SAXS Instrumentation for Synchrotron Radiation then and now

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Abstract. A brief overview is given of the development of instruments and methods for synchrotron radiation small angle scattering and diffraction on biological systems and synthetic polymers. It is shown that many of the developments were largely accidental and although there were a number of innovations, in most cases other fields provided the sources of novelty.

1. The road to the tipping point

The present article aims at giving an – inevitably biased - overview of the development of instruments for small angle X-ray scattering (SAXS) and diffraction (SAXD), in particular for applications in biology and synthetic polymers with an emphasis on time resolved measurements. It does not cover important areas where I have no experience like inorganic applications, anomalous scattering, grazing incidence scattering or coherent applications. Since many things happened in parallel the story is not linear and frequent backtracking is unavoidable.

As noted by Patricia Fara in her recent book on the history of science, during the 20th century, (big) science was driven by the 5M (military, money, manpower, machines, media) [1]. This is perhaps not surprising as the Greek philosopher Heraclitus (600BC) had noted more generally that war is the father of all things and somewhat later Thucydid (400BC) had diagnosed very human characteristics, honour, fear and interest, as the causes of war. Is this really what drives our activity?

The nearly simultaneous development of synchrotron radiation in Europe, the USA and the Soviet Union (for a short history see http://xdb.lbl.gov/xdb.pdf) apparently – but only apparently - followed the 5M pattern. The first synchrotron was built in 1946 by a group of the British Admiralty [2] and the second one at the General Electric labs, where work on betatrons as potential X-ray sources had been going on for some years (reviewed in [3, 4]). Both machines were intended to produce X-rays by sending the accelerated electrons to a target like in conventional sources. Although early synchrotrons were built from surplus radar sets and capacitors the aim was actually to develop non-weapons facilities after world war II [5]. Synchrotron radiation was only observed later and its properties as light source were only fully realized in the 1960s (see [4]). Further accelerator developments took place in high energy physics (HEP) laboratories, among others at CERN. The change of mood and funding patterns in those years is best illustrated by the fact that the decision to join CERN by the British government, for example, was based on the assumption that no work of military importance would be done there [6]. With insertion devices there is a slightly different story. The first undulator built in 1953 [7], and the first wigglers used as radiation sources around 1980 were based on electromagnets and soon after on strong permanent magnets, which had become available in the early 1970s, and on superconducting devices [8, 9]. Wigglers and undulators thus existed well before funds
for large devices like those used in free electron lasers later started to flow in the frame of the Strategic Defence Initiative (1983-1992) [10]. SSRL’s first wiggler has now been put to the ultimate peaceful use: it decorates the garden at the SLAC National Accelerator Laboratory.

High energy physicists like to point out that synchrotron radiation was a by-product of their experiments and although this is largely true, it is perhaps more accurate to say that storage rings are the descendents of (commercially) failed X-ray sources.

The development of detectors follows a pattern similar to that for the sources. Multiwire proportional detectors with wires connected in parallel and a readout based on valves had already been used as particle detectors in the Manhattan project (see e.g [11]) and delay lines had been developed for early radar and computer applications [5]. These developments were, of course, only described in the late 1940s but were a source of inspiration for high energy physicists trying to replace bubble chambers and photographic methods. After spark chambers, which had very low count rates, various forms of multiwire chamber readouts, including some involving delay lines, were proposed in the 1960s. Electromagnetic delay lines, which were capacitively coupled to the wires, were introduced by V. Perez-Mendez and his colleagues at Berkeley [12]. Two events which had an influence on detectors occurred in 1968 – but remember that events mark the end of a process, not its beginning: G. Charpak and coworkers using newly available solid state amplifiers developed the readout of individual wires [13], which was very successful in high energy physics and for a while also in protein crystallography, whereas C. Borkowski and M. Kopp developed the RC delay line readout for various types of detectors [14]. The propagation of signals along a delay line (i.e. Kelvin’s 1855 model and Heaviside’s modern form of the telegrapher’s equation), the electrostatic field around a wire or a grid and the properties of RC and LC delay lines (ladder networks) were all standard textbook knowledge at that time [15]. It was essentially progress in electronics, made for entirely different purposes, which enabled an accurate readout of the position of the events. This led to the success of multiwire chambers in HEP and in X-ray detection. The mere existence of such devices was, however, not sufficient, they had to be brought in a new context. For SAXS this occurred a few years later when the experiments on lipids made in V. Luzzatti’s laboratory with an RC delay line detector built by A. Gabriel [16], following a suggestion of M. Chabre, attracted the attention of biophysicists to these devices. Due to this transfer delay, the first experiments with SR were still done with film, but as from the mid-1970s they were made with gas detectors (see e.g. [17]). What made delay line detectors a success for SAXS with synchrotron radiation was the introduction of LC readout with inductances directly connected to the cathode strips by A. Gabriel [18]. The replacement of the resistive wire of the RC detectors by metal wires gave the new detectors a much higher radiation resistance (For an introduction to these detectors see [19]).

The proceedings of the 1977 synchrotron radiation instrumentation conference in Orsay [9] and of the 1980 conference on X-ray detectors for synchrotron radiation in Hamburg [20] give a good overview of the detector work going on at that time at the different facilities worldwide. What is striking with hindsight is that there was only a brief mention of the potential of CCD detectors and that imaging plates and pixel detectors, the disruptive innovations of the next decade, do not even appear. It is also useful to realize, when reading such documents, that many more devices got proposed, or even built, than were actually used afterwards for any meaningful measurements.

Efforts were also underway in the late 1970’s to develop integrating detectors. These were based on vidicons, and although they were useful for strong scatterers like muscle or polymers [21, 22], their high background made them unsuitable for weak scatterers. Fortunately, the development of gas detectors survived a bout of exuberant but fruitless enthusiasm for TV-based detectors at the IPPC (Instrumentation policy planning committee) and the instrumentation division of the European Molecular Biology Laboratory (EMBL) in Heidelberg.

Apart from a source and a detector a SAXS instrument is conceptually very simple as it consists of some optics, slits and vacuum pipes. These all existed and the instruments at synchrotron radiation sources, not unexpectedly, naturally evolved from instruments used on conventional sources. The history of some of the early devices and their designs have been recently described [23-25].
The story is thus very complicated and essentially illustrates that scientists quite flexibly and, forced by circumstances, sometimes somewhat deviously tap the flows of money in society. No wonder thus that even historians may get confused about the way things work. Sociologists [26] and evolutionists [27] therefore often prefer diffusion models to explain how effectively uncorrelated events are associated at another level of complexity with apparently ordered patterns in a system. Sociologists also distinguish between innovation (i.e. the process by which a new idea is discovered or created) and invention (i.e. an idea, practice, or object that is perceived as new by an individual or other unit of adoption, regardless of its objective novelty). Diffusion of ideas and practices depends on the environment in which it takes place and because of the majority’s aversion towards novelty, resistance or friction is highest just before things start moving. Diffusion models of successful projects lead to sigmoid growth curves as illustrated in Figure 1. The two most important points in this curve are the tipping point, where the process of growth or acceptance becomes self-sustained, and the point of diminishing returns. The best time to move on for a scientist is somewhere between these two points since as Rutherford observed “when the man in the street starts believing it, the man in the lab knows that it is finished”. In other words, when the hill is taken, the commandos are replaced by the infantry. Of course, most projects are unsuccessful and peter out even before they reach the tipping point. This well-known Christmas turkey effect [28] is also illustrated in Figure 1. For how long a given type of instrument (or species) survives depends on so many largely uncorrelated factors that selection can be considered a random process, The only constant is the need to work. This view also better reflects my personal experience and I have come to believe that at the more practical level science is driven by the five F’s: Funds, Freedom (there is none without funds), Fun (there is none without freedom), Fortune and Fame. For completion, at least in the case of experimenters, one should perhaps add one more F on which one rarely insists in more romantic presentations. As pointed out by J. Gleick: “The experimenter’s lovers sweat, complain, and fart” [30].

I joined the EMBL outstation on the site of the Deutsches Elektronen Synchrotron (DESY) in Hamburg in 1977, soon after H. Stuhrmann, with whom I had collaborated for several years on neutron small angle scattering, had become the head of outstation. Part of the attraction was the stated purpose of the EMBL, which was (and still is!) to “promote cooperation among European States in fundamental research, in the development of advanced instrumentation …..in molecular biology…”.

Clearly, by then most of the equipment and concepts to do small angle diffraction and scattering with synchrotron radiation had already been available in some form or other in different places. Developments in SAXS/SAXD were also under way at LURE (Orsay) [31], the Stanford synchrotron radiation laboratory (SSRL) [32], Novosibirsk [33, 34], Daresbury, where H. Huxley had installed a camera [35], and among other SAXS devices, a white beam camera using an energy dispersive
detector had been built [36], and in Japan where soft X-ray SAXS had been done [37]. Of course, as a newcomer in the field I – perhaps fortunately - did not yet know this.

The closure of NINA at Daresbury in 1977 not only brought J. Bordas, now director of the ALBA synchrotron source in Barcelona, and somewhat later P. Clout, now president of Vista Control Systems in Los Alamos, who had, respectively, experience in synchrotron radiation instrumentation and computer control and data acquisition, to Hamburg, but also a steady stream of visitors and some equipment from Britain. The storage ring DORIS at DESY was starting to work for colliding beam experiments and a tunable wavelength instrument for fibre diffraction (X11) designed by G. Rosenbaum already existed in the experimental area of the EMBL in Bunker IV, but it had not been foreseen to have other instruments in this hall or to operate a multipurpose facility. Installation of additional instruments and shielding in the hall thus had to be planned so that X11 could remain in place [38] as illustrated in Figure 2. To complicate matters, and give the engineer, the late H. Ludwig, quite a few headaches, all of this also required the a posteriori, installation of an overhead crane. As the HEP program at DORIS was somewhat unpredictable, one of the main practical problems was that as the energy increased from 3 to 5.6 GeV and the current in the ring from 10 to over 100 mA, the shielding, which consisted of large barite concrete blocks, had to be regularly modified and reinforced to cope with the higher radiation levels.

![Figure 2. Layout of the instruments in Bunker IV at the EMBL outstation in Hamburg at the end of the 1970s. X15: anomalous scattering camera. S11: EXAFS spectrometer, X11: tunable wavelength mirror-monochromator camera. X13: fixed wavelength mirror-monochromator camera- M1 vacuum box: M2 vacuum mirror - monochromator box for X11 and X13](image)

For a while, the tunnel on the ground floor was shared between the EXAFS spectrometer and H. Huxley’s camera which had been brought from Daresbury. Later this camera was replaced by the dance floor instrument of the Risoe group, who could test their instruments while HASYLAB V was under construction. On the roof of the tunnel there was the anomalous scattering camera X15 [39] and a Mössbauer experiment.

The experimental area of X13, a fixed wavelength double focusing mirror monochromator camera [40], was only accessible over the tunnel, but this had the advantage that it was a rather quiet place. At the front end the mirrors and monochromator were located in the original X11 mirror box (the second one in Figure 2) which was a low budget design. The optical system was based on geometrical considerations as ray tracing programs were not available. Mirrors were not readily available and for the first set, made by Astron, a subsidiary of Ferranti, the special tools required to make them also had to be paid for. These two companies no longer exist and subsequent mirrors were made by Zeiss. X13 had a simpler design than X11. The DC motors were controlled with a multiplexer rather than with individual potentiometers for each motor as in the original design of X11. Note that the
monochromators were located after the mirror which consisted of eight flat quartz segments in a bicycle chain arrangement. No attempt was made at bending the segments. The initial X11 design used a four point bender for the monochromator which gave some problems and could only be used with short crystals. The main source of progress is often imitation with modification. Hence, as the classical mechanical solution for bending implemented in the triangular monochromator at LURE gave satisfactory results [41] we also used it, but replaced the micrometer screw of the bender by an eccentric shaft to avoid breaking the rather expensive 18 cm long asymmetrically cut triangular Germanium monochromator. A similar monochromator was later also installed at the Photon Factory [42]. The plexiglass tubes filled with helium were soon replaced by metal vacuum tubes with mica front windows instead of Kapton, which much improved the background. The advantage of instruments with sideways deflection rapidly became clear. Since they were outside the cone of the radiation shower which might have occurred in case of electron beam loss in the hall, with an absorber in the beam all adjustments in the hutch could be made manually. The fact that this is no longer allowed only proves that safety regulations are not based on accident statistics.

X-ray monochromators have a narrow bandpass, and especially those who had done neutron scattering dreamed of larger bandpasses. All sorts of techniques were tried out ranging from ion implantation to soap films (for a review of early proposals see [43]). It took a while for some to understand that although bent monochromators gave a wavelength spread this did not result from a higher bandpass but from the fact that each volume element reflected a slightly different wavelength with the same narrow bandpass as the flat crystal. There was also a proposal for a white beam camera at the EMBL, which was, however, not implemented [44]. Pink beam cameras were only implemented much later at the APS (Advanced Photon Source, Argonne) and the ESRF (European Synchrotron Radiation Facility, Grenoble), where they are used for ultrafast time resolved measurements. There are hitherto too few applications [45, 46] to judge how generally useful such devices will be for work on biological systems.

Multilayer monochromators, with a much wider bandpass, had been patented in 1974 by D. Caspar and B. Schoenborn, based on their experiments on nerve fibers [47] (but see earlier references in [48]). It was, however, only in 1998 that H. Tsuruta and his colleagues at the SSRL installed a routinely usable multilayer monochromator for SAXS [49].

The main thing that remained to be done after the successful feasibility and demonstration studies in the late 1970s was to show that SAXS with synchrotron radiation could really contribute something useful to a number of scientific questions of the time. The crucial factor in making use of the available intensity was to increase the readout rate of the data acquisition system. With the first system, based on a time to pulse height converter (TPHC) and a programmable multichannel analyzer (Intertechnique IN90), the total count rate was limited to about 10 kHz. The data were stored on tape and had to be transferred to a PDP 11/45 (248kB) computer for data analysis. The IN90 was, however, sufficient to do experiments on unstriated molluscan muscle which required a time resolution of 0.5 s and where sufficient statistics could be accumulated from about ten contractions. The results of these experiments were, however, only published much later [50]. To speed up the appraisal and interpretation of what was for the time a rather large amount of data some software was also needed as none of the modern packages existed and most users were not as familiar with computers as later generations. This was the origin of the OTOKO program [51, 52], which was quite popular for a while, and still exists in a Windows version.

To make best use of the parasitic time which corresponded to single bunch operation of the storage ring J. Hendrix and the late H. Fuerst built a drift chamber [53] which was, however, never put into operation because soon after the high energy physicists settled for multibunch operation, which rendered the device unusable. This was obviously an example of an interesting idea, rendered obsolete by an unpredictable change of circumstances.

A new data acquisition system based on CAMAC, a standard developed in the early 1970s, soon replaced the IN90. The CAMAC serial highway [54] connected to the PDP 11/45 served three experiments. The data acquisition system consisted of commercial modules for the amplifiers, the
TPHC, the analog to digital converter (ADC) and the 64K histogramming memory. The decisive jump in performance was made by replacing the TPHC/ADC by a time to digital converter (TDC) which directly digitized the time differences between the arrival of the start and stop pulses from the delay line in the detector. The first TDC was a module designed at CERN [55] which had been adapted by C. Boulin to the readout of delay line detectors [56]. The timing of the experiments was controlled by a time frame generator (TFG) and ancillary data like temperature, force etc. were recorded as analog signals, digitized with voltage to frequency converters and stored in a calibration channel unit (CCU).

The first prototypes of these modules were built by E. Dorrington in Hamburg [57] and a second version, which could also be distributed, was designed by C. Boulin at the EMBL-Heidelberg [58]. The system was programmed in CATY [59], a BASIC-like language for CAMAC control and data acquisition by F. Golding and D. Dainton.

The CAMAC system was used for more than 20 years with various upgrades. The local intelligence provided initially by the LSI 11 (32K and later 64K), later by more powerful auxiliary controllers (CES, Starburst) was replaced by an IBM PC (AT) in 1988. This was not necessarily a popular development and even the EMBL council briefly took interest. As PCs became more powerful the serial highway could be replaced by other connections and the data acquisition programs were rewritten in C++ by F. Golding. These developments, which also made it possible to improve display and data appraisal were also passed on to other experiments at the EMBL and to other labs using this system.

When the CAMAC system became difficult to maintain at the turn of the century it was replaced by National Instruments cards [60] and the N110 TDC developed at the ESRF [61]. Although this system is still in use in a number of places, its maximum count rate, which is limited by the data transfer to the PC, and its flexibility in terms of timing and control of the experiment are lower than that of the CAMAC system, a clear case of regression.

As soon as X13 was equipped with the new acquisition system the stage was set to make the first millisecond time resolved measurements on muscle, which had been a Holy Grail for so many years, possible [21]. In London, the Times even reported the event (March 14, 1980). These and similar experiments have been extensively reviewed [23, 35]. The data acquisition system was very flexible and could be used not only with the delay line detectors but also with the parallel readout detector built by J. Hendrix [62]. This detector had a lower spatial resolution (1 mm) than the delay line detectors (0.2 mm) but could cope with very high count rates which made sub-ms time resolutions possible with muscle [63] or lipids [64]. Its lower spatial resolution was not necessarily a handicap because methods were available to increase the resolution of a scattering pattern by small horizontal displacements of the detector [65]. Unfortunately, with time this device could no longer be maintained.

Experiments on frog muscle necessitated the accumulation of the results of many contractions and thus required long periods of stable beam, which were only available during a limited number of main user shifts. The parasitic time, which was available during colliding beam experiments, was very unpredictable, which made most biological experiments impossible. Nevertheless it seemed a waste of our most important asset not to use it. A very effective use for it was found through collaboration with the group of the late G. Zachmann at the University of Hamburg, who worked on synthetic polymers. With these systems useful time resolved experiments could usually be done in single shots [66, 67] and unlike biological samples, polymers are stable and usually available in large quantities. In the following years a number of people, among them C. Riekel, R. Gehrke, P. Boesecke and S. Seifert, who would later contribute to the development of SAXS at DESY, the ESRF and the APS acquired experience in this group.

Not everything had been perfect with X13. The effect of heat load and radiation damage on various components showed up when the energy and current of DORIS were increased. The mirrors, which were fortunately not coated, were exposed to white radiation in a poor vacuum which resulted in cracks. There were also deposits of cracked oil on their surface which degraded their performance and they regularly had to be dipped in aqua regia to clean them. The insulation of electric cables was damaged and finally even the lead slits melted (see Figure 3). The heatload was in some instances also
a problem in the ring and one day we chased the beam for hours until one had to admit that there was an obstruction in the beampath inside the ring. Indeed a piece of stainless steel had melted! This all resulted in quite a lot of maintenance and a steep learning curve.

Figure 3. Left: Lead slits exposed to white radiation in vacuum melted away. Removal of heat with copper straps in contact with the mirror box cured the problem. Right: Mirrors exposed to white radiation in poor vacuum rapidly developed cracks and were coated with cracked oil deposits.

Fortunately, we soon could – or rather had to - build a new instrument (X33) in HASYLAB V because dedicated beamtime was only going to be available there. One great advantage of the new construction was that Al/Pb sandwich plates replaced concrete blocks for shielding. Given the previous experience, when X33 was built the relative position of the mirror and monochromator were inverted. Stepping motors were used which facilitated computer control and the mirror boxes and other vacuum components were designed with more care. Airpaths were reduced to a minimum while retaining the flexibility required to handle very different sample environments. Some things were somewhat more difficult than now. As no stepping motors for vacuum nor affordable rotary feedthroughs were available, for example, the motors had to be disassembled to replace all lubricants and re-magnetized in a dipole magnet that was made available for this purpose by DESY. We could also not afford reliable position encoders, which would in any case not have been very useful because of regular changes in the position of the beam when one switched from HEP operation to dedicated beam.

The real difficulties were, however, of a political or managerial nature with the delegations of some countries very directly interfering in purchasing procedures. Moreover, due to staffing limitations at the outpostation, imposed as a condition for the participation of Italy to the EMBL, some of the designs had to be made in the instrumentation division in Heidelberg, which did not simplify matters. Despite their enormous good will those involved never really got used to the deadlines and strict schedules in Hamburg, but they still remember this as their most interesting project (H. Wittman, private communication, 2006). As illustrated in Figure 4, X33 was a sturdy instrument which served in its original version for over twenty years.

Besides muscle there were several other scientific projects mostly with external collaborations, which dealt with the assembly of fibers (microtubules, actin, collagen) and in-house research on the superstructure of chromatin with L. Perez-Grau. Promising results had also been obtained with a USAXS camera. The use of magnetic orientation had been tested by A. Fowler at the EMBL in Heidelberg, but the purchase of a strong in-line magnet was turned down. Such experiments were later done on tubulin in Daresbury [68]. Recent experiments on actin indicate that strong magnetic fields give a better orientation than previous methods [69]. Right- or left-circular orientation of tobacco mosaic virus was also observed in time resolved measurements using periodic magnetic fields and
This all suggests that a somewhat more systematic investigation of these methods may be worthwhile.

The first T-jump used in the assembly studies was an extremely simple device which allowed jumps up or down in the appropriate temperature range – usually 4 to 40°C [71]. It used four water baths [very hot, hot, cold, very cold] and a switching system based in the final version on washing machine valves. By appropriately adjusting the switching points it was possible to avoid over- or undershoots. A device based on Peltier elements with rapid current reversal, which would nowadays be the preferred solution, was used at LURE for studying phase transitions in lipids [72].

The development of stopped flow techniques illustrates how imitation with improvements rapidly led to better devices and how technology diffused between facilities. On X13 the size of the beam at the sample was too large to make use of commercial stopped flow devices or those adapted for work with lasers and the first attempts therefore did not lead to anything useful. The first useful experiments were done with the group of M. Moody from the EMBL Heidelberg using a purpose-built device [73, 74]. The postdoc doing the hard work was P. Vachette. Some of these experiments used a circular delay line detector, the predecessor of the quadrant detectors. The experiments on assembly of tubulin and other proteins were done with a slower mixer based on motor driven syringes [71]. A new mixing device was designed a few years later by the late C. Berthet at the EMBL-Grenoble [75] for studies on the assembly of viral capsids [76]. After some very preliminary experiments [77] in Hamburg H. Kihara went back to Japan and developed a system [78] which was first used at the Photon Factory to study protein folding and the allosteric transition of aspartate transcarbamoylase (ATC-ase) [79] and later at the SSRL for, among others, iconic studies on virus assembly (see e.g. [80]). At third generation sources commercial devices made for optical measurements can be used without difficulty. We therefore also discontinued this type of work when beamlines like ID02 at the ESRF became...
available. Very fast mixing (<150 µs) using microfluidic mixing devices has been achieved on third generation sources [45, 81]. It is, however, unclear from these applications whether such devices are generally usable.

The end of the beginning
With all the ongoing activity at the EMBL in the early 1980s it thus looked for a brief while as if further progress might be made rather rapidly. All this changed abruptly and following a number of reorganisations the EMBL decided – like everybody else- that it would put the emphasis on protein crystallography. This also meant that, perhaps more than elsewhere, support for further development in SAXS instrumentation was halted and the outstation was reorganized into independent groups. Many years later I found a quotation which George Hampton, a former administrative director of CERN, circulated to his colleagues after a discussion of a reorganisation in that institution (CERN Courier, May 2004, p4): "It seemed that every time we were beginning to form up into teams, we would be disbanded. I was to learn later in life that we tend to meet any new situation by reorganizing; and a wonderful method it can be for creating the illusion of progress while producing confusion, inefficiency and demoralization. Petronius Arbiter 57 AD.” I did not check the authenticity of the quotation but it certainly very well describes what happened at regular intervals at the EMBL outstation in subsequent years.

H. Stuhrmann went to the GKSS (Geesthacht) where he pursued his work on resonant and soft X-ray scattering in HASYLAB. P. Laggner went back to Graz and later built the AustroSAXS beamline at ELETTRA [82] and J. Bordas returned to the SRS at Daresbury to set up the Biology Support Laboratory (BSL) [83]. The rivalry between the EMBL and the SRS, which some in the media would have liked to see [83], never occurred – one should not always believe the media - and good collaborations including transfer of equipment and software and common projects continued until the BSL became fully operational.

In 1984, Zehra Sayers, who had been a regular user for many years, joined my group. Together with an enthusiastic young biochemistry technician, A-M Michon and later P. Brouillon, and at times a postdoc or PhD student we concentrated on biophysical projects. By that time the polymer community worldwide had realized the potential of synchrotron radiation for SAXS and new approaches were rapidly being developed. As an example, the first experiments combining results of differential scanning calorimetry (DSC) and time resolved SAXS at the SSRL [85] and in Hamburg [86], which were going to be followed by many others, were published within months of each other. As intensities increased, the ability to collect short time frames even for projects which did not strictly require time resolution became an important asset in detecting the onset of radiation damage to which nucleic acids are even more sensitive than proteins. Radiation damage of synthetic polymers or even inorganic systems [87], although also often observed, remains much less well documented.

Over the following years, the EMBL detectors and data acquisition systems were made available to LURE, the SRS, SSRL, the X27C beamline at the NSLS and DUBBLE at the ESRF. More recently D2L, the company which A. Gabriel created after retiring from the EMBL, also delivered linear and area detectors to the NSRRC [88] and other facilities. The need to produce more detectors for X-rays and neutrons prompted A. Gabriel and F. Dauvergne in Grenoble to turn to more industrial means of production. Initially, the delay lines had been handmade. As this limited the production, delay lines with surface mounted technology (SMT) were designed as illustrated in Figure 5. Not every novelty is an improvement and although the SMT delay lines can be produced rapidly and very reproducibly, they have significantly higher resistance (8 Ohms) than the hand wound lines (3 Ohms). This was going to take its revenge ten years later when the demand for simultaneous SAXS/WAXS experiments on lipids and polymers arose, as we shall see later.

In the process of our work and that at Daresbury the detectors and data acquisition systems were further developed, especially large quadrant detectors which were more adapted to solution scattering experiments. The first TDC was replaced by the combination of modified Lecroy TDCs and a
purpose-built readout module depending on the type of detector used (linear or area) [89]. When Lecroy proposed to commercialize a data acquisition system for LC delay line detectors in 1982, the UC Berkeley administration informed them that they thought that this might infringe patents taken by V. Perez-Mendez in 1973, which they owned (U.S. patents 3,842,373 and 3,772,521). The matter was not pursued as the coupling methods used in the two types of devices were sufficiently different, but with humour A. Gabriel still regards this as the highest recognition he received during his career. The project also never really took off because in the mid 1980s the firms involved in fast electronics for data acquisition lost interest in such developments as they moved to the much more lucrative telecommunications market.

The area detectors had less impact in time resolved measurement than initially believed. Several factors contributed to this. Rapid accumulation of frames required large histogramming memories, which were not readily available. A proposal in 1982 to have an external company build such a large memory had been rejected partly due to the opposition of the instrumentation groups. We fortunately later had access to such a memory built in Daresbury [83] which allowed us to carry out some projects on Limulus and frog or fish muscle (only the Limulus work could be published [90]). Although some of the data looked quite acceptable, as illustrated in Figure 6, it was claimed that the resolution and efficiency of the detectors were too low. Later improvements in these two parameters, when other types of detectors became available, also did not bring the breakthroughs that some had promised in fibre diffraction, suggesting that the problem was at least partly lying elsewhere.
The detectors were usable even for quite difficult experiments like electric field scattering, where tobacco mosaic virus or DNA could be fully oriented in solution using a short electric pulse [91]. This experiment was only possible because we were lucky enough to be able to borrow a high voltage pulse generator from one of the DESY groups.

When large CAMAC memories [92] based on new and much less expensive technology and new TFG [93] and CCU [94] modules with extended capabilities, based on field programmable gate arrays (FPGA), became available at the EMBL ten years later, they were very useful but the emphasis had shifted to applications which did not require area detectors. The EMBL area detectors were much more extensively used elsewhere, e.g. on the JUSIFA beamline [95], the soft X-ray scattering instrument [96] or BW4 [97] in HASYLAB and later at the DUBBLE beam line at the ESRF [98].

An unexpected event changed the course of things in 1986. Y. Maeda, whose group worked on muscle, brought back from Japan some imaging plates developed by Fujifilm for medical applications, which were in use at the Photon Factory. Initially these plates could only be scanned at a hospital in Hannover, a 2hr car drive from Hamburg. The results convinced J. Hendrix and his group to abandon their work on gas detectors and to build a scanner, which two years later became a very successful device for protein crystallography. This success also marked the end of all detector development in Hamburg.

Imaging plates did not have a significant impact on solution scattering from biological macromolecules. Their slow readout and the difficulty to guarantee full erasure of the previous pattern contributed to an uncertainty on the background to be subtracted, especially in the case of solutions. They were, however, briefly used a few years ago at the EMBL [99] but rapidly replaced by other detectors and are, apparently also still in use for solution scattering on BL08B2 and BL45XU at Spring8. (www.spring8.org.jp).

X13 was rebuilt by G. Rapp during an eighteen months shutdown in 1987-88. This time the segments of the mirror were halved in length and placed on a continuous Aluminium bender with the aim of improving the vertical focusing [100]. The gains compared with the previous system were not spectacular but it was a very good instrument. Soon after, it was decided that DORIS would become a dedicated source, which finally happened in 1993. This also meant that instruments like the new X13, which were now pointing in the wrong direction, had to be dismounted, mothballed for a year, and turned around following a period of extensive remodelling of the buildings. By that time several good instruments had been built at different facilities, as illustrated by the fact that whereas in 1988 about ten SAXS instruments were operational worldwide [101], ten years later the number was already three times larger [102] and it continues to grow (see e.g. [103, 104]). It is therefore not possible in a limited space to give a fair account of all contributions and I shall therefore concentrate on the ones I followed most closely.
A lot of good work was done with the new X13 including some on muscle, lipids and bacteriorhodopsin as well as some of the first SAXS pressure experiments on lipids [105] and solutions. The first pressure experiment on solutions was actually done at SPring8 [106], where the conditions were, of course, much better and in Europe too this type of work soon moved to third generation sources.

Although formally belonging to different groups G. Rapp and I had several productive collaborations and during the time that X13 was unavailable we also shared beamtime on X33.

One of G. Rapp’s strengths was in the construction of UV/visible flash lamps for time resolved studies based on photolysis of caged compounds and laser infrared light sources. Such a flash lamp was used to study the structural changes during the photocycle of bacteriorhodopsin [107] which had previously been detected by neutron scattering on frozen samples [108]. One of his erbium infrared laser was used to follow structural changes upon temperature jumps of 10K in 1-2 ms with sub-ms time resolution in phospholipid phase transitions [64]. Such studies in the non-equilibrium non-linear regime still offer many opportunities, especially in materials science. Previous studies on lipid phase transitions using microwaves had achieved jumps of 30Ks$^{-1}$ [109].

By the mid-1990s research on muscle had migrated to 3rd generation sources and some of us briefly regretted the late night frog legs with garlic or occasional lobster. Measurements on overexpressed proteins have definitely less to offer in this respect! The next reorganisation at the EMBL was, however, around the corner and the new X13 was dismantled again and converted into another protein crystallography instrument. Its crew was dispersed. Later G. Rapp set up a very successful company (www.rapp-opto.com), S. Funari is now responsible for HASYLAB’s most productive SAXS beamline (A2) and M. Rappolt joined the AustroSAXS beamline at ELETTRA.

At about the same time a similar fate struck the X12B SAXS beamline at the NSLS where over the years the groups collaborating with M. Capel had produced many interesting results using gas detectors with delay line readout built by G. Smith [110].

It was also clear by the mid-1990s that more demanding work on synthetic polymers could better be pursued at specialized beamlines such as those at the ESRF or the NSLS, where B. Hsiao, also a frequent visitor in Hamburg, and his colleagues had started a very successful program and several advances in instrumentation were made [111]. New detectors like the cooled CCD combined with an image intensifier developed by Y. Amemiya and his group [112] were also becoming realistic alternatives to proportional area detectors for time resolved measurements, even if they were less straightforward to use and required quite a few corrections [113].

With hindsight some of the early beam lines at the ESRF look somewhat like “missing links” in as much as a double monochromator was followed by a horizontally focusing bent triangular monochromator and gas detectors with delay line readout were used beside imaging plates [114]. In contrast, the new beamlines at 3rd generation sources usually have a tunable double monochromator, sometimes with sagital focussing which deliver much more flux at the sample than those of the previous generation. They were fortunately also built with budgets that one could only have dreamed of even a few years earlier and are equipped with solid state detectors which cost orders of magnitude more than delay line detectors. Recent visits at some of the newer facilities have, however, sometimes reminded me not only of X13 (see Figure 7) but also of R. Feynman’s comparison between the MIT and Princeton cyclotrons [115] The first one was a new, beautifully engineered, machine, the other one was a setup run by scientists, which was so chaotic that it finally burned down, but it had produced lots of interesting results. Fortunately, nothing as drastic happened to X13.
The most complex and expensive instruments are not always the most useful which is also what gives recent instruments on some of the smaller sources [116] a fair chance to compete, especially for static measurements. The best example of this was probably D24 at LURE, which for many years produced very high quality data mainly on protein solutions. The device was very compact. Its optical system was limited to a curved triangular monochromator and it was equipped with a gas detector. D24 was probably the first beamline specialized for solution scattering of biological macromolecules which was equipped with a sample cell in vacuum [117]. New experiments suggest that a further reduction in the background may be possible by working with microdrops [118] or even in the gas phase [119].

In contrast with D24, some of the other early beamlines at a number of facilities have recently received a new lease of life. X33 was upgraded [99], after my departure from the EMBL in 2006, largely automated for solution scattering [120] and equipped with a PILATUS pixel detector [121]. Around the same time, BL4-2 at the SSRL was also upgraded and equipped with an additional USAXS device [122]. High throughput systems aiming at obtaining low resolution models of proteins are also being installed at other facilities [123]. The future will show to what extent this flurry of description will help to understand biological systems.

2. Delay line readout
The reconstruction of DORIS in the early 1990s was accompanied by a long period of beam instability until the ring was switched to positrons. Shutdowns and periods when the beam was unusable were always some of the most productive periods in terms of instrumentation as they gave the opportunity to explore some new ideas.
Figure 8. Top: The avalanches in a gas detector induce two pulses travelling in opposite directions on a delay line with delay $\delta$. The spatial position of a single avalanche (e.g., the starting position of the pair of black runners) is readily obtained from the time difference between the arrivals of the two pulses at the ends of the delay line. The position of simultaneous avalanches cannot be unambiguously determined with such a standard time to digital converter, because pulses from different avalanches are used as start and stop signals. Middle: With space-time-space conversion the circuit is closed with a second delay line of the same total delay ($\delta$). If the clock is started by the prompt anode pulse and a snapshot is taken after a time $\delta$, the pairs of pulses correctly recombine on the lower part of the track. Bottom: In practice, the circuit is implemented by triggering a set of comparators at a time $\delta$ after the arrival of the anode pulse.

During one of these periods A. Gabriel and I visited K. Kuroda at CERN to talk about multianode photomultipliers but came out of there with an idea for a system with two back to back delay lines which could be used for the readout of delay line detectors [124]. Over a period of about ten years this was going to lead step by step to the solution, at least for linear detectors, of a problem which had been considered a major drawback for delay readout i.e. its inability to deal with multiple events as illustrated in Figure 8.

The feasibility was first shown with the help of F. Cipriani [125], who had been hired for the project, but soon after was asked to build a microdiffractometer for protein crystallography. The next step, which involved the production of application specific integrated circuits (ASICs), was only made possible by a collaboration with Smart Silicon Systems in Lausanne. Tests with a prototype data acquisition system based on a PC card [126] proved the good performance of the ASICs which were then used in two NIM data acquisition modules. These devices performed very well and were used for a number of experimental projects (e.g. [127]). They also simplified the read out of multianode detectors, without loss in performance, by connecting groups of eight wires to a short delay line segments connected to one ASIC as illustrated in Figure 9.

A different type of readout was tested with the prototype of a multihit time-stamp TDC, developed for the COMPASS experiment at CERN [128]. The results were very promising as these devices made it possible to detect double events and fluorescence events and, using the signal of the bunch clock, to observe the time structure of the beam [129]. This feature may be useful for measurements on pulsed sources.

The possibility of using gas detectors for measurements where energy resolution matters was also briefly explored. For this, the beam must enter through the side of the detector rather than through the
front and one measures the number of photons absorbed as a function of depth in the detector. This is a topic which may be worth investigating in more detail for special applications (e.g. harmonic detection, or SWAX with two wavelengths) [130]. Some may see these developments as a case of undue persistence but delay lines have had so many applications in data acquisition that it would be astonishing if some of this technology would not also find other applications.

Gas detectors may in some cases still have an advantage over integrating detectors for fast (sub-ms) measurements, especially, if like the RAPID detector [131] or other recent detectors [132], they can cope with high count rates. With these detectors the readout is sufficiently fast to collect n successive frames without significant deadtime. Repeating the sequence m times to achieve statistics uses a total sample volume of $mV$, where $V$ is the volume used for each shot. In contrast, the relatively long readout times of integrating detectors (about 60-200 ms for the FReLoN detector at the ESRF [133] and 2.5s for a full image or a few ms in frameshift mode for the latest MarCCD (SX165) (www.mar-usa.com)) has hitherto imposed to collect frames at each time point and hence uses a volume $mnV$ of sample. In the first case the sample is, of course, irradiated for a time $nt$, whereas in the second case it is only irradiated for a time $t$. The best choice between the two approaches will thus depend on the radiation sensitivity of the sample and on the relative efficiency of the detectors. Time resolutions of the order of 2.5 ms exposure and 2.5 ms readout have recently been achieved in continuous stopped flow experiments with a PILATUS detector [121] at the SSRL (H. Tsuruta, private communication). The readout performance of integrating and pixel area detectors for SAXS could perhaps still be improved by taking into account that the number of photons in a single shot does not require the large number of bits used in present devices.

3. Simultaneous small and wide angle scattering (SAXS/WAXS)

The development of simultaneous SAXS/WAXS or SWAX which was perhaps less accidental than some other projects, clearly illustrates that the most successful ideas in terms of acceptance are not necessarily the cleverest but often the simplest. Around 1990 a number of time resolved projects on lipids and polymers required to measure SAXS and WAXS patterns. Rather than measuring those separately it was obviously more efficient to measure them simultaneously. One of the first projects to use SWAX was that of the late K. Westesen from the institute of pharmaceutical technology in
Braunschweig investigating lipid nanoparticles as potential drug carriers [134]. The project, which yielded interesting physical chemistry beside practical applications, implied making a large number of measurements to obtain e.g. phase diagrams. Sample cells with several compartments were moved in the beam at the end of each measurements and the temperature of the cells was remotely controlled, a very modest first step towards automation. Over the years, many such mechanical and electronic improvements were made by the technical staff of the outstation, and in particular R. Klaering and B. Rohbranh, to meet the requirement of different types of projects. These included various sample cells and holders for ancillary equipment, the use of a photodiode in the beamstop to measure absorption, which was especially useful with polymers samples where the thickness can change (e.g. during heating or upon stretching), mini-shutters to protect samples from unnecessary irradiation, various control modules and other useful gadgets. They were sometimes mentioned in the methods section of some papers but never independently published.

Various approaches to the problem of simultaneous SAXS and WAXS recordings had been proposed in different laboratories around that time (see [101]) but delay line detectors certainly offered by far the least expensive solution [135] and also solved the problem of exact synchronization between the SAXS and WAXS patterns. This was, however, not a novelty as delay line detectors in series had already been used more than ten years earlier for a fluctuation X-ray scattering experiment on frozen particles [136]. To circumvent the problem of the resistance of the new SMT delay lines the signals from the new detectors had to be delayed as illustrated in Figure 10, rather than by simply connecting the detectors in series.

SWAXS became very popular especially among polymer scientists (e.g. [137]), so much so, that under the influence of W. Bras at the SRS a beamline was dedicated to these applications [138]. One of the important results of SWAX was the proof that under appropriate circumstances one can circumvent Babinet’s principle in SAXS and unambiguously decide whether the crystallinity of a polymer is above or below 50% [139].

In the meantime, SAXS/WAXS with two area detectors is available at the ID02 at the ESRF [140] and at the BioCAT beamline at the APS (T. Irving, private communication).

Figure 10. Alternative SAXS/WAXS connection of linear detectors. The signals at the output of the detector preamplifiers are first input to a constant fraction discriminator (not shown). One of the signals from each detector is delayed by a time corresponding to the delay line of the other detector to produce a circuit which is equivalent to two detectors connected in series. This avoids the damping of the signals due to the higher resistance of SMT delay lines (R!) as well as the gap due to impedance mismatch (see [17]) when delay line detectors are simply connected in series with cables.
4. Data analysis

Unforeseen events in the east of Europe at the end of the 1980s, which resulted in the collapse of the Soviet Union and the reunification of Germany, a bit later led to the development of the ATSAS suite of programs [141]. In 1988 I started a collaboration with the group of A. Schellenberger from the University of Halle [142], which was at the time still in the German Democratic Republic. Two years later this had changed and D. Svergun from the Institute of Crystallography from the (by then) Russian Academy of Sciences had joined the group. The projects with the Halle group served as test cases in the further development of shape determination methods using spherical harmonics, which describe models in terms of a few parameters, proposed by Stuhrmann [143]. The huge progress in computers and display facilities made over the previous twenty years certainly also contributed to the success of this project. Starting from there the programs of the ATSAS suite were successively developed. This process will not be described in detail here as D. Svergun will certainly some time in future provide a better historical overview. Spherical harmonics are now only used to speed up the calculations but they provided an indispensable stepping stone towards the current methods. Significant progress was made when Chacon et al. introduced ab initio bead modelling based on a genetic algorithm [144] and this prompted D. Svergun to write the program DAMMIN [145]. Bead modelling had previously been extensively used by several authors but not for ab initio modelling, whereas the simulated annealing techniques [146] used in the ATSAS programs had also been used in previous work on phasing of crystal structures [147]. A survey of the literature suggests that, unlike the early 1970s when H. Stuhrmann first proposed shape determination against strong resistance, times were ripe for such developments, as they took place in different laboratories over a few years (see [148, 149]) (i.e. a sufficient number of people believed that one could restore a three-dimensional model from a one-dimensional scattering curve).

The success of modelling methods (see e.g. [150]) and the ease with which higher resolution data can be collected from protein solutions with appropriate protocols at 3rd generation sources [151] have recently led to interesting empirical [152] and theoretical [153] approaches to the interpretation of high angle scattering using also molecular dynamics calculations with explicit solvent models [154]. The properties of protein solutions can be strongly affected by crowding [155, 156] or cosolutes like urea or trimethylamine-N-oxide (TMAO) [157] and it may be difficult to separate the effects due to changes in solvent structure and in the protein structure. For such problems isotopic substitution neutron scattering methods and the EPSR (Empirical Potential Simulation Refinement) method [158], which also makes extensive use of molecular dynamics calculations, may provide additional information at least on the structure of the solvent. This technique recently gave the explanation for the antagonistic effects of urea and TMAO [159].

The effects of crowding on the properties of biological macromolecules, which is probably one of the most important questions at this stage, could probably usefully be studied by neutron scattering using a deuterated protein in high concentrations of a protonated protein. Alternatively, heavy labels, as used in some recent studies on the structure and dynamics of DNA [160], at the C- and N-terminals of an unstructured protein may be useful to monitor structural changes in a crowded solution by X-rays. The combination of molecular dynamics simulations and high angle X-ray scattering data also plays a major role in the analysis of fast reactions triggered by a laser pulse (see e.g. [161]). It thus seems that this is an area where further progress could be made, especially as scattering patterns contain information about longer range interactions than molecular dynamics can accurately reproduce.

The success of a program suite like ATSAS is certainly also due to the fact that it was made easily available, maintained and improved over the years. This is where a problem may lie in future, since as J. Monnet once said in a different context, “nothing gets done without the individuals, but nothing remains without the institutions”, but where are the institutions where useful documentation about hardware like detectors or software are being conserved and made available to those interested?
Unfortunately, no suite of programs comparable to ATSAS has yet been developed for time resolved measurements on polymers or colloidal systems, although bits and pieces of software exist in many groups. The result is that large amounts of data remain un-interpreted. This situation certainly provides an opportunity waiting to be taken.

5. Questions for the near future

The drive towards high throughput at most facilities has put a strong emphasis on routine static measurements, at the expense of more experimental work and instruments have become more specialized. This will sooner or later raise the question whether the use of synchrotron radiation from high brilliance sources, is the most cost-effective way of performing these measurements, especially as considerable progress has also been made with instruments on conventional sources like the optimized NanoSTAR [162] from Bruker (www.bruker-axs.com), the S3-Micropix system of HECUS (www.hecus.at) or the SAXSess of Anton-Paar (www.anton-paar.com).

For an analytical technique like SAXS to be useful for longer than academic fashions last, it must yield information which has operational value. This is where time resolved measurements during the processing of materials in close to industrial conditions offer many opportunities (see e.g. [163]). High brilliance sources will remain indispensable for microfocus applications [164] and ultrafast kinetics [165] where much progress in instrumentation has recently been made. For these methods to become generally useful ways will have to be found to deal with radiation damage. In the case of solutions of biological macromolecules it may help to move the sample in the beam [166] but it is also increasingly important to check the samples (e.g. by in-line chromatography) as introduced recently on a number of beamlines [167-169]. This may also help separating species which are in slow equilibrium in solution. It is more difficult but also useful to check the samples after irradiation.

For synthetic polymers other means like differential scanning calorimetry must be used to check, before and after exposure to X-rays, whether samples undergoing the same processes in the absence of beam behave identically.

Ultrafast kinetic experiments with X-ray scattering are hitherto usually performed on small molecules where total sample volumes are not limiting (see e.g. [157]). This may not be the case for biological macromolecules, which are also easily damaged by the laser trigger pulses [46].

6. Looking back into the future

Looking back, many things, even the collective fears (nowadays: climate, pandemics, energy…) have changed during the last 30 years. In instrumentation, computers and software, sensors, modularization and miniaturization have simplified many things. In the environment there were some very positive changes, like the opening of borders in and around Europe and much easier travel and communication which facilitate the diffusion of ideas and practices. There were, of course, also less positive developments like the increasing bureaucratization of science and changes in attitudes towards intellectual property in public research. One may regret that, as a consequence, facilities are perhaps less open and prone to share their developments with others than in the past. This slows down imitation with amelioration and hence also progress. Most facilities have also evolved towards a service model, including “Fedex” operation rather than a scientifically much more efficient and personally more satisfying collaborative model, and emphasize metric-driven rather than curiosity-driven research. One can only hope that the driving force for developments in instrumentation will remain curiosity and that the deeper motivations for automation will not become boredom and laziness.

We have had the good fortune at the EMBL outstation in Hamburg to have been a small group of enthusiastic scientists, engineers and technicians with access to one of the best storage rings and to the best detectors at a time when synchrotron radiation was taking off. There were lots of innovations to be made, perhaps because we knew so little. Being embedded in an established large organization like DESY, without being part of it, gave us some freedom, at least for a few years, and the fun we had made up for the relative lack of funds. Nowadays, there are more funds and many opportunities, which
are admittedly somewhat more demanding than in the early days, but unfortunately also less freedom. If any lessons can be drawn from history the recent evolution of some HEP laboratories into photon science laboratories suggests that the best way to prepare the future is to set up some niches where things slightly beyond ones remit, and in which the majority does not yet believe, can be freely tried out. Instrumentation alone will, however, not guarantee success because, ever since Roger Bacon was walking down the streets of Oxford, the main question when building instruments has remained “What is the question?”

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