A Monte Carlo Study on the Spatial Resolution of Uncollimated $\beta$ Particles with Silicon-based Detectors for Autoradiography

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Abstract—Traditional Autoradiography is an imaging modality used in life sciences where thin ex-vivo tissue sections are placed in direct contact with autoradiographic film. High resolution autoradiograms can be obtained using low energy radioisotopes, such as $^3$H where an intrinsic 0.1-1 $\mu$m spatial resolution can be achieved due to limited $\beta^-$ path length. Several digital alternatives have been presented in recent years to replace conventional film as the imaging medium, but the spatial resolution of film remains unmatched. Although silicon-based imaging technologies have demonstrated higher sensitivity compared to conventional film, the main issue that remains is spatial resolution. We address this here with an investigation into the design parameters that impact on spatial resolution when imaging uncollimated $\beta^-$ found in Autoradiography. The study considers Monte Carlo simulation of the energy deposition process, the charge diffusion process in silicon and the detector noise, and this is applied to a range of radioisotope $\beta$ energies typically used in Autoradiography. Finally an optimal detector geometry to obtain the best possible spatial resolution for a specific technology and a specific radioisotope is suggested.

Index Terms—Digital Autoradiography, Spatial Resolution, CMOS, CCD, Geant4.

I. INTRODUCTION

Autoradiography (AR) is a method used to map the distribution of radio-labelled biomolecules deposited in a thin ex-vivo tissue specimen. Film emulsion has been traditionally used as the imaging medium for AR. This is comprised of a gelatin base with a density up to 10 silver halide crystals per 10,000 $\mu$m$^2$, placed between two protective layers [1]. The size of the halide crystals, 0.1-0.4 $\mu$m diameter, results in excellent spatial resolution. However, this technique presents a number of problems including low sensitivity and poor linearity among the most important. In recent years, silicon-based imaging technologies have demonstrated some of the best overall performance in AR imaging. Work has already been published using CCD and CMOS detectors demonstrating higher sensitivity compared to film emulsion [2], [3], [4], [5], [6]. The main problem that remains unresolved is to match the outstanding spatial resolution exhibited by conventional film. In this work we study the effect of various design parameters of undepleted silicon detectors by means of Monte Carlo simulations. Using the Geant4 toolkit, we address the design trade-offs in achieving the best possible spatial resolution. Several other obfuscating factors, such as charge diffusion, detector noise and noise correction, are implemented in order to obtain realistic results.

II. MATERIALS AND METHODS

A. Monte Carlo toolkit

Geant4 [7] has been selected for use in this work as the Monte Carlo toolkit of choice because it has reliable accuracy in modelling physical interactions with electrons down to 250 eV using the low energy cross-sections. This is particularly important in order to understand energy loss processes of low energy electrons ($^3$H), and the low energy interactions associated with higher energy electrons.

Absorption depth, i.e. range, is an important parameter to consider to study spatial resolution in silicon-based detectors. The National Institute of Standards and Technology (NIST) provides tabulated values for absorption depth of electrons. However, these values of absorption depth do not consider multiple scattering. These fundamental consideration makes these absorption depths provided by NIST potentially disagree with real absorption depths measured with electrons in silicon, given the tortuous path that low energy electrons exhibit. To obtain a more realistic approximation of the absorption depth of $\beta^-$, a point source of monoenergetic electrons placed in the centre of a slab of silicon has been simulated, for a typical range of energies found in AR (5-80 keV). The range obtained from these simulations, with and without multiple scattering, are shown in Figure 1, also with the range values provided by NIST for the same energies. Multiple scattering is present in a realistic scenario, therefore all the simulations presented in this work include multiple scattering.

This initial electron range study was extended for a wide variety of energies to cover the average and maximum energies of the most typical radioisotopes used in AR, such as $^3$H, $^{14}$C, $^{35}$S and $^{33}$P, with a range of average energies from 5.7 keV ($^3$H) up to 694 keV ($^{33}$P), as shown in Figure 2.

B. Detector description

The basic simulation geometry used in this work is illustrated in Figure 3 and represents the digital sensor that we have used in previous works [8]. This geometry contains the most important layers for the Monte Carlo simulations undertaken in our work: the sample (glass slide and tissue sample), the possibility of an air gap between the sample and the detector,
This charge diffusion process may have a significant impact on the achievable spatial resolution, possibly affecting neighbouring pixels. Charge diffusion is not modelled by Geant4, thus it has been studied and implemented separately.

Charge diffusion processes have been extensively studied in the literature. The final shape that charge takes if projected on the charge collection layer of a solid state device has been a matter of discussion for some time. A Gaussian-like shape is assumed by some works [9], [10], [11]. Later analytic studies questioned Janesick’s model by claiming that the projected shape exhibits a more peaked distribution with longer tails [12], [13]. These studies demonstrate that Janesick’s initial work underestimates the charge projection affecting more pixels than initially thought. Pavlov’s work was later validated with experimental data by Prigozhin et al [14] resulting in successful agreement between the analytic predicted projection and the experimental projection measured from X-ray photons absorbed at different absorption depths in a CCD detector.

Figure 4 shows the results of each of the three models plotted together, Prigozhin’s model (blue), Hopkinson’s model (red) and Janesick’s model (black). It is observed how the results obtained by the three models are very similar in almost the whole active volume, but as the absorption depth approaches to the boundary with the substrate, dissimilarities appear. These differences are exacerbated at the extreme situation where the absorption depth is 20 μm, as shown in Figure 4(d), where Hopkinson’s model and Janesick’s model produce similar results, but Prigozhin’s model shows a significantly broader shape.

C. Charge diffusion

It is well known that in absence of electric field, when a β-interacts in silicon, the deposited charge diffuses spherically.

Following this comparison, we observed how Janesick’s model can be considered as a good approximation for thin detectors. For thick detectors (~10-20 μm), as the charge is
deposited further from the charge collection element, the
differences between Janesick’s model and the charge
distribution measured by Prigozhin becomes more significant.
Hopkinson’s model also seems to underestimate the charge
distribution in the tails compared to Prigozhin’s model.
Finally Prigozhin’s model has been implemented in this work
given that it obtains a good level of agreement between experimental and
simulated data.

D. Detector noise

To realistically implement detector noise, each pixel is
independently modelled by acquiring a blank set of 3200
images with the CMOS detector described in [6]. Each pixel
exhibits an assumed Gaussian noise distribution, with model
parameters $\mu_{i,j}$ and $\sigma_{i,j}$, $(i,j)$ being the spatial coordinates of
a specific pixel. After the charge diffusion model is applied
to the raw simulated data, noise in each pixel is added by
randomly sampling the distribution with particular pixel noise
parameters $\mu_{i,j}$ and $\sigma_{i,j}$. After detector noise is included in
the simulated data, the image is subsequently corrected with
the same method used experimentally in [5]. The resulting
charge deposited after each step described above is shown in
an example in Figure 5. This example represents the charge
deposited by a $\beta$- with 66 keV of kinetic energy entering the
detector in a non-orthogonal direction.

![Fig. 5](image)

III. RESULTS: SPATIAL RESOLUTION MAPS

To study spatial resolution a $^{14}$C point source is placed in
direct contact with the top passivated layer (see Figure 3).
To study spatial resolution with a $^3$H point source a back-
thinned detector geometry has been used. This geometry is
very similar to that shown in Figure 3, but the substrate is
replaced by a ~100 nm thick dioxide passivated layer and a
new substrate is grown on top of the passivated layers (dioxide
and nitride layers). These simulations assume a complete field-
free epitaxial layer given the negligible electric field present
in the charge collection point in CMOS technology.

These $\beta$- emitting point sources simulated by the Geant4
toolkit produce a Point Spread Function (PSF), which is later
post-processed to include charge diffusion, detector noise and
noise correction, for a variety of detector geometries, varying
the pixel size and the epitaxial layer thickness, resulting in
what we call here spatial resolution maps.

Charge diffusion, detector noise and image correction are
applied to each simulated event to build a realistic PSF for
each geometry. We now study their effect in the form of the
resulting spatial resolution maps.

A. Intrinsic spatial resolution map

The resulting intrinsic spatial resolution (no charge diffusion,
system noise and noise correction included in the model),
for a point source of $^{14}$C using a detector with an epitaxial
thickness of 5, 15, 20 and 30 $\mu$m and a pixel size of 5, 10,
15 and 25 $\mu$m, is shown in Figure 6. Similarly, the intrinsic
spatial resolution map resulting for a detector with thickness
of epitaxial layer 1, 2, 5, 10 and 20 $\mu$m and pixel size 1, 2,
5 and 10 $\mu$m, for a point source of $^3$H is shown in Figure 7.

![Fig. 6](image)

![Fig. 7](image)

Fig. 6. Simulated spatial resolution map of the digital sensor
exposed to a point source of $^{14}$C with no air gap between the surface
of the sensor and the source.

Fig. 7. Simulated spatial resolution map of the digital sensor
exposed to a point source of $^3$H with no air gap between the surface
of the sensor and the source.

It is observed how in both examples, the data point with the
smallest pixel size and thinnest epitaxial layer, 5 $\mu$m and 5 $\mu$m
respectively for $^{14}$C and 1 $\mu$m and 1 $\mu$m respectively for $^3$H,
shows the best spatial resolution, ~15 $\mu$m for $^{14}$C and ~1 $\mu$m
for $^3$H, which corresponds in both cases with approximately
the average range of $\beta$- electrons for each emitter (~10 $\mu$m
for $^{14}$C and ~1 $\mu$m for $^3$H). It can be observed how the
dependence of this intrinsic spatial resolution on the thickness
of the epitaxial layer is very low, as oppose to the dependence
with the pixel size in both cases.

B. Spatial resolution map with charge diffusion

The results shown in Figures 6 and 7, were obtained using
the data generated by the Geant4 Monte Carlo toolkit, where
charge diffusion, system noise or noise correction are excluded
from the model. Nonetheless, these represent a baseline level
of performance, against which the effect of further performance degrading processes can be measured. To obtain a more realistic study of the resulting observed spatial resolution based on the variation of the detector geometry, the charge diffusion model described in [13] has been implemented. The resulting spatial resolution variation, used for the same geometries used in Figures 6 and 7 is shown in Figures 8 and 9 for $^{14}$C and $^3$H respectively.

![Figure 8](image1.png)  
Fig. 8. Simulated spatial resolution map of the digital sensor exposed to a point source of $^{14}$C, with charge diffusion process (red) and without charge diffusion process (blue).

![Figure 9](image2.png)  
Fig. 9. Simulated spatial resolution map of the digital sensor exposed to a point source of $^3$H, with charge diffusion process (red) and without charge diffusion process (green).

It can be observed in Figures 6 and 7 how, without charge diffusion, the variation in epitaxial thickness does not provide a significant impact on the spatial resolution. However, when charge diffusion process is considered, it is now observed in Figures 8 and 9 how the epitaxial layer thickness represents an important parameter in the detector design, having a negative impact when a thicker epitaxial layer is used.

Both Figures 8 and 9 show a significant degradation of the spatial resolution as both the pixel size and the epitaxial layer increase in size due to the charge diffusion process. This process is more critical for $^{14}$C, attributed to the higher amount of initial deposited charge (higher ionising energy) over a larger volume.

In the specific case of $^{14}$C (Figure 8), it is observed how the rate of spatial resolution degradation as the pixel size increases, is higher for a pixel size $<10$ μm along the entire range 5-25 μm. This is due to the higher impact of the charge diffusion process on the spatial resolution for a pixel size below the average $^{14}$C mean energy. On the other hand, the rate of spatial resolution degradation holds a linear relationship with the epitaxial layer thickness. It is also worth commenting that the charge diffusion has a marked global effect across both radioisotopes considered here.

The specific case of $^3$H (Figure 9) does not show such high degradation of the spatial resolution compared to the previous scenario with $^{14}$C. The diffusion caused by thicker epitaxial regions has a more pronounced effect on the spatial resolution for small pixel sizes ($<4$ μm) than for larger pixel sizes.

C. Spatial resolution map with detector noise and noise correction

This study is further analysed by including the effect of dark current noise and fixed pattern noise (FPN), and subsequent noise correction. It has to be noted that the noise model applied to the raw images, obtained from the Monte Carlo simulations, was previously experimentally measured from an available detector, having 25 μm pixel size and 20 μm thick epitaxial layer. This is expected to change for other geometries but the absence of other available detector geometries limited the implementation of geometry dependent noise models. However, the FPN is not expected to change significantly by changing the dimensions of the pixel size and the epitaxial layer thickness. Dark current noise, on the other hand, is expected to increase with pixel size given that this is proportional to the pixel area $A_p$ and an empirical constant specified by the manufacturer, representing the dark current noise at 300 K. In this respect, the noise implementation here may be somewhat overestimated for pixels $<25$ μm and underestimated for pixels $>25$ μm.

![Figure 10](image3.png)  
Fig. 10. Simulated spatial resolution map of the digital sensor exposed to a point source of $^{14}$C with no air gap between the surface of the sensor and the source, without charge diffusion process (blue) and with charge diffusion process, noise addition and the FPN correction method (red).

![Figure 11](image4.png)  
Fig. 11. Simulated spatial resolution map of the digital sensor exposed to a point source of $^3$H with no air gap between the surface of the sensor and the source, without charge diffusion process (green) and with charge diffusion process, noise addition and the FPN correction method (red).

In Figures 10 and 11 the spatial resolution map, obtained after including the detector noise in the model and applying the FPN correction method described in [5] for $^{14}$C and
$^3$H are shown respectively. Figure 10 represents the intrinsic spatial resolution map for $^{14}$C (blue), and the spatial resolution map obtained after applying the correction method (red) to the diffused charge with pattern noise superimposed. Note the change in scale compared to Figure 8. Similarly, Figure 11 represents the intrinsic spatial resolution map for $^3$H (green), and the spatial resolution map obtained after including charge diffusion and detector noise and applying the correction method (red). In this case, as might be expected from the small path length, the diffusion and noise effects make very little difference, except for thick epitaxial layers.

IV. CONCLUSIONS & FURTHER WORK

Spatial resolution is a key performance parameter that requires further development on the need to produce a viable alternative to conventional autoradiographic film. The best achievable spatial resolution for $^3$H with film is $\sim 1 \mu m$ but this is subsequently degraded by the digitisation process. For comparison, the best (claimed) spatial resolution currently obtained with a digital system for $^3$H is $15 \mu m$ using the $\mu$-Imager 2000T M2 [2].

A thorough study on the spatial resolution of silicon detector has been presented. Given that the Monte Carlo simulations have been previously validated, we can now propose an optimum detector geometry for two typical radioisotopes ($^{14}$C and $^3$H) used in $\beta$-AR. Observing the intrinsic spatial resolution maps it seems clear that for $^{14}$C a pixel size $< 10 \mu m$ does not improve the spatial resolution. From this baseline value up to larger pixels, the spatial resolution then linearly scales with pixel size. A similar effect has been observed for $^3$H albeit with a smaller range of pixel sizes. This indicates that, perhaps unsurprisingly, spatial resolution is strongly related with the mean range of the electrons emitted by each radioisotope, over and above pixel dimension.

When charge diffusion is considered in the model it is observed how its effect greatly degrades the spatial resolution. This could be reduced by applying an electric field to the active volume to collect the deposited charge, as observed in CCD technology, or by using a thinner detector.

Using a FPN correction method [5], sufficiently thresholded to produce a low rate of false events, results in a spatial resolution map similar to the intrinsic spatial resolution map for low energies ($^3$H). For medium energies ($^{14}$C) some differences arise as the effects of the epitaxial layer thickness on spatial resolution decreases, due to higher levels of multiple scattering.

In all cases shown above, when charge diffusion, system noise and noise correction are included in the final model, it has been shown how the best spatial resolution always corresponds to the smallest range of pixel sizes. In the case of $^{14}$C, this represents pixels up to $10-15 \mu m$ as being optimal when associated with an epitaxial region up to around $10 \mu m$. Above this range, the degrading effects of pixel dimension and epitaxial thickness somewhat degrade spatial resolution performance. Below this size, one might expect to see greater significance in the per pixel statistical uncertainty produced due to finer sampling of the total charge. For $^3$H, the charge diffusion effect appears to be proportional to epitaxial thickness and pixel size. In this case, the optimal pixel dimension appear to be $\sim 1 \mu m$ with epitaxial thickness of a few microns.

REFERENCES