The Spatial Resolution of Silicon-Based Electron Detectors in β - Autoradiography

Jorge Cabello[‡] and Kevin Wells[§]

Centre for Vision, Speech and Signal Processing, Faculty of Electronics and Physical Sciences, University of Surrey, Guildford, Surrey, GU2 7XH, UK.

E-mail: k.wells@surrey.ac.uk

Abstract. Thin tissue autoradiography is an imaging modality where *ex-vivo* tissue sections are placed in direct contact with autoradiographic film. These tissue sections contain a radiolabelled ligand bound to a specific biomolecule under study. This radioligand emits β - or β^+ particles ionising silver halide crystals in the film. High spatial resolution autoradiograms are obtained using low energy radioisotopes, such as ^3H where an intrinsic 0.1-1 μm spatial resolution can be achieved. Several digital alternatives have been presented over the past years to replace conventional film but their spatial resolution has yet to equal film, although silicon-based imaging technologies have demonstrated higher sensitivity compared to conventional film. It will be shown in this work how pixel size is a critical parameter for achieving high spatial resolution for low energy uncollimated beta imaging. In this work we also examine the confounding factors impeding silicon-based technologies with respect to spatial resolution. The study considers charge diffusion in silicon and detector noise, and this is applied to a range of radioisotopes 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.

Keywords: CMOS/CCD, Electron, Silicon Charge Diffusion, Monte Carlo, Autoradiography, Spatial Resolution.

1. Introduction

Autoradiography is an extended imaging modality used in the life sciences to measure and localise the density distribution of radiolabelled molecules within thin *ex-vivo* tissue sections. Autoradiographic film is the conventional detection medium most often used. This is comprised of a gelatin base with a density up to 10 silver halide crystals per 10,000 μm^2 , placed between two protective layers (Stumpf 2003). The size of silver halide crystals, 0.1-0.4 μm diameter, results in an excellent spatial resolution, as yet unmatched by any digital system. However, this technology exhibits a number of undesirable qualities, such as poor linearity, low dynamic range and low sensitivity, resulting in long exposure times, depending on the radioisotope/ligand used varying from ~ 4 days for ^{35}S and ^{125}I to 4-5 weeks for ^{14}C and ^3H .

To address these issues, a number of alternative imaging technologies to conventional film have appeared in the last few years claiming superior performance

[‡] Now at Institute for Corpuscular Physics (IFIC), University of Valencia/CSIC, Spain
(E-mail: jcabello@ific.uv.es)

[§] Also affiliated to King Saud University, Riyadh, Saudi Arabia

in some aspect (mainly sensitivity) to the point that may make these viable options to replace autoradiographic film. Phosphor plates have been seen as a very attractive alternative to conventional film for life scientists, wherein a spatial resolution of $50\text{ }\mu\text{m}$ for ^3H imaging has been demonstrated (Yamane et al. 1995). A thin sheet of scintillator with a $5\text{ }\mu\text{m}$ pixel size Charge-Coupled Device (CCD) detector has been used such as in (Barthe et al. 2004), where a spatial resolution of $15\text{ }\mu\text{m}$ is claimed for ^3H imaging using the μ -Imager 2000TM†. Another approach presented in (Chen et al. 2008) uses a lens-coupled cooled CCD camera ($20\text{ }\mu\text{m}$ pixel size) with a $3\text{ }\mu\text{m}$ thin phosphor film placed next to the sample under study. The spatial resolution is estimated at $60\text{ }\mu\text{m}$ assuming a $^{90}\text{Y}/^{90}\text{Sr}$ point source, and a theoretical $50\text{ }\mu\text{m}$ Full-Width-Half-at-Maximum (FWHM) (2.5 pixel size) is obtained assuming an ideal $70\text{ }\mu\text{m}$ FWHM $^{99\text{m}}\text{Tc}$ disc. The application of Multiwire Proportional Chamber (MWPC) (Charpak et al. 1968, Charpak & Sauli 1978, Bateman et al. 1985, Bellazzini et al. 1985, Petegnief et al. 1998) is another approach also adapted for autoradiography that resulted in the commercial system β -Imager 2000TM (Tribollet et al. 1991), achieving a spatial resolution of $50\text{ }\mu\text{m}$ with unrivalled sensitivity. Micro Channel Plates (MCP) have also been proposed for use in autoradiography: Lees *et al* work in this area is extensive using a wide variety of radioisotopes (Lees et al. 1999, Lees et al. 2002). The best spatial resolution achieved using MCP technology is $\sim 60\text{ }\mu\text{m}$ (Lees et al. 1998). However, it is silicon-based detector technology that has achieved the greatest advances in recent years compared to these other approaches.

Several silicon-based alternatives operating in direct-detection mode can be found in the literature such as DEPFET (Klein et al. 2000, Ulrici et al. 2005), claiming a potential spatial resolution of $7\text{ }\mu\text{m}$ with ^3H , silicon strip detectors (Overdick & et al. 1997, Bertolucci et al. 1996, Sanghera & Ott 1993, Orbom et al. 2007), where $50\text{ }\mu\text{m}$ has been achieved as the best spatial resolution so far, hybrid technology (Amendolia et al. 1997, Mettievier et al. 2003, Mettievier et al. 2004*a*, Mettievier et al. 2004*b*, Mettievier et al. 2005, Russo et al. 2008), CCD (Bonazzola & Ropolo 1985, Ott et al. 2000, Kokkinou et al. 2003, Cabello^a et al. 2007) or Complementary-Metal-Oxide-Semiconductor (CMOS) technologies (Deptuch 2005, Cabello^b et al. 2007). These tend to offer superior sensitivity, higher dynamic range and more linear response compared to film, and spatial resolution of a few tens of μm or more.

However, to the best of our knowledge, there has been no systematic study on the physics of the image formation process that might examine how to optimise the performance of silicon imaging technologies for autoradiography applications. This is addressed here, where in we describe a Monte Carlo study on spatial resolution effects with silicon-based detectors. Several considerations, such as charge diffusion, detector noise and noise correction, are implemented in order to obtain a best estimate of practicable performance.

2. Materials and methods

For physics-based simulation, there are several Monte Carlo toolkits available: Geant4 (Agostinelli, S. 2002), MCNPX (Briesmeister 2000), Penelope (Baro et al. 1995) and EGSnrc (Rogers & Bielajew 1995) are among the most important implementations. For this study Geant4 has been used, together with its low energy package, because it has reliable accuracy in modelling interaction physics with electrons down to 250

† Biospace Measures, 10 rue Mercoeur, Paris Cedex 75011, France

eV. This is particularly relevant for studying ^3H imaging (average energy 5.9 keV and maximum energy 18 keV), along side higher energy emitters. Geant4 is a complex Monte Carlo package developed in C++, structuring all the different modules interacting in the simulation in C++ classes, making this toolkit both powerful and flexible.

A variety of detector architectures shown in this work, have been simulated to demonstrate that the architectures and the physical processes involved in the detection of β particles are well understood. The detector structures used in these simulations are typically comprised of (from bottom to top) a substrate, epitaxial layer (sensitive layer) and overlying passivated structures. Above these layers an air gap is included between the top surface and the sample, the tissue sample itself and finally the glass microscope slide which is used to carry the tissue sample, as shown in Figure 1.

Figure 1. 3D cutaway of a digital detector used in these Monte Carlo simulations.

The tissue thickness can take two different values, either $120\ \mu\text{m}$ (microscale thickness), for validation purposes, or $20\ \mu\text{m}$ which is the typical tissue thickness found in experimental use. When a point source is used it is placed at the bottom surface of the tissue layer, to consider the best case scenario.

The dimensions of the common structures in CCD and CMOS detectors are shown in Table 1. Note that although the air gap is variable, in this work we only consider idealised point sources placed directly above the detector, i.e. zero air gap. We have considered the problem of air gap variation elsewhere (Cabello & Wells 2007), demonstrating a significant impact of this parameter on the spatial resolution. However, experimental work applying different amounts of pressure on a $\sim 1 \times 1\ \text{mm}^2$ piece of ^{14}C , to reduce a possible air gap between the sample and the detector, did not produce differences in the edges of the final image. This can be explained by the negligible air gap existing between the sample and the detector surface with only the own weight of the sample itself.

Table 1. Common dimensions used in the CCD and CMOS architectures

Layer	Glass slide	Tissue	Air gap	Sensitive layer	Substrate
Thickness	1.0 mm	$120.0\ \mu\text{m}$ $20\ \mu\text{m}$	variable	$20.0\ \mu\text{m}$	$500.0\ \mu\text{m}$

Ignoring read out techniques, the physical structures where CCD and CMOS detectors differ are the pixel size and the structure and thickness of the overlying layers, see Table 2.

A special mention has to be made for back-thinned devices. In this case the usual overlying layers of a front-illuminated device, are located between the sensitive layer

Table 2. Typical dimensions used in the CCD (left) and CMOS (right) architectures

Structure	Dimension	Structure	Dimension
Pixel size	22.5 μm	Pixel size	25 μm
Poly-Si	0.5 μm	SiO ₂	4 μm
SiO ₂	0.1 μm	Si ₃ N ₄	1 μm
Si ₃ N ₄	0.1 μm		

and the substrate in order to facilitate direct access to the sensitive region for any incident radiation. An extra passivated ~ 100 nm layer is usually present on top of the active layer, representing the residual SiO₂ layer remaining on the epitaxial layer after etching the substrate in the back-thinning process.

3. Monte Carlo validation

The validation of any Monte Carlo package is a critical issue to assure reliable results are produced. A thorough validation of the electromagnetic model applied to photons, electrons, protons and alpha particles in Geant 4 is presented in (Amako et al. 2005). In the aforementioned article the standard package, the low energy package and an alternative low energy package based on the Penelope analytical approach (Baro et al. 1995) are considered. The conclusion for electrons, the particle of interest in this work, is that the three packages show an excellent agreement in the energy range 1 keV to 100 TeV when compared to the NIST reference data (NIST 1901).

To validate the results obtained from the experimental setups shown here, the electron stopping power and continuously slowing down approximation (CSDA) ranges have been measured, and these have been compared with those tabulated in ICRU Report 37 (ICRU 1984). In this work only the CSDA range of electrons from 10 keV up to 500 keV is considered, as this corresponds to the range of energies of the typical isotopes used in β - autoradiography. The measured range for each energy using the standard package (red diamonds) with its corresponding error margin (standard deviation of the measurement), and using the low energy package (blue triangles) is compared to the range obtained from ESTAR[‡] (red points) in Figure 3. The error measured does not exceed 3 % for any energy. The error bars shown in Figure 2 represent $\pm 1\sigma$ of the electron ranges measured with Geant4 using the standard package, being very similar for the low energy package. The way to measure the electron range is identical to how it is measured in (Amako et al. 2005). An isotropic point source is simulated in the centre of a box of silicon, and the range is measured as the distance between the point where the electrons are generated and where they are stopped.

This experiment was undertaken with multiple scattering and the energy loss fluctuations that electrons suffer while they traverse the detector disabled, in agreement with ESTAR (Amako et al. 2005, NIST 1901). To neglect the energy loss fluctuations is the same as to assume that the rate of energy loss at every point along the track is equal to the same as the total stopping power. Secondary particles are *killed* also in agreement with (Amako et al. 2005). We conclude from this comparison

[‡] Stopping-power and range for electrons (NIST 1901)

Figure 2. Measured electron range obtained with Geant4 using the standard package (red diamonds), using the low energy package (blue triangles) and NIST electron range (red points) in silicon as a function of the electron incident energy.

and that of Amako *et al* (Amako et al. 2005) that Geant4 is a reliable tool for studying β electron interactions in the energy range 1-500 keV.

3.1. Absorption Depth

The absorption depth, also known as range, is where a specific particle with a specific kinetic energy is absorbed in matter. In the particular case of β - electrons in digital autoradiography, these interact with (in our case) silicon, depositing charge in each interaction, hence generating electron-hole pairs. These β - electrons slow down as their kinetic energy decreases, ultimately to a stopping point where no more energy is contained in the particle (other than thermal energy). The trajectory of these β -electrons in silicon is tortuous, in contrast to the typical straight line trajectories obtained with X-ray photons. Electrons can undergo sharp deflections or maybe stopped completely in a single interaction. Electron ranges are highly variable even for electrons with the same energy (Cherry et al. 2003). In order to characterise this behaviour, the range is conventionally defined as the straight-line distance between the coordinate where the β particle initially interacted with the target material (silicon) and the coordinate where it was finally absorbed.

A tabulated measurement of absorption depth is found in the NIST website (NIST 1901). This information is also published in the International Commission on Radiation Units and Measurements (ICRU) report 37, which defines the *Stopping Powers for Electrons and Positrons*. As has been previously mentioned, this measure neglects energy-loss fluctuations and multiple scattering. In the case of low energy β electrons, scattering is a significant process. Therefore the ranges provided by NIST may show large differences from those particle ranges observed in the Monte Carlo simulations obtained here.

To obtain a better approximation of the absorption depth of β electrons, a point

source of monoenergetic electrons placed in the centre of a slab of silicon has been simulated, for a wide range of energies (5-80 keV). The ranges obtained from these simulations neglecting/including scattering are shown in Figure 3, also with the range provided by NIST. This 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 autoradiography, as shown in Figure 4.

Figure 3. Electron range in silicon provided by NIST (blue), obtained with the Monte Carlo simulations without scattering (red) and with scattering (green).

It can be observed that NIST does not provide any information for energies below 10 keV. It can also be observed how the ranges provided by NIST are longer than those obtained in the simulations due to the absence of models for energy-loss fluctuations and multiple scattering in the NIST data. The difference shown by these sets of data (with and without scattering) becomes higher as the energy increases due to a higher multiple scattering effect. Therefore, whilst we observe agreement with NIST and ICRU data when scattering and energy loss mechanisms are removed, we should note that when enabled, those processes lead to significantly reduced absorption depths in the simulation work described in the rest of this paper.

4. Monte Carlo simulations

In order to devise an optimum detector geometry for a specific technology and a specific radioisotope, typical CCD and a CMOS geometries have been simulated, varying the pixel size and the thickness of the field-free layer. In all the experiments shown here a point source has been placed as described above at the interface between the tissue layer and the detector surface, and after simulating 10^5 particles for each different geometry to have statistical validity, three processes have been subsequently applied to the resulting deposited charge in the active volume of the detector. First, the

Figure 4. Electron range obtained from Monte Carlo simulations with energy loss scattering mechanisms enabled, for a range of energies 5-1710 keV. The average and maximum energies of ^3H , ^{14}C , ^{35}S and ^{32}P , typical radioisotopes used in β -autoradiography are denoted.

deposited charge in the detector diffuses in the silicon in the absence of an electric field. This important detector process is not modelled by Geant4. Therefore it is independently applied to the deposited charge distribution using a bespoke Matlab-based software routine (Section 4.1). Secondly, to obtain realistic results, detector noise derived from experimental measurement is then applied to the resulting diffused charge (Section 4.2). Finally, a fixed pattern noise (FPN) image correction scheme used routinely in our foregoing work, was applied to the resultant noisy images (Section 4.3).

4.1. Charge diffusion model

Consider a β particle interacting in silicon and depositing charge. Provided this charge is not exposed to an electric field (as in the depletion layer in a CCD detector), it will tend to diffuse spherically in the silicon until it recombines or is collected. Ideally all the charge should be collected to maximise the detection efficiency. Manufacturers also make use of some mechanisms to increase the probability of collecting the charge before recombination. These include using low doping levels in silicon to increase the recombination time, by using more than one or large charge collection points and by using p-type silicon in the active volume and p+ silicon in the substrate (underneath the active volume). The latter will *reflect* charge that reaches the substrate boundary, and diffuses back towards the active volume. Charge diffusion is an important process to consider because it potentially influences neighbouring pixels, and can yield considerably larger pixel event clusters compared to a situation where charge diffusion is absent.

Charge diffusion is not modelled by Geant, and thus it has been studied and implemented separately. A few charge diffusion models available in the literature can be found. A well accepted model used by a variety of authors in the literature (Bootsma et al. 2000, McCarthy et al. 1995) determines that the charge diffusion can be approximated to a Gaussian, with standard deviation σ_{ff} (1), if projected on the charge collection layer (Janesick et al. 1985).

$$\sigma_{ff}(x) = \frac{z_{ff}}{2} \sqrt{1 - \left(\frac{z_a}{z_{ff}}\right)^2} \quad (1)$$

where x is the dimension parallel to the surface of the detector, z_a is the depth of interaction (distance from the point of interaction to the deepest side of the field free layer) and z_{ff} is the thickness of the field free layer. This approximation was obtained after simulating multiple electron random walks until reaching the charge collection layer. The projection obtained in all the cases was approximately a Gaussian distribution with standard deviation σ_{ff} empirically fitted by equation 1.

This model has been subsequently demonstrated by other analytical studies (Hopkinson 1987, Pavlov & Nousek 1999) to have limitations. Other studies demonstrate that the assumed Gaussian charge exhibits longer tails and a more peaked shape, affecting the charge diffusion in greater number of pixels than that predicted by Janesick's model.

However, it appears relatively little experimental work has been undertaken to validate these analytical approaches though. Relatively recent is the work of Prigozhin *et al* (Prigozhin et al. 2003) where the analytical solution detailed by Pavlov *et al* (Pavlov & Nousek 1999) was successfully validated, using a cooled CCD detector (all sources of noise except read-out noise were effectively suppressed) exposed to a ^{55}Fe source. By isolating the signal deposited by X-ray photons absorbed in the field free layer at different depths of interaction, the charge deposition shape of such events was studied and compared with the analytical distribution proposed by (Pavlov & Nousek 1999). Another conclusion of Prigozhin's work is that the charge diffusion suffered in the depleted layer in CCD detectors can be neglected without significantly distorting the final charge distribution. The resulting charge distribution observed by Prigozhin *et al*, assuming recombination in the field free layer is negligible (diffusion length is much larger than the thickness of the field free layer) and that the substrate works as a reflecting body (active volume is p doped and substrate is p+ doped), produces:

$$q_{ff1}(x) = \frac{1}{2\pi} \sum_{m=-\infty}^{\infty} \frac{z_a - 2mz_{ff}}{p_m(x)^3} \quad (2)$$

where p_m is defined by (3):

$$p_m(x) = \sqrt{x^2 + (z_a - 2mz_{ff})^2} \quad (3)$$

This charge distribution has been compared with Hopkinson's *et al* work (Hopkinson 1987) obtaining very similar results. The charge distribution as defined by Hopkinson's *et al* follows (4):

$$q_{ff2}(x) = \frac{z_a}{2\pi u(x)^3} \left(1 + \frac{u(x)}{\frac{1.15z_a}{z_{ff}} + 0.13}\right) \exp\left(-\frac{u(x)}{\frac{1.15z_a}{z_{ff}} + 0.13}\right) \quad (4)$$

where $u(x)$ is described by (5):

$$u(x) = \sqrt{(x^2 + z_a^2)} \quad (5)$$

Figure 5 compares the results of each of the three models: 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 the depth of the boundary with the substrate, then differences appear. These dissimilarities are exacerbated at the extreme situation where the absorption depth is $20 \mu\text{m}$, as shown in Figure 5(d), where Hopkinson's model is not too far from Janesick's model but Prigozhin's model shows clear differences.

Figure 5. Analytical charge distributions of an X-ray absorbed at different absorption depths in a $20 \mu\text{m}$ thick field free layer, obtained with Prigozhin's model (2) (q_{ff1}) shown in blue, obtained with Hopkinson's model (4) (q_{ff2}) shown in red, and approximated Gaussian distribution proposed by Janesick shown in black.

In this study it has been observed how Janesick's model appears to represent a good approximation for thin detectors. However, for thick detectors, as the charge is deposited further from the charge collection element, the differences between Janesick's model and the real charge distribution measured by Prigozhin have more significant differences. Hopkinson's model also seems to underestimate the charge distribution

in the tails compared to Prigozhin's model. Thus, Prigozhin's model has been implemented in this work given that it is the only work found in the literature (to the best of the authors knowledge) that compares the analytically developed model with real data and demonstrates a high level of agreement.

4.2. Detector noise

For the Monte Carlo simulations presented here, experimentally-measured pixel *mean* and *standard deviation* images have been used in order to evaluate the effects of sensor manufacturing tolerances and the effect of internal (detector) and external readout electronic noise. The image produced by the Geant4 Monte Carlo simulation can be considered noiseless apart from quantum charge fluctuations. The physics-based simulation therefore represents each pixel values in units of eV. But as noise is usually perceived in digital numbers (DN), every pixel value is transformed to DN. For this transformation, the ratio between the number of electrons per DN (e-/DN), i.e. sensor gain, is necessary. In order to obtain this, a physical detector was calibrated with a ^{241}Am point source as described in Appendix A.

After the deposited energy image has been converted to DN, the instantaneous noise $n_{i,j}$ is then independently obtained for each pixel at location (i,j) , sampling a random number from a Gaussian distribution with parameters $\mu_{i,j}$ and $\sigma_{i,j}$ derived from prior experimental dark field images. For a given pixel signal intensity $x_{i,j}$, the noise $n_{i,j}$ is added to obtain an observed pixel value $y_{i,j}$, given by equation 6.

$$y_{i,j} = x_{i,j} + n_{i,j} \quad (6)$$

where $n_{i,j}$ is a random number sampled from a Gaussian distribution with mean and standard deviation $\mu_{i,j}$ and $\sigma_{i,j}$ respectively, derived from experimental data acquired from a CMOS sensor operating at room temperature, and with an integration time of one second. This process is illustrated in Figure 6(a-c).

4.3. Simulated image correction

The resulting Point Spread Function (PSF) obtained with the simulated point source, after charge diffusion is applied to every simulated particle and system noise is added to the resulting image, the FPN correction method described in (Cabello^a et al. 2007), and briefly described below, has been implemented.

For the FPN correction method, first a set of blank frames is simulated to compute for each pixel located at location (i,j) , the mean dark current offset or pedestal ($\mu_{i,j}$), the standard deviation ($\sigma_{i,j}$), and the global mode of a set of blank frames (m_{ref}). As dark current corruption is principally a bias effect, $\mu_{i,j}$ attempts to model this bias level for each pixel.

After the set of blank frames has been acquired, new images are simulated and the correction, defined by equation 7, is applied.

$$y_{i,j} = x_{i,j} - [\mu_{i,j} - (m_{ref} - m_c)] \quad (7)$$

where $x_{i,j}$ is the raw pixel value, $\mu_{i,j}$ is the mean value of the pixel (i,j) obtained from the reference set of blank images, m_{ref} is the mode of all the images in the reference data set, m_c is the mode of the current frame and $y_{i,j}$ is the new pixel value.

After this first step, a threshold $t_{i,j}$ proportional to the standard deviation of each pixel, defined by equation 8, is then applied to each pixel:

$$t_{i,j} = m_{i,j} + k\sigma_{i,j} \quad (8)$$

Figure 6. In Figure (a) a 66 keV β electron without any diffusion entering the detector from a non orthogonal direction is observed. The implementation of the diffusion process produces a slight reduction in the peak, with a spread of charge around this central pixel, is shown in (b), noise is added in (c), initial correction is observed in (d) and this is finally transformed to keV in (e).

where $m_{i,j}$ is the mode dark signal of the pixel, averaged over the blank set of images, and $\sigma_{i,j}$ is the dark level standard deviation for each pixel obtained from the aforementioned blank frames, which defines the pixel threshold individually. The pixel threshold is then globally defined in terms of the coefficient k . This parameter is experimentally set for a certain radioisotope, hence k does not have to be changed between experiments given similar environmental conditions. The resulting binary images are then labelled using 8-connectivity analysis and the location, size and intensity of each event cluster are saved. In order to obtain a useful composite image, the thresholded images, described above, are accumulated and summed.

4.4. Validation of the simulated setup

The approach used in this work to evaluate the similarity of the simulated data compared to experimental data, is by comparing the cluster distribution obtained from the detector and the corresponding Monte Carlo simulations.

The experimental data acquired with the CMOS detector is comprised of a 6 hours acquisition exposure to a ^{14}C microscale, resulting in a total of 18360 images acquired. The number of events that were detected is 6570 events. The number of simulated events was 10^6 . The FPN correction method implemented in both experiments is that

described in (Cabello^a et al. 2007).

In Figure 7 the cluster distribution obtained from the acquired images from the detector and the cluster distribution obtained from the simulated setup are shown. Both distributions show very similar results, noticing how most of the events are concentrated in the first 4 bins, which means that most of the events are 1-4 pixels in size in both experimental and simulated results. In comparison to the situation where charge diffusion is not implemented, where most events are 1-2 pixels in size due to the closeness between the average electron range ($\sim 11 \mu\text{m}$) and half of the pixel size ($12.5 \mu\text{m}$), in this case the charge diffusion process makes the charge to be collected in 1-4 pixels, depending on the depth of interaction.

Figure 7. Experimental normalised cluster distribution for the digital detector (left) and result from Monte Carlo using the same sensor geometry (right).

Besides the random behaviour of the dark current in the pixels of the detector, which has been modelled, it was also observed how the experimental noise exhibits a time-dependant random component. This random component was basically comprised of an apparently random change of the global bias in the image i.e. random change of dark current, and also in the random increase of noise that some pixels exhibit in the detector i.e. random change of FPN. This effect has not been modelled as no reliable pattern of behaviour has been found. This will result in some minor level of discrepancy between cluster distributions.

After these results of the Monte Carlo simulations of the β - particles interactions in silicon and the implemented charge diffusion process, it is considered that the simulations are sufficiently close to the experimental case, making possible a plausible set of predictive and/or analytical investigations in detector geometries and their effect on the spatial resolution and charge deposition.

The resulting spatial resolution has been measured as the FWHM obtained with a ^{14}C and a ^3H point source, for a variety of detector geometries, by systematically varying the pixel size and the epitaxial layer thickness, resulting in a set of spatial resolution maps. Two different technologies have been simulated regarding the epitaxial layer. First an entire field-free epitaxial layer, representing the CMOS technology (wherein the small ($\sim 0.5 \mu\text{m}$) electric field produced by the applied pixel voltage is ignored), and secondly an epitaxial layer where half is depleted (an electric field is applied) and the other half is field-free, representing a CCD type of detector.

Charge diffusion effects, detector noise and image correction are applied to each simulated event to build a realistic Point Spread Function (PSF) for each geometry. The image correction method detailed in (Cabello^a et al. 2007) is implemented to understand its effect on the resulting spatial resolution maps.

5. Results

5.1. Intrinsic spatial resolution

The intrinsic spatial resolution is considered as the resulting spatial resolution in a (field free epitaxial layer) sensor where charge diffusion effects, system noise and noise correction are not included in the model. This is therefore the best case scenario for spatial resolution, if no post-processing techniques, such as centroiding or other algorithms (Cappellini et al. 2008), are later applied to individual hits to improve spatial resolution.

The spatial resolution map resulting from a simulation of the variation of the spatial resolution with the thickness of the epitaxial layer (5, 15, 20 and 30 μm) and the pixel size (5, 10, 15 and 25 μm) for a point source of ^{14}C with no air gap is shown in Figure 8. Similarly, a spatial resolution map resulting from a simulation of the variation of the spatial resolution with the thickness of the epitaxial layer (1, 2.5, 5, 10 and 20 μm) and the pixel size (1, 2, 5 and 10 μm) for a point source of ^3H with no air gap is shown in Figure 9.

Figure 8. 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.

Figure 9. Simulated spatial resolution map of the digital sensor exposed to a point source of ^3H with no air gap between the surface of the sensor and the source.

The uncertainty measured in these experiments was between 0.1% and 2.3% depending on the detector geometry simulated. It is observed how in both examples, the data point with the smallest pixel size and thinnest epitaxial layer, (5 μm) for ^{14}C and correspondingly (1 μm) for ^3H , produces the best intrinsic spatial resolution, $\sim 15 \mu\text{m}$ for ^{14}C and $\sim 1 \mu\text{m}$ for ^3H . It can be observed how the dependence of the spatial resolution on the thickness of the epitaxial layer is very low, as oppose to the dependence with the pixel size in both cases. Note, this high dependence is absent in Figure 8 for ^{14}C below a pixel size of $\sim 10 \mu\text{m}$, which corresponds approximately with the average range of ^{14}C β electrons, demonstrating the effects of multiple scattering. By contrast the dependence of spatial resolution on pixel size appears linear for ^3H due to the short range (max $\sim 1 \mu\text{m}$) in silicon.

5.2. Spatial resolution including charge diffusion

Those results shown in Figures 8 and 9, were obtained using the data generated by the Geant4 Monte Carlo toolkit, where no charge diffusion, system noise or noise correction are included in 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 accurate study of the resulting observed spatial resolution based on the variation of the detector geometry, the charge diffusion process has been implemented. The resulting spatial resolution variation, used for the same geometries shown in Figure 1, is shown in Figure 10 and 11 for ^{14}C . For ^3H a slightly different geometry compared to that shown in Figure 1 has been used, i.e. back thinned geometry. The only difference of a back-thinned geometry is the thin dioxide entrance window (~ 100 nm) that the particles have to traverse to reach the sensitive layer, compared to the ~ 5 μm of passivated layers that front-illuminated devices exhibit.

Figure 10. Simulated spatial resolution map of the digital sensor exposed to a point source of ^{14}C without charge diffusion process (blue) and with charge diffusion process implemented (red). Note that the data point corresponding to the smallest spatial resolution corresponds to a 5 μm thick epitaxial layer and a 5 μm pixel.

Figure 11. Simulated spatial resolution map of the digital sensor exposed to a point source of ^3H without charge diffusion process (green) and with charge diffusion process implemented (red). Note that the data point corresponding to the smallest spatial resolution corresponds to a 1 μm thick epitaxial layer and a 1 μm pixel.

It can be observed in Figures 8 and 9 how, without charge diffusion, the variation in epitaxial thickness does not provide a significant impact on the spatial resolution. The surfaces from Figures 8 and 9 respectively have been reproduced in Figures 10 and 11 as blue and green planes respectively. If the charge diffusion process is considered, it is now observed in Figures 10 and 11 how the epitaxial layer thickness represents an important parameter in the detector design, having a negative impact when a thicker epitaxial layer is used, assuming there are no depletion field effects present.

Both Figures 10 and 11 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 being process more critical for ^{14}C due to the higher amount of deposited charge (higher ionising energy), spread over a larger initial volume.

In the case of ^{14}C (Figure 10), it is observed how the rate of spatial resolution degradation as the pixel size increases is higher for a pixel size $< \sim 10$ 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 (49 keV). After this point, the rate of spatial resolution degradation holds a linear relationship with the epitaxial layer thickness.

For the case of ^3H , Figure 11 shows some interesting differences compared to the previous case. In this case, the charge diffusion process does not show such a pronounced overall degradation of the spatial resolution compared to the previous scenario. Nonetheless, the epitaxial layer thickness appears to have a higher effect on the spatial resolution for small pixel sizes ($< \sim 4 \mu\text{m}$) compared to larger pixel sizes. But for a pixel size $> 4 \mu\text{m}$, there appears to be no significant effects due to charge diffusion irrespective of epitaxial layer thickness. Once again, this may be attributed to this larger thickness (layer/pixel size) being larger than the maximum range of these electrons in silicon.

5.3. Spatial resolution including detector noise and noise correction

This study is now extended to include the effects of dark current noise and FPN (as these are significant if working at room temperature) and a subsequent noise correction stage. The FPN correction approach, described in (Cabello^a et al. 2007), is implemented to observe how this affects the spatial resolution. It should be noted that the noise model applied to the raw energy deposition images was derived from previously measured experimental data from an imaging sensor, having $25 \mu\text{m}$ pixel size and $20 \mu\text{m}$ thick epitaxial layer. The magnitude of this corrupting influence is expected to change for other geometries or grades of device. Dark current noise is expected to increase with pixel size given that this is proportional to the pixel area. In this respect, the noise implementation here may be somewhat overestimated for pixels $< 25 \mu\text{m}$ and underestimated for pixels $> 25 \mu\text{m}$.

Figure 12. 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 single threshold FPN correction method (red).

Figure 13. Simulated spatial resolution map of the digital sensor exposed to a point source of ^3H 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 single threshold FPN correction method (red).

In Figures 12 and 13 the resulting spatial resolution map for ^{14}C and ^3H are shown respectively, obtained after including the detector noise in the model and applying the FPN correction method described in (Cabello^a et al. 2007). Figure 12 represents the intrinsic spatial resolution map for ^{14}C shown in blue, and the spatial resolution map obtained after applying the correction method shown in red. Similarly, Figure 13 represents the intrinsic spatial resolution map for ^3H in green, and the spatial resolution map obtained after including detector noise and applying the correction method in red.

This demonstrates that for ^{14}C imaging, provided either pixel size and epitaxial thickness are minimised to 10-15 μm , then the correction method can successfully recover close to the idealised uncorrupted spatial resolution. However as either parameter increases, the FPN correction struggles to recover the true charge distribution. Nonetheless it provides a significant resolution recovery when compared to Figure 10. This demonstrates that the FPN correction method is able to recover the spatial resolution, compared to the intrinsic spatial resolution shown in Figure 8, for a thin epitaxial layer or a small pixel. However, as any of these parameters increase in size, the FPN is unable to cope with the significant spatial resolution degradation due to charge diffusion. Tables 3 and 4 summarise the resulting spatial resolution for each detector geometry shown in Figures 8 and 12 respectively.

Table 3. Intrinsic spatial resolution for ^{14}C imaging

Pixel size Epitaxial layer	5 μm	10 μm	15 μm	25 μm
5 μm	14.1 μm	16.0 μm	20.2 μm	29.6 μm
15 μm	15.3 μm	16.9 μm	21.2 μm	30.8 μm
20 μm	15.5 μm	16.9 μm	21.4 μm	30.9 μm
30 μm	15.5 μm	16.9 μm	21.3 μm	31.1 μm

Table 4. Post-processed spatial resolution for ^{14}C imaging

Pixel size Epitaxial layer	5 μm	10 μm	15 μm	25 μm
5 μm	15.3 μm	20.5 μm	25.6 μm	37.1 μm
15 μm	16.8 μm	27.0 μm	35.2 μm	52.6 μm
20 μm	17.4 μm	27.7 μm	37.6 μm	55.9 μm
30 μm	17.0 μm	28.6 μm	39.9 μm	60.8 μm

In the case of ^3H spatial resolution map in Figure 13, the FPN correction has a far more marginal effect, although this is consistent with the results shown in Figure 11. This is due to the low energy of the β electrons emitted by ^3H and subsequent short range and little deposited charge, and therefore low spatial resolution degradation compared to ^{14}C . Tables 5 and 6 summarise the resulting spatial resolution for each detector geometry shown in Figures 9 and 13 respectively.

Table 5. Intrinsic spatial resolution for ^3H imaging

Pixel size Epitaxial layer	1 μm	2 μm	5 μm	10 μm
1 μm	1.1 μm	2.0 μm	5.0 μm	10.0 μm
2.5 μm	1.1 μm	2.0 μm	5.0 μm	10.0 μm
5 μm	1.1 μm	2.0 μm	5.0 μm	10.0 μm
10 μm	1.1 μm	2.0 μm	5.0 μm	10.0 μm
20 μm	1.1 μm	2.0 μm	5.0 μm	10.0 μm

Table 6. Post-processed spatial resolution for ^3H imaging

Pixel size Epitaxial layer	1 μm	2 μm	5 μm	10 μm
1 μm	1.3 μm	2.2 μm	5.0 μm	10.0 μm
2.5 μm	1.6 μm	2.5 μm	5.0 μm	10.0 μm
5 μm	2.0 μm	3.0 μm	5.1 μm	10.0 μm
10 μm	2.6 μm	3.6 μm	5.4 μm	10.0 μm
20 μm	3.0 μm	4.5 μm	5.8 μm	10.1 μm

5.4. CCD vs. CMOS technology

There exist several works published in the literature comparing different aspects of CCD and CMOS technologies, such as quantum efficiency, noise or charge collection efficiency (Janesick 2002, Magnan 2003). However no quantitative comparison between technologies regarding the achievable spatial resolution has been found (to the best of our knowledge). In this work the spatial resolution of a typical CCD architecture and the CMOS VANILLA architecture are compared. From a detection stand point, the structures where CCD and CMOS detectors differ are in the pixel size and the structure and thickness of the overlying layers. The dimensions used here are based on two detectors used in prior work (Cabello^a et al. 2007) with similar pixel dimensions (shown in Table 2), although it should be noted that a variety of different pixel sizes from ~ 1 -100 μm may be found in different devices.

Moreover, a key difference between CCD and CMOS technology is that in CCD technology the epitaxial layer is subject to a significant electric field. This electric field acts on the initial cluster of ionised charge producing rapid drift and subsequent collection at the overlying electrode. This means that within the depletion region produced by the electric field, there is negligible thermal charge diffusion. In this comparison study, where a wide range of detector geometries were simulated, it is assumed that the depleted layer corresponds to half the epitaxial thickness, although we are aware that this assumption may not always be fulfilled, especially for thin CCD detectors.

Figure 14 shows the spatial resolution map achieved with CCD and CMOS technologies without charge diffusion, with charge diffusion and with detector noise and the noise correction technique.

It is observed in Figure 14(a) how the intrinsic spatial resolution obtained with CCD technology appears superior to that obtained with CMOS technology for all detector geometries simulated in this work. This effect may be well explained first by the thinner (0.7 μm) passivated layers present in this CCD geometry compared to CMOS technology, where a total 5 μm thick passivated layers are modelled, as observed in Table 2. This positions the point source farther from the sensitive region, allowing the β electrons to suffer more dispersion before they deposit charge in the epitaxial layer. Secondly, the CCD detector has a 22.5 μm pixel size compared to 25 μm of the CMOS detector, causing a slightly finer sampling of the charge and possibly producing better spatial resolution measurements.

However, Figure 14(b) shows significantly different spatial resolution maps, principally attributed to the higher charge diffusion observed by the undepleted CMOS architectures compared the CCD architectures, and thus associated with thicker field-

Figure 14. Comparison of simulated spatial resolution map of the CMOS sensor (red) and the CCD sensor (green) exposed to a point source of ^{14}C , without charge diffusion (a), with charge diffusion (b) and system noise and noise correction (c).

free regions present in the CMOS architectures. This spatial resolution degradation is also observed in the subsequent processes after system noise and noise correction are included in the simulations.

These results have shown that using the FPN correction to room temperature devices is a vital step in recovering spatial resolution and mitigating the effects of charge diffusion and electronic system noise. Applying the FPN step to such room temperature devices allows almost complete recovery of the resolution that might otherwise achieved under cooled conditions. However, with thicker undepleted sensors imaging longer range β emitters (i.e. other than ^3H), deep beta penetration into the sensitive region may induce significant charge diffusion effects that may still be problematic. This may also be exacerbated by high energy and/or oblique entry particles traversing more than a single pixel. Maintaining epitaxial and pixel dimensions below $10\ \mu\text{m}$ minimises these obfuscating diffusion effects, once the FPN correction has been applied. However it is also worth commenting that once very large dimensions are employed, in particular epitaxial dimensions of $40\ \mu\text{m}$ and above, then the effectiveness of the FPN method at recovering resolution is slowly diminished.

6. Discussion and Conclusions

Enhancing the spatial resolution of digital detectors is a key issue in developing a viable alternative to conventional autoradiographic film. The best achievable spatial resolution for ^3H with film is $\sim 1\ \mu\text{m}$ but this is subsequently degraded by the digitisation process. The best spatial resolution currently obtained with a digital system for ^3H is $15\ \mu\text{m}$ (Tribollet et al. 1991), using the μ -Imager which is comprised of a thin sheet of scintillator and a CCD detector with $5\ \mu\text{m}$ pixel size. Other approaches, such as phosphor imaging plates (Yamane et al. 1995) and the commercial β -Imager (Tribollet et al. 1991), imaging ^3H have claimed a spatial resolution of $50\ \mu\text{m}$. A more extended research is found in ^{14}C imaging where a spatial resolution of $20\ \mu\text{m}$ has been claimed by DEPFET (Neeser et al. 2000), $50\ \mu\text{m}$ has been claimed by the commercial β -Imager, $70\ \mu\text{m}$ using MCPs (Lees et al. 1999) and $110\ \mu\text{m}$ with hybrid technology using Medipix-II (Mettivier et al. 2004b).

A detailed study on the spatial resolution of silicon imaging detectors has been presented. A variety of different detector geometries have been modelled to obtain an optimised detector geometry for two key radioisotopes (^3H and ^{14}C) representing the energy ranges of the most commonly used radioisotopes used in β autoradiography.

From this set of experiments an optimal detector geometry can be chosen depending on the radioisotope used. Observing the intrinsic spatial resolution maps it seems clear that for ^{14}C a pixel size $< 10\ \mu\text{m}$ does not improve spatial resolution performance. From this value up to larger pixels, the spatial resolution then linearly degrades with pixel size. A similar effect has been observed for ^3H albeit with a smaller range of pixel sizes. This indicates that spatial resolution is strongly related with the mean range of the β electrons emitted by each radioisotope, over and above pixel dimension.

When charge diffusion is included in the model it is observed how its effect can significantly degrade the observed spatial resolution. This could be reduced by applying an electric field to the active volume to collect the deposited charge, as shown with CCD technology, or by using a thinner detector. It has been observed that the outer pixels affected by the deposited charge in an arbitrary event only contain charge of a few electrons. These few electrons will be easily masked by dark current noise.

Using the FPN correction method, a single threshold, high enough to produce a low rate of false events, results in a spatial resolution map similar to the intrinsic spatial resolution map for low energies (^3H). For medium energies (^{14}C) some differences arise as the effects of the epitaxial layer thickness on spatial resolution increases, 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 $10\text{--}15\ \mu\text{m}$ as being optimal. 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 ^3H , the effect of charge diffusion on spatial resolution appears to be proportional to epitaxial thickness and pixel size. In this case, the optimal pixel dimension appears to be $\sim 1\ \mu\text{m}$.

The limits of CCD and CMOS technology have also been studied and compared in this work. These demonstrated that, due to the attenuated charge diffusion in

CCD technology, compared to thicker field-free layers in CMOS technology, better spatial resolution measurements are obtained for CCD technology, for the imaging of uncollimated β particles found in autoradiography in imaging sensors of similar pixel and epitaxial dimensions.

It is also probably worth mentioning that in practice the choice of technology (CCD vs. CMOS) may also be governed by other factors such as cost, noise performance, read-out speed, radiation hardness and available sensor area.

One further issue, ignored so far, is the amount of deposited charge produced by a β^- in the epitaxial layer. This has a significant impact on the contrast to noise ratio, resulting in higher expected contrast for thicker detectors. This is one area worthy of further study to ultimately understand the final image quality that can be produced by an *optimal* image sensor.

The study presented in this work can also be extended to β^+ sources, such as ^{18}F , ^{11}C or ^{15}O , due to the similar behaviour of β^+ particles exhibited in silicon. The only difference in this case is the higher energy of β^+ particles emitted by β^+ emitter radioisotopes (0.64 MeV, 0.96 MeV and 1.7 MeV maximum energy respectively), producing more interactions in silicon (assuming that the β^+ do not escape the epitaxial layer) given the lower stopping power of silicon to particles in this range of energy.

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Appendix A. Calibration

A CMOS sensor (previously described in (Cabello^a et al. 2007)) was exposed to a point source of ^{241}Am (activity of 41 kBq) situated approximately 30 mm from the surface of the detector with a layer of insulating tape to absorb the associated α particles. The geometry was set up such that the chances of obtaining overlapping event clusters within a single image frame was considered negligible.

The peaks corresponding to the ^{241}Am photon energies of 13.9 keV, 17.5 keV, 22 keV and 26 keV were observed in the reconstructed energy spectrum. Further details appear in (Cabello^a et al. 2007).

From these data a fitted calibration line is shown in Figure A1 with a slope of 24.1 DN/keV (0.041 keV/DN) and an intersection point of -295.7 DN. Assuming 3.6 eV is required to liberate 1 electron in silicon, then this yields a slope of 11.5 e-/DN units and an intersection of 3400 electrons.

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Figure A1. Energy calibration curve for the CMOS Vanilla sensor. X axis represents the energy in keV and Y axis represents the signal in DN units.

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