Development of an Economical, Position-Sensitive Detector for High Performance Liquid Chromatography

BME 200/300

UW-Madison

Department of Biomedical Engineering

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Abstract

High performance liquid chromatography (HPLC) is a method of chemical separation often used to separate radioactive products produced by a cyclotron from a chemical synthesis. These products are often used in PET imaging for diagnosing and treating various diseases. Most current HPLC systems utilize only a single detector at the end of the separation column to signal when the radioactive product has passed through the system. Our clients, Dr. Nickles and Dr. Barnhart, request we design a device that can track the position of the radioactive band continuously through the column, report the data to a computer, and provide an audio or visual cue as to the band's progress. We have selected a linear motor system to satisfy the design requirements that utilizes a linear motor with a scintillator-photodiode detection unit mounted on the motor. The motor-detection unit will travel along the axis of the HPLC column and provide continuous data about radioactivity and position. For the remainder of the semester we will begin programming the software necessary, fabricate the required housing, and begin testing the prototype.

Background

Gamma Radiation

Gamma radiation is a high-energy result of nuclear decay. With wavelengths often less than the size of an atom, gamma radiation is an ionizing radiation that is imbedded in the excretion of 511 keV photons[1]. This occurs by the process of beta decay within an atom, which releases a positron. The positron then travels one to two millimeters before colliding with an electron, annihilating both, and producing two coincidental (travelling in equal and opposite directions) 511 keV photons[2]. While one typically thinks of photons as nothing more than harmless "light" particles, gamma radiation is so high in energy that it can ionize and destroy strands of DNA. This leads to either mutagenesis or cell death[3].

Medical Imaging

Despite the obviously harmful effects of ionizing radiation, gamma radiation is an effective tool used by modern medical imaging modalities, including Single Photon Emission Computed Tomography (SPECT) and Positron Emission Tomography (PET). By specifically radiolabeling drugs that mimic those naturally found in the body with minute amounts of radiation, researchers can track concentrations of labeled drugs throughout the body. This is often done to track metabolic processes [4].

Figure 1: A standard PET Scanner

In both SPECT and PET, subjects are given doses of radioactive supplement, typically by injection, and then placed in a scanner as seen in Figure 1. This process images the body or brain to track the movement of the chemicals. In this way, doctors and researchers can use PET and SPECT for clinical value both in diagnosing diseases as well as monitoring treatment[5].

High Performance Liquid Chromatography

Unfortunately, synthesizing labeled drugs with the ability to emit gamma radiation that can garner valuable biological information is a difficult process. Products of this process often include species that would be more chemically harmful to subjects than the radiation itself. In order to isolate the radioactive species, a process called High Performance Liquid Chromatography (HPLC) is used upon the conclusion of synthesis.

HPLC works by integrating a cyclotron-synthesized product with a standard called a "mobile phase" throughout a highly pressurized column, as seen in Figure 2[6]. As the product passes through the lipophilic compound on the inside of the column, product species are separated based on their unique polarities. As species leave the column, they can be directed to either a waste container or collected as product. Through careful calibration, scientists can identify retention times for a wide variety of species and selectively isolate desired products.

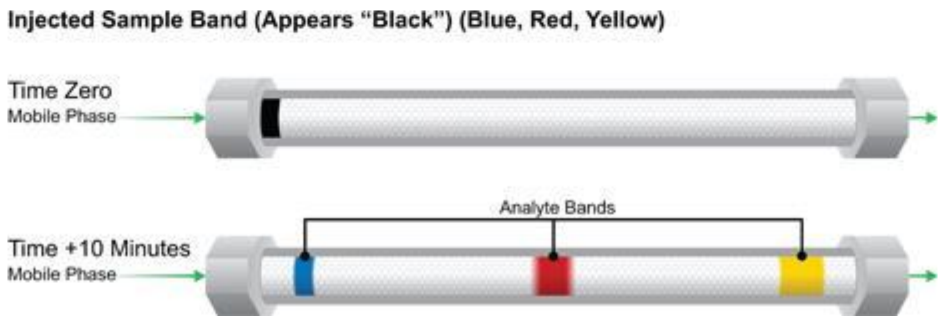

Figure 2: Image depicts the "end of synthesis" chemical entering HPLC, and the separation of species as they pass through the column.

Design Motivation

Motivation

Despite closely calibrated retention times, alterations of the species incurred during synthesis can result in variant retention times. As a result, researchers are often required to closely monitor a single detector located at the end of the column in order to accurately acquire the desired product(s). Even with close monitoring, a passing peak of radioactivity by the detector can occur in a matter of seconds. This event can be easily missed over the entire 10 to 15 minute process. Missing any of this peak can result in inadequate amounts, if any, of radioactive product being collected, demanding the synthesis process be repeated.

The demand for a self-monitoring detection system of radioactive materials throughout the HPLC column is one that has yielded few successful designs. By implementing such a design, researchers and physicians would be able to conduct more consistent and efficient synthesis.

Problem Statement

The Cyclotron Group in the Medical Physics department at the University of Wisconsin - Madison lab routinely uses HPLC on cyclotron-irradiated materials in order to separate the radioactive product from the target stock. During this process, it is important to know when the radioactive band is passing through the column. Various systems are in place to do this currently, but the client requests a device that will detect the passage of the gamma-emitting product throughout the column, record its passage digitally, and send out either an audio or visual cue to indicate the product's progress before leaving the column.

Client Requirements

Regarding the hardware of the device, the detector should detect the peak wave at around 500 nm, the green portion of the visible spectrum. Once the radiation level passes the 10 milliCurie threshold, the signaling system should give a simple, reliable readout accompanied by an audio or visual cue. Since the purpose of the design is to locate radioactive components inside the HPLC column, high position accuracy is required; the device should be able to measure the movement of the components in real time and report its position within a two-millimeter tolerance. The entirety of the device must fit within a lead tube with an inner diameter of 5.08 cm.

Physically, four functional parts are required to achieve the design: a detector, a transducer, a cue (audio or visual), and software for observing and recording the data. The first two must be purchased for less than $500 and fixed together, and the last two will be coded using National Instruments LabView software. The irradiation time of the detector should be at least 1,200 seconds so that it can cover the length of time necessary for completion of the HPLC process. The software should be able to record the data in real time, save the data, and activate the cue device when the radiation level surpasses the threshold.

Figure 3: National Instruments LabVIEW software[7]

Existing Devices

There are devices commercially available that measure gamma radiation and output simple and clear signals, but many of these programs are specific to certain scenarios and not optimized for measuring radiation from HPLC columns. For example, the C12137 (pictured in Figure 5) high sensitivity radiation detector module from Hamamatsu is a design that detects gamma rays using a scintillator and an ultra-high sensitivity semiconductor sensor (MPPC). A signal processing circuit, an Analog-Digital Converter (ADC), and a USB interface are included in the device so that measurement of radiation could be shown on a Windows PC easily and with high accuracy. However, this device is not optimized for measuring radiation from an HPLC column for several reasons. First, the device has a

Figure 4: The Hamamatsu C12137 Gamma Radiation Detector[8]

Figure 5: The Hamamatsu C9692 Photon Detector[9]

relatively large size (111mm by 55mm by 30mm) and therefore would not fit into the 5.08 cm shell. In addition, the C12137 also has a high radiation sensitivity and accuracy, which is not necessary in the HPLC detector design. However, the required position sensitivity is not achieved in this device. Also, the price of this device is over $4000, significantly more than the project budget.

The C9692 series from Hamamatsu (pictured in Figure 5) is another photon detection unit that, when connected to a scintillator, could perform high sensitivity photon detection and provide a simple output signal through a USB interface. This design, however, has a large size, which makes it difficult to attach to the HPLC system. Similar to the C12137, it also has a high cost, low position sensitivity, and unnecessarily high radiation sensitivity.

There is also precedence for the use of a large detector array to track high sensitivity radiation through the passage of a chromatographic column. The sensitivity for detection is on the order of nano-Curies. Although this has high radioactive detection sensitivity, it lacks a strong ability to separate peaks[10].

Design Proposal

The design alternatives center around the use of static or dynamic systems and the amount of detectors utilized. Numerous factors were considered including but not limited to: band passage tracking or point-specific tracking, detector size and cost, designs in use, detector sensitivity, and feasibility in programming.

Design 1: Linear Motor

Our first design involved a single scintillator/detector complex mounted on a linear motor or actuator. The motor would move back and forth along the length of the HPLC column at a constant frequency, tracking radiation levels at points specific to the passage of radioactive material through the column as opposed to a single point exterior to the column. The primary advantage of this system is its low cost; a single detector complex coupled with a linear motor will cost far less than the other designs that

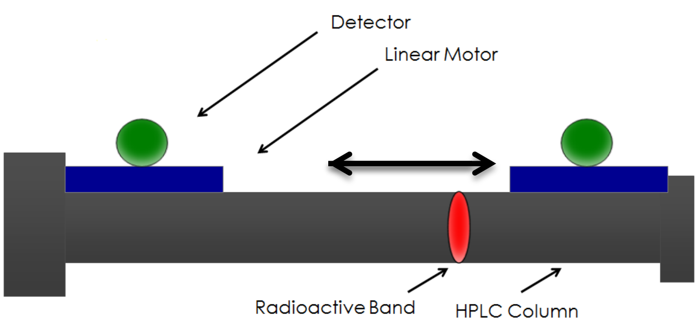

Figure 6: Linear Motor Design

involve multiple detectors. Also, because the detector moves with the radioactive band, accurate position sensitivity of the radioactive band can be achieved with a low-sensitivity detector utilizing this method. This prevents the need for higher-sensitivity photon detectors, further lowering the cost. One of the primary disadvantages of this system is that it involves moving parts, likely shortening the lifetime of the device. Unlike the other static designs, the use of a linear motor in this design introduces room for malfunction, but this factor is offset by the low cost. According to the client, at the price they would pay for a device of this design, they could afford to replace it every two years, which should be well within the lifetime of even a low-quality motor. Another potential disadvantage may be the microcontroller programming involved in getting a linear motor to move back and forth at constant frequency. This introduces a factor of difficulty on the part of the engineers and lowers the feasibility of the design, but this difficulty can be overcome. An additional disadvantage may be the size of the linear motor. With the constraint of 5.08 cm, the inner diameter of the lead protective casing that the design must fit into, it could be difficult to find a linear motor system that thin. However, preliminary research reveals that such motors do exist. Also, even if the motor does not fit, it is permissible to slot the inside of the lead tube to fit the design into the tube.

Design 2: multiple detectors

Our second design is a static system of four or five detector/scintillator complexes mounted on the outside of the HPLC column. The detectors would sense the radiation levels at their respective positions exterior to the column and all of the data could be fed to a computer. In order to utilize point detection specific to the passage of the radioactive band, an algorithm would have to be written that combined the radiation data from each of the detectors and compared the readings against each other to determine, in real time, the point of high radiation output. The primary advantage of this system is that it does not involve moving parts, greatly increasing its longevity and reliability. Additionally, without a linear motor or a large volume of detectors, as utilized in design three, the device would be relatively small, likely easily fitting within the lead casing without rendering any modification necessary. Also, it is believed this design would be the most simplistic from a programming standpoint. Creating an algorithm for coalescing radiation data to give position data would be difficult, but is believed to be mathematically well within the ability of the engineers. The primary disadvantage of this system is the high cost. Using multiple detectors greatly increases the cost of the device, especially when that cost is multiplied over the five to ten devices that the client eventually wants produced. Also, more sensitive detectors would have to be utilized in order to track the position of the band because the readings of detectors that are relatively far away from the band must be factored into the position tracking algorithm for it to be accurate, again raising the cost. Even with an algorithm in place, the design will still have lower position sensitivity than the linear motor design because the motor allows a detector to track the moving point directly rather than indirectly through mathematical means.

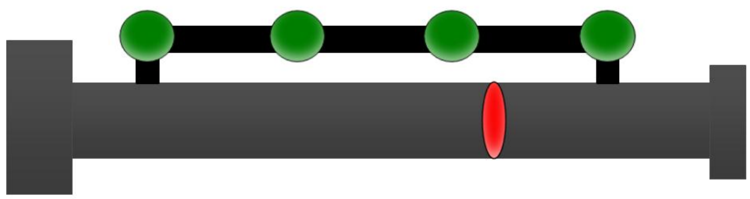

Figure 7: Multiple Detector Design

Design 3: Detector Array

Our third design is similar to the multiple detector design except many more detectors are utilized in an array that would run the length of the column. This design was included because there is much precedence for it in the research we have conducted on radiation sensors as they relate to imaging[11]. However, many of the studies found using this detector array design were concerned with radiation sensitivity, which is not what we are looking for. Due to our interest in position sensitivity, this design is simply not practical as many of the disadvantages for design two also apply here, especially high cost. The algorithm for combining the data to determine position, although much more accurate due to increased detector density, would be more difficult to implement. In addition, the utilization of so many detectors would make for a very large device as well as introduce increased possibility of malfunction of at least one of the detectors.

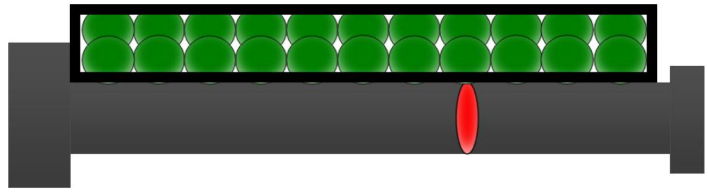

Figure 8: Detector Array Design

Design Criteria

The weight of the categories of the design matrix reflects the best interests of the client and his expectations for the device. The categories, their respective weights, and the rating of each design in each category can be seen in Figure 9. Cost and position sensitivity were given high weight because the client wasn't interested in many of the expensive products on the market that have high radiation sensitivity. Not only was it too much to pay, but he was not even interested in radiation sensitivity because the passage of the radioactive band is an event that is clear to even the lowest resolution detectors. Position sensitivity was the goal and is the factor reflected in the design matrix. Lifetime was given a medium weight because the client was willing to replace and update the devices every two years, but it would be ideal if they lasted longer than that. Size/weight also received a medium weight because although the lead tube presents a size constraint, it can be modified. Ease of use received a low weight because the client and his research fellows have a high level of technical knowledge, so it was not a large concern. The only ease of use issue could potentially be the programming component of the device, but this is not a part of the device the client should have to interact with, so it is also of little concern. Reliability and safety received low weight because this device doesn't present any dangerous elements such as heavy or sharp objects. It has been surmised that the device could harbor small amounts of radiation, but the system will be contained in a lead tube, so any human exposure would not only be minimal in amount but highly limited in time. The main issue is the reliability of the hardware, but ordering from legitimate sources and adequate testing will ensure that our final design works when and how it is intended.

Design	Multiple Detectors	Linear Motor System	Detector Array System
Cost (30%)	3	5	1
Accuracy/Sensitivity (30%)	3	5	4
Lifetime (15%)	4	2	4
Ease of Use (5%)	4	3	4
Reliability/Safety (5%)	3	2	2
Size/Weight (15%)	4	2	1
Total	3.35	3.85	2.55

Figure 9: Design Matrix

Final Design

Design Selection

As can be seen in Figure 9, the linear motor design was determined to be the most practical for this project. The use of only one detector on a linear motor greatly lowers the cost of the device as well as maximizes its position sensitivity. Although the use of the motor increases the likelihood of malfunction and the size of the device, both of these factors can be compensated for and thus do not significantly detriment the practicality of the design.

Design Development

Our final design, thus far, will utilize a Cesium Iodide (Thallium activated) scintillator that is mounted onto the Hamamatsu S9269 Silicon Photodiode (with preamp). This detection unit will be mounted on a to-be-determined linear motor that will either have a track along the HPLC column axis, or will utilize a linear actuator with the detection unit mounted at the end. The linear motor and detection unit will be attached to the HPLC column via clamps. Because the size of the linear motor is subject to large variability, re-fabrication of the lead shielding outside of the HPLC column may be necessary. The electrical current signal emitted from the Si Photodiode will need to be converted into a signal that can be processed by a computer using an adapter. The last component of the final design is the program interface that will use LabView to plot the activity data with the position data and provide an audio/visual cue.

Future Work

At this point, we have selected our photon detection element and ordered it from Hamamatsu. The photodiode will take approximately six to eight weeks to arrive. During the shipping layover, there are still a number of things that need to be accomplished.

The software component of this project will utilize LabView for the primary programming. The electrical signal from the photodiode, in the form of a current, will have to be displayed as a radioactivity. The position data from the linear motor will have to be combined with the radioactivity data to display a visual plot of activity versus position in real time. This graphical interface should be both easy to use and visually simple. In addition, some coding will be necessary to include an audio/visual cue to let lab members know where the radioactive band is in the column and the estimated time of passage through the column. Once the photodiode arrives, it will be attached to the scintillator using optical glue (both provided by the client) and mounted to the selected linear motor.

A housing will need to be fabricated to contain the detection unit and the motor. The housing will be mounted safely onto the HPLC column without exceeding the space allowed by the lead shielding. The housing will be made of aluminum and feature two clamps that can be adjusted to fit various sizes of HPLC columns.

Once the prototype is complete, the device will be mounted on one of the HPLC columns used in the Cyclotron Lab in the Department of Medical Physics at the University of Wisconsin-Madison. From there, position accuracy, radiation sensitivity, and ease of use tests will be administered to determine whether or not the prototype is an acceptable product.

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Appendix A: Product Design Specifications

Development of an Economical, Position-Sensitive Detector for High Performance Liquid Chromatography

Client: Professor RJ Nickles
Advisor: Chris Brace
Team: Sarvesh Periyasamy, periyasamy@wisc.edu (Leader)
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Date: September 19th, 2012

Problem Statement:

The Cyclotron Group in the Medical Physics department at the University of Wisconsin - Madison lab routinely uses high-pressure liquid chromatography (HPLC) on cyclotron-irradiated materials in order to separate the radioactive product from the target stock. During this process, it is important to know when the radioactive band is passing through the column. Various systems are in place to do this currently, but the client requests a device that will detect the passage of the gamma-emitting product through the column, record its passage digitally, and send out either an audio or visual cue to indicate the product's progress before leaving the column.

Client requirements:

- Hardware:
  - The device should detect the peak wave at around 500 um, green area.
  - The device should give simple, reliable readouts, and either an audio or visual cue when it detects an amount of radiation at the peak wave that surpasses the threshold level of 10 milli-curie.
  - The device should be able to measure the movement of the radioactive components in real time and the position of the components within 2 mm of tolerance.
  - Three functional parts are required: detector, transducer, a cue (audio or visual), and software for observing and recording the data. The first three will be purchased, and the last will be coded using LabView (see below).
  - The irradiation time of the detector should be more than 1200 seconds so that it can cover the length of time necessary for completion of the high-pressure liquid chromatography process.
- Software:
  - A software component corresponding to the hardware should be programmed which shows the amount of radiation in real time.
  - The software should be able to record the data in real time and save as a file.

  - The software should also activate the cue device when the radiation level surpasses the threshold.

Design requirements:

- 1. Physical and Operational Characteristics
  - Performance requirements: The device must consist of a detector, a transducer, and a cue device that sense and alert the researcher to the passage of a radioactive band in a chromatographic tube and report this reading to a computer.
  - Safety: It is possible that the components of the device could absorb radiation. Care should be taken to minimize exposure to both the device and the chromatographic tube it is attached to.
  - Accuracy and Reliability: The device should be sensitive enough to detect low level radiation as little as several milli-curie,
  - Being used for scientific purposes, the data acquired from the device must be highly reliable. Specifically, the measurement of the band's position should be exact to within 2 mm and should have a resolution better than 1 second.
  - Life in Service: at least 5 years
  - Shelf Life: N/A
  - Operating Environment: The device will be attached to a chromatographic tube in a research lab and will be subject to potentially high amounts of radiation.
  - Ergonomics: The device should be easy to implement and use. The accompanying software should be easy to understand and learn.
  - Size: the device must fit around the 10 mm diameter column and together with this column, fit into a shell of 5.08 cm inner diameter.
  - Weight: less than 0.5 lb.
  - Materials: detector, transducer, cue device (optical or visual), possibly a linear motor, attachment device.
  - Aesthetics: The device must look professional and simple. It is being used in a research lab so it has to look like what it is: a scientific piece of equipment.

- 2. Production Characteristics
  - a. Quantity: 2
  - b. Target Product Cost: $500

- 3. Miscellaneous
  - a. Standards and Specifications: N/A
  - b. Customer: The client stressed the use of a cueing device to alert the researcher to the passage of the radioactive band. The client also stressed the necessity of a simple readout in real time.
  - c. Patient-related concerns: N/A
  - d. Competition: The sensors currently used by the lab only detect the radioactive band at one point. They do not track the passage of the band. Products that do this are available, but lack a cue to notify the researcher of the band passage. Current devices that are

available and fulfill the functions needed are too expensive and have features not necessary for the clients' purposes.

Appendix B: S9269 Data Sheet

HAMAMATSU
PHOTON IS OUR BUSINESS

Si photodiode with preamp

S9269 S9270

Photodiode and preamp integrated with feedback resistance and capacitance

S9269 and S9270 are low-noise photosensors consisting of a Si photodiode, op amp, and feedback resistance and capacitance, all integrated into same package with a surface size equal to our standard ceramic packages. These photosensors are ideal for a wide range of photometric applications including analytical equipment and measurement equipment. The active area of the photodiode is internally connected to the GND terminal making it highly resistant to EMC noise. Combinations with various photodiodes such as UV sensitivity enhanced type, IR sensitivity suppressed type and IR sensitivity enhanced type are also available. (Custom order products)

Features

- **Si photodiode for visible to near IR Si precision photometry**
- **Small package**
  S9269: 10.1 × 8.9 × 40 ^{t} mm
  S9270: 16.5 × 15.0 × 4.15 ^{t} mm
- **Active area**
  S9269: 5.8 × 5.8 mm
  S9270: 10 × 10 mm
- **FET input operational amplifier with low power dissipation**
- **Built-in Rf=1 GΩ, Cf=5 pF**
- **Low noise and NEP**

Applications

- **Precision photometry**
- **General-purpose optical measurement**

Absolute maximum ratings (Ta=25 °C)

Parameter	Symbol	Value	Unit
Supply voltage (op amp)	Vcc	±20	V
Power dissipation	P	500	mW
Operating temperature	Topr	-20 to +60	°C
Storage temperature	Tstg	-20 to +80	°C

Note: Absolute maximum ratings are the values that must not be exceeded at any time. If even one of the absolute maximum ratings is exceeded even for a moment, the product quality may be impaired. Always be sure to use the product within the absolute maximum ratings.

Electrical and optical characteristics (Ta=25 °C, Vcc=±15 V, RL=1 MΩ)

Parameter	Symbol	Condition	S9269			S9270			Unit
			Min.	Typ.	Max.	Min.	Typ.	Max.	
Spectral response range	λ		-	340 to 1100	-	-	340 to 1100	-	nm
Peak sensitivity wavelength	λp		-	960	-	-	960	-	nm
Feedback resistance (built-in) *	Rf		-	1	-	-	1	-	GΩ
Feedback capacitance (built-in) *	Cf		-	5	-	-	5	-	pF
Photo sensitivity	S	λ=λp	0.5	0.62	-	0.5	0.62	-	V/nW
Output noise voltage	Vn	Dark state, f=10 Hz	-	7.3	-	-	9.7	-	μVrms/Hz$^{1/2}$
		Dark state, f=20 Hz	-	6.5	-	-	9.1	-	
Noise equivalent power	NEP	λ=λp, f=10 Hz	-	12	-	-	16	-	fW/Hz$^{1/2}$
		λ=λp, f=20 Hz	-	12	-	-	17	-	
Output offset voltage	Vos	Dark state	-	±4	-	-	±4	-	mV
Cut-off frequency	fc	-3 dB	-	32	-	-	32	-	Hz
Output voltage swing	Vo	RL=10 kΩ	-	13	-	-	13	-	V
Supply current	Icc	Dark state	-	0.3	0.6	-	0.3	0.6	mA

* Custom devices available with different Rf, Cf, etc.