

IN VIVO XRF SPECTROSCOPY: SUMMARY OF WORKSHOP II

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Introduction:

This is a brief summary of the second workshop on "*In Vivo* XRF Spectroscopy", the first one was held in the 1994 Denver Conference on Applications of X-Ray Analysis [1-11]. Although, *in vivo* XRF spectroscopy is not widely spread it is, nevertheless, an established methodology used in several centers for *in vivo* elemental analysis. It is a particularly difficult type of XRF analysis because: one, no sample preparation is possible and repetitive measurements are limited; two, the matrix is a low *z* material resulting in considerable Compton scattering; and three, the incident photon flux, for inducing the characteristic x-rays, is limited by the radiation dose allowed to a person. These constraints require special considerations in the design and data analysis of *in vivo* XRF systems, which were the objective of this workshop. It is also felt that *in vivo* XRF will benefit greatly from recent technological developments in the fields of x-ray detectors, nuclear electronics and collimating systems.

General Considerations:

The overriding constraint that must be considered, in the design of an *in vivo* XRF systems, is the radiation dose delivered to a person during the measurement. A good guideline to use, for radiation entrance (skin) dose, is about 0.01 Gy (j/kg)[12,13]. The consequences of this, combined with the fact that the human body presents, to the XRF analyzer, a sample that is thick and made of a low *z* material, are a poor signal-to-noise ratio (SNR) and a large background, resulting in poor minimum detection limit. Furthermore, due to the high Compton scattering, the XRF spectra are usually collected under high count rate conditions resulting, inadvertently, in pile-up spectral distortions that need to be corrected for. Thus, two approaches are needed to optimize an XRF system, one is instrumental and two is analytical.

The first consideration when designing an *in vivo* XRF system is to decide whether K x-rays or L x-rays should be used for the measurement. This decision depends on the element in question

and its distribution in the human body. Once this decision has been made, an excitation source that maximizes the signal, i.e., maximizes the photoelectric interaction, while at the same time minimizing the background, is selected. The background can be reduced by moving the characteristic x-ray peaks away from the Compton peak, or by using polarized incident radiation [14]. It is important to point out that low energy x-rays can be polarized to a higher degree more readily than high energy x-rays. This is another consideration that under certain conditions will favor the use of L x-rays for the analysis.

When designing the geometrical configuration of the system two important aspects need to be considered. One, the system has to be compact to maximize the counting efficiency and reduce the source intensity, and two, the set-up has to allow for reproducible patient positioning. In addition, the system has to be properly collimated and shielded to reduce the radiation dose to parts of the body outside the target area. In order to take advantage of polarized radiation the beam paths between the source and the polarizer, the polarizer and the target, and the target and the detector must be mutually orthogonal. Finally, sufficient space between the source and the target for beam modifying devices and collimators has to be provided.

The basic requirements from the detection system are high counting efficiency, high energy resolution and compactness to satisfy space requirements. Depending on the characteristic lines measured, either Si(Li) or pure Ge detectors are used, both of which operate at liquid nitrogen temperature. A new generation of very compact detectors operating at room temperature with acceptable energy resolution are now available. A novel Si drifted detector with exceptional energy resolution of 140 eV at room temperature holds great promise [15]. Recent developments in detectors for XRF are discussed in a subsequent section.

Analytical aspects of the XRF system include: first, intensity (area) determination of the characteristic lines in the measured x-ray spectrum [16]; second, determination of the elemental concentrations from the measured intensities; and third, error analysis. The first step may involve, prior to peak area determination, to be discussed below, corrections for pulse pile-up distortions [17]. The second step requires proper intensity calibration, and the last step involves proper error propagation analysis [18], also to be discussed below. Calibration of the *in vivo* XRF systems requires special consideration because of the usually non-uniform trace element distribution in the human body and high self attenuation of the incident and characteristic radiations. It is very difficult to create proper tissue equivalent phantoms, in this energy range of x-rays; instead, it is more accurate to use amputated human limbs or animals in which samples are subsequently analyzed using conventional destructive methods, as, for example, atomic absorption.

Finally, comprehensive dosimetry, using, for example, thermoluminescence dosimeters (TLD), must be performed in order to get approval for using such system on humans. The dosimetry includes in beam dosimetry and patient survey to estimate total body dose. Typically, the entrance dose at the target area should not exceed 0.01 Gy. However, it may vary depending if these are children, adults or sick patients that are being measured. These type of measurements will require proper Institutional Human Study Committee or FDA approval.

Developments in Detectors for XRF Analysis:

The use of miniaturized XRF instrumentation for in-vivo applications imposes specific requirements on the choice of detector technologies which can be used, and on the design and

construction of the instrumentation. For example, operation of the detector at liquid nitrogen temperature necessitates cryogenic Dewar vessel that complicates the design. Another issue is the bias voltage and current of the detector, which impact on the safety design. Issues related to complexity of the device, ease of use, and options for sterilization between uses are also important considerations impacting the choice of detector technology. Recent advances in detector technologies, which open up new possibilities in *in vivo* applications of XRF, are presented. In particular we discuss the characteristics of HgI₂, CdTe, Si (p-i-n), and SDDs including their basic material properties, suitable detector structures, and their performance.

Detector Technologies:

There has been a continuous effort to develop non-cryogenic energy dispersive compound semiconductor x-ray detectors for XRF applications. With advances in material characteristics and detector design, excellent results have been achieved with HgI₂, CdZnTe, and CdTe (p-i-n) x-ray detectors. Resolution of better than 200 eV FWHM for HgI₂ detectors (at 0° C) [19] and better than 250 eV FWHM for both CdZnTe and CdTe(p-i-n) detectors (at -40° C) [20,21] have been measured at 5.9 keV. The above results were obtained with the use of a miniaturized, low-power thermoelectric cooler and dry nitrogen atmosphere. The active area of these detectors was about 10 mm². With the availability of high quality, high resistivity silicon and better surface passivation techniques, encouraging results have also been obtained recently with Si(p-i-n) detectors. We have obtained energy resolution better than 220 eV FWHM at 5.9 keV with a device operating at about -40° C [21]. The active thickness of the device was about 0.3 mm. Thus the device has limited efficiency (less than 63% absorption) above 13 keV. In addition, the small thickness of the Si(p-i-n) structures limits their active area to only 6-7 mm². Larger active areas would have too high detector capacitance resulting in increased electronic noise. This limitation can be overcome by using a novel structure, namely the silicon drift detector (SDD) structure [22]. This structure has a small charge collection anode and cathodes which are designed to focus the charge (electrons) to the small anode. The device capacitance (anode capacitance) is minimized and is independent of the detector size because the collection anode can be very small. On the other hand, the active area of these detectors can be 1 cm² or larger. In addition, the individual devices can be hexagonal shaped to allow aggregates of the detectors to be constructed with minimal dead space between the elements. Theoretical calculations [22] for the series, parallel and 1/f noise indicates that 8 e- RMS (68 eV FWHM) noise level is achievable at the optimum peaking time of 90 ns. However, to obtain the optimal performance, the first stage FET must be integrated into the device.

SDD structures with 145 eV (FWHM) at 5.9 keV have been exhibited [23] at an operating temperature of -20° C and active area of 3 mm². However, large SDD structures (close to 1 cm²) have been fabricated and tested with an external FET. The devices exhibited excellent charge collection over the whole active area of the detector, and the energy resolution (obtained by scanning a collimated source over the active area) was uniform over the whole active area.

Discussion:

Use of a particular detector technology for a given practical application depends on many factors. The most important factors include: a) energy resolution, b) spectral quality (peak symmetry, tailing, peak-to-background ratio, etc.), c) detection efficiency, d) maximum detector

active area, e) maximum count rate, f) detector and input electronics operating temperature, g) stability and reliability, i) ability to reduce weight, size, and power consumption; and j) cost. The requirements for the design and construction of instrumentation for medical applications impose additional restrictions. These are: a) ease of use (miniaturization), b) maximum solid angle and efficiency to minimize both radiation dose and measurement time, c) low operating bias voltages for safety reasons, and d) capability for sterilization.

At present, all these detectors (HgI_2 , CdTe, CdZnTe, Si(p-i-n and SDD) offer very similar spectral characteristics for the detection of x-rays. Thus a practical selection of a particular detector for a given application is dictated by the stopping power (inverse of the photoelectric linear attenuation coefficient). Si diodes 0.3 mm thick have a good detection efficiency up to 10 keV (90%). However, for higher energies the detection efficiency drops very rapidly making them impractical for the majority of applications above 10 keV. Instead, CdTe and HgI_2 with significantly higher detection efficiency due to their high average atomic numbers are more appropriate at higher energies. CdTe and HgI_2 with similar detection efficiencies, up to 88 keV, differ in their spectral responses due to different x-ray absorption edges of the detector absorbing elements. Above 88 keV, the mercury K-absorption edge, the stopping power of HgI_2 is significantly higher than that of CdTe. Thus, for example, at 140 keV, which corresponds to the gamma-ray energy of the most widely used isotope in nuclear medicine, $^{99\text{m}}\text{Tc}$, an easily attainable thickness of < 3 mm of mercuric iodide ensures efficiency of 90% whereas for CdTe, almost 7 mm thick detectors are needed in order to obtain the same efficiency.

An important feature of the HgI_2 detector is its operation at a temperature of 0° C with excellent spectral results. Cooling below -5° C gives very little benefit since properly fabricated detectors can attain leakage currents of $< 10^{-13}$ A at 0° C. Further cooling only reduces input FET noise and eventually enhances charge collection (through an increase in the mobilities of carriers) that can only be seen with thick detectors. The SDD detectors can be operated between -10° C and -20° C. In the case of CdTe, CdZnTe, and Si(p-i-n) the best results are obtained at -40° C. The primary reason for the lower temperature is to keep the dark leakage current below 10^{-13} A. The difference in operating temperature has a large impact on the design of hand held portable instrumentation. Whereas truly miniature systems are possible using -5° C detector technologies, systems operating at -40° C will be significantly more bulky, primarily due to additional battery requirements. Future improvements will rely on use of more efficient battery technologies and switched temperature regulators.

Another issue of importance for any practical application is the stability and reliability of the detector technology. Silicon technology, of course, has achieved the highest degree of maturity; however, CdTe and HgI_2 technologies have made great advances with improvements in lattice perfection, a decrease in impurities, and better detector surface passivation and encapsulation.

The SDD detectors when completely developed including integrated input FETs offer large active areas $> 1\text{cm}^2$, unparalleled high count rates $> 10^6$ counts per second, due to small electronic noise at short peaking times (0.1 ms), and high energy resolution. The performance of the detectors discussed above is comparable to that of cryogenically cooled Si[Li] or Ge systems without the need for liquid nitrogen. Parallel developments in miniaturization, low-noise and low-power processing electronics allows one to construct very compact instruments for a variety of applications. The reduced weight, power, and size of the spectrometers makes them extremely attractive as portable

x-ray fluorescence instruments for medical research, environmental pollution, geological exploration, marine mineral analysis, archeometry, space exploration, and industrial material quality assurance.

The Library Least-Square Method For XRF Spectrum Analysis:

The aim of X-ray fluorescence (XRF) spectrum analysis is to extract analytically relevant information from measured spectra, for example, identifying elements from peak locations and obtaining elemental amounts from the peak areas. XRF spectrum analysis is not straightforward because the spectral data are contaminated with background noise and interfered with by other signals. If XRF spectrum analysis can be seen as a signal process, the signals are the characteristic X-rays of the objective elements and the noise and interference are (1) background, (2) characteristic X-rays of the non-objective elements, (3) escape peaks, (4) pileup and sum peaks, and other artifacts. In the *in vivo* XRF trace analysis work, background has been a major obstacle to lowering the minimum detection limit. Background of the XRF spectra is mainly due to Compton scattering of the excitation radiation by the sample. The shape of background can be very complex and depends on the shape of the excitation spectrum, the sample composition, and the incomplete charge collection effect within a detector.

Traditional spectrum analysis involves spectrum processing (such as filtering techniques), background estimation (such as peak stripping or function fitting), and then peak area determination. The spectrum peak analysis methods have the disadvantages that: (1) they are not reliable for estimating small peaks on a high background as well as in the proximity of a matrix line, and (2) they are not free of user-adjustable parameters. However, these difficulties can be overcome by the library least-squares (LLS) spectroscopy method. The LLS method has the advantages that (1) it combines spectrum evaluation and quantitative analysis, (2) it uses all available spectral data (including what was background in other treatments), (3) it gives the best attainable accuracy, (4) it automatically provides estimates of the accuracy, and (5) it is capable of separating overlapping peaks.

The LLS method is based on the fundamental assumption that a measured spectrum of a sample can be described as a linear combination of spectra of the pure elements constituting the sample [24]

$$y_i = \sum_{j=1}^m x_j a_{ij} + e_i$$

with y_i the counting rate in channel I of the sample XRF spectrum, a_{ij} the counting rate in channel I of the library spectrum of element j , and e_j the error in channel I , then x_j is the amount of element j in the sample. x_j can be obtained by linear least-squares fitting, minimizing the reduced chi-square value with respect to all the parameters x_j

$$X_v^2 = (1/v) \sum_{j=n_1}^{n_2} e_i^2 / \sigma_i^2$$

where σ_i are the standard deviations of y_i , n_1 and n_2 are the limits of the fitting channels, ν is the number of degrees of freedom given by $n_2 - n_1 - m + 1$. This assumption is valid: (1) generally for the characteristic X rays without apparent matrix effects, but not necessarily for the continuum background, and (2) especially for all spectral components if the library spectra come from a sample which has a composition close enough to the sample being analyzed.

The library spectra may be obtained either by experiments or by Monte Carlo calculations. The measured library spectra include all spectral components that may be complex or difficult to model. A library spectrum must be acquired for each element present in the unknown, which may be difficult or impossible in some cases by experiments. The library and unknown spectra must be acquired under strictly identical spectrometer conditions. The Monte Carlo library spectra are easy and economical to generate. The unique aspect of the Monte Carlo library spectrum method is that all the spectral information (characteristic lines and scattered radiation) is considered in the analysis. The simulations require an accurate Monte Carlo code and spectrometer response function describing the application in detail.

Based on Monte Carlo simulation, the Monte Carlo - Library Least-Squares (MCLLS) analysis approach was developed [25]. In this approach, a spectrum is simulated starting from an initial guess of the composition of an unknown sample. During the simulation one keeps track of the response of each element to construct library spectra. After the simulation these library spectra are used to obtain the elemental amounts by the linear least-squares fitting of the measured spectrum of the unknown sample. If the composition differs significantly from the initial assumed one, the simulation is repeated. In contrast to the normal library least-squares method, this approach has the advantage that the library spectra are simulated for a composition close to the composition of the sample to be analyzed, rather than measured from standards. Like the normal library least-squares method, the MCLLS approach combines spectrum evaluation with quantitative analysis, but it can handle the nonlinear XRF spectrum analysis due to matrix effects. Our study on ^{109}Cd -based KXRF measurement of lead in bone showed that, compared to the peak area method, the relative standard deviation was reduced by a factor of from three to 22 for the bone phantoms with 25-108 ppm lead using the MCLLS method [16].

In summary, the library least-squares method is a powerful XRF spectroscopy analysis tool combining spectrum evaluation and quantification. This method can give the best attainable accuracy since all the spectral information is used.

Error Analysis of *In Vivo* XRF Spectroscopy Including Pulse Pile-Up:

In developing *in vivo* XRF measurement equipment and measuring amounts of certain elements in the human body using already developed measurement equipment, studies of errors inherent to the measurement are required. In the workshop, sources of errors of *in vivo* XRF spectroscopy based on the general peak area approach are described and their characteristics are presented. Approaches to minimize these errors were suggested and discussed with workshop participants in detail.

Essentially, *in vivo* XRF spectroscopy has two sources of errors: one is general to all XRF spectroscopy and the other is specific to the *in vivo* measurement. Errors concerning counting statistics, signal-to-noise ratio, matrix effects and pulse pile up can be categorized as general errors. Errors which come from variations in skin thickness, source-to-sample (or sample-to-detector)

distance, sample movement, sample shape and lead concentration profile in bone are specific to the *in vivo* measurement (in this case the lead in bone measurement).

In general peak area approaches, peak area information is extracted from measured spectra by fitting, and are then used in calculating the amount of the element of interest. Existing commercial programs or PEAKSI developed at NCSU can be used for this job. When a target element exists in the sample in trace amounts, or the peaks of interest are located in a very high background region, or two or more peaks are convolved, great care should be taken in peak analysis. Gaussian peaks should be de-convolved by software and an appropriate background model should be used and its fitted parameters should be checked carefully.

Error which comes from counting statistics is the unavoidable Poisson distributed random error. It can be reduced by adopting high counting rates and long measurement times, both of which are restricted by the nature of the *in vivo* measurement. As absorbed dose in human is controlled strictly, it limits measurement time and source intensity (so does counting rate). Reasonably achievable *in vivo* measurement time would be less than an hour because the usual patient would not be able to sit any longer without significant movement. The highest possible counting rate is also controlled by the pulse pile up phenomenon.

Minimum Detectable Concentration (MDC) is usually determined by the signal-to-noise ratio. In peak area approaches, signal means the net peak area of interest and noise means the background counts in the peak region. To lower MDC, one should reduce the background count where the peak of interest lies. When a measurement system is devised for trace element analysis, measurement geometry and x-ray source selection should be optimized for better signal-to-noise ratio to reduce the MDC. For this kind of optimization, Monte Carlo codes like CEARXRF are very useful.

For trace element analysis usually linearity between intensity (peak area) and amount of trace element is assumed when inter-elemental (or matrix) effects are negligible. But existence of certain elements where x-ray absorption edges are just above the peak energy of interest or characteristic x rays lie just above the x-ray absorption edge of the element of interest can reduce or enhance the peak intensity greatly. The range of this error can be estimated by adopting the Monte Carlo simulation and general peak analysis approach. If considerable error is expected, some ways to correct the matrix effect should be used. Matrix effect correction is well established for infinitely thick samples in certain fixed measurement geometry, but its application to *in vivo* measurement with geometry variation is not an easy job and might require Monte Carlo simulation.

The highest possible radiation detection counting rates are presently controlled by the pulse pile up characteristics of the detection system of interest. While it is possible to reduce pulse pile up with hardware based pulse pile up rejection, one can never completely eliminate pulse pile up by this approach. In addition, the spectrum distortion caused by pulse pile up can be increased by the use of hardware based pulse pile up rejections. Therefore, it is highly desirable to use software based pulse pile up models which can, in principle, correct for any amount of pulse pile up. Pulse pile up modeling based on Monte Carlo simulation was described and its results were presented in comparison with actual measurement.

Errors specific to *in vivo* lead measurement are studied through the CEARXRF Monte Carlo simulation which can more easily separate one factor from all the other factors than actual experiment. Both of the currently available K- and L- XRF systems are simulated. By using different input parameters for skin thickness, source-to-sample distance, bone shape, lead concentration profile

in bone, etc., peak area changes coming from input variations are obtained and analyzed.

The overlying soft tissue is one of the major error factors for both K- and L-XRF systems. Due to the larger attenuation of the 10.5 keV x rays associated with skin, L-XRF analysis is more adversely effected by skin thickness variation than K-XRF when the L and K x-ray intensities are used directly. However in the L-XRF system a simultaneous measurement of two of the L x rays can be used to minimize this effect. For the K-XRF we can use the ration of the K x ray to the source incoherent scattering peak to reduce this effect.

The change in sample-to-detector distance by 5 mm from a reference position results in a 17% intensity change in L-XRF and 19% in K-XRF. But when the ratio of the K x ray to the source incoherent scattering peak is used for the K-XRF response, the change is reduced to 6%. So sample (patient) movement during measurement can give rise to significant overall errors.

As the half-value thickness of lead L x rays in bone is 0.35 mm and that for K x rays is 9 mm it is expected that the L-XRF approach will suffer more severely from non-uniform lead distribution than the K-XRF approach. A study on the effect of non-uniform lead distribution of the L-XRF system demonstrated that over 99% of its measurement is coming from the outer 1 mm of bone in the path of the source beam. Important to the K-XRF technique is that with the strong penetration of source gamma rays and lead K x rays, it effectively measures the average lead concentration over a considerably wider range than the L-XRF technique.

The use of the ratio of the K x ray to the coherently scattered source photon peak provides an excellent technique which renders the peak intensities less sensitive to many crucial factors, most important among them, the thickness of soft tissue, sample-to-detector distance (sample movement) and instrument instability for K-XRF system.

In the workshop, peak intensity changes from changes of bone density, bone dimension and size were also presented and discussed.

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