Calibration of Gamma Counters for PET

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Dynamic brain positron emission tomography (PET) is a cutting-edge brain imaging modality used in psychiatric research to get a full view of relevant physiological parameters in-vivo. This technique requires the sampling of arterial blood throughout the scan and the counting of radioactivity concentration in these samples. For this purpose, the clinical and translational sciences (CaTS) lab at the Douglas Research Institute uses a Hidex AMG automatic gamma counting system, which includes a NaI-based well counter as its detector. This study aimed to thoroughly characterize the count rate linearity, the sample volume effects, and the efficiency of the Hidex AMG gamma counting system. It also aimed to cross-calibrate this device with a simpler well counter, the Capintec CAPRAC-R, as a demonstration of their linearity as well as demonstrating the possibility of using this detector as an alternate counter in the lab in case of a malfunction of the main detector during a PET study. All experiments in this study used samples of fluorine-18 (^{18}F), as it is a common isotope used in PET imaging. It was found that the two detectors have good linearity with a conversion rate of $H \approx 1.23C$, where H is the measured activity on the Hidex AMG in CPM and C is the same decay-corrected measurement on the CAPRAC-R counter. The Hidex AMG shows good deadtime correction, with under 5% error, for deadtime factors under 1.70 $\pm$ 0.07 or measured activities under (3.59 $\pm$ 0.16) $\times 10^6$ CPM. The absolute error in measurements increases linearly with increasing sample activity, indicating that a secondary deadtime correction is easy and necessary to implement to avoid carrying a large error for larger activities. It was also found that the Hidex AMG has strongly nonlinear behavior for sample sizes above about 3 mL in standard 13-mm diameter vials. Above this threshold, the geometric efficiency dips below 95% for this device. Finally, for polystyrene vials with samples of 0.3 mL and 0.6 mL, it was determined that the Hidex AMG has an efficiency of 33.459 $\pm$ 0.003 %, although secondary deadtime correction is needed to ensure this number is valid for a broader range of activities.

Radiation counting | Cross-calibration | Positron Emission Tomography

Introduction

Brain positron emission tomography (PET) is a neuroimaging modality that allows the quantitative study of proteins in-vivo. To do this, a trace amount of a radioactive material called a radioligand is injected into the bloodstream and allowed to circulate in the body. A radioligand is a pharmaceutical molecule, designed to bind to a particular receptor in the brain in the context of neuroimaging, that is tagged with a positron emitter radioisotope (typically ^{11}C or ^{18}F). As this radioligand travels throughout the brain and the body, its radioactive atom may undergo $\beta+$ decay and emit a positron, which travels at most about 1 mm in tissue before annihilating with a nearby electron and emitting two photons with an energy of 511 keV (1). The detection of these photons in the bore of the PET scanner is what allows the reconstruction of the distribution of radioligand, and by extension of the protein it binds to, in the brain of the patient.

The specific "gold standard" technique that allows for full quantification of physiological parameters relevant to research, called dynamic PET, requires the sampling of arterial blood throughout the scan (2). These samples are sent to the wet lab during the scan to obtain a time series of the radioactivity present in the plasma and the whole blood, allowing researchers to perform full kinetic modeling. Due to constraints on the amount of blood that can be collected from a subject during a study, and the low activities injected in the first place, it is crucial to have a well-calibrated device that can count 511 keV gamma photons accurately in small amounts. Thus, all measurements in the current work are done in the 400-600 keV energy window to encompass this peak.

Linearity. An important limitation of digital gamma counting systems such as those investigated here is the finite response time of the electronic components to each decay event. While the system processes a detected event, it cannot detect any new events – this is called the *dead time*, τ (3). Due to the stochastic nature of radioactive decay, there is always a probability that an event occurs during this time following another one, and this probability is high when trying to detect higher counts rates. As such, at high count rates, some fraction of the photons are ignored or "lost", and the system becomes unresponsive at high enough count rates. We can estimate the true count rate R_t from the measured count rate R_0 if the dead time is known:

$$R_t = \frac{R_0}{1 - R_0\tau} \quad [1]$$

where τ is the system's dead time (3). We can measure this loss as a percentage or a factor called the dead time factor, denoted d_t, which is estimated by the counter software to indicate to the user how many photons are lost:

$$d_t = \frac{R_t}{R_0} = \frac{1}{1 - R_0\tau} \quad [2]$$

This quantity is useful to monitor during data acquisition since it is unitless and captures the counting performance of the system in a single number that requires no calibration. This work aims to estimate the upper limit of dead time factors that constitute an acceptable value for the Hidex AMG gamma counting system by characterizing the linearity of its response to increasing count rates and estimating the accuracy of its internal dead time correction for different counted rates.

Sample volume effects. In well-type counters such as the Hidex AMG and CAPRAC-R discussed in this study, the geometry of the detector and shield necessitates a hole at the top where samples can be inserted. When the sample volume is large, the photons also have a higher probability of escaping through the top of the detector, as illustrated in figure 1 (4). More formally, we say that the geometric efficiency g is proportional to the solid angle subtended by the detector (from the point of view of the source):

$$g = \frac{\Omega}{4\pi} \qquad [3]$$

where Ω is the solid angle, in steradians. The geometric efficiency effectively indicates what fraction of the "field of view" of the source is occupied by the detector. Hence, for a given specific activity, there is an optimal volume which will produce enough photons to have a signal above the noise threshold of the detector, but not so large that a significant portion of the signal is lost through this geometric effect. This work seeks to find a range of optimal sample volumes for the Hidex AMG system to have a reference that can be used for dynamic PET studies.

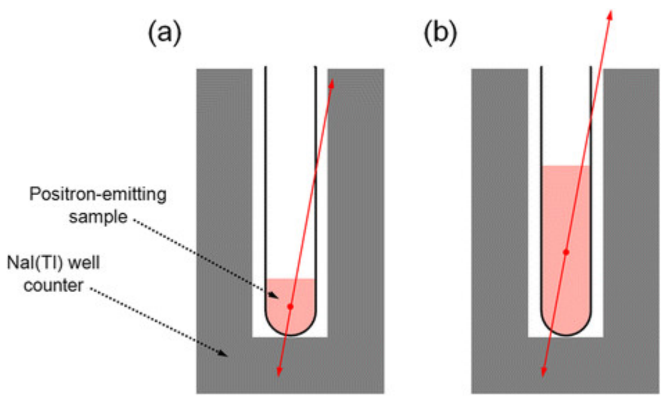

Fig. 1. The effect of sample volume on the detection of gamma photons. Photons of an annihilation event coming from the center of a small sample, as in (a), will have a small chance of escaping through the hole at the top of the well counter where the sample is placed. For a larger sample, as in (b), an annihilation event occuring at the center and sending photons at the same angle will be much more likely to have one "escape" through the hole of the well. Figure from Lodge et al. (4)

Efficiency. The absolute efficiency of a counting system is simply the ratio of the measured count rate over the true activity of the sample, typically expressed in becquerels per counts per minute (Bq/CPM) or curies per counts per minute (Ci/CPM), or as a percentage if the units are the same (4). The true activity of the sample is calculated from knowing the specific activity of the original solution from a well-calibrated detector. The efficiency is the crucial piece of information needed to convert measured activities, in counts per minute, into emitted activities in physical units (Bq or Ci). To obtain the optimal efficiency of a system, one must use sample activities below the threshold where dead time loss becomes significant, and volumes in the "sweet spot" between low signal-to-noise and high geometric loss.

Hidex AMG automated gamma counter. The Hidex AMG Automatic Gamma Counter (Hidex Oy, Turku, Finland) is an automated system for measuring nuclides emitting gamma radiation composed of a conveyor that takes racks of samples, a robotic arm that transfers the samples to the load position, and a detector unit. This unit contains a scintillation well-type detector made of a sodium-iodide crystal (NaI) with a photomultiplier tube and other detector electronics. The system also contains a balance which allows the weighing of empty and full tube vials to calculate the theoretical activity in each sample if the original concentration is known. It contains 2047 energy channels calibrated by matching the position of the 662 keV peak in the spectrum of a Cs-137 source to the 662nd channel. Counts may be kept in a window of these channels to include specific energy peaks of interest. According to the manufacturer, this counter reaches 30% deadtime at about 25 000 counts per second (CPS) or about 0.7 μC assuming ideal efficiency.

Carpintec CAPRAC-R well counter. The CAPRAC-R well counter (Capintec, Mirion Technologies, Inc., Atlanta, GA, USA) is a general purpose drilled-well gamma counter that uses a NaI detector to measure counts per minute in six self-calibrated energy channels. For radionuclides used in PET, the 400 to 660 keV channel is most useful as it includes the 511 keV peak that accounts for most of the gamma energy emitted in a sample. This detector is reported by the manufacturer to handle high count rates, of about 60 000 CPS, before exceeding 30% deadtime. Such a high count rate corresponds to about 1.6 μC, and the typical activities in dynamic PET blood sample are in the order of nanocuries.

Materials and methods

Cross-calibration of Hidex and CAPRAC-R counters. A 3 mL ^{18}F sample of approximately 1 μCi in a 6 mL EDTA tube was obtained in the morning and its activity was measured throughout the day at approximately 1-hour intervals, three times per run, with both counter consecutively. The time of measurements was recorded in UTC to allow for decay correction, effectively making the measurements simultaneous in both counters. Both detectors were calibrated with the same Cs-137 source. A linear correlation was then performed to determine the conversion rule between activities measured with either detector.

Linearity. The linearity of the Hidex AMG system's response was calculated similarly to the cross-correlation above. Four 1-mL samples were taken from the same solution with an unknown activity of ^{18}F. These samples, along with an empty vial to monitor the background activity, were placed in a rack of the system and each counted for 1 minute at 30-minute intervals over the course of about 33 hours. The raw count rates and the dead time corrected count rates were first corrected by the background activity (about 50 CPM), then compared to the theoretical count rate of the sample over time. This ideal count rate was calculated by fitting an exponential decay function to the data points from the lower 50% of the count rate distribution. These low count rate data from the last few hours of the experiment are considered on average the most accurate and the most linear with the true activity of the sample, with minimal dead time loss. All processing was done with the Scipy package in Python 3.

Volume effects. Two vials of ^{18}F solution were prepared with an initial volume of about 0.2 mL and placed in 13 mm tube holders. These samples were each counted for 60 seconds and a background measurement was taken for 60 seconds. Then, 0.1 mL of the original solution was added to each sample vial and the process was repeated 40 times for a final volume of about 4.2 mL. The background activity was then subtracted from each vial measurement and the activity in each sample was decay-corrected to the time of start of the experiment to isolate the effect of the sample volume on the measurement.

Efficiency. The last experiment involved picking an optimal sample volume and activity to calculate the absolute efficiency of the Hidex AMG counter. The calculation of the optimal activity of the sample and the optimal volume serve as building blocks to the measurement of the highest achievable efficiency for the Hidex AMG system while counting positron emitting nuclides. A stock solution of 9.15 nCi/mL of ^{18}F was prepared and divided into six 5-mL polystyrene vials (three with about 0.3 mL and three with about 0.6 mL of solution) and six 4-mL EDTA vials (eight samples between 0.3 mL and 4 mL). All vials were tared then weighted twice for an accurate estimate of the mass of each sample. It was assumed that the density the solution is 1 g/mL. All vials were counted in the Hidex AMG for 30 seconds each, a total of 22 times over the course of about 19 hours, and 30-minute background readings were taken between sets of measurements. In post-processing, the background readings (about 50 CPM) were removed from all the measurements. The theoretical activity in each vial at the time of counting was calculated using the half-life of ^{18}F, and was used to divide the measured activity to obtain the efficiency of the Hidex AMG counter for various activities of ^{18}F. This experiment was repeated at a later date with a solution with a specific activity of 0.489 nCi/mL, where both sets of vials were counted five times.

Results

Hidex counter linearity. The measured and corrected data acquired with the decaying samples of ^{18}F are shown in figure 2, along with the theoretical value decay that should be measured if dead time loss did not occur at higher count rates. We observe the expected underestimation and saturation of the signal in the uncorrected data, most prominent at the highest count rates (at the earliest times). The highest dead time factor recorded was over 3.5.

There is also a slight underestimation of the count rates at high values even in the corrected data, suggesting some imperfection in the dead time correction of the Hidex software. This is illustrated more clearly in figure 3, where we see that there is a good one-to-one match between the dead time corrected measured count rates and the theoretical count rates at low values, but the discrepancy grows at increasing count rates.

Figure 4 shows a very large variance at the lowest activities and a steady increase in the underestimation of the activity thereafter. The dashed line in figure 4 represents a 5% error in the measurement, an arbitrary but useful rule of thumb to use during experiments to avoid errors generally deemed too large in PET. This threshold corresponds to a measured activity of $(3.59 \pm 0.16) \times 10^6$ CPM. The line of best fit has the parameters $y = -1.36x - 0.10$, which may be used as a second correction to the built-in deadtime correction system.

Finally, figure 5 shows the correlation between this underestimation of the activity with the dead time factor. The dead time factor at 5% error is 1.70 ± 0.07. The best-fit line, found with `numpy.polyfit`, is $\delta_A = (-6.81 \pm 0.12)d_t + (6.6 \pm 0.3)$ where δ_A is the percent error on the activity measured and d_t is the dead time factor.

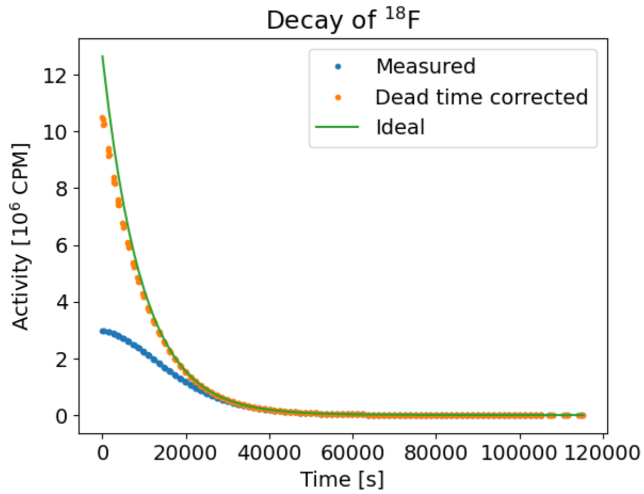

Fig. 2. Comparison of the raw count rate data taken with the Hidex AMG system (blue), the dead time correction on this data provided by the software (orange), and the theoretical underlying count rates that would be detected in the absence of such an effect (green).

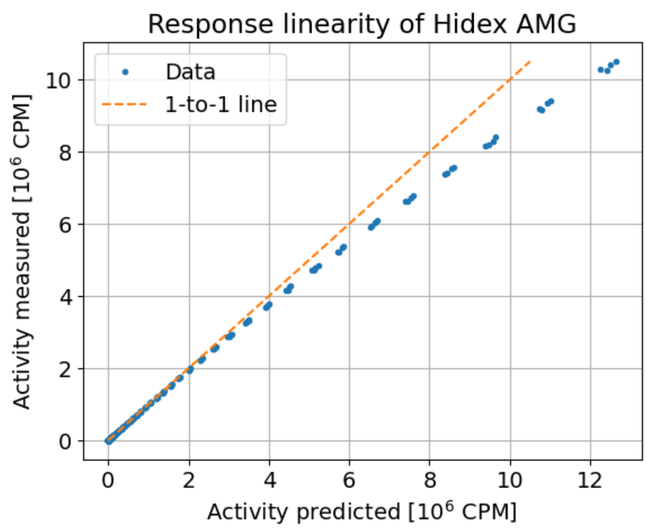

Fig. 3. The measured activity here refers to the dead time-corrected count rate of the sample. Notice that despite the correction, there is a considerable underestimation of the count rate and it is correlated with the count rate.

Hidex counter sample volume effects. Figure 6 shows the effect of increasing sample volume for a constant activity on the measured activity. The efficiency remains within 5% of the ideal value at volumes below about 3 mL, and then sharply falls off as the vials become more full, with visibly nonlinear behavior near 4 mL.

Efficiency. First, it was determined that volumes of 0.3 and 0.6 mL were well within safe limits of geometric efficiency, as calculated in the previous experiment, to minimize and sample volume effects. Measurements with a dead time higher than 1.63 were discarded, as these potentially correspond to

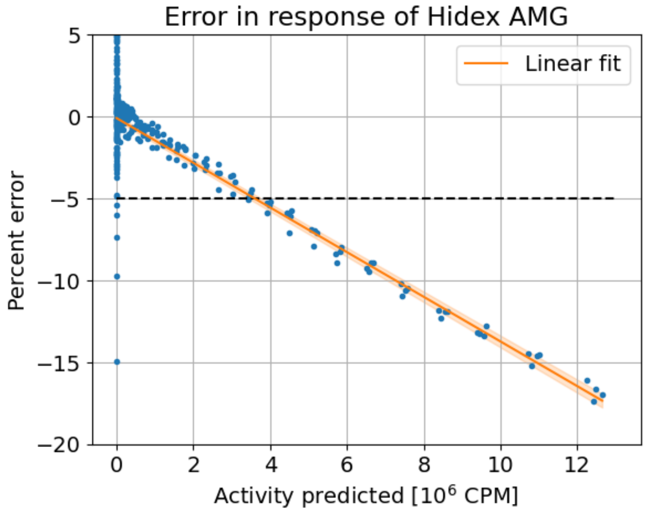

Fig. 4. A close up of the dead time loss effect observed in the residuals of the data shown in figure 3. The dashed line represents the 5% error mark for reference. The high residuals at low activities are cropped as they show a high variance at very low signal intensities from the background noise and the random nature of radiation counting. We observe a good linear fit if we ignore this very noisy portion of the data. The shaded area represents one standard deviation on the linear fit.

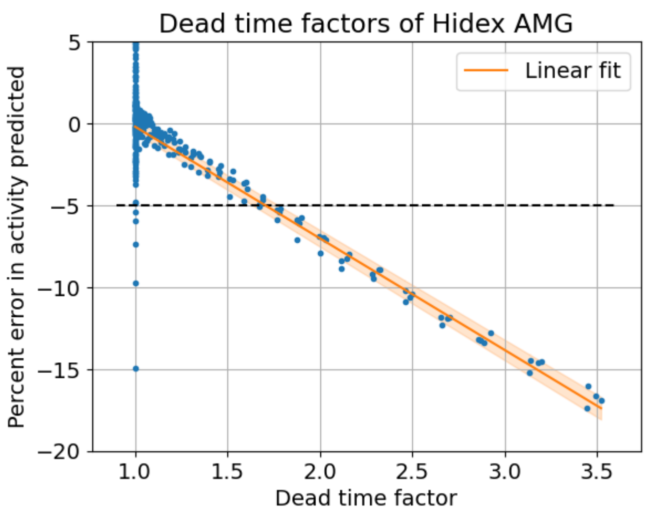

Fig. 5. A comparison of the percent error in the activity measured by the Hidex AMG counter with the corresponding dead time factor. The dashed black line shows again the 5% error mark, and the shaded area represents one standard deviation of the linear fit.

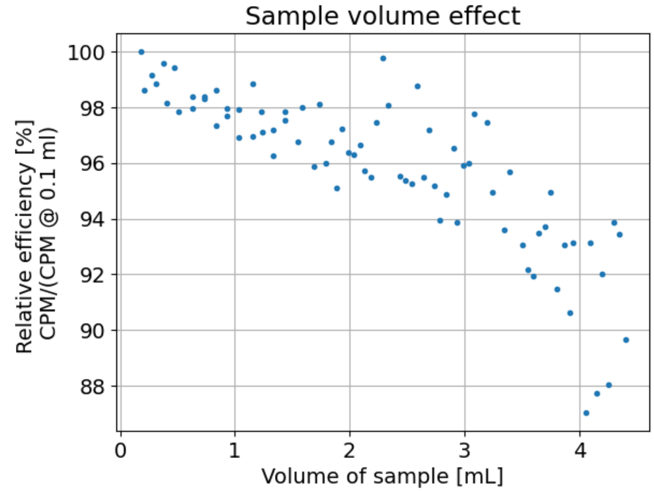

Fig. 6. Demonstrating the effect of sample volume on the measured activity, as an efficiency where we assume the ideal sample volume is 0.1 mL, as it is suffiencently small to have minimal loss due to geometry..

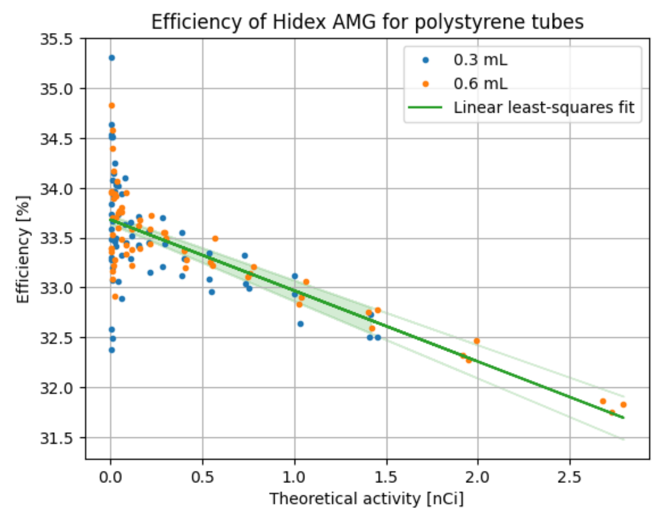

Fig. 7. Efficiency of the Hidex AMG for all volumes in the polystyrene vials. We observe that the data does not differ between the 0.3 mL samples and the 0.6 mL samples and as such these two datasets can be combined to produce a more robust estimate of the efficiency. The shaded area represents one standard deviation on the linear fit.

an error higher than 5%. The efficiency calculated for the polystyrene vials in the first experiment is shown in figure 7, where we observe a linear relation between the efficiency and the activity with a best-fit line of $y = -0.71x + 33.68$.

If we plot the theoretical activities on a logarithmic scale to more clearly see the constant portion at low activities (figure 8), we observe that the flat portion up until about 1 nCi corresponds to an efficiency of 33.459 ± 0.003 %.

Preliminary results for the second efficiency experiment, which used a range of sample volumes of the same original solution in EDTA tubes instead of polystyrene tubes, show a much broader range of efficiencies, as shown in figure 9. Two volumes above 3.1 mL were counted (3.7 mL and 4.0 mL), but these data were discarded due to the known large error that is introduced by geometric effects. These values range ideally (i.e. without deadtime) between about 24% and 30%.

Cross-calibration of Hidex and CAPRAC-R counters. Figure 10 shows the comparison between measurements performed on the same sample with both counters. The linear regression yields $H = 1.23C + 61.4 \approx 1.23C$ where H is the measured activity in CPM by the Hidex AMG system and C is the measured activity with the CAPRAC-R well counter. Both counters were calibrated with the same caesium-137 source prior to measurements.

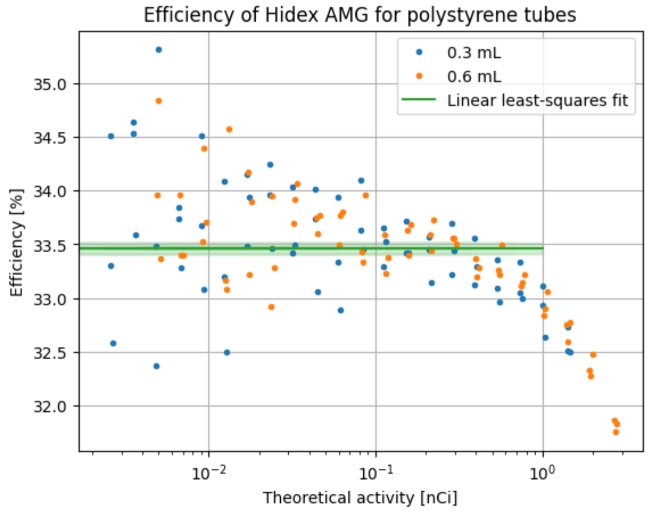

Fig. 8. Efficiency of the Hidex AMG plotted on a log scale to show the constant portion at low activities. The shaded area represents one standard deviation on the linear fit.

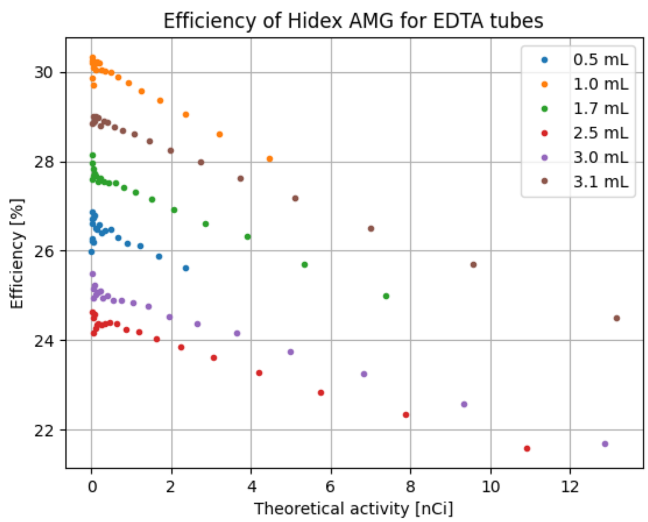

Fig. 9. Efficiency of the Hidex AMG for samples in 4-mL EDTA tubes.

Discussion

A closer look at the residuals in the activity of the Hidex counter (figure 4) reveals a very large variance at the lowest activities, as expected due to the noise. Although the last 11 samples were counted for 5 minutes instead of 60 seconds like all the others, it seems that this measure was not effective in mitigating the low signal-to-noise ratio at these low activities. A 5 minute counting time would perhaps have shown improvement if used for the last 100 or so measurements; however, this long counting time is rather impractical in a lab setting as it would have increased measurement time by over 8 hours (after which there would be little activity left in the samples). At higher activities, we see a steady increase in the underestimation of the activity that starts immediately after 0. Namely, there is no plateau where the activity would be perfectly dead time corrected, as one might guess by looking at figure 3 with the naked eye. Instead we observe a linear correlation between the percent error and the activity, hence for a given

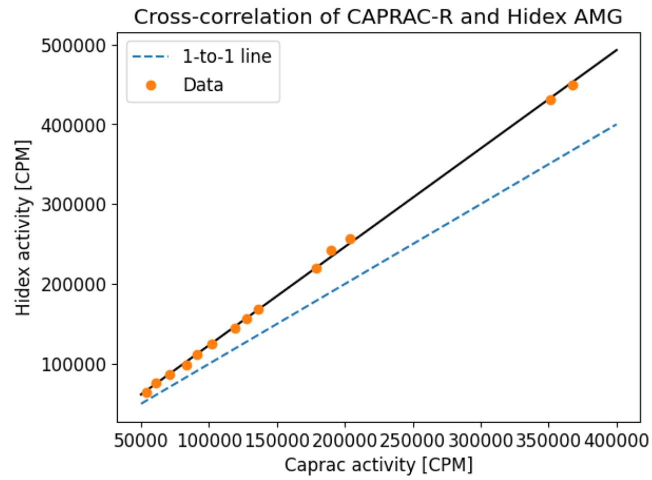

Fig. 10. Cross-calibration of the two counters. We observe a linear correlation between the activities measured when they are calibrated with the same Cs-137 source.

experiment we must pick an activity that is safely below the error that is acceptable for a given application. Similar logic applies monitoring the dead time factor: choosing a maximum acceptable dead time factor means picking an acceptable error in the activity, regardless of how low this activity is. Table 1 shows a quick reference summary for the dead time factor to reach for a given percent error. The linear fit presented above can be used as a correction rule for further fine-tuning of the measured activity after dead time correction has been performed by the Hidex software.

Percent error	Dead time factor
1	1.12 ± 0.53
3	1.41 ± 0.22
5	1.70 ± 0.07
10	2.43 ± 0.82
30	5.37 ± 3.80

Table 1. Summary of dead time factors modelled for a given percent error in the count rate measured by the Hidex AMG

Furthermore, the decreasing linear trend in efficiency with increasing sample activity, in both experiments, is likely explained by this linear error in the deadtime correction. This indicates that a secondary correction is needed to ensure a constant efficiency across a wide range of activities. Without it, as seen in figure 8, there is only a narrow range of activites for which we can consider the efficiency to be constant at 33.459 ± 0.003 % for that vial geometry. Thus, for future use of this gamma counter, if one chooses to not correct for deadtime any more than the manufacturer recommends, the activities of the samples should be between about 0.1 and 1 nCi to simultaneously avoid large noise from low activity samples and poor dead time correction due to high activity. This efficiency is comparable in magnitude to the 34.4 ± 0.18 % reported by Lodge et al. for a similar detector with fluorine-18 (4). Although analysis for the second efficiency experiment is not complete, we notice a few key features in the results. First, that the same linear deadtime correction is needed to verify that the efficiency is constant for various activities. Second, that the efficiencies reported in this experiment are lower by about 3%, or one-tenth, than the efficiency calculated for the polystyrene vials. Seeing as both the polystyrene and EDTA tubes have a similar geometry (13 mm diameter), we should expect to see similar results at least for the 0.5 mL samples. It is thus unclear where this discrepancy comes from, and further investigation is needed. Finally, that although we expect the efficiency to be higher for smaller samples due to geometric effects, this is not what we observe in figure 9: the order of the data series does not follow the order of decreasing sample volume. This may be an artifact of the post-processing of the data, either in the background subtraction or decay-correction steps. It is unlikely that it is purely statistical noise, as the variability in the efficiency for each data series is much smaller than the difference between the series.

The threshold for 5% error in deadtime correction found in this work, $(3.59 \pm 0.16) \times 10^6$ CPM, is about three times greater than the one found by Lodge et al. (4), indicating that the deadtime correction of the Hidex system is robust at a wider range of activities than for the 2480 Wizard (PerkinElmer, Waltham, MA, USA (5)) system that they investigated. The sample volume effects, however, are pronounced at a lower volume in the Hidex system (about 3 mL) than in the one investigated by Lodge et al., which only shows a 5% loss of geometric efficiency for fluorine-18 near 4 mL. However, the diameter of the vials they used was 10 mm, as opposed to 13 mm in this work, and thus the data found for different geometries may not be comparable without an analytical model.

Conclusion

In conclusion, this work shows a full characterization of the Hidex AMG gamma counter with the intention to serve as a useful guide in brain PET studies that involve the counting of blood samples. It was determined that cylindrical liquid samples placed in a standard 13 mm diameter tube have a less than 5% error induced by the difference in geometric efficiency for volumes under 3 mL. Users should be warned, however, that too small of a volume may come with the drawback of a small activity and thus a large counting error. Sample activities under 1 nCi suffer the most from this. However, sample activities above 1 nCi show a drop in efficiency that can potentially be corrected by a secondary deadtime correction. The counting efficiency has been investigated for volumes of 0.3 mL and 0.6 mL in polystyrene tubes, which are typical for radiometabolite analysis, but have yet to be investigated robustly for 4 mL samples in EDTA tubes. The next step in this project will be to complete the analysis of efficiency with this different vial type, as well as to include the newer set of measurements as a test of these results. Users of this counter should keep in mind that the efficiency found here, although it is within the range of acceptable volumes and activities for this detector, is considerably smaller than the 46% reported by the manufacturer for ^{18}F in the provided manual. For the sake of rigor, these experiments, particularly the portion which estimates the efficiency of counting, should be repeated for ^{11}C as it is the other most commonly used radionuclide in our laboratory. It is expected that gamma counters will have the same efficiency for different nuclides so long as they are all positron emitters; thus, one can expect that ^{11}C will also have a counting efficiency of about 33.5%. As a next step in this project, full analysis of the efficiency data in EDTA tubes has also yet to be performed. This testing condition is valuable as it is commonly used in the laboratory's PET studies.

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