Quantifying Maximum Potential Impurity Ratio In Radiopharmaceutical Applications

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Introduction

Radiopharmaceuticals are an important and growing application of radionuclides. Radionuclides for pharmaceuticals can be produced by numerous methods, including neutron irradiation, cyclotron production or extraction from existing long-lived radionuclides, and often includes chemical separation to ensure the product is as pure as possible. Quality assurance measurements are performed to evaluate the sample for the presence of radionuclidic impurities. In this application, the critical metric for impurity evaluation is the ratio of the activity of the radionuclidic impurity to the target radionuclide activity of the sample. To distribute product in the FDA or similar regulated industry, producers must demonstrate that the impurity ratio is below a maximum value. When the impurity is below detectable levels, it is common to use the minimum detectable activity (MDA) divided by the primary radionuclide activity to report the impurity ratio. However, this use is not ideal for several reasons. In this paper, Mirion proposes an alternate analysis algorithm that calculates an upper limit, or maximum potential percent impurity (MPPI), of the ratio of a radionuclidic impurity activity to the target radionuclide activity using Bayesian statistics and taking uncertainties of both radionuclide activities into account. The method works when the signal is not present, is weak, and when the signal is large without the need to change metric. The MPPI can be used to conclude with a specified confidence that the ratio of the activities of the two radionuclides is below a defined limit.

Using the Minimum Detectable Activity

The minimum detectable activity (MDA) is one of three concepts introduced by Currie [1] and more recently expanded on in ISO11929 [2]. The first concept is the critical level LC. This is defined as the size of the signal from a radionuclide that is large enough that one is 95 % sure that it is larger than the signal from background alone. The intention of the critical level is to determine if a radionuclide is present in the sample or not, with 95 % probability. If the signal from the radionuclide is larger than the critical level, it is with at least 95 % probability from the radionuclide and not from the background. The second concept is the a priori detection limit LD which is defined in counts and if converted to activity is the MDA. The MDA is defined as the activity that will with 95 % of measurements give a measured signal that is larger than the critical level. The purpose of the critical level is to determine if the radionuclide is present in the sample with 95% probability and the purpose of the MDA is to determine if a measurement system is suitable for a specific measurement objective. The third concept is the quantification limit which is not further discussed in this presentation. These concepts are illustrated in Figure 1. Currently, most radionuclidic analysis uses the MDA as the activity of an impurity radionuclide if the radionuclide is not identified in the sample. The MDA is then divided by the activity of the primary radionuclide or total sample activity, will be referred to as the primary activity, to get an activity ratio. The definition of the MDA does not support this interpretation and using the MDA is overly conservative, leading to unnecessary long measurement times.

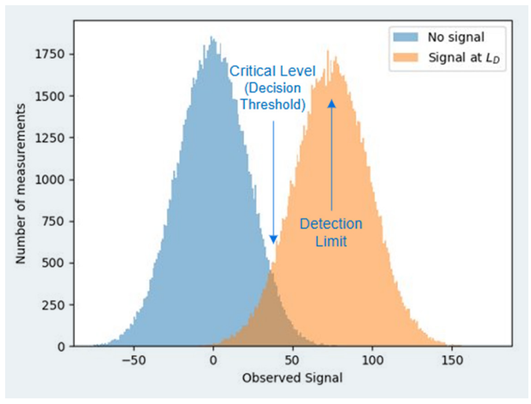

Figure 1, The histogram shows the distribution of the observed signal from a radionuclide when the radionuclide is not present. The orange histogram shows the distribution of the observed signal from a radionuclide when the activity is at the MDA.

The Maximum Potential Percent Impurity Method

Analysis goal

The question that we want to answer is: is the activity of an impurity radionuclide less than a specific fraction of the primary activity with at least an acceptable probability. Alternatively, if the specific fraction is not defined, we want to determine what is the potential largest fraction the activity of an impurity radionuclide to the primary activity with a specified probability. Showing that the impurities are below a specified fraction is an important goal to avoid injection of undesired radionuclides during treatment.

Activity determination

In gamma spectrometry, the activity of a radionuclide is determined from the peak area using a conversion factor. It's always possible to calculate a peak area for a potential peak at any energy and therefore it is also possible to calculate an activity. Figure 2 shows a potential peak at the energy of an emission from an impurity. The channels in blue are part of the ROI for this potential peak, the channels in orange are used to estimate the continuum in this part of the spectrum and the black line shows the estimated continuum in the ROI using the assumption that the continuum is linear. The gross number of counts in the ROI, G, is the sum of the continuum C and the signal S.

G=S+C

We can rearrange and calculate the signal.

S=G-C

Table 1 shows the peak area and uncertainty, L_C, and L_D as defined by Currie and these values converted to activity using the same conversion factor as in Figure 8. The peak area is negative but with the uncertainty it is consistent with 0 or positive. If we wanted to determine that given this measurement is the signal present or not with 95% certainty, one should not conclude that is because the observed signal is less than L_C. The relevant decision for impurity measurement is, given the measurement is the activity of the radionuclide less than a fraction of the primary activity. Let's explore how we can make this decision.

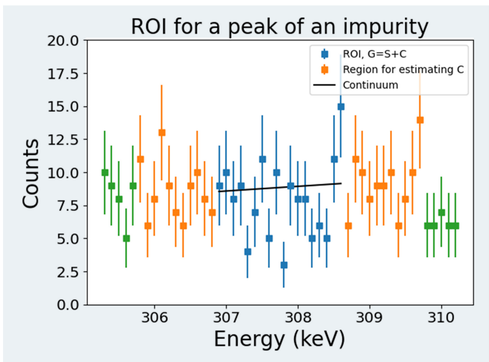

Figure 2, The blue region channels show the region of interest for the signal that may be present at 307.7 keV. The orange channels show the left and right regions of the spectrum that are used to determine the continuum in the region of interest. The black line shows the estimated continuum assuming that the continuum is linear. The observed signal in the region of interest is calculated by tallying the counts above black line and subtracting the counts below it.

Peak Area (counts)	Uncertainty (counts)	L_C (counts)	L_D (counts)	Activity (Bq)	Uncertainty (Bq)	L_C activity (Bq)	L_D activity (Bq)
-16.75	16.56	28.1	58.7	-10.7	10.6	17.9	37.5

Table 1, peak quantities and activities calculated from the peak in Figure 2. The conversion factor from counts to activity was taken from the Lu-177 example in Figure 8.

Definition of the Maximum Potential Percent Impurity

Assume that we have two radionuclides with measured activities of 1 Bq with uncertainty of 0.7 Bq and 1000 Bq with an uncertainty of 20 Bq and that the probability densities are normally distributed. The probability densities are shown in Figure 3. The probability density in the left figure is non-zero for negative activities but we know a priori that negative activities are unphysical. We don't know the true value of the activities of either radionuclide and therefore we don't know the true value of the ratio of the activities either.

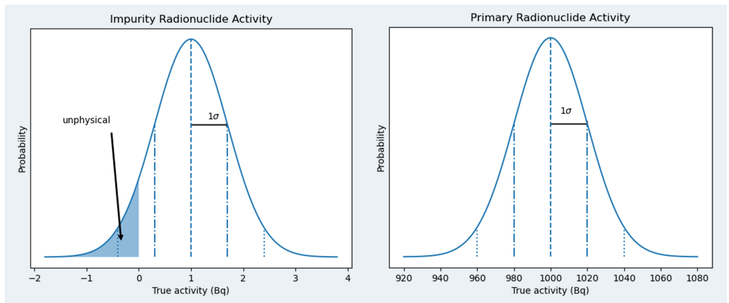

Figure 3, The probability density functions of the activities of two radionuclides.

We can take the ratio of the two probability densities, and this will give us a new probability density which in general is not following the normal probability density. When the uncertainty of the activity in the denominator is small it can be approximately normally distributed, but it is not guaranteed that this is the case. Again, the probability density of the ratio can include non-zero probabilities for negative ratios which is unphysical. Following the ISO11929 [2] standard we can set the probability density for negative activities to be zero and then re-normalize it so that the probability that the ratio is zero or larger is 1. Integrating the probability density from 0 to x will give us the probability that the ratio is less than x. We can now define a Maximum Potential Percent Impurity (MPPI) as the value of x where the probability of the activity ratio to be less than x is 1-α where α is the acceptable false negative rate. A typical value of α is 0.05 which means that the probability of being below x is 95%. This is shown in Figure 4. We can now compare the MPPI to any limit of the activity ratio and if the MPPI is below the limit we can conclude with at least 95% certainty that the true activity is below the limit.

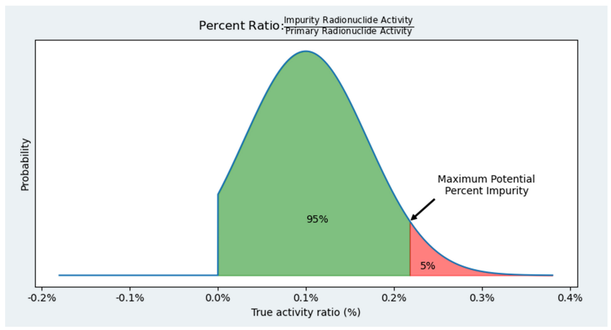

Figure 4 The probability density of the true activity ratio taking the a priori knowledge that it cannot be negative into account. The green part represents 95% of the probability and the red part represent 5%. The MPPI is defined as the value of the activity ratio that given the measurements, we are 95% certain that the true activity ratio is below.

Mathematically the MPPI can be calculated as follows. The ratio Z of two normal distributions X and Y is

$$Z = \frac{X}{Y} = \frac{N_X(\mu_X,\ \sigma_X)}{N_Y(\mu_Y,\ \sigma_Y)}$$

The ratio can only be approximated with a normal distribution under certain conditions, not necessary fulfilled in these measurements. The full solution is

$$f_Z^*\left(z|\mu_x,\sigma_{u_x},\mu_y,\sigma_{\mu_y}\right) = \frac{b(z)d(z)}{a^3(z)}\frac{1}{\sqrt{2\pi}\sigma_x\sigma_y}\left(\Phi\left(\frac{b(z)}{a(z)}\right) - \Phi\left(-\frac{b(z)}{a(z)}\right)\right) + \frac{1}{a^2(z)\pi\sigma_x\sigma_y}e^{-\frac{c}{2}}$$

$$a(z) = \sqrt{\frac{1}{\sigma_x^2}z^2 + \frac{1}{\sigma_y^2}}, b(z) = \frac{\mu_x}{\sigma_x^2}z + \frac{\mu_y}{\sigma_y^2}, c(z) = \frac{\mu_x^2}{\sigma_x^2} + \frac{\mu_y^2}{\sigma_y^2}, d(z) = e^{\frac{b^2(z) - ca^2(z)}{2a^2(z)}}$$

It is another probability distribution, and it was shown in [3] that the probability density function PDF is

$$f_Z^\dagger(z|\mu_x,\sigma_{u_x},\mu_y,\sigma_{\mu_y}) = \frac{1}{\sqrt{\pi}}\frac{\mathrm{p}}{\mathrm{erf}\,(\mathrm{q})}\frac{1}{\mathrm{r}}\frac{1+\frac{\mathrm{p}^2}{\mathrm{q}^2}\frac{\mathrm{z}}{\mathrm{r}}}{\left(1+\frac{\mathrm{p}^2}{\mathrm{q}^2}\frac{\mathrm{z}^2}{\mathrm{r}^2}\right)^{\frac{3}{2}}}\mathrm{e}^{\frac{\mathrm{p}^2\left(\frac{\mathrm{z}}{\mathrm{r}}-1\right)^2}{1+\frac{\mathrm{p}^2\mathrm{z}^2}{\mathrm{q}^2\mathrm{r}^2}}}$$

$$\mathrm{p} = \frac{\mu_X}{\sqrt{2}\sigma_X}, \mathrm{q} = \frac{\mu_Y}{\sqrt{2}\sigma_Y}, \mathrm{r} = \frac{\mu_X}{\mu_Y}$$

And the cumulative distribution function CDF is

$$F_Z^\dagger\left(z_0|\mu_x,\sigma_{u_x},\mu_y,\sigma_{\mu_y}\right) = f\left(z < z_0|\mu_x,\sigma_{u_x},\mu_y,\sigma_{\mu_y}\right) = \frac{1}{2}\left(1 + \frac{\mathrm{erf}\left(\frac{p\left(\frac{z_0}{r}-1\right)}{\sqrt{1+\frac{p^2}{q^2}\frac{z_0^2}{r^2}}}\right)}{\mathrm{erf}\,(q)}\right)$$

The cumulative distribution function is the integral from negative infinity to z_0 of the probability density function. Following the steps in ISO11929, we can define a non-negative prior distribution by

$$f_Z(z|Z \geq 0) = H(z) = \begin{cases} 1\ (z \geq 0) \\ 0\ (z < 0) \end{cases}$$

Multiply it and renormalize

$$f_Z\left(z\middle|\mu_x,\sigma_{u_x},\mu_y,\sigma_{\mu_y},Z \geq 0\right) = N f_Z\left(z\middle|\mu_x,\sigma_{u_x},\mu_y,\sigma_{\mu_y}\right) f_Z(z|Z \geq 0)$$

With a normalization factor of

$$N = \frac{1}{\int_0^{z=\infty} f_Z dz} = \frac{1}{1 - \int_{z=-\infty}^{0} f_Z dz} = \frac{1}{1 - F(0)}$$

The final probability density and cumulative distribution functions becomes
We can define the MPPI as follows.

$$f_Z\left(z\middle|\mu_x,\sigma_{u_x},\mu_y,\sigma_{\mu_y},Z \geq 0\right) = \begin{cases} \frac{f_Z}{1-F_Z(0)} & z \geq 0 \\ 0 & z < 0 \end{cases},$$

$$F_Z(z_0|\mu_x,\sigma_{u_x},\mu_y,\sigma_{\mu_y},Z \geq 0) = \begin{cases} \frac{F_Z(z_0) - F_Z(0)}{1-F_Z(0)} & z_0 \geq 0 \\ 0 & z_0 < 0 \end{cases}$$

Finally, we need to solve for the MPPI which can be done numerically, for example using a bisection method.

$$\int_{z=0}^{\mathrm{MPPI}} \frac{f_Z}{1-F_Z(0)}dz = \frac{F_Z(\mathrm{MPPI}) - F_Z(0)}{1-F_Z(0)} = 1 - \alpha$$

Validation of the Method

The first test of the method involves drawing 20 million pairs of activities from two normal distributions with activities of 10 ±0.7 Bq and 1000 ±100 Bq, shown in Figure 5.

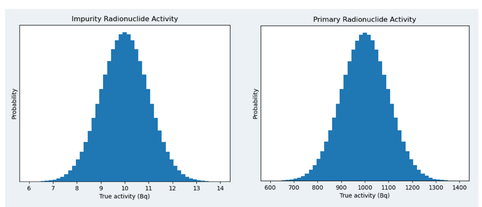

Figure 5, Random numbers drawn from 2 normal distributions.

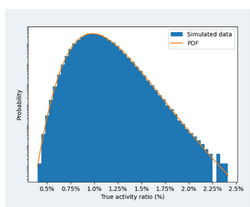

Figure 6, the probability density of the 20 million pairs of random numbers.

The ratio of the 20 million pairs is computed and the probability density of the ratio is shown in Figure 6. The probability density is asymmetric, and it is not following the normal distribution. The probability density function as defined in [3] is plotted in orange and reproduces the simulated distribution very well even at the high ratio tail. The value of the MPPI calculated from the simulation, using the method described in this poster, and assuming that the probability density of the ratio is normally distributed. The value of the MPPI calculated using the method in this poster reproduces the simulated value almost exactly.

Method	Maximum possible impurity	Relative difference from simulation
Simulation	1.265 %	N/A
This method	1.265%	0.0009 %
Using normal distribution	1.232%	-2.57 %

Table 2, MPPI calculated from simulations, using the method in this poster and assuming that the activity ratio is normally distributed.

The next test is using spectral data with known activity ratios. For this Monte-Carlo simulations using MCNP-CP [4] was used to generate realistic spectra for two measurements of Lu-177 with no impurity and an impurity of Yb-169 at the limit from the European pharmacopeia at 0.01% Yb-169 to Lu-177 activity ratio. The geometry simulated was a 20 ml liquid scintillation vial at 10 cm from the end cap of a 30% relative efficiency HPGe detector. The simulated activity of Lu-177 was 500 kBq and 360 10 second measurement was simulated and summed to get a 10 second measurement, 20 second measurement and so on. The last measurement was an hour-long measurement. The simulated spectrum is shown in Figure 7.

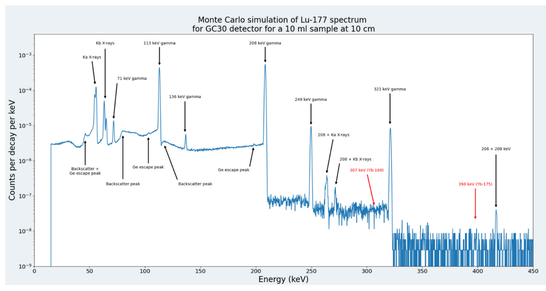

Figure 7 The simulated spectrum of Lu-177 without any impurities using MCNP-CP

All 360 simulated measurements were analyzed and the time evolution of the MPPI, MDA divided by primary activity and the ratio of the two estimated activities. Figure 8 shows the time evolution for the simulation without Yb-169 impurity. The MPPI is always lower than the MDA divided by the primary activity, and it goes below the activity limit after a measurement of about 700 seconds while the MDA divided by primary activity doesn't go below the limit until about 2400 seconds. This leads to a reduction in measurement time when using the proposed method with as much as a factor of 3-4. We can also see that the estimated activity ratio fluctuates around 0 as expected.

Figure 9 shows the same quantities as Figure 8 but for the simulations with an Yb-169 to Lu-177 activity ratio of 0.01%. The estimated activity ratio is only shown when the gamma spectrometry analysis identified Yb-169. The MPPI never goes below the limit which means that regardless of which time the measurement is stopped, using the MPPI method will never draw the incorrect conclusion that the activity ratio is below the limit. The MDA divided by the primary activity continues to decrease and will eventually go below the limit. This is because when the analysis finds a peak at the energy of interest the MDA calculation changes and uses the regions next to the peak to calculate continuum and the MDA. Once this happens the MDA quantity is not appropriate to use for impurity analysis. One would then have to switch to using the estimated activity and if the uncertainties are not included, we see that one would draw the incorrect conclusion that the activity ratio is below the limit.

The final test was done by simulating 100 1-hour measurement of an activity ratio at the limit of 0.01%. The MPPI was calculated for all 100 measurements and the distribution of the measurements are shown in Figure 10. The results range from 0.008 to 0.027% with only 3 analyses of the measurements showing a MPPI value of less than 0.01% which would lead to an incorrect decision that the impurity is below to limit when it is not. This is consistent with the 5% acceptable error rate that we used in the calculation of the MPPI. It should be noted that the 5% error rate is only for samples where the true ratio is exactly at the limit. If the true ratio is higher than the limit the error rate decreases fast with increasing ratio. If a 5% error rate is not acceptable for samples exactly at the limit, a smaller error rate can be chosen. The drawback of this is that longer measurement times are required to be certain that the true activity ratio is below the limit when the true ratio is small.

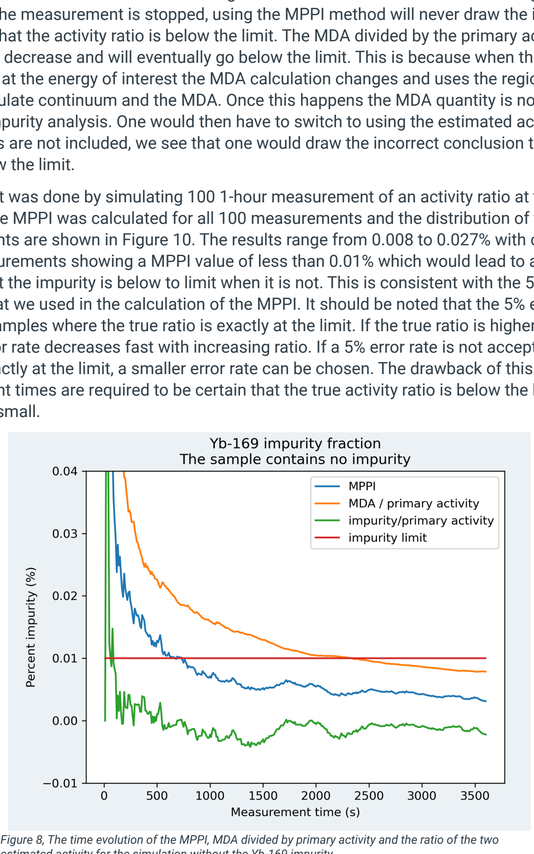

Figure 8, The time evolution of the MPPI, MDA divided by primary activity and the ratio of the two estimated activity for the simulation without the Yb-169 impurity.

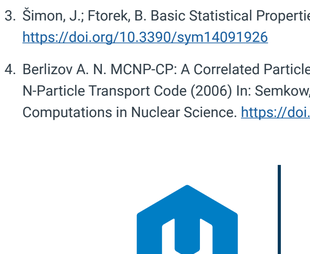

Figure 9, The time evolution of the MPPI, MDA divided by primary activity and the ratio of the two estimated activity for the simulation with the Yb-169 impurity with an activity ratio of 0.01%.

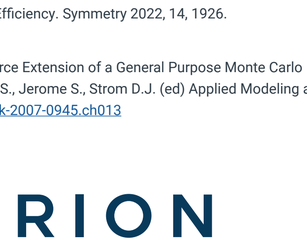

Figure 10, distribution of the MPPI calculated for 100 1-hour measurement of an activity ratio of 0.01%.

Conclusions

We have proposed a new method for determining an upper limit of the ratio of the activity of two radionuclides. The upper limit of the ratio can be used to determine if the activity of an impurity is below a fraction of the activity of the primary radionuclide in a sample. The new method is based on the measured values and the uncertainties of the activities of the two radionuclides and considers Bayesian statistics and the a priori knowledge that the activity ratio cannot be negative. The targeted application is radionuclidic purity measurements for radiopharmaceuticals. The main benefits include shorter measurement times of as large as a factor of 3-4 when the impurity is not present in the sample and a reduced risk of false negative results when the impurity is present with an activity close to the desired limit, compared to using the MDA as the activity of the impurity radionuclide when it is not identified and not taking the possibly very large activity uncertainties into account when the radionuclide is identified.

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