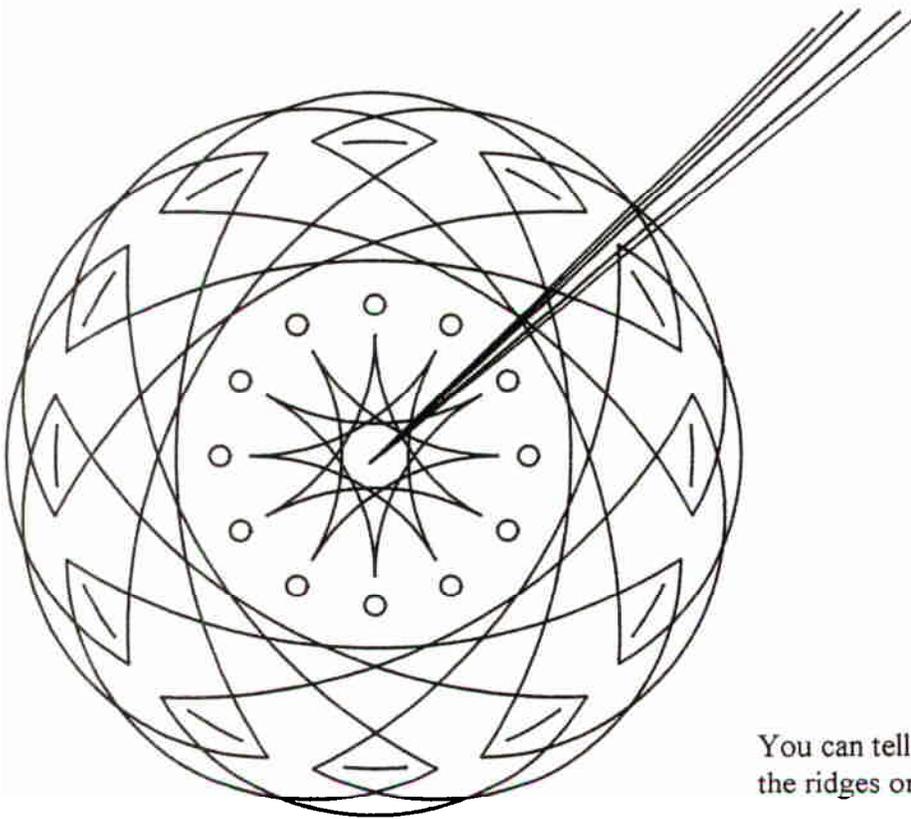


Session V

## Isotope Processing and Automation

Moderators: J.M. Link, J.C. Clark



You can tell the age of a clam by counting the ridges on its shell.



## SESSION V ISOTOPE PROCESSING AND AUTOMATION

Jeanne Link and John Clark Co-Chairs

### Moderator Comments on the Automation Session:

The emphasis in automation presented at this meeting has changed over the last two years. While the work of automating a synthesis remains important, there are more reports of automation of procedures other than the synthesis and there were more feedback sensors reported. For example, metabolite analysis at Brookhaven, radiopharmaceutical dosing at Michigan and pneumatic transport at Philadelphia.

Sensors for radiation detection for production, synthesis and quality control remain of interest, but other sensors are being used. In this meeting sensors for dryness and for liquid levels were presented and discussed. Hopefully this trend should continue and we will see more sensors used to make decisions as to when activity has peaked (TRIUMF) or the target is full (Brookhaven). This use of sensors, if reliable, will improve overall yields and reliability of syntheses.

### What is happening in automation?

Automated non-robotic commercial systems, CTI-Siemens, G. E. Medical Systems, Danatec, and IBA are available for radiochemical synthesis. These units are primarily developed for FDG synthesis and methylations. The number of suppliers of robotic automation has also expanded. However radiochemistry will remain a small part of their market and probably never receive enough attention to have dedicated systems unless supplied by PET companies, i.e. Siemens, General Electric, EBCO and IBA. Zymark, Hudson Robotics, and HP(ORCA), Source for Automation and others, are good choices, but these systems are built to do a few tasks again and again. Typically this task is an analytical test which doesn't have the space restrictions of the radiochemistry hot cell. Use of these robots for radiosynthesis requires either considerable time and effort in the individual radiochemistry lab, or considerable expense to have the company build special modules for radiochemistry. The robotic companies are moving to even more modular systems. Many market the multiple sample xyz cartesian systems which are more useful for biotechnology but less so for radiochemistry. There are robotic units for the pharmaceutical industry, such as that made by Bohdan Automation, but they are far too large for use in a hot cell. One class of automated systems which may prove useful in radiochemistry are the automated pipettors/ diluters marketed by Cetus(Propet); Hamilton (microlab); Packard (Oximate); Gilson (401); and Tecan (RSP5000). In summary, commercial automation, robotic and non-robotic, affords more options than two years ago, but still doesn't fill all the needs of the radiochemistry lab. The future should bring more modular units which are probably less adaptable and perform only one or two functions per module. Systems which are useful in our field are supplied primarily by the accelerator manufacturers.

An interesting source of automation ideas is the field of flow injection analysis. (Analytical Chemistry and Talanta are good journal sources). Flow injection is a technique which



which uses the principle that in very thin tubing, ~0.5 mm ID, liquids pass through the tubing without much mixing between sequential boluses of liquid. This principle has been used to develop multiple injection automated systems for different kinds of chemical analyses. Flow injection is evolving so that rather than using many feet of tubing; syringe pumps and centrally ported multiple position valves are used for distribution of the reagents to effect the chemical reactions for analysis. These systems are similar to those developed in our field, for example the system described by R. Iwata at this meeting. The flow injection literature should be worth perusing for automation ideas.

As discussed by R. Ferrieri at this meeting, supercritical fluid extraction is coming into our field. The use of supercritical CO<sub>2</sub> has the potential to solve a lot of the time, solvent and dilution problems which PET radiochemists face, because CO<sub>2</sub> is easily removable from the analyte or the product in synthesis. Several companies now market supercritical fluid extraction and chromatography systems: Varian, Horizon Technologies, Hamilton, ISCO, Dionex and Zymark. It will be interesting to see if this technology is further developed for use in radiochemistry.

Some of the most exciting advances in automation are going to be in miniature sensors, both optical and nonoptical. Will they be useful for both chemistry and radiochemistry? With regard to optical sensors, the future is here. Hewlett Packard and Hitachi market diode array detectors which have multiple UV and visible diode sensors in a given detector. These instruments will be useful for analytical quality control rather than synthesis. They can monitor multiple wavelengths for a single time point on the effluent of an HPLC. With this information, if the synthesis has appropriate chromophores, the chemist can determine if the product is pure or has contaminants eluting with the product peak. Use of this type of detector at the beginning, middle and end of a product collection, may allow a single preparative chromatography injection to serve as a valid measure of product purity and specific activity. A simpler system, but also potentially useful, is the scanning UV-visible detector marketed by Konik Instruments. Spectra-Tech has developed the "ReactIR system" consisting of an FTIR internal reflectance sensor positioned at the bottom of a reaction vessel. The IR beam is bounced to the internal reflectance sensor and then to the IR sensor positionable below the bottom of a reaction vessel. Rein and Sheriden (Research & Development, Oct. 1991, pp. 100-102) have used this system to monitor phosgene and isocyanate at low concentrations.

Nonoptical chemical sensors are further in the future. One of the sensors which appears promising is the field effect transistor (FET). FETs are tiny. Many fit on a single computer chip and are currently used to monitor chemical emissions in cars. There are many modifications to FETs, but perhaps the most interesting to our field are the ion selective ISFETs. These devices are made to detect single chemical species. On a single chip many of these devices can be used to determine concentrations of many ions. Commercially, UNIFET Incorporated has developed a pH meter which uses a FET as the pH electrode and contains a small reference and temperature sensor. The device is rugged and stable with time. The problem with the device is that the tiny FET is packaged in a unit the same size as conventional pH probes, losing the advantage of miniaturization. Other ISFET devices remain in the future. Problems with interferences, references, electrical drift and fouling of



the FET in solution remain to be solved. It will be interesting to revisit these detectors in a few years.

Another nonoptical chemical sensor which might have application in targetry / radiochemistry automation is the piezoelectric thermal sensor. These sensors are also tiny, generally the size of a coin or smaller, but can be more accessible to the average PET laboratory, because they don't require knowledge of chip fabrication technology, although some are constructed as part of silicon chips. The components are inexpensive. The quartz piezoelectric crystals vibrate at a certain frequency as part of an electrical circuit. This is the basis of most quartz watches. The vibration frequency changes in response to temperature. An extension of this principle is that the crystal resonance also depends on the mass of the crystal. Absorption of mass can be detected as a change in frequency. This is the basis of the Surface Acoustical Wave sensor (SAW). The surface of this crystal is chemically modified to contain a sensor which absorbs either a specific chemical or many types of chemicals. Their sensitivity with 1994 technology is about 10 ppm for individual compounds. The combination of these two properties has been used to detect specific gases in air. A commercial SAW system is available from ING (-301 Vapor sensor). This field of research is just beginning, but ppb sensitivities should be possible. FET and SAW sensors will not work inside the cyclotron vault because they are semiconductor based. In the vault, optical devices should be best because the detector signal can be sent through fiberoptics to electronics outside the vault. An article which reviews most of these sensors is: Microfabricated nonoptical chemical sensors. J. N. Zemel. Rev. Sci. Instrum. 61(6). June 1990, pp. 1579-1606. Miniature sensors are showing up in many journals, but Analytical Chemistry is also a good source of these articles.

An area of automation which was discussed in Switzerland (Targetry IV) is the lack of cross compatibility of software and different instrument systems. There has been some progress since that meeting. First, more than half of the chromatography-related lab instrument companies worldwide have agreed to adopt the Chromatography Data Communications Standard issued in June 1992. According to this standard, complying equipment will be able to "transfer data from one vendors chromatography data system to another, to be able to transfer data from a chromatography data system to third party commercial software application and to transfer data from a chromatography data system to individual user-chosen targets"(ie. computers or instruments). Systems that comply with this standard are DOS, DOS - Windows, VMS, UNIX, GEM, Macintosh and OS/2. The standard can be used to transfer data between instrument systems, LIMS, spreadsheets, statistics applications and archives. There are 69 key words divide into five information classes covering administration, sample description, detection method, raw data and peak processing results. The vehicle the standard employs is netCDF, a software utility tool that transfers the data. "Net CDF provides the simple commands and internal algorithms to make the format translations between the instrument systems involved in the transfer of data". (LC-GC, Volume 11(9) pp. 657-666, Sept, 1993). This should make interfacing systems much easier.

Related to this is the automation of data management in the laboratory. Regulatory work in the radiopharmacy is increasing and there is reason to believe that good laboratory manufacturing practices will be required to be implemented in many PET radiochemistry labs.



Laboratory information management systems (LIMS) are part of this implementation. There are several commercial suppliers: FISIONS, Beckman, and Harley Systems ("Matrix") for DOS, and Beckman and BBM for Vax and Unix. The usefulness of these systems in the radiochemistry lab has still to be tested.

While there are exciting things happening in sensor technology the use of sensors in synthesis and their effect on reliability is a point of disagreement between the comoderators. John Clark believes that sensors may be useful for measuring dryness and for monitoring radioactivity but the use of other sensors in synthesis is likely to lead to more problems than advantages. The simpler the system, the more robust. Jeanne Link agrees that a system should be designed to be as simple as practical but she argues that the information provided by sensors can prevent failures and that sensors can be reliable. It will be interesting to see what the future brings. One thing the comoderators agreed on is that there are still lots of areas for improvement. Now that FDG appears to be automated and fairly routine, one of the most glaring needs in radiochemistry is an automated, nonliquid, synthesis of [C-11]CH<sub>3</sub>I. We look forward to further progress at the next meeting.



## Detectors and Transducers for Target Operation and Automated P.E.T. Chemistry

S. K. Zeisler, T. J. Ruth, M. P. Rektor, G. A. Gschwandtner  
TRIUMF, 4004 Wesbrook Mall, Vancouver, B.C., Canada V6T 2A3

### Abstract

Remote target operation as well as automated PET chemistry syntheses generally require feedback from the target or synthesis module to the computer control unit. Transducers such as pressure sensors and conductivity probes can be used to indicate the filling status of gas or liquid targets. Many radiopharmaceutical preparations involve the transfer of liquids containing radioactivity and the evaporation of solvents. Our goal was the automation of a production system for [ $^{18}\text{F}$ ]-FDG consisting of a low-volume high pressure target and a synthesis module based on the TBA- $\text{HCO}_3$  method by means of three recently developed devices:

- a non-invasive bolus detector to ensure complete filling of the water target,
- a small photodiode radiation detector to monitor trapping of the  $^{18}\text{F}$ - fluoride on the ion exchange resin and its elution from the column,
- a thermistor probe to determine the endpoint of solvent evaporations from the reaction vessel.

The detectors deliver a signal suitable for processing in the Optomux<sup>TM</sup> control system. They show excellent reliability and have been successfully tested in [ $^{18}\text{F}$ ]-FDG, [ $^{18}\text{F}$ ]-FDOPA, and [ $^{13}\text{N}$ ]- $\text{NH}_3$  production.

### 1 Introduction

In automated syntheses of radiopharmaceuticals labelled with positron emitters compact sensors and transducers are widely used as part of a process control system. Many commercial instruments such as radiation detectors based on small volume geiger tubes, scintillation or semiconductor detectors are often considered to be either too large or too expensive which can become a problem if an apparatus needs to be equipped with several detectors. Therefore a number of simple, efficient, and reliable sensors for monitoring different process parameters have been developed over the last few years.

It is recognized that there are two main reasons for automating a radiochemical synthesis, to reduce radiation exposure to personnel performing the synthesis and to increase the reliability of the procedure. While there are a number of ways of reducing radiation exposure to personnel handling short-lived nuclides, the most practical means for synthesizing P.E.T. radiopharmaceuticals involves some combination of hot cells



with a system composed of solenoid valves remotely controlled either by an operator or with a computer (PLC or PC) performing the control or having the total synthesis controlled by robotics.

Making use of remote control operation where the chemist is deciding when to activate a valve or proceed to the next step is prone to operator error. The successful application of computer control is dependent on feedback loops that can be used to check the condition of the process and for decision making. Many parameters such as temperature, pressure, vacuum, gas and liquid flow need to be monitored to provide data for process control. All detectors and transducers for synthesis modules have to give a reliable output signal to eliminate errors of the control system. They should be kept as small as possible to minimize space requirements.

Every radiopharmaceutical synthesis – like the one for [ $^{18}\text{F}$ ]-FDG – starts with the production of the radioisotope. The activity produced has to be transferred from the target to the synthesis unit in which the labelling of the desired biomolecule is to be performed. The labelled compound often undergoes several purification reactions before it is finally worked up and prepared for application. All these steps can be automated, provided that suitable sensors to ensure continuous control of the process are available.

In the following we briefly present three detectors especially designed for automation of radiopharmaceutical syntheses. Since the most part of the extensive tests has been performed with a module for FDG preparation, we have chosen this synthesis as an example.

## 2 Bolus Detector

A titanium target with an internal volume of 300  $\mu\text{L}$  is used to produce [ $^{18}\text{F}$ ]- $\text{F}^-$  from 95% enriched  $^{18}\text{O}\text{-H}_2\text{O}$ . The target chamber is filled from the hot lab (distance approx. 30 m) by injecting 750  $\mu\text{L}$  of enriched water into a 1/16" polypropylene tube connected to the lower solenoid valve on the target. The water bolus can be pushed forward with helium pressure.

To ensure complete filling of the target a special bolus detector is located on top of the upper solenoid valve that closes the target chamber. It consists mainly of a small incandescent lamp (6.3 V, 40 mA) and a photoconductive cell (NSC-6140; Silonex Corp., Montreal) placed opposite to one another in an aluminum block that holds the polypropylene tube. When the water arrives in the upper tube after having filled the target from the bottom the resistance of the photoconductive cell drops due to higher incidence of light from the incandescent lamp. The signal can trigger switches in the control system to stop the filling procedure.

Compared to a conductivity probe the detector described is non-invasive, avoiding possible contamination of the target solution with trace metals. It also eliminates the need of a high pressure feed-through, and it works with aqueous solutions as well as non-conducting organic solvents which is important if the target system needs to be cleaned with ethanol or acetone. Since the detector head contains no semiconductors it is not destroyed in fields of particle radiation.



Fig. 1 shows the circuit diagram, Fig. 2 the location of the bolus detector in the high pressure target system. Fig. 3 gives a sketch of the detector head.

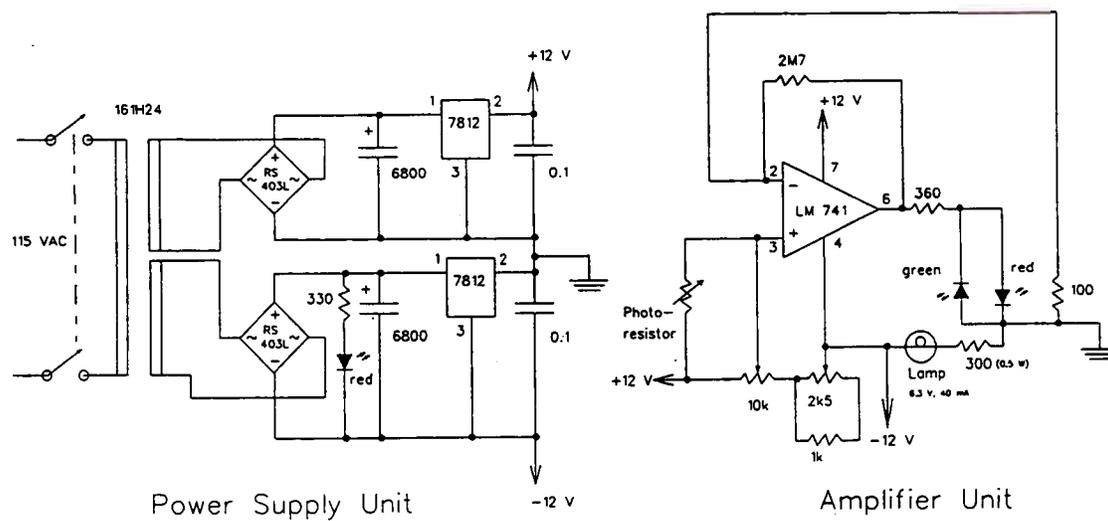


Fig. 1: Bolus Detector Circuit Diagram

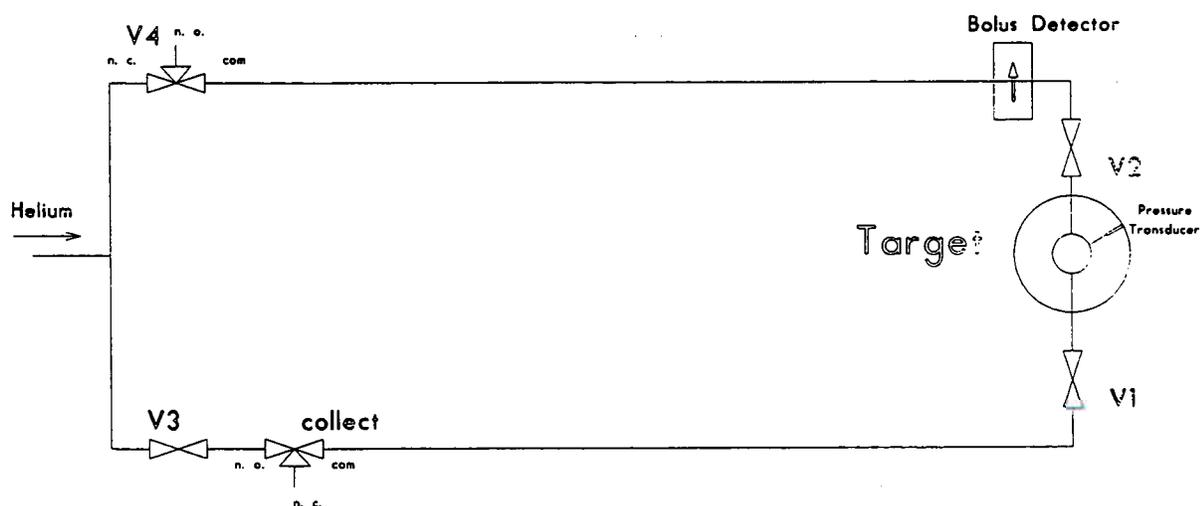


Fig. 2: Location of the Bolus Detector in the High Pressure Target System

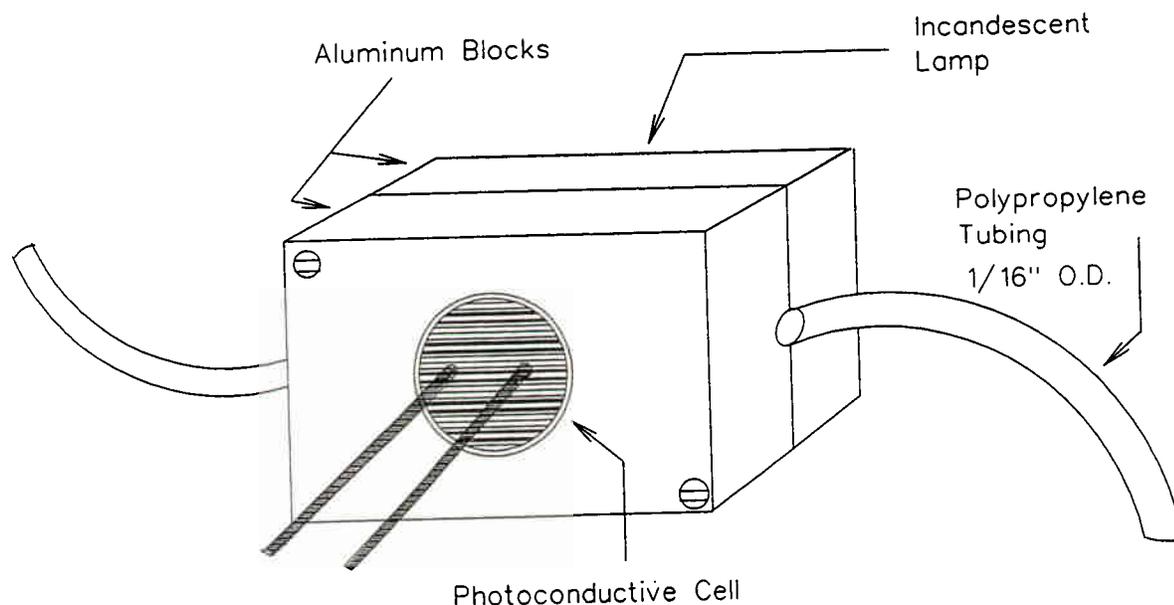


Fig. 3: Bolus Detector with Photoconductive Cell

### 3 Photodiode Radiation Detector

After the irradiation the target solution containing  $^{18}\text{F}$ -fluoride is transferred back to the lab and pushed through an anion exchange column (10 mg BIO-RAD AG 1X8, 100-200 mesh,  $\text{HCO}_3^-$  form) to collect the activity. In order to monitor the trapping a radiation detector is placed close to the ion exchanger. It is composed of a large area photodiode (S2386-8k; Hamamatsu Corp.) and a dual fet op-amp circuit, both fitting in a cylindrical aluminum case (60 mm length, 19 mm o. d.). The amplifier requires only a low supply voltage of  $\pm 15$  VDC provided by the computer control system, and it delivers a signal suitable for direct processing and display in arbitrary units or, after calibration, in mCi. The photodiode detector shows linear response in the range of one to several hundred mCi and is much less expensive than many other commercially available systems (cost per unit less than \$100).

The stability of the output signal is affected by temperature. We assume that it is a combination of the effect on the dark current of the photodiode and the performance of the op-amp circuit. Fig. 4 presents a picture of the photodiode detector with the aluminum case removed. Fig. 5 shows the amplifier circuit diagram.

### 4 Miniature Thermistor Sensor

In nucleophilic replacement reactions the radioactive fluorine is eluted from the ion exchange column with 1 mL of a 93 mM solution of tetrabutylammonium bicarbonate in acetonitrile/water (80:20) into the reaction vessel. Since the labelling must be performed in a non-aqueous solvent, the liquid is evaporated to dryness by applying vacuum and heating the reaction vessel to  $50^\circ\text{C}$ . To remove traces of water, the evaporation is repeated with a small amount of water-free acetonitrile.

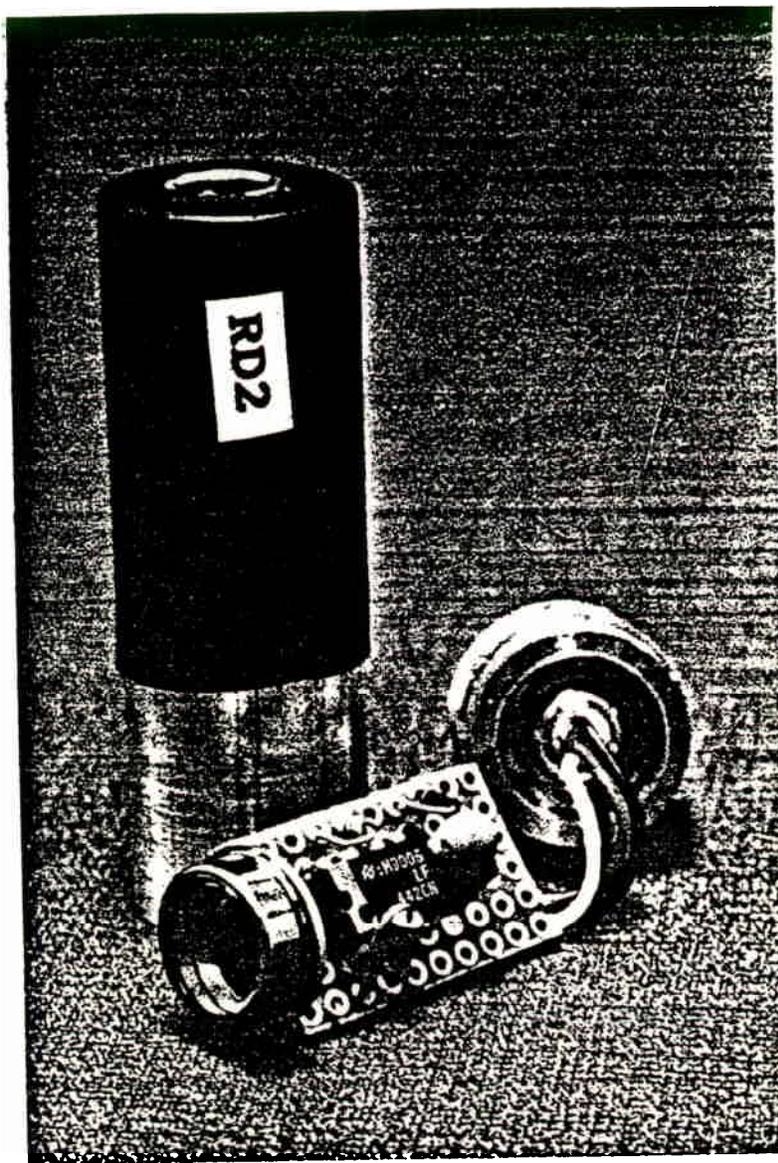


Fig. 4: Photodiode Radiation Detector with Protective Sleeve Removed

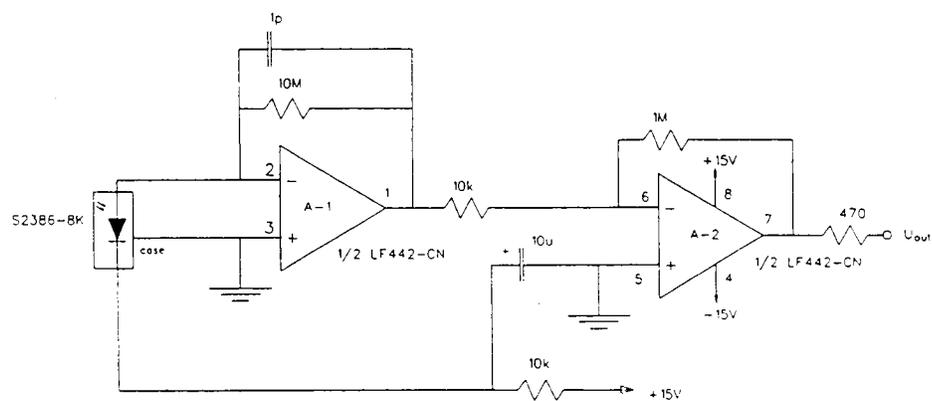


Fig. 5: Amplifier Circuit Diagram

The endpoint of the evaporation steps can be reliably monitored by means of a thermistor probe placed on the bottom of the tapered reaction vessel. While the solution boils the thermistor delivers a constant signal according to the temperature of the solution. As soon as the evaporation is finished, the temperature inside the vial rises quickly, resulting in a sudden change of resistance in the sensor. This signal is decoded in the Optomux control system and is utilized to terminate the procedure by switching off the heater and closing the vacuum line.

The thermistor sensor is based on a simple two wire resistance measurement, and it delivers a high output signal. It is very small (o. d. 1.1 mm) and shows a fast response which can be essential if the substance in the reaction vial is instable at higher temperature.

Fig. 6 gives an example of a typical temperature curve recorded with the miniature thermistor bead (112-503JAJ-B01; Fenwal Electronics) which had been inserted into a 1/16" teflon tube and sealed (cf. Fig. 7). The circuit diagram is given in Fig. 8.

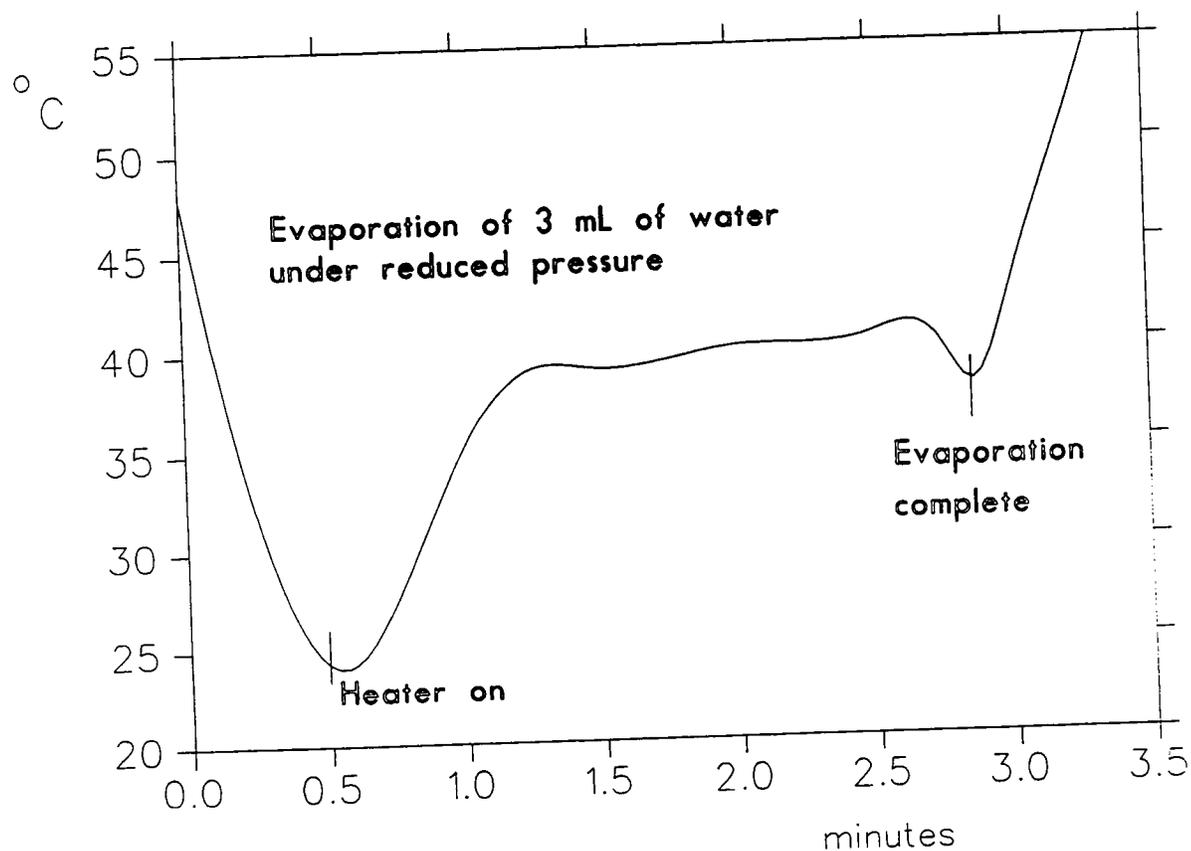


Fig. 6: Evaporation of 3 mL of water: temperature curve

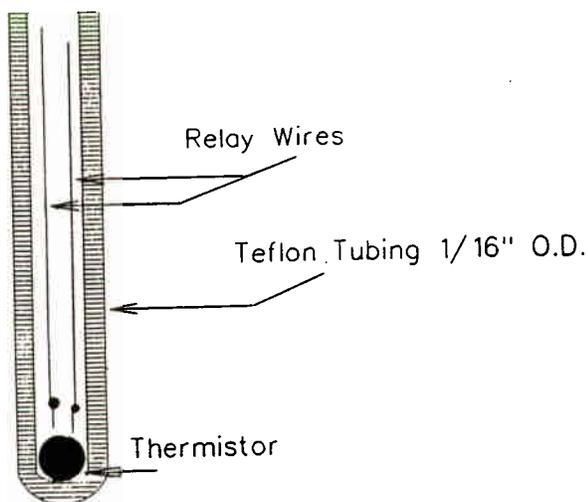


Fig. 7: Teflon Coated Thermistor Probe (Sketch)

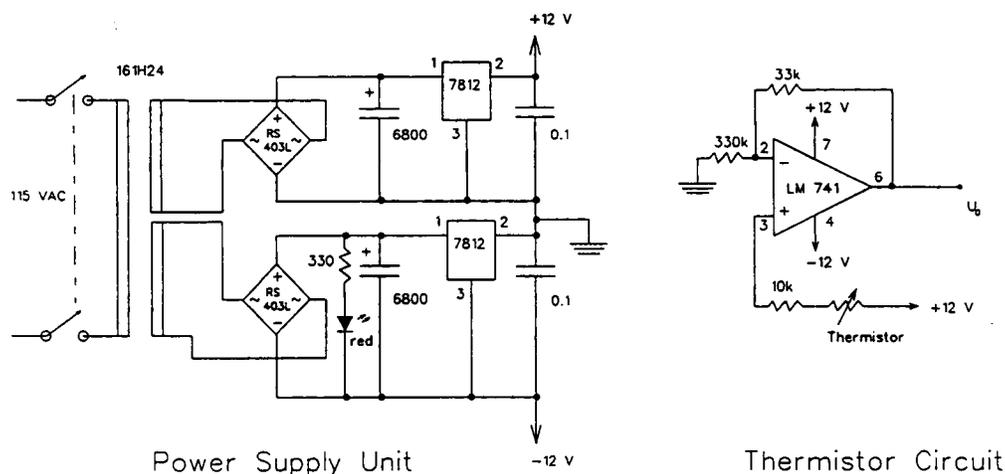


Fig. 8: Op-Amp Circuit with Thermistor Connected to Non-Inverting Input

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## Detectors and Transducers for Target Operation and Automated P.E.T.

Chemistry

S.K. Zeisler, T.J. Ruth, M.P. Rektor, G. A. Gschwandtner - Triumph, B.C.,  
Canada

Discussion of the target filling sensor:

Q: J Clark: How far is the 741 circuit for the sensor from the target?

A: The circuit is located in our lab away from the detector at the target.

Q: How does this detector work when you do not have a bolus of liquid in the tubing but drops are passing by the detector?

A: Then it always switches back and forth between the red and green light emitting diodes (l.e.d.). The Triumph group triggers the switches for the valves only when the red l.e.d. remains on. That means when the tube at the target is full.

Q: Does this detector respond quickly?

A: Yes, the detector response is very fast. The signal changes immediately when the drop passes through the tubing between the photoconductive cell and the incandescent lamp.

Q: B. Weiland: What is the dead volume of your solenoid valve?

A: The dead volume of the solenoid valve is approximately 150 microliters. It is rather large compared to the 300 microliters in the target chamber, but the TRIUMF group tries to recycle the water by passing the target solution through a small ion exchange column that contains only 10 milligrams of resin.

Q: J.-L. Morelle asked if this detector is radiation resistant?

A: Yes, the Triumph group believes that it is radiation resistant. They have placed this detector immediately on top of the target. In the CP42 cyclotron vault, the detector experiences all kinds of radiation, neutrons during production and high gamma fields, and the detector has not failed. The detector contains only the incandescent lamp and the photoresistor in the vault, it contains no semiconductors and, therefore, it is very durable.

Q: J. Clark asked what is the active element in the photoresistor? And what material is it based on?

A: I think it is Cd selenide, or Cd sulfide.

J. Clark commented, that Cd selenide and Cd sulfide are in fact themselves radiation detectors; they were used many years ago. Their resistance alters when exposed to radiation, but they return to normal. You have to use this sensor when the beam is off.

Q: At what pressure do you operate your target?

A: The target described here is rated for pressures up to 250 psi. We want to modify that to run higher currents; and our new target will be run at between 500 and 600 psi.

Q: P. Salvatore: What kind of valves are you using to control filling of the target, and what is their rated psi?

A: The valves are General Valves, Series 9. These are rated for 250 psi, but they are also available rated for 500 and 1250 psi.

Q: R. Ferrieri: I missed the placement where the detector might be relative to the load lines of the target. Is your detector built into the high pressure end of the target assembly? If you intend to operate the target at higher pressures, what is the pressure limitation of the plastic tubing, ie. the burst pressure? At 250 pounds of pressure, I think you are probably at the burst pressure for polyethylene. Will it sustain much higher pressures?

A: T Ruth: This is not a problem because the sensor is operated beyond the valves, in the low pressure part of the system.

C: John Clark had a comment. "I notice that the valves that you showed in the picture are in fact different than the valves that Karl Erdman has on the demonstration target."

A: Yes, S. Zeisler presented a second version, Karl Erdman showed a yet newer version of this sensor system.

C: Continuing comment from J. Clark: Anybody that is interested in a very small volume straight through, one-way valves, two port valves, should have a look at Karl Erdman's prototype target down in the commercial exhibit or contact K. Erdman at EBCO.

Discussion of the thermistor probe for sensing dryness:

Q: J. Clark: In my experience, trying to seal teflon tubing is virtually impossible. How do you actually get the teflon to hermetically seal at the end?

A: We have a rather brutal method for that. We first insert the thermistor, then we put it over an electric fan, melt the teflon, and squeeze it with pliers.

C: J. Clark comment: One thing worries me about all of these sensors. If you input their signal into computers and the sensor actually improves the reliability of the synthesis, that's great; but how many of these sensors actually give you false positives, and ruin the synthesis?

Discussion of the photodiode for detecting radioactivity:

Q: J. Clark: Does this detector measure betas or gammas or mixed flux?

A: We are measuring gamma radiation only.

Q: What is the temperature stability of this detector?

A: Triumf has found that the detector is somewhat unstable with changing temperature. The output signal rises when the temperature rises. This effect is, I think, a combination of the effect on the photodiode itself and also on the performance of the amplifier. For our process control the signal is good enough to monitor the reaction, whether the activity arrives, for example, or not. We use it for monitoring the activity trapped on the anion exchange resin while we collect the fluoride-18, and to decide if it is or is not worth proceeding to the next step.

Q: Jeanne Link: We have made S. Zeisler's photodiode detector, and we are going to use it for monitoring our radiosyntheses. It is easy and inexpensive to build. We have collected data from the decay of a C-11 source and we have a large "dark current" which gives a non-linear signal. The "dark current" is very stable and when we subtract this "dark current" from the signal the data become linear down to about 2 mCi. What kind of a dark current do you find in your detectors at TRIUMF and have you found ways to reduce the dark current besides using coaxial cable and providing a light tight seal?

A: We found that circuit layout is very essential for that purpose. We are talking about an input current of nanoamps and a bad spot when you solder can change the signal completely. We have dark currents, depending on the circuit layout, from 30 to approximately 180 millivolts.

Q: Jeanne Link: I have another question. Dr. Plascjak, from NIH has a detector that he has developed. He has taken a similar diode but added a scintillator. What are the differences between these two detectors?

A: Dr. Plascjak: My unit is similar to the unit being advertised by Bioscan. My detector is different in that it is being operated in the photovoltaic mode and its not reverse biased. The pin diode is actually operating in a manner similar to an actual solar cell and you are turning the light from the scintillator into a very small current that you are then measuring. We have found the unit to be extremely robust and inexpensive. We use 1 cm<sup>3</sup> of cadmium tungstate. This scintillator has about 40 times the light output of sodium iodide and is not hygroscopic. They are very easy to build.

Comment: J. Link: Dr. Plascjak has preprints which describe his circuit for those interested in building one. Bioscan has demonstrated their photodiode based detectors at this meeting. Their detectors appear to have very little noise. This is an option if one doesn't make their own detectors. With regard to the TRIUMF detector, we have also found it to be thermally unstable, but when we put a large thermal shield, ie. a metal mass, around the detector the instability is greatly reduced.

C: Comment from M. Berridge: There was some talk of detectors like this at the last workshop and even a little bit in Vancouver. We have been using one of these types of detectors for quite some time. We have managed to test it up to 5 curies and have found that it was quite linear over the entire range. These detectors work well.

C. McKinney: Also on the photodiode radiation detectors, I have a manuscript in preparation right now using a Hamamatsu 1723 large area photodiode. In the pulse mode rather than in the DC current mode. It uses an AMPTEIC A225 charge amplifier that has about .83 microvolts per electron gain, a simple comparator circuit, and a hybrid frequency to voltage converter, and a voltmeter to round out the circuitry. It has about 5 percent linearity over six decades. The detector itself fits into a 1 by 1 by 0.5 inch housing. As I said, that manuscript is in preparation and hopefully it will be out shortly. So one more alternative to some already very nice radiation detectors.

Q: J. Clark: Is that one gamma sensitive? Or beta and gamma?

A: C. McKinney: I've looked only at gamma and I don't think that below 100 keV you see much but gamma radiation detection. Obviously, it was designed for 511 keV gamma

operation, but I have taken it I believe it was with I-125 and its low energy gamma line.

Q: J. Clark: Could I just ask a little question to all those people using pin diodes? Is the dark current related to how well you can make the little circuit board and maintain it in good leakage conditions, ie. is it a matter of encapsulation and keeping it dry? When you are measuring nanoamps, if you have a small leakage on the circuit board you will have trouble.

A: S. Zeisler: No, I don't think so. I am not quite sure, but we have never experienced that.

Q: J. Clark further commented on detectors made by Hanu Sipila regarding leakages on circuit boards. Turku has had a lot of experience using very high gain op-amps on circuit boards and keeping leakage currents down. They use teflon circuit boards, not PC boards, but one with a teflon backing. Providing they put those little boards into cans that can be really sealed, and dry them out, then a lot of their dark current problems are solved.

Q: Comment from Dave Alexoff about high gain op-amps. We have had about five years experience with a particular op-amp. It's a standard op-amp from Analog Devices. It has about 250 femptoamp of input bias current. We were careful, it was an etched board, and we used clean teflon standoffs on the feedback resistor, but didn't use a teflon backed material for the printed circuit board. The teflon standoffs on the feedback resistor were important and the layout used was that from the book. Analog Devices gives a layout to sort of minimize leakage currents and problems. It has worked well for the Brookhaven group.

Q: J.-L. Morelle: Regarding the generic sensitivity necessary to design a general purpose small detector for positron emission tomography, for instance. We would like to have a sensor that deals with all the possible locations in a PET system where we would like to monitor activity. Of course there are the high activity concentrations e.g. at the output of the water target. but that's not the only place where we would like to measure activity. We would also like to measure activity on gas lines where the activity concentration is far lower, roughly about three orders of magnitude. The ideal sensor would be the one that would have a dynamic range over, let's say five orders of magnitude. I was wondering if anybody had an idea for a sensor that could do that? Besides the usual light detection sensors.

A: J. Nickles: This still uses light, but I have had success with wide-range, about five decades, activity detectors that we build out of Hamamatsu HC 120 CP's. It's a 1/2 inch side on Hamamatsu phototube that's powered by a Cockroft-Walton, and followed by a little current amp, all fit into a box that is about half the size of a package of cigarettes. With this you can detect activity from microCuries up to any high activity.

C: J.-L. Morelle had a warning about an experience J. Nickles had a couple years ago. He asked a student to make a detector for detecting high activity concentrations, and he thought, (and just to tell you, don't try it) of measuring the current coming from the positrons. It worked, but it was really a bad system. First the amplifiers were very sensitive, and second, he used a plastic tube to contain the positrons, because it was electrically insulated, but some of the positrons stop in the insulators. At some time the charges accumulate to the point where they suddenly discharge and it results in an unreadable signal.

Comment from J. Link: I used to think that you needed five orders of magnitude, for a single radioactivity detector but I no longer think that is true. Rarely do our reactions happen in one pot from target to end so there are very few places where we need to be able to detect five orders of magnitude of activity in one location. The use of several detectors with different sensitivities placed in different locations throughout the radioactivity system can provide more information than a single detector particularly if the detectors are insensitive to activity any distance away. This is an advantage of these photodiode/pin detectors. They have a small volume of interaction with the radiation and because of the inverse square law, they are insensitive to most radiation even one foot away from the detector.

## A SIMPLE LIQUID DETECTOR for RADIOPHARMACEUTICAL PROCESSING SYSTEMS.

D.L. Alexoff, K. Hallaba, D. Schlyer, and R. Ferrieri.  
Department of Chemistry,  
Brookhaven National Laboratory, Upton, New York , USA.

### INTRODUCTION

Sensing the presence of liquids in tubing and vessels in radiochemical processing equipment provides information important to the remote or automatic control of the production of clinical doses of radiopharmaceuticals. Although modern commercial automated radiopharmaceutical synthesis machines do not usually include liquid presence as a measured process variable, earlier more complex automated synthesis devices did (e.g., Iwata, *et al.* *IJARI* **35**, 1984); and the inclusion of such feedback can increase system reliability and simplify trouble-shooting tasks carried out by computer software or human operators.

Commercial liquid level detectors are often designed for large-scale industrial processes and are therefore too large or expensive to be useful in many radiochemical hardware systems. An inexpensive miniature optical liquid detector originally by Kramer and Fuchs (*Byte*, Jan., 1986 pg. 263) has been duplicated here for use in monitoring the presence of liquids in teflon tubing (1/16 in. O.D.) in our enriched oxygen-18 water recovery system.

### DESCRIPTION OF DETECTOR

The detector is based on an inexpensive infra-red (910 nm) diode / phototransistor pair purchased from Radio Shack. A custom printed circuit board (1 3/16 in. x 1 3/4 in.) was fabricated to hold the associated electronic hardware inside a small Pomona box (model 2417). The detector's electronic design follows closely the original comparator circuit illustrated by Kramer and Fuchs (ref.) with the exception of the addition of a positive feedback loop to the comparator to provide 10 mV hysteresis. This hysteresis insures a voltage transition suitable for digital interfacing and reduces the probability of detector recognition of fine bubbles passing quickly through a tube at the end of a liquid bolus. The comparator's output is used to drive an open-collector circuit that in turn drives an external light emitting diode (LED) or load resistor for a TTL compatible signal suitable for computer interfacing. Figure 1 illustrates the circuitry contained in the detector's Pomona box.

The diode / phototransistor pair were epoxied to opposite ends of a standard low-pressure 1/4-28 cross that was drilled out to allow a 1/16 tube to pass through the remaining two ports of the cross. This design is similar to the custom block design of Kramer and Fuchs.

### RESULTS and DISCUSSION

The detector's response was characterized using several different liquids. The results of

these experiments are summarized in Table 1. The detector voltages in Table 1 were measured at the test point indicated in Figure 1. The signal voltage in Table 1, derived by subtracting the detector's average output voltage for air from each of the detector's liquid measurements, is used to set the comparator's threshold for indicating a full tube. The detector's sensitivity to the nature of the liquid inside the tube seemed to correlate with refractive index of the liquid as illustrated in Figure 2. This strong dependence on the liquid's refractive index may be explained in part by the following simplified discussion on how the detector operates.

**Table 1.**

medium	ref. index	output (mV)	std.dev.	N	signal (mV)
air	1.0	392	7.7	11	0
methenol	1.326	625	2.1	3	233
water	1.333	612	1.0	3	220
acetone	1.357	576	1.5	3	184
hexane	1.372	553	2.5	3	161
THF	1.404	527	1.2	3	135
cyclohexane	1.443	513	2.7	3	121
CCl <sub>4</sub>	1.459	491	1.5	3	99
toluene	1.494	471	3.1	3	79

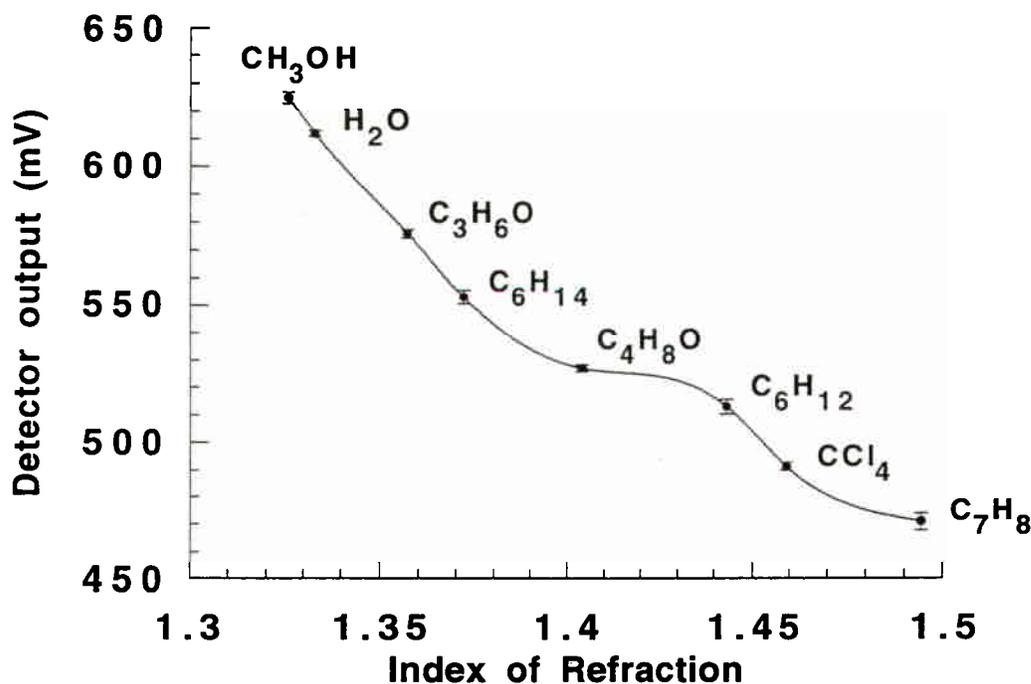


Figure 1. Detector response to liquid presence.

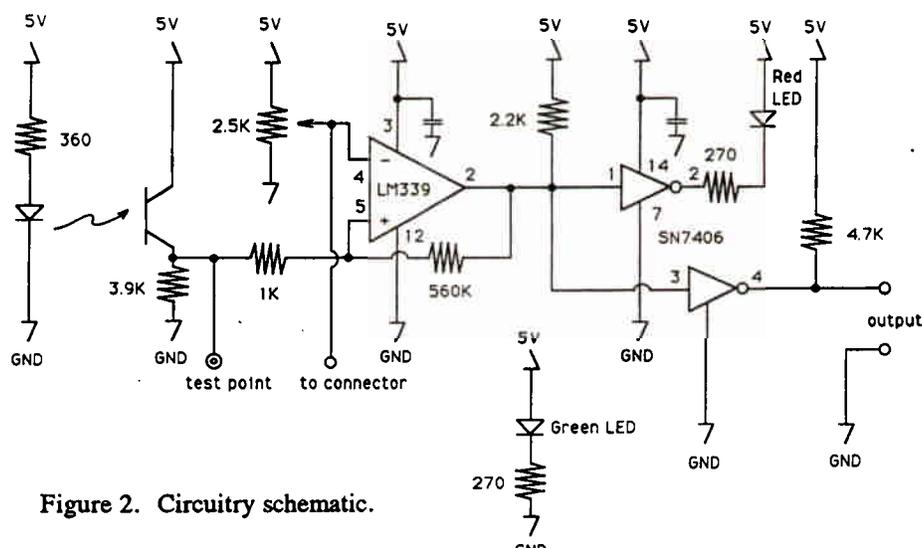


Figure 2. Circuitry schematic.

Infrared light emitted from the photodiode must travel through the wall of the teflon tube, through the medium occupying the space inside the tube, and back through the teflon tube again to be detected. When the refractive index of the medium inside the tube is close to the refractive index of the tube, less light is internally reflected inside the tube and is instead refracted into the liquid. Since the critical angle for internal reflection inside the teflon tube increases as the refractive index of the space inside the tube increases, it is expected that more incident light will pass through the tube when liquids are present.

As the refractive index of the liquid increases beyond the value for teflon (approximately 1.35 for yellow light), internal reflection into the liquid at the exiting liquid/tube interface is possible, and light output to the phototransistor is decreased. The critical angle for internal reflection of light into the teflon tube at the exiting tube/air interface does not change for the cases of air and liquid inside the tube. Therefore it would be expected that liquids with a refractive index close to teflon, at 910 nm, would give a maximum detector output.

This detector has been in use for the past six years in our laboratory. Five of these years the detector was used inside our shielded "hot cells" where our enriched oxygen-18 target was unloaded. The detector was used to indicate when the flow of a bolus of target water or carbonate solution passing through our  $^{18}\text{F}$ -fluoride recovery resin was completed. The detector operated without failure under these conditions. Since installation of our  $^{18}\text{O}$ -water recovery system into our cyclotron vault, a rapid decrease in sensitivity of the diode/phototransistor assembly has been observed. Detector sensitivity - measured as a voltage at the printed circuit board test point - decreased to 50% of its initial value after 4 months of routine operation. During this time the detector resided inside a lead box on the floor next to the cyclotron's target changer.

## CONCLUSION

Because of the detector's lack of radiation hardness, it is not a good candidate for monitoring vault-related liquid operations such as target loading and unloading. It is,

however, suitable for monitoring the presence of liquids in tubing in radiochemical apparatus located away from or shielded from cyclotron vault operations, and may be easily incorporated into many automated synthesis devices. The very reliable performance of this type of sensor under normal operating conditions (i.e. away from high radiation fields and/or high neutron fluxes) allows feedback control of the passage of liquids through tubing.

*Acknowledgement* - This research was carried out at Brookhaven National Laboratory under contract DE-ACO2-76CH00016 with the U.S. Department of Energy and supported by its Office of Health and Environmental Research, and also supported by the National Institutes of Health, Grant NS-15380.

Detector for Recovery of enriched [O-18]-H<sub>2</sub>O. David Alexoff:Brookhaven National Lab

Discussion of Dave Alexoff's IR detector for recovery of [O-18]H<sub>2</sub>O:

Q: Jeanne Link: With the amount of adjusting of the sensitivity and signal change due to drift, how does a drop of liquid, instead of a bolus affect the signal?

A: D. Alexoff: I haven't seen like a false positive or something, where a drop gave me a full tube indication. You will see as a bolus breaks up, some flickering. I put a little hysteresis which may help eliminate some of that, because if the change isn't great enough, it won't even be detected. But I haven't seen a problem with drops giving a false full. You will see some flickering, if you are driving some other circuit directly with this. This was used in a manual remote system, a remote system where a computer monitored it, just for an operator to observe. But if you were driving something directly, you are going to get some transition as the end of the bolus goes, so you have to be aware of that. But it seems pretty immune to a false, a drop, hanging up in there and giving you a full signal.

## REMOTE SENSING OF LIQUID WATER TARGET OPERATIONS

R.A. Ferrieri\*, D.L. Alexoff and D.J. Schlyer  
Brookhaven National Laboratory, Department of Chemistry,  
Upton, New York, 11973-5000 USA.

### INTRODUCTION

One of the key considerations in the design of automated liquid water target systems for reliable  $^{18}\text{F}$  production is the inclusion of adequate sensing devices for remote feedback of individual process operation status. This information allows for smooth transition between process operations that ultimately avoids production inconveniences such as target damage due to empty target irradiation, or loss of  $^{18}\text{F}$  activity due to incomplete recovery of the target contents after irradiation. Such inconveniences can not only result in loss of PET runs, or at least delays in schedule, but result in an increase in the radiation exposure of production personnel as well. The process operations needed to generate, extract and deliver  $^{18}\text{F}$  to the Hot Lab for subsequent chemistry are not really complex. These involve configuring target valves for access during loading of enriched water, filling the target with water, reconfiguring target valves so that it is sealed during irradiation, and finally emptying the target contents after irradiation.

At the lowest level of remote sensing of these operations is the act of determining whether target valves are actually in their correct configuration for a specific step. Electric feedback of whether a solenoid valve is energized or not is entirely inappropriate in these instances because such valves may fail, and remain either opened, or closed, while yielding false feedback to the monitor. Physical displacement valves such as HPLC injector valves are better suited to this task because feedback of the valves configuration can be accomplished through closure of electric contacts on the valves stem.

Sensing the filling or emptying status of the target is perhaps the most crucial feedback for reliable target performance. One must ensure that the entire charge of water has been loaded into the target confines. Irradiation of partially filled targets can be just as devastating as irradiation of empty targets. Likewise, one must ensure that the entire contents of the target has been emptied after irradiation. This is important not only to maximize production levels of radioisotope, but also to minimize losses of enriched water during subsequent processing.

Sensing the presence, or absence, of liquid water can be accomplished by measuring some physical property of the substance in that phase. For example, we demonstrated (Ferrieri R.A. et al., 1992) that 5 ppm levels of metal cations in water will yield a specific resistance of 0.15 MW. This level is more than adequate to detect a response using commercial conductivity meters. Conductivity probes can be easily installed into the high pressure componentry of the target plumbing using standard HPLC fittings.

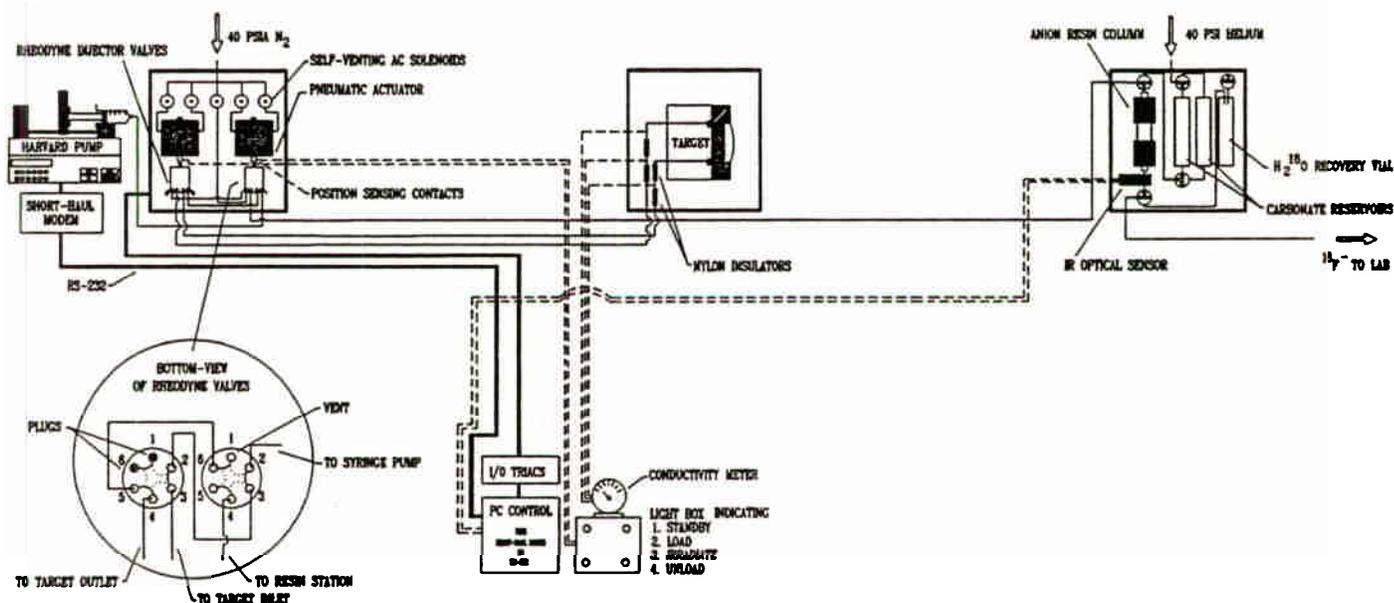
Likewise, refractive index is another property of water that can be harnessed for sensing the liquid's presence (Alexoff D.L. and Hallaba K., 1993). For example, the amount of light transmitted from a source through a transparent cell or tube will vary depending on whether the cell or tube is filled with liquid. This later approach possesses the advantage of being non-invasive in detection. Unfortunately, it is not entirely amenable to operations requiring high

pressure components, and therefore, is limited in use to operations involving manipulation of liquids downstream from the high pressure target.

## $H_2^{18}O$ WATER TARGET SYSTEM DESCRIPTION

The Figure shows a complete schematic of the high pressure liquid water target system that is now in operation on the BNL JSW beamline for routine production of  $^{18}F$ . The target is constructed of silver, and is of a standard keyhole design possessing an active volume of 2.5 mL, and two ports for manipulating the water charge. All operations for configuring target valves, loading the target, and unloading the target are controlled by a PC computer either through an RS-232 interface that couples to a short-haul modem, or through I/O triacs for powering AC solenoids. The computer is located in the cyclotron control room.

Target loading is carried out using an infusion syringe pump (Harvard Apparatus, Inc., Model 22). The pump is connected to the target through two 6-port high-pressure HPLC valves (Rheodyne Model 7010) that are remotely operated using pneumatic actuators. These valves configure the target for receiving water from the pump, for high-pressure irradiation, and for unloading the water charge to the vault located resin/recovery station. In the event of line rupture in the  $N_2$  supply driving the pneumatic actuators, the switching valves remain in their last command state thus avoiding a catastrophic occurrence. Electrical feedback is made to a light box via contact switches located on the valve stems indicating valve status at all times during target operation.



All connections involved in target loading are made using standard HPLC fittings, as well as 1/16" o.d. 316 stainless steel tubing to maintain high-pressure integrity. The total load volume of liquid necessary to fill the active target volume and peripheral plumbing is 3.3 mL.

Electrical isolation of the target is accomplished using high-pressure low dead volume nylon HPLC couplings (Waters) on both lines attached to the target. When paired in series, the short length of stainless tube coupling each insulator serves as an isolated probe for measuring the resistance across the nylon gap of each target line. The target filling status can be monitored by carrying out resistance measurements across the isolation gap of the top port line using a commercial conductivity meter (Crystalab Inc., Hartford CT, 120 V AC, 60 cycle, 1/25 W). The target must fill to capacity before water can exit through the top port and change the resistance across the gap at that location. Likewise, the target emptying status can be monitored in the same fashion across the isolation gap of the bottom port line.

The response range for the above meter covers 3 MW to less than 0.01 MW, corresponding to metal ion levels of 0.1-50 ppm, respectively. The  $^{18}\text{O}$ -enriched water used (Isotec) for  $^{18}\text{F}$ -production generally possesses metal ions in the range of 15-20 ppm, more than adequate for good meter response. However, response does drop upon distilling the water during reprocessing. Adequate response can be reestablished by leaving the distilled water in contact with a silver foil for approximately 24 h before use.

The "handshake" software that is an integral part of the pump's processing software allows the computer to start or stop the pump, and to monitor the volume of water dispensed from the syringe. If the syringe should empty prior to dispensing a complete charge of water to the target, the pump automatically pauses and flags the computer of its status. Once refilled, the computer flags the pump to resume operation.

After loading of the target is complete, the computer places the Rheodyne valves in their proper configuration for sealing the target. As the blow-up of the valve plumbing shows in the Figure, the inlet and outlet ports are coupled during this action. Once the irradiation is complete, the computer reconfigures the valves for unloading. Nitrogen gas forced through the top port of the target during this operation drives the water charge from the target, and into the resin/recovery station.

The resin/recovery station is also located in the cyclotron vault approximately 1 m from the target station. This facilitates target unloading, maximizes  $\text{H}_2^{18}\text{O}$  recovery, as well as prevents long-lived contaminants from reaching the Hot Lab. The station that was previously reported by us (Ferrieri, R.A et al., 1992) has been modified to include a new leak-free resin column assembly that is fabricated from a standard HPLC guard column housing. The inlet and outlet holes to this housing are enlarged slightly to prevent flow restriction. The anion resin (Bio Rad AG1X8 carbonate form; 200 mesh) is packed inside a 1/4" o.d. lucite tube that has a polyethylene liner. Polyethylene frits (Alltech) are placed at both the inlet and outlet to the tube as it is mounted within the guard column housing. Connections to the guard column housing are made with finger-tight nylon HPLC connections (Rainin) on 1/16" o.d. polyethylene tubing.

The outlet tube from the resin column passes through an optical sensor which measures light transmission across the plastic tube. The sensor unit emits 915 nm light through a miniature infrared phototransistor (Radioshack) mounted on one side of the plastic tube, and receives it through an equally small photodetector (Radioshack) mounted diagonally across the tube. The amount of light transmitted changes depending on whether the tube is filled or not with liquid. The current output from the detector is of course proportional to the amount of light received. However, with appropriate circuitry the unit can be configured to transmit either a 0 VDC or 5 VDC signal directly to the computer for remote feedback of the tube's status. This feedback informs the cyclotron operator of when the enriched water recovery is

complete. All target operations are then shutdown, thus transferring control of the resin station via "blackbox" operation to the Hot Lab, where the chemist has complete control of radioisotope delivery.

### SYSTEM PERFORMANCE

In the six months since its installation, the described automatic high-pressure water target system has been able to make and deliver up to 725 mCi of  $^{18}\text{F}$  (EOB) from a 40 minute irradiation on 95%  $^{18}\text{O}$ -enriched water using 15  $\mu\text{A}$  of 17.4 MeV protons on target. The target should be able to tolerate higher beam currents, and thus produce larger amounts of radioisotope, although this aspect has not tested to date. Automatic operations permit target loading and valve configuring for irradiation within one minute. In addition, target unloading and water recovery takes only one minute. Radioisotope extraction from the resin, as well as its delivery to the hot lab in carbonate solution through 40 m x .5 mm i.d. of polyethylene tubing generally takes 5 minutes.

With constant daily use of the system, we have observed significant deterioration in the response of the optical sensor resulting in 50% reduction in sensitivity. Of course, sensitivity of the unit depends on light emission, as well as light detection, both requiring lens that are probably sensitive to neutron damage. While the unit is housed inside a 1" thick lead hot cell that shields the resin station, we have not taken steps to shield it against the high neutron field induced in the cyclotron vault during irradiation. We have compensated for the change in sensitivity by readjusting the threshold setting of the unit that allows it to transmit a 5 VDC signal to the computer. Eventually, the unit will be rendered nonfunctional as the radiation damage becomes overwhelming, and will have to be replaced.

*Acknowledgements:* This research was carried out a Brookhaven National Laboratory under contract DE-ACO2-76CH00016 with the U.S. Department of Energy and supported by its Office of Health and Environmental Research, and also supported by the National Institutes of Health, Grant NS-15380.

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Remote sensing of Liquid Water Target Operations R.A. Ferrieri, D. L. Alexoff, and D.L. Schlyer Brookhaven National Laboratory.

Discussion of the liquid water target operation:

C: J. Clark: In my experience nylon is extremely radiation sensitive, I've had nylon components in back of fluoride targets just turn to dust. So watch those couplings that you use. You may have to make some PEEK ones.

A: R. Ferrieri: These have been in place for six months and I haven't noticed any deterioration. They don't appear to have become brittle in any way. Are you telling me they'll just spontaneously explode?

Q: J. Clark: Well, I had a rheodyne valve with a nylon body, which was preloaded with springs and it just exploded on me. My second question relates to your method to recover water. How big is your anion column and do you start with it wet or dry?

A: R. Ferrieri: The anion column is packed just before the run and installed. I don't know the exact amount in mg, but the column is 7 mm high and the insert is a lucite 1/4 inch tube that replaces the guard column with a polyethylene sock. The inside of the polyethylene provides about a 1 mm ID. So the column size is about 1 mm diameter by about 7 mm in height. We use Biorad AG 1X8 anion exchange resin about 200 mesh.

Q: J. Clark: Is that wet with O-16?

A: We flush it out with distilled water, so it is damp, a little bit.

Q: J. Clark: I just wondered whether anyone has gone through the exercise of calculating the isotope dilution that you get on these columns?

A: R. Ferrieri: Relative to the targets volume, I think that is trivial. Dave Schlyer might have some better numbers on this, but we haven't seen significant dilution effects in the isotopic abundance with 10 redistillations and recoveries.

Q: J. Link: In our lab, we lose 2 percent abundance per run through the ion exchange. We don't distill as often as the Brookhaven Group does.

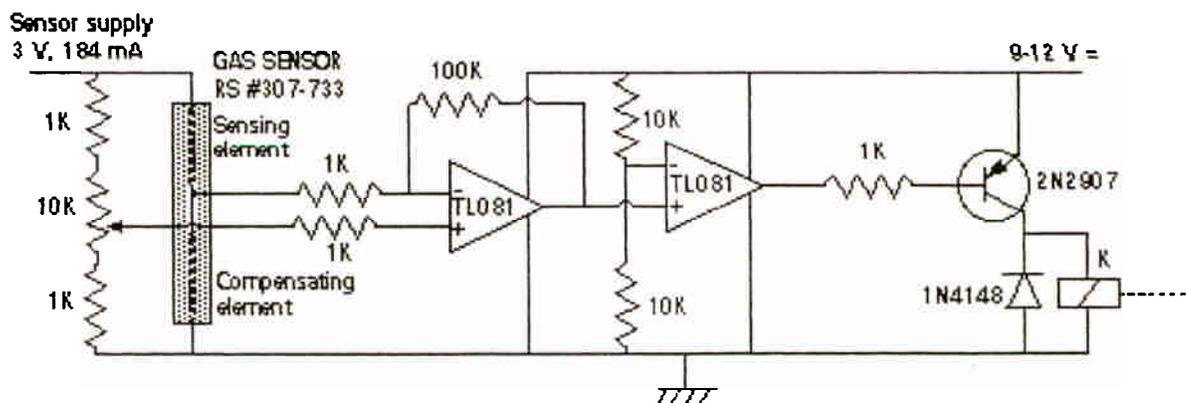
## SOLVENT VAPOR SENSOR & BOLUS DETECTOR FOR RADIOSYNTHESIS

A. DUCRET, L. VEYRE, P. LANDAIS, D. LE BARS  
CERMEP, LYON, France

### 1/ SOLVENT VAPOR SENSOR FOR DRYNESS CONTROL

One of the key points in the Hamacher method of [ $^{18}\text{F}$ ]FDG synthesis, in common with many other chemical reactions, is the need for an anhydrous state of the  $^{18}\text{F}$ /Kryptofix complex before addition of the mannose triflate. This is usually done by ensuring enough time elapses after the additions of acetonitrile for azeotropic distillation of the carbonate / K 2.2.2 solution, with the resulting possibility of overheating the dry kryptofix adduct.

In our system, the entire [ $^{18}\text{F}$ ]FDG synthesis is controlled by a Siemens Simatic S100 PLC; the fluorination takes place in an open Sigradur® vessel. We choose to automate this evaporation step with the control of this little vapor sensor, used otherwise to detect explosive atmospheres. The sensor (scheme 1) is based on a miniature flammable gas sensor designed for detection of propane, butane, natural and "town" gas, using the platinum wire (pellistor) principle. Acetonitrile and organic flammable solvents are easily detected, the difference ( $\sim 30\text{ mV}$ ) between the platinum sensing filament and compensating filament is measured and drives a K relay interfacing the Simatic PLC. Response time is within 3 seconds after complete disappearance of the solvent.

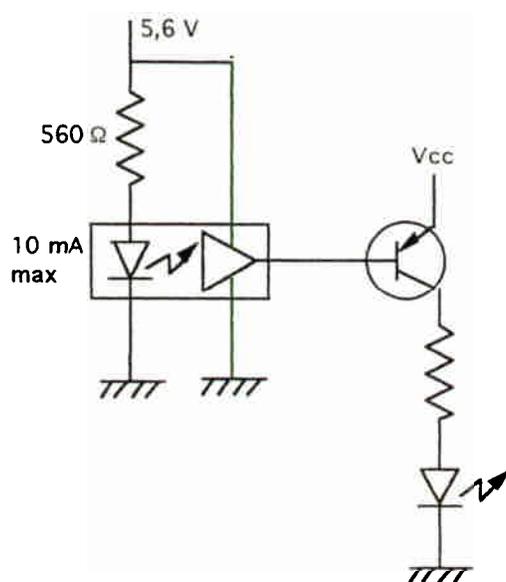


Vapor is sampled over the Sigradur® crucible with a small needle+tube and pumped ( $\sim 2\text{ l.min}^{-1}$ ) to the remote sensor box. The K relay gives a very clear "dry" information to the Simatic S100 PLC which, in turn, adds immediately acetonitrile for the following azeotropic distillation step or mannose triflate solution.

This simple dryness sensor ensures good transition steps, and a small gain in time as well as yield. It could be easily applied to any other reactions where dryness or solvent removal must be monitored, for example fluorination of benzaldehydes.

## 2/ BOLUS & BUBBLES INTERFACE DETECTOR

We also developed a small bolus detector, based on a Honeywell HDA 2003-001 IR fork detector. It is very useful for HPLC injection for example where this device detects the end of the liquid vein in the teflon tubing and lights a LED:



The proper position of the teflon tube inside the fork is difficult to find, but can be blocked with Araldite® when OK.

This small device is used for HPLC injection, elimination of air bubbles and safety checks in our automated oxygen-15 water bolus injector, and will be applied to remote enriched  $^{18}\text{O}$  water target filling.

A bolus and bubble interface detector. Didier LeBars, Lyons, France

Discussion of the fork detector:

Q: D. Alexoff: Is it radiation hard for neutrons as well as gammas?

A: I have not yet put it in the vault. It is not very sensitive to gammas, but I don't know yet about neutrons. I will drop one in the vault for a while and see what happens.

Q: We have experience with the infrared phototransistors, they have a fairly high gains and they are not very hard to neutrons.

Discussion of the Vapor Sensor:

Q: T. Ido: How sensitive is the detector for a mixed solvent such as chloroform and water.

A: I've not used it for chloroform because it is not flammable. I don't know about mixtures. It works with flammables; eg. acetone, acetonitrile, THF.

Q: J. Clark: The principle presumably is a small amount of chemical combustion of the solvent. So you need air there. So if you work in inert atmosphere, you will need to add air.

A: Yes, it requires air.

Q: J-L. Morelle: Would this detector work in a methyl iodide system when you evaporate THF?

A: The group was uncertain but felt it wouldn't work unless you added oxygen or air to the evaporation which is not desirable.

Comment from J. Clark: Combustion requires air, oxygen. In fact the operating principle of this detector is based on two filaments. One is covered with platinum. The other is a reference filament. The combustion of the solvent occurs on the platinum wire and this filament heats a lot. You detect the equilibrium between the two filaments. It gives a 30 millivolt signal and is very easy to use.

### Sensors for indication evaporation of solvents: Experience at the Univ. of Washington

J. Link, K. Krohn, J. Courter  
Radiology Imaging Research Laboratory  
University of Washington, Seattle, WA

We have been developing sensors for indicating dryness and solvent removal in our robotic syntheses. Our first sensor was visual observation. The robotic arm would hold up the reaction vessel and we would observe the sample through lead windows, but we soon realized that looking dry, wasn't dry. We are investigating other types of sensors for indicating solvent removal.

One sensor we have examined involves conductivity. We placed two steel or Pt wires sheathed in fused silica capillaries to electrically isolate them from each other, with less than 0.05 cm of wire exposed to the reaction mix in the reaction vessel. We measured the change in resistance during drying. We hypothesized that resistance would increase as the reaction became dry and become infinite when all solvent was removed. We dried a water / CH<sub>3</sub>CN mixture at 96°C with argon blowing over it. The conductivity changed with drying as shown in figure 1, but not the way we expected. The technique was not very sensitive and in our system was sensitive to changes in the argon blowing across the surface of the liquid. The measured resistance went to 0 and then negative as the solvent disappeared. Also there is the disadvantage of having a probe in contact with the sample, which caused loss of sample due to dried solids staying on the surface of the probe and the potential for contaminating the reaction.

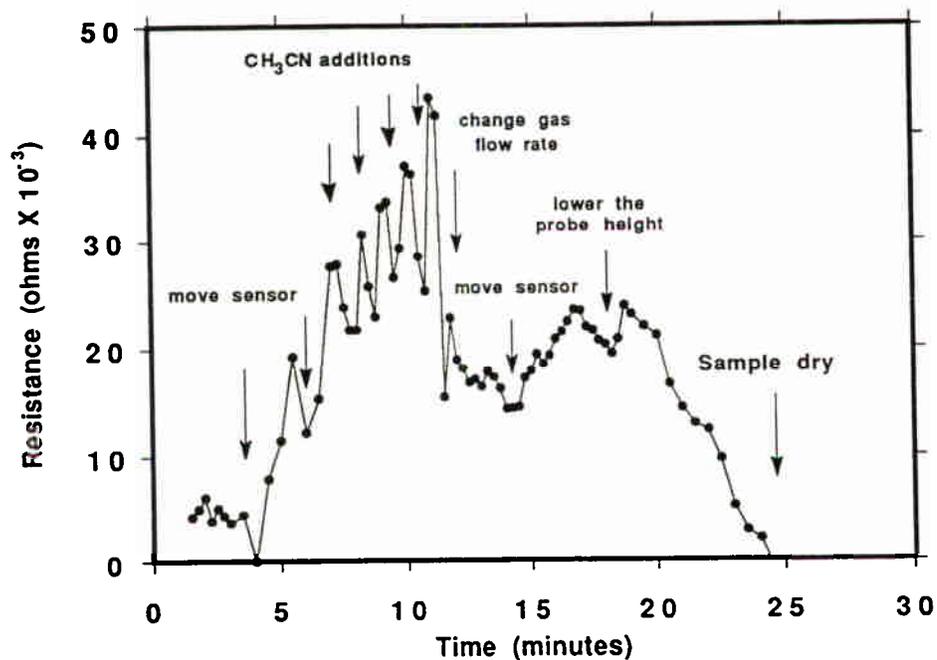


Figure 1: Typical resistance graph.

A thermocouple sensor is currently being used for the synthesis of thymidine. The thermocouple is located near the source of argon in the stream of the gas and evaporated molecules. As long as the thermocouple has solvent molecules hitting its surface, it reads a lower temperature due to collisions of the solvent molecules with the surface of the probe.

Our sensor consists of an ungrounded 1/16" stainless steel sheath J type thermocouple connected to a signal conditioner (Analog Devices thermocouple filter amplifier). The amplified voltage signal is passed into an ADC on a PC computer (Analog Devices RTI815 board) and the 0 to 4096 channel digital signal is signal averaged 20 times per ~1.4 seconds and read by the robot controller as well as displayed on the computer monitor and collected as a data file. When the signal reaches an empirically derived value for dryness, 2349 in our example, figure 2, the robot stops the drying procedure and goes to the next step. This sensor works but has disadvantages. The digital endpoint is dependent on the temperature of the gas stream as it passes over the thermocouple.

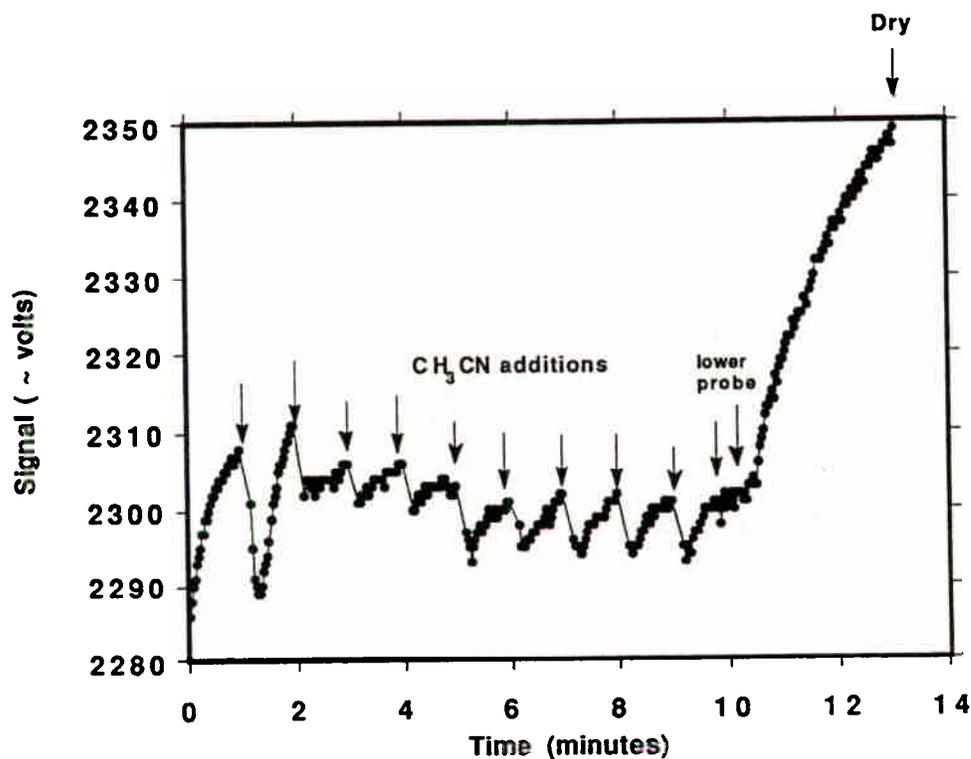


Figure 2: A typical thermocouple graph.

## An Efficient System for the Preparation of [<sup>13</sup>C]-HCN, CO<sub>2</sub>, and CO

J.R. Dahl, R.A. Matakchieri, A. Belakhlef, T.C. Chaly, D. Margouleff,  
North Shore University Hospital/Cornell University Medical College, Manhasset N.Y.,

### INTRODUCTION

<sup>13</sup>C has long been used as a label for a variety of compounds of bio-medical interest, ranging from simple materials such as [<sup>13</sup>C]-CO and [<sup>13</sup>C]-CO<sub>2</sub><sup>(1)</sup> through non-specifically labeled glucose<sup>(2)</sup> to carboxyl labeled amino acids<sup>(3,4,5)</sup> and carbohydrates labeled in specific positions<sup>(6,7,8,9)</sup>, as well as a wide variety of other compounds. Due to the 20 minute half-life of <sup>13</sup>C, its use as a label in compounds for bio-medical investigations requires completion of preparation of the labeled compounds at the appropriate time in the experiment. This in turn, requires a reliable, easy to operate system for supplying the <sup>13</sup>C labeling agent. A number of systems for the routine preparation of the [<sup>13</sup>C]-labeling precursor compounds have been reported<sup>(10,11)</sup> and a number of systems are commercially available which satisfy these requirements with varying degrees of success. Local conditions and techniques often impose new requirements not discernible during the design of a commercial system. Such was the case with the <sup>13</sup>C system at North Shore University Hospital. As supplied, this system was operated remotely by selecting a flow path by means of toggle switches on a control panel. A dummy diagram assisted in selection of the path and appropriate operation of the toggle switches. Skilled, experienced chemists left undisturbed and allowed to concentrate on the task could, with practice, operate the system effectively. However, inappropriate switching of the flow path could easily cause reagents to be sucked into the system, usually with the result that a run was lost and the system rendered inoperative until repaired. The tendency to suck reagents from the output line into the process system was due to unpredictable pressure differences resulting from vacuum pumps installed to rapidly remove process stream waste gas. Another problem was the difficulty of isolating one part of the system from another during preparation of a particular [<sup>13</sup>C] precursor. For example the part of the system used in the preparation of [<sup>13</sup>C]-HCN could not be isolated from the remainder of the system, during the preparation of other [<sup>13</sup>C] precursors. This made it very difficult to maintain catalysts under an inert gas environment in the part of the system not in use. The flow controller for metering NH<sub>3</sub> into the [<sup>13</sup>C]-CH<sub>4</sub> process stream for conversion to [<sup>13</sup>C]-HCN by passage over Pt at 1000°C was not sufficiently sensitive and excess NH<sub>3</sub> appeared in the product. Many of the catalyst tubes and furnace tubes were mounted horizontally, providing a path through which the process stream passed without effectively contacting the reagent. To improve reliability and increase ease of operation, the system was redesigned, taking advantage of the opportunity to increase system automation as much as possible. Since the automatically controlled functions on the MC17F cyclotron and associated systems are controlled through programmable logic controllers (PLC's) it was decided to continue with this method rather than instituting a dedicated micro-computer with interface boards.

### MATERIALS AND METHODS

In this laboratory <sup>13</sup>C is produced via the <sup>14</sup>N(p,α)<sup>13</sup>C nuclear reaction using a target of UHP N<sub>2</sub> containing 100 ppm added O<sub>2</sub>. Usually the <sup>13</sup>C is obtained from the target chamber as [<sup>13</sup>C]-CO<sub>2</sub>,

but experience has shown that occasionally the  $^{11}\text{C}$  is in some other form, assumed to be either  $[^{11}\text{C}]\text{-CO}$  or  $[^{11}\text{C}]\text{-C}_2\text{O}_3$ . This phenomenon has not been investigated, and identity of the chemical form of the species remains speculative, since, when it is produced, the priority is to immediately restore production of  $[^{11}\text{C}]\text{-CO}_2$ . Figure 1 is a diagram of the system showing the relative location of the various operational components. Installation of a furnace (AA in fig. 1) which heats a tube of CuO to  $\sim 650^\circ\text{C}$  and flowing the gas from the target chamber through this tube after bombardment minimizes the occurrence of reduced yields of  $[^{11}\text{C}]\text{-CO}_2$  from the target chamber by oxidizing other species to  $[^{11}\text{C}]\text{-CO}_2$ . A small trap containing molecular sieve 5A pellets (MS5A in fig. 1) is used to trap the  $[^{11}\text{C}]\text{-CO}_2$  in the gas flowing from the bombarded target. A drawing of this trap<sup>(12)</sup>, designed at NSUH/CUMC is shown in figure 2. The trap can be heated to  $250^\circ\text{C}$  from room temperature in less than 4 minutes by a 150W band heater (Omega Engineering Model MB1E1E1A1) surrounding it. It can be rapidly cooled by an air stream directed through cooling holes within it. The target is operated in the batch process mode. Following release of the bombarded target gas through the MS5A to trap the  $[^{11}\text{C}]\text{-CO}_2$ ,  $\text{N}_2$  flowing through the trap sweeps residual  $[^{13}\text{N}]\text{-N}_2$  from the trap. The trap is then heated to release  $[^{11}\text{C}]\text{-CO}_2$  to the flowing gas stream. For the production of  $[^{11}\text{C}]\text{-CO}_2$  or  $[^{11}\text{C}]\text{-CO}$  nitrogen is used as the sweep gas.  $[^{11}\text{C}]\text{-CO}_2$  is used as such or directed to the hot cell for conversion to  $\text{CH}_3\text{I}$ .  $[^{11}\text{C}]\text{-CO}$  is prepared by directing the  $[^{11}\text{C}]\text{-CO}_2$  through a furnace (AA in fig.1) containing zinc near the melting point ( $420^\circ\text{C}$ ). For the preparation of  $[^{11}\text{C}]\text{-HCN}$ , the  $[^{11}\text{C}]\text{-CO}_2$  is swept from the MS5A by a  $\text{H}_2$  stream and carried over a Raney nickel catalyst (in furnace CC, fig. 1) at a temperature between  $100^\circ\text{C}$  and  $250^\circ\text{C}$  depending upon the condition and age of the catalyst. The output stream from the Raney Ni is swept through a NaOH trap (EE) to remove any  $[^{11}\text{C}]\text{-CO}_2$  which was not reduced to  $[^{11}\text{C}]\text{-CH}_4$  before passing through  $\text{P}_2\text{O}_5$  (FF) for removal of residual moisture produced during the reduction. The flow of a small amount of  $\text{NH}_3$  metered with a Whitey SS31RS4 metering valve (MV1, fig. 1) is monitored with a Cole-Parmer N042-15 Rotameter with a glass ball. The ammonia is directed into the flowing  $\text{H}_2 + [^{11}\text{C}]\text{-CH}_4$  stream just before it is introduced into furnace BB containing Pt held at  $1000^\circ\text{C}$ . The output from this furnace contains  $[^{11}\text{C}]\text{-HCN}$ . It then flows through a second  $\text{P}_2\text{O}_5$  trap (GG) to remove any residual moisture and reduce the  $\text{NH}_3$  remaining in the product. All of the tubing in the system except that beyond the output of the Pt furnace is 3mm OD SS tubing. From the output of the Pt furnace to the collection point of the  $[^{11}\text{C}]\text{-HCN}$  3mm OD standard wall Teflon tubing is used. All valves through which reagents pass are stainless steel General Valves, either #9-497-900 3 way valves or 9-270-900 on-off valves. Valve V12 (figure 1) which controls the output from the  $[^{11}\text{C}]\text{-HCN}$  process system is a General Valve model 2-10-900 all teflon 24VDC solenoid valve. Cooling air is controlled with Asco 8210-B20 24VDC piloted valves. To provide an inert atmosphere for reagents in the system when the system is not in use, a shutdown scheme was devised during which the power to all of the furnaces is turned off and air is directed through the furnaces to reduce the time required to cool them to room temperature while UHP nitrogen is flowed through the system being shut down. Simply shutting off the flow of  $\text{N}_2$  and allowing the system to cool results in  $\text{N}_2$  pressure less than 1 atmosphere within the system. Atmospheric moisture and oxygen can then be sucked back into the system, poisoning the reagents. A bypass loop permits sweep gas to be directed through the process portion of the system while the target system is being filled, drained or bombarded, thus allowing the process system to be prepared and maintained in a standby mode while the bombardment is carried out. This provides optimal conditioning of the system.

A Keyence KV40R programmable logic controller was selected because it combines economy, expandability, small size with ease of programming. The ladder diagram can be constructed in a micro-computer (PC), compiled to operational code and transferred to the PLC from the PC.

On the control panel, figure 3, are 12 push-button switches which select the functions of the system. As can be seen in figure 1, V21, the sweep gas bypass valve directs the sweep gas to either the selected process system, or through the MS5A trap to the selected process system. Coupled with the flow of gas from the target chamber through the molecular sieve either to waste or to the process system, the two gas flows dictate which flow patterns can be set simultaneously and which must operate individually. The push-button switches are of the "one button in a set at a time" style. Thus "FILL" or "DRAIN" or "FLUSH" or "BOMBARD" may be selected only one at a time. Only a single  $^{11}\text{C}$  precursor and only one state of the process system may be selected at a time. "STANDBY" or "SHUTDOWN" may be selected and any of the target functions on the top row simultaneously selected. However, when the "DELIVER" function is selected, the PLC is programmed to allow only "FILL" or "BOMBARD" on the top row to be selected. The PLC also turns on the MS5A during delivery, allowing it to heat as rapidly as possible to  $250^{\circ}\text{C}$  to release the  $^{11}\text{C}$ - $\text{CO}_2$  to the flowing gas stream and be carried through the selected process system.

## RESULTS

The heating time for the MS5A trap is about 4 minutes to  $250^{\circ}\text{C}$ . It may prove effective to maintain the MS5A at a temperature slightly elevated above room temperature, perhaps between  $60^{\circ}\text{C}$  and  $110^{\circ}\text{C}$ , to provide a head start to the heater and reduce the required temperature rise. To date, 420mCi of  $^{11}\text{C}$  (EOB) have been recovered following a 10uA, 20 Minute bombardment. Optimization of the system operating parameters is presently underway.

## CONCLUSION

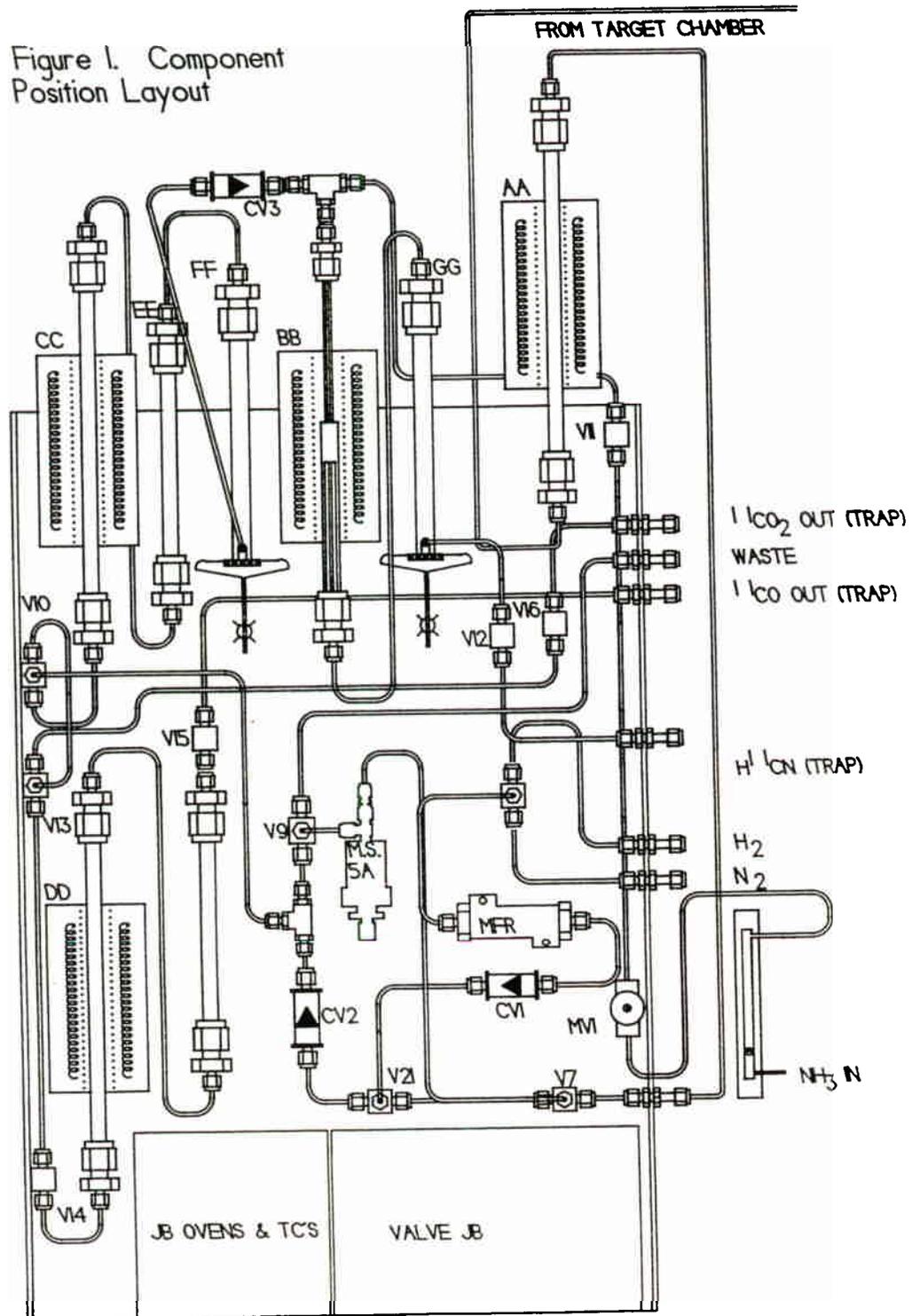
The system, though not yet fully operational, is much easier to operate, and appears less likely to failure.

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Figure 1. Component  
Position Layout



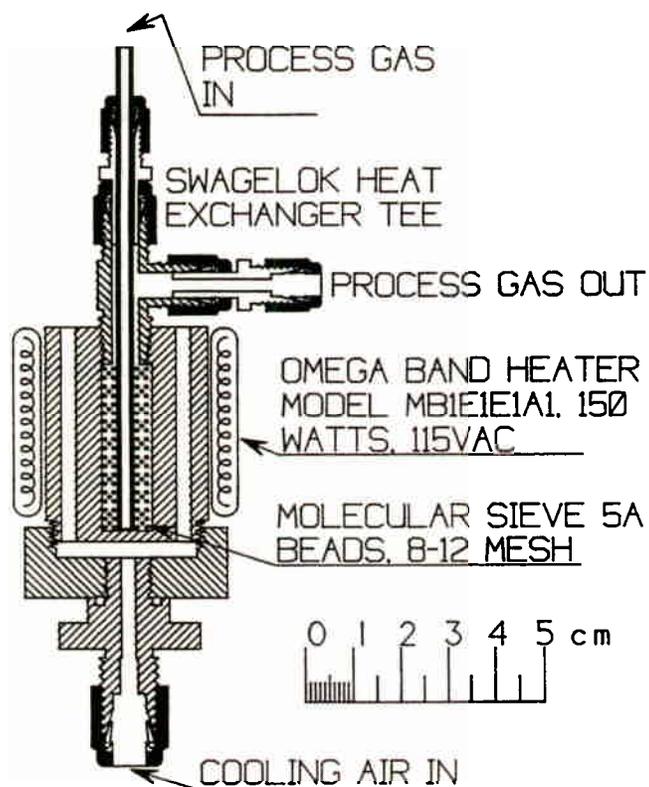


FIGURE 2. NORTH SHORE UNIV. HOSP.  
SCALE DIAGRAM OF MOLECULAR SIEVE TRAP

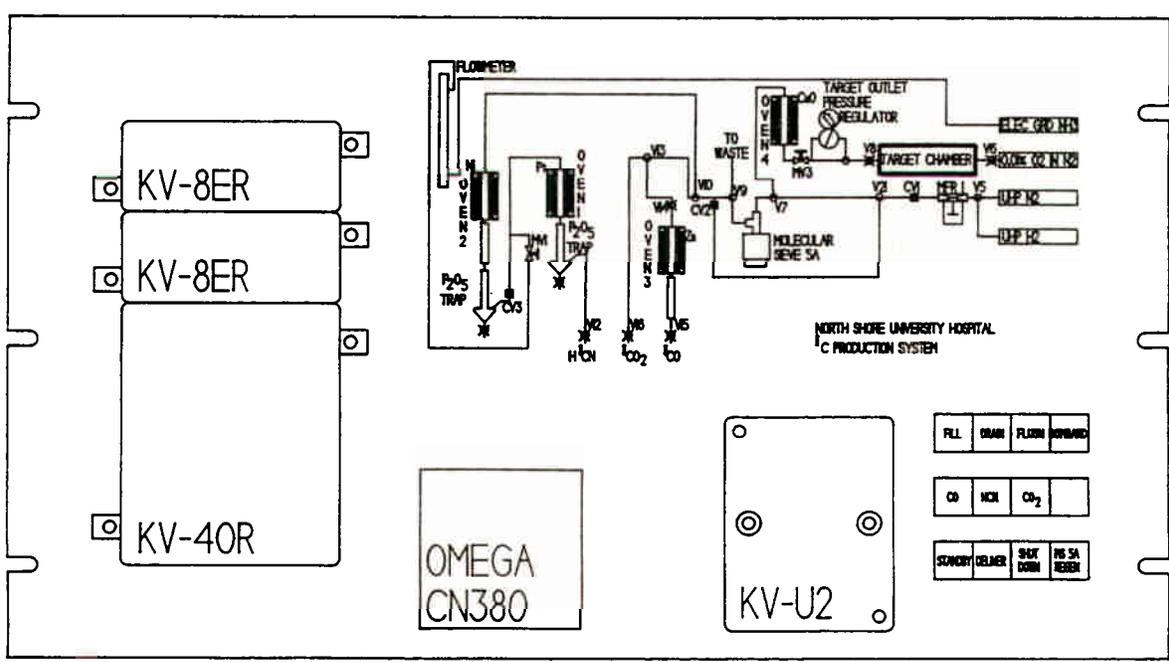


FIGURE 3. CONTROL PANEL SHOWING COMPONENT  
AND SWITCH PLACEMENT

## An Efficient System for the Preparation of [C-11]HCN, CO<sub>2</sub> and CO Ralph Mataccieri:

### Discussion of the North Shore C-11 system:

Q: Tom Ruth: Have you used the molecular sieve system yet?

A: We have not produced any radioactive gas with it yet, it does function.

C: T Ruth: We tried something similar several years ago. We found that we invariably got cold CO<sub>2</sub> included in it which reduced the specific activity.

J. Clark: I think the Upsalla group still uses molecular sieve, but is anyone here able to comment?

B. Dahl: I want to thank Scanditronix, for giving us the inspiration for using the molecular sieve system. With regard to the CO<sub>2</sub> problem that T. Ruth mentioned, one of the things that we've programmed in the system but is giving us just a modicum of difficulty is a regenerate function. We want to be able to regenerate any time we suspect that there is CO<sub>2</sub> in the system. For example if the system has sat for a while or it's not totally prepared we plan to pass nitrogen through it to clear the CO<sub>2</sub> out before we run.

J. Link: What temperature do you use for regenerating the molecular sieves?

Bob: 250 degrees centigrade.

Q: J. Link: My cyanide system requires several rapid valve changes at one time. I haven't had time to automate this. Tom Ruth uses programmed logic and a radioactivity detector to decide when he has finished emptying his target. Are you going to switch you valves by time, or are you using a logic for detection of activity?

A: No, right now we are switching the valves pretty much by time. We allow it to collect, then switch the valves.

Q: M. Berridge: What is the recovery percentage off those molecular sieves?

A: We haven't run the system yet. We haven't recovered any activity yet.

C: J. Kozirowski: We use molecular on the PET trace and it's quantitative. We recover everything off of the molecular sieves.

Discussion of a capacitance bolus detector:

Colin McKinney:

As a result of our discussions here, a concept idea for bolus detection came into mind that would be radiation hard. One could use a capacitive sensor on any type of teflon or polyethylene tubing. A capacitance impedance bridge could be used. That would be made of resistors and capacitors which certainly aren't going to be effected by neutrons. You could couple out to it via coaxial cable to an AC volt meter. I don't know, that is just a concept at this point. So I would like some comments on that because that might be worth going back and working on in the laboratory after the workshop.

J-L Morelle: There have been two systems described, one working on index of refraction, another based on resistivity and conduction, and here is, actually, a third method which is based on the dielectric constant. I have compared the various efficiencies signal to no signal for these three methods. Since the dielectric constant of water, which is the one you usually want to measure, is very high, it is in the vicinity of 80, it is the system that gives the best output. You don't need to do any settings. So I think your idea meets exactly one of the best ways of monitoring the presence of water or the absence of water. detection of water through a tube. Typically what you are measuring it's a variation of 20 picofarads up to 100. Theoretically, it should be 2 to 160, if it were the perfect ratio, but you have, of course, other capacitants on the wire and on the lead, etc. And the internal volume you have to measure is in the vicinity of 30 microliters.

C. McKinney: Is that information in the literature? I would like to get it.

J-L. Morelle: No, not yet, we designed it a few months ago. It operates already on one of our modules.

A: Colin: Great, looks like something to work on.

Comment G. Bida: That was done in Knoxville, as well. We just strapped a couple pieces of metal onto a coax connector and put them across a piece of tube. With a fairly expensive HP reactance meter we saw a third digit change. But it worked very quickly and easily. It needs a lot more work but I think it might be a very handy way and it is radiation hard.

C. McKinney: Yes, an impedance bridge circuit would give you much more sensitivity, because you null it, say without water, and then you'd have very high sensitivity if something came into the tube to change the dielectric constant.

## A SIMPLE SYSTEM FOR REMOTE PROCESSING AND DELIVERY OF $\text{H}_2[^{15}\text{O}]$ PRODUCED FROM A $\text{N}_2/\text{H}_2$ TARGET

R.A. Ferrieri\*, D.L. Alexoff, D.J. Schlyer and A.P. Wolf  
Brookhaven National Laboratory, Department of Chemistry  
Upton, New York, 11973-5000 USA

### INTRODUCTION

By far,  $\text{H}_2[^{15}\text{O}]$  is one of the most widely used radiotracers in Positron Emission Tomography (PET) for assessing regional cerebral blood flow (Ter-Pogossian et al., 1969; Jones et al., 1985; Raichle et al., 1983; Huang et al., 1983; Kanno et al., 1991; Frackowiak et al., 1980). This radiotracer can be prepared by a variety of methods including reduction of  $[^{15}\text{O}]\text{O}_2$  with  $\text{H}_2$  over Pd (Meyer et al., 1984; Clark and Buckingham, 1975; Clark et al., 1987) or Pt (Berridge et al., 1990) catalysts, exchange between  $[^{15}\text{O}]\text{CO}_2$  and water (Welch and Kilbourn, 1975), recoil production via in-target reaction of  $^{15}\text{O}$  atoms generated by the  $^{16}\text{O}(\text{p},\text{pn})^{15}\text{O}$  reaction on natural abundance water (Mulholland et al., 1990), and recoil production via in-target reaction of  $^{15}\text{O}$  atoms with  $\text{H}_2$  generated by the  $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$  reaction on a  $\text{N}_2 + 5\% \text{H}_2$  gas target (Vera-Ruiz and Wolf, 1978; Jackson et al., 1993).

The success and widespread use of  $\text{H}_2[^{15}\text{O}]$  in PET re-emphasizes the need for simple, reliable, as well as, safe systems that can satisfy the PET demands for processing and delivery of this radiotracer in quantities and purities suitable for human studies. We report here a simple system for trapping and processing  $\text{H}_2[^{15}\text{O}]$  produced directly through in-target chemistry from a  $\text{N}_2 + 5\% \text{H}_2$  gas target, and for delivering that radiotracer 300 feet away in an injectable form that is sterile and pyrogen-free. The system does not require electrical power nor extraneous pressurized gas supplies to drive any of the remotely operated process steps, thus facilitating its setup on short order.

### EXPERIMENTAL

**1. RADIOISOTOPE PRODUCTION** Oxygen-15 as  $\text{H}_2[^{15}\text{O}]$  was produced directly from the  $^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$  reaction on a flowing gas target comprised of  $\text{N}_2 + 5\% \text{H}_2$ . The target was of a standard cylindrical design constructed from aluminum, and possessed a 100 mL active volume. The front window was 20 mil thick aluminum (6061) which degraded the 8 MeV deuteron beam down to 7.2 MeV on gas. Typically, the target was operated in a dynamic mode at  $4 \text{ L min}^{-1}$  using 60 psia of gas. Irradiations generally were of 3 minute duration using a 15  $\mu\text{A}$  beam intensity on target. Typically, 300 mCi of  $[^{15}\text{O}]\text{H}_2\text{O}$  accumulated in the bubbler of the radioisotope processing apparatus within 5 minutes time from the start of beam after having transferred through a 120 m x 3.18 mm o.d. Impolene line enroute to the PET facility.

**2. RADIOTRACER PROCESSING SYSTEM** Figure 1 shows a schematic diagram of the radiotracer processing apparatus. The system operates through the actions of two Rheodyne 7010 injector valves (Rainin, Inc., Woburn, MA) which, along with peripheral traps and

plumbing, are mounted on a sliding plexiglass plate that allows all components to fit inside a shielded Capintec Dose Calibrator for direct activity measurement. The shielding is comprised of five 7.6 cm thick interlocking lead rings that are stacked around the chamber. With 300 mCi of  $\text{H}_2[^{15}\text{O}]$  accumulated in the processing apparatus, the background radiation level at contact with the shield never exceeds 20 mR/hr. The valves are operated remotely from behind the shield through 30 cm extension handles thus minimizing exposure to personnel.

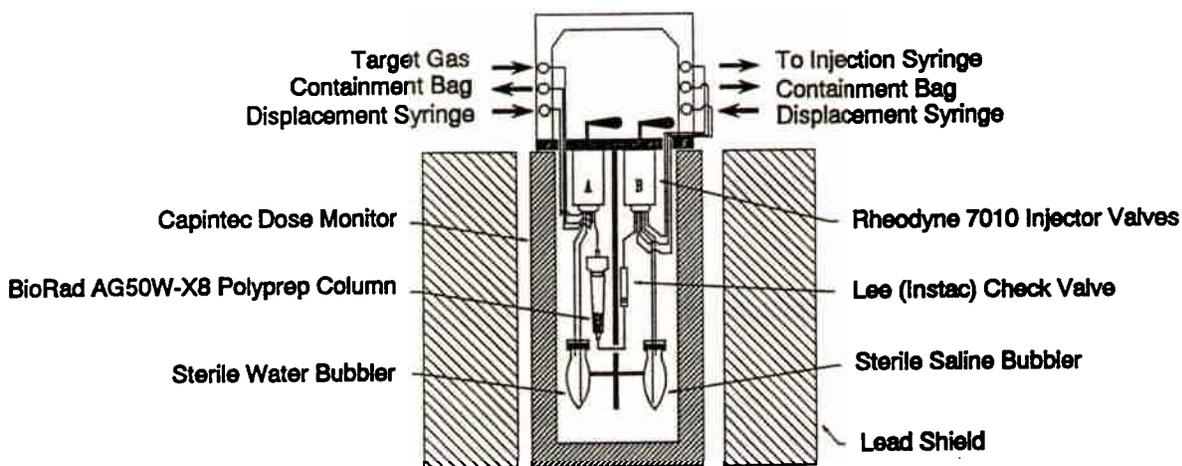


Figure 1. Schematic of  $\text{H}_2[^{15}\text{O}]$  collection and processing apparatus.

Figure 2 shows a schematic diagram of the plumbing configuration for both valves. All fixed transfer lines are made of 1.6 mm o.d. stainless steel tubes, and their connection to the valve ports are made through standard HPLC fittings. Connections to the displacement syringes, as well as the K50L transfer line (Baxter Healthcare Corp., Valencia CA: 3.3 mL capacity, 84 cm length) leading to the injection syringe assembly, are made through stainless steel Luer-Lok connections mounted to a plexiglass slide handle on the apparatus for easy access. Connections to the inlet target gas line and the outlet gas line leading to the containment bag are made through quick-disconnect fittings which are also mounted on the slide handle. This facilitates removal of the apparatus for general servicing or prepping between radiotracer deliveries.

In addition to the above plumbing, the system has two liquid bubblers, one filled with 6 mL of sterile water for trapping  $\text{H}_2[^{15}\text{O}]$  vapor from the gas stream, and one filled with 1.6 mL of 5% sterile saline. This amount and strength of saline is sufficient for making the radiotracer preparation isotonic. The bubblers are connected to the system using long 18 gauge stainless steel needles that attach directly to the Rheodyne valves using HPLC fittings, and enter the bubblers through silicone rubber septa.

The system also has a cation resin column (BioRad AG50W-X8 Polyprep columns;  $\text{H}^+$  form; BioRad, Inc., Melville, NY) for stripping ammonium ions from the preparation. Passage through the cation resin is essential for removal of ammonium ions produced as a consequence of in-target radiolysis of the target gas. If left untreated, the  $[^{15}\text{O}]\text{H}_2\text{O}$  preparation possesses a pH of approximately 9.5. After treatment, however, the pH falls within a range of 5.5-6.0 that is acceptable for patient injection.

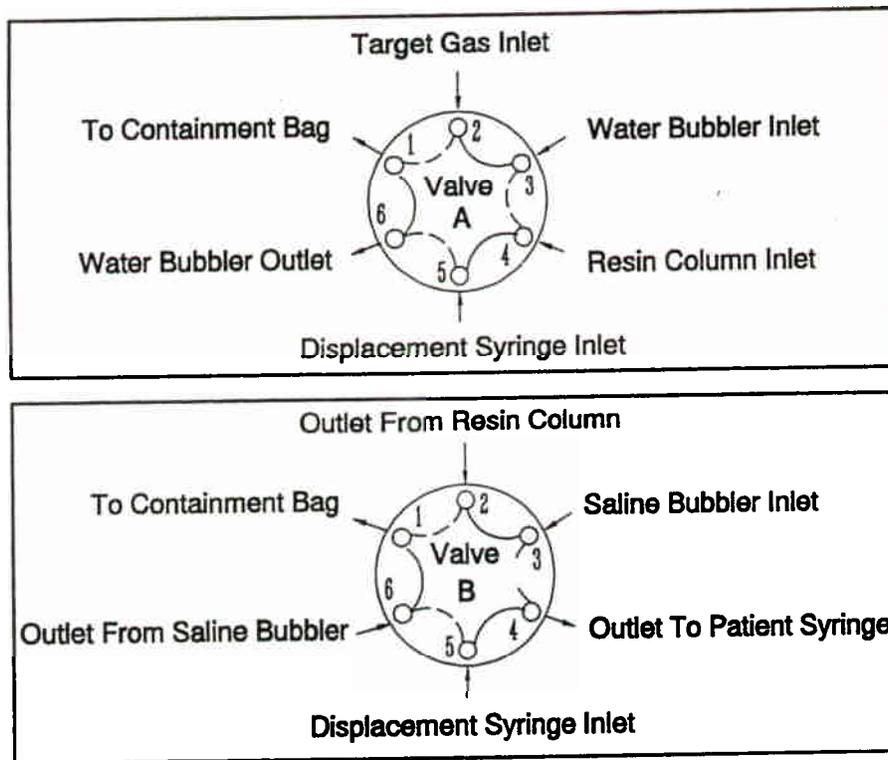


Figure 2. Schematic of plumbing layout to Rheodyne valves.

A test on resin capacity for ammonium ions was carried out using four samples of Milli-Q filtered water; 6 mL volume each, that were titrated with ammonium hydroxide to a pH of approximately 11.5. Each sample was passed, in turn, through the same cation resin column, and the pH of the effluent measured with a pH meter. Table 1 summarizes results from this test. A single resin column has the capacity to strip ammonium ions from three radiotracer preparations before cation breakthrough is observed. Even so, standard operating protocol calls for replacement of the resin column after each radiotracer delivery.

Table 1

**Ammonium Ion Capacity of a Single BioRad Polyprep Column  
Filled with AG50W-X8 Cation Resin<sup>a</sup>**

Sample No.	Sample pH	
	Before Resin	pH After Resin
1	11.5	5.0
2	11.5	5.5
3	11.6	6.5
4	11.7	11.0

a. Samples were prepared by titrating 5 mL of distilled water with ammonium hydroxide to a pH of about 11.6. Samples were passed sequentially through the same resin column.

### 3. INJECTION SYRINGE ASSEMBLY AND SHIELDED TRANSPORT CANNISTER

The radiotracer preparation passes through a disposable sterile K50L line on exiting the system, in addition to passing through a sterile vented Millex-GS 0.22  $\mu\text{m}$  filter (Millipore Products Division, Bedford, MA), and then enters a 10 mL disposable sterile syringe fixed within a Pro-Tec II titanium syringe holder (Biodex, Inc., Shirley, NY). Figure 3 shows a sideview of the syringe assembly, and the shielded transport cannister which sits atop a second shielded Capintec Dose Monitor.

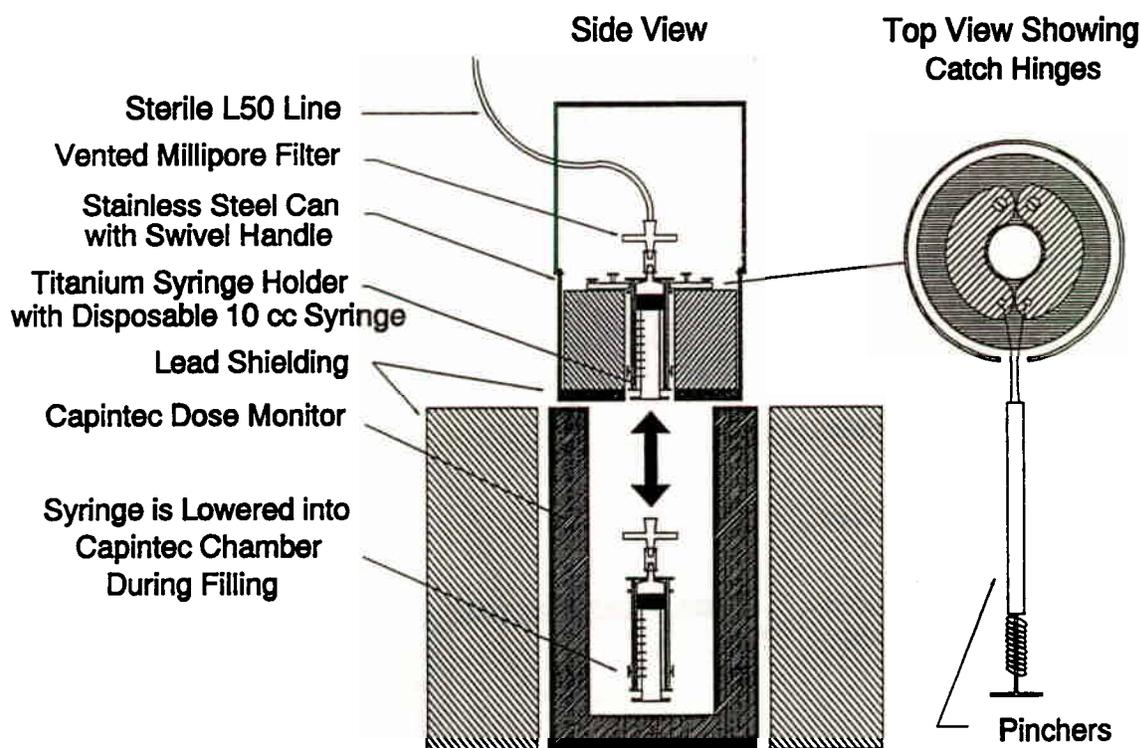


Figure 3. Schematic of injection syringe assembly in the portable shielded cannister.

The syringe holder was modified by brazing a 25 mm o.d. steel washer (10 mm opening) to the end of the syringe holder. The end of the syringe protrudes through the opening of the washer when it is locked into place by the set screw located on the opposite end of the holder. This modification to the holder allows the syringe assembly to be fixed to the shielded cannister during transport by a set of steel wings which clamp onto the holder just beneath the washer. The wings are held in place through the spring tension of remote pinchers located on the top of the cannister (see Figure 3). The wings can be separated by depressing the pincher. This action frees the syringe assembly thus allowing it to be lowered to the bottom of the Capintec Dose Monitor during filling.

The shielded transport cannister consists of a lead glass syringe shield (10 cm long x 3 cm thick wall: Biodex, Inc., Shirley, NY) that was modified by boring out the brass end-caps to the same internal diameter (35 mm) as the shield. A stainless steel can was also brazed to the bottom brass end-cap to allow the shield to sit firmly within the can. This can also extended 1.5

cm beyond the top of the shield to allow room for a 35 cm long swivel handle for easy transport. The extension is notched to allow room for the pincher arm to extend perpendicularly across the top face of the shield. The syringe assembly locking wings are screwed directly into the brass end-cap of the top face, but slide freely across the face.

**4. RADIOTRACER TRANSPORT CART AND HYDRAULIC INJECTOR** Figure 4 shows a sideview of the radiotracer transport cart including the hydraulic injector. The transport cart consists of a 30 cm long x 15.2 cm o.d. (6.35 mm wall thickness) aluminum pipe fixed to the table top of a rolling cart. An additional lead shield (1.9 cm thick) is mounted within the top portion of the aluminum pipe. This shield is bored out to accommodate the shielded transport cannister. The cart allows for easy transport of the radiotracer to the bedside of the patient while minimizing exposure to chemist, as well as, the patient. The height of the cart and assembly is 107 cm which places the radiotracer injection syringe within close proximity to the intravenous line.

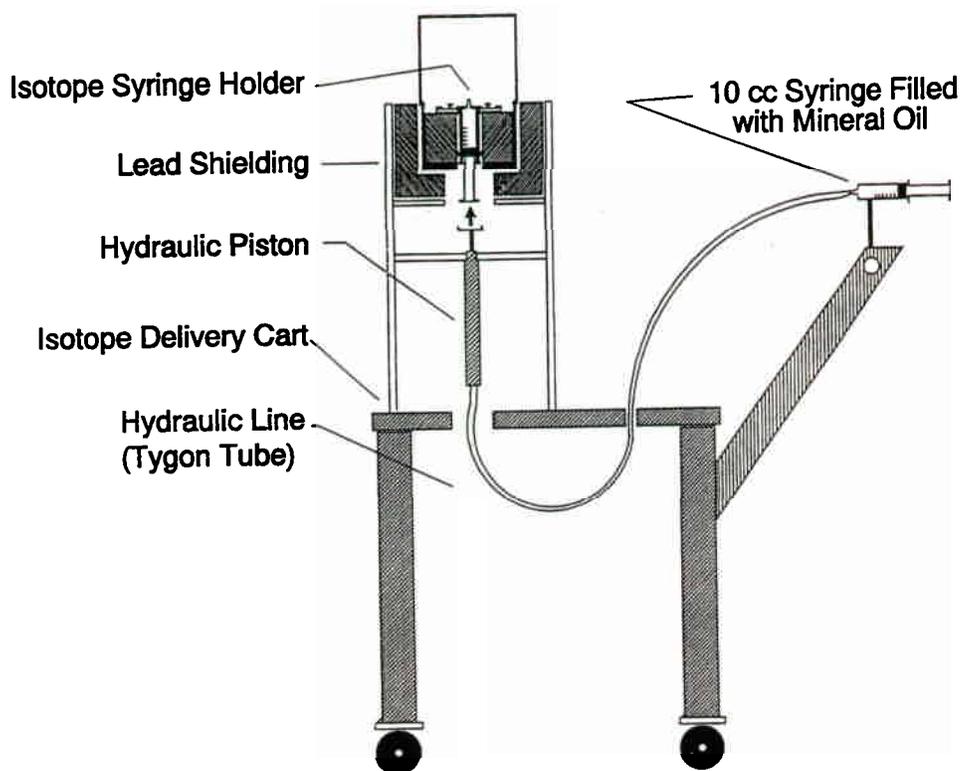


Figure 4. Schematic of shielded isotope delivery cart and remote hydraulic injector.

When the cannister is lowered into the shielded recess of the delivery cart, the plunger of the injection syringe resides approximately 1 cm above the stem of a hydraulic piston (Bimba Manufacturing Co., Monee, IL). The stem tip is modified to accommodate a 2 cm diameter aluminum disk so that the piston pushes uniformly against the plunger during injection.

The hydraulic piston is connected to a remote injection syringe (10 mL volume plastic syringe with Luer-Lok end) via a 6.35 mm o.d. tygon tube (1.59 mm wall thickness). The piston, hydraulic line, as well as, approximately 8 mL of the remote injection syringe are filled with mineral oil. This type oil offers the least effect on the rubber seal of the syringe plunger on prolonged exposure.

Injection is made when the physician depresses the plunger of the remote injection syringe. The travel distance of the hydraulic piston is more than adequate to displace the entire contents of the isotope syringe into the intravenous line. The hydraulic piston stem also offers resistance once the isotope syringe plunger has traveled the full extent of the syringe. The injection is completed by flushing the intravenous line from a saline drip bag.

**5. PROCESS OPERATION** Initially, both Rheodyne valves are placed in the "Load" position when the bubblers are being charged with appropriate liquids, and when the apparatus is ready to trap activity. Under these conditions target gas flows through the sterile water bubbler containing the 6 mL of sterile water, and exits to a shielded containment bag thus preventing radioactivity release to the atmosphere. After accumulation is complete, valve A is repositioned to "Inject", and 60 mL of air from a syringe is used to displace the water through the cation exchange resin and into a saline collector. After accumulation in the saline solution is complete, valve B is repositioned to "Inject", and another 60 mL charge of air from a second syringe displaces the saline solution to the injection syringe assembly.

## SUMMARY

The  $N_2 + H_2$  target can produce more than enough  $H_2[^{15}O]$  to meet the demands of any PET imaging facility. We have shown that the radiotracer can be transported across 300 feet of tubing without significant loss of activity, using fast flows of target gas. An advantage of this method is that the radiotracer is generated directly within the target. Thus, there is no need to maintain an extraneous chemical processing station at the PET imaging facility that involves heating a high temperature furnace, and introducing a potentially dangerous gas mixture such as hydrogen which is required for the catalytic conversion of  $[^{15}O]O_2$  to  $H_2[^{15}O]$ .

A simple remotely operated system is reported here that performs the following three step operation for  $H_2[^{15}O]$  delivery at the PET imaging facility: (i) collection of the radiotracer in water; (ii) removal of ammonia from the preparation, while at the same time making it isotonic for injection; and (iii) delivery of the radiotracer to the injection syringe. The system can process and make available for injection 100 mCi of  $H_2[^{15}O]$  (>99% radiochemically pure as measured by radio GLC), starting with 300 mCi of the radiotracer in the water bubbler. The machine is easily prepped for subsequent deliveries by sliding it out of the Capintec chamber, recharging the water and saline bubblers with appropriate solutions, and replacing the cation resin column. Also, the K50L transfer line, as well as the injection syringe and filter assembly must be replaced with new sterile components. Additional doses of radiotracer can be made available within 12 minutes of the previous injection.

In addition, a general syringe loading device with remote hydraulic injector is also reported here that is compatible for use with any  $H_2[^{15}O]$  radiotracer processing station. The device allows for direct measurement of syringe dose while filling, and for easy, as well as safe transfer of the injection syringe assembly to a delivery cart that houses the remote hydraulic injector. The injection syringe is never handled directly during transport nor during injection except, to connect it to the intravenous line, thus minimizing radiation exposure to personnel.

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### Discussion of the Remote Processing System:

Q: J. Link: Rich, Do you have problem with pyrogens?

A: R. Ferrieri: No problems with that in any of the samples that we sent out.

Q: J. Clark: I just have a couple of comments. Iwakano and Akita published a paper in Japanese, which reports the ammonia production in quite great detail at different dose rates. And also it talks about transport of water vapor under these target conditions over different materials. Quite an interesting paper. If anybody wants a copy, I have the Japanese version, but the figures and the captions are in English, so it is fairly readable.

Q: M. Welch: There is a difference you know. I didn't realize it until I looked at your poster and heard your talk. You are irradiating flowing gas at 4 liters a minute, we're irradiating static gas, and so even if all of the hydrogen in our target was converted to ammonia, our concentration would be very low because we have got such a small volume.

A: R. Ferrieri: Well, you also indicated that the beam strike volume is so small relative to ours.

M. Welch: Right, it is also the fact that you are flowing and we are not. Maybe Jerry Bida could tell us what the radiation chemistry of ammonia is at sort of low and high beam currents, but I bet you that would explain the difference.

Q: B. Wieland: This may be a naive question. What is the proton energy of the BNL 60 inch cyclotron approximately?

A: Rich: It's variable. It will go up to 33 MEV protons.

B. Wieland: Okay, then a comment is: The O-16 (p,pn) O-15 reaction between 20 MEV and 30 MEV, I believe, has ~200mCi per microamp yield. Have you looked into making target O-15 water via the (p,pn) on natural water? I know if you keep the exit energy high enough, you don't make very much N-13 from the (p,alpha) reaction and you can remove the N-13 I think.

A: Rich: No, we haven't. Only because we would have a logistical problem of moving that bolus of irradiated water from the cyclotron vault to the PET facility. It is about 400 feet. We don't have a pneumatic tube that would do anything of that nature.

B. Wieland: I'm pretty sure the Ann Arbor people have done that. If anyone wants to make a comment on that.

J. Link: We use the (p,pn) reaction. We irradiate static oxygen gas at 45MeV and 30 microamps and make the water in the hot cell. Very little N-13 is produced. It is less than 0.3 percent of the radioactivity with no measurable ammonia in our system.

Comment: At Philadelphia, there was a similar system for production. We didn't see any ammonia in that system, and we were also able to easily transport the gas about 1200 feet, I think, from the cyclotron to the scan area.

Q: R. Ferrieri: What were your radiation conditions?

A: Gonzales: We irradiate at lower current not more than about 4 or 5 microamps. The energy was about the same, about 8.5 MeV.

Q: R. Ferrieri: Dynamic, flowing target also?

A: Gonzales: Yes, right.

Q: J. Clark: I don't understand where you get your nitrogen-13 from. Deuteron energy is what energy?

A: R. Ferrieri: It is actually entering the gas at about 7.3 MEV.

Q: J. Clark: Okay. The other comment is I think both Philadelphia and ourselves have run this target system and used the dialysis membrane exchanger technique to do continuous water infusions and I've not seen any ammonia problems either.

A: R. Ferrieri: No. As I said this may be unique to our irradiation conditions. And this what we've done to solve that.

Q: J. Clark: The other query is, what is the maximum permissible pH with something like ammonia that you are allowed to inject anyway? Blood is an excellent buffer.

A: T. Tewson: I can tell you the Merck index quotes an LD50 in rats for ammonium acetate. And presumably what is toxic in ammonium acetate is the ammonium and not the acetate. The LD50 is 17 mg per kg. But a question, have you looked at the gas concentration, I mean 5 percent hydrogen seems a rather large amount. If you drop the amount of hydrogen do you still get water? But then you can't make as much ammonia because there is not as much hydrogen to make ammonia with.

A: M. Berridge: In the system we use routinely, because the hydrogen is being added to the stream, we have a lot of control over how much is added. We find that as long as the hydrogen flow is above zero, we make water with no real difference in yield. The hydrogen flow rate that we use is 20 -30 ml per minute. We don't have the ammonia problem that Brookhaven has, so maybe reducing the hydrogen concentration will help your problem.

Q: R. Ferrieri: What concentration of hydrogen is that, relative to the total?

A: Marc: We are flowing the whole target gas at somewhere between 1-1/2 and 2-1/2 or so liters per minute.

J. Clark: Marc, as I understand it, you are talking about a [oxygen-15] O2 target and then you bleed in the hydrogen.

Marc: No, it's a hydrogen / nitrogen gas target.

R. Ferrieri: What he is saying, with that mixture, he has like a fraction of a percent of hydrogen and he's still getting efficient water production.

J. Clark: The Japanese paper in fact describes all that in detail.

M. Berridge: Right, the point being that you take the hydrogen out.

R. Ferrieri: The experiments that we did several years ago on the ratio showed that 5 percent

Synthetic Application of Column Extraction to Automated Preparations of PET Radiopharmaceuticals. Ren Iwata and Tatsuo Ido. CYRIC Tohoku Univ.

Discussion of the extraction method:

Q: T. Ruth: How flow rate sensitive is this for extracting compounds, just getting the material onto the column?

A: R. Iwata: For Liquid? We just apply the organic solvent and naturally (gravity) it flows down, but you can apply pressure to speed the extraction, no problem.

Q: M. Channing: That was very nice. I was wondering about the second column, when you go to separate out the fatty acid, on silica gel, what do you use? For the hydrolysis with HCl is the HCl a gas or a liquid? For the decomposition of the Grignard, you use HCl? Is that gas?

A: No, liquid. The Michigan group used gas, but we just use dilute HCl solution to decompose all reagents.

# Synthetic Application of Column Extraction to Automated Preparations of PET Radiopharmaceuticals

Ren Iwata and Tatsuo Ido

*CYRIC Tohoku University, Sendai 980 Japan.*

## INTRODUCTION

Organic synthesis generally requires extraction for purification of a reaction product. In PET radiochemistry this liquid-liquid extraction has often been conveniently substituted for solid phase extraction with a commercially available short C18 column to accommodate a procedure to remote control or automation. However, this replacement cannot be applied to all PET radiopharmaceutical preparations, and consequently conventional liquid-liquid extraction is sometimes inevitably employed using a specially designed device to automate this procedure. Figure 1 illustrates a few methods developed so far for this purpose.<sup>1-3)</sup> An aqueous layer containing a reaction product is first shaken with an organic layer by vigorously stirring or bubbling and then the two layers are separated using these devices.

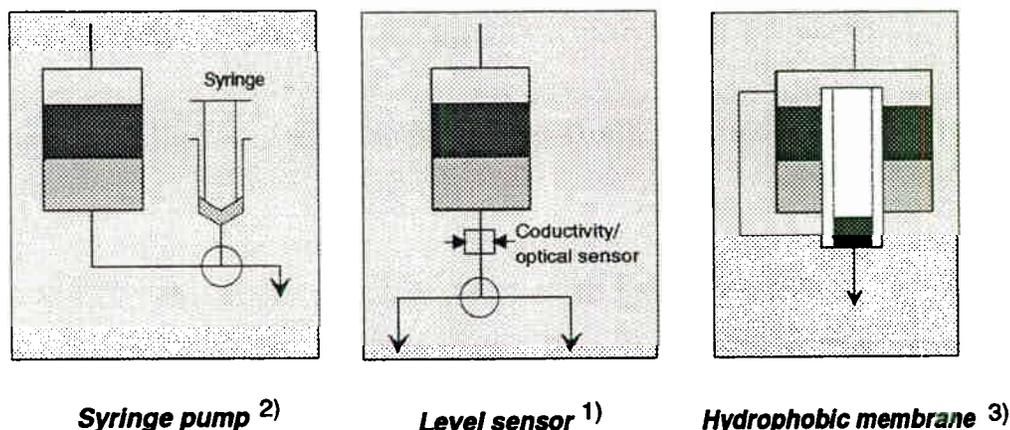


Figure 1. Devices for remote-controlled or automated extraction

*Extrelut* is a commercially available column filled with a large-pore kieselguhr of granular structure and high pore volume, capable of taking up and holding water. As shown in Fig.2 lipophilic substances are extracted from the aqueous phase retained by *Extrelut* with organic solvents not miscible with water.

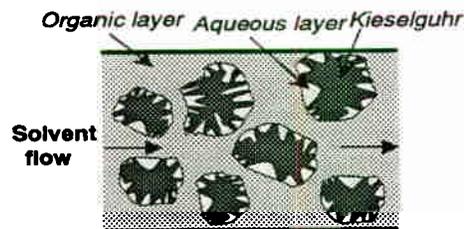


Figure 2. Principle of column extraction



*Preparation of [<sup>11</sup>C]amino acids*

Reaction scheme

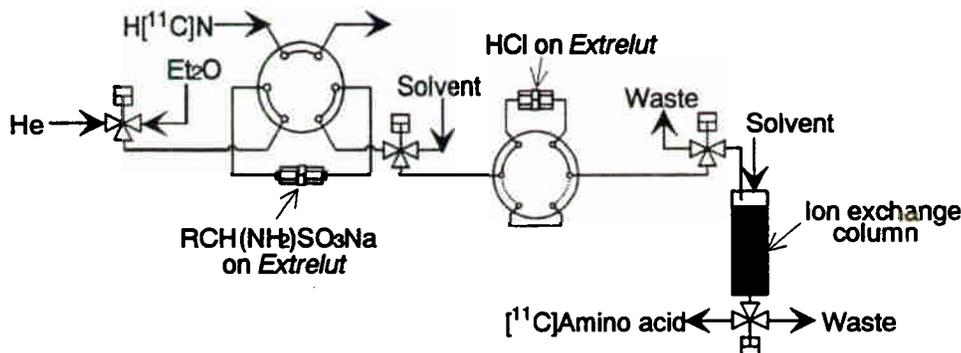
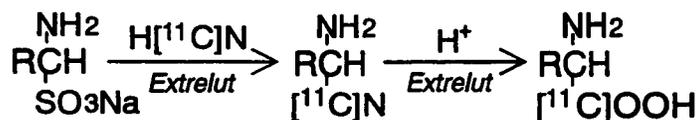


Figure 5. Automated preparation of <sup>11</sup>C-amino acids using *Extrelut*

*Extrelut* offers a very convenient and efficient extraction method for PET radiochemistry. It can be also used for on-column preparations of PET radiopharmaceuticals. Using the present method [<sup>11</sup>C]acetic and [<sup>11</sup>C]palmitic acids were obtained in >80% and 30–40% radiochemical yields, respectively. We are currently trying to apply the method to the preparation of [<sup>11</sup>C]amino acids. Synthetic procedures can be shown to be very simplified and easily automated using *Extrelut*.

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A: No, liquid. The Michigan group used gas, but we just use dilute HCl solution to decompose all reagents.

## USE OF SUPERCRITICAL CARBON DIOXIDE FLUID AS A SOLVENT FOR THE PURIFICATION OF PET RADIOTRACERS

R.A. Ferrieri\*, J.S. Fowler and A.P. Wolf  
 Brookhaven National Laboratory, Department of Chemistry,  
 Upton, NY 11973-5000 USA

### INTRODUCTION

Figure 1 represents a general phase diagram for a pure substance illustrating regions of temperature and pressure where the substance exists as a solid, liquid, gas and supercritical fluid.

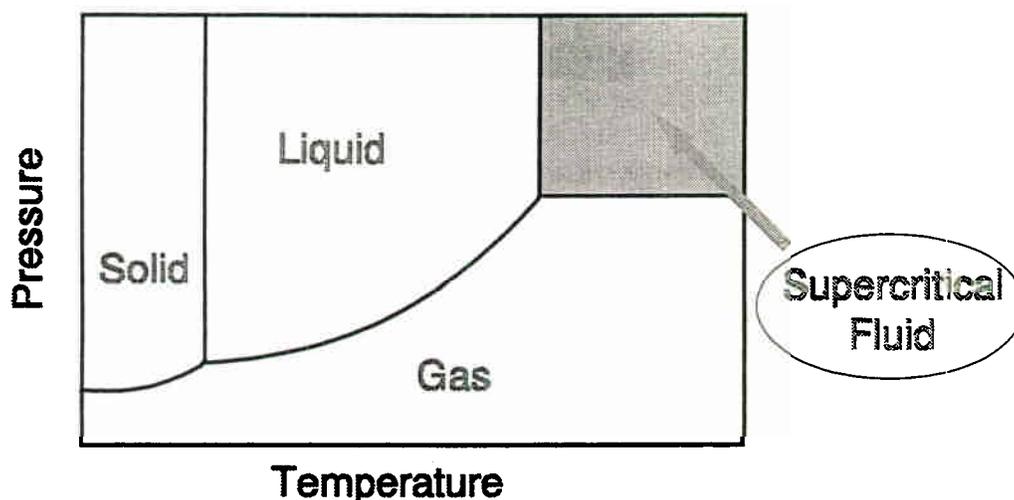


Figure 1. General phase diagram for a pure substance illustrating regions of temperature and pressure where a substance exists as a solid, liquid, gas and supercritical fluid.

A fluid can exist in its supercritical state when its pressure and temperature exceed the critical pressure and temperature of that substance which together define its critical point (CP). Above the critical temperature and pressure, the distinction between a liquid and gas disappears. However, the resulting fluid retains many of the characteristics of both phases. For example, the fluid possesses densities comparable to those of a liquid, but with a much higher diffusivity and a lower viscosity, much like that of a gas, thus affording it increased solvating power. Unlike conventional liquid solvents, supercritical fluids possess the unique feature that the solvating power of the fluid can be altered drastically because of its direct relation to fluid density. Thus small changes in fluid temperature and pressure within the supercritical regime can have large effects on fluid density. Table 1 illustrates this behavior with supercritical carbon dioxide fluid (SF CO<sub>2</sub>).

**Table 1**  
**Properties of SF CO<sub>2</sub> compared to helium gas and liquid water under**  
**conditions where they would be used for GLC and HPLC**

Property	Helium	SF CO <sub>2</sub> (low density)	(high density)	Water
Temperature (°C)	200	100	35	20
Pressure (psi)	20	1200	3000	1000
Density (g mL <sup>-1</sup> )	10 <sup>-4</sup>	0.1	0.8	1.0
Diffusivity (cm <sup>2</sup> s <sup>-1</sup> )	10 <sup>-1</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>
Viscosity (cP)	0.02	0.02	0.1	1.0

The density of SF CO<sub>2</sub> can be varied by nearly an order of magnitude. Comparisons against helium gas and liquid water, as they might be used in GLC and HPLC separations, respectively, indicate that SF CO<sub>2</sub> possesses features similar to both of these substances in their respective phases.

Supercritical fluids have found widespread use in numerous industrial and analytical fields as solvents for compound extraction (SFE)<sup>1-4</sup> and compound separation in chromatography (SFC).<sup>5-7</sup> Process SFE has been used for many years to selectively remove certain compounds in food and chemical processing industries. A classic example of its application here is the extraction of caffeine from coffee beans using SF CO<sub>2</sub>. Analytical sample preparation using SFE is also gaining use as a rapid low-cost method for extracting components from solid matrices prior to their analysis for quantitation and purity. The main advantage SFC has over conventional HPLC is its ability to provide faster compound separation times. This feature is primarily due to the lower viscosity of the SFC mobile phase affording it faster effective flow velocities through the column material.

SF CO<sub>2</sub> is one of the most widely used supercritical fluids because it is inexpensive, nontoxic, and can be made to assume different solvent strengths. This substance behaves as a supercritical fluid at temperatures exceeding 31°C, and at pressures exceeding 1050 psi.

Unfortunately, the nonpolar nature of the carbon dioxide molecule can limit its solvating strength in many instances. Its utility as a pure solvent in the SF state has been somewhat limited with regard to the extraction and separation large molecular weight polar compounds. Quite often, its solvating strength can be enhanced through the addition of polar modifiers such as methanol. Many of these modified mixtures are available commercially.

Recently, we initiated a feasibility study to determine whether existing technology in SFC could be applied to PET radiotracer purification as well. Specifically, we were interested in whether pure SF CO<sub>2</sub> could be used as a solvent in this step. SF CO<sub>2</sub> offers a feature that is particularly appealing to PET radiotracer purification. That is, the mobile phase will disperse as a gas once depressurized from the SF state, and easily vented since it is nonflammable and nontoxic. This action would eliminate the need for solvent removal prior to formulation of the radiotracer for injection; a step that can take as long as 10 minutes to accomplish depending on

the solvent volume, and no doubt result in product loss during the manipulation. With regard to carbon-11 labelling, a 10 minute delay reduces the amount of radioactivity delivered, as well as the specific activity.

## EXPERIMENTAL

**SFE SYSTEM DESCRIPTION:** Recently, we acquired an ISCO model 260D syringe pump that is capable of delivering 260 mL of solvent at pressures up to 7500 psi, and flowrates ranging between 1  $\mu\text{L}/\text{min}$  and 40 mL/min. The unit is designed for use in SFE as well as SFC. Figure 2 illustrates a schematic layout of the SFE system. The pump and control box are modular, which is a feature that is highly desirable for eventual installation into a production hot cell.

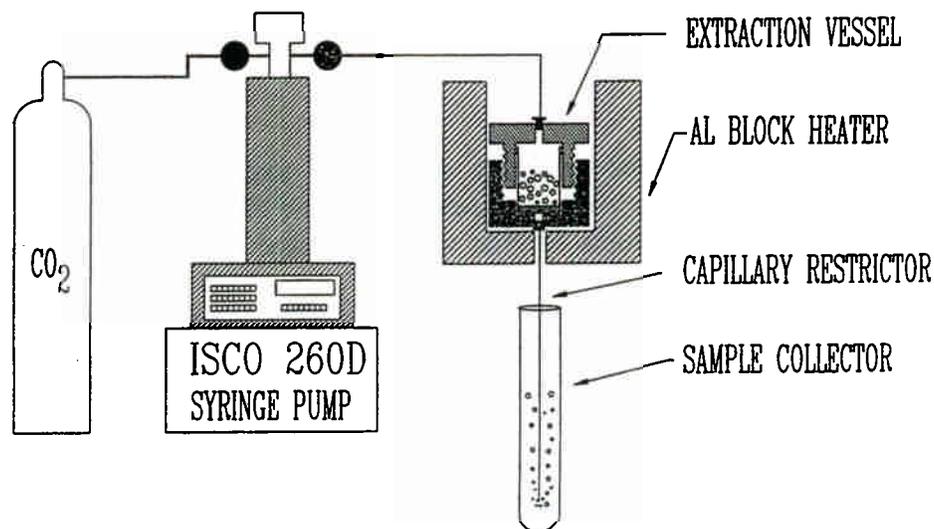


Figure 2. Schematic layout of supercritical fluid extraction system.

Solubility measurements were carried out in pure SF CO<sub>2</sub> at 5000 psi and 55°C on a host of PET radiotracers that are routinely prepared at BNL. This was accomplished by placing 3 mg samples of the hydrochloride salts of each of the compounds tested into a 0.5 mL volume extraction vessel outfitted with a 0.5 micron frit (Suprex Corp. SFE/10). The inlet to the extraction vessel was plumbed directly to the syringe pump via small-bore 1/16" OD stainless steel tubing. The outlet was connected to a 1 m length of 0.375 mm OD x 0.015 mm ID fused silica capillary tubing which acted as a restrictor in order to attain SF pressures within the vessel. The vessel was independently heated within a well-insulated aluminum block heater to insure thermal stability. Samples were solubilized in 10-12 mL of SF CO<sub>2</sub>, and collected in 1 mL of acetonitrile solvent at the restrictor outlet for later quantitation against standards using gas chromatography (GC) with flame ionization detection (FID).

**SFC SYSTEM DESCRIPTION:** Figure 3 illustrates a schematic layout of the SFC system. For operation in this capacity, the outlet of the syringe pump was connected to a Rheodyne 7125 injection valve via small-bore 1/16" OD stainless steel tubing. The Rheodyne seal was tightened to provide leak-free operation at pressures exceeding 5000 psi. The valve was connected to the separation column via 0.375 mm OD x 0.040 mm ID fused silica capillary tubing. The valve was installed as close to the separation column inlet as possible, but outside the column oven. We used an Eppendorf HPLC column heater to maintain SFC columns at appropriate temperatures. The outlet of the column was connected to Valco tee via 0.375 mm OD x 0.040 mm ID silica tubing. One outlet of the tee was connected to the FID of a HP 5890 GC through a 3 m length of 0.010 mm ID silica capillary tubing. The other outlet fed to a collector via a short length of 0.040 mm ID capillary tubing.

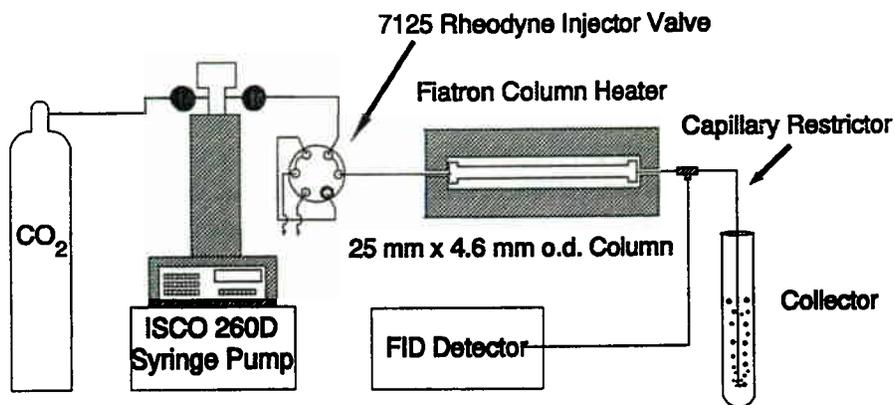


Figure 3. Schematic layout of supercritical fluid chromatograph.

Several advantages are offered in using FID in SFC. It is less expensive to purchase a FID than it is a high-pressure UV absorbance detector. Self-contained FID's complete with electrometer are available commercially. FID is also insensitive to  $\text{CO}_2$ , and therefore, would not exhibit baseline drift during SF pressure gradient operation. In addition, the detector is installed on the depressurization side of the SFC thus eliminating concern over maintaining proper SF pressures. Absorbance detectors, on the other hand, must be installed on the high-pressure side of the SFC because they are extremely sensitive to bubble formation within the flow-cell. Fortunately, FID is extremely sensitive to detect minute amounts of material, and therefore, would only sacrifice a minute fraction of the collected eluent for on-line mass measurement.

## RESULTS AND DISCUSSION

As seen in Table 2, results from the solubility tests have shown that organic compounds of interest in PET are sufficiently soluble in pure SF  $\text{CO}_2$  for purification as PET radiotracers. Typically, radiotracer synthesis yields compound masses of less than 20 micrograms.

Table 2

Compound solubilities in SF CO<sub>2</sub> at 5000 psi and 55°C

Compound	Solubility µg/mL
Raclopride	68
L-deprenyl	85
Cocaine	108
Ritalin	45
Cogentin	250
Flumazenil	61

We have also demonstrated in two instances that separation of the compound of interest from the labelling substrate is possible. Figure 4 shows SF CO<sub>2</sub> chromatograms of nor-raclopride and raclopride using a 75 mm x 4. mm ID, 3 micron silica column at 60°C with a pressure ramp of 500 psi/min (2000 to 7000 psi). Baseline separation is achieved on this analytical column with between 30 and 50 microgram amounts of material introduced in 20 microliter volumes of acetonitrile. Figure 5 shows SF CO<sub>2</sub> chromatograms of nor-deprenyl and deprenyl using a 250 mm x 1 mm ID Ultracarb 5 ODS (30) column maintained at 150°C and operated across a pressure gradient from 2000 to 5000 psi at 150 psi/min.

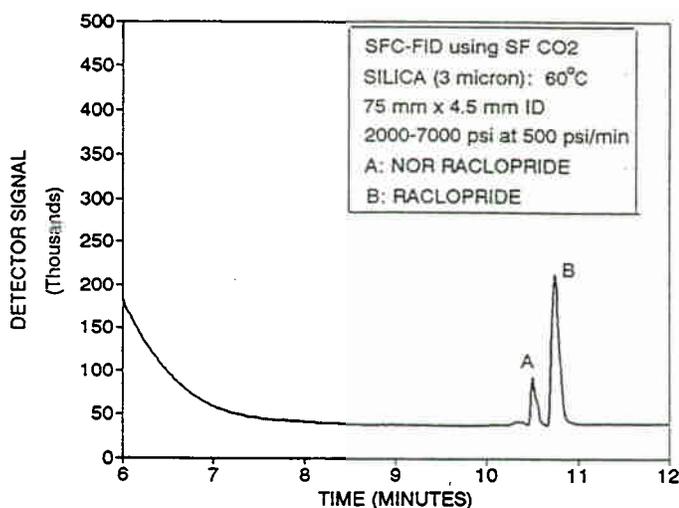


Figure 4. Supercritical CO<sub>2</sub> nor-raclopride and raclopride. Separations achieved on a 75 mm x 4.5 mm i.d. (3 micron) silica column at 60 °C using a pressure ramp of the CO<sub>2</sub> mobile phase of 500 psi/min starting a 2000 psi and ending at 7000 psi. Samples of nor-raclopride (30 micrograms) and raclopride (50 micrograms) were injected in 5 microliter volumes of acetonitrile. A flame ionization detector was used with a 0.1 % sample split on the column outlet.

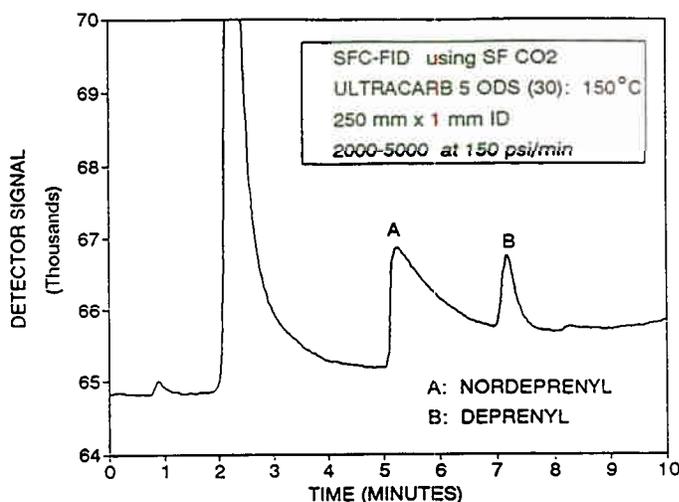


Figure 5. Supercritical CO<sub>2</sub> fluid chromatograms of nor-deprenyl and deprenyl. Separations achieved on a 250 mm x 1 mm i.d. Ultracarb 5 ODS (30) column maintained at 150 °C and operated across a pressure gradient from 2000 to 5000 psi at 150 psi/min.

Pressure programming of the mobile phase offers one of the most convenient ways to affect compound resolution in SFC. Most commercial SF compatible pumps offer this feature, as well as flowrate programming as standard features in equipment. As mentioned earlier, slight changes in operating temperature within the supercritical fluid regime can also affect compound resolution. Slight changes in column temperature can yield striking changes in solvating strength of the mobile phase as well as inverse changes in linear flow velocity. Both effects work in unison to either increase or decrease resolution between low molecular weight and high molecular weight compounds. This behavior is illustrated in Figure 6 where repeated injections of (L)-deprenyl dissolved in acetonitrile were made on a 250 mm x 1 mm ID Ultracarb 5 ODS (30) column maintained at temperatures ranging from 50°C to 150°C. The column was operated across the same pressure gradient in all instances ranging from 2000 to 5000 psi at 150 psi/min. At 50°C no resolution is achieved between solvent and compound. However, as the column temperature is raised by fixed amounts, one observes a decrease in the solvent elution time in accordance with an increase in linear flow velocity, and an increase in compound elution time in accordance with decreased solvating strength of the mobile phase. Interestingly, this later behavior reverses above 125°C indicating that other factors, such as surface interactions with the stationary phase are equally important.

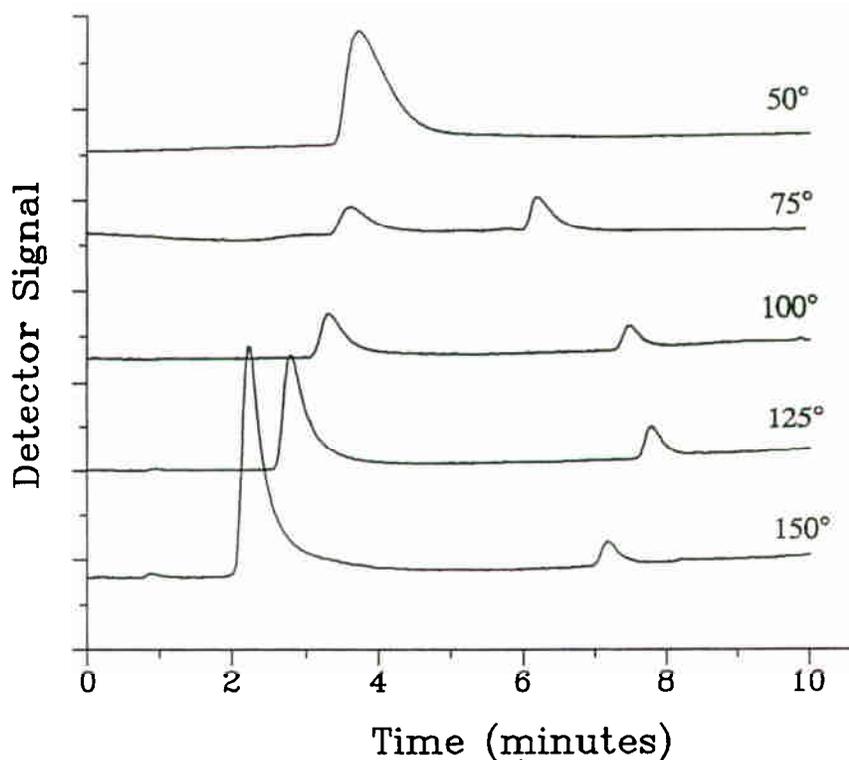


Figure 6. Supercritical CO<sub>2</sub> fluid chromatograms of (L)-deprenyl in acetonitrile. Separations achieved on a 250 mm x 1 mm i.d. Ultracarb 5 ODS (30) column maintained at temperatures ranging from 50 C to 150 C, and operated across a pressure gradient from 2000 to 5000 psi at 150 psi/min.

Not all compounds are well suited for purification by SFC. We discovered that ester groups are vulnerable to hydrolysis on passage through unmodified silica in SF CO<sub>2</sub>. For example, cocaine underwent complete hydrolysis to benzoyl ecognine during SFC separation, but remained intact during the simple solubility tests. This suggests that surface interactions play a key role in this chemistry. The silyl hydroxyl groups of the silica support can be strong sites for hydrolysis of esters. End-capping of these sites by passing tetrahydrofuran through the column at 1000°C for 12 hours suppressed the hydrolysis somewhat, although not entirely. This procedure yields a permanently bound layer of carbon and oxygen arising from the thermal decomposition of the organic substrate. Methodologies of this nature are essential if optimized radiopharmaceutical recovery is ever to be gained.

## SUMMARY

The advancement of radiotracer development depends critically on the implementation of new technology which offers advantages over the standard methodologies in the field. We have identified SFC as a promising method which could offer advantages in radiotracer purification through rapid separation, as well as, improved recovery and purity of labeled product. Using SF CO<sub>2</sub> as the mobile phase for chromatographic separation of labeled product would eliminate the need for solvent removal from product prior to delivery. Since large volumes of HPLC-grade solvents would not be needed operating costs for the purchase of these solvents, as well as for their safe disposal would be reduced.

Of course, challenges remain before this technique can become useful. Typically, SFC is an analytical tool and not a preparative one. Scaling up the analytical separations demonstrated here to semi-preparative levels necessary for radiopharmaceutical purification will be difficult owing to the fact that the increased column bore size that would be needed for increased sample throughput could yield uncontrollable pressure gradients within the column resulting in irreproducible elution times, as well as poor product recovery.

However, we are encouraged by a recent report which showed that <sup>11</sup>C-methylations using <sup>11</sup>CH<sub>3</sub>I can be carried out with reasonable efficiency in certain model compounds using supercritical ammonia fluid.<sup>8</sup> One of the striking features of this work was that the amounts of labelling substrate, as well as organic solvent used was significantly less than those used in standard practices for carrying out <sup>11</sup>C-methylations. This suggests that analytical scale SFC separations may be adequate for chromatographic purification of the labelled products when synthesized in the supercritical medium.

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**Supercritical Fluid Extraction: Rich Ferrieri. Brookhaven National Lab.**

**Discussions of Supercritical Fluid Extraction:**

**Q: B. Weiland: How do you creep up the pressure on the rheodyne valve?**

**A: R. Ferrieri: There are little set screws underneath. Read the instruction manual, they give you a little allen wrench, and you just turn it carefully. If you tweak too far, you can break the seal on it.**

**Q: J. Link: I think supercritical fluid extraction chromatography is going to be used more in our field because you can get rid of the solvent, i.e. CO<sub>2</sub> so easily and I think maybe compounds that people have trouble separating in final preparation could be taken through these columns, instead of the current situation of having to use a few percent ethanol in buffer for the mobile phase or getting rid of the solvent. I know that extraction works, but I don't know whether swelling and pressures prevent preparative chromatography or how much sample you can really put on these systems.**

**A: R. Ferrieri: That is going to be a limitation. The work I'm doing, is purely on an analytical basis. The column will certainly handle the loading with compound. I don't think there will be a problem with that. Actually, if you look at the solubility numbers, 50 to 60 micrograms per milliliter and you subject the flushing of say your reaction mixture onto the column, set the time limitation there. You are only going to take a certain cut of the compound. Usually we put in 1 milligram of the starting material in an alkylation. So you are not going to be putting that entire sample onto the column. There is going to be a problem though, while you can get the sample through the column, it is the outlet where the restrictor is. Those capillary columns are not amenable to high sample load and they tend to plug up. So what I am looking at right now is trying to multiplex a number of these capillaries to take the sample through put to the collector.**

**Comment J. Link: Also I know you don't need to use an FID detector. You need the restrictor, but there are a lot of detector options on those systems.**

**Rich: Yes, there are a number of options. You can use radiation detectors or other detectors to take your product cut. We just like the FID from the standpoint of measuring specific activity that has some kind of mass detector right on our analytical separation system.**

**Q: J. Clark: Rich, just to sort of complete the education process, what other solvents are potentially useful in this area?**

**R. Ferrieri: Nitrous oxide. Bengt Langstrom in fact has an abstract at Kyoto where he's demonstrated some chemistry in a supercritical fluid ammonia. Water. In fact the literature is chock full of references where supercritical fluid water does all sorts of neat chemistry, so that's something else that might be worth looking at.**

**Q: T. Ido : It is very interesting Rich. Do you know of any other other examples for the (chemical) reaction with CO<sub>2</sub> during the separation of some compounds?**

**A: R. Ferrieri: I've seen some reference to condensation reactions. Not in structures similar to deprenyl. I don't know whether that alkyne group has introduced some kind of a highly**

active site there. As I say, until I can fully identify what that product is, I'm not going to stick my neck out and say that there is any type of reaction going on, but there are examples in pure CO<sub>2</sub>.

Q: Doug Channing: Did you measure the number of theoretical plates and do you know the flow or linear velocity in columns like this?

A: R. Ferrieri: I have not measured the number of theoretical plates in the column. The flow is pressure ramped, usually start at about 1 milliliter per minute, and never exceed 4 milliliters per minute at the high pressure end of the ramping.

Comment: J. Link: Just a comment about other fluids. I think the limitation is fluids or things that have critical points at room temperature and a reasonable pressure. The ones that people typically talk about using, around 30, 40, 50 degrees centigrade, are nitrous oxide, CO<sub>2</sub>, sulfur hexofluoride, and ethane.

## PRESENTATION OF THE FDG MicroLab

Jacek Koziorowski, GEMS PET Systems AB, Husbyborg, Uppsala, Sweden

The initial report on the MicroLab was presented at the IV<sup>th</sup> target workshop at PSI, Switzerland in 1991. It was a technical description and a presentation of the specifications, yet no experimental data was presented. This presentation is based on data and experience from the clinical sites and is therefore an experimental data presentation and not a product specification. The synthesis is based on the solid-phase Mulholland method. The yield and radiochemical purity depends on the quality (purity) of the target water. The nature of the target water impurities is, at the time being, not known.

### Installed base

Uppsala University PET Center, Uppsala, Sweden

Rigshospitalet, Copenhagen, Denmark

Duke University, North Carolina, US

John Hopkins University Hospital, Baltimore, US

Praxisgemeinschaft RNS, Wiesbaden, Germany

### Data

This data is based on a total of 201 syntheses performed with MicroLab.

Yield(not decay corrected)	35%
Radiochemical Purity	97%
Failures <sup>1</sup>	2%
Acetonitrile	<50ppm
CIDG	20g/ml
"cold" FDG	3g/ml
4-methylpiperidinium	<2ppm
Synthesis time	52min
Synthesis setup time	10-40min

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<sup>1</sup> Failure; yield < 20 % or radiochemical purity < 90%. The FDG MicroLab executed the synthesis without any problems (= failure not due to mechanical malfunction).

### Problems/bugs

The cassette is symmetrical from a vial point of view; there are two possibilities to ~~add~~ the vials containing the chemicals needed for synthesis, either: 1,2,3,4 (the correct way) or 4,2,3,1. If you apply the vials according to the latter schedule the synthesis will not work (you start with HCl and finish by adding precursor).

Action: the vials are now both numbered and color coded for easy recognition.

To close the front lid one has to push two buttons, simultaneously which are placed on the top of the sides. This may cause some problem if the unit is placed in a high hot cell; a short person may not reach the buttons.

Action: a dedicated, shielded box was designed (which also takes care of the used cassettes).

### Comments from the audience

Duke: agreed with the results presented. Made a remark that the failure rate might be somewhat misleading since it did not include the "unbegan" syntheses where the cassette was rejected due to leak (leak in the cassette and/or in the syringes), these failures were quite uncommon (no statistics reported) according to the customer. They have had some trouble in depositing all activity in the receiving vessel; they use a 300µl target, the box is designed to receive 0.5 to 2.5ml of water.

Uppsala PET Center: agreed with results; no further comments.

University of Michigan, Ann Arbor: said that results presented ( yield, failure rate etc. etc.) were virtually identical with their results; the machine is as good as a person.

Results from the Clinical Use of the FDG Microlab. J. Kozirowski. GE Medical Systems. Uppsala, Sweden.

#### Discussion of the Microlab:

Comment from J. Clark: This system is based on the solid phase Mulholland chemistry which many people have tried and I think we have all been skeptical that it could really be commercialized. I wondered if any of the customers who use the microlab are willing to comment on their experience with it?

Comment: C. McKinney: I agree with the data presented by Jacek Kozirowski. We have had very good synthesis results. Everything you presented is correct for yield. However, you list zero mechanical failures; this is misleading. Once the synthesis starts that is true, but there are failures before the synthesis begins. Occasionally we have failures when a cassette is inserted into the mechanism (box) and does automated pressure testing to make sure there are no leaks. Occasionally we have problems with this test and we have to discard the cassette. Once we get the cassette out of the box it is common that it is functioning (ie. pressure tight) and we wouldn't have had a synthesis failure using that cassette. This is a minor problem, in general our experience has been very good.

Comment J. Moskwa (Michigan): For comparisons sake, the results of the microlab are identical to those yields we get by hand labeling.

R. Reineck- PET Centre , Uppsala. We are now completely relying on the microlab to make FDG.

Q: T. Ruth : Has the failure rate anything to do with the extraction onto the column resin?

A: It is hard to tell because most of the people who buy this unit are absolute beginners. Sometimes they have little errors and they don't know why, and I mean there are small things for which I can't tell what happened. Maybe after a couple of years when people have used it we will be able to answer this question. I intend in our factory to run it on a daily basis but we have the entire results of everything run and we haven't any general trend in what goes wrong. For example, if you store it in a very dry atmosphere the resin column gets broken up and it is hard to pass fluoride through?

Comment J. Clark: I think taking equipment out in the field in the commercial sense is fraught with all sorts of pitfalls and traps but I think this group ought to be willing to feedback the sort of information we take for granted from people like Jacek Kozirowski, so that the field can be more reliable.

Q: Mike Channing: Has there been any modification of the resin since Mulholland's publication and a second question, has anybody looked for piperidine in the product?

A: As to residues from the column in the product, 4-methylpiperidinium, at a maximal level is 2 ppm, is the only thing we find from the column. I can't answer about changes in the

resin.

Comment from Michigan: The resin is much the same, it's just the manufacturer from whom you buy the resin that is the question. There was a general group debate as to how stable the resin would be with storage, that was not resolved.

Q: B. Wieland: Will shielding be available for the unit?

A: Yes, we have shielding or a hot cell you can buy.

Q: J-L Morelle: What is the price for replacement card cassette?

A: Uno Zetterberg, GE. The price is approximately \$100.

Q: J. Link: You present the final product yields which are good. However, this is a system just entering the market and you could use more information to understand failures and improve reliability. Are any of your data sites trying to get more information? Is anybody doing HPLC? Is anybody measuring the activity in the water that isn't retained on the resin? It would be nice to get a good database on these parameters.

A: C. McKinney. We do very minimal testing at Duke. The efficiencies are based on final mCi yield. We look at the product activity and what's left in the box at various places. In general the extra activity is on the resin or there is a purification problem. Bruce is saying that I should mention a small problem that we have had with yield is using a small volume target with 300-350 microliters of water. The GE microlab was designed for use with their systems, i.e. for 1 mL target volume. We have had trouble in depositing the entire 350 microliters from our target into the receiver vessel on the box because with that small volume it is easy to trap a drop or two and we lose a 100 mCi in the delivery sequence. So there is some improvement that could be made.

Comment J. Nickles, Madison: If you want to do a perfect analysis of the activity, the simple thing is to image the cassette in a scanner or gamma camera.

## Advances in the Robotic Production of Radiopharmaceuticals

Mallinckrodt Institute of Radiology  
Washington University School of Medicine  
510 S. Kingshighway  
St. Louis, MO 63110

Greg Gaehle and Michael J. Welch

### Introduction

A variety of robotic systems, including Zymark, Hudson Control Group, Anotech, and Questech formerly U.M.I, have been used as a reliable and safe way to produce radiopharmaceuticals. A robotic system's ability allows it to produce a variety of radiopharmaceuticals on a routine basis including final preparation and quality control. With proper scheduling, a single robotic system can synthesize  $^{18}\text{F}$ -fluorodeoxyglucose,  $^{18}\text{F}$ -estradiol,  $^{11}\text{C}$ -acetate,  $^{68}\text{Ga}$ -citrate and at the same time control black box type syntheses such as  $^{15}\text{O}$ -butanol in a single day. A robotic system's flexibility allows it to be used in designing and testing new syntheses, thus making the development of the new radiopharmaceuticals safer for the chemist.

The development of Windows<sup>TM</sup>, a multi-tasking operating system for PC computers, allows a robot controlled by that computer to function simultaneously with a large variety of other systems. This increases the system's ability to communicate with other systems and it allows for change without replacing the entire system.

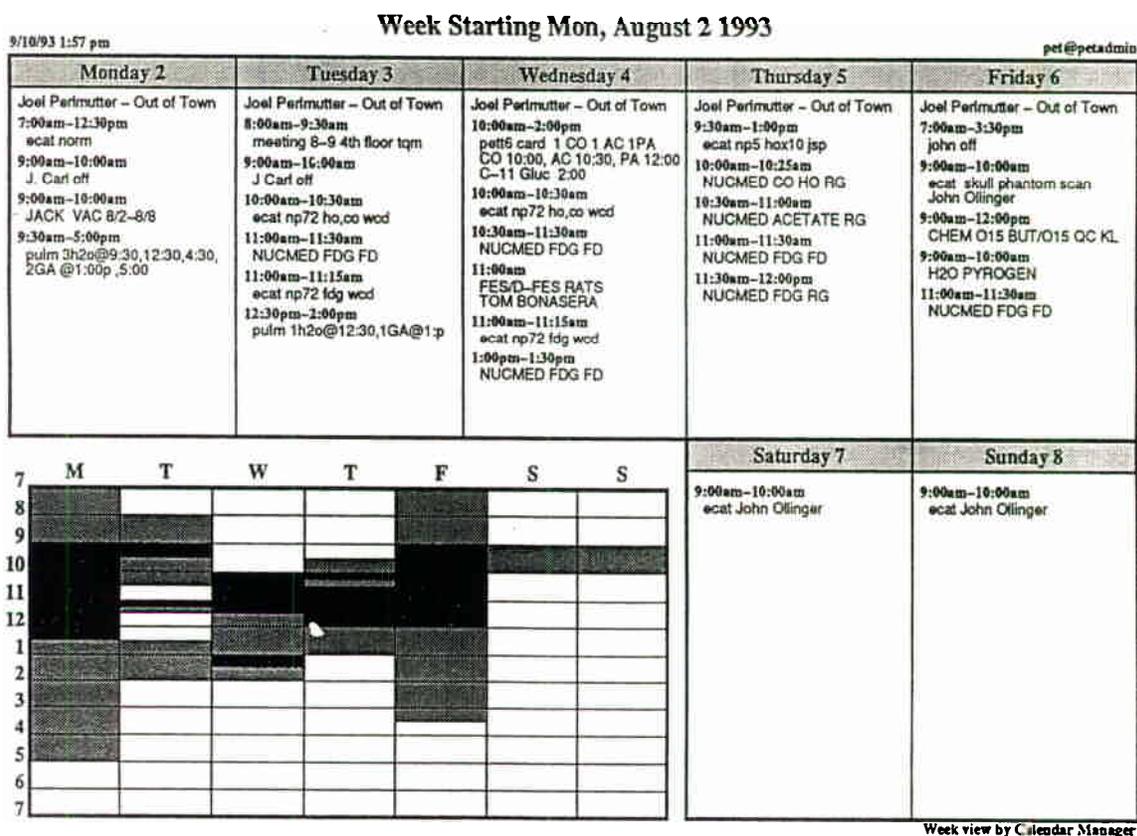
Improvements in robot technology has increased their reliability while making them competitive in price to other means of automation. Today a robotic system to produce  $^{18}\text{F}$ -fluorodeoxyglucose can cost as little as \$55,000 U.S. depending on the cost of the hot cell.

### Communications

The improvements that have occurred in the hardware of PC computers and their operating systems have made the robots they control more useful and flexible. Improvements in Windows<sup>TM</sup> have enhanced a robotic systems ability to communicate with the outside world and other peripherals. The development of software written specifically for Windows to control a robotic system allows the system to operate simultaneously with other applications. At Mallinckrodt Institute of Radiology we use Total Control for Windows a software package developed for Windows by Hudson robotics to control our robot and a variety of other PC controlled devices.

Being able to communicate with other computer systems can simplify paper work and scheduling. Figure 1. represent a schedule pulled off a workstation at Mallinkrodt. All of our PET scanners are controlled by different workstation that are also used to keep patient records. The robot and accelerator/cyclotron are controlled by PC computers. The drug manufacturing reports (Figure 2.) that are needed by the manufacturer and the doctors are generated on PC used to control the robot. By hooking up lines of communications between these systems, the amount of time and effort needed to coordinate and keep tracked of all the activities involved in a PET study is reduced. Our line of communication was set up using a ethernet board 3COM 3503 and using Chameleon NFS to hook up to the network. Chameleon NFS (NetManage) written for Windows makes it easy to transfer files from a windows application into Chameleon NFS. Then Chameleon NFS can make the files available to the network.

Figure 1



Being able to communicate with a variety of computer systems can simplify management but the ability to multi-task has increased the versatility of robotic systems. Working in a Windows environment using the software package Total Control for Windows, makes it possible to run one application while improving or developing another. The user can also run multiple applications allowing the integration of a large variety of peripherals into their system.

Figure 2

**MALLINCKRODT INSTITUTE OF RADIOLOGY  
RADIOPHARMACEUTICAL COMPOUNDING RECORD  
2-[<sup>18</sup>F]FLUORODEOXYGLUCOSE**

DATE: 8-4-93  
 PHARMACY CONTROL NUMBER: 000518  
 QUANTITY PREPARED: 9.35 ml  
 EXPIRATION: 8/4/93 16:23

PROCEDURES: See master formulary card

INGREDIENT	MANUFACTURE	LOT	EXP. DATE	QUANTITY	INT.
D-18 WATER	Isotec	84.6%	-----	1.2 ml	
DOWEX 1 RESIN	MIR	CRT-1	-----	15 mg	
AG11A8 ION RETARDATION RESIN	BioRad	45898A	-----	3 g	
ALUMINA	Aldrich	03809H7	-----	100 mg	
1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethanesulfonyl-beta-D-mannopyranose	Aldrich	04221JZ	-----	20 mg	
4,7,13,16,21,24-Hexaaza-1,10-diazabicyclo-[8.8.8] hexacosane	Aldrich	0552KW	-----	8.0 mg	
Acetonitrile	Aldrich	04840CF	-----	2.1 ml	
Diethyl ether	Fisher Scientific	923942-15	9/93	3.0 ml	
0.02 M K <sub>2</sub> CO <sub>3</sub>	M.I.R.	PC-4	11/19/93	1.0 ml	
1 M HCl	M.I.R.	CA-6		3.0 ml	
0.1 M HCl	M.I.R.	DA-7	11/19/93	10 ml	
Ethanol	M.I.R.	A-8	6/11/93	20 ml	
3 N NaCl	M.I.R.	S-3	12/16/93	3 ml	
Sterile Water	Abbott	69-903JT	4/1/94	1000 ml	

Type of container:  Glass (clear)  Plastic

Appearance of final product: clear and colorless

Product concentration: 6.25 mCi in 3 ml = 20.83 mCi/ml at 10:23 (time)

pH of Preparation: 6.0

Radiochemical purity: 99.62%

Checked by (R.Ph): \_\_\_\_\_

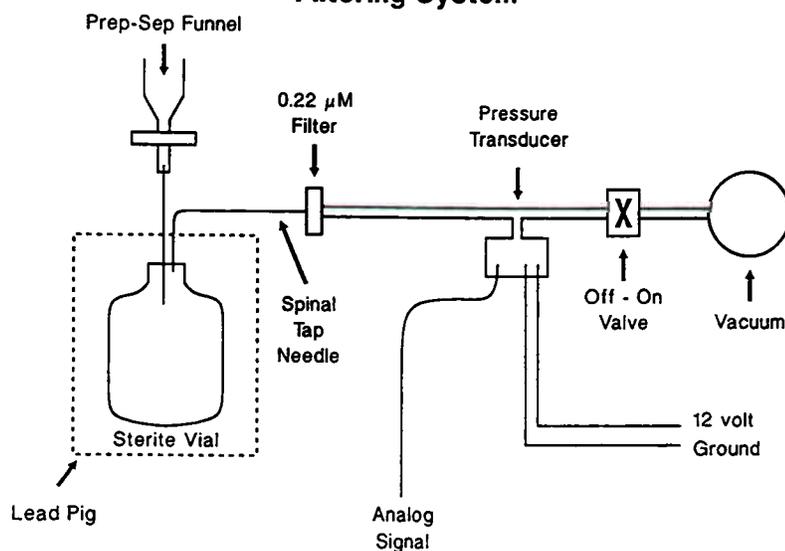
Date released: 8-4-93

Comments:

Patient Numbers: \_\_\_\_\_

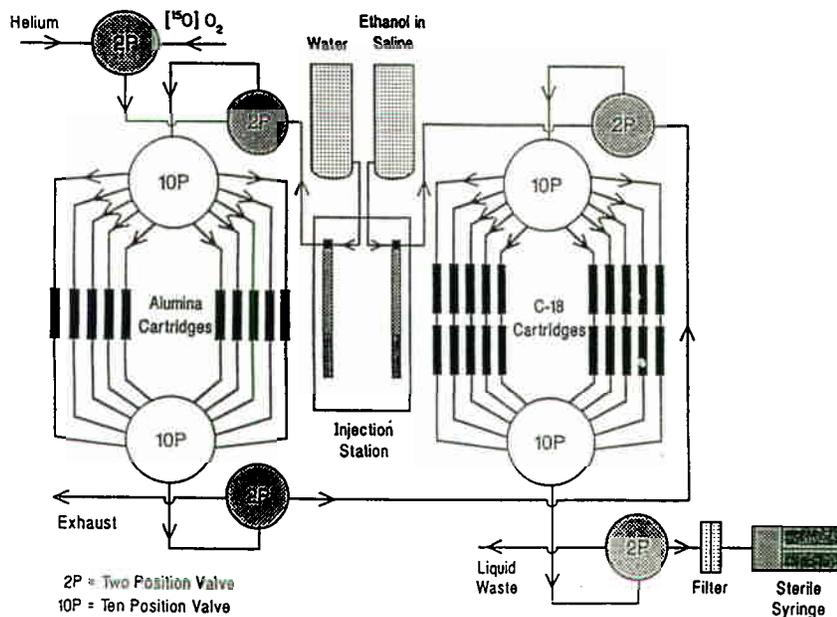
Figure 3 represents a filtration device used on all of our robotic systems. In order to use this device the loss of vacuum over time must be determined. After the filtration is complete the vacuum is cut off from the system by a two way valve. The loss of vacuum is then determined over time using a pressure transducer that measures vacuum. Determining vacuum loss requires a little time, but it can be determined while a synthesis is in progress if the robotic system is controlled by a PC operating with Windows. Thus a robot being used for routine production of radiopharmaceuticals can also be programmed to perform other syntheses while in use.

**Figure 3**  
**Filtering System**

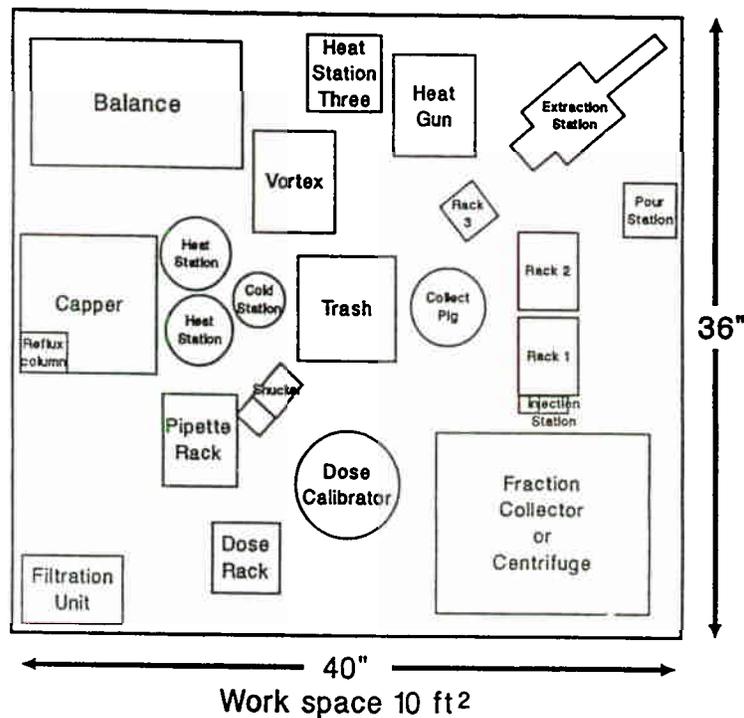


Multi-tasking with Total Control for Windows allows the user to operate multiple systems simultaneously. Figure 4. represents a system developed to produce ten  $^{15}\text{O}$ -butanol doses with a single setup and Figure 5. represent the Hudson robotic system with all of its stations. Both of these systems can be operated simultaneously with one computer by one operator using a multi-tasking environment like Windows.

**Figure 4**



**Figure 5**  
**Hudson Robotic Hot Cell Layout Ceiling Mount**



Multi-tasking also allows two systems that run under completely different software packages to operate simultaneously. This is the case with our Hudson robot and SSI HPLC systems. This also allows one to use the computer for other task like word processing or data analysis while the robot is operating.

#### Cost

The cost of robotic systems have remained stable over the years while becoming more reliable and flexible. In practical terms the actual cost is less with inflation. Figure 6. represents the estimated cost of a robotic system to synthesize  $^{18}\text{F}$ -fluorodeoxyglucose and a variety of similar syntheses.

**Figure 6**  
**Robotic System Cost List for the Synthesis of FDG**  
**Washington University Hot Cell**

Equipment	Cost in U.S. Dollars
Hot cell Wash. U. machine shop	18,000.00
Robot system (CRS)	19,525.00
Servo-Gripper	2,300.00
Digital I/O rack	530.00
Digital isolators	400.00
Expanded memory	1,300.00
Homing Bracket	500.00
Robcomm II	700.00
Hamilton dispensing station	3,425.00
Capping Station	4,200.00
Racks depending on preference	1,000.00
Hot plates *3	240.00
Heat controllers *3	825.00
Pipetting Hand Unit	1,000.00
<b>Total Cost</b>	<b>53,945.00</b>

### Conclusion

Robots are becoming more economical and useful as technology improves. Improvements in system controllers (PC computers) have made management for clinical production and implementation of a variety of syntheses simpler.

A robotic system that costs less than \$60,000 can be set up to produce a radiopharmaceutical such  $^{18}\text{F}$ -fluorodeoxyglucose, perform quality control, and then generate a production report providing full details on progress of the synthesis, quality of the product and chemicals used in production. The robot will then be able to send this information on to the end user and the producer. The Pharmacist can use this information to verify quality and track cost, while the producer can use this information to verify quality, track inventory and assist in billing.

As technology changes, robots remain useful because they can change. Robots controlled with a PC can change and add stations as necessary without affecting the functions of the arm. Software changes can be accommodated by simple installations. And failed arms can be replaced by a newer version without upgrading the entire system within the hot cell.

Advances in the Robotic Production of Radiopharmaceuticals. G. Gaehle. Washington Univ., St. Louis.

**Discussion of Robotic Production of Radiopharmaceuticals:**

**Q: What pressure do you regularly run your bubble test at?**

**A: We don't do a bubble test, but we test integrity with 15 psi of pressure.**

**Q Yes but is 15 psi high enough to do a filter integrity test?**

**A It depends on the rating of that membrane.**

**Q: Is there is a specific rule that if you are going to do a bubble test you have to use a specific pressure?**

**C: Mike Welch: Barry Siegel at Washington University was head of the USP radiopharmaceutical subcommittee for many years and he is satisfied with the way that we verify our filter integrity. I have a question. How many people in this room when they make things like O-15 water, test their filter integrity? I know it doesn't happen often that a filter fails, but it is something that we have been made to verify. (Very few groups responded that they were doing this measurement).**

**Comment from Duke: We use a sterile filter before injection and we opted not to use the test kit. Millipore sells a test kit. They have a little hand pressure pump which you can put a pressure guage on . I believe their bubble test on a wet filter is no bubbles below 40-50 psi. There is no sense in going to 50 psi to see the bubbles because we are only putting a tender 12 psi on it in operation, so there wouldn't be any source of pressure higher than that on the membrane.**

**Comment from J. Link: The United States Pharmacopeia (USP) has sections on sterility, test procedures using membrane filtration, and sterilization by filtration which discuss the methods to test the filters used for sterility assurance and for membrane integrity. Integrity tests described are bubble point test, diffusive airflow test, pressure hold test and forward flow test. All of these tests should be correlated with microorganism retention.**

## **Application of an Industrial Robot to Nuclear Pharmacy**

Jeff Viola  
University of Michigan  
Ann Arbor, MI

### **ABSTRACT**

Increased patient throughput and lengthened P.E.T. scan protocols have increased the radiation dose received by P.E.T. technologists. Automated methods of tracer infusion and blood sampling have been introduced to reduce direct contact with the radioisotopes, but significant radiation exposure still exists during the receipt and dispensing of the patient dose. To address this situation we have developed an automated robotic system which performs these tasks, thus limiting the physical contact between operator and radioisotope.

### **INTRODUCTION**

The chemistry laboratory is located in a building fourteen hundred feet away from the hospital. The vial is shipped to the hospital in a plastic casing called a rabbit which rides in a tube under the ground between the buildings. When it arrives the person receiving it must extract the multi-dose vial, possibly containing several hundred mCi, from the rabbit and then prepare a dose. Prior to the installation of this robotic system the preparer would have to manually unscrew the lid from the rabbit then draw off the compound into a syringe by hand. After multiple tries between assays the proper amount was obtained. To eliminate this unfortunate circumstance we have developed a hands off system to receive and prepare patient doses. This system utilizes a Unimate Corp. Puma 260 six-axis robot arm with a two-finger gripper. This model has a 46.2 cm (18 in.) reach and 1 kg (2.2 lb.) payload. The robot arm acts solely as a transfer mechanism. All complex operations such as dose reception and measurement are performed by eight separate specialized stations, they are; receiving, separation, vial cup, dose calibrator, weighing, dock, draw off, vial store. Control and actuation of all station functions is provided by Humphery Series S410 stackable pneumatic control valves coupled with Compact Air Products, Inc pneumatic cylinders. Banner optical sensors are located at each station to assure task completion and to track the location of the vial. A menu driven user interface facilitates ease of operation.

### **PROCEDURE**

The user must first decide whether a dose is needed from the vial immediately or stored for future use. Then the compound/isotope is chosen from a list. As the rabbit enters the environment the robot moves to the receiving station to retrieve it. It then places it in the separation station, where the rabbit is pulled apart and the vial is obtained. The vial is now assayed. It is placed in a Capintec well and then placed on a balance for the purpose of obtaining volume (the density of water and the average tare weight of a vial and label is used for this calculation). If the user chooses to use the vial now he or she have the option to automatically (or if necessary, manually in the case of minimal activity or O-15) draw the dose. In an automatic draw off the vial is

placed in a gripper on the pump-station. An empty syringe is also placed on the station. The station then performs a single needle draw off, based on the concentration and the amount requested for a user-specified future time. For an average dose of 2mL, the draw off procedure takes approximately two and one half minutes to complete including vial handling. One minute of that is for actually drawing the dose (i.e. approx. 0.5 min./mL). After the dose is in the syringe it is placed in the Capintec for verification of the requested activity. Finally, the syringe is placed in a lead shield for transport to the patient. The full procedure of receiving a new vial and delivering a dose to the user takes around three and one half minutes. At this time the vial is re-assayed as upon reception and then placed in lead shielded storage. The robot's computer maintains the identity, contents, and position of each dose vial in memory for subsequent re-use, this information is available in tabular form on the operator's console. From here the user can now choose one of these vials for an immediate draw off, reflecting only the time to pick up the vial and syringe then place them on the draw off station and complete the draw off itself. The entire assembly is compact and can be housed in a standard chemical hood - with only strategically located lead bricks, a movable lead window, and the Capintec's own environmental shield for radiation protection.

### STATION DESCRIPTIONS

The following is a brief description of the specially developed hardware components that support the operation of the robot system.

**RECEIVING STATION:** This device is affixed to the rabbit delivery line and includes a sliding trap door and an elevating cup for the assembled rabbit to drop into. Upon successful reception of the rabbit the robot is able to remove the rabbit from this station and place it into the separation station.

**SEPARATION STATION:** This device includes a vertically displaceable three finger gripper to grasp the rabbit body and a guillotine like blade to hold the base. Successful rabbit separation allows the multi-dose vial to be grasped by the robot and removed from the base for further processing.

**VIAL CUP STATION:** This is simply a cup to accept a multi-dose vial which itself is placed in a socket atop a tower. This simple device serves two purposes. One is to establish a precise and repeatable elevation position for the multi dose vial. The other is to facilitate fitting the multi dose vial into the dose calibrator station.

**DOSE CALIBRATOR STATION:** This station incorporates a Capintec brand dose calibrator well with a simple elevator system that includes a special socket. The socket is designed to accept the plunger end of the Syringe/Holder and maintains the holders rotational configuration. A hole board in the socket to accept the plunger allows for the insertion of a bare syringe in a needle-first orientation for manual use of the dose calibrator. The socket also accepts the Vial/Cup for assay (the cup stops the multi-dose vial from falling through the hole).

**WEIGHING STATION:** An A & D model:EK120A small foot print balance with an RS-232

interface has been modified to include a light weight plastic receptacle for precision placement of the multi dose vial.

**DOCK STATION:**An aluminum stand to support the lead syringe shield; which is explained below. This device houses micro-switches and optical sensors for verification of shield and syringe placement.

**DRAW-OFF STATION:** This apparatus is based on a commercially-available syringe pump that includes an RS-232 interface. The original V-block syringe slot was modified with a saddle like fixture. It incorporates a conical locking plunger to securely attach the Syringe Holder in a vertical orientation - needle up. Because operation of this system requires both compression and extension of the syringe plunger there is another short stroke gripper which engages and holds the plunger base. In addition, there is also a device to grasp and hold a multi dose vial in an inverted position. This device moves the vial downward to allow the syringe needle to pierce the resealable rubber septum of the dose vial. It then withdraws upwards, disengaging the needle to allow the robot to remove both the Vial/Cup and the Syringe/Holder for further processing.

**VIAL STORE:** This station is a ten-well lead enclosure designed as a shielded storage area for dose vials. As doses are received the robot places each vial in a storage well and the software designates each well position by isotope and compound type. Individual pneumatic elevators for each well raise vials to allow the robot arm to remove doses from storage.

### **ADDITIONAL SUPPORT HARDWARE**

**RABBIT MODIFICATIONS:** The standard pneumatic rabbit originally in use is about 3-1/2 inches long, 1-1/4 inches in diameter and includes a simple screw-on base. This base was replaced with a snap-on unit that includes a socket to receive a standard multi-dose vial and a special slot to enable a guillotine-like blade to hold the base during separation from the body.

**SYRINGE SHIELDS:** These hinged clam-like lead devices shield the PET Technologists from the loaded syringe containing the radioisotope. When mounted in the robot cage the top lid is open to allow the robot grippers to grasp and manipulate the Syringe Holder as it readies a patient dose. They are moved in and out of the robot cage as well as transported from the Nuclear Pharmacy to the scanning room. Additionally, they then mount directly in the socket of the Auto Injector System for remote administration of the patient dose in the scanner room. When transporting and injecting the dose the top is locked shut to reduce personnel exposure from the radioisotope.

**SYRINGE HOLDERS:** These devices are aluminum bodied enclosures designed to house 5 and 10 ml Becton Dickinson sterile syringes. They feature a pivoting access door for loading and unloading new syringes, a conical hole docking port for alignment and stabilization in the Syringe Pump station and a square edged protrusion to block axial movement in the Syringe Shield. They were developed to enable the robot to handle the syringes without direct contact between the robot gripper and the syringes.

## SOFTWARE

Menu driven software allows the user to choose via lists virtually all of the necessary information needed to perform its function. Only activity quantities need to be entered explicitly. The software incorporates error algorithms which check ahead at each station for debris left behind by human or robot. After the task (i.e. move the multi-dose vial to the balance) is assumed complete, a check is made to make sure this is true. If an error occurs a message and a standard style three option menu is given. The user can then choose to retry, override and continue, or return to the main menu.

## CONCLUSION

The robot system has been used successfully for three months. In automatic mode the robot system receives a multi-dose vial which has been shipped from the chemistry laboratory inside a rabbit. The vial is removed from the rabbit and a calibrated dose is drawn into a syringe with a single try. The operator's hands experience minimal radiation during this process. The operator's total radiation dose can be drastically reduced by the performance of the robot system and its shielding.

## **Control of Radioactive Material Pneumatic Transport System using an Inexpensive Programmable Logic Controller**

**Barry Dembowski and Carlos Gonzalez-Lepera  
Center for Functional And Metabolic Imaging  
Hospital of University of Pennsylvania  
Philadelphia, Pa 19104**

### **Introduction**

The Flexo-Rabbit Pneumatic Transport System provided by Intertech Nuclear Products Division was installed at the University of Pennsylvania Cyclotron Facility in 1987-88 connecting the Cyclotron Facility to the PET center with 390 m of tubing. The original transport system had two receiving stations, one for the PET center in the University Hospital and one in a Radiochemistry Research Lab located in a Medical Research Building. A diverter station located in line controlled the destination of the transport capsule.

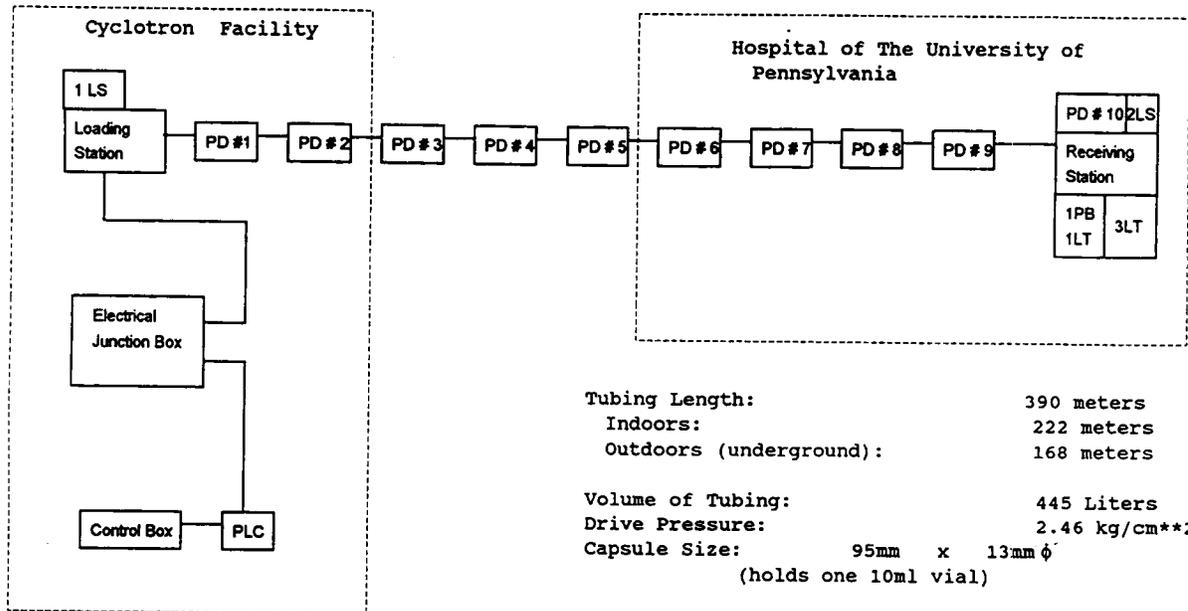
With the removal of the research lab station and diverter, modification of the control system was necessary. Space restrictions around the Cyclotron Radiochemistry Lab also demanded a better solution to the Personal Computer/interface box control system, without jeopardizing the systems safety interlocks.

We selected a Programmable Logic Controller (PLC) and a small control box of our own design to replace the original equipment. In addition, we introduced a new loading station in an effort to reduce radiation exposure during operation.

The requirements for the replacement system were:

1. Reconfigure the system controller for one loading and one receiving station.
2. Reproduce the Safety interlocks from the old system controller.
3. Minimize the size and space requirements for new hardware.
4. Provide a system controller that can be easily modified in the future.

## Block Diagram



### Requirements for interlocks:

Because of the nature of the transport material, particular attention was directed to insuring that the control system operate with the following interlocks:

- A. In order to initiate the transfer of a capsule, personnel are required at both the sending and receiving station.
- B. The receiving station port must be closed before one can initiate a transfer and the sending station port must be closed before sending a capsule.
- C. During the transfer of a capsule if either station port is opened the air supply will immediately be cut off.
- D. Before sending a capsule, the ballast tank air pressure must be 85 psi or above. This is sufficient air supply so that a capsule may be sent every two minutes

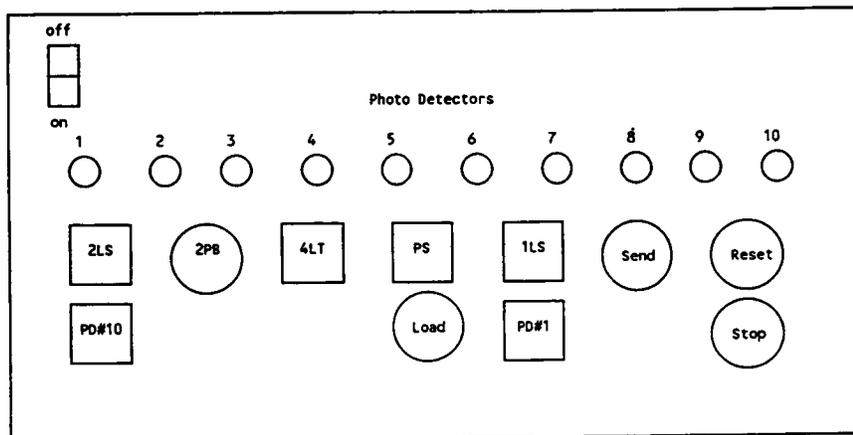
### Equipment Selection:

- A. Programmable Logic Controller (Cutler Hammer D100)  
20 I/O Total 12 Input 8 Relay Output 2A 115/230V
- B. D100 PLC Software (Cutler Hammer) \*Programs are stored on floppy disk.
- C. Control Box (BUD) 260mm x 60mm x 150mm

### Major Existing Components ( Supplied by Intertech):

- A. Transport Tubing 38.1 mm i.d. x 44.5 mm o.d. x 390 meters Polyethylene Tubing
- B. Ballast Tank 757 Liters
- C. Load and Receive Stations
- D. Control Valves, Photo Detectors, Regulators, Pressure Switch.

### Control Box



## Operational lights and push buttons at send station (Cyclotron Facility Radiochemistry Lab)

Key:           LT = Indicator Lamp                           PB = Push-button  
                   PDLT = Photo Detector Light            LSLT = Limit Switch Light

<u>Light</u>	<u>Function</u>
Power ON/OFF	Turns power on and off to the Control box, Programmable Logic Controller (PLC), and all switches associated with the system.
2LSLT	On when 2LS is closed (receiver door is closed). Otherwise Off.
10PDLT	On when photo detector at receiving station detects an object is present. Otherwise Off.
2PB	Sends signal to receiver station that permission is requested to send a capsule
2PBLT	Lamp is lit flashing while waiting for permission to be granted. Lamp is steady when permission is granted
4LT	Lamp is on when permission to send is granted by the receiver station (similar to 2PBLT)
PSLT	On when ballast tank pressure is sufficient to send a capsule (85 psi and above). Off when this condition is not met.
LOAD(PB)	Not connected. It will provide a signal to the sending station to remotely load a capsule when the option is required.
1LSLT	On when 1LS is closed (sending station door is closed). Otherwise Off.
1PDLT	On when photo detector at sending station detects an object is present.
SEND(PBLT)	On when all the conditions necessary to send a capsule are met. When on, SEND(PB) power is provided to the Push-button. Pressing the Push-button will open 1SOL and send a capsule.
RESET(PB)	By pushing the reset button the operator will reset all input all output conditions of the PLC. This means that the operational sequence of the PLC is at start.
* STOP(PB)	By pushing the stop button the operator will cut all power the Pneumatic Transport System. This includes the control box, the PLC, and all signals and switches associated with the system.

Light

LED 1,2,3,4,5,6,

Function

LEDs are lit as the capsule passes through the respective photo-detectors. 7,8,9,11 - LED's remain lit for three seconds before resetting themselves.

Operational lights and push buttons at receiver station (Pet lab Hot Cell Room, Silverstein Pavilion).

Key: LT = Indicator Lamp, PB = Push-button

Light

1LT (Red)

Function

Light is flashing while capsule is in transit. Light is steady when capsule is present

3LT (Yellow)

Light is flashing while permission requested to send is activated. Light is steady after permission to send capsule is granted

1PB

Push-button sends (permission granted) signal to the sending station.

Operational Sequence:

1. Sending station: Control Box Power on Switch (green LED)
2. Programmable Logic Controller (PLC) checks for proper initial conditions at the receiver station. The receiver station must be empty (no capsule present) , and the door must be closed (2LS) .If the receiver station status is not correct, the operator must call the PET center to correct the situation. The PLC will continue to interrogate the sensors so that the operation can continue when the error condition is cleared.

On the control box: If 2LSLT is lit (yellow) and 11PDLT is off (red) the conditions are correct and the operator can proceed to the next step.

3. 2PBLT is lit when conditions in step one are correct. Operator requests permission to send a capsule to receiver station by pushing 2PB\*. When 2PB is pushed, 2PBLT changes to Flashing. A flashing display will confirm that the permission request was made. \*If a capsule has been previously sent, you will have to press the reset button.

4. Receiver Station: 3LT is flashing indicating that a permission request was made. By pushing 1PB the receiver station operator grants permission to send a capsule. If the operator is not ready, he or she may delay pushing 1PB indefinitely.

5. Sending Station: PLC waits for the receiver station permission switch to be pressed. Once 1PB at receiver station is pushed. 2PBLT goes steady and 4LT lights (yellow) \*The receiving station

is ready\* \*Note: If any of the conditions change at the receiving stations prior to sending a capsule, the operator will have to hit reset and repeat step 3.

6. The PLC has been monitoring the pressure switch and when the ballast tank has the required pressure, PSLT will light (yellow) on the control box. The operator cannot send a capsule unless PSLT is lit.

7. The operator may proceed to load the capsule. Note the capsule may be loaded at any time during this sequence.

Once the capsule is loaded, and the loader door closed 1LSLT will be lit. If all of the previous conditions have been met, the send button will light.

Conditions for send button to light:

- A) Power on
- B) 2LSLT lit(yellow) 10PDLT off(green)
- C) Permission requested and received 4LT lit(yellow)
- D) Tank Pressure OK PSLT lit(yellow)
- E) Loading station door closed 1LSLT lit(yellow)
- 8) Send conditions are set. The operator may now send

the capsule by pressing the send button. 1SOL will remain open until the capsule is detected at PD#9 or PD#10. This takes about 12-15 seconds.

Receiver Station: 1LT lights flashing while the capsule is in transit. 1LT lights steady when the capsule is received.

Sending Station: Observing the Photo Detectors LED's will indicate the position of the capsule. The LED's will remain lit for approximately two seconds after the capsule has passed.

If the capsule becomes jammed, 1SOL will turn off 45 seconds after the send button has been pushed. The operator should note the last photo detector that was lit in the event that it becomes necessary to locate the capsule in the transport line.

**Pressure vs. Time of Complete Transfer in Seconds**

Pressure	20 psi	30 psi	35 psi
1	14.6	13.5	12.8
2	14.4	13.7	12.6
3	14.6	13.4	13.0
4	15.1	13.8	13.1
5	15.3	14.3	12.6

### Discussion of Loading Station:

We designed the main component of the loading station so that the capsule of radioactive material will be sitting in the base of a Capintec Well awaiting delivery. The Capintec along with additional 50 mm lead provides a substantial amount of shielding for delivery samples of less than 100 mCi. for PET radio-pharmaceuticals.

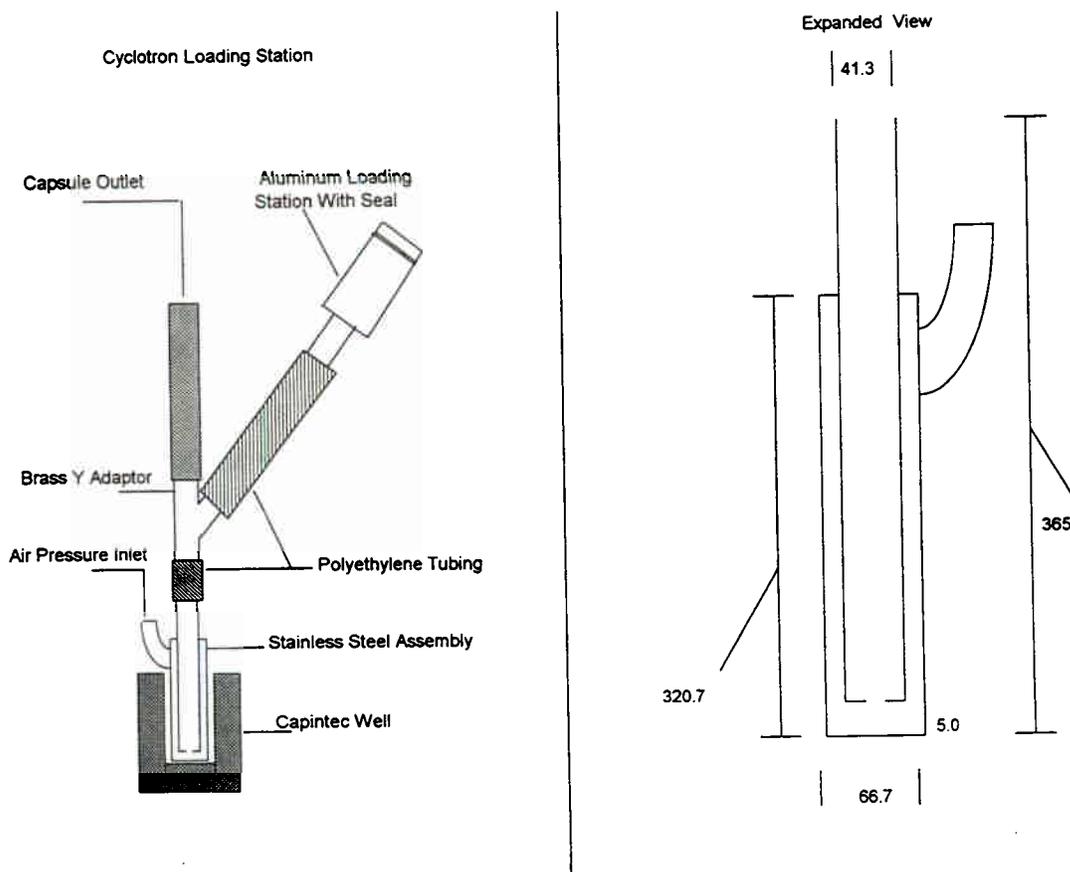
The main component of the loading station is made of two-part stainless steel tubing with one inlet port (ss elbow) and one outlet. The inner tubing holds the capsule less than 5 mm away from the base of the Capintec well. An additional 1/4" tubing port was provided at the neck to monitor pressure during testing and is now sealed.

The drop-in design loading station requires less handling of the capsule and provides us with a means for measuring our sample before leaving the facility.

### Conclusion:

We have successfully completed over 100 transfers of non-radioactive material without failure. We hope that our licensing agreement with the University will soon permit us to run radioactive samples through the system, mainly N-13, C-11 and F-18.

\*The majority of the equipment used in this system was originally provided by Intertech, Nuclear Products Division, 155 Eleanor Drive, Woodside CA, 94062. We appreciate their services



## REMOTE/LOCAL CONTROL CIRCUIT FOR ACCELERATOR TARGETS

Abdelfatihe Belakhlef, Ph.D. J. Robert Dahl, Ph.D.  
North Shore University Hospital/Cornell University Medical College  
Manhasset, New York

Operating experimental accelerator targets for radioisotope production requires a system which permits manipulation of the apparatus from a position adjacent to the targets during setup, and from the accelerator operating console during irradiation. Targets for producing different radioisotopes are mounted vertically on a target exchanger with vertical motion. These targets produce short-lived radioisotopes that are the basis for synthesizing the tracers used in positron emission tomography. Targets for radioisotope production are filled to specific volume and pressures from as many as five different tank gases, imposing the need for a reliable control of valves with continuous visual monitoring of the valve state. Appropriate signals to indicate the status of the controlled apparatus must be presented visually at both locations. The transient nature of experimental setups requires a highly adaptable control system. Apparatus setup suitable for the system herein described are readily adaptable to microprocessor control, once the operational procedure is developed using this system.

### Design Circuits

Figure 1 shows the remote/local control circuit with its four distinct blocks. Momentary contact switches are connected to debouncing circuits for each location from which the electrical instrument is to be controlled. The debouncing circuit is made of a set of two AND gates (7400) connected in an R-S type latch. The inputs of the R-S latch are connected to a SPDT switch with the single pole connected to ground. The outputs of the R-S latches, one for each location, are then connected to the inputs of the OR gate (7432) whose output feeds the T latch of the second stage.

The second stage is a dual T latch made of J-K latches (7476) whose inputs are connected to logical high. The timing clock of the T latch receives its input from the output of the first stage, the OR gate. Reset switches with indicating lights are provided to monitor the states of each latch.

The third stage consists of a HEX open collector driver with high output voltage circuit (7407). This circuit allows interfacing with high-level circuits or driving high current loads. By properly choosing the voltage and the resistance at the output of the driver, different relays requirements can easily be met. LED's are connected in parallel with the buffers to monitor the circuit states.

Relays driving resistive loads make up the fourth stage. The relay input voltage and current requirements are met in the previous stage. Although individual reset switches can be used, a single reset switching circuit was implemented as shown in Figure 1. The single reset switch is particularly important during power up of the control circuit where each controlled output load should be in an off state.

## Timing Diagram

Figure 2 Shows the timing diagram of the remote/local circuit when relay 1 is to be energized. With either SW1 or SW2 activated a low to high signal is transmitted from either B or D NAND gates through the OR gate E to the T flip flop clock input setting its output QT to a logical high. This drives the open collector output high to yield the output voltage which will turn the relay on driving the resistive load.

## Applications

The resistive loads that can be used with this control circuit include solenoid valves, electric fans, recirculating pumps and heating elements. A surge absorber, i.e. a capacitor and a resistance in parallel with the resistive load inputs must be used to eliminate the transient states.

## Advantages

TTL technology was used in implementing this control circuit, but because of its compartmental characteristics this circuit allows substitution of any existing technology, and facilitates operation of the whole process using a microprocessor. This simple and inexpensive control circuit can easily be modified to accommodate more control locations using multiple input OR gates. By taking the complement of the O-C output and connecting it to a relay then to an alarm, an audio signal can be generated when ever failure in the system occurs. Also the digital nature of this control circuit make it well suitable for automatization.

## Conclusion

In a cyclotron environment where radiation damage is a threat to both human and machine, extra attention must be taken to ensure proper and prolonged functioning of the control systems in use. Remote control circuits and automation are being developed more and more to minimize human health hazards. This remote/local control circuit is now been used at North Shore University Hospital/Cornell University Medical College in our cyclotron/PET facility.

**Acknowledgement** This work was supported in part by a grant from Scanditronix N.A.. The authors are grateful to Dr. D. Margouleff for his enthusiastic support of this project.

Figure 1. Remote/Local Control Circuit(TTL technology)

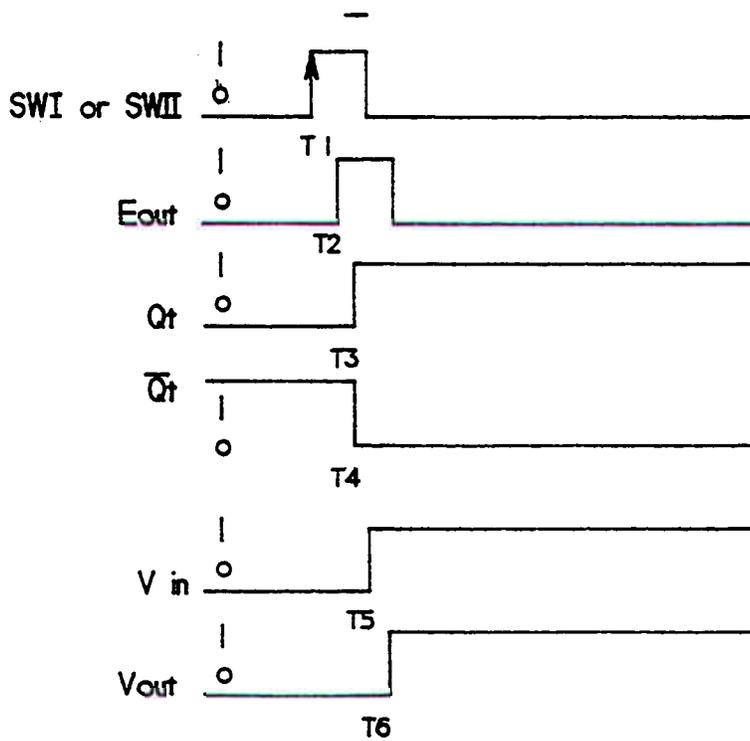
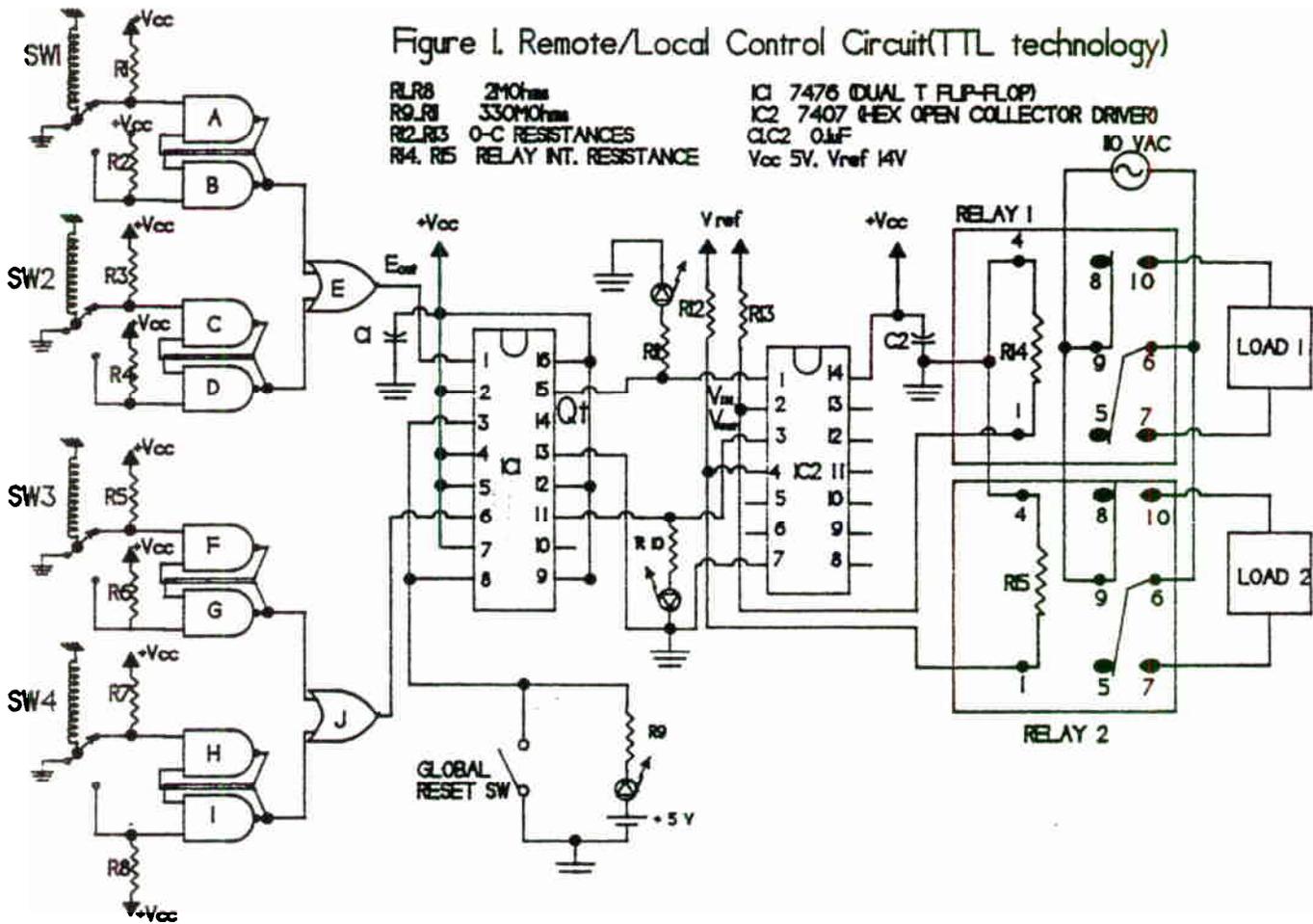


FIGURE 2. REMOTE/LOCAL CONTROL CIRCUIT TIMING DIAGRAM

**Radiation Effects on Polymers**  
 Jeanne Link  
 University of Washington, Seattle

There has been a lot of speculation on radiation sensitivity of materials. Some of the comments about materials problems due to radiation sensitivity made no sense given the radiation fields and time for which these materials were exposed to those radiation fields. Radiation sensitivity of polymeric materials has been studied. Publications of which I am aware are from CERN- European Organization for Nuclear Research.

There are several publications: Effects of Radiation on Materials and Components I. Radiation effects on polymeric materials and II. Radiation problems relating to high-energy accelerators, publication CERN 70-5 ; 26 February 1970, editor: M.H. Van de Voorde. Also: Selection guide to organic materials for nuclear engineering Authors: M.H. Van de Voorde and C. Restat. Cern 72-7, Laboratory I , Intersecting Storage Rings Division, 17 May 1972. These publications may still be available from CERN or CERN may have newer publications on this subject. Some brief radiation sensitivity data for polymeric materials used in targetry is presented below. It should be noted that the following sensitivities will be affected by the way the material is produced and its dimensions. Other stresses will also weaken the materials, such as exposure to chemicals and physical conditions such as temperature.

Gamma dose to produce damage in material	mild (rads)	moderate (rads)	severe (rads)
<b>THERMOPLASTIC RESINS:</b>			
teflon TFE	$1 \times 10^4$	$2 \times 10^4$	$5 \times 10^4$
polyamide	$4 \times 10^5$	$2 \times 10^6$	$6 \times 10^6$
polymethyl methacrylate	$5 \times 10^5$	$8 \times 10^6$	$3 \times 10^7$
Kel-F	$7 \times 10^5$	$1 \times 10^7$	$4 \times 10^7$
polymethyl alpha-chloroacrylate	$9 \times 10^5$	$2 \times 10^6$	$3 \times 10^6$
vinyl chloride-acetate	$9 \times 10^5$	$2 \times 10^6$	$3 \times 10^6$
ethylene propylene polyallomer	$2 \times 10^6$	$5 \times 10^7$	$5 \times 10^8$
Cellulose acetate	$2 \times 10^6$	$1 \times 10^7$	$4 \times 10^7$
teflon FEP	$2 \times 10^6$	$7 \times 10^6$	$2 \times 10^7$
polyvinylidene chloride	$2 \times 10^6$	$2 \times 10^7$	$9 \times 10^7$
Polyvinyl butyral	$2 \times 10^6$	$1 \times 10^7$	$4 \times 10^7$

polycarbonate	3X10 <sup>6</sup>	9X10 <sup>7</sup>	2X10 <sup>8</sup>
Teflon TFE and FEP (vacuum)	3X10 <sup>6</sup>	5X10 <sup>7</sup>	1X10 <sup>8</sup>
polyvinyl formal	1X10 <sup>7</sup>	7X10 <sup>7</sup>	3X10 <sup>8</sup>
polyvinyl chloride	1X10 <sup>7</sup>	8X10 <sup>7</sup>	3X10 <sup>8</sup>
polyethylene	1X10 <sup>7</sup>	7X10 <sup>7</sup>	6X10 <sup>8</sup>
polyvinyl carbazole	5X10 <sup>7</sup>	1X10 <sup>9</sup>	5X10 <sup>9</sup>
acrylonitrile/ butadiene/styrene (ABS)	7X10 <sup>7</sup>	6X10 <sup>8</sup>	3X10 <sup>9</sup>
polyimide	2X10 <sup>8</sup>	3X10 <sup>8</sup>	1X10 <sup>9</sup>
polystyrene	4X10 <sup>8</sup>	3X10 <sup>9</sup>	6X10 <sup>9</sup>
THERMOSETTING RESINS:			
mylar	4X10 <sup>6</sup>	1X10 <sup>8</sup>	1X10 <sup>9</sup>
silicone, unfilled	1X10 <sup>8</sup>	9X10 <sup>8</sup>	4X10 <sup>9</sup>
polyurethane	1X10 <sup>9</sup>	1X10 <sup>10</sup>	
epoxy	2X10 <sup>9</sup>	9X10 <sup>9</sup>	1X10 <sup>10</sup>
phenolic, glass laminate	9X10 <sup>9</sup>	1X10 <sup>10</sup>	
ELASTOMERS:			
butyl rubber	1X10 <sup>6</sup>	3X10 <sup>6</sup>	1X10 <sup>7</sup>
silicone rubber	8X10 <sup>6</sup>	3X10 <sup>7</sup>	1X10 <sup>8</sup>
neoprene rubber	2X10 <sup>7</sup>	9X10 <sup>7</sup>	4X10 <sup>8</sup>

ref: Figures I.1, I.2, I.3 Van de Voorde, M.H., Effects of Radiation on materials and Components CERN 70-5, 1970.

Advances in the Robotic Production of Radiopharmaceuticals. G. Gaele. Washington Univ., St. Louis.

**Experience with the IBA Automated Chemistry Systems**  
Steve Toorongian. SUNY, Buffalo, N.Y.

A discussion of the IBA chemistry systems was initiated by this presentation which resulted in the following questions and comments:

Q: J Link: How much experience have you had with the FDG system?

A: We have used it since December 1st, 1992.

Q: Where is your FDG unit located.

A: It is in the hot cell. Actually each IBA module is in a separate hot cell.

There were many comments on the F-18 target and the fact that the SUNY 50 micrometer thick Ti foils ruptured with >19 microamp on target:

Comment B. Dahl: The 19 microamp limit for the water target means you are running right on the ragged edge where a 5% change in your beam current will cause a rupture. We are holding to 19 microamp, an empirically derived number, in the target that we are using right now because we also have problems with our foil. We believe there are beam profile problems because we have a problem with our gradient power supplies. The point that I am trying to make, is that if you get to the point in running your water target that a 5% difference will cause a failure, you have got some problems which I would not necessarily relate to market design or anything else. You had better look into your system because you should have much more latitude than your operational parameters give you now.

Comment: V Bechtold, Karlsruhe: We also have two small volume targets and one large volume target from IBA and we had the same problems with the small volume target but not the large volume targets. We believe that the small volume target is too thin and you lose your beam on the back of the target.

C: JL Morelle: I think that statement is correct. If the target is not deep enough, it was initially designed for lower energy and it is not designed to be run at 15MeV, it should be made deeper.

C: V Bechtold : I would like to make some comments on the use of the IBA FDG system. Some problems have been mentioned with targets. We also have the FDG module. We had no knowledge of fluorine-18 production and synthesis of FDG (when we started) and taking this into account I think that the target of IBA is working rather nicely. We overcame a tubing problem in the beginning and since then the target is working very reliably. We are doing routine labeling and produce 300 to 500 mCi of FDG.

C: B Wieland: We ran a couple of meters of polyethylene delivery line through a detector and then into the synthesis box and everytime we do that we lose about 1 percent of the activity. This is a diagnostic method you can use.

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