra are given as an output for not only the total dose, but for LET distributions for n, alpha, ^7Li and ^{10}B . Hit distribution as well as dose distribution are also made available for analysis.

The key difference, and asset, in this program deals with the final line of output. The survival fraction of the cell layer or suspension is calculated as a function of fluence, concentration and energy deposition. This fraction is coded specifically for V79 hamster cells and yet the calculational methods can be applied to any tumor strain as will be shown [15]. The equations for survival become:

$$\begin{aligned} \text{Average Survival} &= \exp(-D/D_0); \quad D_0 = -d/\ln[1-1/n_0]; \quad L = -T/\ln[1-1/n_0] \\ L &= 108.0 - 0.97 \cdot \text{LET} \quad [50,100] \text{KeV/um} \\ L &= 10.7 \quad [100,190] \text{KeV/um} \\ L &= 58.0 - 0.25 \cdot \text{LET} \quad [190,] \text{KeV/um} \end{aligned}$$

Where T represents the chord length of the path through the cell nucleus. L represents the mean free path of the particle through the nucleus. D is the average dose to the cell nuclei and D_0 is the specific lethal dose, calculated using d as the dose per passage. The average number of passages, n_0 , the mean free path and the thickness of the nuclei have been found by experiment. Appendix K gives the full output from the TNC6 program using 10000 cells with a fluence equal to that at the Brookhaven Medical Research Reactor. A concentration of 33.6ppm is used in tissue and is equally distributed throughout the cellular compartments. A suspension was used instead of a monolayer which could

explain the 3% survival rate. If the fluence or boron concentration is increased slightly, the survival rate drops significantly. Note the average number of passages per cell is 11.13 in this case. The results are similar to those reported by BNL and are given in the results section.

Petten Microdosimetry Code

A final option to microdosimetry calculations comes from the PETTEN BNCT Facility in the Netherlands. A published program to perform these calculations was received from Dr. Peter Watkins, albeit missing the stopping power tables and configuration files. It is written in PC based PASCAL and I have been able to successfully recompile it in its entirety. The next step is to recreate the input files containing the particle stopping power tables. Dr. James Ziegler of IBM has a current version of his Stopping and Range of Ions in Matter, SRIM program at: <http://www.research.ibm.com/ionbeams>. Once complete this program will provide many features not currently available in BCT. A block diagram in the published paper will complete our description of this package [83,84].

Analytical Methods

One last methodology review should definitely be mentioned as a reference to all other programs. Kobayashi and Kanda provide an accurate and complete analysis method for estimating boron dosage to the cell nucleus. Their analysis differs from all others in the fact that it is an analytical approach and has been solved exactly

BORON AND NITROGEN NEUTRON CAPTURE MICRODOSIMETRY

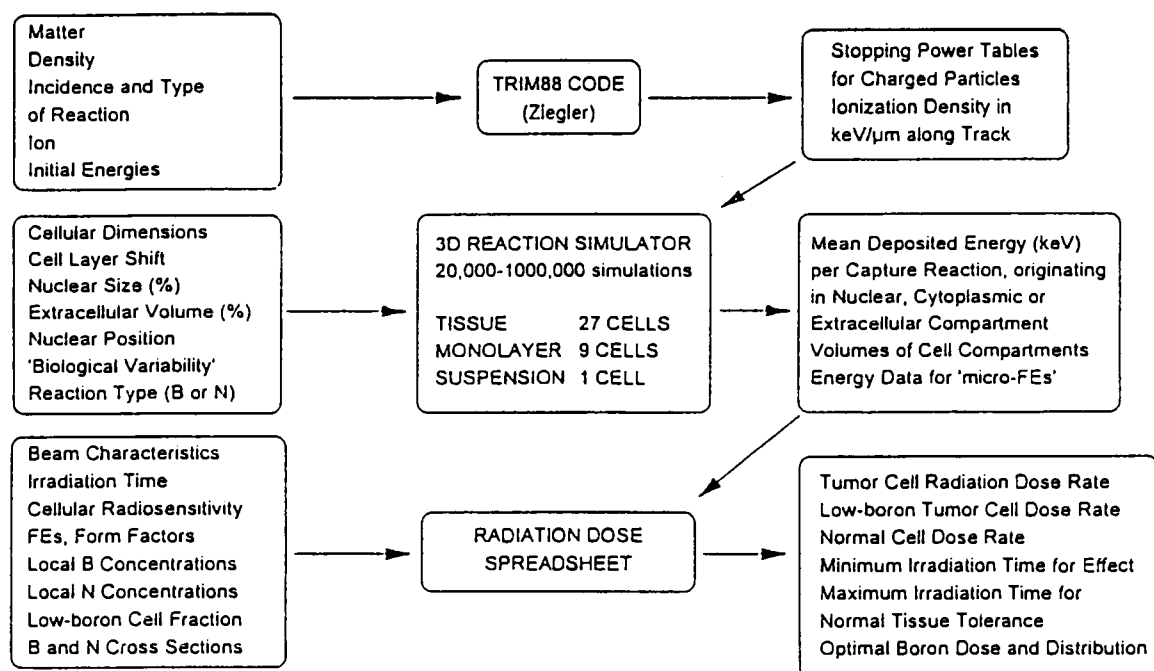


Figure 46. Petten BNCT Microdosimetry Program Block Diagram

for a specific geometry of cells. A spherical cell with a spherical nucleus at the center is assumed. Assumptions made in the model include that particle movement is linear and isotropic, production rate is isotropic, and the range-LET equation can be expressed in linear form. 6 different cell regions and 12 different hit scenarios are dealt with through analytical solutions. A close packed or cubic structure may also be approximated [46].

A further analysis of their model and implementation into a spreadsheet, as they have accomplished, would also provide another simple method to confirm dose

calculations on the cellular level. A fairly comprehensive synopsis of microdosimetry directly related to Boron Neutron Capture therapy has been compiled by Zamenhof at Harvard and should be read as a reference [87].

Results

Literature Confirmation

To begin the results section confirmation of the reliability of the BCT program will be stated. The author has compared results with other published experiments and has obtained results that reproduce the data within statistical variation [13-15]. For basic analysis we take a standard run with a fluence of 5.0×10^{12} n/cm², a nitrogen content of 2% and a boron concentration of 15ppm. The results yield the following where D_n , represents the nitrogen dose component, D_b , represents the boron component and D_t the total dose given by: $D_t = D_n + D_b$.

$$D_t = 2.94\text{Gy}; D_n = 0.811\text{Gy}; D_b = 2.135\text{Gy}$$

If the fluence is reduced by half to 2.50×10^{12} n/cm² all of the dose components should be reduced by half as well. The results become:

$$D_t = 1.523\text{Gy}; D_n = 0.395\text{Gy}; D_b = 1.129\text{Gy}$$

$$0.5\phi = 0.5\text{Dose}$$

If the fluence is returned to its original value and the boron concentration is decreased by a factor of 2/3 to 10ppm we find the following:

$$D_t = 2.214\text{Gy}; D_n = 0.758\text{Gy}; D_b = 1.456\text{Gy}$$

$$0.667 \text{ }^{10}\text{B} = 0.667 D_b$$

The same results occur for linear variance of the nitrogen concentration. Therefore, within statistical error, that is related to the number of cells simulated in the population, the program gives results that are reasonable and expected.

One other check on the reliability of the program was performed on a recent in-vivo cellular dosimetry paper using BPA injected into tumor bearing mice [63]. The crux of this paper formulates a linear fit relating survival fraction to neutron fluence for BPA BNCT. The final least squares fit to their data, is presented below:

$$-\ln SF = -0.052 + 13.0 \times 10^{-13} \text{ Fluence}$$

Using the TNC6 program we may now input data from the BNL clinical trials and compare the predicted survival fractions. The input value of boron concentration stated 1500 mg/kg body weight of BPA was administered [13]. Prior to that statement they claim the preparation of BPA was 100mg/ml of water. This last value converts into 51.67ppm of ^{10}B in solution. They state that the concentration in the tumor reached a maximum of 11ppm after a period of 3 hours.

For a fluence of $1 \times 10^{12} \text{ n/cm}^2$ the formula above yields a survival fraction of 27%. With a 52ppm input function of BPA, the TNC6 package predicts a survival fraction of 23.4%. For a fluence of $3.7 \times 10^{12} \text{ n/cm}^2$ as at BNL, the result was 0.86%. With a 52ppm input function of BPA, the TNC6 package predicts a survival fraction of 0.474%. Although the package was used initially for V79 tumor cells in hamsters, the correlation between the results and experimental data is still very comparable.

Adjustments in the calculation of survival fraction to take into account the different strain of tumor cells is needed to further correct the survival fraction calculations. The calculations are performed by using the average survival equations quoted earlier from Charlton. Given chord length in the nucleus is a factor, it is a high possibility that if more accurate cell sizes were placed in the model, that the results would correlate to a better degree with those of Ono's.

One final result from Ono.,et.al. relates to a tumor eradication graph that was published. Figure 47 plots the tumor control rate as a function of neutron fluence using nine mouse tumors per data point. The results state that a fluence of 10.2×10^{12} n/cm² produced a 50% control rate in comparison to the 3.7×10^{12} n/cm² fluence at BNL. Obviously variance in beam strength must be examined with extreme detail in human treatment planning. One option to test this result would be to increase the fluence slightly and then perform a PET scan after irradiation. Comparison to a control PET scan as well as a standard fluence irradiation PET scan would provide information about tumor control. Also, given the fact that each patient has a different uptake value for BPA a number of data points would need to be accumulated to eliminate statistical error.

BNL Results Comparison

The true test of this package is to see if the doses obtained macroscopically at the BNL clinical trials may be simulated microscopically with BCT. The parameters

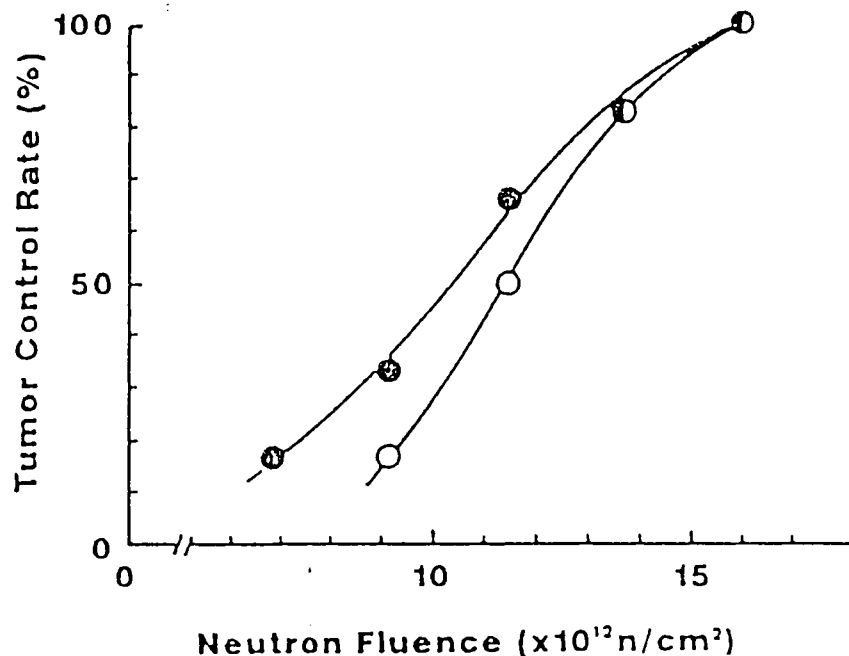


Figure 47. Tumor Control Assay Plot

used at the BMRR reactor are as follows: $3.7 \times 10^{12} \text{ n/cm}^2$ fluence, 250ppm BPA dose yielding approximately a 33.6ppm dose in the tumor region. The output from an overnight BCT run with a 10000 cell simulation is given in Appendix L.

The results from the Brookhaven Clinical Trial yield a value of 1.4Gy-eq for the Nitrogen dose and 4.3 Gy-eq for the boron dose for a sample patient done under the current protocol. The Relative Biological Effectiveness factor, RBE, must now be divided into the above doses to convert to Grays. The RBE for ^{10}B in blood is 1.3 and that of ^{14}N is 3.2. This then yields doses of 3.308Gy for the boron dose and 0.438Gy for the nitrogen component. This is in comparison with a dose of 3.577Gy for the boron dose and 0.583Gy for the nitrogen dose from the BCT

program. The results are within 10% for the boron dose and 33% for the nitrogen dose. The amount of nitrogen could be decreased in order to compensate for this difference, although this is an average value and is not patient specific. One final note is that in the simulation of 10000 cells, which would correspond to approximately 10uL of tissue assuming a standard packing of 1×10^6 cells/ml, 100% of the cells were hit. The average number of hits/cell is 25.19 as shown in the hit distribution plot of Figure 48.

Cellular Size Variance Study

A cell size study, in Table 2, was also performed to determine slight variation in dose due to nuclear size. The runs consisted of 200 cells and 8 migrations with the standard BNL protocol. Run A used the original method for cell radius distribution that ranged from 5-7um. Runs B and C fixed the cell radii at 5um and 7um respectively. Run D ran overnight with 10000 cells at 7um to insure statistical accuracy. One can see that changes on the order of 20% in cell radius affect the dose components to some degree. Further simulations varying the cell size and shape as discussed from a pathology perspective should be examined. BCT does provide a tool which allows compartmental distributions to be examined as a result of minor changes in geometrical structure.

ACBC/Lung Cancer Cell Verification

Analysis of Tom Byrne's experimental data can now be undertaken given the BCT

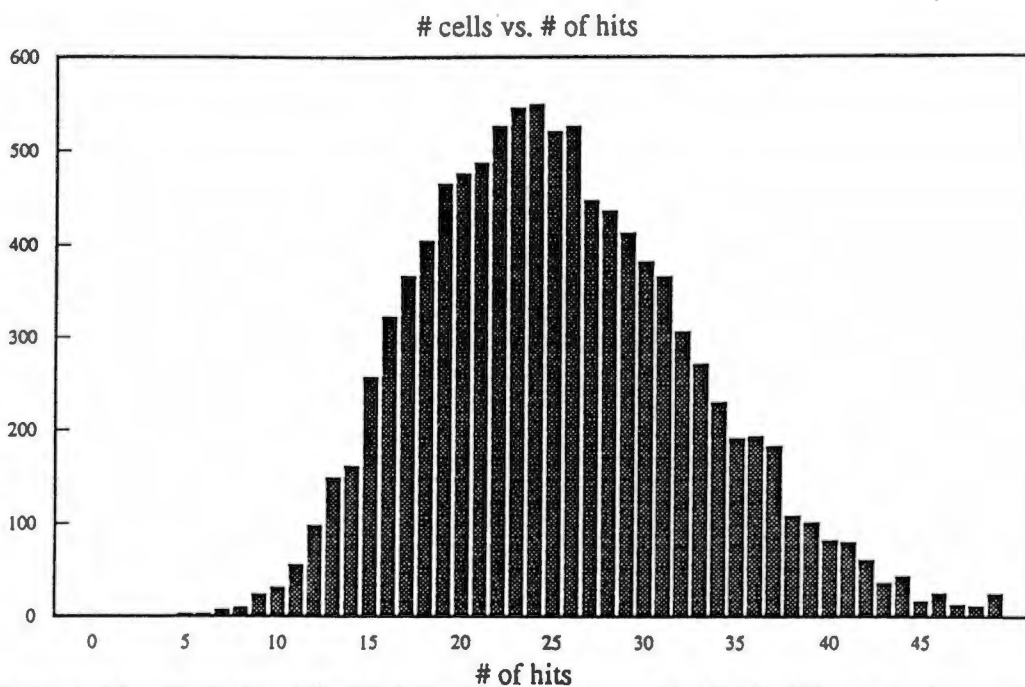


Figure 48. Cellular Hit Distribution Pattern for BNL Microdosimetry Run

Table 2. Cellular Size Variation Dose Results

	RUN A	RUN B	RUN C	RUN D
¹⁴ N nuclear interactions	144.6	130.4	153.3	257.7
¹⁴ N cytoplasm	48.2	43.5	51.5	85.9
¹⁴ N external	528.7	547.3	516.7	377.9
¹⁰ B nucleus interactions	107.1	96.6	113.6	190.8
¹⁰ B cytoplasm	35.7	32.4	38.2	63.6
¹⁰ B external	391.6	405.2	382.5	279.8
¹⁴ N nuclear dose - Gy	0.22	0.199	0.279	0.286
¹⁴ N cytoplasm dose	0.044	0.046	0.053	0.066
¹⁴ N external dose	0.304	0.31	0.249	0.228
¹⁰ B nuclear dose - Gy	1.169	0.95	1.079	1.073
¹⁰ B cytoplasm dose	0.165	0.165	0.144	0.178
¹⁰ B external dose	0.444	0.465	0.333	0.345

program has been verified to a reasonable degree. This experiment irradiated lung cancer cells exposed to boronated ACBC with a ^{252}Cf source having a fluence of $2 \times 10^8 \text{ n/cm}^2\text{s}$ at a concentration of 10ppm. One note of verification includes the data collected by Fairchild [21]. Dr. Tom Byrne's M.S. thesis references similar results to this paper.

Using TNC6 to simulate the experiment on V79 hamster cells conducted at the BMRR by Fairchild with a fluence of $2.8 \times 10^{11} \text{ n/cm}^2\text{min}$ at a concentration of 30ppm yields a surviving fraction of 77.7% for a 1 minute irradiation and 8.96% for a 10 minute irradiation which is similar to that seen for BSH and BSSB. Figure 49 for BOPP shows the steeper slope for the survival curve.

Table 3 gives the results from Tom Byrne's experiment at Oak Ridge. The results are drastically irreconcilable in survival fraction percentage. The fluence used in this experiment is a factor of 10 lower than that of Fairchild, even at the point of greatest irradiation time. The other disturbing factor is that all of the control cells are below the LD37 even at only a 1 minute irradiation time. Fairchild's control cells reach this point after approximately 5 minutes irradiation and there is always a surviving fraction even at the point of greatest irradiation time.

One idea for future study would be the simulation of tumor regrowth on a microdosimetry level to study the effects of fractionated treatment planning.

Table 3. Survival Result Comparison for ACBC Lung Cancer Irradiation

Tumor % Survival	Control % Survival	TNC6 % Survival	Fluence 10^{10}n/cm^2	Time Minutes
0.00002	0.007	0.986743	4.8	4
0.004	0.023	0.993102	2.4	2
0.065	0.243	0.996709	1.2	1
0.211	0.465	0.998019	0.6	0.5

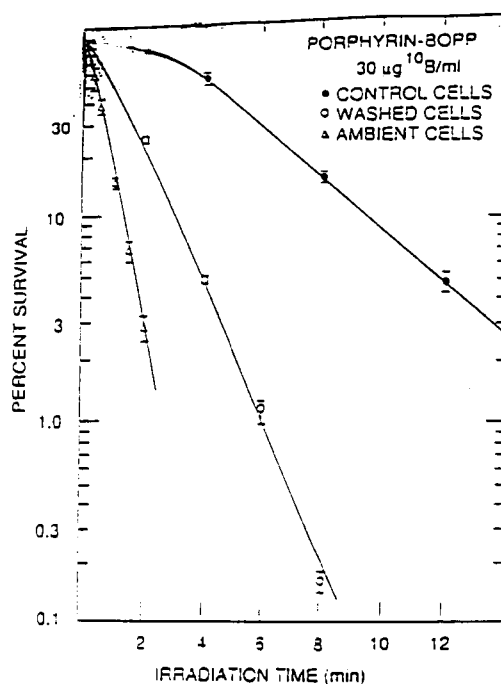


Figure 49. BOPP V79 Hamster Cell Survival Curves

Figures have been presented for cell motility and regrowth rates specifically for glioblastoma multiforme. Pathology studies have been done that examine cell proliferation and invasiveness studies of GBM in-vivo. Necrosis studies on a microscopic level have been published for GBM tumor strains. If a lower time interval for irradiation could be simulated, the possibilities would exist to reduce tumor necrosis. Lower intervals imply that a repeated procedure would be applied at a later time interval. BCT2 could simulate the initial dose prescription and record the positions of cells that were not eradicated by the irradiation.

Using these cells as a primary vertex, an isotropic simulation of regrowth, knowing the doubling rates in-vivo could be performed. The resulting cell colony would then be exposed to a simulated dose treatment, and the process cycled until complete eradication was achieved. Although a fairly straight forward idea in itself, the additional programming would need to be carefully implemented. Alongside this simulation, a battery of experiments with either cell cultures or small animals would need to accompany this study to provide substantive data. The opportunity does exist to simulate the dose prescription on a patient specific basis prior to neutron irradiation that could theoretically provide approximate information about treatment efficacy.

Conclusions

In conclusion, the microdosimetry analysis of BNCT agents in-vivo and in-vitro will remain an integral part of patient specific treatment planning. Programs exist that

allow accurate simulation of various geometrical constructs that may be modelled to improve physiological accuracy. There does exist room for refinements in all models as the knowledge about the specific tumor and BNCT agent increases. The addition of microdosimetric calculations through PET compartmental models will be dealt with as the model is defined and its compartments related to the areas of cellular dosimetry defined above.

Chapter IV

Macrodosimetry

Introduction

The need for radiation treatment planning on the macroscopic scale does not need to be explained. This step is taken on a patient specific basis to determine the logistics needed to administer a specific dose to a specific tumor in 3 dimensional space. The tumor has already been debulked by the surgical team and has been approved for irradiation. It is now that the theory of dose calculations must be practically applied to the well being of a real patient. Idaho National Engineering Lab in conjunction with Montana State University have developed a treatment planning package specifically for Boron Neutron Capture Therapy [62]. This package is in current use at Brookhaven National Laboratory to provide the patient specific treatment planning in their clinical BNCT trials.

Problem Definition

This dissertation has as a primary goal, the inclusion of Positron Emission Tomography images into the treatment planning code. The goal has immense importance as the PET images provide ^{10}B concentration information on a per pixel basis. It is this accurate concentration distribution that is markedly different from the previous homogeneous ^{10}B assumptions. This factor combined with the inherent metabolic uptake and pharmacokinetic information provided by the PET scan make the introduction of this modality into the treatment planning spectrum of ultimate importance. The metabolic uptake information is unparalleled by any other modalities at the present time. Although lacking in anatomical information, the PET scans show the "true" center of the tumor as the point of highest uptake. The results section then deals with the data comparison between the standard MR/CT prescribed dose contours and those of the PET results. One last comment about future study using PET in BNCT will be discussed in the section on the radiation transport code.

There are two components to the program that will be examined separately. The first component of the software package is the Boron Neutron Capture Therapy Treatment Planning Environment, Bnct_rtpe. It is through this interface that the physicist is able to import medical images from any modality in order to define the geometrical construct required by the radiation transport code. Figure 50 shows the control panel for Bnct_rtpe.

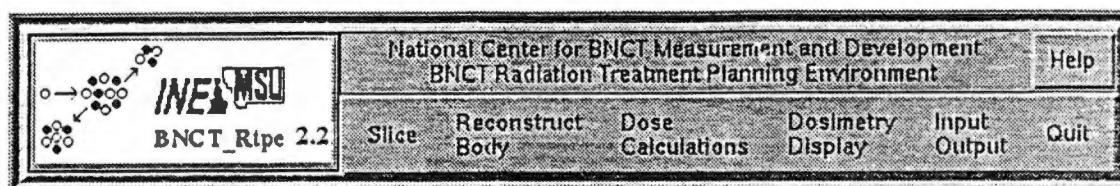


Figure 50. BNCT Radiation Treatment Planning Environment Control Panel Methods

Methods

Image Series Input

This process begins by importing data into the Bnct_rtpe package. As PET data had never been used in pre-treatment planning prior to this dissertation, there was no a priori Graphical User Interface to input data. One of two options must then be employed to allow the data to be properly read in. The first involves conversion of the data into qsh image format. A conversion routine with a graphical user interface, GUI, has been written that will allow input of raw data into qsh format. QSH was developed by a joint collaboration between the Dept. of Computer Science at Columbia University and the Dept. of Radiology at NYU in 1990 as a standard for digital image exchange following the AAPM image file format. (<http://nucmed.nyu.edu/NucMed/qsh.html>)

Figure 51 represents the user input area to convert PET data into qsh format. The advantage of this process is the creation of a single file that contains the entire series. A header is created using a GUI by inputting such standard information as number of slices, thickness, view, dimensions and other parameters.

QSH Header File Configuration		
Patient Name	Reference Location	0
	: 0.0	Number Of Beads
Date	Image Locations	Beads
: 09-26-97		
Number of Slices Selected	Uniform Thickness	
0	: 3.375	
Size of Dimension X (Pixels)	Number Of Echos	
: 256	: 0	
Size of Dimension Y (Pixels)	Dimensionality	
: 256	mm	
X Pixel Size	View	
: 2.1098	axial	
Y Pixel Size	Modality	Unrecognized Recognized
: 2.1098	Unknown	More Done

Figure 51. QSH Header Edit - Image Import Utility

Pixel size is obtained from the following basic equation:

$$\text{Pixel size} = \text{FOV/matrix size} = (27\text{cm})(10\text{mm/cm})/(128 \text{ pixels}) = 2.11\text{mm/pixel}$$

One last note about the conversion is that the "Image Locations" button can be set to auto-slice assuming a uniform slice thickness. This allows automatic z-axis assignment of each plane which eases calculation later on. The one disadvantage not outlined in the QSH documentation concerns that fact that it does not work at all times. The conversion routine is not without glitches.

I would recommend the following method to import PET data into Bnct_Rtpe. An in-house program, **zoom_img** has been modified to assist in this process. Appendix M gives a screen output from a sample conversion which as an end result will separate each plane of the PET file into an individual 8-bit raw format with no header.

These images may be read directly in to the **slice viewer** and may be automatically incremented by setting the **Auto Z Value** option under the **Make New Slice** button. The **zoom_img** program also scales the images up from 128x128 to 256x256 using 4 point smoothing in pixel replication, which is standard for the MR images usually read into Bnct_rtpe. This also allows for zooming of the images while drawing regions of interest in the **slice viewer**. Notice that output name of the file should be designated as follows:

filenamep#.img

the program will then automatically insert the appropriate plane number for the # symbol. The quantification scale factor is multiplied by the ECAT cps values from the raw PET data to give uCi/ml with a normalized 8bit maximum value of 255. The author would like to thank Dr. Hedley Bond for his work in modifying his original code to meet this need.

Bnct_rtpe ROI Definition

The data is now in an acceptable format and may be ftp'd over to curie.ipl.utmck.edu into the bnct user account. Curie holds the only copy of the dosimetry code under licensure agreement between Dr. George Kabalka and INEEL/MSU. In order to clarify the following steps a tree diagram, given in Figure 52, provided by INEEL/MSU, depicts the functionality of each section in the program.

A detailed description of use starting with image acquisition and ending with reconstruction specifically for UTMCK, will now be given. As a note, full documentation on bnct_rtpe and rtt_MC_106 is provided via the internet at:

<http://curie.ipl.utmck.edu/~bnct>

with a login ID of "bnct and a password of "me".

Starting the software by entering "bnct_rtpe" on curie allows the volume definition to take place. Using the **Slice** button to **Make New Slice** opens a browser which

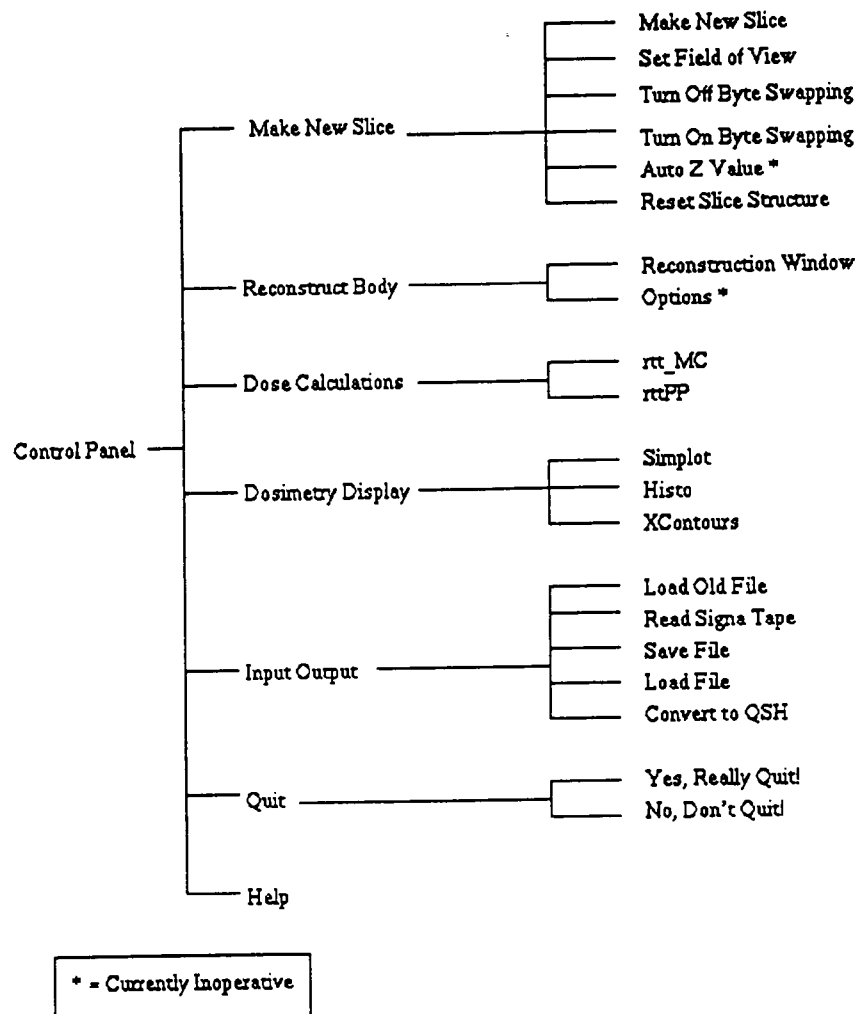


Figure 52. Bnct_rtpc Operations Tree Diagram

enables input of the image created with zoom_img. A field of view and z-coordinate must now be set dependent on the scan. The **Auto_Z Value** option is then set to the uniform slice thickness of the PET scan as stated earlier to simplify input of the image set. Once all of the images are loaded, the **Input/Output** and **Save File** options should be exercised prior to ROI definition.

The slice viewer allows two possible methods for ROI definition. The first is entered under the **Edit** option in the slice viewer as **Automatic Edge**. The options menu is shown in Figure 53.

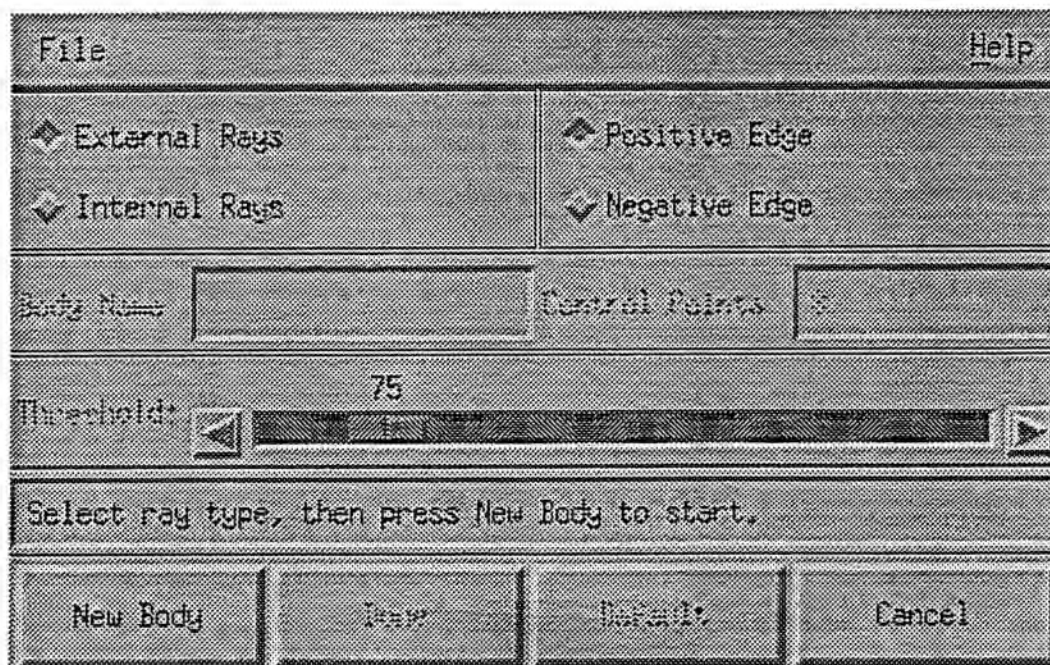


Figure 53. Automatic Edge Detection Menu of Bnct_rtpc

The standard regions of interest drawn by Brookhaven National Laboratory starting from the outside are as follows: scalp, skull, brain, target and tumor. This author questions the scalp definition in a PET scan given the anatomical boundary is essentially non-existent. The target region is defined as a uniform 2cm boundary outside the tumor itself that will be used as a general beam focus point. The automatic edge method is based on defining the ROI using a threshold of the image intensity level. For example, setting the external rays button allows the edge to search from the outside towards the center of the image which is ideal for the skull ROI. One then inputs the body name, ie. skull, and a value of **20** control points. The number of control points corresponds to the number of points in the ROI itself. 20 has been found to be an ideal value to minimize computational time as well as insure accurate regional definition. Allowing the threshold to vary on the slider bar gives the appropriate ROI. One then continues for each slice of the image. The auto edge command also periodically works using the internal rays on tumor definition but, the signal to noise must be fairly high in order for this function to give accurate edge definition.

If the noise is too great due to the backprojected streak artifacts found in PET images, one must then define a new body and manually enter the points for the ROI in a clockwise direction allowing for 20 control points. The ROI can then be copied to other slices within the same body to speed input time. All points whether defined with the automatic edge or manually can be edited after definition with the

edit points button. Points may be individually repositioned to a more accurate location following which the program will recompute the spline between adjacent points. In general, this is a fairly time consuming process for each patient.

All of the ROI files will have the extension of .bs and may then be loaded at a later date with **Load File** for further modification. Following ROI definition and saving the file once again, the reconstruction menu may now be entered from the main console. This is the process by which each of the defined regions is assigned a material definition to be used in the actual radiation transport analysis. The reconstruction process begins by selecting a body from the **bodies** list. The scalp or the outermost region should be selected first. The .rm files created in the reconstruction menu by using File and Save illustrate which materials and parameters to choose for the PET scan regions.

```
regn_in "regn name" "matl name" regn_out cap_style min_z max_z type color
1 "buffer" "buffer" 0
2 "scalp" "Fairchild_tissue" 1 0.0000 0.0000 interp 2
3 "skull" "Duck_cranium" 2 1 0.0000 0.0000 interp 4
4 "brain" "brain_MIT+10ppm" 3 1 0.0000 0.0000 interp 5
6 "tumor" "brain_MIT+10ppm" 4 1 0.0000 0.0000 interp 0
-1 "eof" "eof" -1 -1 -1.0 -1.0 "eof" "eof"
```

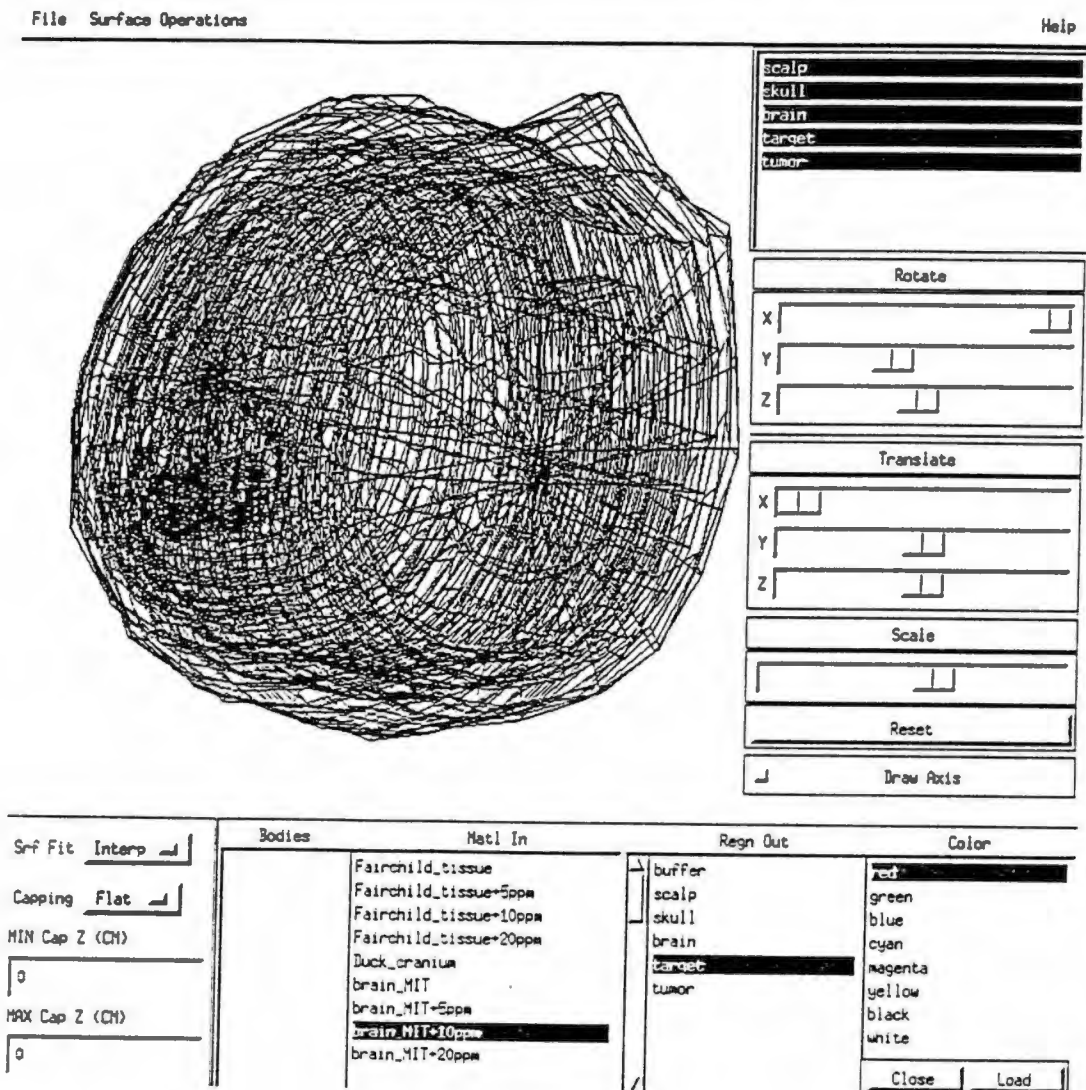
The material definition uses Fairchild_tissue plus a concentration of assumed boron in that region at 5ppm level increments for normal tissue, duck_cranium for skull, and brain_MIT for tumor and brain tissue. The program does allow for design of specialized tissue or material files if needed.

Notice that the concentration of boron in each region is fixed. If the level of boron is less than 50ppm in a region, then the affect on the neutron transport calculation becomes negligible as there is no appreciable thermal flux depression. The **Regn Out** must be then set as the region outlying the current body to be used for boundary identification. The body may now be loaded and the entire image may be reconstructed into a wire frame B-spline image that can be rotated, scaled or translated if needed as seen in Figure 54.

Once the information defining the geometrical B-spline construct is defined, a file will be created which will be used as a target for the Monte Carlo radiation transport section of this code by choosing the **make rtt interface file** option in the reconstruction window. This ends the application of the Bnct_rtpc package. Attention is now turned to the rtt_MC_106 program that is used to perform the actual Monte Carlo stochastic neutron transport simulation.

Neutron Transport Calculations

At the heart of all macrodosimetry code exists the capability to solve the 3D Boltzman transport equation for neutral particles. Figure 55 gives for reference, the Boltzman equation with definition of the variables involved. The basic assumption in macrodosimetry modelling is that it is possible to solve the above equation by randomly selecting neutrons from an incident source with a specific spectrum. These neutrons are then tracked until they either become captured



Srf Fit <u>Interp</u> Capping <u>Flat</u> MIN Cap Z (CM) 0 MAX Cap Z (CM) 0	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th>Bodies</th> <th>Matl In</th> <th>Regn Out</th> <th>Color</th> </tr> </thead> <tbody> <tr><td></td><td>Fairchild_tissue</td><td>buffer</td><td>red</td></tr> <tr><td></td><td>Fairchild_tissue+5ppm</td><td>scalp</td><td>green</td></tr> <tr><td></td><td>Fairchild_tissue+10ppm</td><td>skull</td><td>blue</td></tr> <tr><td></td><td>Fairchild_tissue+20ppm</td><td>brain</td><td>cyan</td></tr> <tr><td></td><td>Duck_cranium</td><td>target</td><td>magenta</td></tr> <tr><td></td><td>brain_MIT</td><td>tumor</td><td>yellow</td></tr> <tr><td></td><td>brain_MIT+5ppm</td><td></td><td>black</td></tr> <tr><td></td><td>brain_MIT+10ppm</td><td></td><td>white</td></tr> <tr><td></td><td>brain_MIT+20ppm</td><td></td><td></td></tr> </tbody> </table>	Bodies	Matl In	Regn Out	Color		Fairchild_tissue	buffer	red		Fairchild_tissue+5ppm	scalp	green		Fairchild_tissue+10ppm	skull	blue		Fairchild_tissue+20ppm	brain	cyan		Duck_cranium	target	magenta		brain_MIT	tumor	yellow		brain_MIT+5ppm		black		brain_MIT+10ppm		white		brain_MIT+20ppm			Close Load
Bodies	Matl In	Regn Out	Color																																							
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	Fairchild_tissue+5ppm	scalp	green																																							
	Fairchild_tissue+10ppm	skull	blue																																							
	Fairchild_tissue+20ppm	brain	cyan																																							
	Duck_cranium	target	magenta																																							
	brain_MIT	tumor	yellow																																							
	brain_MIT+5ppm		black																																							
	brain_MIT+10ppm		white																																							
	brain_MIT+20ppm																																									

Figure 54. Geometrical 3D Splined Reconstruction of ROI Defined Volumes

$$\frac{1}{v} \frac{\partial \phi}{\partial t} + \Omega \cdot \nabla \phi + \Sigma_t(r, E) \phi(r, E, \Omega, t) - \int \int \Sigma_s(r, E' \rightarrow E, \Omega' \rightarrow \Omega) \phi(r, E', \Omega', t) dE' d\Omega' = \frac{1}{4\pi} \chi(r, E) \int \int \nu(r, E') \Sigma_f(r, E') \phi(r, E', \Omega', t) dE' d\Omega' + S(r, E, \Omega, t).$$

where,

E	= neutron energy	[J]
r	= position	[cm]
t	= time	[s]
v	= neutron velocity	[cm s ⁻¹]
S	= extraneous neutron source	[cm ⁻³ s ⁻¹]
ν	= mean number of neutrons produced per fission	
Σ_a	= macroscopic absorption cross section	[cm ⁻¹]
Σ_f	= macroscopic fission cross section	[cm ⁻¹]
Σ_s	= macroscopic scattering cross section	[cm ⁻¹]
Σ_t	= macroscopic total cross section	[cm ⁻¹]
χ	= normalised fission spectrum	
ϕ	= forward neutron fluence rate	[cm ⁻² s ⁻¹]
Ω	= unit direction vector	
∇	= gradient	

Figure 55. 3D Boltzman Neutron Transport Equation

or exit the volume of distribution [64]. The steps to accomplish this are simple in concept. The process starts by pseudo-randomly selecting a particle from the flux distribution and assigning it a position and velocity vector. Another pseudo-random number determines whether the particle interacts within the medium or passes through one of the boundaries. If the particle remains in the volume it may then be scattered or captured. If captured, then the history is finished. If scattered, then a new position and velocity vector must be calculated and the cycle restarts. The key to the concept of this simulation is to obtain enough particles to statistically determine the particle flux in each region of interest.

Practically this is achieved via one of three methods. The first uses the standard MCNP package produced by Los Alamos National Laboratory. This allows modelling of structure using simple geometric volumes which are then exposed to the simulated flux. This method has, as a key advantage, a fast running and computationally simple simulation. A disadvantage is that the primitive geometrical shapes do not model the actual anatomical structures to any great level of accuracy. One approach to improving the accuracy of the model incorporates the use of a voxel approximation method. Allowing information to be read from CT images, density and structure is defined on a much finer level.

A thresholding technique, based on ranges of Hounsfield units, allows density assignments to each voxel in the image. As a note, a standard "voxel" size for MCNP simulation is 1cm^3 not 1mm^3 based on the camera resolution due to restrictions on computing time. Dr. David Nigg points out that although this method has as a primary advantage the possibility to be easily automated, the voxels themselves do not realistically allow curved surfaces to be modelled. He states that this is the case regardless of how small the voxels become in size.

I have proposed an idea for future study in the area of voxel reconstruction that would simplify the density assignments and allow finer resolution of material definition based on medical images. The INEEL code is evolving into a voxel based system that will eventually replace the B-spline method, in all its elegance,

as time progresses. The opportunity exists to use a PET scan to both enter the concentration data as well as the density data on a per pixel basis. For each PET scan that is taken there are 2 image sets. The first is called an absorption or "attenuation" scan which is taken using a rotating source to simulate a CT scan on the PET bed. The pixel values are related to e^{-ux} where u is the attenuation factor that is related to the material density. The next scan is the emission scan which is produced from the radiotracers emitting positrons from within the patient. The emission scan divided by the attenuation scan becomes the actual PET scan.

The per pixel density information from the attenuation scan, in conjunction with the metabolic information from the emission scan would provide all of the needed data about the patient from a single set of scans in one modality. Coregistration of the images would be straightforward given the exact same positioning parameters and scan variables.

A second method uses discrete ordinates deterministic routines, such as TORT, originally developed at ORNL, to provide distinct numerical solutions of the transport equation. This approach solves one of the basic difficulties in all Monte Carlo methods. If a detailed spatial dose distribution is required, then the statistics needed to reach a convergence in this method often requires vast amounts of time. The discrete ordinates method provides an analytical solution that numerically converges without the effect of statistical variance. The method

divides the geometry into a fine spatial mesh and then proceeds to discretize the angular flux as well. The program then iteratively calculates the energy dependent particle intensity at each point and then integrates to determine the scalar flux data.

The method chosen by INEEL is currently based on a nonuniform rational B-spline fit to the geometric surface. As stated in the `bnct_rtp` section above, the ROI's are drawn on the medical image and the fit is performed on each plane for each region. Within the calculation itself, steps of much smaller sizes may then be taken along this fit, given it is fully described as an analytical equation. A subelement mesh is placed over the geometrical construct composed of 3 orthogonal planes of consisting of parallelepipeds. Typically the volume of these sections is 1cc, but again are placed in conjunction with the geometrical spline fit of the anatomical structure. Depending on the number of control points in use, very curved surfaces may be modelled in a precise way. These subelements are then used to calculate the flux across a boundary through the mesh. The Monte Carlo code was derived by INEEL/MSU and is independent of the MCNP package.

In a personal communication with Dr. Chuck Wemple of INEEL, he mentions that the `rtt_MC_106` code almost decouples the dose components within the simulation through the partitioning of the volumes. The other advantage of the code is that the voxel grid placed on the surface allows particle tallies to be carried out very

rapidly. This gives rtt_MC_106 an order of magnitude factor of efficiency over MCNP.

Configuration File Parameters

Specifically once the user has defined the ROI's on the medical image and created a reconstructed mesh volume, the run parameters may now be set as shown in the rtt.input configuration file given in Appendix N. It is this file that contains the only parameters that can be altered prior to running the neutron transport calculation. A brief description of the variables that need to be altered for differing runs will be given. At the present time one of the most important factors regarding this input file concerns the format. The second line contains the number of batches to process and the number of particles per batch and **MUST** retain the FORMAT 3E20.8 structure. Any extra spaces or numbers will result in incorrect runs being processed or run-time errors.

The target point definition is placed on line number 3 in cm. The BNL positioning protocol **REVERSES** the x and y axis in their orientation structure. In order to determine the target point, the slice viewer in bnct_rtpc may be used. By loading the central slice and using the location button in the lower left corner of the window, an x and y coordinate will be displayed and the slice offset or z position is fixed on the image itself. These may then be placed in the rtt.input file directly, again noting that the units are cm as default independent of the units defined in

the slice viewer.

The next line contains the beam orientation with regard to the patient position and is the most critical line in the entire file. A diagram, provided by Dr. Floyd Wheeler of INEEL, that depicts the physical orientation of each of the variables is given. Following each diagram is a view file generated by rtt_MC_106 and viewed in xcontours. These gif files show the reconstructed volume in 2D at the beam position that was defined in the rtt.input file. These files are created almost instantaneously upon starting a run and should be used to confirm beam positioning. As a first run, the number of batches and number of particles should be set very low in order to obtain a short run time and view the resulting orientation of the patient. At Brookhaven National Laboratory, fiducial markers are used and may be referenced by the program to insure correct patient positioning. This has been done at UTMCK using a stereotactic MR head apparatus to allow accurate image comparison back at BNL.

Beam Positioning Methods

View3.gif is created as a **coronal** cut through the patient and is directly related to Zb in the input file. Zb is the distance from the target point to the source in cm. This is shown in Figure 56 in both a theoretical diagram as well as an actual slice volume taken from the tumor planes of one of our BPA patients that underwent BNCT at BNL. The second parameter phi becomes the angle between the top of

the head to the current beam location as is directly related to the **sagittal** view. Figure 57 shows primarily the tumor planes that were used in the reconstruction. In general, the entire head should be used to aid in positioning as well as to simulate a realistic amount of back scatter and interactions from adjacent planes. The angle theta is related to the **axial** view1.gif and can be seen in Figure 58.

The ninth line in the rtt.input file defines the origin of the mesh. The standard defaults are 30x30x30 cubes with a user defined origin and voxel dimension. If the model were centered at 0,0,0 and the origin placed at -15,-15,-15 the volume would inclose a 27 liter box assuming 1cc voxels. If the mesh is not given a large enough size or is placed inaccurately errors will be displayed during the run:

```
point outside of subelement mesh -1.5964E+01 -3.2835E+00 7.0875E-01  
point outside of subelement mesh -1.5964E+01 -3.0347E+00 7.0875E-01
```

The contours will then not be produced and the initial image size, target point, angles and mesh origin must then be reexamined. These are the basic essential parameters that must be changed between different runs. I have placed an online manual, with permission, at:

<http://curie.ipl.utmck.edu> , login: bnct, password: me

that should be consulted as a reference, as there is no printed manual available for the current version of the code.

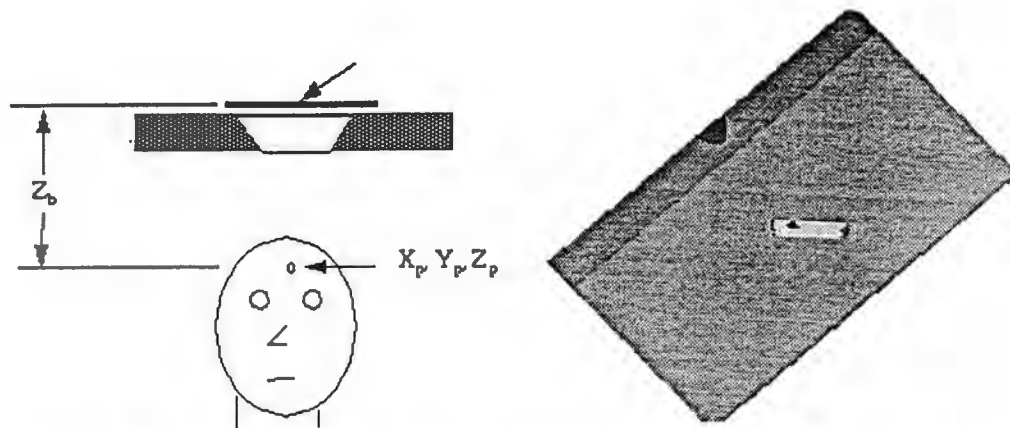


Figure 56. Zb - Coronal View: Beam Positioning Alignment Diagram

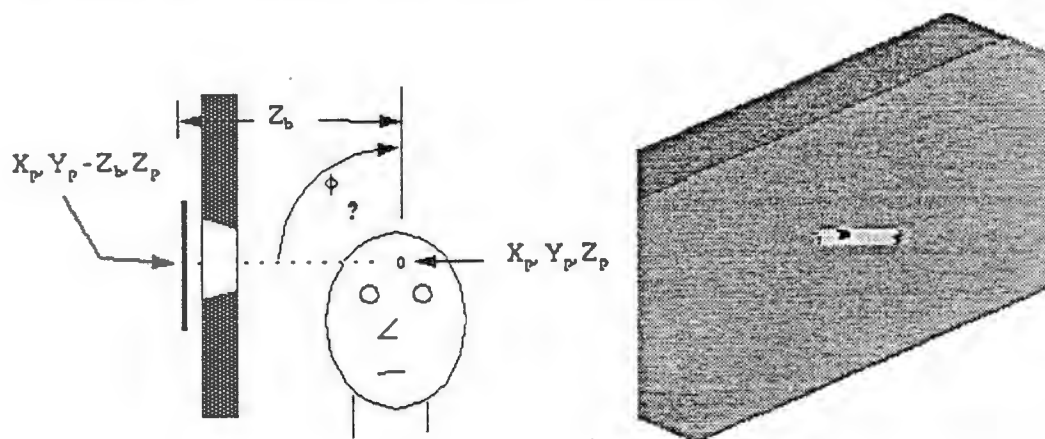


Figure 57. Phi - Sagittal View: Beam Positioning Alignment Diagram

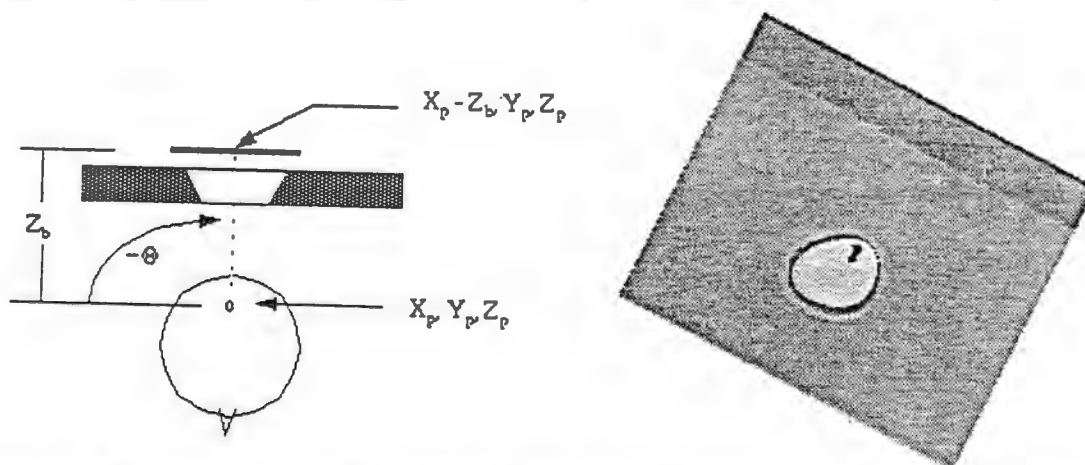


Figure 58. Theta - Axial View: Beam Positioning Alignment Diagram

Results

Macroscopic Tumor Heterogeneity

The primary difficulty concerns the relation of the concentration distribution of the boron in-vivo to the pixel intensity. Bnct_rtpc assumes a uniform concentration of boron throughout the defined region that was assigned in the slice viewer. At present, BNL uses direct atomic emission spectroscopy to determine boron levels in-vivo from tissue samples taken from the patient during debulking surgery [17]. Absolutely no pharmacokinetic information can be gained from this method due to the limited number of time points. The question that must be initially addressed then is whether the boron distribution is heterogeneous or homogeneous at the tumor site. This may be fully visualized in a 3D surface plot generated with MATLAB from raw PET data of a tumor plane from our second patient as shown in Figure 59.

It can then be easily seen that although the tumor is concentrated primarily in one specific region, that the distribution of F-BPA-Fr is definitely not homogeneous. In fact, it can be seen that a peak arises in the tumor that gradually dissipates near the tumor rim. This uptake plot does NOT correlate with the MRI data as the MR gives no information about the metabolic uptake of the compound only of that of proton density of the region or of a Gd-DTPA contrast agent.

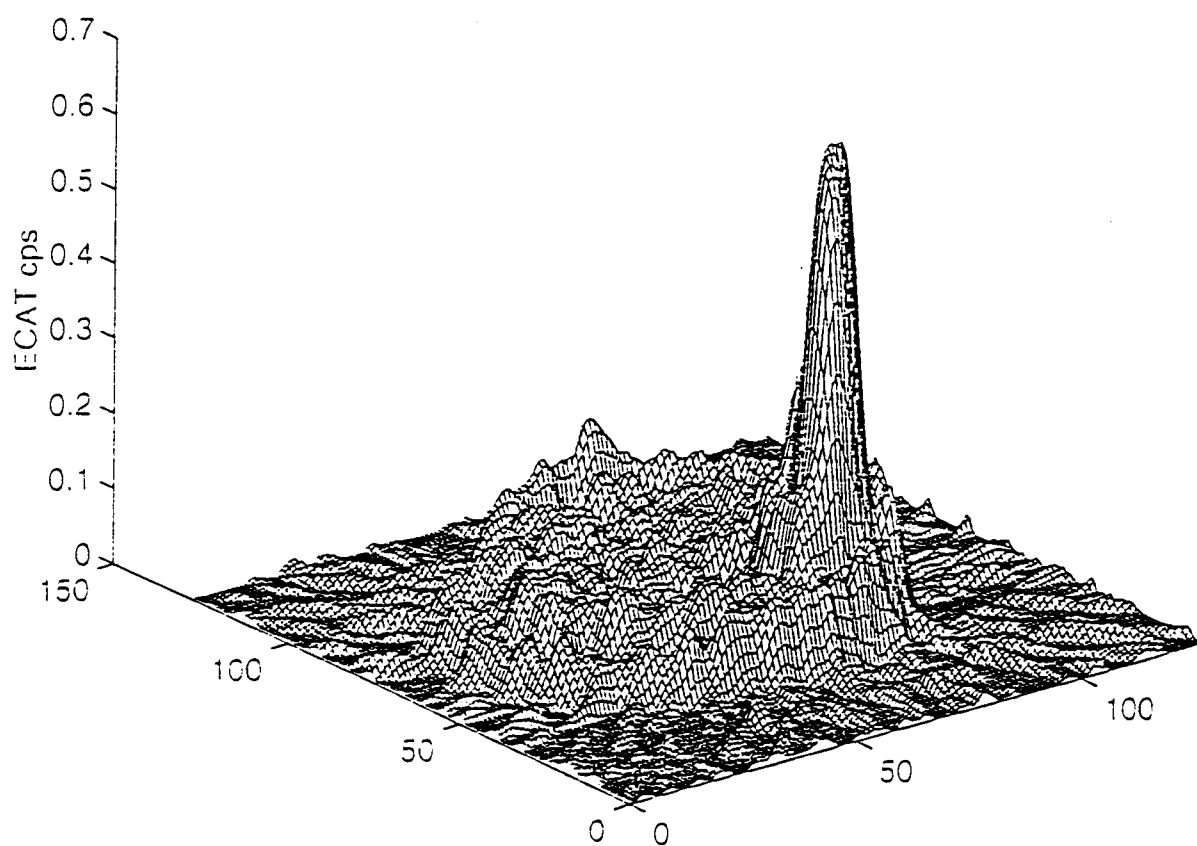


Figure 59. PET Raw Activity Data Showing Tumor Heterogeneity

Image Coregistration

A process has been developed here at UTMCK to coregister the MRI and PET scans and actually interleave the pixels of each into a single image. A dual color look-up table is defined whereby the MRI is assigned values between 0-127 in shades of red. The PET scan is then assigned values from 128-255 in shades of blue. The images are interleaved in a manner identical to that of a checkerboard pattern where every other pixel belongs to every other image. In this way one can analyze in 2D or through an Analyze volume rendering the extent of the tumor. The MR yields anatomical information and definition unavailable in the PET scan while in converse the PET reveals the uptake and distribution information.

Chad Wight, an undergraduate research student for Dr. George Kabalka was assigned to assist me in this project. Through some guidance from Hedley Bond and myself, Chad has developed a step by step guide to perform this procedure given in Appendix O. Figure 60 is a slide containing a sample result showing the original MRI, the original PET and the combination of the two. Notice that the tumor in the MRI is larger than that shown in the PET scan. Anatomical information does not correspond exactly to uptake results. Correlations between the modalities allow treatment efficacy to be more accurately gauged and the combined set of information will help to prevent erroneous interpretations from arising.

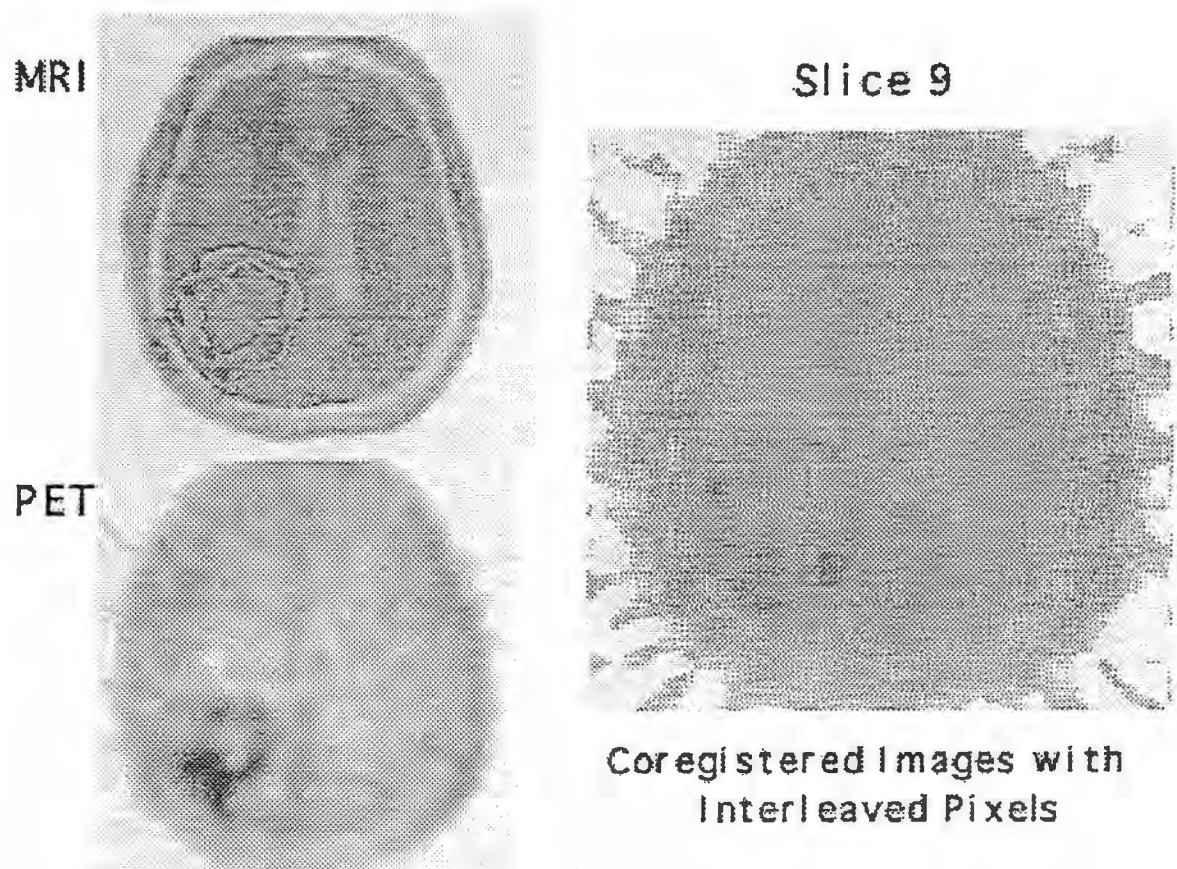


Figure 60. Coregistered and Interleaved PET/MRI Post-BNCT Images

The following equation converts the PET raw output in units of ECAT counts per pixel per second to number of boron atoms per pixel.

$$\frac{[x \text{ ECAT cps}] [20.7 \text{ uCi/ml}] [3.7 \times 10^4 \text{ Disintegrations/s}] [1s] [\# \text{ ml}]}{[\text{ECAT cps}] [\text{uCi}] [1.11 \times 10^{-4}]} = \frac{\# \text{ B atoms}}{\text{pixel}}$$

The minimum level of boron atoms per cell needed to produce a capture reaction capable of killing the nucleus is approximately 1×10^9 boron atoms. The assumptions made in the above conversion relation are that the boron does not disassociate from the ^{18}F in-vivo which has been shown to be the case in animal experiments utilizing ^{19}F -BPA. Given this fact, knowing that there is a 1:1 ratio between boron and fluorine in F-BPA-Fr it stands that each annihilation corresponds to 1 molecule of F-BPA-Fr and therefore 1 molecule of boron. Then by knowing the number of disintegrations and the decay factor of the compound, the number of boron atoms can be estimated.

An estimate has also been made to convert the number of boron atoms to a more usable unit such as ppm which is standard in MRI. This is given below to be:

$$\frac{[\# \text{ B atoms}] [1\text{mol}] [10.8\text{g}] [1.0\text{ml}] [1 \times 10^6 \text{ ug}]}{[\text{pixel}] [6.022 \times 10^{23} \text{ atoms}] [1\text{mol}] [1 \text{ g}] [1 \text{ g}]} = \frac{\text{ppm } 10\text{B}}{\text{pixel}}$$

Blood Pool Convolution Studies

One of the primary differences between the pre-BNCT PET scans done at UTMCK and the actual BNCT treatment at Brookhaven National Laboratory is reflected in the administration and dosage of F-BPA-Fr. BNL administers a dose of 250mg F-

BPA/kg body weight of the patient. The drug is prepared to 0.14M or 30mg BPA/ml, which for an average patient of size 70kg would yield a dose of 17.50g or a dose volume of 0.5833 L [17]. The large volume of the dose necessitates that an i.v. must be used over a longer period of time. The Phase I/II Clinical Trials protocol from BNL uses a standard of 2 hours for their infusion of the BNCT agent.

UTMCK prepares an ^{18}F -BPA-Fructose radiopharmaceutical for use in Positron Emission Tomography scans with a dose of 0.15uCi/kg at a volume of approximately 5-10ml. This injection is given immediately as a bolus which has a peak rise time of about 30s. This blood curve can be fit using a linear ramp up to the peak and a bi-exponential washout after the peak as given in the following equations:

$$[t \leq t_{\text{peak}}] Cp(t) = mt$$

$$[t > t_{\text{peak}}] Cp(t) = A\theta^{-Bt} + C\theta^{-Dt}$$

The linear ramp is created using an intercept of 0.0 and a slope of $Cp_{\text{peak}}/t_{\text{peak}}$, as shown in the following MATLAB code (Mathworks, Inc., Natick, MA.):

```
[y,i]=max(Data(:,2));
k=1;
while (k<i),
Data(k,2) = (Data(i,2)/Data(i,1))*Data(k,1);
k=k+1;
end
```

where Data(:,1) holds the time values and Data(:,2) holds the activity values stripped off the .cpt file from the PET scan.

The bi-exponential fit has 4 distinct independent parameters that must be optimized to yield the minimum least squares error given by:

$$\sum (Cp(t_i)^2 - (A\exp(-Bt_i) + C\exp(-Dt_i))^2)$$

MATLAB is used to fit the bi-exponential washout of the blood curve using an unconstrained multivariable function: fmins. This function minimizes the least squared error or normal error between the true and fitted data. The normal error is defined here as the maximum difference between the true and fitted data. The fmins function uses a standard Simplex search algorithm to optimize the parameter vector. Given initial estimates for B and D, which are the exponential powers denoted as lambda, the algorithm proceeds to optimize the fit using code given in Appendix P. This routine works by taking the initial estimate given by lambda and determining the exponential multipliers by taking the ratio of the exponential over the function, ie.:

$$y_i = c_i e^{-\lambda_i t_i} : c_i = \frac{y_i e^{\lambda_i t_i}}{1}$$

It then creates the fitted curve z and places the normal error into the minimization routine, fmins which returns an iterated value for lambda. When called in MATLAB by the following lines, a fit is produced.

```

global c
c=[.0114 .241];
lambda=fmins('fits',lambda,[0 .1]);

```

This blood curve can now be extrapolated to any time point using the resulting equations:

$$\begin{aligned}
 [t < 0.808 \text{ min}] \quad C_p &= 0.0622 \, t \\
 [t > 0.808 \text{ min}] \quad C_p &= 0.0114 \, e^{-0.0072t} + 0.2307 \, e^{-2.2012t}
 \end{aligned}$$

Now that the blood curve is fitted, the bolus approximation can be convolved with a step function of size equal to the 2 hour time interval used for infusion at BNL.

A convolution integral is defined as follows:

$$a(t) \otimes b(t) = \int_0^t a(\tau) b(t-\tau) d\tau = b(t) \otimes a(t)$$

A discrete computational method to evaluate convolution integrals is given by Ctrl-C (Palo Alto,CA.):

```

Y(k) = Convolution(a(i),b(j))
If the sequences A and B are defined as
A = a(i) i=1,2...p; B = b(j) j=1,2,...q; N = p+q-1
then the sequence Y is formed as

```

$$Y(k) = \sum_{i=1}^k \{ a(i) * b(k-i+1) \}, \quad i < p, \quad k-i+1 < q, \quad k = 1, 2, \dots, N$$

These formulas have been placed in a Lotus 123 spreadsheet as a secondary method to check the accuracy of the convolution integrals and also as a method that is highly portable and that requires only minimal computing facilities. For example, if a 2 hour infusion is to be simulated in minutes, the spreadsheet would calculate:

$$Y_i = @sum(Cp_1..Cp_i) \quad \text{for } i=1..120$$

$$Y_i = @sum(Cp_{i-120}..Cp_i) \quad \text{for } i=121..$$

which would yield a "convolved" blood pool plot.

Given the PET data has a much lower concentration of F-BPA-Fr and is measured in Activity(uCi/ml), the peak of the PET curve must be normalized to that of the actual BNL blood sampling curve. Given the PET dose is much smaller in volume, the number of boron atoms at a specific voxel is much less than the needed dose for successful irradiation. The dose is great enough to provide accurate information on the biodistribution of the compound in-vivo. Once this is accomplished, the infusion times are then identical and the scales on both curves are the same.

Is the above method of convolving a bolus with a step function a good simulation of actual patient data from BNL? Dr. Jacek Capala, the treatment planning physicist at BNL, has provided us with the venous blood boron concentrations at various time intervals. BNL uses both prompt gamma and/or direct current plasma atomic emission spectroscopy to determine the blood boron concentrations. When both methods are available, an average is taken. Figure 61 shows a pre-surgery PET blood pool time activity curve that has been exponentially fitted and extrapolated. This same curve is now normalized to a peak value of 1.0 and plotted on the same axis with the actual BNL BNCT venous sample data as shown in Figure 62. The curves are very close until after about 4 hours. One possible

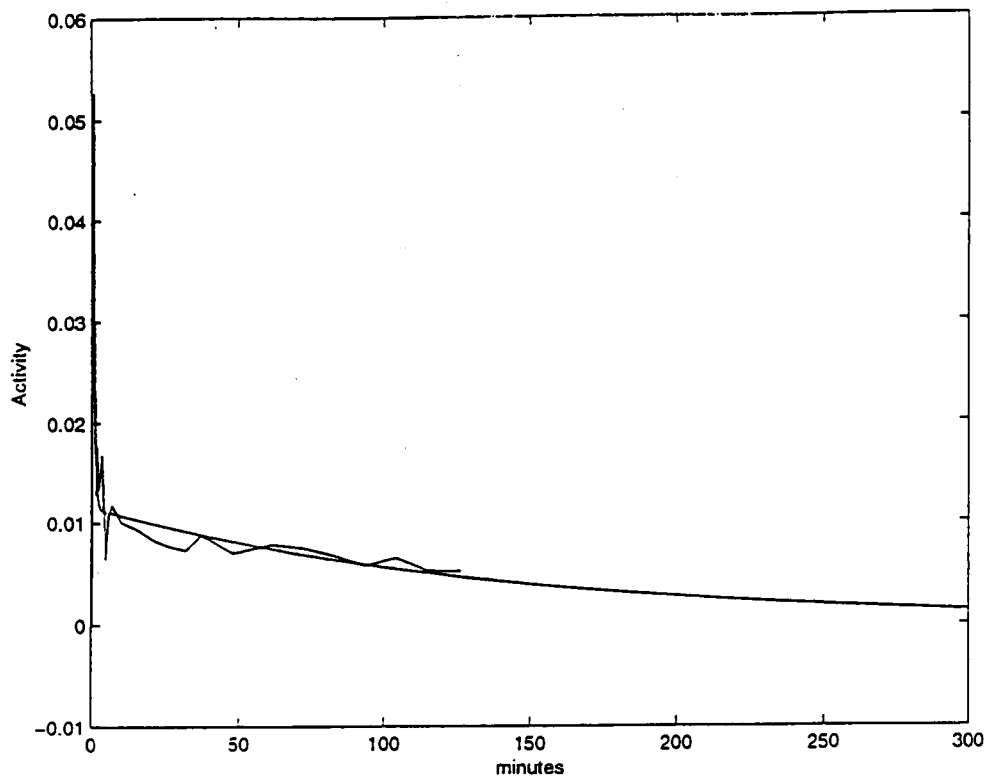


Figure 61. Pre-Surgery Exponential Bolus Fit and Extrapolation

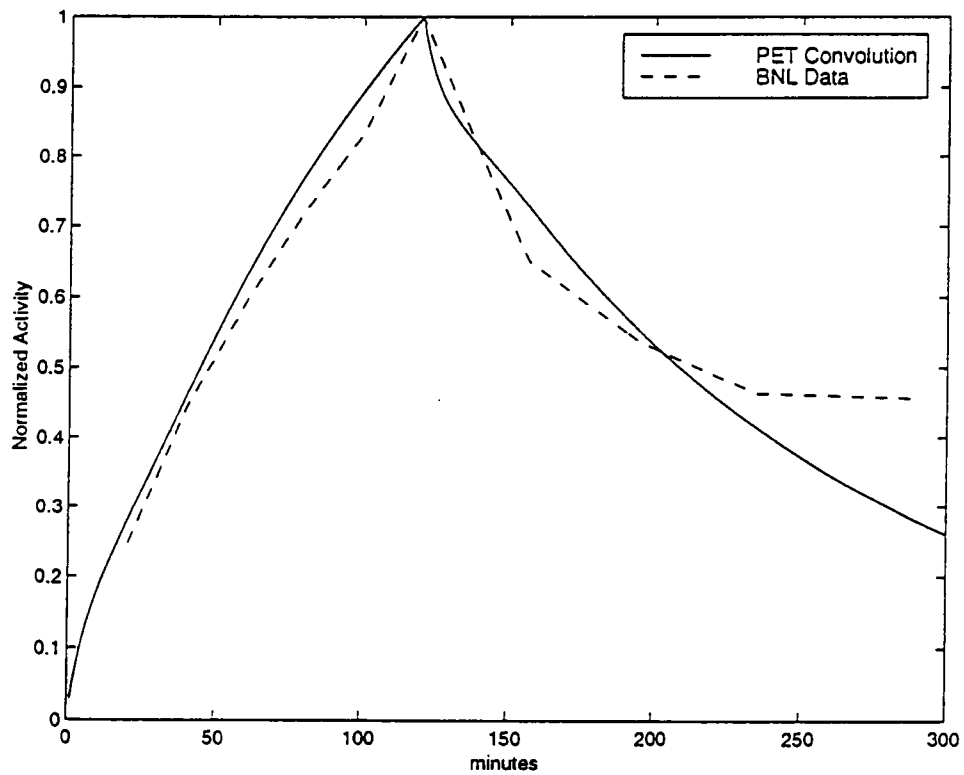


Figure 62. Pre-Surgery Convolved Bolus Blood Pool Comparison

reason for this could be that a small variation in the bolus exponential fit is increased an order of magnitude when convolved and extrapolated to a much longer time axis than the PET scan actually occurred in.

The same graphical analysis routines were performed on the post-surgery PET scan bolus blood pool data using MATLAB (Mathworks, Inc., Natick, MA.) Figure 63 should actually produce a closer fit, given the PET scan occurred after debulking surgery. The scan was also almost 2 months prior to the actual irradiation done at BNL. A possible cause for error would be spillover from the brain to the blood pool data. Figure 64 gives the convolved blood pool curve normalized and plotted against the BNL venous samples.

The data from BNL is patient specific and does not represent an average blood boron curve. Figure 65 represents results taken from an 11 patient study showing the standard deviations [17]. One interesting fact to note is that the ratio of the peak to that of about 4 hours is at approximately 2:1 for all patients. A study needs to be carried out at UTMCK that would infuse an actual dose identical to that at BNL into a possible patient. Obviously the radiotracer level would yield a constant dose of approximately 10mCi identical to that given in the bolus, but the biodistribution of a large scale volume study could be examined experimentally.

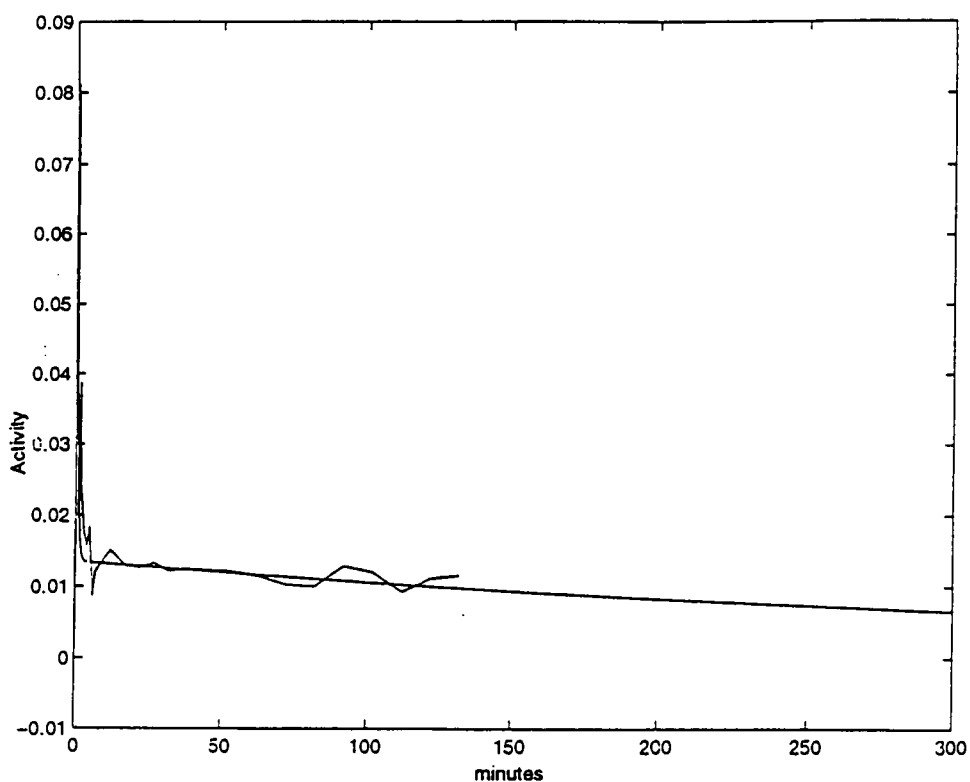


Figure 63. Post-Surgery Exponential Bolus Fit and Extrapolation

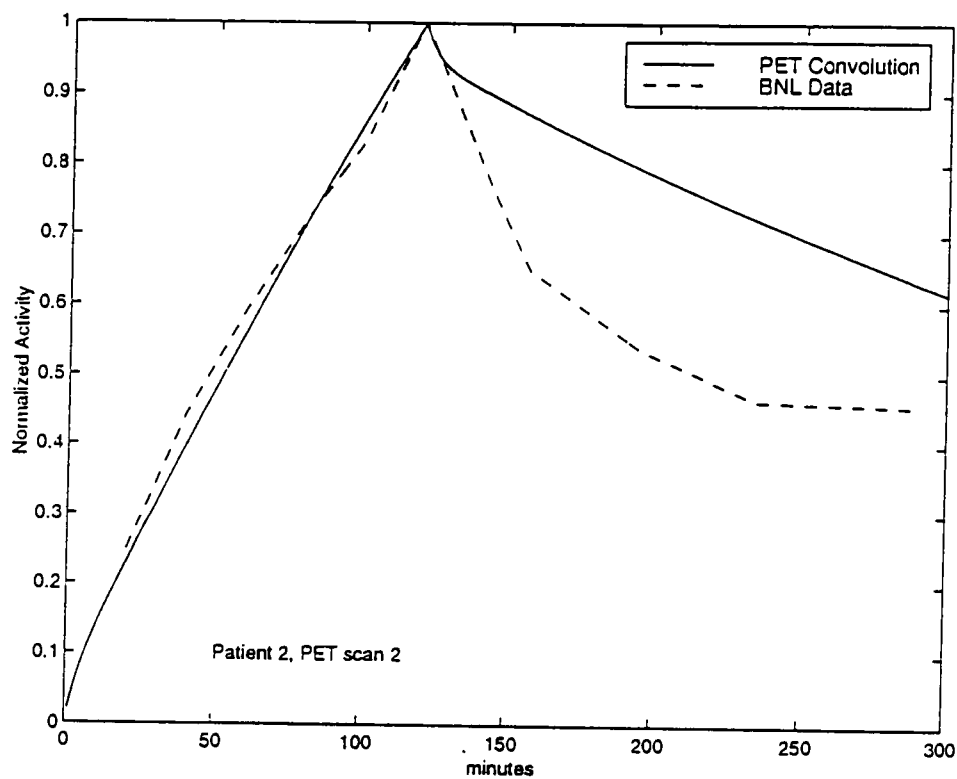


Figure 64. Post-Surgery Convolved Bolus Blood Pool Comparison

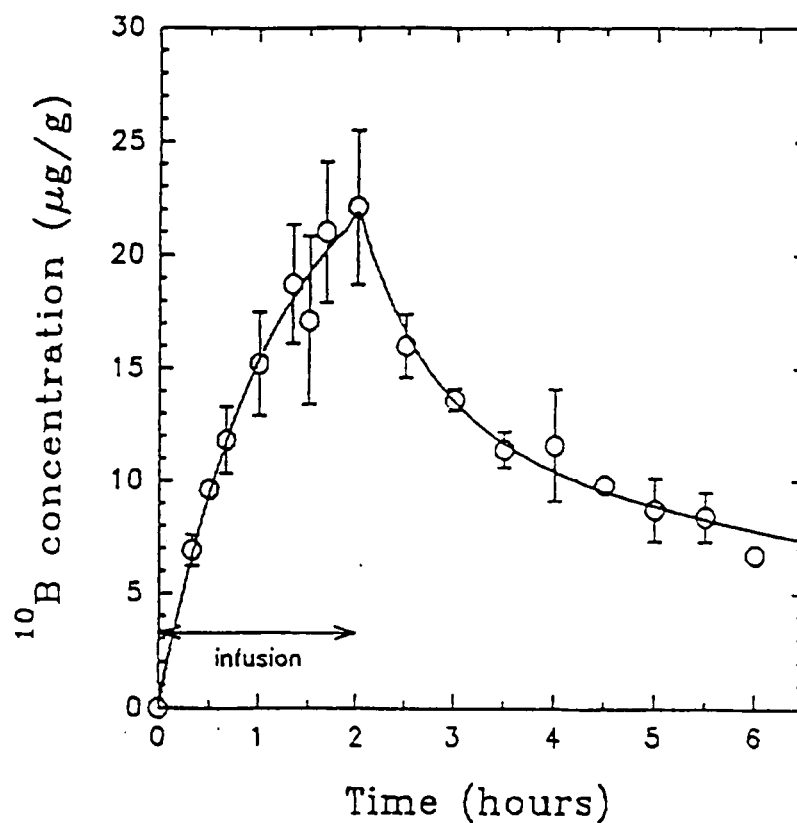


Figure 65. BNL Protocol Average Blood Time Activity Curve

Treatment Planning Dose Contours

The PET data has been successfully imported into the Bnct_rpe package and the rtt_MC_106 program has also been configured. The actual results from the UTMCK PET runs can now be examined. The second BPA patient underwent BNCT on 2/1/96 and had three PET scans. BNL, using the same software, imported MRI scans from SUNY in order to perform the dose prescription prior to irradiation. These scans produced the following dose contours, in Figure 66, the first representing the total dose from all beam components, the second just the boron dose.

Figure 66 represented ROI's drawn from the MRI images directly assuming a homogeneous concentration of boron throughout the defined tumor region. Figure 67 gives identical contours from our second BPA patient taken on 12/15/95 approximately 2 months prior to BNCT. The first scan is again the total dose component and the second represents the boron specific dose. Another study of the same series of contours for the pre-surgery PET scans are shown in Figure 68. The concentration of boron in the tumor region prior to debulking surgery was slightly higher in these images. This resulted in clearer dose contours with less noise. This will be highly apparent in the per pixel PET boron concentration contours. A striking contrast with the BNL data will then be examined.

One aspect that should be addressed is the process by which these contours are created and may be further analyzed after the neutron transport calculation is finished running rtt_MC_106. The program, xcontours, provided by INEEL/MSU, allows post-processing of the contours through a GUI. The first step is to load the image plane desired and then the corresponding dose contours which will have a .contour file extension. The final file to load for a plane is optional but allows more focused viewing. As in the reconstruction windows, different regions may be displayed individually with their separate dose contours. The "mask" file as it is called allows the user to select distinct regions for display and also to exclude regions outside the volume of distribution. A mask is displayed in Figure 69 for one of BPA patients.



Figure 66. BNL Post-Surgery Dose Contours - Homogeneous Distribution

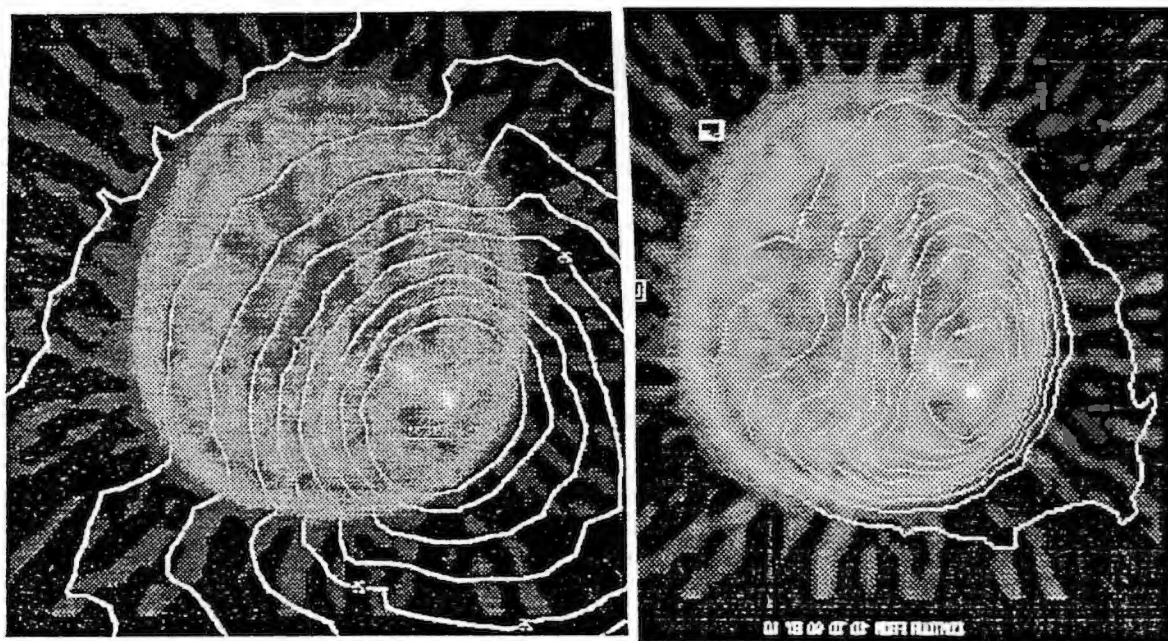


Figure 67. Post-Surgery PET Dose Contours - Homogeneous Distribution

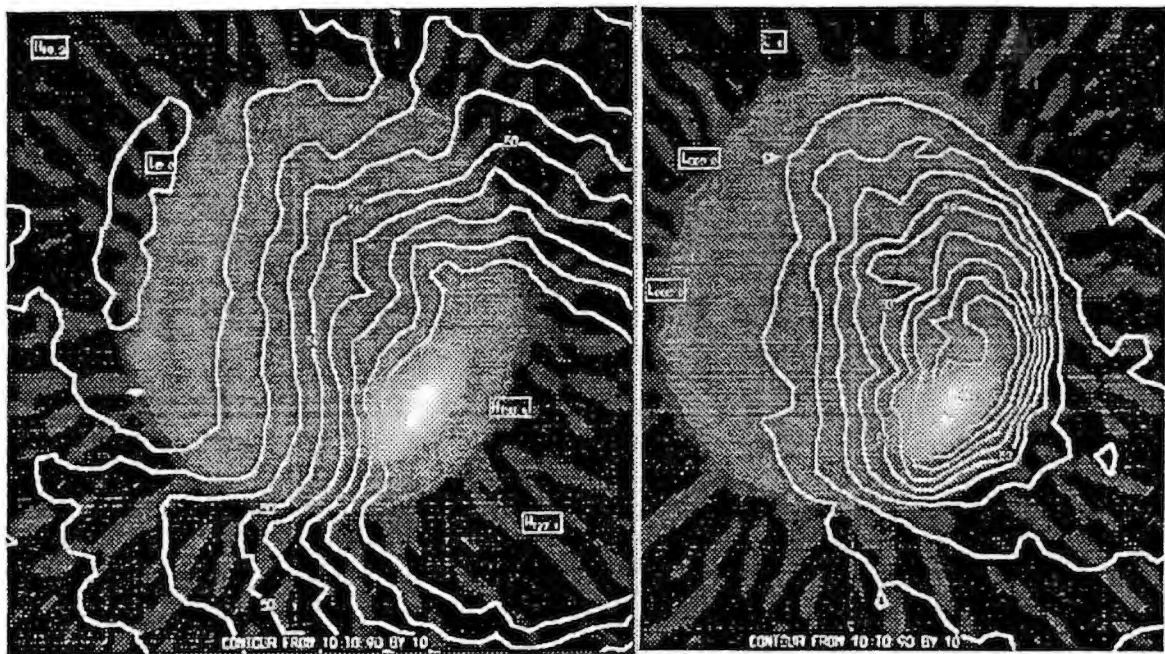


Figure 68 Pre-Surgery PET Dose Contours - Homogeneous Distribution

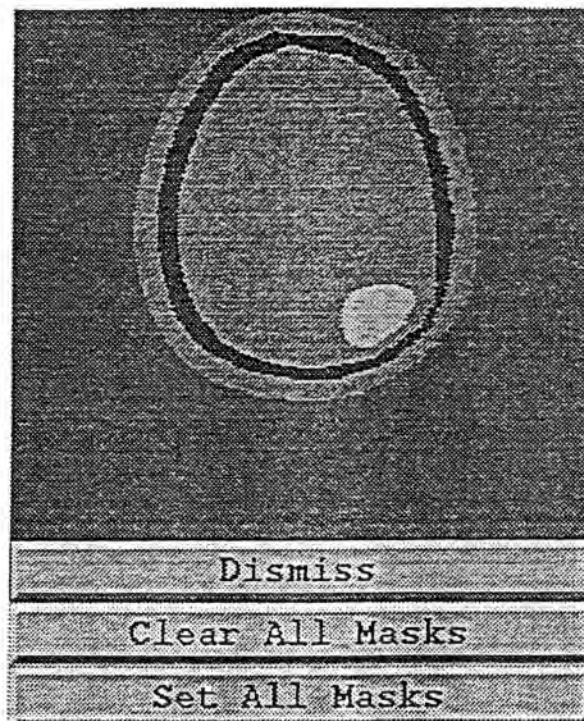


Figure 69. Contour Masking Options for Display

The next step is to choose a dose component of interest from the following options: Boron Dose, Gamma Dose, Nitrogen Dose, Fast Dose, Group 1 Fluence, Group 2 Fluence, Thermal Fluence and Total Dose. This may be selected from the "Select Dose Component" pull down menu within xcontours. The current image selected with the mouse will then displayed the corresponding contour map. Post-processing of the contours to allow dose modifications may be done in the dose factors window as shown in Figure 70.

The window displays a factor, concentration and reference value. The factor is usually defined as the RBE or relative biological effectiveness factor and may be set at a desired value. The BNL protocol gives the following RBE factors for BNCT peak dose in normal brain:

Boron (11.2ppm in blood):	1.3
Gamma:	1.0
Fast Neutrons:	3.2
Nitrogen:	3.2

The concentration value in the second column is in units of ppm for the boron dose, unity for the gamma dose, percent by weight for nitrogen and percent by weight of hydrogen for the fast dose. The reference values are those values for the edit voxel, or 1cc region of peak neutron flux. It is standard practice to run the transport calculations at 1 MW reactor power and set all the factors to 1.0 with 1.0ppm of boron and the actual nitrogen and hydrogen concentrations. Then, all doses are uniform and may be scaled afterwards.

Dose Name	Factor	Concentration	Reference Value
Boron	1.000000	1.000000	0.038740
Gamma	1.000000	1.000000	0.482200
Nitrogen	1.000000	1.940000	0.065650
Fast	1.000000	10.570000	0.102700
total			0.689290
Set to Default	Apply	Dismiss	

Figure 70. Xcontours Dose Factor Modification Window

The key item to note in this menu is that the boron concentration may be increased from within xcontours, but all regions are scaled uniformly. A standard practice is to run the neutron transport calculations defining a 10ppm boron level in tumor and normal brain. This corresponds to an average blood boron level in-vivo. The contours are then displayed, as a preference, with concentrations of 1ppm so the dose contours will yield a dose/ppm curve. The boron dose contours are percent contours and relative to the concentration. Therefore, a 90% dose contour line will remain at the same position whether the boron level is 10ppm or 30ppm. This is also assuming that the concentration level was below the 50ppm limit that would have no significant effect on the thermal flux depression in the neutron transport calculations as described earlier.

Knowing how the contours are produced now allows us to take the final step in dose analysis. All of the above contours, including the PET scans have assumed a homogeneous boron concentration. We may now incorporate the per pixel boron concentration from the PET data into the dose contours without affecting the neutron transport calculations. I have written a short subroutine in C to strip off the raw data from the PET scan, find the maximum pixel value and scale the image accordingly writing the raw data out in floating point format. This code uses `img_sel` by Dr. Hedley Bond as a base and is given in Appendix Q. Dr. Chuck Wemple of the INEEL/BNCT team has worked with me to incorporate the data created by my subroutine into the `xcontours` files. The input needed to run his short code is given in Appendix R.

The first line in Appendix R gives the image prefix followed by the image and contour directories respectively. The average intensity in the blood is now given next. Note, that this is in ECAT cps and gained from an ROI over the carotid artery from the `.cpt` file. Line 5 contains the position of the reference voxel which may be found by doing a:

grep Norm rtt.output

The next two lines give the image file name above and below the reference point. The last set of data in the input file contains the maximum pixel values from the image planes. These may be determined by running my subroutine as shown previously. The program `pet_boron` is then run with the input file to produce the

desired contours. The actual code written by Dr. Chuck Wemple is given in Appendix S.

Figure 71 shows the first image taken from the pre-surgery PET scans on a per pixel concentration basis as described above. Comparing this set of contours with the homogeneous boron dose curves from BNL shows the unbelievable difference in treatment planning. The PET dose as given below shows a very tight set of contours that are actually focused on the metabolic center of the tumor region. The increased amount of signal, due to the increased amount of tumor prior to surgery, allows better contours to be produced on a per pixel basis.

An identical procedure was performed on the post-surgery PET scans, prior to BNCT, in Figure 72. Notice that although the curves are slightly noisier, that the contours still remain tightly focused around the remaining metabolic center of the tumor.

One final tool that should be run is an ancillary program to rtt_MC_106 called histo. This package reads the rtt_MC output file and invokes an xmgr plot at each volume edit. Different dose components may be selected and the output gives the dose/volume plot for the specific run. This allows a quantitative analysis of dose distribution throughout the volume. For the second BPA patient study, prior to BNCT, Figure 73 shows the dose/volume histogram was created.

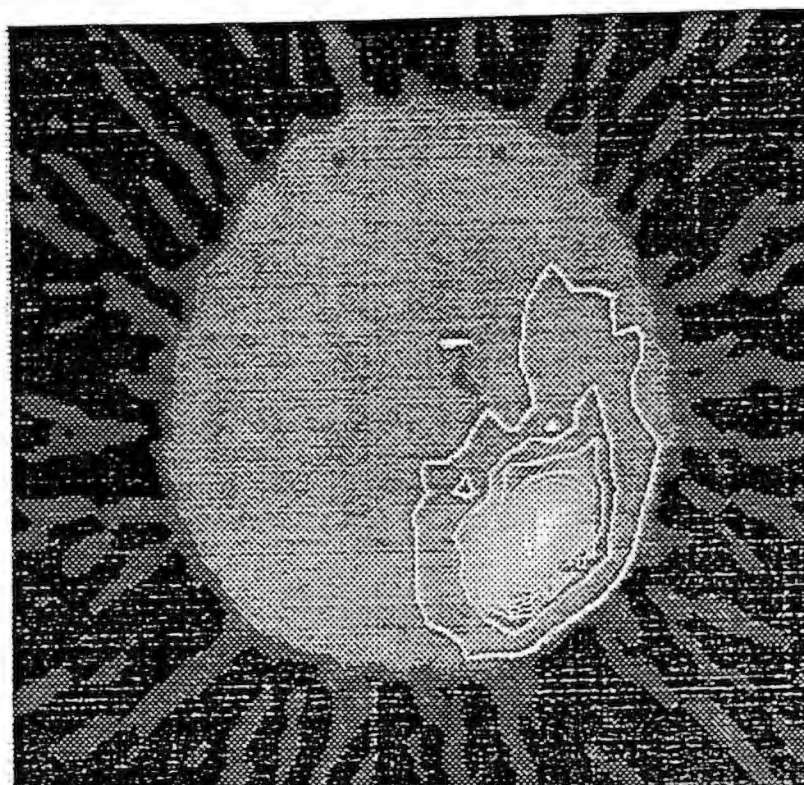


Figure 71. Pre-Surgery Dose Contours - Concentration/Pixel Data

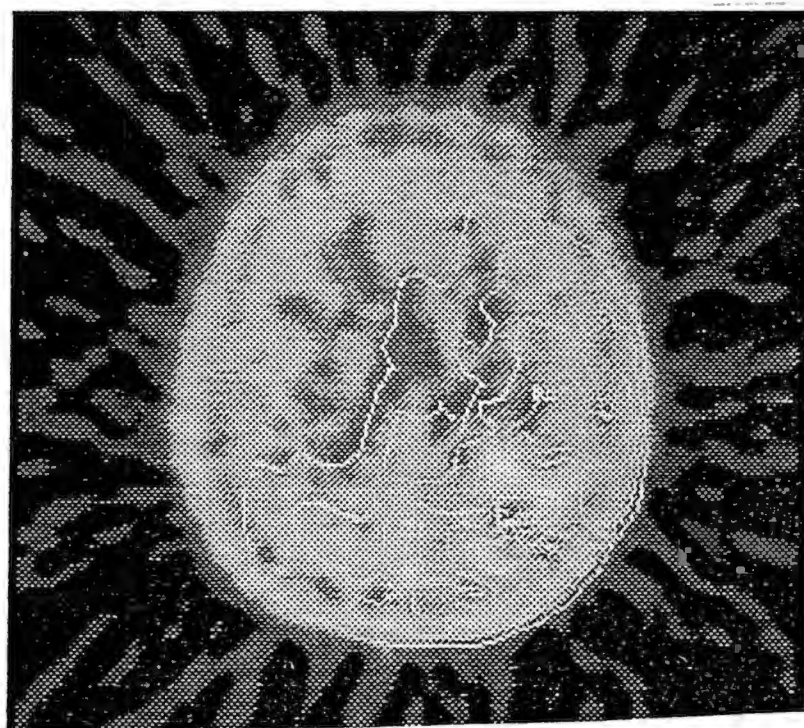


Figure 72. Post-Surgery Dose Contours - Concentration/Pixel Data

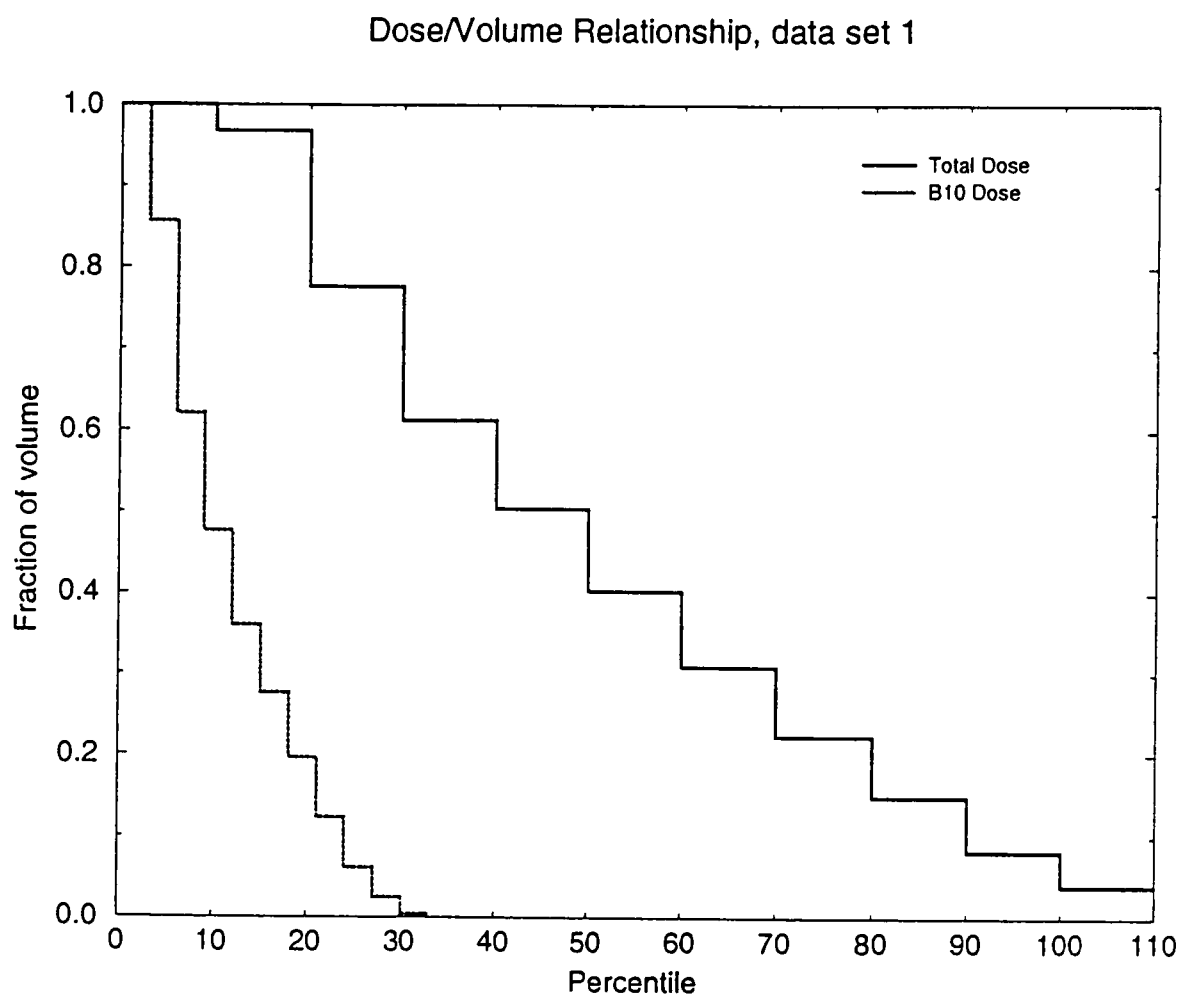


Figure 73. Dose/Volume Histogram Total/¹⁰B Dose Analysis

Conclusion

In conclusion, this method of per pixel incorporation of the boron concentration from the PET studies yields a patient specific planning method that produces significantly more accurate dose prescriptions. In the BNL contours, a much higher percentage of healthy tissue was allowed for irradiation. The bnct_rtp package does incorporate certain dose protection limits for healthy tissue and other specific regions such as the optic chiasm. There is no danger in the current BNL dose prescription package. Yet, the PET data shows that the beam focus will not be at the position defined by the MRI, but is dependent on the metabolic uptake of the BNCT agent. This cannot be generalized among a large patient population and the need for patient specific uptake analysis combined with dose prescription is apparent.

The PET data does allow a more accurate beam positioning method that will allow the peak flux to be directed at that specific portion of the tumor that has the maximum uptake value of a specific BNCT agent. This could improve results and efficacy, given the central tumor portion will be exposed. This is also highly important due to the pixel specific concentration curves. The curves indicate that the dose is much more concentrated than previously believed and that accurate planning and possibly fractionated or repeated treatments are even more crucial in view of this evidence. This study has shown the benefits of non-invasive boron distribution as applied to BNCT treatment planning.

Chapter V

Compartmental Modelling

Introduction

Compartmental modelling allows the clinician and the research scientist to gain pharmacokinetic information from the PET data which is unavailable from the standard emission images. PET is one of the few modalities to allow time dependent parameter estimation of metabolic uptake values [31]. Tracer kinetic modelling enables one to extract quantitative or "useful" data from the standard image set. Parameters such as extraction, flow rates, regional glucose metabolism and inter-compartmental transfer rates that represent physiological or biochemical processes may be obtained through various modelling techniques. The goal for F-BPA-Fr modelling is to maximize treatment planning as well as to better evaluate candidates for Boron Neutron Capture Therapy.

Compartmental models treat the parameters as time independent and the compartments as homogeneous. In principle, it is a relatively simple matter to produce a model that will simulate the Time Activity Curve, TAC, generated from a Region of Interest, ROI, in the PET scan. Factors that complicate this procedure are: the physical structure, assumptions taken, the physiological correctness of the underlying model, the number of compartments and variables possibly leading to dependency, the noise characteristics of the data, the estimation technique and algorithm, and the statistical tests that are chosen.

Richard Carson comments on this by stating, "All of these factors can make the parameter estimation problem as much craft as science." [9-10]. With this in mind then, our "coven" of researchers have studied and developed a number of models and techniques specific to F-BPA-Fr uptake in relation to BNCT.

Problem Definition

Figure 74 gives a pictorial diagram of the three models explored in this dissertation. These pictorial models can be converted to a set of linear differential equations. The standard form of the problem in state-space analysis methods is:

$$\begin{aligned} dX/dt &= A X + B U \\ Y &= C X + D U \end{aligned}$$

where X is the compartmental activity vector, U is the input function and Y represents the measured PET activity from the scan which allows us to fix $C=1$, $D=V$, where V represents a vascular fraction. An estimate can be made of the vascular fraction by drawing an ROI over the carotid artery during the first frame of activity. This allows the entire signal to arise strictly from the blood pool. This value gives an estimate of how much activity from the blood has spilled into adjacent parts of the brain. This parameter is generally assigned as an independent variable in the optimization routines. From the second equation above, the theoretical curve can then be compared to the true data. The vascular fraction can then be adjusted to increase or decrease the amount of blood activity included in the ROI.

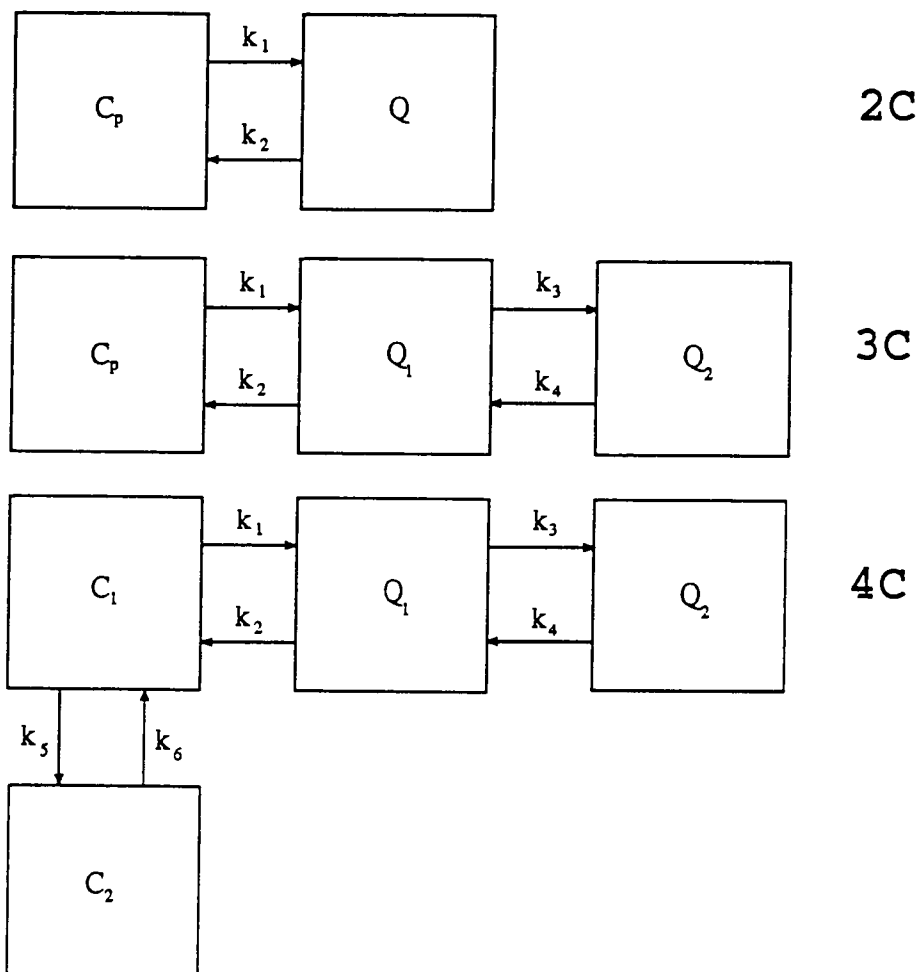


Figure 74. Compartmental Model Pictorial Definitions

Results

Assuming equilibrium or steady state of the parameters, allows us to write each of the three models in the form:

$$2C: \quad A = [-k_2], B = [k_1]; X = [Q];$$

$$3C: \quad A = [-(k_2+k_3) \quad k_4; k_3 \quad -k_4]; B = [k_1; 0]; X = [Q_1; Q_2];$$

$$4C: \quad A = [-(k_2+k_3) \quad k_4 \quad -k_1; k_3 \quad -k_4 \quad 0; 0 \quad -(k_5+k_6)]; B = [k_1; 0; k_5]; X = [Q_1; Q_2; C_2];$$

This allows a simple and compact way to analyze the 3 linear, homogeneous, first order differential equations. The computational linear optimization methods require that the differential equations be presented in this matrix form for input to the algorithm.

There are three basic ways to solve these models in order to obtain the desired parameters. The first depends primarily on the complexity of the model or number of compartments that have been defined. A graphical approach such as the Patlak method may be applied to both the 2 and 3 compartment models if the tracer does not wash out rapidly [64]. A second approach involves solving the model equations from first principles to obtain a complete analytical solution at all time points. The result may be in terms of $C_p(t)$, the blood pool or input function, or a specific form of $C_p(t)$ may be substituted. The last method of solving the set of equations is a numerical linear optimization method which iterates through an algorithm to approach the set of parameters that gives a "best" fit.

2C Graphical Analysis

The multiple linear regression graphical method can be formed for the 2 compartment model and is easily derived as shown below:

$$\frac{dQ}{dt} = k_1 C_p - k_2 Q$$

$$\frac{dC_p}{dt} = -k_1 C_p + k_2 Q$$

Integrating the second equation and rearranging yields:

$$k_2 \int Q = C_p + k_1 \int C_p$$

The last step places the equation in a linear form:

$$\int Q/C_p = \frac{k_1}{k_2} \int C_p/C_p + \frac{1}{k_2}$$

This is then in the form of $Y = mX + b$ and may be solved quite readily on a simple spreadsheet. The standard approach is to integrate the first equation describing the biodistribution in the tissue compartment to yield:

$$\frac{Q}{C_p} = k_1 \int C_p/C_p - k_2 \int Q/C_p$$

2C Analytical Solutions

The set of coupled linear differential equations may also be solved analytically using Laplace transforms. Taking the transform of the tissue compartment:

$$S Q = k_1 C_p - k_2 Q$$

$$Q = k_1 C_p / (S + k_2)$$

knowing the following inverse transform allows us then to write our solution as:

$$e^{-At} = \text{Inverse Laplace} [1 / (S + A)]$$

$$q(t) = k_1 \exp(-k_2 t) \otimes C_p(t)$$

This may also be solved directly using the symbolic manipulation package Maple V Release 4. This package has the ability to solve differential equations analytically in general form. This author feels that it is far superior mathematically to the package Mathematica produced by Wolfram. The defining equations are input into Maple and the initial condition of 0.0 activity at time 0.0 is applied to yield the results in Appendix T. This is then placed in a Lotus spreadsheet as an approximation tool for parameter estimation. The k values in the model can be easily changed and the results immediately seen in Figure 75 and compared with the mean squared error. This can also be done in MATLAB using the ode45 solver which will be discussed later. Figure 75 shows a 2 compartment fit of our most recent BPA patient.

2C Linear Optimization Methods

The method of manual spreadsheet entry of the model parameters is time consuming and inaccurate, albeit portable and simplistic. A full understanding of the particular model is needed to understand the effects that a single parameter produces on the time activity curve. The next level of parameter optimization leads

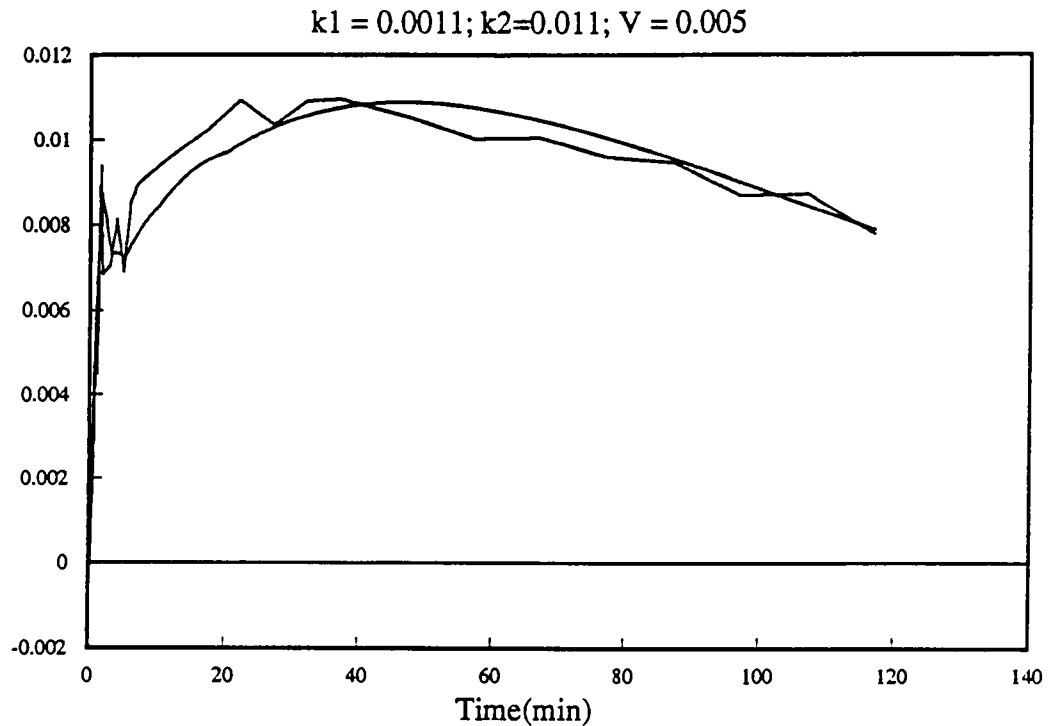


Figure 75. 2C Analytical Solution using Spreadsheet Analysis

to computational algorithmic numerical solutions of the differential equations. Initial parameters are defined for the problem and an initial fit is produced by numerically solving the set of differential equations. At this point we can simulate what the algorithms accomplish by using a short piece of code in MATLAB:

```
for k1=1:20,
for k2=1:20,
k(1)=.00008*k1;
k(2)=.0024*k2;
[T,Y]=ode45('2comp',t3,[0;0;0],'',k,bp2);
Ym = Y(:,2) + Y(:,3) + 0.0032*bp2;
s(k1,k2)=q'*q-Ym'*Ym;
end
end
```

The resulting vector, s , will then contain the squared error between the estimator

Ym and the true data, q. If this problem converges then the resulting vector, when plotted on the z-axis vs. k_1, k_2 plotted on the x and y axes respectively will yield a surface plot. There will theoretically be only one absolute minimum, but the possibility exists for many local minimum. These local minimum can be mistaken by the algorithm as the absolute minimum which will then produce erroneous and irreproducible results. The choice of local minimum will vary on the initial parameters chosen in analogy to the placement of a marble on the surface. Noisy data will compound this problem immensely. It is only the quality of the computational package and the choice of minimization algorithm that protects the researcher from this pitfall. Figure 76 shows the described surface plot for a 2 compartment model on our most recent BPA patient. This surface plot was created using MATLAB and was rotated in 3D to provide the best overall view. Figure 77 shows a mesh plot that was also created with MATLAB from the identical data set. The z-axis was zoomed to provide a much clearer view of the absolute minimum of the surface. Each point represents a numerical solution to the set of compartmental differential equations. The plots were created using the following lines of MATLAB code.

```
k1=1:20; k1=k1*0.00016; k2=1:20; k2=k2*0.0048; surf(k1,k2,s)
```

The two packages currently in use to compute the parameter estimation are Ctrlc, (Palo Alto, CA.) and MATLAB (Natick, MA.). Ctrl-C has been successfully used to model various compartmental systems here at UTMCK. Advantages of the

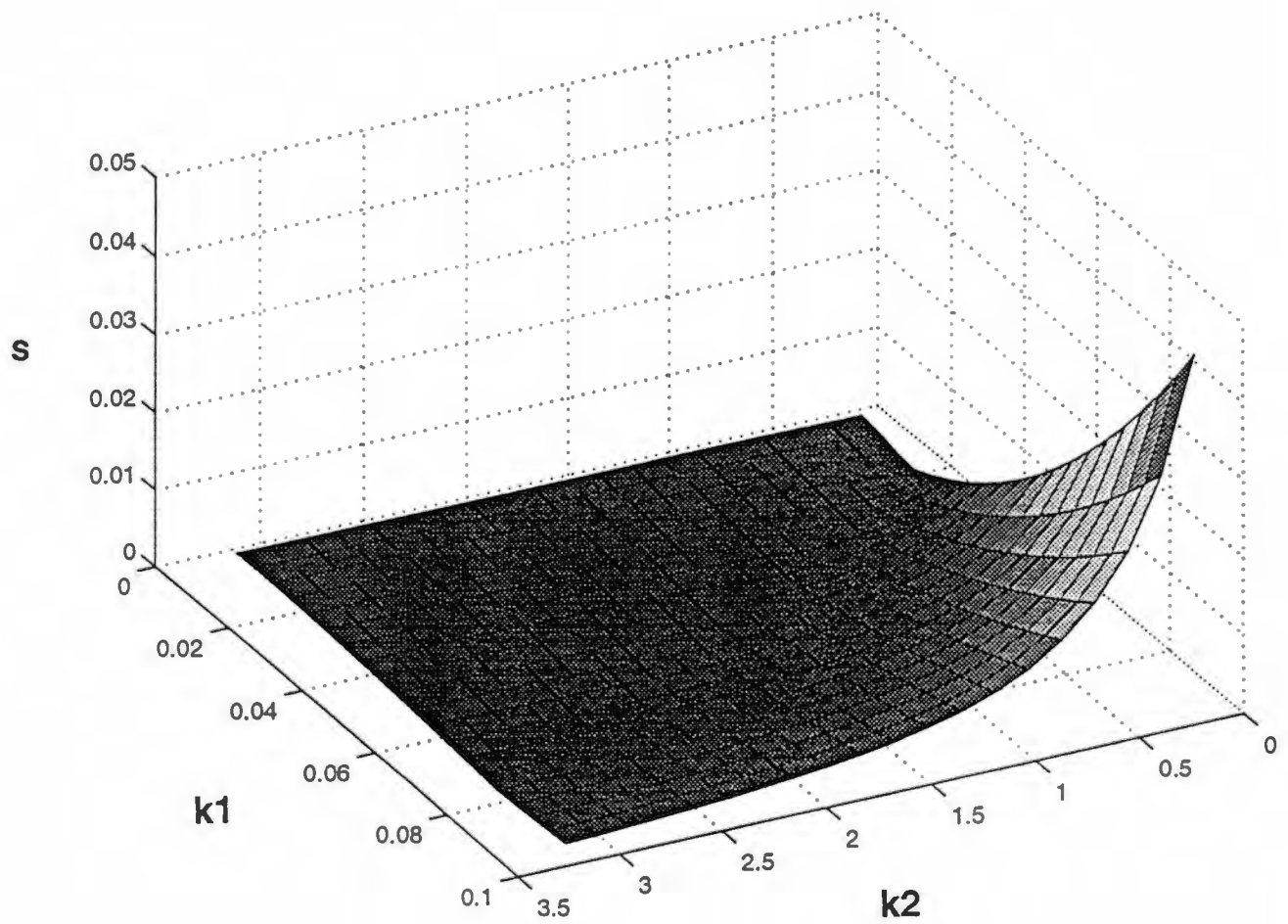


Figure 76. Coarse Scale Squared Error Parameter Estimation Plot

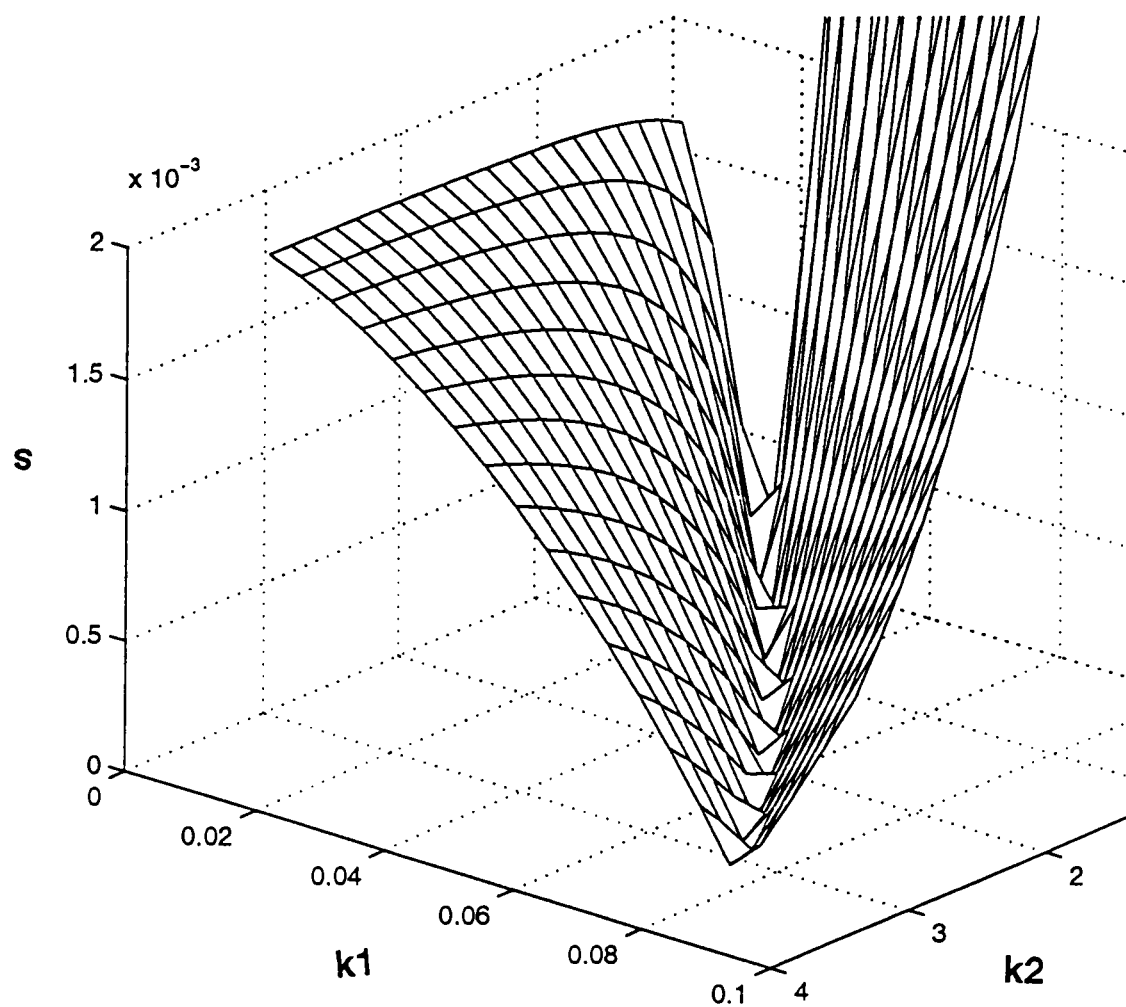


Figure 77. Fine Scale Squared Error 2C Parameter Estimation Plot

program include speed of computation, and ease of model alteration. The model definition takes place in a "p2ss" file and is identical in matrix form to that described earlier. The package uses a maximum likelihood method combined with a Levenberg-Marquardt search algorithm to minimize the parameters [48,51]. A full mathematical description of this procedure is beyond the scope of this dissertation. As that aspect is not the focus of this problem, a set of references to the original works and later implementations is provided.

Figure 78 gives a 3 parameter, 2 compartmental fit of the data using Ctrl-C.

Ctrl-C does have a number of disadvantages that should be mentioned. A primary restriction on data input pertains to the definition of the time interval. Only equal time partitions are allowed as valid input into Ctrl-C.

To illustrate the conflict with PET data, we can examine the frame lengths of our most recent BPA patient. The scan had 12 frames of 10 seconds in length, followed by 5 frames of 1 minute in length, followed by 6 frames of 5 minutes in length, finished with 9 frames of 10 minutes in length. Ctrl-C requires that both the blood and tissue curves must be of equal time points. In order to maintain the resolution of the time frames, the shortest interval of 10 seconds was chosen. MATLAB then fit the blood pool data with a bi-exponential curve as outlined in the macrodosimetry section of this dissertation [28,42]. The tissue curves were either linearly interpolated or fitted with a low order spline from within MATLAB. The

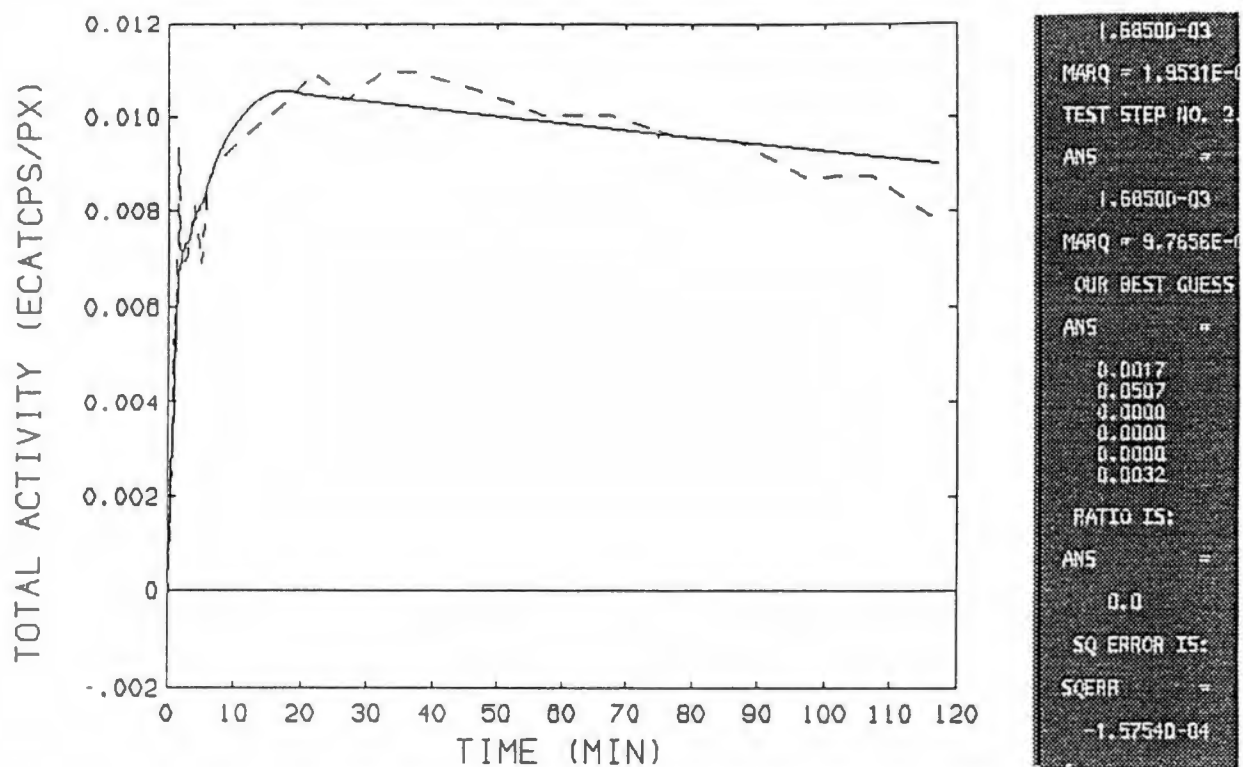


Figure 78. 2C Ctrl-C Linearly Optimized Fit

spline tended to minimize the noise of the data but also produced false oscillations at large discontinuities.

The second disadvantage of Ctrl-C involves the minimization problem. The zoomed scale surface plot created for the simulated 2 compartment fit revealed many peaks and valleys. The noise within the data created the numerous steps in the surface plot that would be categorized as local minimum. Ctrl-C does not, in every situation, have the ability to resolve the differences between a local and absolute minimum. It has in the past produced false minimum parameter values that, when re-run at different points of initial estimation, could not be reproduced.

Overall, Ctrl-C is an excellent package for non-linear optimization and should be used to check the results obtained with other software such as MATLAB. The Ctrl-C code used in the above runs is provided in Appendix Y.

The current choice for parameter estimation is MATLAB with an additional Optimization Toolbox. The actual solution of the set of differential equations is found using the subroutine **ode45**. The command line to call this solver for the 2 compartment case is:

```
[T,Y]=ode45('2comp',t3,[0;0;0],'',k,bp2);
```

The MATLAB file 2comp.m contains the problem definition in its simplest form:

```
function dy = dme2(t,y,flag,k,bp2)
global t3 ;
bp3=interp1(t3,bp2,t);
dy = [0; 0; k(1)*bp3-k(1)*y(1)-k(2)*y(3)];
```

This produces an immediate solution to the 2 compartment model assuming the parameters of $k(1)$ and $k(2)$ as previously defined. The variable $t3$ contains the starting points of the frames as given in the .cpt file. The variable $bp2$, likewise, is the activity data from the same input file. Stripping off the first 5 text lines of the input file allows the .cpt file to be read directly in to MATLAB in matrix form.

The ode45 solver is a simple non-stiff solver based on an explicit Runge-Kutta formula, the Dormand-Prince pair. The solution of the equations will be determined specifically at the initial time points defined by the PET scan frames. The solver itself will take smaller steps in regions of the function where the

derivative is sharper or more discontinuous. This is reason for the linear interpolation of the input activity into the ode solver. Although a linear interpolation is needed as in Ctrl-C, the solver is not limited by the step size of the input time vector. This allows a much more accurate determination of the solution at the given time points and also leads to a more accurate determination of the absolute minimum as a general method.

There are 5 different ode solvers specific for non-stiff or stiff problems having different levels of discontinuities. The number of specific options for the ode solver can also be specified with `odeset`. Options such as initial step size, maximum step size, relative or absolute tolerances, Jacobians and statistics may also be set to improve accuracy and speed. The "refine" option is also present which allows the user to input a refinement factor in the step sizes at which the solver proceeds. Statistics such as the number of successful steps, the number of failed attempts and other measures are also given. All the above functions are provided within the basic MATLAB package. The speed of the solver and any function call can be measured directly from within MATLAB using the following statement:

```
m=cputime; [T,Y]=ode45('2comp',t3,[0;0;0],',k,bp2); m1=cputime-m
```

The speed and accuracy must be weighed carefully when designing a routine.

The optimization routine itself calls upon the ode45 solver at different parameter values as determined within the optimization algorithm. Two choices for optimization routines have been successfully explored: `constr` and `curvefit`. The `constr` routine finds the minimum of a constrained nonlinear multivariable function. The routine can be called by the following command:

```
[k,options] = constr('2constrme',k,options)
```

with the function `2constrme.m` defined as:

```
function [err,g] = fun(k,t)
global t3 bp2 q
[T,Y]=ode45('2comp',t3,[0;0;0],',',k,bp2);
Ym = Y(:,2) + k(3)*bp2;
g = -k ;
plot(T,Ym,T,q)
drawnow
err=norm(Ym-q)
k
```

This example calls the ode45 solver and uses the output to create the steady state space equations simulating the actual measured PET values. It includes a vascular fraction defined as an independent parameter, `k(3)` which is multiplied by the input function, `bp2`. Upon each iteration the results are plotted and the error and parameter list displayed on the screen.

The `constr` routine uses Sequential Quadratic Programming methods in non-linear design. The addition of equality constraints sets this method apart from `Ctrl-C` in the fact that the restriction that `g = -k` can be implemented. This produces the desired effect that all of the `k` values within the model must remain positive

throughout the iterations. This was not always true in Ctrl-C. Negative parameter values are fictitious and have no relevance in a correct solution of the optimization problem.

Options available to the user in problem definition include display accuracy, worst case scenario termination values for x, f, g , gradient definition and checks, equality constraints, maximum number of function evaluations, step size and perturbation size. Another key difference is the ability to define v_{lb} and v_{ub} . These are upper and lower bound vectors on the parameters themselves. Knowing an approximate range on each of the parameters from various patient studies allows a limitation of the attempted parameters throughout the optimization run which increases the speed of the goal attainment. For further accuracy the lambda values of the Lagrange multipliers and the Hessian matrix may also be returned if desired.

The other preferred choice of nonlinear optimization methods mimics that of Ctrl-C. The **curvefit** routine is designed specifically for data-fitting problems in the area of least squares optimization. The primary difference between this and the **constr** function is the ability to choose various search algorithms. The default is the Levenberg-Marquardt algorithm, as in Ctrl-C but can be changed to a Gauss-Newton method which is generally faster with smaller residuals but is also more sensitive to noise [56]. The optimization manual provided by MATLAB states that the only limitation of **curvefit** is the fact that it may provide only local solutions if the

surface has discontinuities.

Overall, the routine of choice is the `constr` function which allows optimization of many variables and will be explicitly defined for each model. In general, the definition could be made as follows in the most general sense which would allow solutions of all the models to be accomplished simply by setting the undesired variables to zero.

The general function `constrme.m` is given as:

```
function [err,g] = fun(k,t)
global t3 bp2 q
[T,Y]=ode45('dme2',t3,[0;0;0],'',k,bp2);
Ym = Y(:,2) + Y(:,3) + 0.0036*bp2;
g = -k ;
plot(T,Ym,T,q)
drawnow
err=norm(Ym-q), k
```

where the vascular fraction of 0.0036 can be defined as $k(6)$ and left as an independent variable to be fitted if desired. The specific `ode45` function, in general form, `dme2.m` is defined as:

```
function dy = dme2(t,y,flag,k,bp2)
global t3 ;
bp3=interp1(t3,bp2,t);
dy = [-k(5)*y(1)+k(5)*bp3; k(3)*y(3)-0.002*y(2);
k(1)*bp3-k(1)*y(1)-(k(2)+k(3))*y(3)+0.002*y(2)];
```

The variable $k(4)$ has been fixed at 0.002 as in Ctrl-C for various runs. A 2 parameter optimization run fixing V at 0.0032 has been in Figure 79. Letting the vascular fraction vary as an independent parameter yields Figure 80.

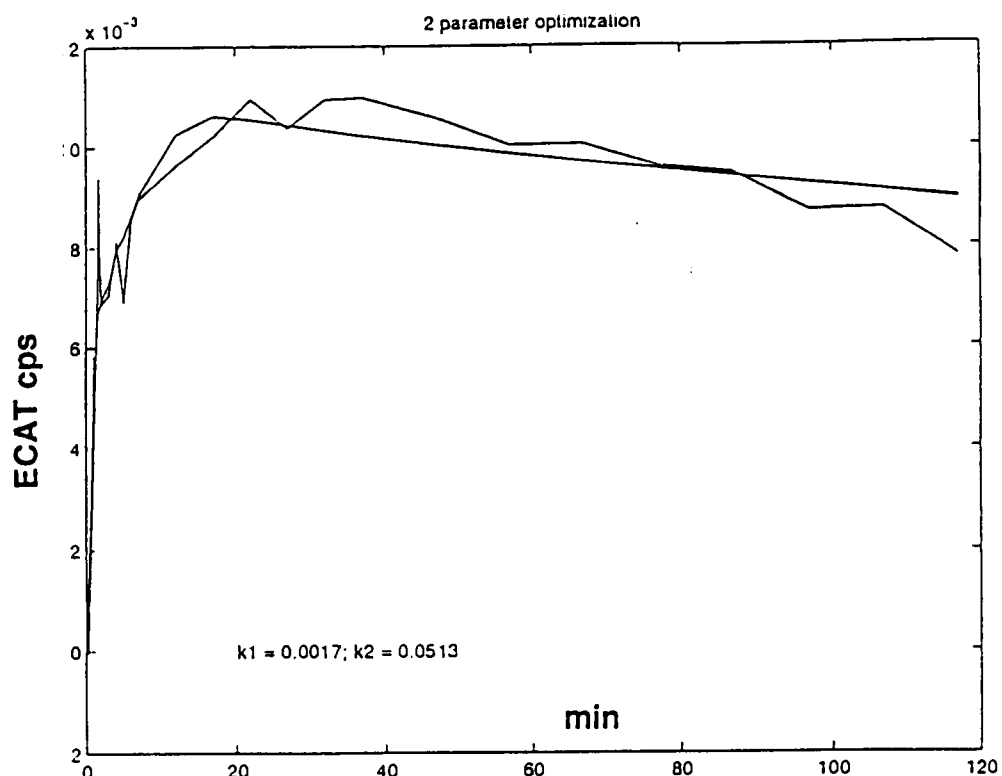


Figure 79. 2C MATLAB Linear Optimization 2 Parameter Run

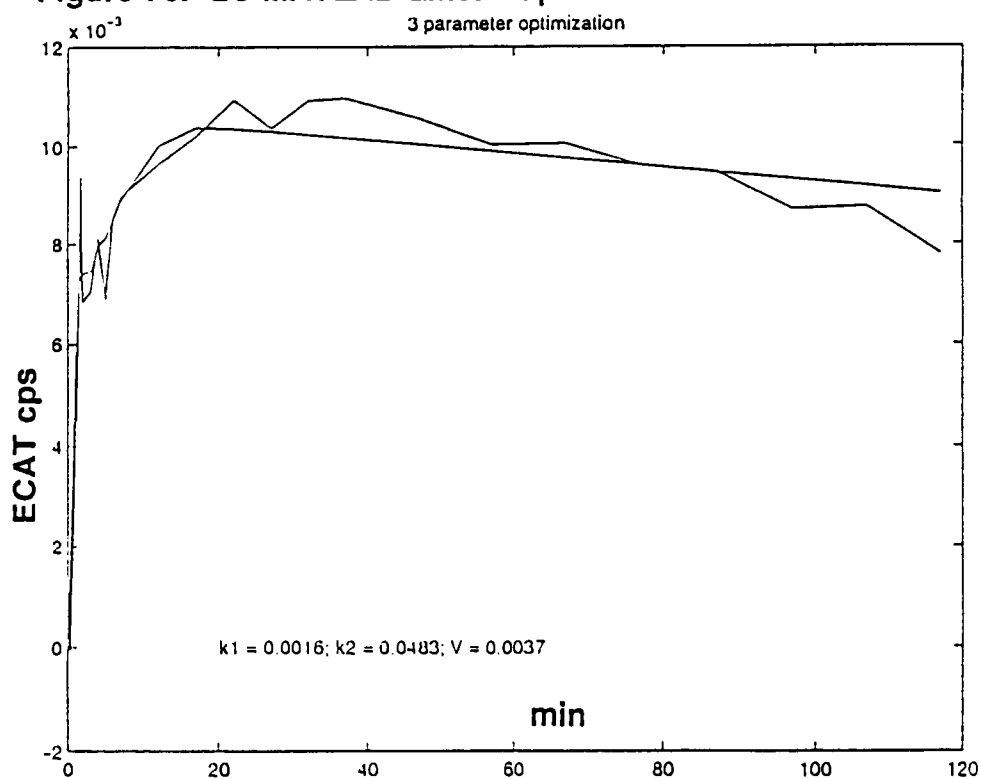


Figure 80. 2C MATLAB Linear Optimization 3 Parameter Run

3C Graphical Analysis

These runs, yield identical parameters, within statistically accepted ranges, to those of Ctrl-C for this specific example. The curves are essentially the same for both packages which also aids in confirming the accuracy of the optimization methods used in each case.

The three compartment model, identical in form to the FDG model proposed by Huang and used by Ishiwata for BNCT work may now be analyzed [31,35]. As in the two compartment model, a graphical method is available for the three compartment model. The analysis is known as the Patlak approach and may be fully derived from the three compartment model. The two tissue compartments may be written in differential form as:

$$1) \quad dQ_1/dt = k_1 C_p + k_4 Q_2 - (k_2 + k_3) Q_1$$

$$2) \quad dQ_2/dt = k_3 Q_1 - k_4 Q_2$$

$$3) \quad dQ/dt = dQ_1/dt + dQ_2/dt = -k_2 Q_1 + k_1 C_p$$

Solving for Q_1 and dQ_1/dt from equation 3 and substituting back into equation 1 yields:

$$4) \quad (k_1 dC_p/dt - d^2Q/dt^2)/k_2 = -(k_2 + k_3)(k_1 C_p - dQ/dt)/k_2 + k_4 Q_2 + k_1 C_p$$

Solving for Q_2 and substituting into equation 2 yields a form in just Q , C_p :

$$5) \quad d^3Q/dt^3 + d^2Q/dt^2 (k_2 + k_3 + k_4) + dQ/dt (k_2 k_4) = d^2C_p/dt^2 k_1 + dC_p/dt k_1 (k_3 + k_4)$$

Assuming minimal contribution from the third derivative of Q and integrating:

$$(k_2+k_3+k_4)Q+k_2k_4\int Q=k_1C_p+k_1(k_3+k_4)\int C_p$$

This can be placed in a linear form and graphed analytically. This Patlak approach is shown in Figure 81 on data from our second BPA patient. Again the slope of the Patlak plot would be equal to the macro parameter $k_1k_3/(k_2+k_3)$.

3C Analytical Solutions

The analysis by first principles or direct analytical solution of the FDG model can be shown in MAPLE in Appendix U. As cryptic as the output may appear, it actually gives a quick and concise solution that may be written as a convolution integral and correlates exactly with the Laplacian form given in Huang's original paper [31]. This has also been placed in a Lotus spreadsheet for simplistic parameter estimation runs. One interesting development in implementing this solution into a spreadsheet is the inclusion of convolution integrals. In general the convolution integral takes the form of:

$$a(t)\otimes b(t)=\int^t a(\tau)b(t-\tau)d\tau$$

In the compartmental models the $b(t-T)$ term can be separated given it is an exponential in all our equations. This fact originates from the form of the solution not from the fit to the input function. The $\exp(t)$ term can then be pulled outside the integral. The integral is then performed numerically using Simpson's rule or

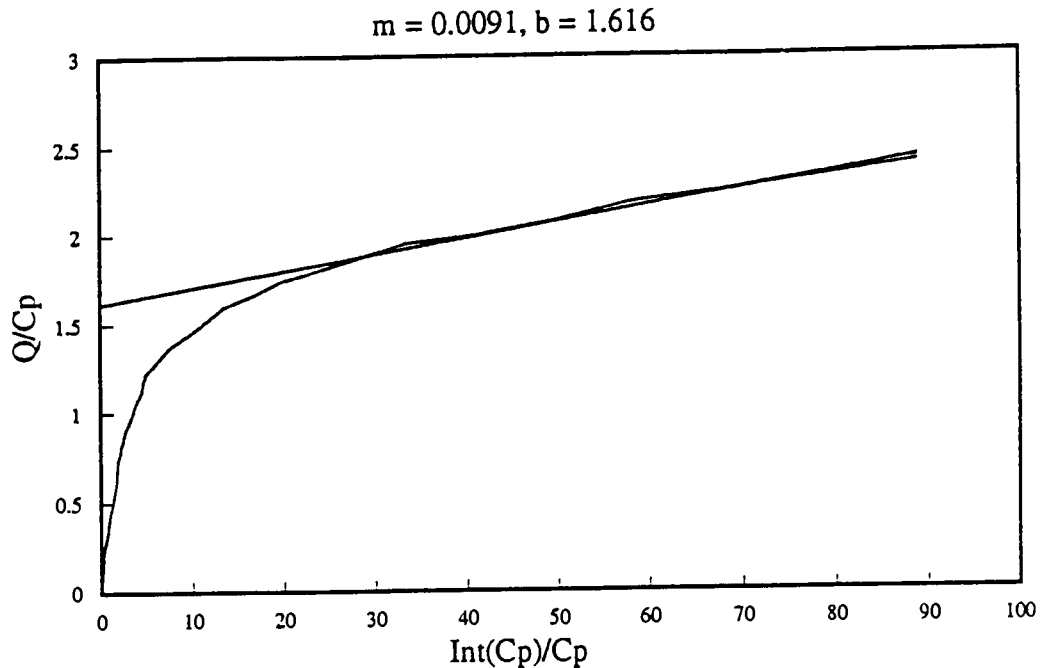


Figure 81. Graphical Patlak Analysis Plot

the trapezoid method and then the result is multiplied by the exponential term as described before. A sample 3 compartment fit with this method is shown in Figure 82.

3C Linear Optimization Methods

Again, the direct spreadsheet analysis method is a good general approximator but adjusting the parameters individually does not yield an optimized solution. Yet, it does serve a great purpose in the fact that it confirms the results from MATLAB or Ctrl-C with the analytical solution. Ctrl-C yields the fit in Figure 83 for the same data set as shown in the 2 compartment model.

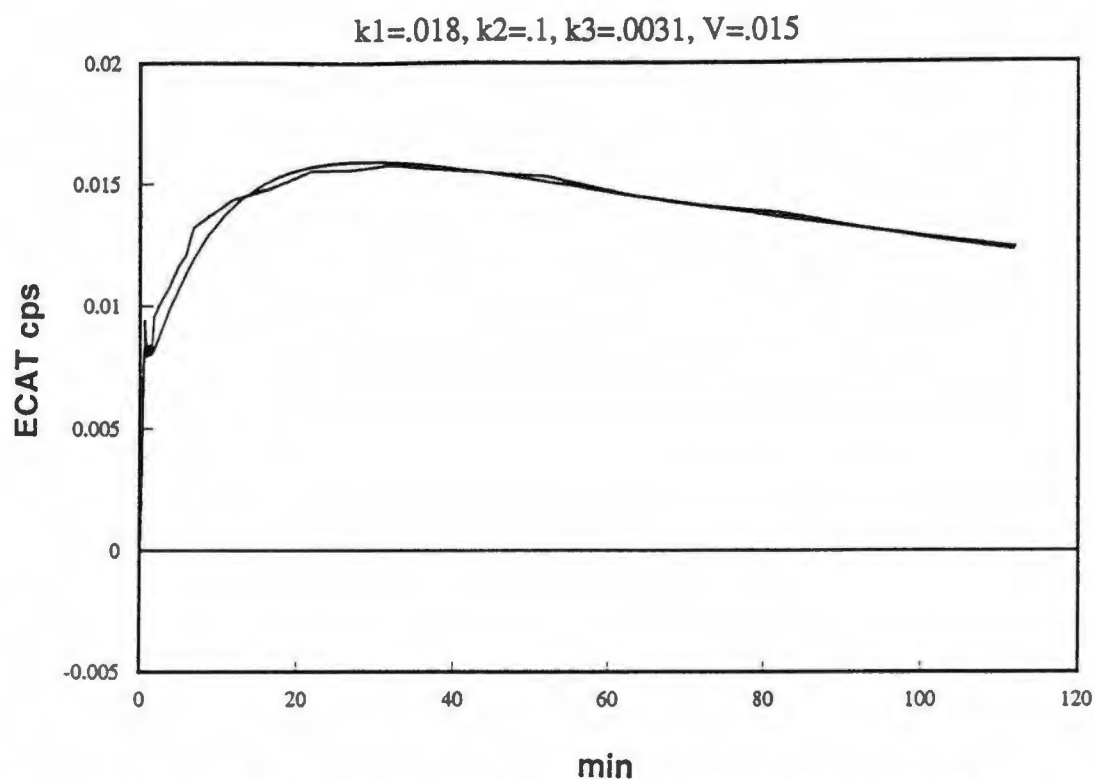


Figure 82. 3C Analytical Fit using Spreadsheet Analysis

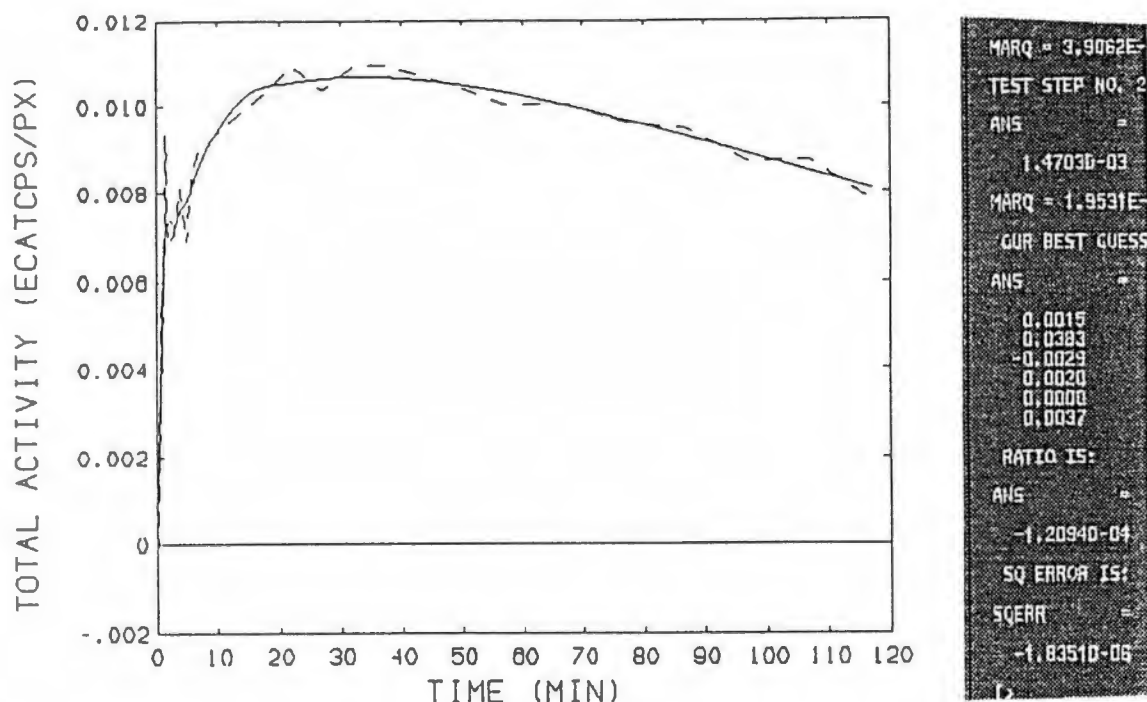


Figure 83. 3C Ctrl-C Linearly Optimized Fit

Note that in this case, the "best" fit parameters yielded a negative value for k_3 . Although the fit appears to be "good", this is not acceptable and can be checked from within Ctrl-C. Similar to MATLAB, a function exists that will solve the system of equations for one specific set of input parameters. This function is called "simu" and takes the form $[Y,X] = \text{SIMU}(A,B,C,D,U,T)$ where the state space equations of $dX/dt = AX + BU$ and $Y = CX + DU$ apply. This function then allows the plotting of each of the compartments of the model individually. One can then plot time vs. $X(1,:)$ and $X(2,:)$, where $X(2,:)$ contains the activity from the non-diffusible tissue compartment. This is what is shown in Figure 84 as an output from Ctrl-C.

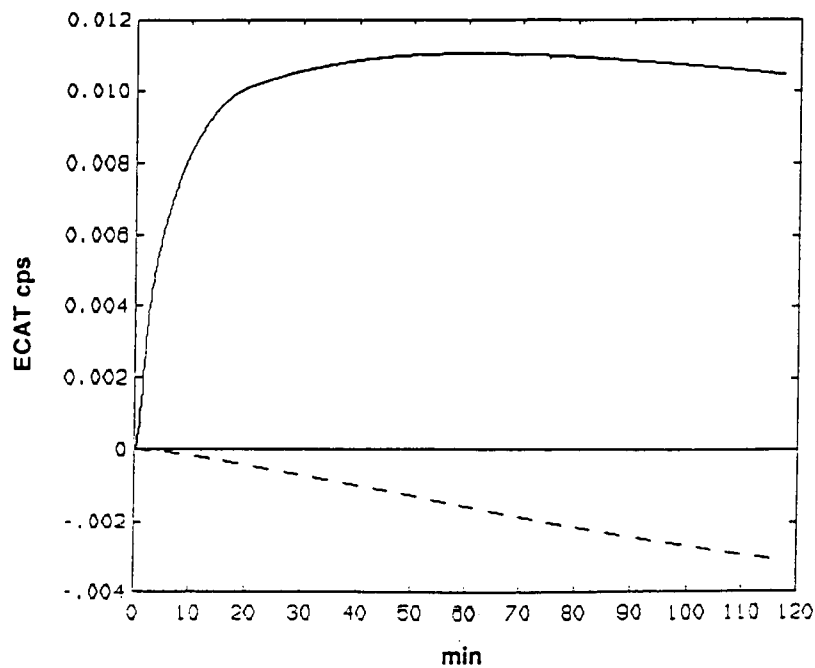


Figure 84. Single Parameter Set 3C Numerical Solution

Notice that $X(2,:)$ drops negative immediately after injection. This is unrealistic and allows us to see in a quantitative way that the optimized parameters, although providing a good fit with $X(1,:)$ must be reexamined. Fixing $k_3=0.001$ as a low positive number and running Ctrl-C again letting k_1 and k_2 vary yields Figure 85.

Notice that although all of the parameters are positive that the overall goodness of fit is still very poor. Repeating this calculation in MATLAB will permit an accuracy check of the Ctrl-C runs. This does occur given MATLAB has a constraint that limits the values of k to be positive in all cases. The following plot allows V to be fixed as well as k_4 just as in Ctrl-C. It can be seen that almost identical parameters are estimated in Figure 86. Possibly, letting k_4 and V vary as well might alleviate the stiffness of the solution. MATLAB then produces Figure 87 with a 5 parameter variance optimization run for the 3 compartment model. It should be noted that, for this set of data, the 3 compartment model failed. For previous BPA patients an adequate 3 compartmental fit was obtained [42].

4C Analytical Solutions

We now finish our model analysis by approaching the 4 compartment BPA model derived from a ^{99m}Tc -HM-PAO study. This model differs significantly from the previous two in the fact that it allows for a portion of the drug to remain in the non-diffusible compartment within the blood pool. Physiologically, a portion of the drug will remain in the diffusible or liquid portion of the blood and some will remain

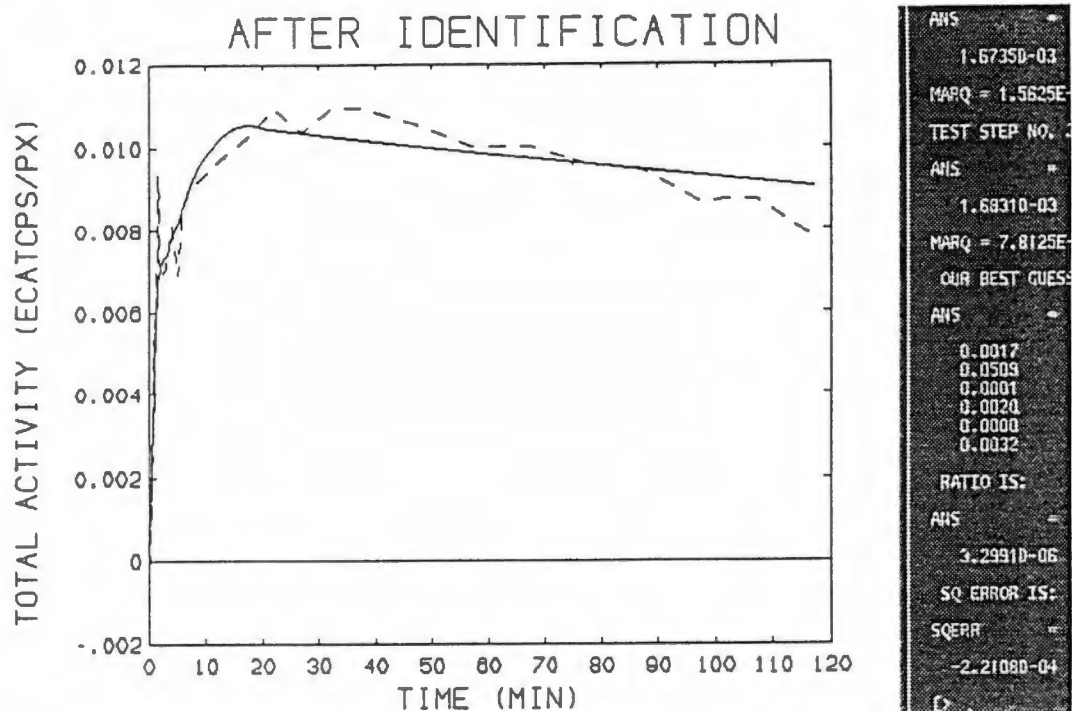


Figure 85. 3C 2 Parameter Ctrl-C Linear Optimization Fit

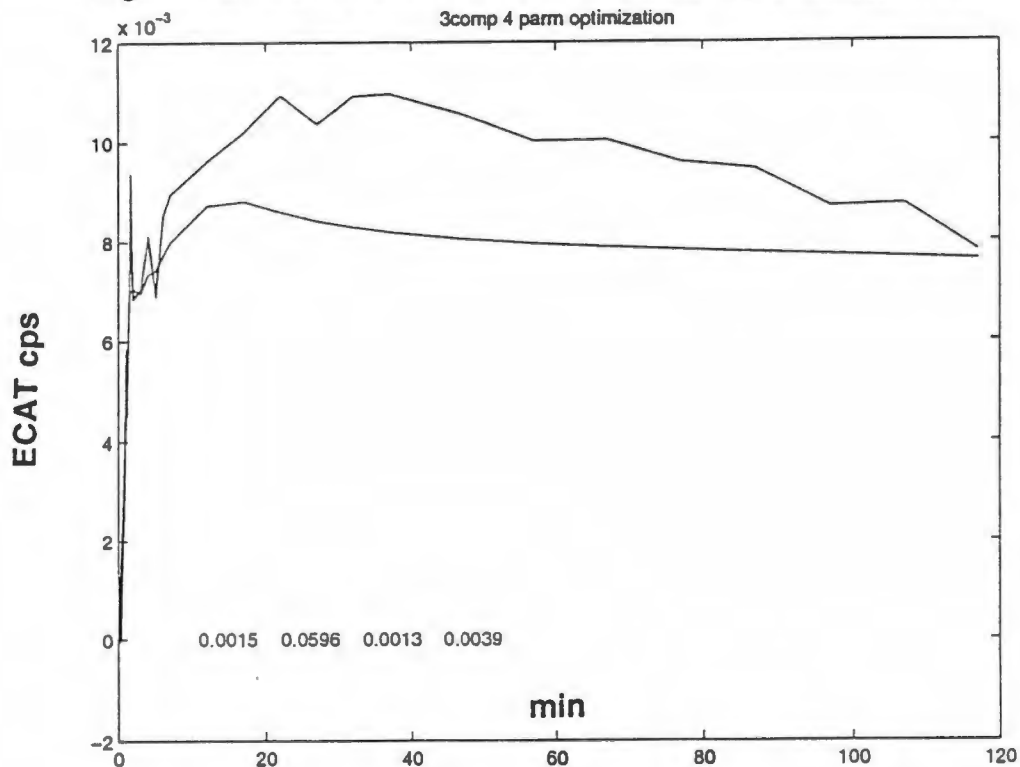


Figure 86. 3C 4 Parameter MATLAB Linear Optimization Fit

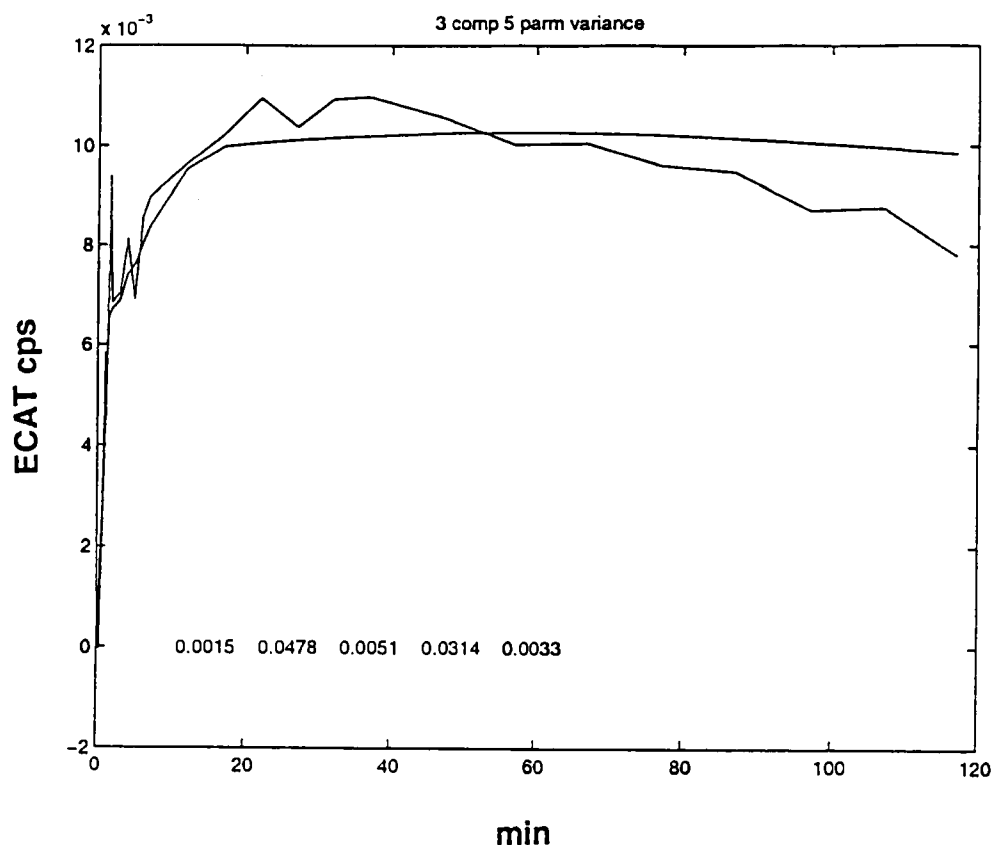


Figure 87. 3C 5 Parameter MATLAB Linear Optimization Fit

trapped or bound to the red blood cells, proteins and other solid components of the blood. This is the primary difference between the model and the standard FDG model proposed earlier [4,31]. The assumption that $k_6 = 0.0$ is given due to the assumption of a low release rate of the drug from the RBC's back to the plasma within the amount of scan time.

This model has not been fit graphically due to the number of assumptions that must be made to reduce the number of parameters. The most recent BPA patient had venous blood samples drawn at time intervals similar to the frame offsets.

This blood data was separated into plasma and RBC components and counted in a well counter. An FDG phantom was also created with identical activity to that of the PET scan and placed in the well counter to achieve a baseline correction factor. After decay correction and normalization with the phantom, Table 4 was produced. Time is in seconds and the activity is in uCi/ml. Figure 88 then shows the data in graphical form from which it is easier to see the appropriate ratios. Also plotted in Figure 89 is the ratio of plasma to whole blood and RBC's to whole blood which has a direct relation on the expected values of k_5 and k_6 respectively.

Table 4. Well Counter Blood Activity Data

Time	WB	Plasma	RBC
Seconds	Activity	Activity	Activity
0	0	0	0
90	30.7	25	5.7
188	16.4	15.3	1.1
307	10.9	9.6	1.3
607	8.1	6.5	1.7
1204	5.6	4.6	1
1800	4.6	3.8	0.9
8503	2.2	1.8	0.3

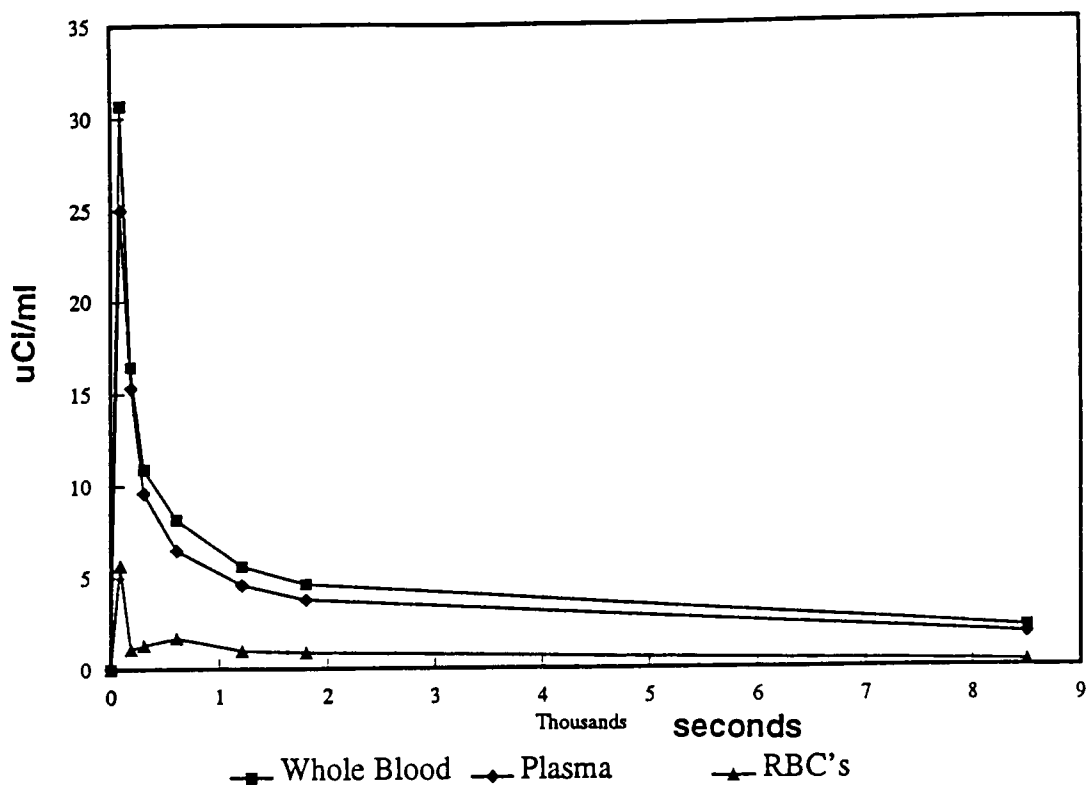


Figure 88. Well Counter Blood Compartment Activity Plots

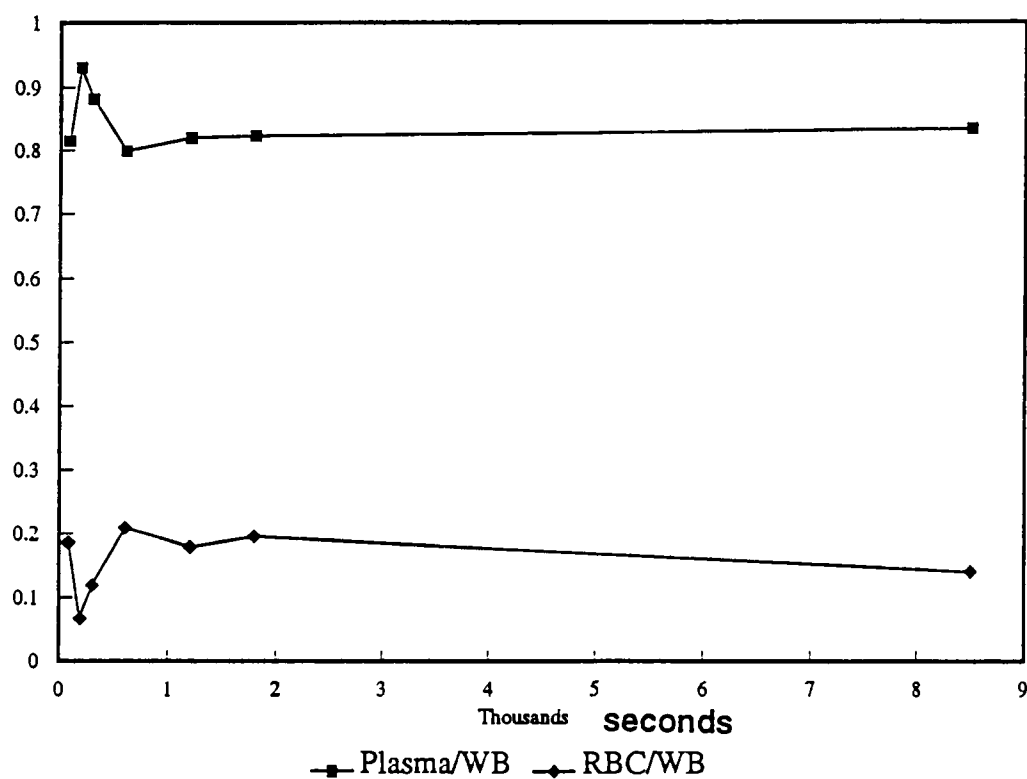


Figure 89. Well Counter Compartmental Activity Ratios

The analytical solution is quite interesting and also mathematically intensive. A first successful approach at the analytical solution was gained by using MAPLE shown in Appendix V. This solution is correct but is rather unruly given that the inverse Laplace transform of a polynomial yields hyperbolic trigonometric terms. We know that:

$$\sinh(x) = 0.5(e^x - e^{-x}); \cosh(x) = 0.5(e^x + e^{-x});$$

therefore it is possible to simplify this solution in terms of pure exponentials.

Let the following constant substitutions be made:

$$A = 2k_5k_3 + k_5(k_2)^2 + 2k_5k_4k_3 + k_5(k_3)^2 + k_2k_3k_4 + k_4(k_3)^2$$

$$B = -k_2k_5 - k_3k_5 - k_3k_4$$

$$C = (-k_5k_2 + (k_5)^2 - k_5k_3 - k_4k_3)\text{Sqrt}(\%1)$$

We can write the final result, after a little simplification, in the following form:

$$Q_1 = I_1 + I_2 + I_3;$$

where Q_1 represents the diffusible portion of the tissue.

$$I_1 = \frac{k_1}{A}(k_5)^2\sqrt{1}\exp(-k_5t)\int\exp(k_5u)C_a(u)du$$

$$I_2 = 0.5\frac{k_1}{A}(A+B\sqrt{1})\exp(0.5(\sqrt{1}-k_2-k_3)t)\int\exp(-0.5(\sqrt{1}-k_2-k_3)u)C_a(u)du$$

$$I_3 = -0.5\frac{k_1}{A}(A-B\sqrt{1})\exp(-0.5(\sqrt{1}+k_2+k_3)t)\int\exp(+0.5(\sqrt{1}+k_2+k_3)u)C_a(u)du$$

The non-diffusible portion of the tissue compartment, Q_2 can also be written in a

similar form:

$$Q_2 = I_4 + I_5 + I_6;$$

$$I_4 = -\frac{k_1}{A} k_3 k_5 \sqrt{1} \exp(-k_5 t) \int \exp(k_5 u) C_a(u) du$$

$$I_5 = -0.5 \frac{k_1}{A} k_3 (k_5 (k_2 + k_3) + 2k_3 k_4 - k_5 \sqrt{1}) \exp(0.5(\sqrt{1} - k_2 - k_3)t) \int \exp(-0.5(\sqrt{1} - k_2 - k_3)u) C_a(u) du$$

$$I_6 = 0.5 \frac{k_1}{A} k_3 (k_5 (k_2 + k_3) + 2k_3 k_4 + k_5 \sqrt{1}) \exp(-0.5(\sqrt{1} + k_2 + k_3)t) \int \exp(0.5(\sqrt{1} + k_2 + k_3)u) C_a(u) du$$

where Sqrt(1) represents the Sqrt(%1) given in the MAPLE solution. This is then the final form of the solution where the measured PET data would then be given by:

$$Y = C_{TD} + C_{TND} + VC_a$$

This solution was actually placed in a spreadsheet to check the results with those of Ctrl-C and MATLAB. The fit in Figure 90 is accurate and corresponds with graphs to be presented for Ctrl-C and MATLAB.

One interesting note that had an affect on this particular analysis was the step size of the input functions. Given that a large amount of numerical integrations were accomplished, a small step size was needed to minimize errors to produce a reasonable fit. The original irregular time steps in the PET data provided a noisy fit that was much less accurate.

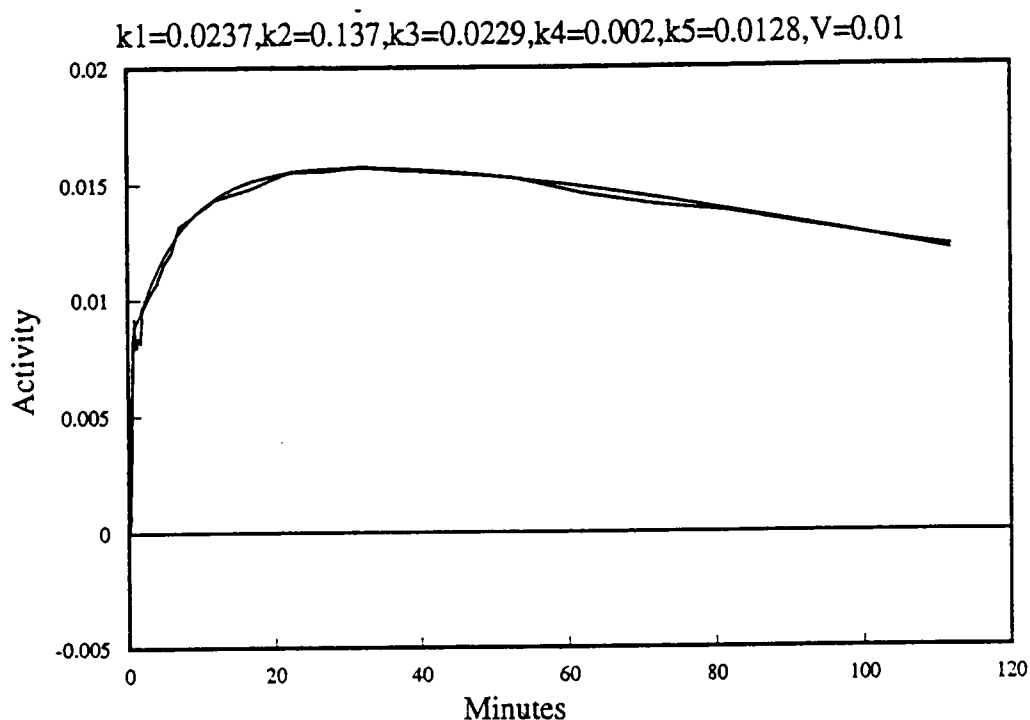


Figure 90. 4C MAPLE Analytical Fit using Spreadsheet Analysis

The second method of direct solutions followed the same steps as above. Dr. Gary Smith discovered that if the differential equations are put into partial fraction forms after Laplace transform, then they can be analyzed using only one inverse transform as given in the 2 compartment analysis. This solution follows the form published by Huang for the FDG model and actually is more mathematically elegant. Knowing the above inverse Laplace transform, and the algebraic method of partial fractions, one can then theoretically solve any number of models from first principles. The results have been placed in a spreadsheet and compared with the previous analytical solution and computational solutions as well and is plotted in Figure 91. The solutions described above have been placed in a Appendix W.

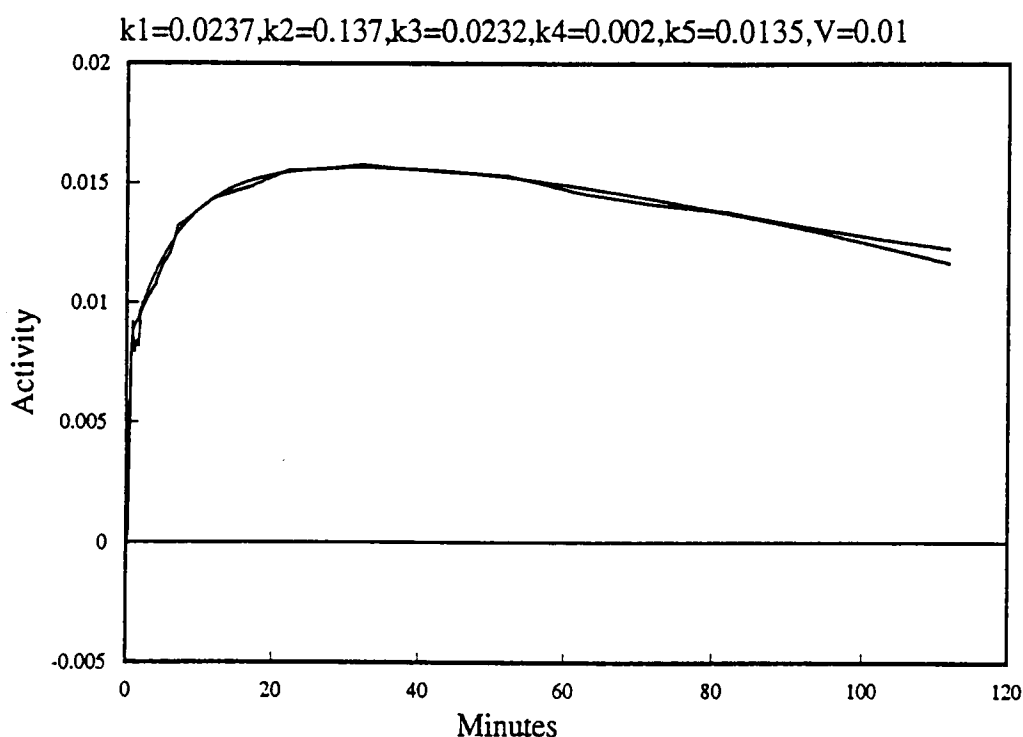


Figure 91. 4C Laplace Analytical Fit using Spreadsheet Analysis

Two other full analytical solutions were also derived. The first derivation that was used as a reference was carried out by Dr. Joseph Thie, a consultant on this project. He used the following form for the blood pool input function:

$$C_p = Nmt \text{ for } t < T; \quad C_p = N[Ae^{-at} + (1-A)e^{-bt}] \text{ for } t > T$$

where T represents the time of peak injection from the bolus. An average value of T for the BPA studies was approximately 30 seconds. His approach contains numerical values for many of the constants and uses series expansion to neglect some of the terms for various time periods. A sample fit is given in Figure 92 which was provided by Dr. Thie. His insight into this analysis has been invaluable and much appreciated.

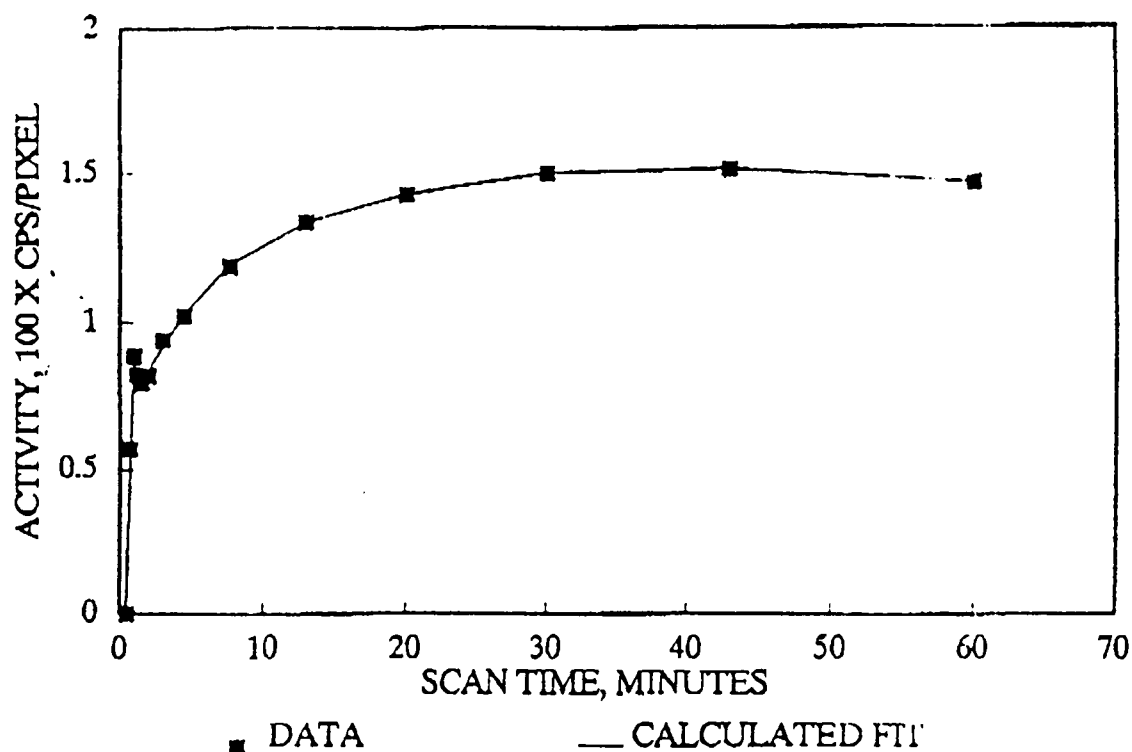


Figure 92. 4C Analytical Fit - Dr. Joseph Thie

The second method is given in as a simplification of the earlier MAPLE model in Appendix X. It is a simplification in the fact that only pure exponential terms are arrived at and the hyperbolic terms are bypassed.

Four different forms of the direct analytical solution have been presented. All yield accurate fits of the data and should be directly reconcilable with the others in the purest mathematical sense.

4C Linear Optimization Methods

The Ctrl-C package is the next package that may again be used to analyze the 4 compartment BPA model for which the code is given in Appendix Y. Again, the

data is from our most recent BPA patient which has been analyzed with the 2 and 3 compartment models. The plot in Figure 93 fixes $k_4 = 0.002$, which yields an excellent fit to the data with all positive parameters.

MATLAB also provides an excellent fit whether k_4 is fixed or whether it is optimized as an independent variable. In this particular case, Figure 94 fixes k_4 and returns a set of parameters with $k_3 = 0.0$. This may be interpreted that the drug is completely captured by the tissue once within the intracellular space and possibly a 3 compartment model might be used. Both plots are presented below with the first having k_4 as fixed. Both plots allow the vascular fraction to be optimized in all cases. For the 4 compartment model, this allows 6 independent variables to become optimized as shown in Figure 95.

Parametric Images

One of the primary goals of the direct analysis methods, that provide a quantitative mathematical solution, is the implementation of the equations into a parametric image routine. The above derivations provide solutions that are simplistic enough to be placed in a spreadsheet and are therefore transferable into C code. A short subroutine was written to perform the 3 compartment Patlak analysis on each pixel of a PET image [25]. The code itself is fairly simple and the crux performs a numerical linear regression on the data set defined by that pixel in each frame of the PET series. Patlak slopes that are negative are set to 0.0 and regarded

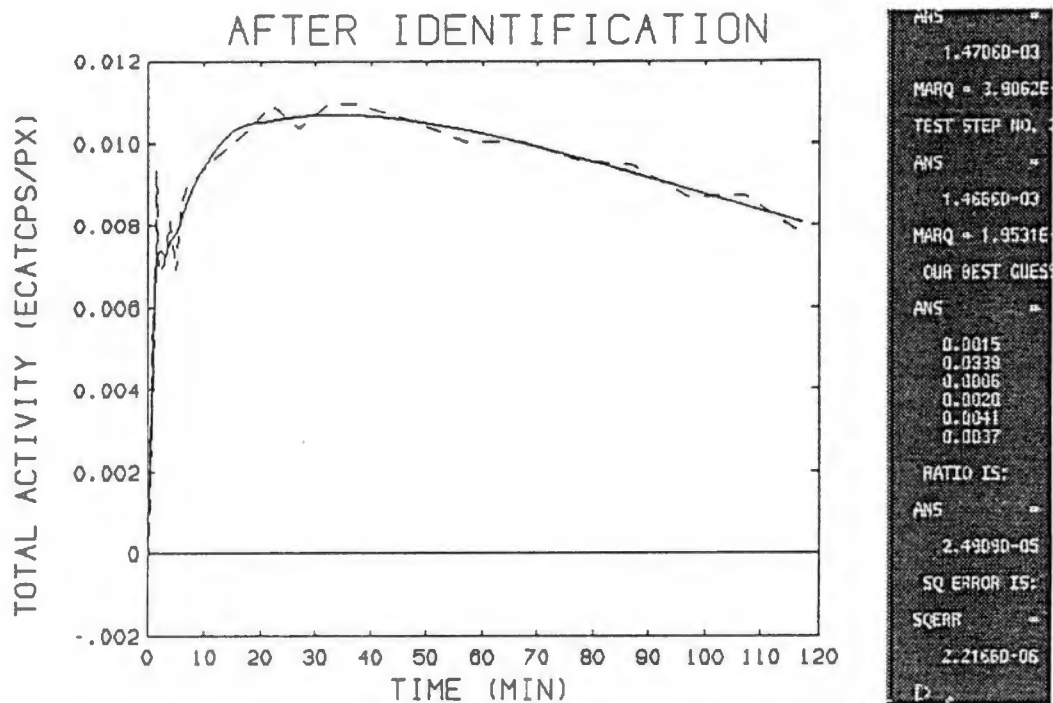


Figure 93. 4C Ctrl-C Linear Optimization Fit

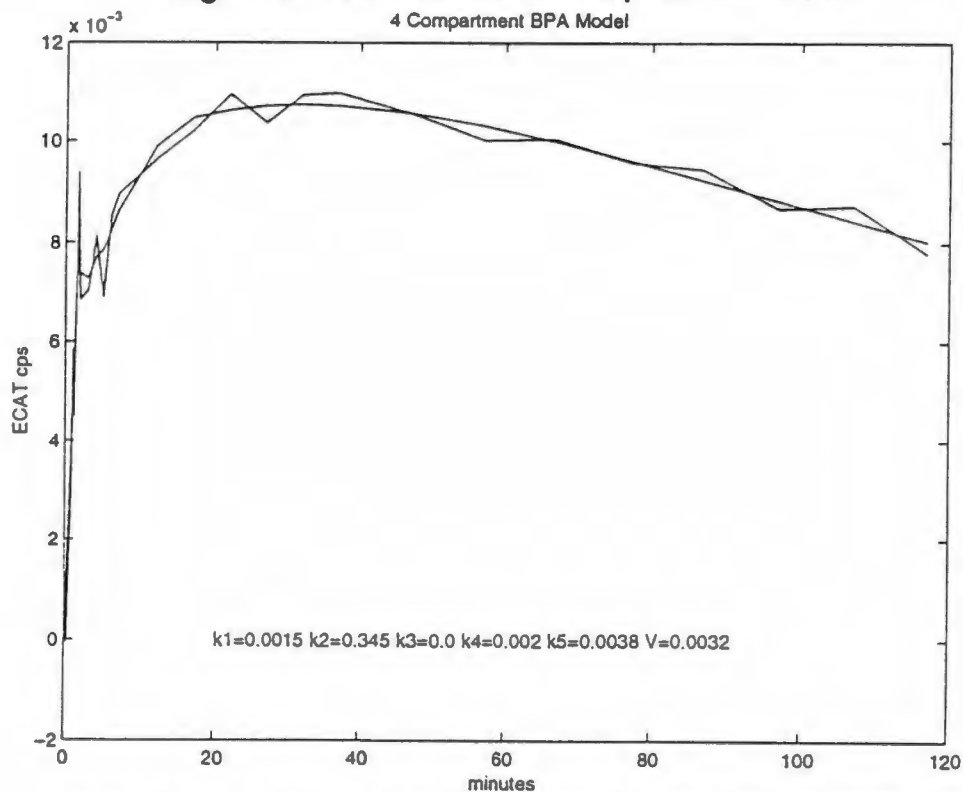


Figure 94. 4C MATLAB 5 Parameter Linear Optimization Fit

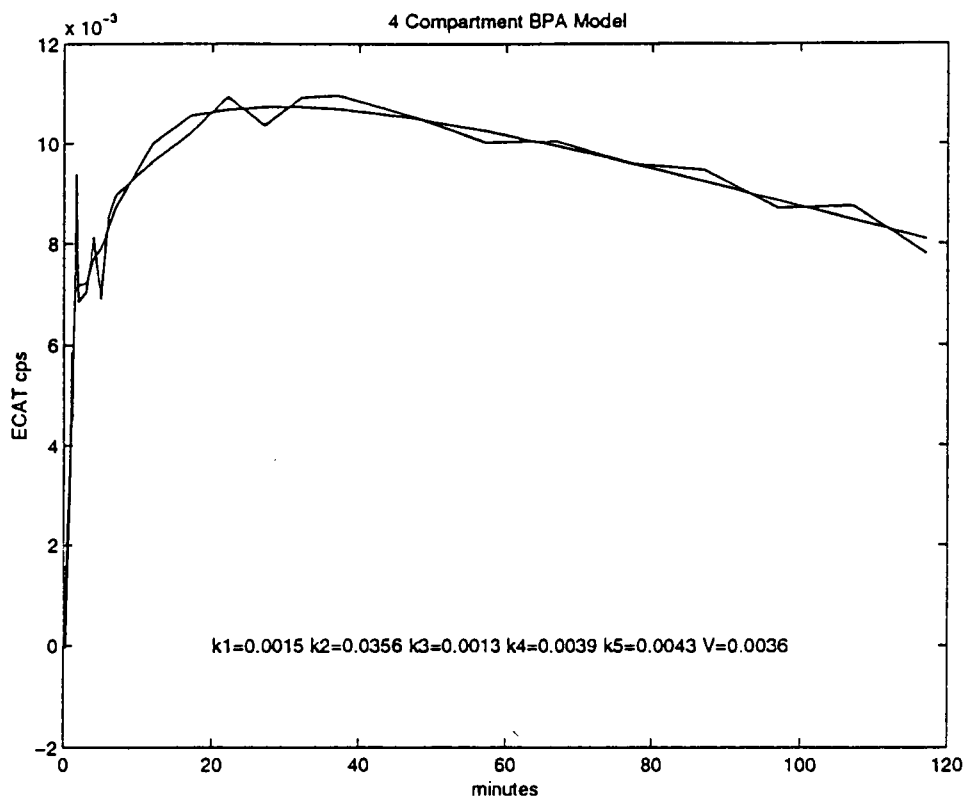


Figure 95. 4C 6 Parameter Linear Optimization Fit

as noise. The resulting values for the slopes are then scaled to standard 8 bit intensity values and written back out into a separate image. This subroutine fits into the program `pet_parm.c` written by Dr. Hedley Bond as an in-house UTMCK analysis routine given in Appendix Z.

Images may be viewed using standard CTI format viewers such as `imagetool`. Regions of steeper Patlak slopes appear brighter on the image. This has been done previously and proves to be useful in eliminating areas of constant uptake. Such regions as bladder reach a constant level and may be filtered out by using

a threshold for the correlation coefficient on the Patlak slopes. Pixels are then commonly retained that have r^2 values of 0.8 or above. Resulting images are cleaner and show increasing regions of uptake on the Patlak slope which is directly related to tumor activity.

Regions that may appear dim in a standard emission image will appear brighter in this parametric image set and provide a more quantitative tool for clinical diagnosis.

Figure 96 shows an image created at a 90% correlation factor between the data and the linear regression fit of the Patlak slope for a prostate scan. Notice the fact that the reconstruction backprojection noise is kept at a minimum while the "true" hot spots stand out from the background noise. It is a future goal to incorporate individual PET compartmental curves into parametric images using the following image method as a baseline.

The key factor in creating parametric images from the compartmental model data involves transference of the parameters to the pixel values. Direct analytical solutions have been formulated and presented in length earlier. Compartmental fits to regions of interest on the PET scans are shown in a summary table published in JNM on our first two BPA patients given in Appendix AA. Fits were accomplished for tumor, healthy brain, marrow and blood pools.

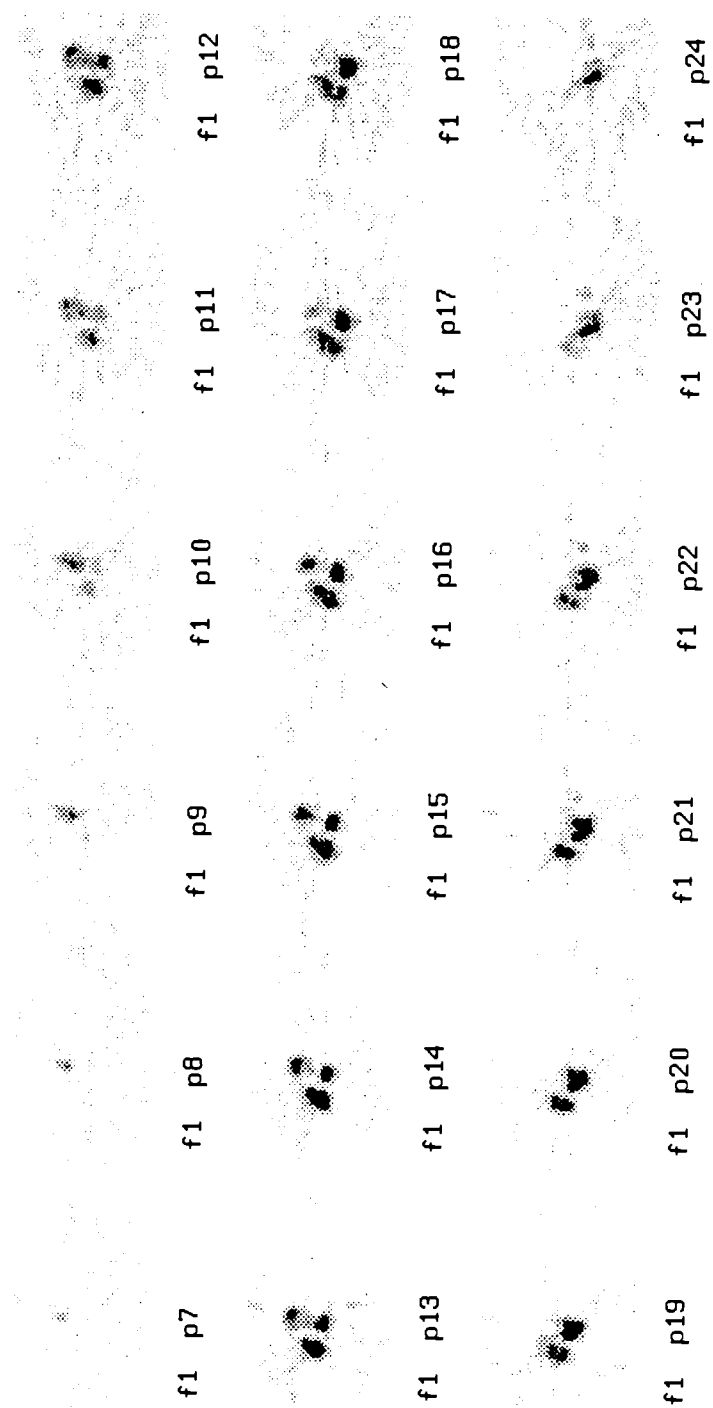


Figure 96. Patlak Parametric Image of a Prostate Cancer Case

We are missing two key pieces of the puzzle needed to create accurate parametric images that would provide intra and extracellular metabolic uptake information of the BNCT agent. The first key is to relate the parameters obtained through an average region of interest to the activity on a per pixel basis. The relationship between a single measured pixel of PET activity and 5 independent model parameters is not trivial. The single pixel value is only for one frame of the image series. In reality, each pixel has a time activity curve, TAC, as was fitted by each of the various models above. Theoretically, one would just have to run the analysis for 128×128 or 16384 different curves for each patient. Estimating a 5 second computation time for each pixel in a 128×128 image, a full 47 plane set would still take over 45 days to run.

There have been two proposed solutions to this difficulty. The first is to take approximately five points at specific times on the TAC for each pixel. One would then compare these points with those in a look-up table generated from a range of parameter variations and find the closest match to that specific pixel TAC. This would provide an accurate choice of parameters based upon a number of points along the TAC. One disadvantage that can be foreseen in this method concerns image noise. A slight variation in the curve could produce a similar variation in the model parameters, any deviation produced by random image noise would force the prediction of false parameters. This could be avoided by a spline fitting of the curve as done in MATLAB to minimize noise and interpolate time intervals.

Figure 97, created by MATLAB from Appendix AB, simultaneously displays a series of curves generated by incremental changes in a single model parameter. It is among a series of curves, as those displayed in the plot shown below, that the look-up table would function from.

A clue to the puzzle is then found when the percent error in each parameter is presented against the percent error in observed activity. Figure 98 is chosen for a specific time point and the results tabulated. At first glance it appears that the relation of:

$$\delta Y / \delta k_i = c \Delta k_i$$

holds true for all time points where Y is the measured PET activity, and k represents the model parameters. This assumption cannot be made and is extremely misleading given the general analytical solutions provided earlier.

If the change in activity is plotted against time for a fixed change in each model parameter, Figure 99 is derived. This holds true with the analytical solutions immediately as can be seen with dY/dk_i . k_i is just a direct multiplier in the exact solutions and therefore the change with time mirrors the actual tissue uptake curve which can be seen below.

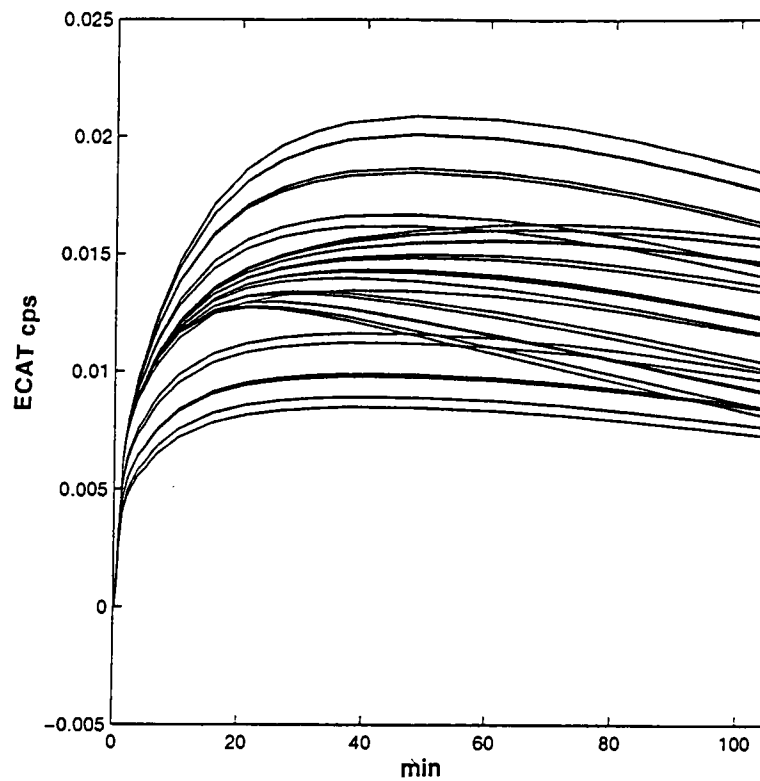


Figure 97. MATLAB Parameter Variance Analysis Plot

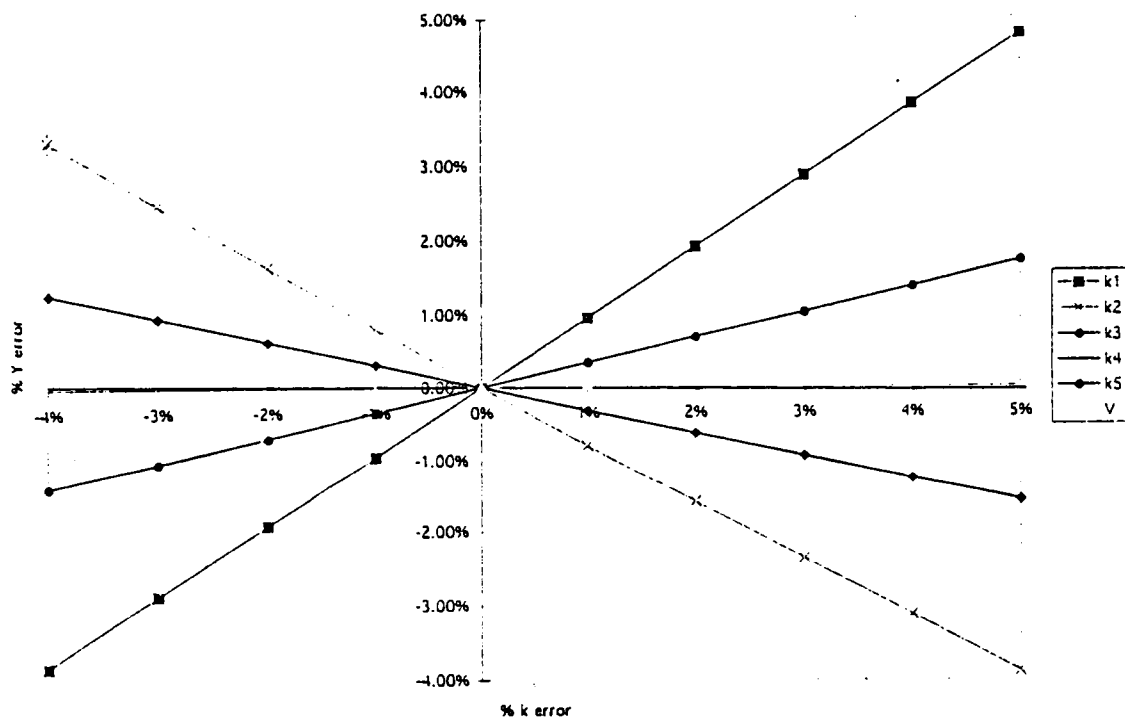


Figure 98. Bolus Injection dY/dk Analysis

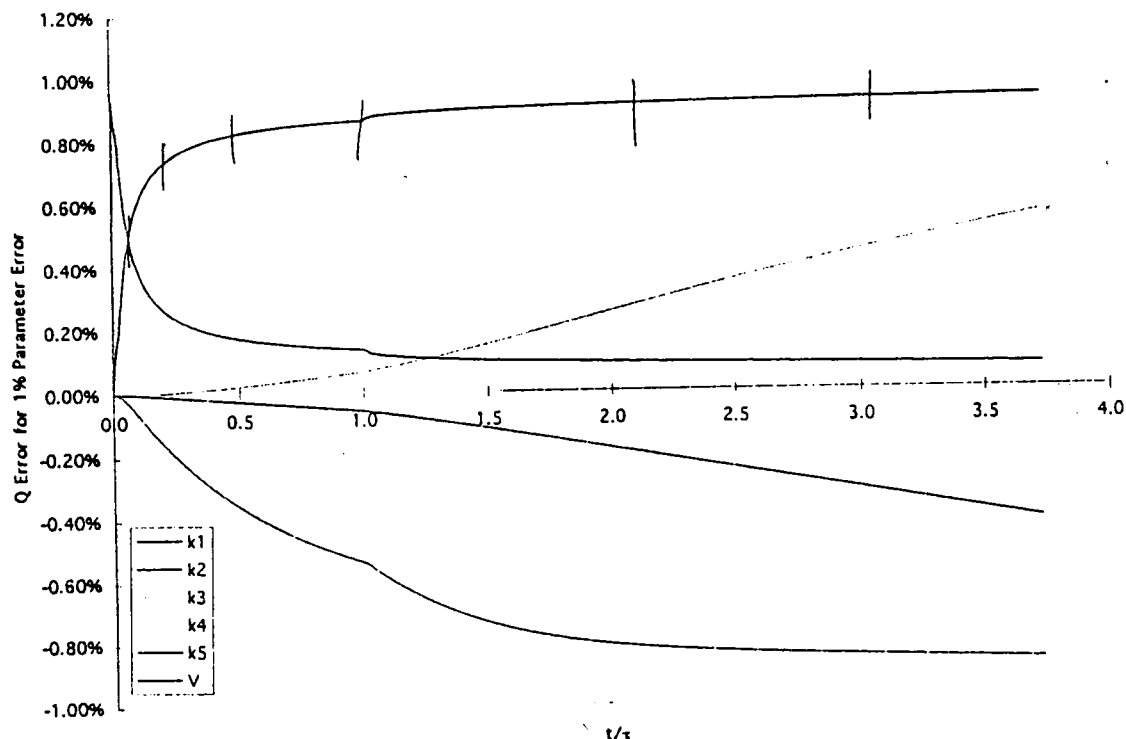


Figure 99. Fixed Parameter Error Activity Variance Analysis

Although the change in model parameters with activity is not linear for all time points, there must be some way to estimate the underlying shift. A direct mathematical analysis of the solutions has been attempted with MAPLE as shown in Appendix AA. The form of the output is absolutely unmanageable and gives no useable information until further simplification is done. Possibly, an examination of Dr. Thie's approximated solution set would provide insight into this area. Huang performed this exact method of error analysis for the FDG model [31]. The question that cannot be answered by this method is whether the observed activity change is produced by a change in more than one model parameter. This is most likely to be the case and would present a difficulty to this direct approach.

The second hurdle to overcome is the translation of a small change in bolus administered activity to that of constant infusion activity. Given the convolution analysis on the time activity curves, we know how a change in bolus activity will affect a change in the convolved time activity curve. What we do not know is mathematically, or numerically, how a change in the model parameters for a bolus fit will affect those parameters in a constant infusion simulation. Again, through a direct iteration of curves, Figure 100 has been created that gives the percent error in the bolus data in comparison with the convolved data for each parameter.

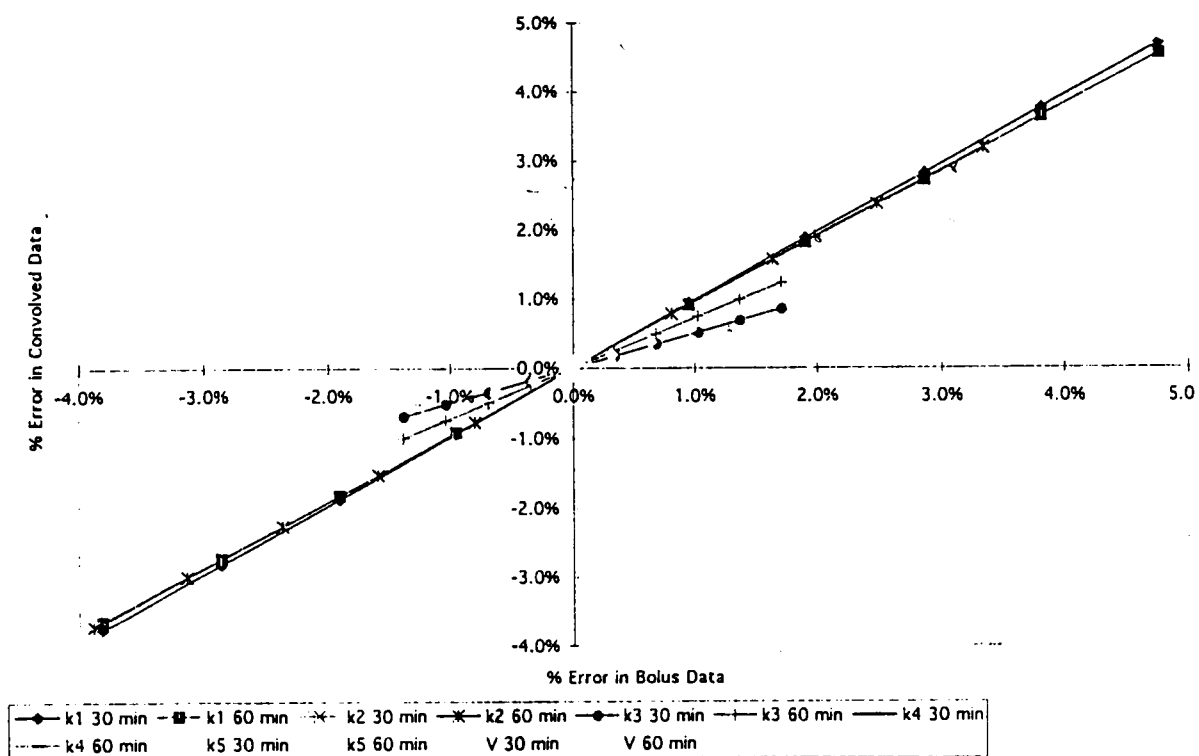


Figure 100. Parametric Error Analysis: Infusion vs. Bolus

This again, is for a single time point on the time activity curve. The linear relationship is evident, but the more striking fact is that k_1 is the major factor in activity deviation. A direct relation between the bolus error and the infusion error is shown in k_1 . The other parameters show a lesser "weighting" towards error in the convolved data. For a 30 minute convolution study, Figure 101 is produced identical to the bolus plot provided earlier that shows the relation between percent activity change and that of the model parameters.

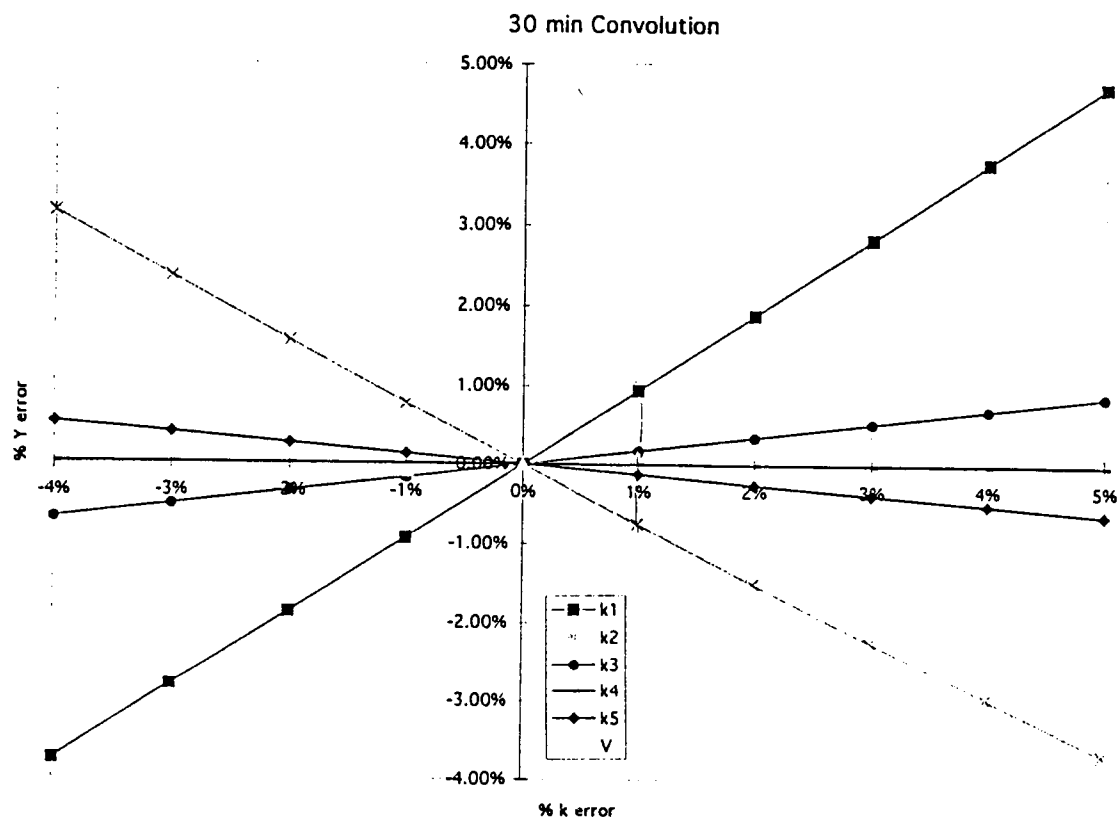


Figure 101. Parametric Error Analysis using a 30 minute Convolution

These are questions that must be answered in order to create a set of parametric images. The single pixel contains an entire time activity curve that must be correctly modelled. One possible solution to the problem would be to estimate the TAC through the direct solution for C_2 . This component contains the intracellular activity information which is assumedly the most crucial in BNCT. Perhaps, this compartment could be analyzed individually to determine dY/dk . It would be difficult to correlate the measured activity with a single compartment unless k_4 was approximately zero.

A simpler solution would be to determine the change in k_1 and k_2 , the primary parameters, and then to provide a limit for the range of the other model parameters. The majority of the change in activity will result from k_1, k_2 as shown in the previous graphs. If these parameters could be determined accurately then the other parameters could be evaluated for a single time point near the end of the scan where the effect would be greatest. The change in activity with respect to k_1 is already known analytically. For early time points this would be an accurate estimator of the total activity change. Points at the end of the scan would then be analyzed to determine an estimation of the outflux of the agent from the different compartments.

The solution to this problem is within reach and once found will provide accurate information about the individual compartments on a per patient basis. These

parametric images will then theoretically show whether the cells at the tumor site are binding the agent to a greater degree within the cell itself or in the extracellular space. One problem with this approach is that the mathematical solution fixes the equation for each of these compartments over time. Figure 102 shows a 4 compartment, 5 parameter fit to the BPA data emphasizing each individual component. This graph is basically representative of all patients. Notice that the extracellular compartment mimics the actual measured PET data while the intracellular compartment gradually increases. This plot states that the compartmental model may or may not be an accurate predictor of actual cellular distribution in-vivo. If it is a true predictor, this states that a far greater percentage of the BNCT agent aggregates in the extracellular space than inside the nuclear compartment itself. This would drastically affect treatment planning and kill ratio predictions.

Cell Kill Ratio Study

One unbiased way to determine the cell kill ratios from the PET scans directly without model biasing is described below. Our second BPA patient received a PET scan post-debulking surgery but prior to BNCT. A third PET scan was also taken post-BNCT to determine the effect the of treatment. These two data sets can be quantitatively compared to yield some estimate of effective kill ratio at the tumor site in-vivo. On the second BPA patient there was a central tumor region that was metabolically active prior to BNCT. This identical region after BNCT did

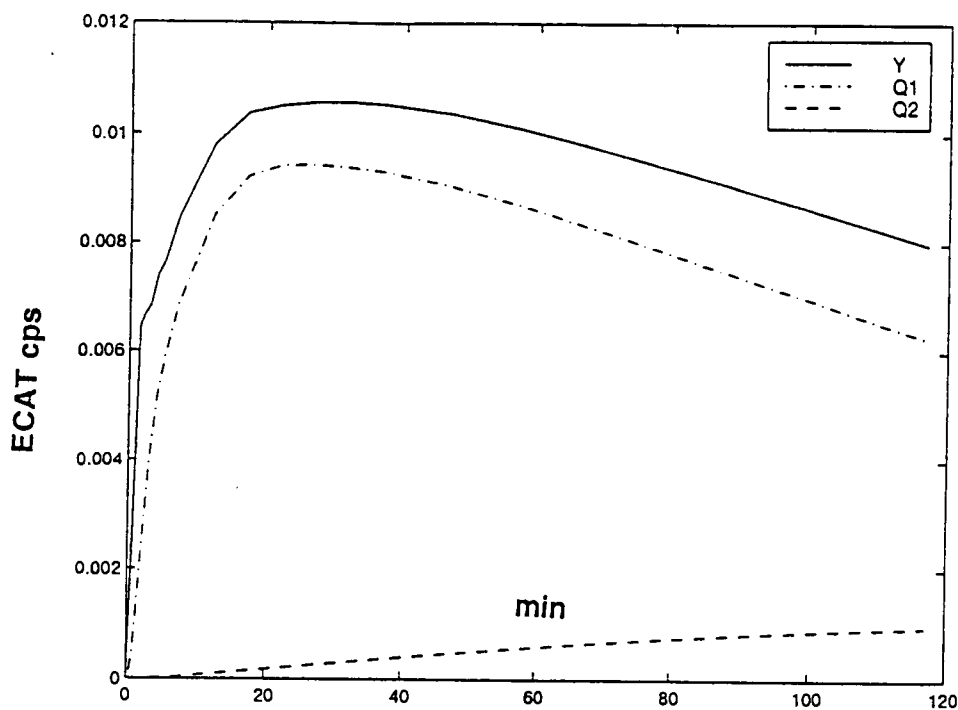


Figure 102. 4C Direct Compartmental Solution Plot

not take up the drug to any large extent. The autopsy showed that tumor regrowth outside of this area had occurred to cause the death of the patient.

Quantitatively, did the BNCT actually kill this region of the tumor successfully? Drawing regions of interest around this specific area pre and post BNCT and normalizing the results to the area of the ROI provided some interesting data. At first, a small circular region of interest was drawn completely within the tumor region to insure a lesser degree of contamination by other regions. This was also compared with contours drawn using isointensity methods. The analysis package provides the option to draw a ROI on a continuous line of intensity within the image. The threshold was chosen to isolate just the tumor region.

Various tumor planes were chosen in the image and the ROI total was weighted by the area of the ROI in the case of the isocontensity contours. The small circular ROI was a fixed size for both PET scans. The results as shown in Figure 103, indicate a definite killing of the tumor centralized in plane 20 of the image in both ROI methods. There is a baseline of approximately 30% throughout the entire image set in the ratio. This is due to the fact that healthy tissue does take up F-BPA-Fr though to a lesser degree. This could also be due to image blurring produced by the reconstruction method. Ideally, if the background noise was the same in both exams, then the ratio would be zero for a perfect kill ratio.

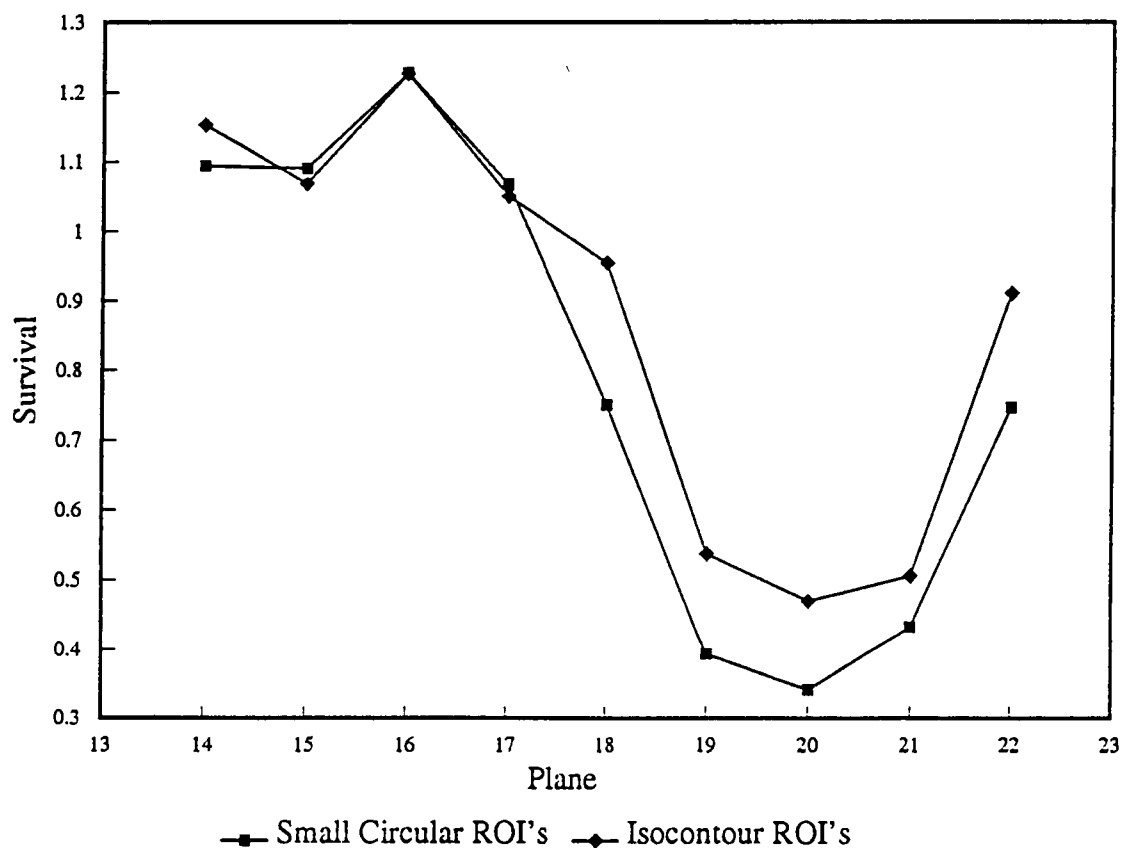


Figure 103. PET Normalized ROI Kill Ratio Analysis

This method could provide information on a macroscopic level as to the effectiveness of the treatment. It could also provide insight to the clinician as to whether further irradiation is needed on a fractionated basis. Areas of concern in this method would relate to the background noise levels in each image. A base ROI in healthy brain tissue could also be taken and subtracted out from the tumor ROI to provide a "noiseless" measurement. Practically, a large ROI should be used in order to minimize local variations caused by the backprojection of the image. Another point of concern would be to examine whether necrotic or edemic tissue actually absorbs or takes up the BNCT drug. Post-irradiation patients develop one of these conditions as a common side effect. This has not been explored as well.

Optimal Time of Irradiation Study

One last area that is similar in nature to this study concerns the optimal time of irradiation on a per patient level. Compartmental model analysis will allow clinicians to predict the optimal treatment time by examining the ratio between either Y/C_p or C_2/C_p . Our second patient was scanned after debulking surgery prior to BNCT. These fitted curves were then convolved with a step function and the ratio of the measured PET activity to that of the blood pool was plotted. Ideally, there should be some peak or plateau visible that would indicate a maximum ratio between the tumor and the blood had been reached. This ratio should also be checked for tumor vs. healthy brain tissue as well.

Figure 104 gives the results for this specific patient post-surgery. BNL irradiates the patients at approximately 90 minutes after the end of infusion which correlates with this as well [17].

Conclusions

In conclusion, compartmental modelling provides information that is very useful in a theoretical and clinically practical sense as well. In the future, this analysis method could provide many answers to questions currently being raised about dose effectiveness, patient candidacy and biodistribution issues. In short, PET could provide a the key to successful BNCT planning and analysis for future clinical trials. The non-invasive, low dose, non-toxic method by which uptake information is gained is rivaled by no other modality. UTMCK provides an opportunity for research that will be of intense value at present and in future studies.

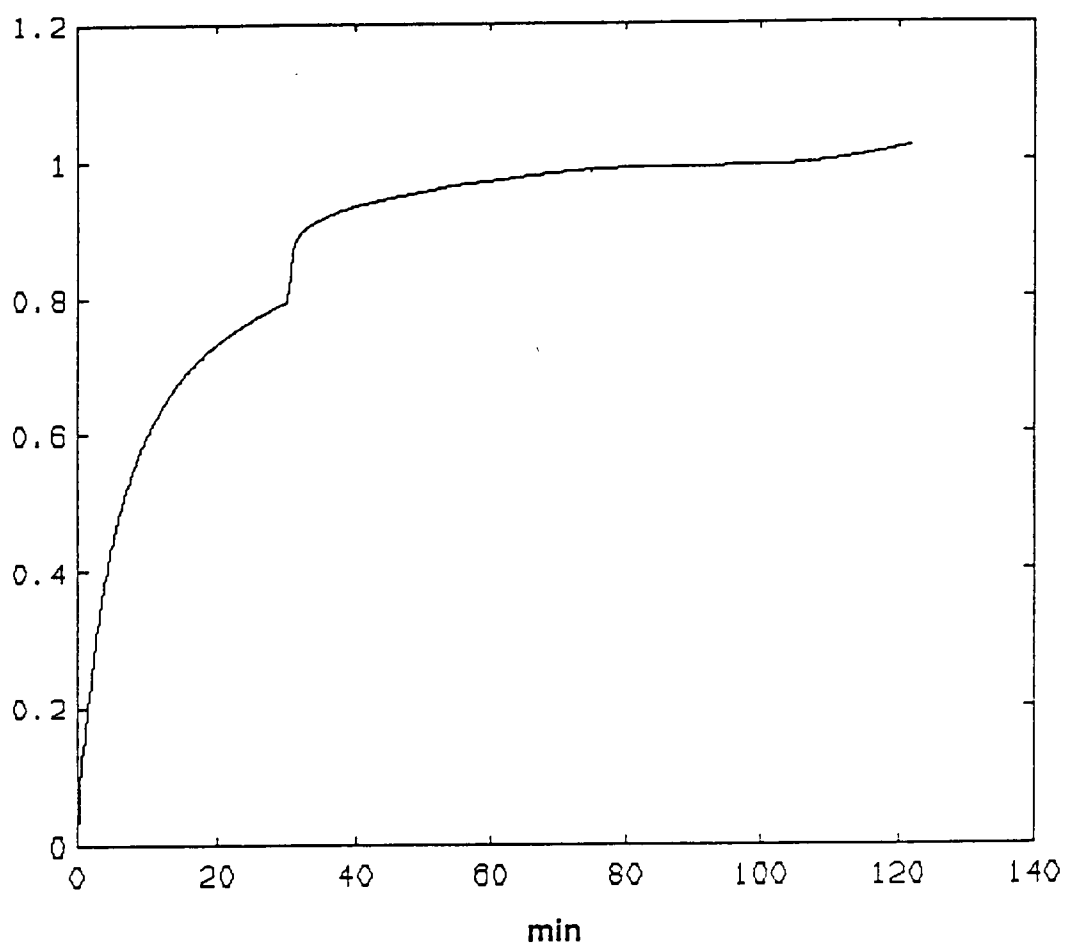


Figure 104. Activity/Blood Pool Ratio Showing Optimal Irradiation Time

References

References

1. Bartels, M., Albert, K. Detection of Psychoactive Drugs Using ^{19}F MR Spectroscopy. *J Neural Transmission* 1995; 99:1-6.
2. Belli, M., Cherubini, R., Finotto, S., et.al., RBE-LET Relationship for the Survival of V79 Cells Irradiated with Low-Energy Protons, *Int. J. Radiation Biology* 1989; 55, 1:93-104.
3. Delli, M., Cera, F., Cherubini, R., et.al., Inactivation and Mutation Induction in V79 Cells by Low Energy Protons: Re-Evaluation of the Results at the LNL Facility., *Int. J. Radiation Biology* 1993; 63, 3:331-337.
4. Biolo, G., Chinkes, D., et.al. A New Model to Determine in vivo the Relationship Between Amino Acid Transmembrane Transport and Protein Kinetics in Muscle. *J. of Parenteral and Enteral Nutrition* 1992; 16:305-315.
5. Bolo, N.R., Hode, Y., Macher, J.P. Comparision of Plasma and in-vivo Brain Levels of Fluvoxamine Measured by Flourine NMR Spectroscopy During Drug Washout. *Proceedings of the Fourth Scientific Meeting of the International Society of Magnetic Resonance in Medicine* 1996; 3:1179.
6. Brix, Gunner. Mapping the Biodistribution and Catabolism of 5-Fluorouracil in Tumor Bearing Rats by Chemical Shift Selective ^{19}F MR Imaging. *Magnetic Resonance in Medicine* 1995; 34:302-307.
7. Brix, G., Bellemann, M.E., et.al. Monitoring of 5-Flourouracil in Tumor Bearing Rats by Metabolic ^{19}F MRI and Dynamic ^{18}F PET. *Proceedings of the Fourth Scientific Meeting of the International Society of Magnetic Resonance in Medicine* 1996; 3:1116.
8. Burger, P.C., Kleihues, P., Cytologic Composition of the Untreated Glioblastoma With Implications for Evaluation of Needle Biopsies. *Cancer* 1989; 63:2014-2023.
9. Carson, R.E., Precision and Accuracy Considerations of Physiological Quantitation in PET. *J Cerebral Blood Flow and Metabolism* 1991; 11:A45-A50.
10. Carson, R.E. Positron Emission tomography and Autoradiography: Principles and Applications for the Brain and Heart. Phelps, M., Mazziota, J., Schelbert, H., ed. New York: Raven Press, 1996; 347-390.

11. Ceberg,C.P., Brun,A., et.al. A Comparative Study on the Pharmokinetics and Biodistribution of BOPP and BSH in the RG2 Rat Glioma Model. *J Neurosurgery* 1995; 83:86-92.
12. Chandra, S., Lorey, D.R., Lessig, S., et.al. Quantitative Imaging of Boron from BPA and BSH in Glioblastoma Cells with Ion Microscopy, Submitted to the 7th Int. Conf. on Neutron Capture Therapy of Cancers.
13. Charlton, D.E., Energy Deposition in Small Ellipsoidal Volumes by High-LET Particles: Application to Thermal Neutron Dosimetry, *Int. J. Radiation Biology* 1991; 59,3:827-842.
14. Charlton, D.E., Kassis, A.I., Adelstein, S.J., A Comparison of Experimental and Calculated Survival Curves for V79 Cells Grown as Monolayers or in Suspension Exposed to Alpha Irradiation from ^{212}Bi Distributed in the Growth Medium., *Radiation Protection Dosimetry* 1994; 52,1-4:311-315.
15. Charlton, D.E., Turner, M.S., Use of Chord Lengths Through the Nucleus to Simulate the Survival of Mammalian Cells Exposed to High-LET alpha-Radiation., *Int. Journal of Radiation Biology* 1996; 69, 2:213-217.
16. Choi,Y.,et.al. Parametric Images of Myocardial Metabolic Rate of Glucose Generated from Dynamic Cardiac PET and FDG Studies. *J Nuclear Medicine* 1990; 32:733-738.
17. Coderre,J., et.al. Boron Neutron Capture Therapy for Glioblastoma Multiforme using p-boronophenylalanine and Epithermal Neutrons: Trial Design and Early Clinical Results. *J Neuro Oncology* 1997; 33:141-152.
18. Dardzinski, B. Rapid Tissue Oxygen Tension Mapping Using ^{19}F Inversion Recovery Echo Planar Imaging of Perfluoro-15-Crown-5-Ether. *Magn Reson Med* 1994; 32:88-97.
19. De Chiro,G.,et.al. Issues in the In Vivo Measurement of Glucose Metabolism of Human Central Nervous System Tumors. *Ann Neuro* 1984; 15:S138-S146.
20. Dorn, R.V. Boron Neutron Capture Therapy (BNCT):A Radiation Oncology Perspective. *Int. J Rad Oncol Biol Phys* 1994; 28:1189-1902.
21. Fairchild, R.G., Kahl, S.B., Laster, B.H., Kalef-Ezra, J., Popennoe, E.A., In-Vitro Determination of Uptake, Retention, Distribution, Biological Efficacy, and Toxicity of Boronated Compounds for Neutron Capture Therapy: A Comparison of Porphyrins with Sulfhydryl Boron Hydrides., *Cancer Research* 1990; 50:4860-4865.

22. Farr,L.E., Sweet,W.H., et.al. Neutron Capture Therapy with Boron in the Treatment of Glioblastoma Multiforme. *Roentgenology* 1954; 71:1279-1293.
23. de Forni,M., Malet-Martino MC., Jaillais,P., et.al. Cardiotoxicity of High Dose Continuous Infusion Fluorouracil: A Prospective Clinical Study. *J Clin Oncol* 1992; 10:1795-801.
24. Fukushima,E.,Roeder,S.B.W. Experimental Pulse NMR, Reading,MA.: Addison-Wesley Publishing, 1981; 395-407.
25. Gambhir,S.,et.al. Simple Noninvasive Quantification Method for Measuring Myocardial Glucose Utilization in Humans Employing Positron Emission Tomography and FDG., *J Nucl Med* 1989; 30:359-366.
26. Gedde,A., et.al., Comparative Regional Analysis of 2-Fluorodeoxyglucose and Methylglucose Uptake in Brain of Four Stroke Patients. With Special Reference to the Regional Estimation of the Lumped Constant., *J.Cerebral Blood Flow and Metabolism* 1985; 5:163-178.
27. Glaholm, B.J., Leach, M.O., et.al. Comparision of 5-Fluorouracil Pharmacokinetics Following Intraperitoneal and Intravenous Administration Using in vivo ¹⁹F Magnetic Resonance Spectroscopy. *Brit. J. of Rad.* 1990; 63:547-553.
28. Graham,M. Physiologic Smoothing of Blood Time-Activity Curves for PET Data Analysis., *JNM* 1997; 38,7:1161-1168.
29. Gupta,N., Gahbauer,R.A., Blue, T.E., Wambersie,A., Dose Prescription in Boron Neutron Capture Therapy, *Int.J. Rad. Oncol. Biol. Phys* 1994; 28,5:1157-1166.
30. Haritz D., Gabel D., Huiskamp R. Clinical Phase-I Study of BSH in Patients with Malignant Glioma as Precondition for BNCT. *Int. J. Radiation Oncology Biol. Phys* 1994; 28:1175-1181.
31. Huang,S.C., Phelps,M.E., Hoffman, E.J., et.al., Noninvasive Determination of Local Cerebral Metabolic Rate of Glucose in Man., E69-E82. 1980.
32. Imahori,Y., et.al., Positron Emission Tomography Based Boron Neutron Capture Therapy Using Boronophenylalanine for High Grade Gliomas, Submitted to *Cancer Research* 1997.

33. Imahori, Y., et al., A Basic Concept for PET-BNCT System, (pre-print), 1995.
34. Imahori, Y., et al. Fluorine-18-labeled Fluoroboronophenylalanine and Positron Emission Tomographic Studies in Patients with Gliomas for Boron Neutron Capture Therapy, (pre-print).
35. Ishiwata, K., et al. A Unique in-vivo Assessment of 4-[10B]borono-L-phenylalanine in Tumor Tissues for Boron Neutron Capture Therapy of Malignant Melanomas Using Positron Emission tomography and 4-borono-2-[18F]fluoro-L-phenylalanine, *Melanoma Research* 1992; 2:171-179.
36. Itoh, YH., Kandori, Y., et al. 19F-MR Imaging of Transplanted Tumor: Perfluorochemicals as a Fluorine Tumor Imaging Agent. *Nippon Acta Rad* 1995; 55:345-7.
37. Jao, J-C., Chen, P-C, Lao, X., Nalcioğlu, O. Oxygenation Changes in Rat Tumors by H-1 T1 Weighted Images at 1.5T in Conjunction with PFB. *SMR* 1996, 1362.
38. Jeffrey, K.R., Armstrong, R.L., Simple Bridge for Pulsed Nuclear Magnetic Resonance, *Rev Sci Instr* 1967; 38,5:634-6.
39. Joseph, Peter M. Design and Evaluation of a Radio Frequency Coil for Nuclear Magnetic Resonance Imaging of Fluorine and Protons. *Med Phys* 1985; 12:679-683.
40. Kabalka, G.W., Davis, M., Bendel, P. Boron-11 MRI and MRS of Intact Animals Infused with a Boron Neutron Capture Agent. *MRM* 1988; 8:231-237.
41. Kabalka, G.W., Davis, M., Bendel, P., et al., In-vivo Boron-11 MRI and MRS using (B24H22S2)4 in the Rat., *J Mag Reson Imag* 1991; 9:969-973.
42. Kabalka, G.W., Smith, G.T., Dyke, J.P., et al., Evaluation of Fluorine-18-BPA-Fr for Boron Neutron Capture Treatment Planning, *JNM* 1997; 38,11:1762-1767.
43. Kabalka, G.W., Tang, C., Bendel, P., The Role of Boron MRI in Boron Neutron Capture Therapy, *J Neuro Oncol* 1996.
44. Kanazawa, Y. Metabolic Pathway of 2FDG Studied by F-19 NMR. *Life Sciences* 1986; 39:737-742.
45. Kassis, A.I. Transient Toxicity of 2FDG in Mammalian Cells: Concise Communication. *J Nucl Med* 1983; 24:1055-1059.

46. Kobayashi, T., Kanda, K., Analytical Calculation of Boron-10 Dosage in Cell Nucleus for Neutron Capture Therapy. *Radiation Research* 1982; 91: 77-94.
47. Kuwabara, H., Gjedde, A., Measurements of Glucose Phosphorylation with FDG and PET are Not Reduced by Dephosphorylation of FDG-6-Phosphate. *JNM* 1991; 32,4:692-698.
48. Levenberg, K. A Method for the Solution of Certain Problems in Least Squares. *Quart Appl Math* 1944; 2:164-168.
49. Longmaid, H.E. In Vivo ¹⁹F NMR Imaging of Liver, Tumor and Abscess in Rats. *Invest Radiol* 1985; 20:141-145.
50. Maki, H., Lethal Effect and Potentially Lethal Damage Recovery in Cultured Mammalian Cells Irradiated by Neutron-Capture Beams, *Int J Radiation Biology* 1989; 55, 3:397-409.
51. Marquardt, D., An Algorithm for Least-Squares Estimation of Non-linear Parameters, *SIAM J. Appl. Math* 1963; 11:431-441.
52. Mason, Ralph P. Non-Invasive Determination of Tumor Oxygen Tension and Local Variation with Growth, *Int. J. Rad. Oncol. Biol. Phys* 1994; 29:95-103.
53. Mattrey, R.F. The Potential Role of Perfluorochemicals (PFC's) in Diagnostic Imaging. *Artif. Cells, Blood Substit., & Immob. Biotech.* 1994; 22:295-313.
54. McKeever, P.E., Hood, T.W., Varani, J., et.al., Products of Cells Cultured from Gliomas. Cytology and Morphometry of Two Cell Types Cultured from Glioma, *JNCI* 1987; 78, 1:75-84.
55. Meyer, Kristen L. Fluorinated Blood Substitute Retention in the Rat Measure by Fluorine-19 Magnetic Resonance Imaging. *Invest. Radiol.* 1992; 27:620-627.
56. More, J.J., The Levenberg-Marquardt Algorithm: Implementation and Theory., Numerical Analysis, ed. Watson, G.A., Lecture Notes in Mathematics 630, New York: Springer Verlag, 1977; 105-116.
57. Nakada, T. Fluorine-19 NMR Imaging of Glucose Metabolism. *MRM* 1988; 6:307-313.

58. Nakada, T. Noninvasive Analysis of Aldose Reductase Activities in Rat Testis: 3-FDG NMR Spectroscopy and Imaging. *MRM* 1993;29:543-545.
59. Nakada, T. Heterogeneity of Regional Cerebral Glucose Metabolism Demonstrated in Situ in Rat Brain by ^{19}F NMR Rotating Frame Zeugmatography: 1D CS Imaging of Normal and Gliosarcoma Implanted Brain. *MRI* 1987;5:259-266.
60. Nakada, T. Noninvasive Evaluation of Effects of an Aldose Reductase Inhibitor in Rat Brain by ^{19}F FDG NMR Spectroscopy. *MRM* 1987;4:366-371.
61. Nakada, T. F-19 Imaging of Glucose Metabolism in the Rabbit. *Radiology* 1988;168:823-825.
62. Nigg, D.W., Methods for Radiation Dose Distribution Analysis and Treatment Planning in Boron Neutron Capture Therapy. *Int.J. Rad. Oncol. Biol. Phys.* 1994;28,5:1121-1134.
63. Ono, K., Masunaga, S.I., Kinashi, Y., et.al., Radiobiological Evidence Suggesting Heterogeneous Microdistribution of Boron Compounds in Tumors: It's Relation to Quiescent Cell Population and Tumor Cure in Neutron Capture Therapy., *Int. J. Radiation Oncology, Biol. Phys.* 1996;34,5:1081-1086.
64. Patlak,C.S., Blasberg,R.G., Fenstermacher,J.D., A Graphical Evaluation of Blood-to-Brain Transfer Constants from Multiple-Time Uptake Data., *J. Cereb.Blood Flow Metab.* 1983;3,1:1-7.
65. Phelps,M.E.,Huang,S.C.,et.al., Tomographic Measurement of Local Cerebral Glucose Metabolic Rate in Humans with FDG: Validation of Method., *Ann.Neurol.* 1979;6:371-388.
66. Pomer, S., Hull, WE., et.al. Magnetic Resonance, A Means for Anatomically Reliable Imaging and Noninvasive Metabolic Studies of Kidney Transplants. *Helvetica Chir. Acta* 1992;59:465-6.
67. Raaijmakers, C.P.J., Konijnenberg, M.W., Dewit, L., et.al., Monitoring of Blood- ^{10}B Concentration for Boron Neutron Capture Therapy Using Prompt Gamma-Ray Analysis, *Acta Oncologica* 1985;34,4:517-523.
68. Ratner, Adam V. Detection of Tumors with ^{19}F Magnetic Resonance Imaging,. *Invest. Radiol.* 1988;23:361-4.

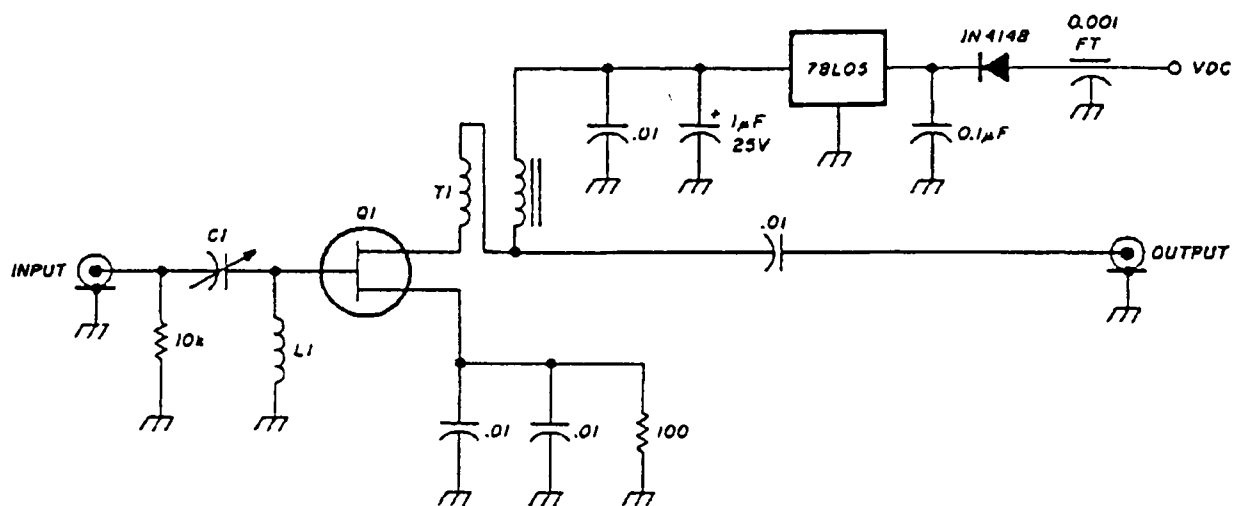
69. Ross, B.D., Radda, G.K., Gadian, D.G., et.al., Examination of a Case of Suspected McArdle's Syndrome by ^{31}P Nuclear Magnetic Resonance, *N.Engl.J.Med.* 304:1338, 1981.
70. Samaratunga, R.C. Implementation of a Modified Birdcage Resonator for $^{19}\text{F}/^1\text{H}$ MRI at Low Fields (0.14T). *Med. Phys.* 1994;21:697-705.
71. Scarpelli, M., Montironi, R., et.al., Quantitative Evaluation of Nucleolar Features on Cytologic Material in Brain Tumor Diagnosis, *Clinical Neuropathology*, 13, 6, 323-328, 1994.
72. Schlemmer, H.P., Bachert P., et.al. Drug Monitoring of 5-fluorouracil: in vivo ^{19}F NMR study during 5-FU chemotherapy in patients with metastasis of colorectal adenocarcinoma. *MRI* 1994;12:497-511.
73. Schmidt, K., Mies, G., Sokoloff, L., Model of Kinetic Behavior of Deoxyglucose in Heterogeneous Tissue in Brain: A Reinterpretation of the Significance of Parameters Fitted to Homogeneous Tissue Models., *J.Cerebral Blood Flow and Metabolism*, 11, 10-24, 1991.
74. Sgouros, G., Barett, G., et.al., Treatment Planning for Internal Radionuclide Therapy: Three-Dimensional Dosimetry for Nonuniformly Distributed Radionuclides. *JNM* 31, 11, 1884-1891, 1990.
75. Shimizu, M. Tumor Imaging with Anti-CEA Antibody Labeled ^{19}F Emulsion. *MRM* 1987;5:290-295.
76. Shinohara, S. Evaluation of Energy Metabolism in Brain Using Epimerization of 2-FDG by ^{19}F NMR: The Effect of Anesthesia. *MRM* 1991;21:191-196.
77. Slosman, D.O., Pittet N., et.al. Fluorodeoxyglucose Cell Incorporation as an Index of Cell Proliferation: Evaluation of Accuracy in Cell Culture. *Euro. J. of Nuc. Med.* 1993;20:1084-8. (Abstract)
78. Smith, D.R., Chandra, S., Coderre, J.A., Morrison, G.H., Ion Microscopy Imaging of ^{10}B from p-Boronophenylalanine in a Brain Tumor Model for Boron Neutron Capture Therapy. *Cancer Research*, 56, 4302-4306, 1996.
79. Smith, G.T., Stubbs, J.B., Hubner, K.F., Goodman, M.M., Dynamic PET Scanning and Compartmental Model Analysis to Determine Cellular Level Radiotracer Distribution In-Vivo, CONF-910529, Fifth International Radiopharmaceutical Dosimetry Symposium, Oak Ridge, TN., 371-383, May 10, 1992.

80. Song, SK., Hotchkiss, RS., et.al. Determination of Intracellular Calcium in vivo via Flourine-19 Nuclear Magnetic Resonance Spectroscopy. *Amer. J. of Physiology*. 1995;269:C318-22.
81. Strauss, W.L., Dager, S.R., Layton, M.E., Hayes, C.E. 19F MRS Determination of Acute and Steady State Brain Fluvoxamine Levels in Obsessive Compulsive Disorder. *SMR* 1996;1:415.
82. Stubbs, J.B., Smith, G.T., Stabin, M.G., et.al., An Approach to Cellular Level Dosimetry Using Compartmental Model Analysis and Dynamic PET, CONF-910529, Fifth International Radiopharmaceutical Dosimetry Symposium, Oak Ridge, TN.,385-395 May 10, 1992.
83. Verrijk, R., Huiskamp, R., Begg., A.C., Wheeler, F.J., Watkins, P.R.D., A Comprehensive PC-Based Computer Model for Microdosimetry of BNCT, *Int. J. Radiation Biology*. 1994;65,2:241-253.
84. Vroegindewij, Corine, Micro and Macroscopic Modelling of Boron Neutron Capture Therapy., Ph.D. Thesis, Delft University of Technology, Petten: Netherlands Energy Research Foundation, 1997.
85. Wesseling, P., et.al., Quantitative Immunohistological Analysis of the Microvasculature in Untreated Human Glioblastoma Multiforme. Computer Assisted Image Analysis of Whole Tumor Sections., *J. Neurosurg*. 1994;64,2:902-9.
86. Wolf, W., Albright, M., et.al. Flourine-19 NMR Spectroscopic Studies of the Metabolism of 5-Fluorouracil in the Liver of Patients Undergoing Chemotherapy. *MRI* 1987;5:165-169.
87. Zamenhof, R.G., Microdosimetry for Boron Neutron Capture Therapy: A Review,*J.Neuro Oncology* 1997;33:81-92.

Appendices

Appendix A

^{19}F Tuned MRI Pre-Amplifier - Advanced Receiver Research



Appendix B
May 24, 1996 - 5 Molar TriFluoro Acetic Acid
1st ¹⁹F MRS at UTMCK

SW=Sweep Width, NEX=Number of Excitations/Averages,
TR=Repetition Time, AMP=Signal Amplitude, TG=Transmit Gain,
SD=Noise Standard Deviation, S/N=Signal to Noise Ratio

SW	NEX	TR	AMP	TG	Angle	SD	S/N	FILE
8	1	1	0.84674			0.007093		27
8	20	1	0.025712			0.001611	2.523071	28
8	20	250	0.01108			0.00077	2.27437	30
8	20	500	0.085076			0.00731		31
16	20	500	0.039429			0.002122	2.9382	24
8	1	500	0.06194			0.007125	6.147201	26
32	20	1	0.54984	0	90	0.015007	5.793119	42
	2	1	0.5005	0		0.046625	5.367292	43
	2		0.49604	20		0.047898	5.178087	44
	2		0.43237	40		0.047679	4.534176	45
	2		0.5348	60		0.04729	5.654472	46
	2		0.42485	80		0.04893	4.341406	47
	2		0.32575	100		0.047857	3.403368	48
	2		0.27463	0	70	0.04646	2.955553	49
	2		0.31347		80	0.050245	3.119415	50
	2		0.28333		90	0.04533	3.125193	51
	2		0.34804		100	0.047678	3.649901	52
	2		0.2269		110	0.048859	2.321988	53
8	100	1	0.11602			0.003627	2.261884	54
4	20		0.40047			0.006048		55

Appendix C

November 13, 1996 - 250mMol TriFluoroAcetic Acid

NEX	AMP	TG	OPFLIP	SD	S/N	FILE
10	4.2309	0		0.113091	8.36545	86
10	3.0156	20		0.133653	5.04521	87
10	16.721	25	90	0.110775	33.7524	90
10	13.782	30		0.107468	28.6759	89
10	1.6168	40		0.137854	2.62253	88
10	18.501		80	0.117692	35.1506	93
10	16.721	25	90	0.110775	33.7524	90
10	17.974	25	100	0.110445	36.3901	91
10	17.33		110	0.135973	28.4990	92

November 13,1996 - 100mMol TriFluoroAcetic cid

NEX	AAMP	TG	OPFLI	SD	S/N	FILE
10	2.5621	15		0.115648	4.95385	97
10	2.4296	20		0.126147	4.30668	95
10	2.9232	25	90	0.121144	5.39562	94
10	2.0248	30		0.12253	3.69508	96
0	2.4827	15		0.077428	7.16982	98
1	6.0527	20		0.116304	36.7993	99
10	5.375			0.065177	18.4402	100

November 13, 1996 - 50mMol TriFluoroAcetic Acid

NEX	AMP	TG	OPFLI	SD	S/N	FILE
1	3.1138	20	90	0.131517	16.7414	101
10	2.8985	20		0.056168	11.5389	102

November 13, 1996 - 10mMol TriFluoroAcetic Acid -65ml

NEX	AMP	TG	OPFLI	SD	S/N	FILE
10	0.72327	20	90	0.052856	3.05981	104
156	0.66977			0.012427	3.051305	105
10	0.66831	15		0.066123	2.26	106
10	0.81844	18		0.067142	2.725677	107
156	0.59356	18		0.01192	2.819104	108
10	0.93323			0.059562	3.503507	111

Appendix D
November 14, 1996 - 36ppm FBPA

NEX	AMP	TG	OPFLI	SD	S/N	FILE
10	2.3695	20	90	0.065157	8.13166	114
10	3.5232	25		0.066412	11.8625	115
200	0.66875	0		0.013795	0.22435	166

November 18, 1996/February 10, 1997 - FBPA Injected RAT - BNL

SW	NEX	AMP	R1/R2/T	SD	S/N	FILE
32	150	0.38814	6/12/28	0.020676		121
16	150	0.19417	6/12/28	0.011267	0.99493	122
	290	0.026719	6/12/30	0.001624	0.68330	154
	290	0.021798	6/12/50	0.001791	0.50540	155
	200	0.022917	6/12/50	0.002093	0.54756	156
	298	0.051083	6/14/60	0.007887	0.26531	157
	300	0.034817	6/14/60	0.006336	0.22435	158

Appendix E
2dfast Imaging Studies - January 24, 1997 - 250mM TFA

NEX	AMP	TG	SD	S/N	FILE
10	7.412	6/15/0	0.051335	32.28551	130
10	10.603	6/15/4	0.056444	42.00444	132
10	11.257	6/15/4	0.057745	43.59079	133
10	8.7187	6/15/0	0.049099	39.70657	134

Appendix F
March , 1997 - R2,TR Optimization - 36ppm TFA

FILE	Noise	Signal	NEX	SW	R2	S/N
169	0.01611	0.16937	200			0.525778
170	0.01554	0.16676	200	16		0.536385
171	0.01176	0.2664	200	16		1.132441
172	0.00599	0.11819	5	32	12	6.242185
173	0.00521	0.070069	5	32	12	4.255543
174	0.00782	0.10526	5	32	13	4.255619
175	0.0169	0.26508	5	32	14	4.958954
176	0.03057	0.5501	5	32	15	5.690631
177	0.08727	0.73452	5	32	16	2.661645
178	0.131	1.911	5	32	17	4.613239
179	0.26101	3.0541	5	32	18	3.700208
180	0.45514	7.0473	5	32	19	4.896388
181	1.02651	12.601	5	32	20	3.881878
182	1.77466	49.301	5	32	21	8.784976
183	4.60432	60.632	5	32	22	4.164246
184	8.72467	126.86	5	32	23	4.598071
185	17.4549	239.78	5	32	24	4.344058
186	2.70592	50.38	50	16	22	1.861844
187	1.93439	66.559	50	8	22	3.440826
188	3.97484	45.096	50	32	22	1.134536

Appendix G
Cell/Nuclear Size Determination Subroutine - BCT Microdosimetry Code

```
C*****
C  SUBROUTINE CELL(XN,RADC,RADN)
C  TO CHOOSE CELL SIZE
C  INTEGER XN
C  R=URAND(XN)
C  IF(R.LT.0.4) THEN
C      RADC=6.0
C      RADN=5.45
C      RETURN
C  ENDIF
C  IF(R.GT.0.4.AND.R.LT.0.6) THEN
C      RADC=6.5
C      RADN=5.91
C      RETURN
C  ENDIF
C  IF(R.GT.0.6.AND.R.LT.0.8) THEN
C      RADC=5.5
C      RADN=5.0
C      RETURN
C  ENDIF
C  IF(R.GT.0.8.AND.R.LT.0.9) THEN
C      RADC=7.0
C      RADN=6.36
C      RETURN
C  ENDIF
C  RADC=5.0
C  RADN=4.54
C  RETURN
C  END
```

Appendix H **OUTPUT FROM BNCT2.FOR**

Number of sections 100
 Number of cycles 100
 Fractional filling of volume
 Nuclei Cells External
 0.3537 0.1175 0.5288

Concentrations in components
 Element Nuclei Cytoplasm External
 Nitrogen (g/100g) 2.0 2.0 2.0
 Boron (ppm) 11.2 11.2 11.2

Neutron fluence (n/cm*cm) 3.7E+12
 Number of cells 10000

Average number of interactions
 Element Nuclei Cytoplasm External
 Nitrogen 255.2 84.8 381.5
 Boron 423.3 140.6 632.7

Average proton dose (including carbon in nucleus) 0.581777 Gy
 Average alpha/lithium dose 3.58415 Gy
 Average dose 4.16592 Gy

Contributions to nuclear dose
 Nitrogen - nuclei 0.286 Gy
 Nitrogen - cytoplasm 0.066 Gy
 Nitrogen - external 0.231 Gy
 Total nitrogen 0.583 Gy

Boron - nuclei 2.394 Gy
 Boron - cytoplasm 0.399 Gy
 Boron - external 0.783 Gy
 Total boron 3.577 Gy

Total average dose 4.160 Gy
 Distribution of doses - 10 rad intervals (including zero)

0	0	0	0	0	0	1	1	0	
5	3	4	8	8	18	27	22	33	48
63	79	80	105	124	153	148	193	195	215
235	238	303	316	328	340	370	341	359	306
346	351	326	355	344	301	286	298	271	211
251	201	199	182	182	154	150	124	108	69
75	78	65	67	45	45	42	19	28	37
13	11	21	6	15	13	5	4	3	3
6	1	3	1	4	2	3	1	1	2
0	1	0	1	0	0	0	0	0	0

 Distribution of hits (including zero)

0	0	0	0	0	3	7	10	24	
32	56	98	149	161	256	321	365	403	464
475	486	526	545	549	521	526	447	436	412
381	365	306	271	230	191	193	183	108	101
82	80	61	37	44	17	25	13	12	25

Fraction of average dose from ions
 Protons Alphas Lithium
 0.131 0.546 0.314
 Fraction of cells hit 1.000
 Average number of hits = 25.1975

Appendix I
Nuclear Energy Agency - Sample Thermal Neutron 10B Cross Section
Results

INSTITUTE (1USAIRT)
REFERENCE (C,75WASH,1,232,7503)
(R,INTEL-RT-7011-001,7402)
AUTHOR (S.J.FRIESENHAHN,V.J.ORPHAN,A.D.CARLSON,M.P.FRICK,

W.M.LOPEZ)

TITLE MEASUREMENTS OF THE 6-LI- AND 10-B PARTIAL CROSS
SECTIONS FROM 1 TO 1500 KEV.

FACILITY (LINAC) ELECTRON LINEAR ACCELERATOR

METHOD (TOF) TIME-OF-FLIGHT. 230-M FLIGHT PATH.

STATUS (APRVD) A.CARLSON, 85/8/5.

HISTORY (730129C)

(740302A) DATA SUPERSEDED. REFERENCE CHANGED.

(770201U) BIB CORRECTIONS.

(830118A) CONVERTED TO REACTION FORMALISM

(841205A) BIB CORRECTION.

(850625A) DATA IN SAN 007 NORMALIZED.

ENDBIB

REACTION (5-B-10(N,A)3-LI-7,,SIG)

DETECTOR B-10 IONIZATION CHAMBER.

(PROPC) CH4 PROPORTIONAL COUNTER FOR FLUX

MEASUREMENT.

MONITOR (1-H-1(N,EL)1-H-1,,SIG)

NORMALIZED TO 611.1 B*RT-EV AT 3.5-4.5 KEV.

ERR-ANALYS (ERR-S) STATISTICAL ERROR.

(ERR-1) SYSTEMATIC ERROR.

STATUS DATA TAKEN FROM PRIVATE COMM.,FRIESENHAHN,75/1.

HISTORY (840824A) EN CHANGED TO EN-MIN AND EN-MAX

ENDBIB

NOCOMMON 0 0

DATA 5 152

EN-MIN EN-MAX DATA ERR-S ERR-1

EV EV B B PER-CENT

2.3500E+03 2.4432E+03 1.2311E+01 4.9837E-01 4.2000E+00

2.4432E+03 2.5243E+03 1.1729E+01 4.8146E-01

Appendix J **Energy Dependent Cross Section - ^{10}B Reaction from ORNL**

' nuclide 5010 process 102 (n,gamma)

0.00000E+00 0.00000E+00 0.00000E+00 0.00000E+00 0.00000E+00
0.00000E+00 0.00000E+00 0.00000E+00 0.00000E+00 0.00000E+00
0.00000E+00 0.00000E+00 0.00000E+00 0.00000E+00 0.00000E+00
0.00000E+00 0.00000E+00 0.00000E+00 2.12530E-05 4.79922E-05
7.23669E-05 9.86601E-05 1.18978E-04 1.35308E-04 1.61010E-04 2.06999E-04
2.67384E-04 3.40356E-04 4.11394E-04 4.61689E-04 4.93441E-04 5.15348E-04
5.81298E-04 7.77375E-04 1.13512E-03 1.64973E-03 2.77274E-03 4.49015E-03
6.53721E-03 1.01974E-02 1.80544E-02 2.93602E-02 4.58156E-02 7.07119E-02
1.03101E-01 1.91126E-01 4.54191E-01

47 neutron-group boundaries (given in eV)

17332+3 14191+3 12214+3 1+7 86071+2 74082+2 60653+2 49659+2 36788+2

30119+2 27253+2 2466+3 23653+2 23457+2 22313+2 19205+2 1653+3
13534+2
10026+2 82085+1 74274+1 6081+2 49787+1 36883+1 29721+1 18316+1
11109+1
67379 40868 31828 26058 24176 21875 15034 71017-1 33546-1 15846-1 454

21445-2 1013-1 37266-3 10677-3 50435-4 18554-4 87643-5 41399-5 1-1 1-5

Appendix K
DOSE TO THE NUCLEI OF CELLS FOR THERMAL NEUTRON
IRRADIATION
TNC6 - VERSION 6 APRIL 1992

Nuclear radii 3.80 3.80 3.80
Radii of cytoplasm = 4.5 4.5 4.5
Nuclear volume (um+3) = 229.9
Treating suspended cells
Number of cells to be scored 10000
Neutron fluence = 3.70E+12

Concentration/Number of interactions for nitrogen and boron
(Concentrations in g/100g and ppm) Region 1; External
2.0/1.32E+02 11.2/1.65E+02

Concentration/Number of interactions for nitrogen and boron
(Concentrations in g/100g and ppm) Region 2; Cytoplasm
2.0/8.73E-01 11.2/1.45E+00

Concentration/Number of interactions for nitrogen and boron
(Concentrations in g/100g and ppm) Region 3; Nucleus
2.0/1.32E+00 11.2/2.20E+00

Number of atoms/interactions for surface boron
0.0E+00/ 0.0E+00

Equilibrium dose from boron outside cell 3.585 Gy
Equilibrium dose from nitrogen outside cell 0.543Gy

Dose contributions to the nucleus from nitrogen and boron from the four regions

Nitrogen in region 1 0.38Gy Number of passages = 2.41
Boron in region 1 1.19Gy Number of passages = 4.06

Nitrogen in region 2 0.04Gy Number of passages = 0.27
Boron in region 2 0.50Gy Number of passages = 0.89

Nitrogen in region 3 0.11Gy Number of passages = 1.31
Boron in region 3 1.89Gy Number of passages = 2.20

Boron in region 4 0.00Gy Number of passages = 0.00

Average dose to nucleus from nitrogen = 0.538 Gy

Average dose to nucleus from boron = 3.576 Gy

Total average dose to nucleus = 4.115 Gy

Average number of passages per cell = 11.13

HIT DISTRIBUTION 0,1,2,etc

0	3	9	27	90	197	349	615	895	1106
1188	1163	1113	935	761	545	411	251	179	81
38	24	9	4	3	3	1			

DOSE DISTRIBUTION IN 0.5 Gy INTERVALS

(DOES NOT INCLUDE ZERO DOSE)

14	96	276	511	739	1066	1177	1200	1148	1019
791	615	487	317	192	155	74	66	27	17
5	3	2	1	1	0	0	1		

LET DISTRIBUTION FOR SINGLE PASSAGES (NITROGEN)

10 keV/um INTERVALS

0	0	518	2856	14680	5598	7325	8545	280	1
---	---	-----	------	-------	------	------	------	-----	---

LET DISTRIBUTION FOR SINGLE PASSAGES (ALPHA)

10 keV/um INTERVALS

0	0	0	0	1387	940	889	900	866	928
953	1053	990	1157	1309	1373	1441	1887	2612	4005
8397	7106	9621	5302	963	3				

LET DISTRIBUTION FOR SINGLE PASSAGES (LITHIUM)

10 keV/um INTERVALS

0	0	4	40	41	460	113	157	853	2144
1675	1307	1185	1162	1222	1060	999	1014	1059	991
1093	7253	995	1034	1014	1015	1111	1059	1109	991
1217	1414	1534	2847	128	143				

DOSE WEIGHTED LET DISTRIBUTION FOR NUCLEI (NITROGEN)

10 keV/um INTERVALS

0	0	10	76	1365	3755	4029	573	3
---	---	----	----	------	------	------	-----	---

DOSE WEIGHTED LET DISTRIBUTION FOR NUCLEI (BORON)

10 keV/um INTERVALS

0	0	0	0	3	0	1	2	6	3
6	9	10	24	26	41	99	177	453	982
1724	2190	2082	1328	468	133	35	9		

SURVIVING FRACTION = 2.92454E-02

Appendix L
OUTPUT FROM BNCT2.FOR - BNL BNCT Comparison

Fractional filling of volume

Nuclei	Cells	External
0.3537	0.1175	0.5288

Concentrations in components

Element	Nuclei	Cytoplasm	External
Nitrogen (g/100g)	2.0	2.0	2.0
Boron (ppm)	11.2	11.2	11.2

Neutron fluence (n/cm*cm) **3.7E+12**

Number of cells **10000**

Average number of interactions

Element	Nuclei	Cytoplasm	External
Nitrogen	255.2	84.8	381.5
Boron	423.3	140.6	632.7

Average proton dose (including carbon in nucleus) 0.581777 Gy)

Average alpha/lithium dose 3.58415 Gy

Average dose 4.16592 Gy

Contributions to nuclear dose

Nitrogen - nuclei	0.286 Gy
Nitrogen - cytoplasm	0.066 Gy
Nitrogen - external	0.231 Gy
Total nitrogen	0.583 Gy

Boron - nuclei	2.394 Gy
Boron - cytoplasm	0.399 Gy
Boron - external	0.783 Gy
Total boron	3.577 Gy

Fraction of average dose from ions

Protons	Alphas	Lithium
0.131	0.546	0.314

Fraction of cells hit **1.000**

Appendix M
zoom_img Raw Image Extraction Example

quark{dyke}134: zoom_img

Enter name of input file > god0926bpa_f24.img

Enter name of output file > god0926p#.img

*** Zoom_img - Image Conversion and Zoom Utility ***

Select conversion type (1-8):

1. - CTI to Analyze - enter frames, planes, flip, zoom
2. - CTI to Analyze - last frame, no zoom.
3. - CTI to BNCT - one image, zoom to 256 x 256.
4. - CTI to BNCT - loop to convert > 1 image to > 1 file.
5. - Analyze to CTI - no zoom, one frame.
6. - Analyze to CTI - enter planes, flip, zoom
7. - Analyze to Analyze - zoom
8. - I don't belong here - exit zoom_img now.

Selection (1-8) [1] > 4

Output filenames will have slice# inserted in place of #.

DATA TYPE: 2

Input file (god0926bpa_f24.img) - 1 frames, 47 planes.

Enter frame & planes to zoom (1 only).

Zoom which plane of frame 1? [23] > 1

Zoom image 1 in frame 1. OK? (y/n) [y] >

Data for first image selected:

Image size: 128 x 128 Pixel size: 2.109mm

Slice width: 3.375mm

Continue? (y/n) [y] >

Zooming 1 images (reading front to back) 1 VAX fmt

Quant scale: 0.000001, correction factor 12208.0186

comp scaler 0.0078 max pixel val 32767

Continue? > y

Image size - 16384

Image saved to god0926p01.img.

Convert more images? (y/n) [y] >

DATA TYPE: 2

Input file (god0926bpa_f24.img) - 1 frames, 47 planes.

Enter frame & planes to zoom (1 only).

Zoom which plane of frame 1? [23] > 2

Zoom image 2 in frame 1. OK? (y/n) [y] >

Data for first image selected:

Image size: 128 x 128 Pixel size: 2.109mm

Slice width: 3.375mm

Continue? (y/n) [y] >

Zooming 1 images (reading front to back) 1 VAX fmt

Quant scale: 0.000001, correction factor 12208.0186

comp scaler 0.0067 max pixel val 32767

Continue? > y

Image size - 16384

Image saved to god0926p02.img.

Convert more images? (y/n) [y] > n

Done.

Appendix N **rtt_MC_106 Neutron Transport Calculation Input configuration File**

```

Gaddis 11/10/95 UTK PET scans - 04/16/97
  700    1000    .10000000E-01
  -.30900000E+01    .35600000E+01    -.23625000E+01
  .25000000E+02    -.45000000E+02    .25000000E+02
./cg.geom
./gad1110.rs
  30      3
  32      72      94
  -.15000000E+02    -.15000000E+02    -.15000000E+02
  .10000000E+01    .10000000E+01
none
gad.rst
/usr/people/bnct/rtt/beam/BPTB_D_12cmBS.source
  1      0
NFGD      01/27/96
/usr/people/bnct/rtt/lib/rtt_008.mat
/usr/people/bnct/rtt/lib/rtt_005.sigma
  521 508 513 .60142600E-07 .63150000E-01 .79110000E-03
rtt_MC.106
# exclude    target
edit_dir
#date      30 Jan. 1997
#beam      BNL_12cm
mw_min      1.0
b10_blood  1.0
refvol      1.0
ref_reg     brain
# point     -3.00 1.00 -3.00
ottocon     40 scalp
delta       0.25
eps         1.0
# dose- volume histogram for brain
in_reg      brain
b10_blood   11
rbe         1.3 1.0 3.2 3.2 1.0 1.0
DVbs
# dose-volume histogram for tumor
in_reg      tumor
b10_blood   38.5
rbe         3.8 1.0 3.2 3.2 1.0 1.0 DVbs

```

Appendix O

PROCEDURE FOR THE COREGISTRATION OF PET AND MRI IMAGES

1. Using "gview" in OpenWindows, convert individual MR's (tumor planes) into cti format, saving them under a different file name.

2. Since gview only saves individual planes, you must combine the planes into

one file. The following illustrates this procedure:

1. Take the first .img file and copy/rename it to the final CTI file name. (All the file names presented are example files). This way the main header from the first image will be used as the main header for the final image set.

2. Strip the first 1024 bytes from the other image files (main header + directory block) and concatenate them to the final image set.

That is, `dd if=in.img bs=1k skip=1 | cat >> out.img`

Repeat this for additional images.

3. The header block must be updated to point to the new images and their subheaders. Do this with `~/bond/src/edit_hdr_blk out.img`

4. The main header must now be edited to correct the number of planes. Use the CTI program `header_edit` (`scanner:/usr/local/cti/bin/header_edit`), change number of planes and save the result.

5. Do the same with PET images if they exist in separate files. If all of the planes are already in one file, use the following to delete non-tumor planes:

```
dd if=in.img of=out.img bs=30976 skip=3 count=22
```

where `bs` is the image size (the example given is $176 \times 176 = 30976$), `skip` is the number of non-tumor images to skip at the beginning of the file, `count` is the number of tumor images to place into the outgoing file.

6. Zoom the mri file down to 128 X 128 so the images can be processed in neurotool.

`zoom_img in.img out.img`, and then follow the directions, choosing to zoom to specific image size

7. Open neurotool, and load the 128 X 128 file in. Choose the brain section by dragging the right mouse button, rotate the images around the z axis using the left button. Also rotate the images around the y axis if necessary

8. Save the transaxial slices.
9. Zoom the pet and mri images up to the same size (somewhere around 280X280),
converting to analyze format at the same time.
10. Run biopsy in Analyze to determine crop boundaries. Crop the images as close to the largest brain image as possible, making sure X and Y dimensions are divisible by 4 (preferably 16). Record X and Y dimensions as well as cursor positions.
11. Crop images and make a header

 crop in.img out.img, and then follow directions
 make a header (using makeaheader) so analyze can recognize the new file
12. Zoom the images to 240X240.
13. Interpolate the images using interp.
14. Using the same technique as in step 5, delete images to where both files have the same number of planes.
15. Splice the two image sets together. Choose to process from front to back, Interleave ALL pixels from both input images (i), First image = difference image (n), number of images = number of images in one file, fill in the correct X and Y axis size, and then follow the defaults from there on out.
16. View the new header with readhdr, noticing that the bits per pixel is said to be 0. Change this to 8 using makeaheader.
17. View the spliced images in Analyze (movie), and use the interactive color tool setting found in /tmp_mnt/home/Ca/Ca/cwright/chad
18. If spliced images of three dimensional sections is desired, use the render volume tool in analyze after step 14. Render each file (PET and MR) by creating 30 planes rotated at 12 degree increments ($12 \times 30 = 360$) and then splice these two files together. However, you must first make sure that interp has interpolated the images into cubic voxels, or volume render will not work correctly.

--CAW

Appendix P
MATLAB - Blood Pool Exponential Fitting Routine

```
function err = fitme(lambda)

global hmm

t = hmm(:,1);
y = hmm(:,2);
A = zeros(length(t),length(lambda));
for j = 1:length(lambda)
    A(:,j) = exp(lambda(j)*t);
end
global c
c = A\y;
z = A*c;
plot(t,y,t,z);
drawnow;
err=norm(z-y);

c
lambda
err
```

Appendix Q

PET Scan Maximum Value/Scaling Code

```

get_b_atoms(fp,qfac,ip,ims)
    short *ip; float qfac; FILE *fp; int ims;
{
    int i,j;
    float *fptr, magic, temp;
    magic=1.0;
    printf(" 11B output file name is: %s\n",fp);
/*    printf(" Inside get_b_atoms \n");
    printf(" size is: %d\n",ims);
    printf(" qfac is: %8.7f\n ",qfac);*/

    fptr = (float *) malloc(ims*sizeof(float));
/*    find maximum value to scale image */
    temp=0.0;

    for (i=0; i<ims;i++)
    {
        fptr[i]= ip[i]*qfac*magic;
        if (fptr[i]>temp) temp=fptr[i];
        if (ip[i]<0) fptr[i]=0.0;
    }

    printf(" maximum value is then: %8.7f\n",temp);
    for (i=0; i<ims; i++)
    {
/*        fptr[i]=255.0*fptr[i]/temp;*/
        fprintf(fp,"%10.7f ",fptr[i]);
/*        printf("%10.7f ",fptr[i]);*/
    }

    return(0);
}

```

Appendix R
Xcontours PET Concentration/Pixel Input Parameters File

gad1215j1d_f24p
\$HOME/bnct2.2/images/utk_gad1215
\$HOME/bnct2.2/images/utk_gad1215
.012242
-3.5 -3.5 5.5 30
\$HOME/bnct2.2/images/utk_gad1215/gad1215j1d_f24p17.img
\$HOME/bnct2.2/images/utk_gad1215/gad1215j1d_f24p16.img
0.0189039
0.0189038
0.0183685
0.0199138
0.0182740
0.0198392
0.0184695
0.0204930
0.0165572

Appendix S

Code to Incorporate PET 10B pixel Concentration Data into Xcontours

blowup.f - Dr. Chuck Wemple, INEEL BNCT Team, 1997.

```

SUBROUTINE blowup(filename,mlen)
  POINTER (PATHNAMp, PATHNAM)
  INTEGER GETVAR,null
  EXTERNAL GETVAR
  CHARACTER*80 filename,newfile,filehead,PATHNAM
  CHARACTER*1 a,blank,cnull
  DATA blank/' '/
  DATA null/0/
  DATA (filehead(i:i),i=1,80)/80*' '/
  DATA (newfile(i:i),i=1,80)/80*' '/
  cnull = CHAR(null)

c
c Expands general pathname - recognizes ~ for home directories, and
c $ for environment variables. Special case for $RTT - include
c $BNCTPATH expansion before adding /rtt at end.
c
c First, find the pathname in the filename - key on $ and ~
c
  len = 1                                cawapr97
  mlen = 0                                cawapr97
  a = filename(len:len)                   cawapr97
  DO WHILE (a.NE.blank)                   cawapr97
    nlen = 0                               cawapr97
    IF (a.EQ.'$') THEN                     cawapr97
      FREEFORM                             FREEFORM
c Set up variable as included in calling argument FILENAME
FREEFORM
c
      DO WHILE (filename(len+nlen+1:len+nlen+1).NE.' ' .AND.
cawapr97
      *      filename(len+nlen+1:len+nlen+1).NE.blank)      cawapr97
      *      IF (filename(len+nlen+1:len+nlen+1).EQ.'$' .OR.  cawapr97
      *          filename(len+nlen+1:len+nlen+1).EQ.'~') THEN cawapr97
        PRINT*,'This is not a valid filename!'               cawapr97
        PRINT*,'Please check your input.'                      cawapr97
        STOP                                                    cawapr97
      ENDIF                                                      cawapr97
      nlen = nlen + 1                                           cawapr97
    END DO                                                       cawapr97
  cawapr97
c
c Get expanded environment variable name                        cawapr97
c
  IF (filename(len+1:len+nlen).EQ.'RTT' .AND. len.LE.1) THEN
cawapr97
  PATHNAMp = GETVAR ('BNCTPATH' // cnull)
cawapr97
  ELSE
cawapr97
  PATHNAMp = GETVAR (filename(len+1:len+nlen) // cnull)
cawapr97

```

```

ENDIF
c
c Strip off trailing blanks in expanded variable name
c
IF(PATHNAMp.NE. null) THEN
    nmlen = 0
    DO WHILE (PATHNAM(nmlen+1:nmlen+1) .NE. blank .AND.
cawapr97
        PATHNAM(nmlen+1:nmlen+1) .NE. cnull)
        nmlen = nmlen + 1
    END DO
    IF (nmlen .GT. 0) THEN
        filehead(1:nmlen) = PATHNAM(1:nmlen)
        IF (filename(len+1:len+nlen).EQ.'RTT'
            .AND. len.LE.1) THEN
            filehead(nmlen+1:nmlen+4) = '/rtt'
            nmlen = nmlen + 4
        ENDIF
    ELSE
        PRINT*,filename(len+1:len+nlen),' is zero-length'
    ENDIF
    ELSE
        PRINT*,filename(len+1:len+nlen),' is zero-length'
    ENDIF
c
c Store expanded variable name in file pathname
c
newfile(mlen+1:mlen+nmlen) = filehead(1:nmlen)
mlen = mlen + nmlen
c
c Expand ~login as home directory for 'login'
c
ELSEIF (a.EQ.'~') THEN
    DO WHILE (filename(len+nlen+1:len+nlen+1).NE.' ' .AND.
cawapr97
        filename(len+nlen+1:len+nlen+1).NE.blank)
        IF (filename(len+nlen+1:len+nlen+1).EQ.'$' .OR.
            filename(len+nlen+1:len+nlen+1).EQ.'~') THEN
            PRINT*, 'This is not a valid filename!'
            PRINT*, 'Please check your input.'
            STOP
        ENDIF
        nlen = nlen + 1
    END DO
c
c Get expanded directory name for ~login
c
filehead = 'echo '//filename(len:len+nlen)//">doGgGgG'
call system(filehead)
open (88,file='doGgGgG',status='old')
read (88,10) filehead
format(a80)
close (88)
call system('rm doGgGgG')
c

```

```

c Strip off trailing blanks, and append to complete filename      cawapr97
c                                                                    cawapr97
    nmlen = 0                                                       cawapr97
    DO WHILE (filehead(nmlen+1:nmlen+1).NE.blank)                  cawapr97
        nmlen = nmlen + 1                                           cawapr97
    END DO                                                           cawapr97
    newfile(mlen+1:mlen+nmlen) = filehead(1:nmlen)                 cawapr97
    mlen = mlen + nmlen                                             cawapr97
c                                                                    cawapr97
c Otherwise, just echo through single character                    cawapr97
c                                                                    cawapr97
    ELSE                                                             cawapr97
        newfile(mlen+1:mlen+1) = a                                  cawapr97
        mlen = mlen + 1                                             cawapr97
    ENDIF                                                           cawapr97
c                                                                    cawapr97
c Set up for next character in loop                                cawapr97
c                                                                    cawapr97
    len = len + nlen + 1                                           cawapr97
    a = filename(len:len)                                           cawapr97
    END DO                                                           cawapr97
c                                                                    cawapr97
c Finish off with check for filename length, and return           cawapr97
c                                                                    cawapr97
    IF(mlen .GT. 80) THEN                                           cawapr97
        PRINT *, HALT -- EXPANDED FILENAME EXCEEDS 80
CHARACTERS' cawapr97
        PRINT *,filename                                           cawapr97
        STOP                                                       cawapr97
    ENDIF                                                           cawapr97
    filename(1:mlen) = newfile(1:mlen)                             cawapr97
    RETURN
END

```

envr.c - Dr. Chck Wemple, INEEL BNCT Team, 1997.

```

/*
 * Below is the set of C routines that I use in PDQ to query user
 * environment variables in a somewhat portable fashion. The calling
 * Fortran routine should assign the "getvar" return value to a
 * Fortran pointer variable. For example:
 *
 *      pointer (PATHNAMp, PATHNAM)
 *      character*64 PATHNAM
 *      integer GETVAR, NULL
 *      external GETVAR
 *      parameter (NULL = 0)
 *
 *      PATHNAMp = GETVAR ('BNCTVAR' // char(NULL))
 *      if (PATHNAMp.ne. NULL) then
 *          ... use the character PATHNAM variable somehow ...
 *      endif
 *      ...
 */

#include <stdlib.h>
#ifdef cray
#include <string.h>
#endif

/*
 * getvar - Searches the environment list for the specified environment
 *          variable. This function serves as a bridge to the 'getenv'
 *          function of the C run-time library.
 */
char *getvar (name)
char *name;          /* environment variable name */
{
#ifdef cray
    int len;
    char *sp, *wp;

    if ((sp = getenv(name)) == NULL)
        return ((char *) NULL);

    if ((len = strlen(sp)) == 0)
        return ((char *) NULL);

    if ((wp = (char *) malloc ((size_t) (((len/8)+1)*8))) == NULL)
        return ((char *) NULL);

    (void) memcpy(wp, sp, len+1);
    return (wp);
#else
    return(getenv(name));
#endif
}

/* Alternative entry point names for 'getvar'. */
char *GETVAR (name)
char *name;
{
    return(getvar(name));
}

char *getvar_ (name)
char *name;
{
    return(getvar(name));
}

```

get_image.c - Dr. Chuck Wemple, INEEL BNCT Team, 1997.

```
#include <stdio.h>
#include <ctype.h>

void getimage_(array, fname, len)
int  array[256][256]; /* 2D array of integer values */
char *fname;          /* the input file name*/
int  len;              /* # characters in fname*/
                        /* len is short for Domain, int for standard FORTRAN*/
{
    int i, j;
    unsigned char buf[256];
    FILE *fp;

    /* fix up the file name */
    for (i = 0; i < len; i++) {
        if (isspace(fname[i])) {
            fname[i] = '\0';
            break;
        }
    }

    /* open the file */
    if ((fp = fopen(fname, "r")) == NULL)
        return;

    /* read in a row at a time -- unpack each row into an array column */
    for (i = 0; i < 256; i++) {
        (void) fread((char *) buf, 256, 1, fp);
        for (j = 0; j < 256; j++)
            array[i][j] = (int) buf[j];
    }

    /* close the file */
    (void) fclose(fp);

    return;
}
```

pet_boron.f (Main Program) - Dr. Chuck Wemple, INEEL BNCT Team, 1997.

```
character*1 blank
character*16 puppy
character*34 mutt
character*80 image_prefix, image_path, contour_path, base_file
character*80 ref_file, ref_file2, contour_file, image_file, a
data blank/ '/'
external getimage
integer b10(256,256), reg(1600)
real dose(1600,8), pos(1600,3), num(8), range(6), ref_loc(3)
c
c Read input information
c
  read (5,10) image_prefix
  call blowup(image_prefix,lenpr)
  read (5,10) image_path
  call blowup(image_path,lenip)
  read (5,10) contour_path
  call blowup(contour_path,lencp)
c  read (5,10) base_file
c  call blowup(base_file,lenbf)
10 format(a80)
  read (5,*) avg_int
  read (5,*) ref_loc, voxel_dim
  read (5,10) ref_file
  call blowup(ref_file,lenrf)
  read (5,10) ref_file2
  call blowup(ref_file2,lenrf2)
c
c Open image files containing reference point and find the relative
c intensity of the reference point by averaging the two pixel values
c Also, divide by 255 (max intensity) to get relative intensity
c
  iref1 = 128 + int(128.*ref_loc(2)/voxel_dim)
  iref2 = 128 - int(128.*ref_loc(1)/voxel_dim)
  call getimage(b10,ref_file)
  dog = (b10(iref1,iref2) + b10(iref1+1,iref2) + b10(iref1-1,iref2)
  *      + b10(iref1,iref2+1) + b10(iref1,iref2-1))/5.0
  call getimage(b10,ref_file2)
  dog2 = (b10(iref1,iref2) + b10(iref1+1,iref2) + b10(iref1-1,iref2)
  *      + b10(iref1,iref2+1) + b10(iref1,iref2-1))/5.0
  ref_val = (dog + dog2)/510.0
c
c Read base_file to get baseline PET intensity for blood
c This is used as the average intensity for scaling the B-10 dose
c
c  open (11,file=base_file,status='old')
c  do 20 i = 1,28
```

```

c 20 read (11,*)
c   read (11,*) (idog,i=1,3),avg_int
c   close (11)
c
c Set up filenames, and start loop over all image files
c
  a = 'ls '//contour_path(1:lencp)//'//image_prefix(1:lenpr)
  a = a(1:lenip+lenpr+4)//'*',contour > doGgGgG'
  call system(a)
  open (99,file='doGgGgG',status='old')
  read (99,10,end=110) contour_file
  call blowup(contour_file,lencf)
  do while (contour_file.ne.blank)
c
c Read image file and contour file
c
    read (5,*) scale
    fac = scale/avg_int
    image_file = image_path(1:lenip)//contour_file(lencp+2:lencf-8)
    lenif = lenip + lencf - lencp - 2
    call getimage(b10,image_file)
    open (10,file=contour_file,status='old')
    read (10,*)
    read (10,*) (dog,i=1,6),idog,idog,i1,i2,idog
    do 30 i = 1,11
30   read (10,*)
    nline = i1*i2
    do 40 i = 1,nline
40   read (10,50) (pos(i,j),j=1,3),reg(i),(dose(i,j),j=1,8)
50   format(1p,3e10.3,i4,8e10.3)
    rewind (10)
c
c Read top of old contour file and copy to new contour file
c
    open (12,file=contour_file(lencp+2:lencf)//'b',status='new')
    do 60 i = 1,5
      read (10,10) a
60   write (12,10) a
      read (10,70) puppy, range
      write (12,70) puppy, range
70   format(a16,1p,6e13.5)
      read (10,10) a
      write (12,10) a
      read (10,10)
      read (10,10)
      read (10,10)
      write (12,80)
80   format(5X,'x',8X,'y',10X,'z',5X,'reg',' total  B-10 '
*   , ' gamma  N-14  Hydrogen  Gp 1  Gp 2  '

```

```

*      , 'thermal',/,3X,'(cm)',5X,'(cm)',7X,'(cm)',10X,'dose',5X,'dose'
*      ,6X,'dose',7X,'dose',6X,'dose',5X,'fluence',3X,'fluence'
*      ,3X,'fluence',/)
      read (10,90) mutt,(rnum(j),j=1,8)
      write (12,90) mutt,(rnum(j),j=1,8)
      read (10,90) mutt,(rnum(j),j=1,8)
      write (12,90) mutt,(rnum(j),j=1,8)
      read (10,90) mutt,(rnum(j),j=1,8)
      rnum(1) = rnum(1) - rnum(2)
      rnum(2) = rnum(2)*fac*ref_val
      rnum(1) = rnum(1) + rnum(2)
      write (12,90) mutt,(rnum(j),j=1,8)
90    format(a34,1p,8e10.3)
      close (10)

c
c Loop through contour file and scale the boron dose for each point
c Determine relative boron concentration at each point - use average
c pixel value of (x,y) and four surrounding pixels
c
      do 100 i = 1,nline
        locx = pos(i,1)*128 + 128
        if (locx.le.0) locx = 1
        locxp = locx + 1
        if (locxp.gt.256) locxp = 256
        locxm = locx - 1
        if (locxm.le.0) locxm = 1
        locy = -pos(i,2)*128 + 128
        if (locy.le.0) locy = 1
        locyp = locy + 1
        if (locyp.gt.256) locyp = 256
        locym = locy - 1
        if (locym.le.0) locym = 1
        favg = (b10(locx,locy) + b10(locxp,locy) + b10(locxm,locy) +
*             b10(locx,locym) + b10(locx,locyp))/5.0
        dose(i,1) = dose(i,1) - dose(i,2)
        dose(i,2) = dose(i,2) * fac * favg/255.
        dose(i,1) = dose(i,1) + dose(i,2)
100    write (12,50) (pos(i,j),j=1,3),reg(i),(dose(i,j),j=1,8)
      close (12)
      read (99,10,end=110) contour_file
      call blowup(contour_file,lencf)
    end do
110 close (99)
      call system('rm doGgGgG')
      stop
      end

```

Appendix T

2 Compartment Analytical Solution

|W| Maple V Release 4 (University of Tennessee at Knoxville)
 ._|N |/_|_ Copyright (c) 1981-1996 by Waterloo Maple Inc. All rights
 \ MAPLE / reserved. Maple and Maple V are registered trademarks of
 <_____ Waterloo Maple Inc.
 | Type ? for help.

> de1:=diff(cp(t),t)-k2*q(t)+k1*cp(t)=0;

$$\frac{d}{dt} \left(-cp(t) - k_2 q(t) + k_1 cp(t) \right) = 0$$

> de2:=diff(q(t),t)-k1*cp(t)+k2*q(t)=0;

$$\frac{d}{dt} \left(q(t) - k_1 cp(t) + k_2 q(t) \right) = 0$$

> dsolve({de2,q(0)=0},q(t));

bytes used=2000312, alloc=1441528, time=1.07

$$q(t) = \exp(-k_2 t) k_1 \int_0^t \exp(k_2 u) cp(u) du$$

Appendix U

3C MAPLE Analytical Solution

```
de1:=diff(ce(t),t)-k1*cp(t)+(k2+k3)*ce(t)-k4*cm(t)=0;
de2:=diff(cm(t),t)-k3*ce(t)+k4*cm(t)=0;
dsolve({de1,ce(0)=0,D(ce)(0)=0,de2,cm(0)=0,D(cm)(0)=0},{ce(t),cm(t)});
```

$$\begin{aligned}
 \{cm(t) = & \frac{(k_3 k_1 \int_0^t cp(u) \exp(1/2 u \%3) du \exp(-1/2 t \%3) - k_3 k_1 \int_0^t cp(u) \exp(1/2 u \%2) du \exp(-1/2 t \%2)) \sqrt{\%1}}{\sqrt{\%1}}, \\
 ce(t) = & \frac{(k_1 \int_0^t \frac{d}{du} cp(u) + cp(u) k_4 \int_0^t \exp(1/2 u \%3) du \exp(-1/2 t \%3) - k_1 \int_0^t \frac{d}{du} cp(u) + cp(u) k_4 \int_0^t \exp(1/2 u \%2) du \exp(-1/2 t \%2)) \sqrt{\%1}}{\sqrt{\%1}}, \\
 \%1 := & k_2^2 + 2 k_2 k_3 - 2 k_4 k_2 + k_3^2 + 2 k_3 k_4 + k_4^2 \\
 \%2 := & \sqrt{\%1} + k_2 + k_3 + k_4 \\
 \%3 := & -\sqrt{\%1} + k_2 + k_3 + k_4
 \end{aligned}$$

Appendix V **4C MAPLE Analytical Solution**

$$\{cand(t) = k_5 \int_0^t \exp(-k_5 _U) ca(t - _U) d_U,$$

$$cbnd(t) = -k_3 k_1 \int_0^t ca(t - _U) k_5 \%3 \%2 k_2 + ca(t - _U) k_5 \%3 \%2 k_3 \\ - ca(t - _U) k_5 \%3 \%4 \%1^{1/2} + ca(t - _U) k_5 \exp(-k_5 _U) \%1^{1/2} \\ + 2 ca(t - _U) k_4 k_3 \%3 \%2 d_U \int ((-k_5 k_2 + k_5^2 - k_5 k_3 - k_4 k_3) \%1^{1/2})$$

$$cbd(t) = k_1 \int_0^t ca(t - _U) k_5^2 \exp(-k_5 _U) \%1^{1/2} + 2 ca(t - _U) k_5 k_3 \%3 \%2 k_2 \\ + ca(t - _U) k_5 k_2^2 \%3 \%2 - ca(t - _U) k_5 k_2 \%3 \%4 \%1^{1/2} \\ + 2 ca(t - _U) k_5 k_4 k_3 \%3 \%2 + ca(t - _U) k_5 k_3^2 \%3 \%2 \\ - ca(t - _U) k_5 k_3 \%3 \%4 \%1^{1/2} - ca(t - _U) k_4 k_3 \%3 \%4 \%1^{1/2} \\ + ca(t - _U) k_4 k_3 \%3 \%2 k_2 + ca(t - _U) k_4 k_3^2 \%3 \%2 d_U \\ \int ((-k_5 k_2 + k_5^2 - k_5 k_3 - k_4 k_3) \%1^{1/2}) \\ \}$$

$$\%1 := k_2^2 + k_3^2 + 2 k_2 k_3 + 4 k_4 k_3$$

$$\%2 := \sinh(1/2 \%1^{1/2} _U)$$

$$\%3 := \exp(-1/2 _U (k_2 + k_3))$$

$$\%4 := \cosh(1/2 \%1^{1/2} _U)$$

Appendix W

Partial Fractions Laplace 4C Analytical Solution

The compartmental model equations for figure 1 are given by the parameter matrix:

$$\begin{aligned}\dot{X}(t) &= AX(t) + BU(t) \\ Y(t) &= CX(t) + DU(t)\end{aligned}\tag{1a}$$

where $X(t)$ is a column vector $[C_{ND}^P(t); C_D^T(t); C_{ND}^T(t)]$, $U(t)$ is the arterial input activity, $C_a(t) = C_D^P(t) + C_{ND}^P(t)$ (mCi/ml), measured from a carotid artery blood pool time activity curve following intravenous injection of ^{18}F -BPA-Fr, and $Y(t)$ is the measured tumor tissue activity. Both $C_a(t)$ and $Y(t)$ are determined using PET region of interest analysis. Matrix A is given by:

$$A = \begin{bmatrix} -(k_5 + k_6) & 0 & 0 \\ -k_1 & -(k_2 + k_3) & k_4 \\ 0 & k_3 & -k_4 \end{bmatrix}\tag{2a}$$

where the kinetic transport constants are defined as in figure 1. B is a column vector $[k_5; k_1; 0]$, C is a row vector $[0 \ 1 \ 1]$, D is a scalar $[V]$, and t is a time variable (min). V is the estimated vascular fraction.

The solution to this set of differential equations for the total activity in a region of interest on the PET image, C_{PET} , can be determined using the tissue activity equations:

$$\begin{aligned}\frac{dC_D^T}{dt} &= -(k_2 + k_3) C_D^T + k_4 C_{ND}^T + k_1 C_D^P \\ \frac{dC_{ND}^T}{dt} &= k_3 C_D^T - k_4 C_{ND}^T\end{aligned}\tag{3a}$$

Using Laplace transforms, these equations can be written:

$$\begin{aligned}sC_D^T &= -(k_2 + k_3) C_D^T + k_4 C_{ND}^T + k_1 C_D^P \\ sC_{ND}^T &= k_3 C_D^T - k_4 C_{ND}^T\end{aligned}\tag{4a}$$

Solving for C_D^T using the method of partial fractions and expressing the result in the form introduced by Huang (REF) yields:

$$C_D^T = \left(\frac{A}{s + \alpha_1} + \frac{B}{s + \alpha_2} \right) C_D^P\tag{5a}$$

where s represents the Laplace transform operator and the coefficients α_1 , α_2 , A , and B are defined as follows:

$$\begin{aligned}
2\alpha_1 &= (k_1 + k_2 + k_3) + \sqrt{(k_1 + k_2 + k_3)^2 - 4k_2k_4} \\
2\alpha_2 &= (k_1 + k_2 + k_3) - \sqrt{(k_1 + k_2 + k_3)^2 - 4k_2k_4} \\
A &= \frac{k_1}{\alpha_1 - \alpha_2} (\alpha_1 - k_4) \\
B &= -\frac{k_1}{\alpha_1 - \alpha_2} (\alpha_2 - k_4)
\end{aligned} \tag{6a}$$

From the model, it is apparent that the total blood pool activity is given by,

$$C_s = C_D^P + C_{ND}^P \tag{7a}$$

Also, assuming negligible back-diffusion in the blood pool, i.e. $k_5=0$, then

$$\frac{dC_{ND}^P}{dt} = k_5 C_D^P \tag{8a}$$

Taking the derivative of equation 7a, combining with equation 8a, and taking the Laplace transform of the result yields,

$$C_D^P = \frac{s}{(s + k_5)} C_a \tag{9a}$$

Substitution of C_D^P from equation 9a into 5a and again using the method of partial fractions to separate the variables yields:

$$C_{ND}^T = \left[\left(\frac{A\alpha_1}{\alpha_1 - k_5} \right) \left(\frac{1}{s + \alpha_1} \right) - \left(\frac{Ak_5}{\alpha_1 - k_5} \right) \left(\frac{1}{s + \alpha_1} \right) + \left(\frac{B\alpha_2}{\alpha_2 - k_5} \right) \left(\frac{1}{s + \alpha_2} \right) - \left(\frac{Bk_5}{\alpha_2 - k_5} \right) \left(\frac{1}{s + \alpha_2} \right) \right] C_a \tag{10a}$$

Now, combining C_{ND}^T from the second equation in 4a with the result in 10a,

$$C_{ND}^T = \frac{k_3}{k_4 + s} \left(\frac{\beta_1}{s + \alpha_1} + \frac{\beta_2}{s + \alpha_2} + \frac{\beta_3}{s + k_5} \right) C_a \tag{11a}$$

where the coefficients β_1 , β_2 , and β_3 are given by:

$$\begin{aligned}
\beta_1 &= \frac{A\alpha_1}{\alpha_1 - k_5} \\
\beta_2 &= \frac{B\alpha_2}{\alpha_2 - k_5} \\
\beta_3 &= -\left(\frac{Ak_5}{\alpha_1 - k_5} + \frac{Bk_5}{\alpha_2 - k_5} \right)
\end{aligned} \tag{12a}$$

Again using the method of partial fractions to separate the variables in 11a gives the following result:

$$C_{ND}^T = \left[(E_1 + E_2 + E_3) \left(\frac{1}{s + k_4} \right) - E_1 \left(\frac{1}{s + \alpha_1} \right) - E_2 \left(\frac{1}{s + \alpha_2} \right) - E_3 \left(\frac{1}{s + k_5} \right) \right] C_a \quad (13a)$$

where

$$\begin{aligned} E_1 &= \frac{k_3 \beta_1}{\alpha_1 - k_4} \\ E_2 &= \frac{k_3 \beta_2}{\alpha_2 - k_4} \\ E_3 &= \frac{k_3 \beta_3}{k_5 - k_4} \end{aligned} \quad (14a).$$

The total activity seen in a region of interest on the PET scan, C_{PET} , is given by

$$C_{PET} = C_D^T + C_{ND}^T + VC_a \quad (15a)$$

Combining equations 10a and 14a with 15a, taking the inverse Laplace transforms, and rearranging variables gives the desired result:

$$C_{PET} = \left(\gamma_1 e^{-k_4 t} + \gamma_2 e^{-k_5 t} + \gamma_3 e^{-\alpha_1 t} + \gamma_4 e^{-\alpha_2 t} \right) \otimes C_a + VC_a \quad (16a)$$

where the coefficients, γ_1 , γ_2 , γ_3 , and γ_4 are defined as:

$$\begin{aligned} \gamma_1 &= E_1 + E_2 + E_3 \\ \gamma_2 &= \beta_1 \left(1 + \frac{k_3}{k_4 - \alpha_1} \right) \\ \gamma_3 &= \beta_2 \left(1 + \frac{k_3}{k_4 - \alpha_2} \right) \\ \gamma_4 &= \beta_3 \left(1 + \frac{k_3}{k_4 - k_5} \right) \end{aligned} \quad (17a)$$

and $\otimes$ represents the convolution operator. Equation 16a reduces to the FDG three compartment model equation described by Huang (REF) when $k_5=0$ and $V=0$.

Appendix X **Alternate 4C MAPLE Analytical Solution**

$$s := \{ \text{cbnd}(t) = \frac{(-\%7 k_3 \%6 + \%7 k_3 \%2 + \frac{1}{2} \%5 \%2 \%1 - \frac{1}{2} \%5 k_2 \%6}{\%1^{\frac{1}{2}} + \frac{1}{2} \%5 k_2 \%2 - \frac{1}{2} \%5 k_3 \%6 + \frac{1}{2} \%5 k_3 \%2 + \frac{1}{2} \%5 \%6 \%1} \} /$$

$$\%6, \text{cbnd}(t) = \frac{(\frac{1}{2} \%7 \%2 \%1^{\frac{1}{2}} + \frac{1}{2} \%7 k_2 \%6 - \frac{1}{2} \%7 k_2 \%2 + \frac{1}{2} \%7 k_3}{- \frac{1}{2} \%7 k_3 \%2 + \frac{1}{2} \%7 \%6 \%1^{\frac{1}{2}} - k_4 \%5 \%6 + k_4 \%5 \%2) / \%1^{\frac{1}{2}}}$$

$$\%1 := k_2^2 + 2 k_2 k_3 + k_3^2 + 4 k_4 k_3$$

$$\%2 := \exp(- \frac{1}{2} (k_2 + k_3 - \%1^{\frac{1}{2}}) t)$$

$$\%3 := \exp(\frac{1}{2} (k_2 + k_3 - \%1^{\frac{1}{2}}) s)$$

$$\%4 := \exp(\frac{1}{2} (k_2 + k_3 + \%1^{\frac{1}{2}}) s)$$

$$\%5 := \int_0^t \frac{k_3 (-\%4 + \%3) k_1 (ca(s) - cand(s))}{\%1^{\frac{1}{2}}} ds$$

$$\%6 := \exp(- \frac{1}{2} (k_2 + k_3 + \%1^{\frac{1}{2}}) t)$$

$$\%7 := \int_0^t (\frac{1}{2} \%3 \%1^{\frac{1}{2}} + \frac{1}{2} k_2 \%4 - \frac{1}{2} k_2 \%3 + \frac{1}{2} k_3 \%4 - \frac{1}{2} k_3 \%3$$

$$+ \frac{1}{2} \%4 \%1^{\frac{1}{2}}) k_1 (ca(s) - cand(s)) / \%1^{\frac{1}{2}} ds$$

APENDIX Y

Ctrl-C Linear Optimization Code

bpa.ctr

```
//graphics=input('Do you really want graphs - 1=yes 0=no: ');
plot_query=1;
print_graph=0;
//recovery=input('Enter partial volume coefficient for artery data: ');
//bp_recov_coeff=recovery;
bp_recov_coeff=1.0;
do cpcurve;..
//ca=cp;
time=t;
sectorm=q;
do bpa_calc;..
```

cpcurve.ctr

```
tf=7020;
load m <bpa.txt -f -c3;
t=m(:,1); cp=m(:,2)/20.1;
q=m(:,3);
// simulate 2 hour infusion time
h=ones(1:360);
ccp=conv(cp,h);
cpconv=ccp(1:tf/10+1);
cq=conv(q,h);
cpconv(1)=.0001;
qconv=cq(1:tf/10+1);
ty=['initial plot -- godwin 09-26'];
plot(t/60,q),title(ty),ylabel ('Total Activity(ECATcps/px)');
//      xlabel ('Time (min)');
//hard = 'hpglf';
//replot;
//redhard -close;
//$hpgl2ps ctrlc.hpgl>conv.ps
cpconv(1)=.0001;
//erase;
//ty=['Ratio Qconv/Cpconv'];
//plot(t/60,ratme),title(ty),ylabel ('Total Activity (ECATcps/px)',...
//      xlabel ('Time (min)');
//hard = 'hpglf';
//replot;
//redhard -close;
//$hpgl2ps ctrlc.hpgl>ratio.ps
```

bpa_p2ss.ctr

```
[ad,bud,bwd,c,d,qd,r,x0] = bpa_p2ss(p)
dt = p(11);
k1 = p(1);          ..initial value of k1
k2 = p(2);          ..          k2
k3 = p(3);          ..          k3
k4 = p(4);          ..          k4
k5 = p(5);          ..          k5
k6 = p(6);          ..          k6
plasma_vol=p(7);    ..plasma volume
//
//define model
a = [-(k2+k3)   k4   -k1 ; ... bpa model
//a = [-(k2+k3)   k4     0 ; ... 3c model
      k3   -k4     0 ;
      0     0  -(k5+k6)];
bu = [k1; 0; k5];
bw = [0; 0; 0];
c = [1 1 0];
d = [plasma_vol];
q = p(15);
r = p(8);
x0= [p(9); p(10); p(10)];
[ad,bd]=c2d(a, [bu bw],dt);
bud = bd(:,1);
bwd = bd(:,2);
qd = q/dt;
```

bpa_calc.ctr

```
plot_query=1;
do cpcurve;
//rec=input(' input recovery coefficient');
//rec=.121;
t=t/60;
qtot=q;
//-----Variable definition-----
line = 1000;
deltat=(t(2)-t(1));
dt = deltat;
//k1=0.0015;          ..initial value of k1
//k2=0.0370;          ..          k2
//k3=0.0001;          ..          k3
```

```

//k4=0.002;
//k5=0.0028;
//k6=0.0;          ..          k6
//plasma_vol=0.0036; .. value of plasma volume
k1=0.001;          ..initial value of k1
k2=0.03;           ..          k2
k3=0.000;          ..          k3
k4=0.00;
k5=0.00;
k6=0.00;           ..          k6
plasma_vol=0.00; .. value of plasma volume

p = 0*ones(15,1);

p(1)=k1;           ..value of k1
p(2)=k2;           ..          k2
p(3)=k3;           ..          k3
p(4)=k4;           ..          k4
p(5)=k5;           ..          k5
p(6)=k6;           ..          k6
p(7)=plasma_vol; ..initial value of p(5)=plasma_volume
p(8)=0.000025;    ..activity noise variance
p(9)=0.0;          ..Ce(0)
p(10)=0.0;         ..Cm(0)
p(11)=dt;          ..increment time
p(15)=0.00004;     ..process noise variance
deff bpa_p2ss;     .. define the p2ss function
u=cp'/20.1; ... bpa model
//u=u/.4; ... hematocrit correction factor 3c model
y=qtot';
ty=[' Prior to Identification'];
ty2=[' During Identification'];
ty1=[' After Identification'];
disp(' initial parms:')
[p(1),p(2),p(3),p(4),p(5),p(7)]
//-----Like call-----
[llf,yest,b,k]=like(p,'bpa_p2ss',u,y);
disp(' Cost Function, llf = '),llf;
if plot_query=1,..
    erase;..
    plot(t,yest,t,y),title(ty),ylabel ('Total Activity (ECATcps/px)'),...
        xlabel ('Time (min)'),...
    hard = 'hpglf',
    replot,

```

```
redhard -close,
$hpgl2ps ctrlc.hpgl>prior.ps
```

```
end;
//----- Maximum-Likelihood identification run
short e;
marq=0.0;
pert=0.001;lold=0; mfc=0.0001;
pid=[1,2];      ..identify
pret=p;
..
pold=pret(pid); nth=prod(size(pid));
for i=1:nth, if pold(i)=0, pold(i)=1.e-6;
..
//-----for loop -----
for j=1:10,..
    disp(' Iteration Number'),j;..
    [pret,marq,llf,grad,hes]=mlstep(pret,pid,'bpa_p2ss',u,y,pert,marq);..
    ngrd=(grad.*pret(pid))/llf;..
    delp=100*(pret(pid)-pold)./pold;..
    std=100*sqrt(diag(inv(hes)))./pret(pid);..
    rc=2*abs(llf-lold)/(abs(llf)+abs(lold));..
    if rc<mfc,exit;end;..
    pold=pret(pid);..
    lold=llf;..
end;
p=pret;
short
[llf,yest,h,k]=like(p,'bpa_p2ss',u,y);
disp(' Our Best Guess at these things is: '),p;
//-----plot the final estimated model-----
if plot_query=1,..
    erase;..
    plot(t,yest,t,y),title (ty1),ylabel ('Total Activity (ECATcps/px)'),..
        xlabel ('Time (Min)'),..
end;
end;
[p(1:5)' p(7)]'
display(' ratio is:')
p(1)*p(3)/(p(2)+p(3))
display(' sq error is:')
sqerr=sum(yest.*yest-q'.*q')
```

Appendix Z

Patlak Parametric Image Analysis Code

```

calc_ptlk_data(nfrms, pln_seq, x, xmin, bp_vals, tau, nu_pln, pln_qsf,
pln_max, pln, sz, seld_val)

short *pln_seq[], pln_max[];
float x[], bp_vals[], tau[], pln_qsf[], xmin, *nu_pln, seld_val;
int pln, nfrms, sz;

{   int i,j,n;
    char resp[4];
    float prod, y[MAX_FRMS], sumx, sumy, sumx2, sumy2, sumxy, m, b, corr;
    short *img_ptr, img_val;

    if (DEBUG)
        printf("\n Plane %2d - ", pln+1);
    if (pln == 0 && DEBUG)
    {   printf("\n   intcp/cp: ");
        for (i = 0; i < nfrms; i++)
            printf(" %6.4f %d", x[i], i);
        printf("\n   tau: ");
        for (i = 0; i < nfrms; i++)
            printf(" %5.1f ", tau[i]);
        printf("\n   Image Max Values (and quant scale factors*10**5): ");
        for (i = 0; i < nfrms; i++)
            printf(" %5d (%5.3f)", pln_max[i], pln_qsf[i]*100000);
    }
    /** i = frame number j = pixel number ***/
    for (j = 0; j < sz; j++)
    {   n=0;    sumx=0;
        sumy=0; sumx2=0; sumy2=0;
        sumxy=0; m=0; b=0; corr=0;
        for (i = 0; i < nfrms; i++)
        {
            img_ptr = pln_seq[i];
            img_val = img_ptr[j];
            if (img_val < 0) img_val = 0;
            y[i] = (pln_qsf[i] * img_val) / bp_vals[i];
            if (x[i] >= xmin) {
                sumx = sumx + x[i];
                sumy = sumy + y[i];
                sumx2 = sumx2 + x[i]*x[i];
                sumxy = sumxy + x[i]*y[i];
            }
        }
    }
}

```

```

        sumy2 = sumy2 + y[i]*y[i];
        n++;
    }
}
if (n>0)
{
    /*printf(" sumy %10.7f sumxy %10.7f frm %d pix
%d\n",sumy,sumxy,i,j);*/
    m = (sumxy - sumx*sumy/n) / (sumx2 - sumx*sumx/n);
    b = sumy/n - m * sumx/n;
    corr = sumxy / sqrt (sumx2 * sumy2);
    if (corr < seld_val || m < 0) m=0;
    *(nu_pln+j)=m;
}
}
/* printf("\n    Continue? > "); gets(resp); */
}

```

Appendix AA

JNM Compartmental Model Parameter Summary

Estimated kinetic parameters for 4 compartment model

Tumor	Study	k_1^*	k_2	k_3	k_4	V^*	$k_1 k_4 / (k_2 + k_4)$
	1a	0.072	1.460	0.127	0.051	0.012	0.0058
	1b	0.083	1.808	0.141	0.062	0.016	0.0060
	2	0.023	0.137	0.023	0.013	0.009	0.0036
	3	0.033	0.304	0.009	0.003	0.017	0.0009
	Average	0.053	0.927	0.075	0.032	0.014	0.0040
Brain	Study	k_1^*	k_2	k_3	k_4	V^*	$k_1 k_4 / (k_2 + k_4)$
	1	0.020	0.668	0.036	0.022	0.014	0.0010
	2	0.009	0.228	0.028	0.009	0.006	0.0009
	3	0.014	0.280	0.024	0.007	0.017	0.0011
	Average	0.014	0.392	0.029	0.013	0.012	0.0010

$\gamma_{k4}=0.002$ and $k_6=0.0$ for all cases

* k_1 and V reflect values corrected for partial volume correction

Appendix AB

MATLAB Analytical dY/dk Error Analysis Routine

```

s1:=sqrt(k2*k2+k3*k3+2*k2*k3+4*k3*k4);
a:=2*k5*k3*k2+k5*k2*k2+2*k5*k4*k3+k5*k3*k3+k2*k3*k4+k4*k3*k3;
b:=-k2*k5-k3*k5-k3*k4;
c:=(b+k5*k5)*s1;
c1:=(k1*k5*k5*s1-k1*k3*k5)/c;
c2:=(k1*(a+b*s1)-k1*k3*(k5*(k2+k3)+2*k3*k4-k5*s1))/(2*c);
c3:=(-k1*(a-b*s1)+k1*k3*(k5*(k2+k3)+2*k3*k4-k5*s1))/(2*c);
i1:=int(exp(k5*t)*cp(t),t);
ctd1:=(k1*k5*k5*s1/c)*exp(-k5*t)*i1;
i2:=int(exp(-.5*(s1-k2*k3)*t)*cp(t),t);
ctd2:=(k1*(a+b*s1)/(2*c))*exp(.5*(s1-k2*k3)*t)*i2;
i3:=int(exp(.5*(s1+k2+k3)*t)*cp(t),t);
ctd3:=(-k1*(a-b*s1)/(2*c))*exp(-.5*(s1+k2*k3)*t)*i3;
ctd:=ctd1+ctd2+ctd3;
ctnd1:=-(k1*k3*k5*s1/c)*exp(-k5*t)*i1;
ctnd2:=-(k1*k3*(k5*(k2+k3)+2*k3*k4-k5*s1)/(2*c))*exp(.5*(s1-k2-k3)*t)*i2;
ctnd3:=(k1*k3*(k5*(k2+k3)+2*k3*k4+k5*s1)/(2*c))*exp(-.5*(s1+k2+k3)*t)*i3;
ctnd:=ctnd1+ctnd2+ctnd3;
Y:=ctd+ctnd+V*cp(t);
dYdk1:=diff(Y,k1);
dYdk2:=diff(Y,k2);
dYdk3:=diff(Y,k3);
dYdk4:=diff(Y,k4);
dYdk5:=diff(Y,k5);
dYdV:=diff(Y,V);

```

Vita

Jonathan Dyke was born in Berea, Ohio on July 30, 1968. He attended schools in the public system of Brecksville, Ohio where he graduated from Brecksville High School in June, 1986. He entered Northwest Nazarene College, Nampa, Idaho, during September 1986 where in June 1990, he received the Bachelor of Science in Engineering Physics, Magna Cum Laude. He entered the Master's program in High Energy Physics at Iowa State University, Ames, Iowa in August of 1990, officially receiving the Master's degree in May 1992 where research was accomplished on the D0 experiment at the Fermi National Accelerator Laboratory. He entered the Master's program in Physics at the University of Cincinnati in June of 1992, receiving the degree in June of 1994. In August of 1994 he pursued the Doctorate of Philosophy Degree in Engineering Science with a major in Biomedical Engineering and Medical Imaging. The doctoral degree was received in December of 1997.

He has accepted a Postdoctoral Fellowship in the NMR/MRI Laboratory at the Memorial Sloan Kettering Cancer Center in New York, NY. beginning January 1998.