*International Tables for Crystallography* (2012). Vol. F, Section 7.2.4, pp. 186–187.



To map the nonuniformity in response, one would ideally use a uniform source of X-rays of the proper energy placed at the position of the sample. This would calibrate the detector with the proper energy and angle of incidence for the diffraction data to be corrected. Correction factors are computed from a series of images taken of this uniform source. Sufficient numbers of X-rays per pixel must be collected to reduce the shot noise in the X-ray measurement to the required level (*e.g.* 40 000 X-rays per pixel must be acquired to correct to 0.5%).

Providing a truly uniform source with an arbitrary X-ray energy and angular distribution is difficult at best. Other sources can be used, however, with good results. Amorphous samples containing a variety of elements can be fabricated which produce X-ray fluorescence at various wavelengths when excited by a synchrotron beam (Moy *et al.*, 1996). These can be placed at the position of the sample, thereby mimicking the angular distribution of X-rays from the experiment. The fluorescence is not uniform in space, however, so that the actual distribution must be mapped by some means. Once mapped, however, these samples provide a stable calibration source.

Another alternative is to separate the calibration procedure into several parts, mapping the dependence at normal incidence and treating the angular dependence as a higher-order correction. By moving an X-ray source sufficiently far away, the detector can be illuminated at near-normal incidence with excellent uniformity. For example, an X-ray tube at 1 m distance can produce a field with uniformity better than 0.5% over a $10 \times 10$ cm area. A sum of images with sufficient X-ray statistics, taken with the area dilation of each pixel computed through the geometric distortion calibration, can be used to compute a pixel-by-pixel normalization factor. Again, this should be determined for the X-ray energy of interest. In practice, the appropriate energy may be approximated by a linear combination of several energies. However, the proper coefficients will need to be determined empirically. This can be judged in diffraction having broad diffuse features, because imperfections in the phosphor stand out clearly when the data are corrected using factors derived from the wrong X-ray energy.

#### 7.2.3.5. *Obliquity correction*

It has been found empirically that the light output for a given X-ray energy has a quadratic variation with the angle of incidence. The quadratic coefficient varies with X-ray energy and may be either positive or negative. The angular dependence may be measured by illuminating the detector with a small stable spot of X-rays and recording the integrated dose at various angles of incidence. Given the placement of the detector in relation to the beam and sample, the angle of incidence at a particular pixel can be computed and can be used to find the correction factor needed. With this method, a change in the experimental setup does not require a new calibration, just the computation of a new set of coefficients. The combination of energy and obliquity sensitivity varies slowly and may be approximated by a quadratic or cubic fit to a surface as a function of X-ray energy and angle. The few coefficients defining this surface allow quick computation of the combined energy and obliquity factor with which to multiply the local flat-field correction for X-rays of known incident energy and angle.

The obliquity correction is often ignored, since the solution of structures from X-ray diffraction typically includes a temperature factor which also varies with angular position. Uncorrected angular dependence of detector response will be convoluted with the true temperature factor and often does not impede the solution of the structure.

These procedures do not allow correction to arbitrary accuracy, however. The calibration data are taken with uniform illumination, whereas diffraction spots are localized. Given a nonzero point spread in the detector, the computed correction factor arises from a weighted average of many illuminated pixels. The signal from a diffraction spot only illuminates a few pixels, so the true factor might well be different. This should be less of a problem as diffraction spots become larger, becoming more like a uniform illumination. Measurement for one detector showed 75 µm spots could be measured to 1% accuracy, whereas 300 µm spots could be measured to 0.3% accuracy (Tate *et al.*, 1995).

#### 7.2.3.6. *Modular images*

The size of available fibre optics and CCDs and the inefficiencies of image reduction limit the practical imaging area of a single CCD system. Closely stacked fibre-optic taper CCD modules can be used to cover a larger area. Although the image recorded from each module could be treated as independent in the analysis of the X-ray data, merging the sub-images into one seamless image facilitates data processing. Each module will have its own distortion and intensity calibration. It is no longer possible to choose an arbitrary lattice onto which each distorted image will be mapped: the displacement and scaling must be consistent between the modules. This would be accomplished most easily by having a distortion mask large enough to calibrate all modules together, although it is possible to map the intermodule spacing with a series of mask displacements.

Flat-field correction proceeds as in the case of a single module detector after proper scaling of the gain of each unit is performed. There can potentially be a change in the relative scale factors between modules, since each is read though an independent amplifier chain. Multimodule systems emphasize the need for enhanced stability and ease of recalibration.

### 7.2.4. Detector system integration

*Hardware interfacing.* CCDs are operated, during both data acquisition and readout, by a dedicated hardware controller attached to a host computer, generally a PC. The requirements for the controller are complex and quite stringent in order to obtain low-noise operation. As with any high-speed electronics, noise increases with speed. Typically, pixel read rates of 100–500 kHz are used, although higher read rates can be used (and still preserve low-noise performance) for CCDs with multistage on-chip amplifiers. Some CCDs have multiple output amplifiers that increase pixel throughput by using parallel digitization channels. The entire CCD can also be read at reduced resolution by analogue summation of adjacent rows and/or columns on the chip (binning). This has the added benefit of increasing the signal-to-noise ratio for signals with low spatial frequency since there are fewer digitizations. Binning is highly recommended whenever the reduced resolution can be tolerated.

The time resolution of the detector can be further increased if the CCD array is used as frame storage. In this case, a portion of the imaging area is masked to X-rays, making it available for storage. The exposed area can be shifted rapidly into the masked area and a second exposure begun. Storage for five to ten subframes can easily be configured before readout is necessary. The time resolution is ultimately limited by the phosphor decay time and the time needed to shift the image. Although most

 

CCDs are capable of being operated in very flexible ways, flexible CCD controllers are expensive. The consequence is that few commercial CCD X-ray detectors permit use of all the available options.

The detector itself is contained in a cryostat with the low-noise parts of the controller nearby, either in a separate box connected by a short cable or mounted inside the cryostat itself. A longer cable carries the time-multiplexed digitized data to the computer. High-speed serial data technologies are under investigation to simplify this connection and will become imperative for the much larger format detectors that are being developed.

Several installations have constructed a safety shield in front of the detector that opens only when data are being collected. This device helps to protect the delicate front surface of the detector and is highly recommended.

*Data acquisition software.* There is a wide spectrum of computer configurations surrounding CCD detectors. The major tasks to be performed are operating the detector, controlling the beamline, storing raw data, correcting images and analysing diffraction patterns. In home laboratories, where exposure times are relatively long, a single PC typically handles these tasks. In another arrangement, the detector controller is really an embedded system, mostly unseen by the operator, making the detector a remote image server. The raw data or corrected images come to the user's workstation where subsequent analysis is performed. This circumvents the problem that the detector computer may be running a different operating system from the workstation. At storage-ring sources, where the data volume is very large, the detector is almost always configured as a remote image server; the user's workstation does not even need to be nearby. Clusters of remote computers that can perform tasks in parallel become attractive for streamlined data collection, correction and analysis from large data sets. Remote analysis over the internet is being explored by several storage-ring facilities.

Control software should be easy to use, but flexible and extensible. It should be easy to set up experiments and sequence the individual steps in an experiment: exposure, readout, correction, storage and crystal movement, and wavelength change for MAD experiments. Extensible software would permit a user-written macro to be run at each step in place of the detector primitive that is provided. For instance, if it were desired to collect two images at different exposure times for each position of the crystal, extensible software would make it easier to set up the experiment. Finally, the software should permit access to all of the readout modes of the detector. For instance, a detector may be capable of rapidly scanning a small region of interest for alignment purposes, or it may be capable of streak-mode operation for certain types of time-resolved experiments. Available CCD detector software for macromolecular applications has room for much improvement. Hopefully, software will continue to undergo rapid development. Standardization is especially needed.

### 7.2.5. Applications to macromolecular crystallography

*Storage rings.* CCD detectors have gained widespread acceptance for macromolecular crystallography at storage-ring sources, in part because of the high-quality data they give, but more for their speed, convenience and efficiency. Accurate data to high resolution are especially important for MAD phasing, and CCD detectors excel in this application. In the past with film, or even storage phosphors, teams of perhaps ten people were required to perform a synchrotron experiment; today, a single person per shift can perform an experiment. With increasing beam flux, improved X-ray optics and faster CCDs, it is often possible to collect full data sets in little more than an hour. Anticipated improvements in speed for CCD detectors should soon make it feasible to collect fine-sliced rotation data routinely; these data are expected to yield better structure solutions.

*Home laboratories.* Acceptance of CCD detectors for macromolecular crystallography at home laboratories has been slower, in part because there is not such a premium on speed, and in part because of cost. Diffracted spot sizes are larger than at synchrotrons, so highly accurate data should be obtainable. Fully automatic storage phosphor systems work quite well with conventional sources and at this time are lower in cost than large CCD detectors. However, they have a minimum cycle time, caused by the mechanics of the readout scheme, and the required exposure for a strongly diffracting crystal can best this time by a wide margin. Thus, for strongly diffracting specimens, CCD detectors can be significantly more efficient.

### 7.2.6. Future of CCD detectors

The basic principles of CCD detector technology are now well developed, but various incremental improvements have already been demonstrated and may be expected in commercial detectors. These include larger detector areas, faster read times (owing to both faster electronics and multiamplifier CCDs), more flexible control electronics, better optimized phosphors and calibrations, and, especially, better software. Lower-cost CCD detectors would certainly be welcome. It is easily predicted that the application of CCD detectors will continue to increase rapidly for at least several more years until displaced by even better technologies, such as pixel array detectors (see Section 7.1.4 in Chapter 7.1).

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