A New Generation of Space X-Ray Imagers that Could Help Fight Cancer

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A new generation of X-ray imagers for future space-science missions is being developed by ESA in cooperation with European industry. These devices were initially intended for X-ray astronomy and remote planetary sensing, but have now been found to have immediate applications in clinical radiology. In particular, the devices are ideally suited for the imaging of low-density, low-contrast media such as breast tissue, making them invaluable in the diagnosis and clinical support in the fight against cancer.

X-ray imaging is an essential tool for a wide range of disciplines, from astrophysics to material science. Whilst the majority of applications rely on film, phosphor storage screens or other analogue integrating formats, the future development of this field lies in the exploitation of spatially resolved spectroscopy. Commercially available systems generally utilise secondary detection media, such as phosphor plates or scintillator conversion layers.

However, these methods have a number of shortcomings related to resolution and light collection efficiency, and consequently they do not offer much improvement in imaging performance, in terms of 'detective quantum efficiency' (a figure of merit describing a system's ability to resolve imaging detail in weak signals) over more traditional film-screen systems. Additionally, such systems do not make use of 'colour' information and therefore do not lend themselves easily to advanced techniques employing differential absorbtiometry.

While astrophysics has pioneered the utilisation of semiconductor detectors based on silicon at soft X-ray energies (below 10 keV or longward of 1 Angstrom), the hard X-ray band (10 to 200 keV) has proved particularly difficult to develop and has remained relatively unexplored. This band is important because it bridges the transition between thermal and non-thermal emission processes predicted to occur throughout the galaxy. By coincidence, this band is also of crucial importance in medicine and encompasses all the main energies used in clinical radiology. However, while astrophysics can, at least for now, use data from lower X-ray energies to interpolate the underlying high-energy physics, medical applications are not so lucky, since the human body is essentially opaque below 10 keV. In fact, all clinical investigations are carried out in the hard X-ray region, for example at 20 keV for mammography, 60 keV for thoracic radiography, and 140 keV for nuclear medicine (Table 1).

Table 1 shows the key X-ray energies used in space sciences and medicine. Even though the two disciplines are literally worlds apart, they clearly share a lot of common characteristics and an X-ray imager designed for space

Table 1. The various space and clinical applications of X-ray imaging

Space-science radiology	X-ray energy (keV)	Clinical radiology	X-ray energy (keV)
Earth observing (Auroral)	1–20	Mammography	17–20
Planetary	0.2–7	Dental	60–70
X-ray astronomy	0.1–10	Thoracic	50–70
Hard X-ray astronomy	10–200	Nuclear medicine	30–300

science can also be used for medical applications. However, observationally the similarity ends. Astrophysicists, for example, need only to observe for a longer time to improve image quality – in other words the higher the dose the better. In medicine, the converse is true, in view of the risk to the patient. Therefore in clinical radiology other methods have to be found to enhance contrast whilst simultaneously reducing dose. The simplest solution, however, is also the most beneficial to astrophysics – simply detect each photon with 100% efficiency and record its energy, arrival time and position.

It has been clear for some time that the next major step forward in this region of the electromagnetic spectrum will be made through the development of an efficient imaging detector, operating at room temperature, which converts X-rays directly into electrical signals whose amplitudes are proportional to their energies or colour. Alternatively, one may think of this as an X-ray camcorder. The potential market is enormous, not only for space sciences, but also in all branches of medicine, particularly mammography, general radiography, fluoroscopy and nuclear medicine.

At soft X-ray energies, the power of such a system has already been dramatically demonstrated in astrophysics by ESA's XMM-Newton and NASA's Chandra X-ray observatories, which have produced some of the first very high resolution 'colour' images of the X-ray sky using silicon charge-coupled devices (CCDs). As an example, Figure 2 shows two images of the Crab Nebula, the remains of an exploded star known as a supernova remnant. An old star, at the end of its life, exploded in 1054 AD leaving behind the diffuse gaseous nebular we see today, together with the core of the star – known as a 'pulsar' or, more specifically, a neutron star. The event was memorable because Chinese astronomers and probably the ancestral Pueblo Indians recorded it. The left-hand image of Figure 2 is an optical photograph showing the expanding nebula with its characteristic filamentary structure. This is known as a synchrotron nebula. The light we see is simply the radiation from energetic electrons, spiralling in the remnant's magnetic field. The electrons, in turn, are accelerated by (and beamed out of) the central pulsar. Using the world's first superconducting camera, also developed by ESA,

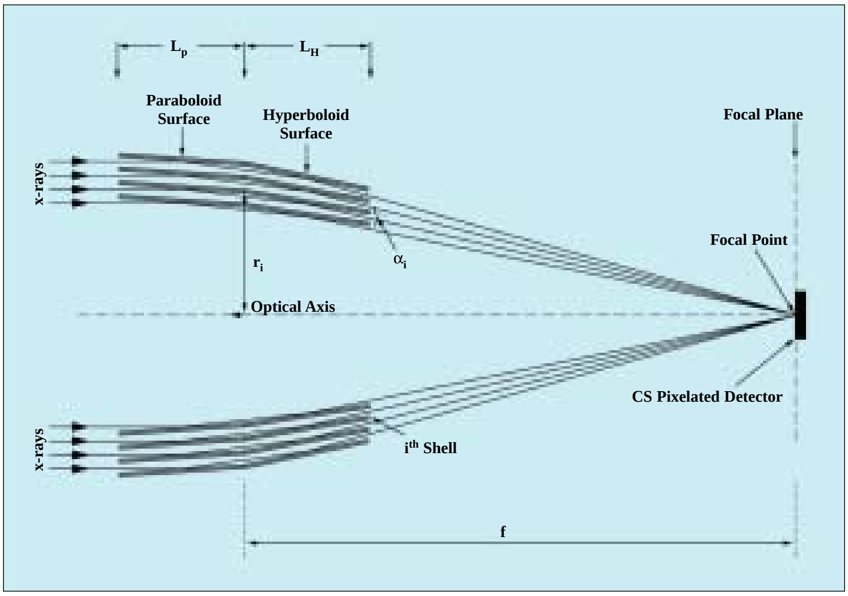

Figure 1. The astrophysicists' approach to soft X-ray imaging through the use of an X-ray telescope and imaging detector

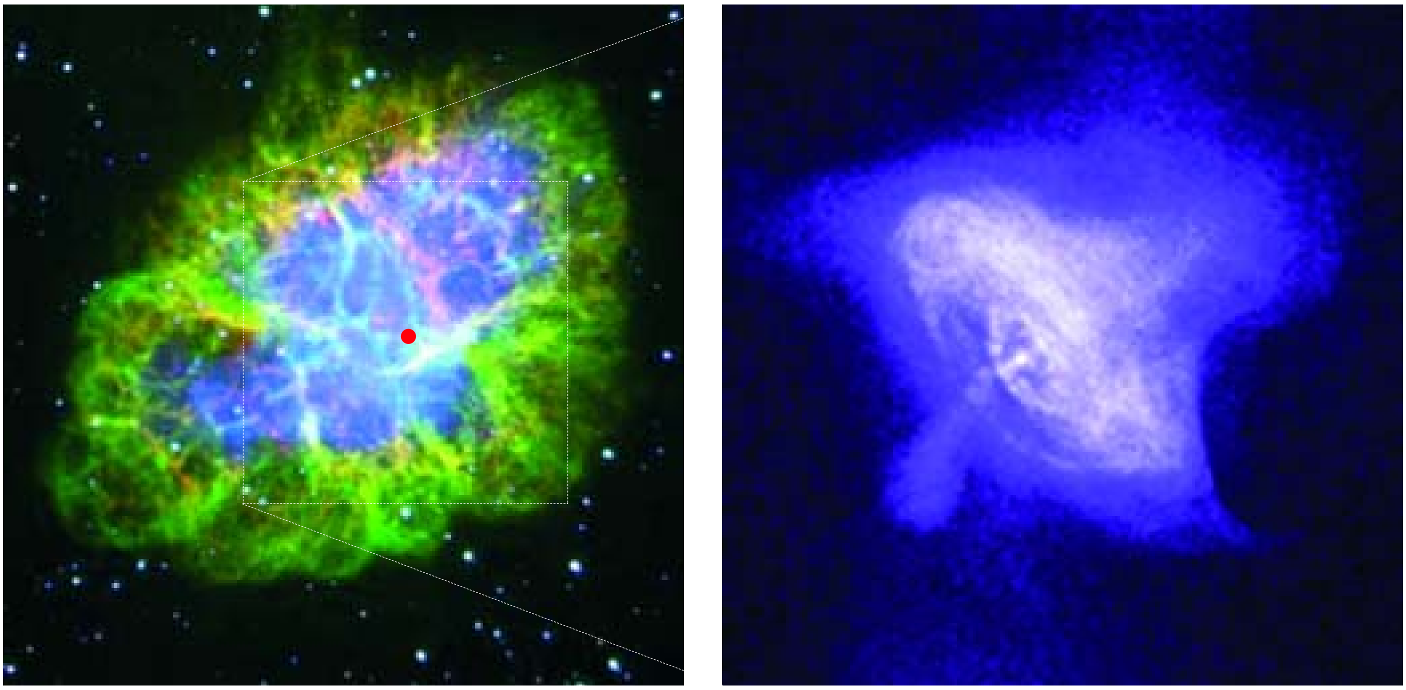

Figure 2. The Crab Nebula at optical (left) and soft X-ray (right) wavelengths. The red dot indicates the position of the pulsar – the remnant of a dead star which powers the nebulae through electron injection

astronomers observed this pulsar in visible light in early 2000 using the William Herschel Telescope in La Palma, Spain. The camera performed pulse phase spectroscopy on the light beamed from the tiny pulsar, only about 10 km in diameter, with unparalleled precision (cf. ESA Bulletin No. 98).

By contrast, the right-hand image of Figure 2 shows the central portion of the nebula viewed at soft X-ray wavelengths. The structures seen at these wavelengths are considerably hotter and are not at all apparent in the optical image. A swirling disk of hot particles and jet-like structures blasting out from the central pulsar are clearly visible. By using the spatially resolved colour information in this image, astrophysicists are now able to disentangle and isolate the energetically different emitting regions.

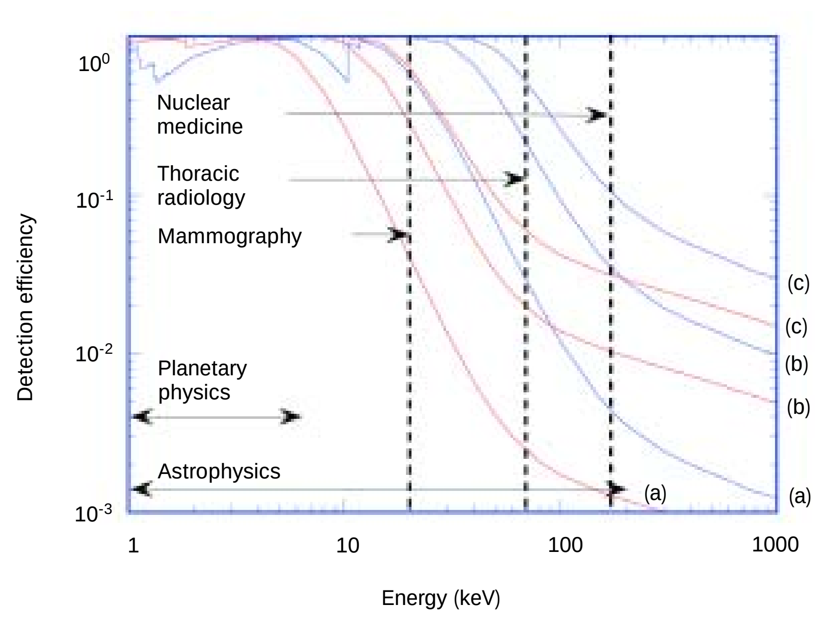

Figure 3. The calculated detection efficiency for three GaAs detectors (blue curves) with thicknesses of 40 microns (a), 325 microns and 1000 microns (c), compared to conventional silicon (red curves). The horizontal solid lines indicate the energy ranges of interest for space-science applications. The vertical dotted lines indicate the peak tube energies commonly encountered in clinical applications, such as mammography, thoracic radiology and nuclear medicine. The important point is that a system based on GaAs and specifically designed for astrophysics applications is also optimally designed for medical applications

Whilst the current generation of semiconductor devices based on silicon has provided sub-keV energy resolution near 1 keV, they are only sensitive in the UV and soft X-ray bands up to ~10 keV because of the low absorption power of silicon (cf. Fig. 3). For example, it is impossible to acquire the X-ray image shown in Figure 2(b) at energies above ~10 keV with ESA's XMM-Newton, simply because the telescope and the silicon CCD detectors lack efficiency at these energies.

Another point of note is that silicon detection systems require cooling to achieve low noise, which in turn means that the devices are quite bulky. For example, XMM-Newton's silicon-based CCDs are cooled passively by large radiators dumping the heat to space so as to achieve an optimum working temperature of minus 100°C. Clearly, this system is inappropriate for say intra-oral applications. These very practical considerations are crucial for the widespread use of new diagnostic instruments in medicine.

The key material requirements for future systems are: (a) high density to provide high detection efficiency, (b) a wide enough band-gap to ensure room-temperature operation, (c) a time response matched to the expected photon fluxes (potentially up to 10 million photons/mm$^{2/}$s for diffraction-enhanced imaging), and (d) a uniformity in spatial response in excess of 99.99% (a precision dictated by the dynamic range required for low-contrast imaging, e.g. mammography). Of the available materials suitable for hard X-ray detectors, compound semiconductors are the most promising, and in particular gallium arsenide (GaAs). Its band-gap is high enough that it does not require cryogenic cooling, but low enough that sub-keV spectral resolution is achievable at hard X-ray energies. The former attribute is highly desirable in a number of applications, e.g. intra-oral radiography, while the latter quality, when coupled with the inherent fast response of semiconductor detectors, offers real advances in fluoroscopy. Room-temperature operation is also an important consideration for X-ray systems designed for planetary exploration, since heat rejection is a real problem, especially for probes exploring the inner planets. The constituent elements of GaAs have high enough densities that its hard X-ray responsivity is much more closely matched to the spectral output of the standard X-ray tubes than either classical film or silicon-based detectors. This is illustrated in Figure 3 which shows the expected quantum efficiency for three thicknesses of GaAs imager as a function of X-ray energy, compared to silicon. All three thicknesses shown are under active development by ESA.

Note from Figure 3 how quickly the response of silicon (red curves) falls-off with energy above 10 keV, in fact a factor of 10 more than for GaAs (blue curves). The lower solid horizontal lines in Figure 3 indicate the energy ranges of interest for astrophysics and planetary fluorescence studies, while the vertical dotted lines indicate the peak tube energies commonly encountered in mammography, thoracic radiology and nuclear medicine. As can be seen, the 40 micron device is particularly well suited for planetary applications, whereas the 325 and 1000 micron devices would be suited for astrophysical and clinical applications. Specifically, a 325 micron device would have an efficiency at 20 keV of over 98%. This should be compared to 1% for radiographic film, or 60% for film-screen combinations. Thus, by default, an imaging system developed for ESA's planetary and astrophysics missions could have immediate medical applications. In fact, since medical imaging requirements are generally more stringent and global than those for space sciences, they make good yardsticks for future mission studies.

The Science Payloads Technology Division and the Agency's Directorate of Technical and Operational Support have worked for a number of years with industry (Metorex International Oy of Finland) to develop GaAs arrays for astrophysics and planetary applications, beginning with an extensive monolithic detector programme designed to probe basic material and technological issues. Steady progress has been achieved, with average room temperature full-width-at-half-maximum (FWHM) energy resolutions at 60 keV decreasing from ~10% keV at the start of the programme to ~1% eV at the present time. The FWHM is a very useful figure of merit for characterising a spectrometer system and essentially describes its ability to resolve colours. The FWHM is usually expressed in terms of a percentage or, alternately, in units of energy (keV). For both space science and medicine, 10% is good, 1% is excellent. As a precursor to producing large arrays, we have also produced a series of small-format pixel arrays. Information on this material-science and detector programme can be found at: http://astro.estec.esa.nl/SA-general/Research/Detectors_and_optics/home.html.

Detailed measurements are routinely carried out in ESTEC's laboratories and in close cooperation with synchrotron research facilities: HASYLAB in Hamburg (D), BESSY II in Berlin (D) and ESRF in Grenoble (F). These key European facilities are three of the few in the world that can produce highly monochromatic X-ray beams extending from 0.1 up to 100 keV. From a space science point of view, they provide the 'cleanest' X-ray sources with which to calibrate satellite-borne detectors, whereas from a medical point of view they allow scientists to experiment with advanced imaging techniques designed to reduce patient doses whilst also improving image contrast. In both cases, the information acquired can be used to better interpret astrophysical and planetary X-ray maps.

Figure 4 shows the first small array produced. The purpose of this phase of the research was to explore array fabrication techniques, particularly masking and etching, as well as possible implementations of the readout and front-end electronics. The array was fabricated by growing an ultra-pure 40 micron epitaxial layer onto an n+ semi-insulating substrate using the same chemical vapour-phase deposition (CVPD) techniques developed for the semiconductor industry. To reduce leakage currents, a 10 micron thick p+ layer was then deposited directly onto the epitaxial layer, forming a p-i-n structure. This layer was then patterned by etching, to create a 5 x 5 pixel structure surrounded by a guard ring (see figure). The pixel sizes are 250 x 250 micron^2, with an inter-pixel gap of 50 microns. The guard is 200 microns wide and is used to control surface leakage currents. The chip was bonded to a ceramic substrate and coupled to a two-stage Peltier cooler capable of cooling the array to -40°C. Two pixels were actually instrumented, contact with the chip being achieved by wire bonding. Measurements from 5.9 to 98 keV were carried out at HASYLAB, yielding room-temperature energy resolutions of 660 eV FWHM at 5.9 keV and 380 eV FWHM with only modest cooling (-40°C).

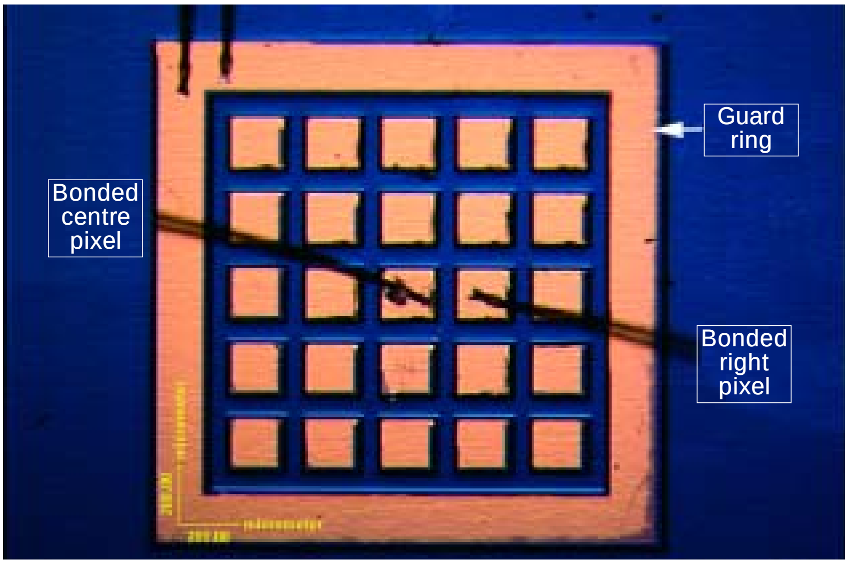

Figure 4. Nomarski photomicrograph of the first array produced. The device is 40 microns thick and has a pixel size of 250 x 250 microns. The bond wires to two instrumented pixels and the guard ring are clearly visible. This early prototype allows the array-processing techniques to be rapidly developed

Figure 5 shows a second-generation device produced in essentially the same way as the 5 x 5 device. In this case, a 4 x 4 array was patterned on thicker (325 micron) epitaxial material. However, unlike the previous device, all pixels were instrumented and read out by individual hybrid resistive feedback pre-amplifiers mounted directly onto an aluminium-nitride substrate along with the chip. To ensure low noise, the input stages utilise state-of-the-art low-capacitance tetrode FETs, also mounted directly on the substrate, but closer to the array. The mechanical layout of the chip, hybrid preamplifiers and substrate is shown in Figure 5.

The optimum performance in terms of energy resolution was found for pixel biases of +50 V, although the device would operate satisfactorily for biases as low as +5 V. The leakage currents

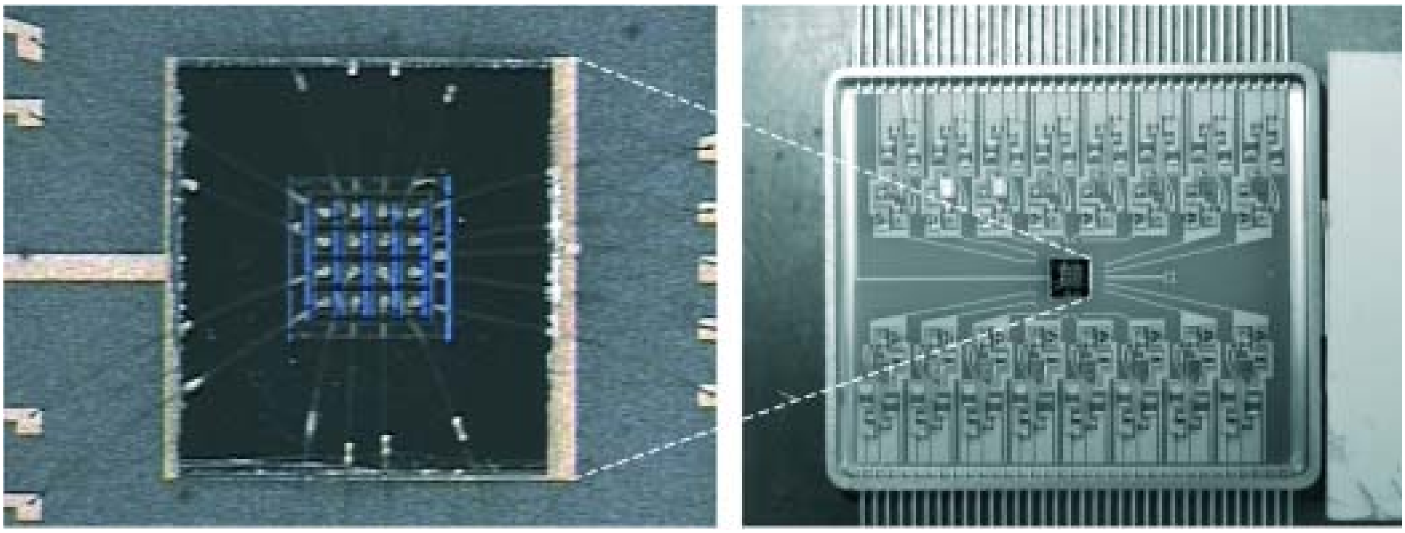

Figure 5. Left: Photomicrograph of a second-generation 4 x 4 GaAs detector assembly. The device is die-attached to the substrate, which in turn is mounted on a two-stage Peltier cooler. Right: Photograph of the completed GaAs array/hybrid/substrate assembly. While such an array is too small for space science or medical applications, it does allow issues related to pixel performance and inter-pixel communication to be studied. Note any large-format device would also use a dedicated ASIC rather than specific components for the electronic readout chain of each pixel

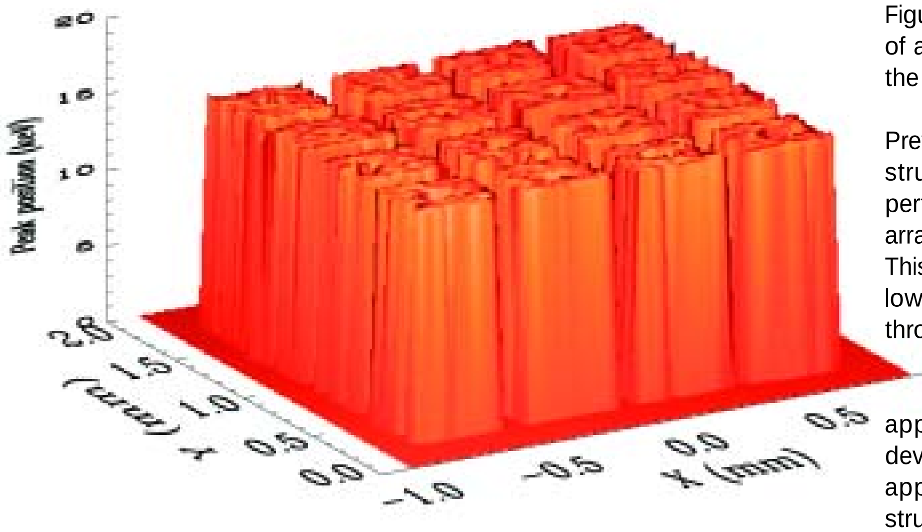

Figure 6. A surface plot of the spatial variation of the gain (i.e. the fitted centroid position) across the 4 x 4 GaAs array measured at HASYLAB using a 15 keV, 20 x 20 micron pencil beam. The spatial sampling in X and Y was 10 microns

were low enough to permit room-temperature operation (RT), with typical FWHM energy resolutions of 600 eV at 5.9 keV and 700 eV at 59.54 keV (pulse width = 550 eV). The energy resolution was found to improve with decreasing detector temperature. At ~ +5°C, for example, typical energy resolutions of ~410 eV FWHM were found at 5.9 keV with an electronic noise component of ~390 eV FWHM. At 59.54 keV, the corresponding resolutions were ~ 640 eV. The spatial uniformity of the array was tested explicitly at HASYLAB using a 15 keV 20 x 20 micron pencil beam, normally incident on the pixels. The beam was raster-scanned across this area with 10 micron spatial resolution in both dimensions. It was found that, apart from a slight depression in these parameters directly under the bond wires, their spatial distributions were very uniform over the surface of each pixel and the array. In fact, the average non-uniformity is typically no worse than 1% and is consistent with a flat response. Specifically, the variations seen in the gain across the array are consistent with the expected statistical variations alone to a level that would satisfy the uniformity requirements of low-contrast imaging. The fact that both the count rate and centroid responses are zero in the inter-pixel gaps, with no evidence of cross-talk, proves that it should be possible to replicate isolated and identical pixels, and thus potentially mega-pixel arrays. Figure 6 shows the resultant map of the 4 x 4 pixel array when illuminated with 15 keV X-rays.

Given that small arrays have demonstrated excellent performance, designs for practical applications in astrophysics, planetary remote sensing and medical imaging can now be considered. Figure 7 shows the first of these attempts, a 32 x 32 pixel array, produced as a technology demonstrator for a planetary mission. As with the 4 x 4 array, it was fabricated on 325 micron-thick epitaxial material. The left-hand image in Figure 7 shows the photo-lithographic mask, which contains the patterns of three 32 x 32 arrays and a large variety of small-format arrays and monolithics. The smaller devices are used to evaluate the quality of masking, lithography and etching as well as assess the electrical and isolation properties of potential detectors via IV measurements, X-ray testing and microscopy. The right-hand image in Figure 7 shows a Nomarski photomicrograph of a single 32 x 32 pixel array after dicing from the wafer.

Previous studies have shown that the p-i-n structure could produce near-Fano-limited performance in monolithic and small-format arrays by drastically reducing leakage currents. This in turn allowed the use of increasingly lower noise preamplifier designs, read-out through the p+ contact and positively biased via the n+ contact to ensure the efficient collection of holes. While such an approach is acceptable for research and development using small arrays, any practical application requires modifications to this structure for large-format arrays as well as

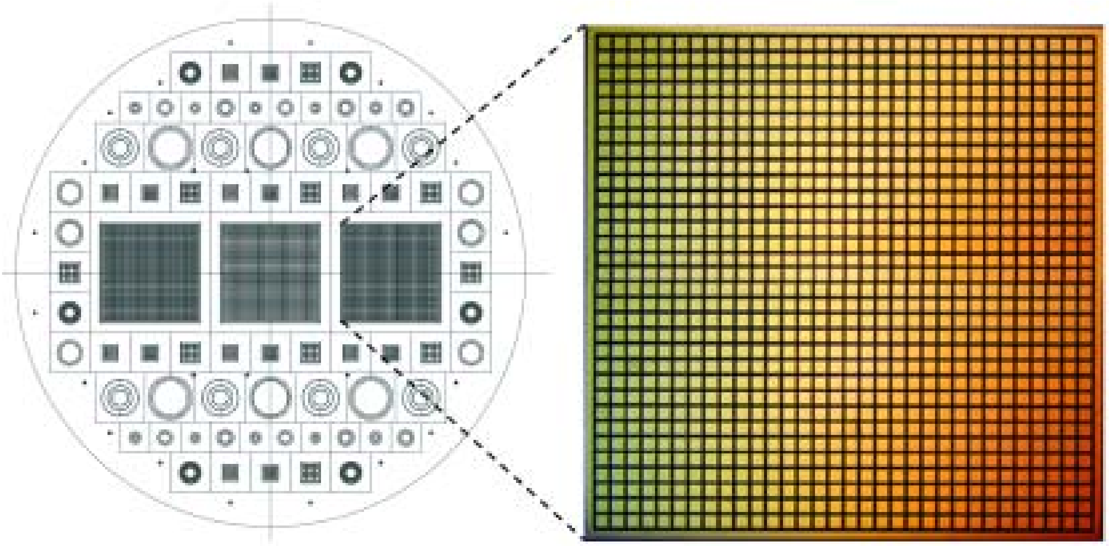

Figure 7. Left: The lithographic mask used to produce the large-format array. Note that a wide variety of smaller arrays, monolithics and test structures are also produced on the same wafer.
Right: A photograph of the array after dicing and prior to electrical probing and bonding of individual pixels

changes to the readout. It will be necessary to illuminate the arrays through the n+ electrode. Since each pixel in a large-format device must be read out individually, with its own electronic chain, the packing density is prohibitive for conventional electronics. Instead, the Division is developing a custom-built microchip to do this. The device is known as an ‘Application Specific Integrated Circuit’ or ASIC, which will be flip-chip, bump-bonded to the pixelated side of the detector. To avoid excessive X-ray extinction in the n+ layer, this layer will have to be substantially thinned or removed. Whilst the thinning process is being developed, the material and electronics development programme has continued by retaining a p-i-n structure on these prototype arrays and reading out the pixels via wire bonding to the p+ layer.

For the initial tests, four pixels were instrumented. The preliminary characterisation of the detector over the energy range 5.9 to 100 keV was carried out at ESTEC and HASYLAB. Typical FWHM energy resolutions of around 300 eV at 5.9 keV and ~550 eV at 59.5 keV were recorded for all four pixels at +24°C. For comparison, the electronic system noise was measured to be ~280 eV FWHM. The resolutions were found to decrease with decreasing temperature to ~250 eV at 5.9 keV and ~500 eV at 59.54 keV at ~+5°C. Below this temperature, there was no statistical improvement in resolution. Note, these results are representative of all pixels. It should be noted that the expected Fano noise at these energies (the limiting resolution given by the physics of the photo-absorption process) is ~130 and 410 eV, respectively.

Conclusion

This GaAs sensor research and development programme, originally intended for astrophysics and planetary exploration missions, has yielded such excellent performance figures that serious clinical applications can now be considered. In particular, the demonstration of good performance at room temperature, coupled with the fact that standard integrated-circuit fabrication techniques can replicate isolated and identical pixels, means that practical large-format compact cameras are not far away. The next key step is the coupling of the current, or even larger format, arrays with a readout system based on ASIC technology, leading to the volume production of compact X-ray cameras for routine radiological procedures.

An example of such a task is the detection and treatment of breast cancer. This cancer is best treated when detected at a rather early stage in its development, in particular before the disease has a chance to spread into to the lymphatic node system from a primary tumour. A compact X-ray camera based on a large-format GaAs array would allow the physician, through radio-isotope imaging, to determine the location of those nodes that are malignant. The GaAs array shown in Figure 7 is entirely suitable for this task. In the event of the detection of ductile carcinomas, the device could be used for staging, i.e. to assess how far the disease has spread by probing the auxiliary lymph nodes, as well as pin-pointing diseased nodes for surgical removal, in real time. Whereas present commercially available devices locate such tumours to a spatial accuracy of several millimetres, the array shown in Figure 7 would have a worst-case accuracy of 250 micron and, depending on statistics, potentially a lot higher.