Considerations in the Use of Automated Well Counters for PET Quantitation

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Although the use of automatic well counters with deadtime and decay correction capabilities has simplified the quantification process in PET, inaccurate correction of data may still occur. In our study, an 18% window resulted in deadtime undercorrections of 25.3% and 5.1% at deadtime rates of 75% and 10%, respectively, due to pulse pile-up and a subsequent rightward shift in the photopeak. Because the number of sumpeak interactions also increases with deadtime, differences between reported and predicted values were best minimized when the window was set to include the sumpeak. Detected counts varied 2% when volume was increased from 0.1 ml to 1.0 ml at the 18% window setting and varied only 0.3% when the window was set to include the sumpeak. Despite the relatively high energy of positrons and the resulting annihilation photons, no significant breakthrough of photons into the well from adjacent samples was observed.

The well counter has long been a fixture of the nuclear medicine laboratory. As such, the effects of sample volume, system deadtime, crystal size, and isotope energy on detection efficiency are well understood and accepted (*1–3*). However, in the PET environment, the use of high-energy short-lived radionuclides presents unique challenges to those using well counters for quantification. Blood sample data must be corrected for decay as well as for differences in count rate (deadtime) and volume (*4*).

Fortunately, technological advances in automated counting instrumentation enable the on-line correction of samples for decay and deadtime, thus alleviating much of the previously necessary data manipulation. Still, due to the inherent limitations of detector electronics and the nature of positron decay (two 511 keV photons are emitted simultaneously as a result of positron annihilation), counting inaccuracies may persist even in state-of-the-art well counters. Specifically, automatic deadtime correction values can be affected by the inadequate response of detector electronics at high count rates, as well as the number of sumpeak photons detected by the crystal. In addition, a change in the relationship between sample volume and count rate efficiency has been observed as window width is varied. Finally, because of the high energy of positron emitters, breakthrough may present an additional problem in the PET environment.

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MATERIALS AND METHODS

Deadtime Effects

A 7-μCi aliquot of fluorine-18 (^{18}F), an amount sufficient to result in a nonparalyzable deadtime of greater than 95%, was placed in a plastic scintillation vial. The sample was continually counted in 300-sec intervals for at least 10 half-lives using a commercially available automatic well counter (LKB-Wallac CompuGamma 1282, Turku, Finland). An 18% window centered on the photopeak of 511 keV was employed. Automatic decay correction was not utilized so that deadtime would be the sole system-corrected parameter.

Raw counts (C_r, no correction for decay or deadtime), deadtime-corrected counts (C_d), and predicted counts (C_p) were graphed as a function of time. Predicted counts were derived from a log-linear fit of the final four background-subtracted raw data points. Differences between the predicted and the actual system-derived deadtime-corrected values were determined using the following equation.

$$[(C_p - C_d)/C_p] * 100$$

The experiment was repeated with an 18% window for the positron emitters carbon-11 (^{11}C), oxygen-15 (^{15}O), and nitrogen-13 at counting intervals appropriate for the isotope and again with ^{18}F using discriminator settings that corresponded to the energy ranges of 470–788 keV and 470–1295 keV.

As an adjunct to the deadtime experiment, ^{18}F, technetium-99m (^{99m}Tc), and iodine-131 (^{131}I) spectra were also obtained at high (greater than 90%) and low (less than 30%) deadtime rates using a system-provided spectrum generation program and normalized so that the integrals of the area under each set of curves were equivalent.

Volume Effects

100 μl aliquots of ^{18}F were autopipetted into 48 preweighed plastic scintillation vials. Vials were reweighed to correct for differences in absolute activity. The activity was diluted with water in 16 volume increments from 0.1 ml to 3.0 ml (3 samples per volume measurement) and weighed a third time. Samples were counted for 30 sec using the automatic decay and deadtime correction features and a preset 18% window centered over the 511 keV photopeak. Measured deadtimes for all samples were 8.7% or less. Total measured volume was graphed as a function of detected cpm per μCi. The experiment was repeated using a single window wide enough to include both the photopeak and the sumpeak.

Spectra representing the 0.1-ml, 0.5-ml, 1.0-ml, 2.0-ml, and 3.8-ml volume levels were obtained as previously, using ^{11}C and normalized to account for decay.

Breakthrough Effects

Background activity was measured in the well counter by placing a scintillation vial containing water but no activity in the counting chamber. Breakthrough, or the amount of activity in cpm penetrating the lead shielding and detected in the well, was determined by placing increasing amounts of ^{18}F into a vial occupying the adjacent position of the counting rack and noting the change in measured background activity in the well. Background cpm was plotted as a function of both activity and deadtime of the adjacent sample.

RESULTS

Deadtime Effects

When well counter data are acquired serially from high to low deadtime, with an 18% window, marked differences between reported C_d and theoretical C_p result (Fig. 1). Underestimations of 5.1% and 25.3% were observed at deadtimes of 10% and 75%, respectively. When the upper discriminator was increased to 788 keV to ensure inclusion of the entire photopeak, differences between calculated and predicted values diminished (Fig. 2). An error of only 7.2% resulted at the 75% deadtime level. Widening the window to include all counts from both the photopeak and the sumpeak improved the deadtime correction capability of the well counter even further. Differences between reported and predicted values were 0.5% or less over the entire deadtime range from 0%–90%, and even at the highest recorded deadtime of 96%, an overestimation of only 3.7% was noted (Fig. 3).

Fluorine-18 spectra data demonstrated a marked rightward shift in the photopeak and a corresponding increase in the ratio of sumpeak/photopeak interactions as deadtime increased from 29% to 90%. The ^{99m}Tc spectra showed a leftward shift in the photopeak as deadtime increased and no sumpeak interactions at the low deadtime rate. For ^{131}I, only a slight rightward shift in the photopeak was noted at the high deadtime (Fig. 4).

Volume Effects

Using the conventional 18% window setting, a 2.0% decrease in detected fluorine-18 activity was seen over the volume range from 0.1 ml to 1.0 ml. However, from 1.0 ml to 3.0 ml, an 8.9% increase in average detected cpm/μCi was observed (Fig. 5). At the wide window setting, the relationship between sample volume and detected activity differed remarkably. Although the average cpm/μCi was 4.7% higher at the 0.1 ml volume than at the 0.2 ml volume, a difference of only 0.3% was noted as volume was increased from 0.2 ml to 1.25 ml, while over the range of 1.25 ml to 3.0 ml, a 1.3% decrease in detected cpm/μCi resulted (Fig. 5).

Breakthrough Effects

A 10-μCi aliquot of ^{18}F located in the adjacent position of the counter rack and in sufficient quantity to cause greater than 99% deadtime when counted, resulted in an increase in measured background activity of <1 s.d. from the mean background of 48 cpm. Even when activity levels exceeding the counting capacity of the system were present outside the well, little breakthrough activity was noted. A 60-μCi aliquot

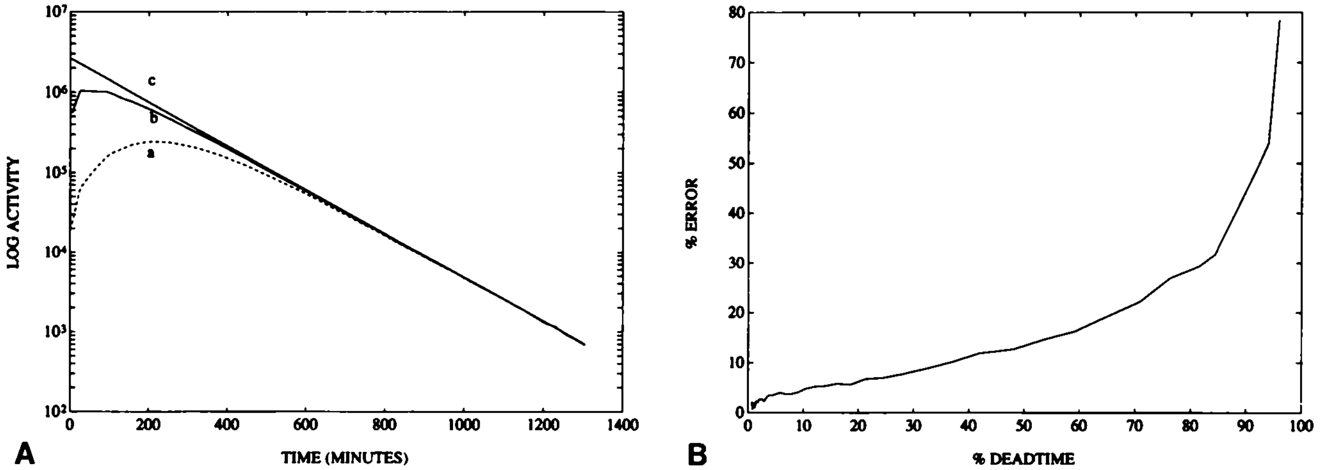


FIG. 1. (A) Time-activity curves of reported uncorrected raw cpm (a), reported deadtime-corrected cpm (b), and predicted cpm (c) for ^{18}F using an 18% window. (B) The error in the deadtime correction function measured as the percent difference between reported deadtime-corrected and predicted cpm.

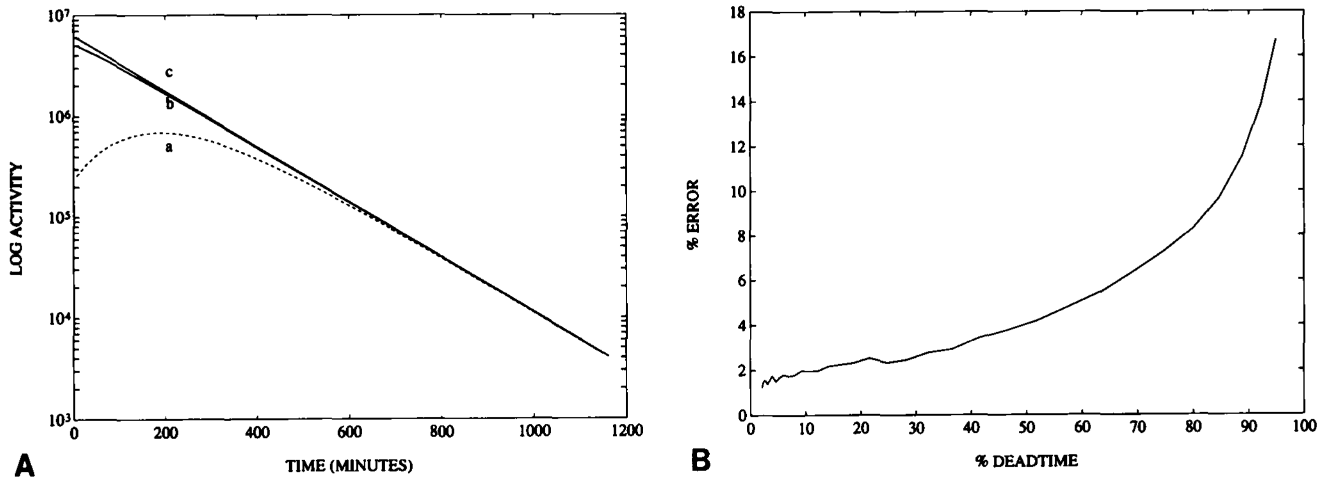


FIG. 2. (A) Time-activity curves of reported uncorrected raw cpm (a), reported deadtime-corrected cpm (b), and predicted cpm (c) for ^{18}F when the upper level discriminator is increased to account for the shift in the photopeak. (B) The error in the deadtime correction function measured as the percent difference between reported deadtime-corrected and predicted cpm.

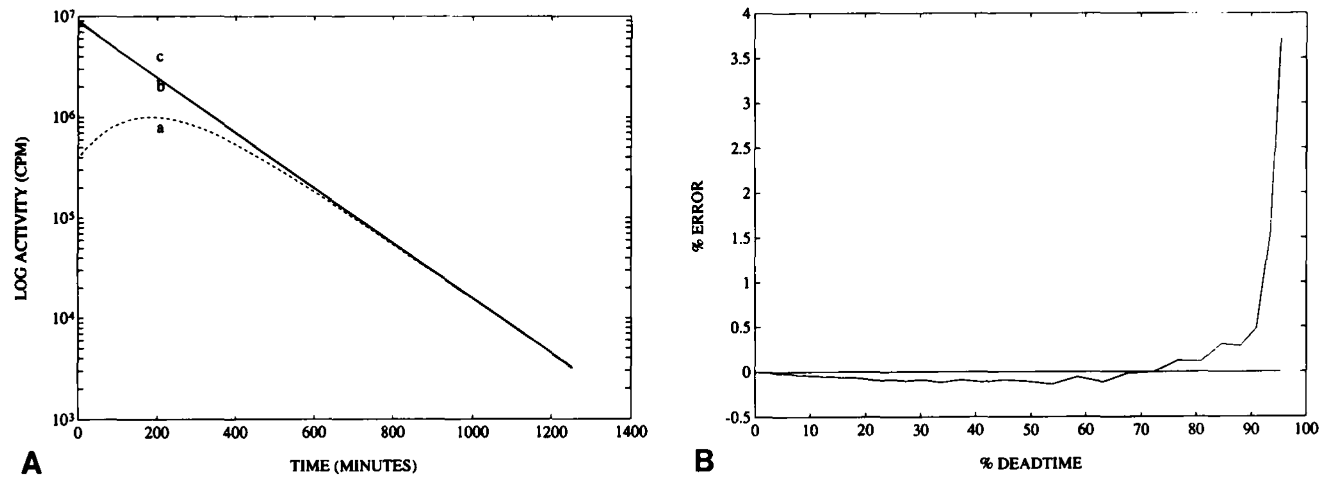


FIG. 3. (A) Time-activity curves of reported uncorrected raw cpm (a), reported deadtime-corrected cpm (b), and predicted cpm (c) for ^{18}F when the upper level discriminator is increased to include the sumpeak. (B) The error in the deadtime correction function measured as the percent difference between reported deadtime-corrected and predicted cpm.

of ^{11}C resulted in less than a threefold increase in detected background cpm (Fig. 6).

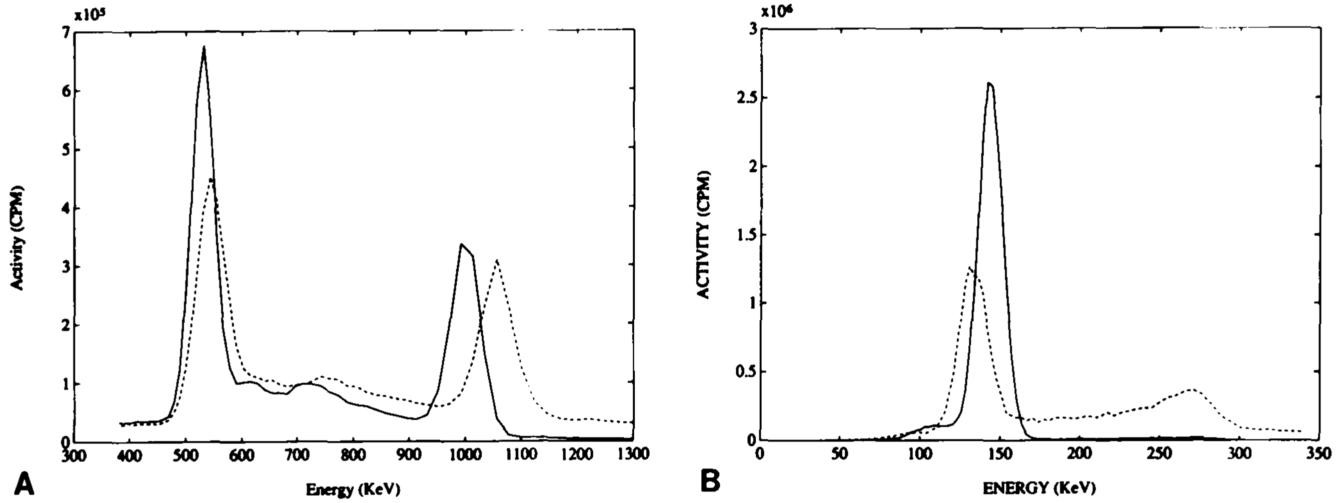
DISCUSSION

Window Width and Deadtime Correction Performance

Deadtime is a function of all pulses interacting in the crystal and not merely those that fall within a predefined window. Yet, deadtime *correction* performance is not independent of window width. This apparent contradiction is due, in part, to the spectrum changes that accompany high counting rates. Since the photopeak shifts and broadens as count rate increases, the number of photopeak interactions that register beyond narrowly set energy discriminators increases. Thus, the number of counts which are reported decreases, since only those photopeak counts falling within the selected window are deadtime-corrected.

The errors resulting from failure to account for this shift effect can be especially devastating in studies that utilize rapidly decaying isotopes such as ^{15}O ($T_{1/2}$ = 123 sec), since within a single set of blood samples, the amount of activity detected in the well may range from a peak of two or three μCi (or a deadtime of 70%–80%) to only a few nCi (or a deadtime of <2%) by the time the last sample is counted. Considering a maximum sample deadtime of 75%, a counting error of 25.3% can be reduced to approximately 7.2% merely by widening the window enough to account for the shift in photopeak (Figs. 1B and 2B).

Widening the window to account for photopeak shift does not completely alleviate deadtime undercorrection problems, although errors are greatly diminished. The concomitant increase in the number of sumpeak interactions occurring in the detector as count rate increases must also be taken into account. This can be illustrated by comparing ^{18}F spectra at low and high counting rates to similarly acquired spectra from



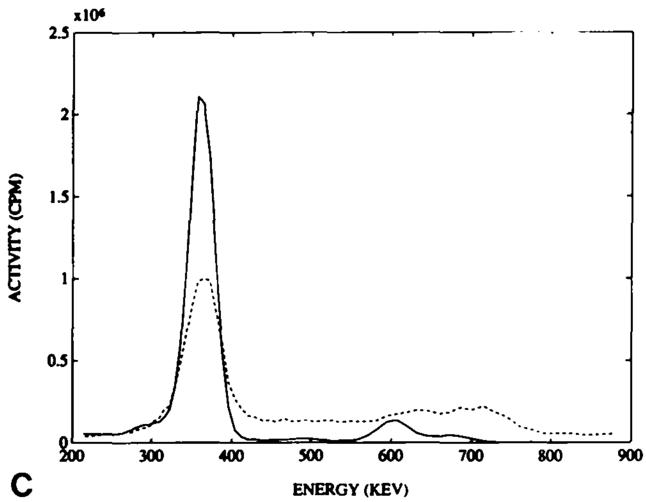


FIG. 4. (A) ^{18}F energy spectra at low deadtime (solid line) and high deadtime (dashed line) rates. As count rate increases, counts which would have registered within the photopeak at the low deadtime rate, appear in the sumpeak or the Compton scatter region, due to pulse pile-up and coincidence summing. Both the photopeak and sumpeak broaden and shift to the right as count rate increases. (B) ^{99m}Tc energy spectra at low deadtime (solid line) and high deadtime (dashed line) rates. The photopeak broadens and additional counts are noted in the region above the photopeak due to coincident summing. However, detected photopeak events are perceived as having a lower energy, due to vagaries in electronics, causing a leftward shift in the photopeak at high counting rates. (C) ^{131}I energy spectra at low deadtime (solid line) and high deadtime (dashed line) rates. The photopeak broadens and additional counts are present in the region above the photopeak. However, there is little shift in the photopeak.

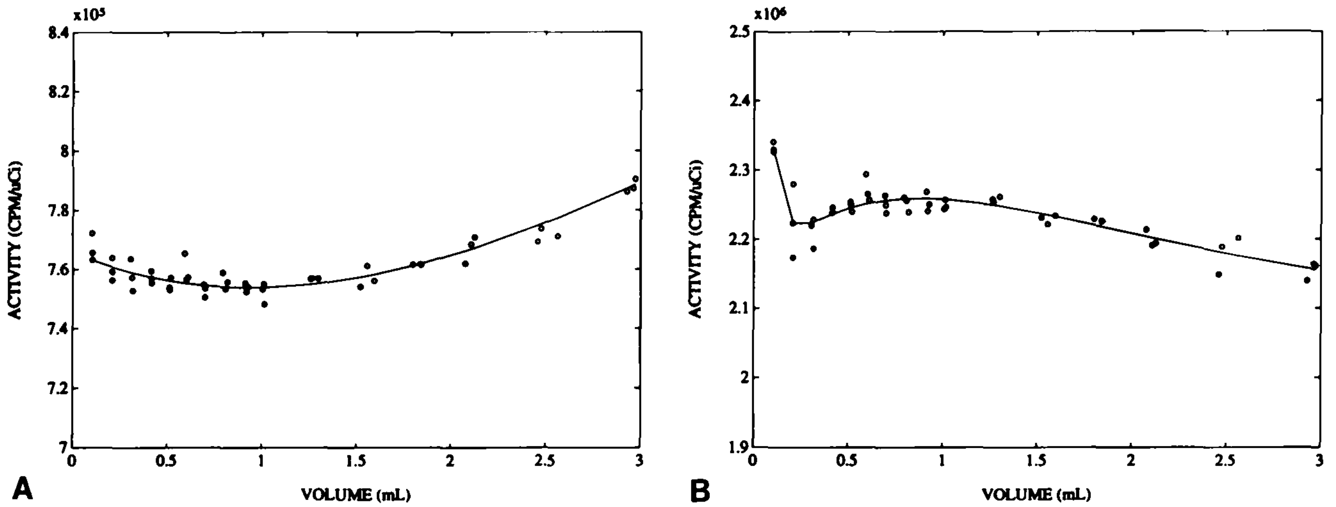


FIG. 5. (A) The change in detected cpm/μCi observed when, using an 18% window, a sample of ^{18}F is diluted with increasing amounts of water. (B) The change in detected cpm/μCi observed when the same samples are recounted using a window which encompasses the sumpeak.

a nonpositron emitter such as ^{99m}Tc (Fig. 4). At a low deadtime, no sumpeak events are seen with ^{99m}Tc. However, at the same deadtime rate with ^{18}F, considerable sumpeak interactions are evident. These differences arise from the increased likelihood of sumpeak phenomena brought on by the simultaneous emission of two 511 keV photons per positron annihilation. At a high counting rate, some sumpeak interactions are seen for single-photon emitters such as ^{99m}Tc. However,

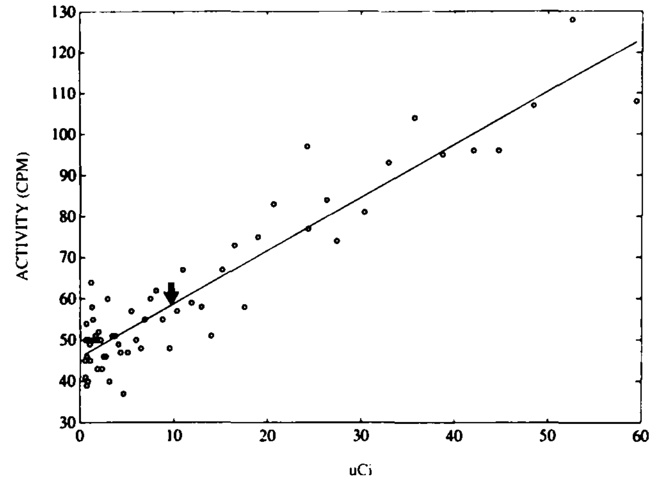


FIG. 6. The increase in measured background counts in the well counter, represented by the solid line, is a result of breakthrough radiation from an adjacent sample. The arrow indicates the point at which deadtime would equal 100% if the sample was counted in the well. Practical activity levels (less than 10 μCi) result in an insignificant change in measured background counts.

for ^{18}F, the number of detected sumpeak interactions is greatly magnified at the higher count rate.

Although quantitative problems introduced by sumpeak interactions are easily avoidable or correctable in the case of ^{99m}Tc or other nonpositron emitters, the sumpeak does present a more formidable threat to the counting accuracy of positron emitters. Not only does the ratio of photopeak to sumpeak interactions change with a change in count rate and deadtime, but the photopeak/sumpeak ratio changes constantly as well. This is because over the course of a multisample assay, count rate and deadtime decrease continually due to rapid decay. Therefore, if an 18% window is used, the number of counts in the window to which deadtime correction is applied decreases as count rate and the number of detected sumpeak interactions increase. These count losses are independent of any additional count losses resulting from the photopeak shift.

Considering a sample with maximum deadtime of 75%, error is now reduced to less than 1% when the window is widened to include the sumpeak (Fig. 3B). Furthermore, when such a window is employed, counting inaccuracies due to deadtime correction problems are eliminated over nearly the entire deadtime range.

Differences in Photopeak Shift

Photopeak shift itself is related to limitations in well counter electronics. Pulse pile-up and baseline shift commonly occur in amplifiers at high count rates and result in a leftward shift of the photopeak in the case of ^{99m}Tc (*5*). However, quite unexpectedly, the photopeak shift observed with positron emitters is to the right.

One possible explanation for this discrepancy is the differences in pulse height (140 keV ^{99m}Tc pulses are nearly one-third of the height of 511 keV annihilation photon pulses). Normally a ^{99m}Tc pulse will rise above baseline, peak at 140 keV and fall below baseline, as is the case in amplifiers that employ double delay-line bipolar outputs (*5*). However, at count rates exceeding the timing resolution of the electronics (a measurable deadtime), a second pulse will be detected before the first pulse recovers to baseline. Since pulse pile-up occurs below baseline and because energy is measured as the difference between baseline and maximum pulse height, the perceived energy of the second pulse is less than the first. Hence 140 keV pulses appear to be lower in energy at high count rates and the spectrum shifts to the left (Fig. 4B). For a 511 keV photon, however, the pulse does not cross the baseline before the ensuing pulses arrive in the detector because its amplitude is three times that of ^{99m}Tc. Therefore, pile-up occurs above baseline and the spectrum shifts to the right (Fig. 4A).

Taking this hypothesis one step further, in the case of ^{131}I, which has an energy (and a corresponding pulse height) nearly midway between that of ^{99m}Tc and positron annihilation photons, very little shift in the photopeak would be expected, even at high deadtimes, since pulse pile-up would occur very near to baseline. Indeed, this is what is observed (Fig. 4C).

Sample Volume Effects and Windowing

Although sample volume is of less concern in PET quantitation, since small samples of uniform volume are usually withdrawn in order to limit blood loss and minimize activity levels, the effect of window width on detected activity as volume varies is of some relevance. Window width appears to have little effect on counter efficiency over the normal range of sample withdrawal volumes from 0.2 to 1.5 ml. However, when a narrow window is employed, an increase in counts occurs as volume increases; this observation is incongruous with known data. Usually, *decreased* counter efficiency is observed with increasing volume (*5*). However, this inverse trend is not observed for all window widths. Rather, a predictable pattern of decreasing count rate with increasing volume occurs when a wide window, encompassing both the photopeak and the sumpeak, is used. In addition, the wide window results in considerably greater count rate stability than the narrow window, both within the range of normal sample withdrawal volumes and as volumes are increased beyond that range.

Changes in the number of detected sumpeak interactions may be the basis for these observed differences (Fig. 7). As volume increases, the attenuation of photons by the water may also increase, so fewer annihilation photon pairs arrive at the crystal simultaneously. In addition, it seems plausible that as volume increases, the chance of one but not both of the photons of an annihilation pair escaping the well, due to geometry alone, increases, thereby diminishing sumpeak events even further. As a result, the actual number of counts in the photopeak increases with increasing volume, and a narrow window centered around the photopeak reflects this. At the wide window setting, count rate decreases with increasing volume due solely to geometry losses, because both photopeak events and coincidence sumpeak events are counted.

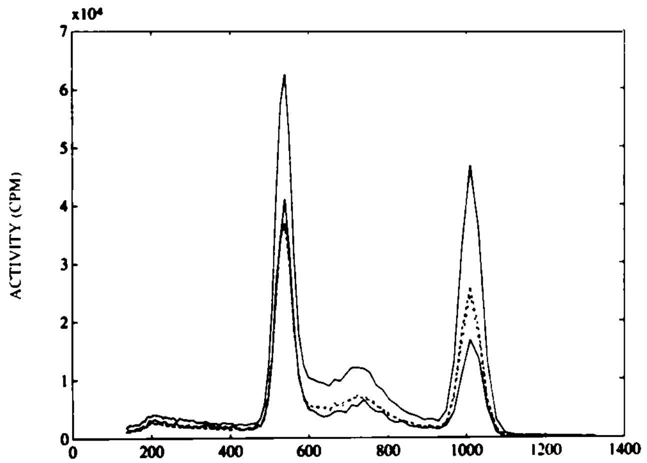


FIG. 7. Decay-corrected energy spectra representing a constant amount of ^{11}C at five different volume levels. The top solid line, corresponding to the highest detected activity, represents the lowest volume (0.1 ml). The lower solid line represents the 3.8-ml sample. The three spectra corresponding to the 0.5-ml, 1.0-ml, and 2.0-ml volumes differ very little and are represented by the dashed, dotted, and dash-dotted lines, respectively.

CONCLUSION

The accurate measurement of blood or other samples of interest is fundamental to any quantitative effort in nuclear medicine. Consequently, the performance characteristics of measurement instruments, such as well counters, and the effects of the operating environment on performance must be fully understood.

In the PET environment, window width has been shown to play a critical role in the accuracy of deadtime correction performance in a state-of-the-art well counter. Since observed counts and accompanying deadtime values from positron emitters are inherently nonlinear, energy discriminators should be set to encompass the photopeak, the sumpeak at its furthest point of shift, and the Compton continuum in between. Use of a conventional 18%–20% window centered around the 511 keV photopeak results in an undercorrection of data at high deadtimes, due to the pulse pileup, increase in the number of sumpeak interactions, and subsequent shift in the energy spectrum. Undercorrection errors are less apparent, but not completely eliminated, when the upper level discriminator is increased.

Errors can be minimized at the narrower window settings by counting only at low deadtime rates. However, such a methodology adds considerable technical complexity to the quantitative process. Samples may have to be recounted if deadtimes are found to be suboptimal, and accounting for timing differences between sample withdrawal and measurement may be more difficult. Moreover, use of a wide window setting allows one to take better advantage of the deadtime correction feature of the counter, thereby reducing the amount of data manipulation. Deadtime correction errors of 0.5% or less are calculated at deadtimes below 90%, and errors of only 3.7% occur at the 96% deadtime level.

Although use of a wide window results in some unexplained count variations at volume levels below 0.2 ml, few differences are evident from 0.3 ml to 1.5 ml, which is the usual volume range for sampling done with PET. In addition, the wide window setting appears to offer no disadvantage in count rate performance for volumes exceeding this range. Errors from differences in volume can be minimized or even eliminated completely by withdrawing uniform sample volumes.

In addition, breakthrough of photons from adjacent samples does not appear to present a problem for PET quantitation. Little breakthrough of activity is noted even at the highest practical counting rates. However, to ensure optimal counting accuracy, the counter should not be placed in an area where unshielded radioisotopes could affect well background activity.

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