

Development of ^{18}F Radiochemistry for Positron Emission Particle Tracking (PEPT)

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Abstract. Positron Emission Particle Tracking (PEPT) is a radioactive tracer technique used to track the trajectory of a radioactively labelled macroscopic particle using a variant of Positron Emission Tomography (PET). The primary application of PEPT is to study dynamic flow systems under varying conditions; including a wide range of particle size distributions, physical, and chemical properties, with applications across the science disciplines. For radiochemical tracer particle production, we are interested in utilising ion-exchange techniques to label small phase-representative resin particles (diameter < 1 mm). For physical activation we will primarily be looking at the novel reaction $^{16}\text{O}(\alpha, \text{pn})^{18}\text{F}$ to produce positron emitters in-situ for larger particles (diameter > 5 mm). This work will develop iThemba LABS specific tracer particle production mechanisms using ^{18}F for the first time, and will provide insight into the effects of tracer particle properties in PEPT applications including optimisation of the PEPT technique and enhanced tracer production mechanisms.

1. Introduction

Positron emission particle tracking (PEPT) is a non-invasive technique used to obtain dynamic information within multiphase dynamic systems. Of particular value to science and engineering, this technique obtains information on the motion and flow fields of fluids and/or granular materials in three dimensions and often in dense and opaque media. PEPT enables tracking of a single tracer particle moving within the field-of-view of a modified Positron Emission Tomography (PET) scanner. The basis of the technique is to radiolabel a tracer particle with a suitable positron emitting radionuclide. Positrons that originate from the tracer radionuclide annihilate with local electrons and produce back-to-back 511 keV gamma photon pairs. When both gamma photons are detected simultaneously (defined as coincident with a typical 12 ns time window), a line of response (LOR) can be formed with the tracer particle located somewhere along that line. Multiple LORs are used to calculate the tracer location as shown in figure 1; an iterative location algorithm is employed to calculate the position of the particle based on the detection of a consecutive series of back-to-back gamma photons, within limits set by the spatial resolution of the camera.

In principle, only two lines of response are necessary, but a larger number (100s – 1000s) of measured LORs are required in practice as the acquired data contains a certain fraction of corrupt LORs, due to scatter, attenuation, and random coincidences [1].

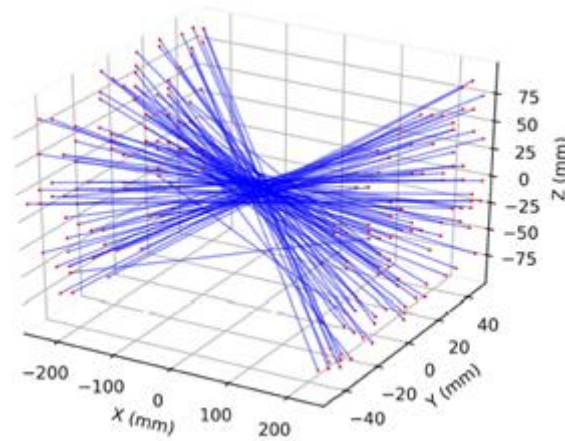


Figure 1. Example LORs from a point source of positron activity placed at the origin. The majority of lines converge at the source position, forming the basis of the technique. Some outliers are visible, being corrupt LORs from scatter or random coincidences.

The acquisition rate of LORs depends upon the emission rate of positrons from the tracer particle (itself a function of activity and the branching ratio for positron decay), multiplied by the sensitivity for detecting coincidence pairs of annihilation photons (proportional to the square of the intrinsic efficiency for detecting single photons). Typical sensitivities for the detector systems at PEPT Cape Town are of the order 5 – 10 % absolute (including solid angle terms) [2]. The data acquisition rate, and hence location reconstruction rate, primarily depends on the tracer particle activity for a fixed geometry. For low activity, the rate of event detection is insufficient to measure a continuous trajectory, and dynamic information is lost. Conversely, with activity too high, effects of pulse pileup and acquisition deadtime degrade the measurement [3]. To ensure that the measured PEPT data is reflective of the motion under study, the radioactivity in a single particle must be sufficient irrespective of the tracer size and physical properties of the material under study which itself must be representative of the media under study.

In addition to the instrumentation, application and data processing, a crucial aspect of the PEPT technique is the production of a suitable representative tracer particle. Currently, the primary radionuclide used at PEPT Cape Town is ^{68}Ga with a half-life of 68 minutes, produced at iThemba LABS through the use of $^{68}\text{Ge}/^{68}\text{Ga}$ radioisotope generators. We have extended the application of PEPT by producing ^{18}F -based tracer particles with the longer half-life of 109 minutes. Advantageously, ^{18}F is a pure β^+ emitter with no additional gamma emissions, thus its use intrinsically increases the signal to noise ratio in PEPT studies.

2. Tracer Production Mechanisms

Radiochemical and physical methods are both being explored to produce ^{18}F based tracer particles. Two methods of tracer production used are direct activation and chemical sorption, with the latter comprising surface modification and ion exchange radiolabelling, as illustrated in table 1. If the materials in the system contain natural oxygen, are thermally stable and greater than 1 mm in diameter, tracer particles may be directly produced by activation in a suitable cyclotron beam. For routine work, and for tracer particles below 1 mm in diameter, PEPT Cape Town utilises chemical sorption methods to produce tracer particles. Ion exchange radiolabelling relies on controlling the uptake of a desired radionuclide (here: ^{18}F or ^{68}Ga) by an organic or inorganic resin which exchanges

non-radioactive counterions for the required species. The Birmingham group has demonstrated that commercially available ion exchange resins of 600 μm diameter can adsorb up to 1500 μCi of ^{18}F [3]. Unfortunately, ion exchange resins are typically not representative of the particles of interest due to differences in density or surface chemistry properties; however, applying suitable coating layers to modify these properties improves representation. Figure 2 highlights a range of various PEPT Cape Town tracer particles that have been developed [5].

Table 1. A summary of different types of PEPT tracers.

	Direct Activation	Ion Exchange	Surface Modification
Typical activity (μCi)	2600	800 - 1000	± 600
Typical size range (μm)	>1000	50 - 1200	100 - 1000
Typical material	contain oxides, heat tolerant, matches bulk	ion exchange resin, tuned to match bulk density	reacts with radioisotope selective to material



Figure 2. A selection of PEPT Cape Town tracer particles from left to right: moulded, density modified, mineral coating, silica coating, coal particle, glass bead with ion-exchange inset. The images have a global scale with the tracer on the far left approximately 300 μm in diameter, up to 1 mm diameter on the far right.

2.1. Radionuclide production

Irrespective of the production method chosen to fabricate tracer particles with the required properties, nuclear activation techniques are used to produce the required radioactive species. Typical reaction pathways for oxygen bearing targets are illustrated in figure 3. Production typically utilises positive ion beams produced by cyclotron, with the majority of global ^{18}F production utilising the $^{18}\text{O}(p, n)^{18}\text{F}$ reaction on an enriched ^{18}O water target with proton beam energy above 7 MeV threshold [6]. Disadvantageously, this production method requires enriched ^{18}O targets (90 – 95% is typical) and therefore cannot be used on natural oxygen bearing substances such as water or oxides. For PEPT, where activation of natural materials is required, both Birmingham and Cape Town groups [2, 3] have explored alternative pathways. Reactions on naturally occurring ^{16}O bearing targets utilise ^3He or alpha particle beams above 20 MeV. For radiochemical synthesis, ^{18}F dissolved in aqueous solution is required. In this scenario the reaction pathway does not affect the chemical properties of the produced solution, and both methods are used with Birmingham preferring the $^{16}\text{O}(^3\text{He}, x)^{18}\text{F}$ reactions, and iThemba LABS using the $^{18}\text{O}(p, n)^{18}\text{F}$ reaction on a dedicated 11 MeV cyclotron used for medical grade ^{18}F (^{18}F FDG) production. PEPT Cape Town has historically utilised the $^{68}\text{Ge}/^{68}\text{Ga}$ radioisotope generators produced by iThemba LABS for routine tracer particle production [4]. In these generators, the long lived (271 day half-life) ^{68}Ge is produced by (p, xn) reactions on natural Ga targets with proton beam energy 66 MeV using the iThemba LABS $k = 200$ Separated Sector Cyclotron (SSC). The ^{68}Ge is loaded into an exchange column, and decays to ^{68}Ga (68 min half-life) which can be eluted on a daily basis to form an aqueous solution. Ion exchange techniques similar to those discussed below have been developed and optimised to produce PEPT tracer particles via radiochemical means using this solution.

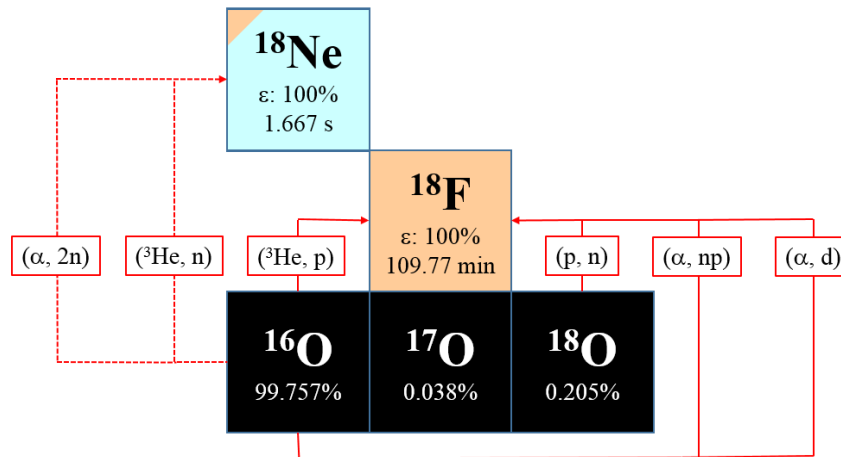


Figure 3. Typical reaction pathways for ^{18}F production from oxygen targets, using proton, ^3He and alpha particle beams. Note many competing reactions contribute to the ^{18}F end-product, sometimes through intermediate short lived stages.

2.2. Direct Activation

The physical-chemical properties of the tracer particle are of extreme importance to accurate representation of results. Ideally, an original particle of the operational bulk material is extracted and radiolabelled. In the context of iThemba LABS the reactions on natural ^{16}O bearing targets with high-energy alpha particle beams are preferred. Up to 10 silicon dioxide (SiO_2) glass spheres of diameter 5 - 10 mm were placed in an aluminium target holder with active water cooling. The target was irradiated in the “Elephant” target station [7] using a 100 MeV alpha particle beam averaging 800 nA current over approximately 2 hours. Radioisotope activation yields were characterised by half-life measurements and gamma photon spectroscopy, with the highest yield being < 3 mCi of ^{18}F on a single glass sphere. Few impurities from other nuclear reaction channels were observed, and the activity was produced firmly embedded in the matrix of the material thus negating radiological contamination issues. Figure 4 illustrates the typical cyclotron target and main conclusions, detailed analysis can be found in [8, 9]. This method complements existing techniques as a benchmark. Typical materials of interest across physics and engineering include: Glass/silica (SiO_2), Mullite ($3\text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2$), Magnetite (Fe_3O_4), and Chromite (FeCr_2O_4).

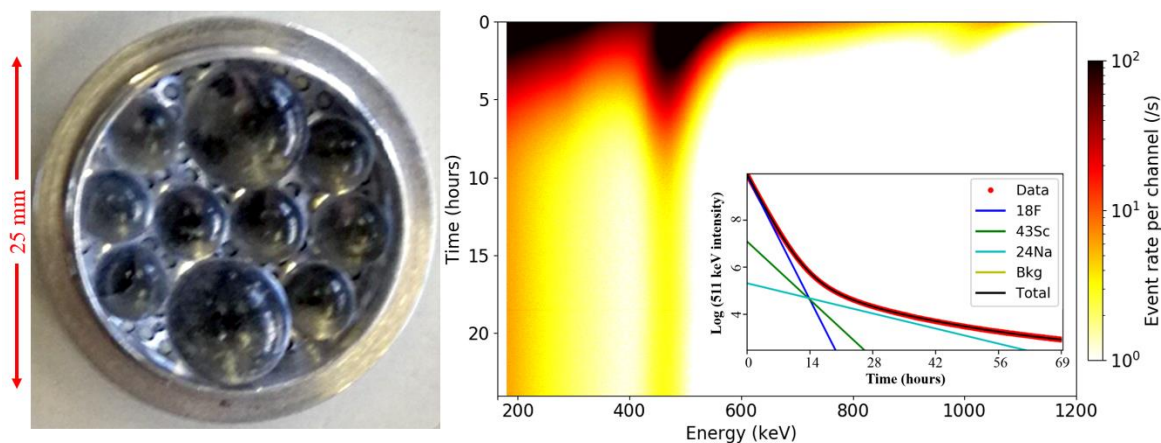


Figure 4. Left: target holder with SiO_2 glass beads of 5 – 10 mm diameter. Right: time-series spectroscopy recorded over 24 hours (vertical axis) showing the principle 511 keV photopeak from positron annihilation, there are very little contaminant species at other gamma energies. The inset shows the 511 keV peak area decaying over time, fitted to half-lives of ^{18}F and the theorised contaminants. These data are consistent with over 95% of the produced activity being due to ^{18}F .

2.3. Ion exchange radiolabelling

Two types of anion exchange resins: weak-base and strong-base, can be used as sorbent resin structures to concentrate and fix suitable radioactivity, and on which to deposit additive layers to control physical material properties. Ion exchange techniques are used to make a resin tracer when particle diameters are required below 1000 μm , and when suitable oxygen bearing substances are not available. The resins consist very small porous plastic beads with functional groups attached to the styrene divinylbenzene copolymer lattice [10]. Each fixed ion is neutralised with a counterion to preserve the overall electrical neutrality of the resin. The basis of ion exchange labelling is to then use radioactive ions to replace the counterions attached to the functional groups on the resin surface. In order for the process to occur, the radioactive ions must have a higher affinity for the resin than the counterions. The functional groups for anion resins are quaternary ammonium cations, shown in figure 5 as N^+R_3 where R is the organic backbone. The mobile counterion in the anion resin beads are chloride anions, and the resin is used in an ionic form with a lower selectivity for the functional group than the sample ions to be exchanged [8], where only ions of the same electrical sign are exchanged. The ion exchange process normally happens in aqueous solution, and here with $^{18}\text{F}^-$ ions dissolved in the high purity deionised water solution used as the cyclotron target.

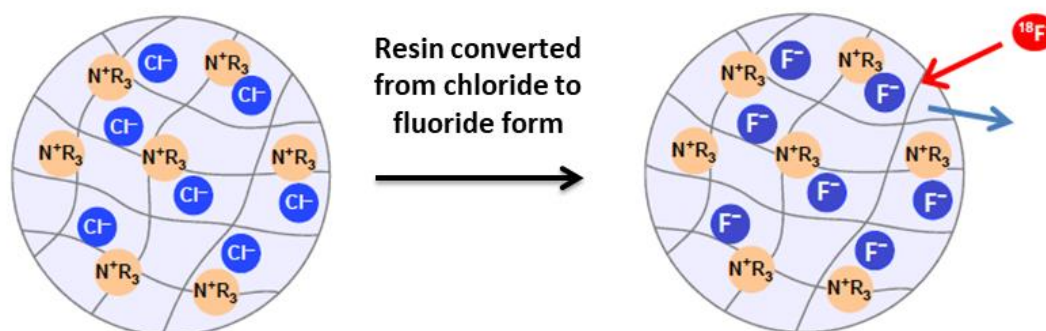


Figure 5. Schematic representation of strong-base anion exchange resin converted from chloride to fluoride form, followed by F^- ion exchange with $^{18}\text{F}^-$ in an anion resin bead to gain radioactive uptake [11].

The uptake of ^{18}F on weak-base anion exchange resins is strongly controlled by water pH. The free-base amines in the weak-base anion exchange resins, eg. $\text{RCH}_2\text{N}(\text{CH}_3)_2$, interact with water and form $\text{RCH}_2\text{N}(\text{CH}_3)_2^+\text{OH}^-$ in which the OH^- acts as a counter ion and can be exchanged by $^{18}\text{F}^-$. The dissociation of the hydroxide ions from the functional group is very weak [3]. As the process progresses, the hydroxyl concentration increases in solution causing the resin to convert back to the undissociated free-base form and inhibiting the anion exchange capacity. The affinity of ^{18}F ions to weak-base anion exchange resin is much weaker than hydroxide ions. Therefore, the use of weak-base anion exchange resins are limited as ^{18}F absorption can only perform at a low pH [3]. Alternatively, strong-base anion exchange resins are less affected by water pH or hydroxide ions since the affinity of $^{18}\text{F}^-$ ions is stronger than hydroxide ions of resins [3]. The strong-base anion exchange resins used are quaternary ammonium derivatives in chloride form: $\text{R-CH}_2\text{N}(\text{CH}_3)_3^+\text{Cl}^-$, where chloride is the counter ion. However, because the affinity of the $^{18}\text{F}^-$ ion to the functional groups is much weaker than the Cl^- ion, the resin particles must first be converted into fluoride or hydroxide form e.g. $\text{R-CH}_2\text{N}(\text{CH}_3)_3^+\text{F}^-$. The conversion is achieved by pouring a resin slurry into a column and eluting with 8 – 10 bed volumes of 1 M KF solution and rinsing with 10 bed volumes of deionised water, the converted F^- ions act as counter ions that exchange with $^{18}\text{F}^-$ ions as illustrated in figure 5.

3. Summary and outlook

We are presently improving the uptake of $^{18}\text{F}^-$ through altering the resin characteristics in which they are based using a polystyrenic or polyacrylic matrix with either gel or macroporous structures [12]. Polystyrenic based resins are hydrophobic relative to polyacrylic based resins, meaning the styrene matrix will retain organic molecules more efficiently. Gel resins offer higher activity levels as increased porosity results in easier ion diffusion through the resin bead. Novel resins under study include mixed base and ion selective functionality, with some having higher chemical and temperature stability, and others with higher capacity and easier regeneration. We have successfully pre-treated a selection of strong-base anion exchange resins for radiolabeling with ^{18}F , and we have demonstrated direct activation using iThemba LABS facilities. In future work we will produce a full kinetic model to explore the change in yield over time as the radioactive species decay and as ions exchange with the introduced media. This work will develop iThemba LABS specific tracer particle production mechanisms, and will provide insight into the effects of tracer particle properties in PEPT applications.

Acknowledgments

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