Physica Medica 49 (2018) 58–76

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Review paper

K-edge subtraction synchrotron X-ray imaging in bio-medical research

W. Thomlinson[a,b,*], H. Elleaume[c], L. Porra[a,d], P. Suortti[a]

[a] Department of Physics, University of Helsinki, Helsinki, Finland
[b] Department of Physics, University of Saskatchewan, Saskatoon, Canada
[c] Université Grenoble Alpes, EA-7442 Rayonnement Synchrotron et Recherche Médicale, F-38058 Grenoble cedex 9, France
[d] Helsinki University Hospital, Helsinki, Finland

ARTICLE INFO

Keywords:
Synchrotron
Bio-medical imaging
K-edge subtraction

ABSTRACT

High contrast in X-ray medical imaging, while maintaining acceptable radiation dose levels to the patient, has long been a goal. One of the most promising methods is that of K-edge subtraction imaging. This technique, first advanced as long ago as 1953 by B. Jacobson, uses the large difference in the absorption coefficient of elements at energies above and below the K-edge. Two images, one taken above the edge and one below the edge, are subtracted leaving, ideally, only the image of the distribution of the target element. This paper reviews the development of the KES techniques and technology as applied to bio-medical imaging from the early low-power tube sources of X-rays to the latest high-power synchrotron sources. Applications to coronary angiography, functional lung imaging and bone growth are highlighted. A vision of possible imaging with new compact sources is presented.

1. Introduction

Conventional clinical X-ray imaging is based on absorption contrast. The contrast arises from variations in the elemental composition and density of the object. There is a striking difference between absorption in bone and absorption in soft tissue, as demonstrated by the sensational images of Mme Bertha Roentgen's hand [1]. In the first months of 1896 X-rays were already used for imaging bone fractures and for locating embedded objects in a body, and even cine-radiography and use of contrast agents were demonstrated (see Dr. MacIntyre's_X-ray_-film.webm). X-ray imaging started a revolution in medical diagnosis. The good contrast for bone is due to calcium and phosphorus, which make the mass attenuation coefficient of bone much larger than that of soft tissue. On the other hand, the elemental composition of soft tissue is rather uniform, and the absorption contrast is weak and largely due to variations in tissue density. The small differences in attenuation are emphasized by modifying the spectrum of the radiation by varying the tube voltage, anode material and filtering. There are also many methods of contrast enhancement in data analysis. However, weak absorption contrast in soft tissue imaging remains a major challenge, and new methods based on phase contrast are being developed.

Subtraction imaging is a generic term of X-ray radiography where an organ is visualized by the distribution of a contrast medium. Ideally, two images are acquired, the images being identical except in places where the beam or beams have traversed volumes containing the contrast medium. In radiography the difference is due to attenuation of X-rays in the contrast medium, and the subtraction image is the image of the contrast medium distribution. The difference may be *temporal* when the reference (mask) image is acquired before introduction of the contrast agent to the organ being imaged. In theory, the subtraction image cancels out the anatomic densities not carrying the contrast agent. In practice, motions due to breathing, pulse, etc. produce a non-uniform residual image, which blurs and shadows the contrast agent image. The motion artifacts can be reduced in sequential imaging when each image is subtracted from the previous one. However, this *differential* image is that of the time derivative of the concentration of the contrast agent. The subtraction images are very different from the radiographs. In *K-edge subtraction* (KES) *imaging*, two images are acquired simultaneously or in rapid succession with X-ray beams of energies that bracket the K-absorption edge of the contrast agent. The motion artifacts are eliminated from the subtraction image, and the contrast due to anatomic details of tissue and bone disappears if the difference in the X-ray beam energies is sufficiently small.

2. Early days of KES imaging

The X-rays from a tube source contain continuum radiation and narrow bands of characteristic radiation. The relative bandwidth $\Delta E/E$ of the characteristic lines is of the order of 10^{-3} and their portion of the total emission of radiation is a few percent. There are several

* Corresponding author at: Physics Department, University of Helsinki, PL 64, FIN-00014 Helsinki, Finland.
E-mail address: william.thomlinson@gmail.com (W. Thomlinson).

https://doi.org/10.1016/j.ejmp.2018.04.389
Received 19 January 2018; Received in revised form 12 April 2018; Accepted 16 April 2018

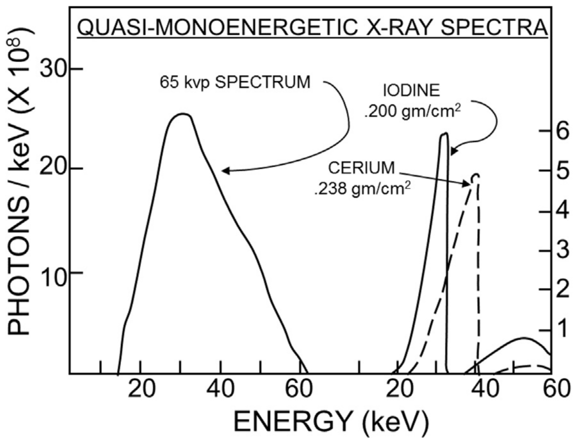

Fig. 1. Computer calculated spectra obtained by filtration of a conventional x-ray source [2]. Copyright 1973, with kind permission from Wolters Kluwer Health. Inc.

possibilities of extracting energy bands that bracket the K-absorption edge of a suitable contrast agent. These include: solutions of iodine (I), gadolinium (Gd) and nanoparticles loaded by heavy elements (Au, Bi, Gd, Fe) for imaging vasculature, stable xenon gas (Xe) for imaging airways and lungs, strontium (Sr) and barium (Ba) compounds for imaging bone or the gastrointestinal tract. By selective *filtering,* energy bands of about 20% relative width can be extracted from the continuum radiation as illustrated in Fig. 1 [2]. Characteristic lines or bands of continuum radiation can be extracted by *Bragg reflection* from single crystals [3,4]. Another possibility is to use secondary radiation from a *fluorescent* source illuminated by X-rays from a rotating anode, high power tube. There are several variants of this method. In the original work by Jacobson [5] a double source of $K(\alpha+\beta)$ radiation from a rotating target coated by iodine (I) and cerium (Ce) compounds was used. The α-lines are separated by 6.1 keV and bracket the iodine K-absorption edge at 33.17 keV. The object is exposed alternatingly to characteristic iodine and cerium radiation, and the detector is read out synchronously. There are a few cases where the α_1 *and* α_2 lines of a single element fluorescent source are on opposite sides of the K-edge of the contrast agent, most notably the lanthanum (La) lines at the iodine K-edge [6], and the cerium lines at the xenon K-edge.

K-edge subtraction imaging of iodine distributions with filtered radiation was studied by Mistretta and coworkers [2,7–10]. The apparatus for two-spectrum absorption edge fluoroscopy is shown in Fig. 2 [7]. The X-rays pass alternately through filters of cerium and iodine which are periodically inserted into the X-ray field. The transmitted X-rays are detected by a conventional image intensifier. It turns out that the necessary large energy separation of the broadband X-ray beams, 7.2 keV in this case, leads to incomplete suppression of bone absorption in the subtraction image. For extraction of the bone signal a third energy band is added to the alternating beams.

The limitations of the broadband KES technique were studied in detail by Rutt et al. [6], who concluded that for imaging at the iodine K-edge the energy separation of the two beams should be 1 keV or less to eliminate the bone signal in the subtraction image. Even the Kα lines of Ba and Ce from a dual source [11] would be too far apart (2.5 keV). However, there is an ideal pair of energies, namely the $K\alpha_1$ and $K\alpha_2$ lines of La at 33.44 keV and at 33.03 keV, respectively, shown in Fig. 3 [6]. Fluorescent radiation from a La target was excited by X-rays from a high-power rotating anode pulsed source. Predominantly $K\alpha_1$ or $K\alpha_2$ beams were obtained by alternating filtering by barium and iodine compounds. The advantage of the fluorescent source is the spectral purity, but the conversion ratio (fluorescence/primary X-rays) is of the order of the solid angle fraction subtended by the fluorescent source for the primary radiation, probably 0.1 to 1%.

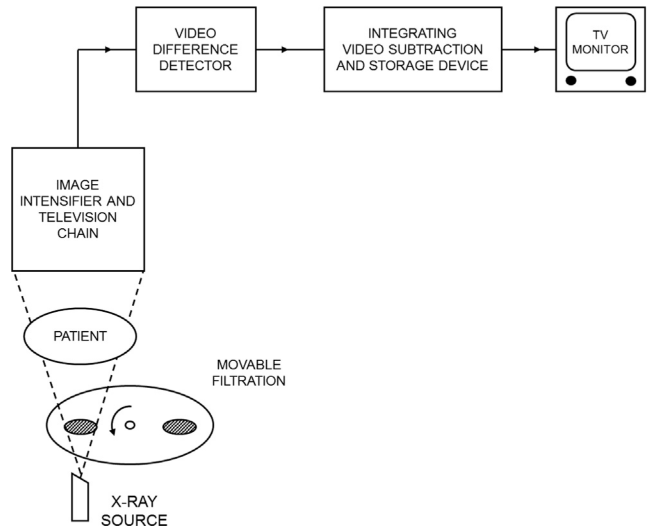

Fig. 2. Apparatus for two-spectrum absorption edge fluoroscopy [7]. Copyright 1976, with kind permission from American Association of Physicists in Medicine.

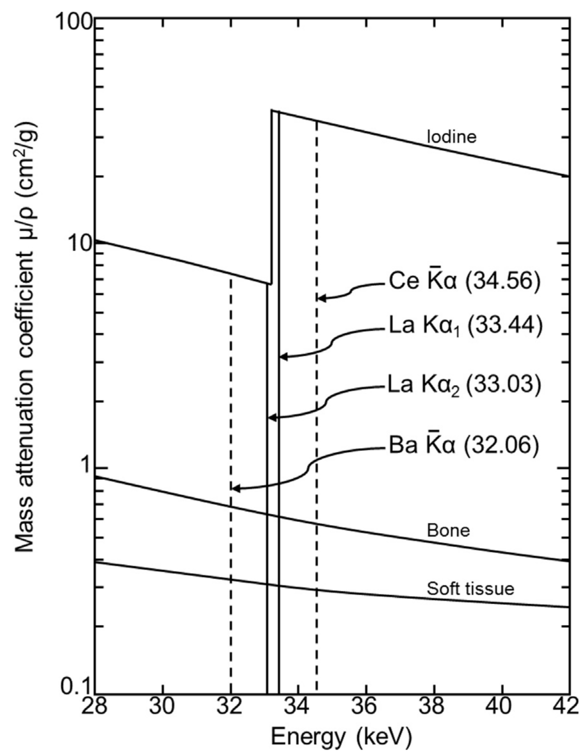

Fig. 3. Mass attenuation coefficients of iodine, bone and soft tissue plotted as a function of energy, showing the energies of barium and cerium K x-rays and lanthanum Kα1 and Kα2 X-rays [6]. Copyright 1983, with kind permission from American Association of Physicists in Medicine.

The early KES imaging studies discussed above are all based on alternate filtering of the X-ray tube radiation or on selection of fluorescent radiation by absorbers. The available X-ray energies are limited and their filtering or selection is incomplete. The image intensifiers have inherent noise, which limits the minimum detectable signal. These limitations may be alleviated by the use of new photon-counting area detectors and new, intense X-ray sources. Future prospects are discussed at the end of this review.