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Published in:
Measurement Science & Technology

DOI:
10.1088/0957-0233/12/11/304

2001

Citation for published version (APA):
Svanberg, S. (2001). Some applications of ultrashort laser pulses in biology and medicine. *Measurement Science & Technology*, *12*(11), 1777-1783. https://doi.org/10.1088/0957-0233/12/11/304

Total number of authors:
1

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2001 Meas. Sci. Technol. 12 1777

(http://iopscience.iop.org/0957-0233/12/11/304)

Institute of Physics Publishing Measurement Science and Technology
Meas. Sci. Technol. **12** (2001) 1777–1783 PII: S0957-0233(01)26180-3

Some applications of ultrashort laser pulses in biology and medicine

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Received 19 June 2001, accepted for publication 18 July 2001
Published 9 October 2001
Online at stacks.iop.org/MST/12/1777

Abstract
Ultrashort laser pulses are finding increasing applications in biology and medicine. Such pulses can be used directly or after non-linear modification. Direct utilization includes propagation studies in scattering media with applications in optical mammography, dosimetry for photodynamic therapy and species concentration assessment. Intense continua of electromagnetic radiation of very brief duration are formed in the interaction of focused ultrashort and intense laser pulses with matter. Two different kinds of experiment using such radiation are described, employing visible radiation and x-rays, respectively. Focusing into water leads to the generation of a light continuum through self-phase modulation. The propagation of the light through tissue was studied, addressing questions related to specific tissue chromophore absorption. When terawatt laser pulses are focused onto a solid target with high nuclear charge Z, intense x-ray radiation of few ps duration and with energies exceeding hundreds of keV is emitted. Biomedical applications of this radiation are described, including differential absorption and gated-viewing imaging.

Keywords: electromagnetic continua, laser spectroscopy, optical mammography, time-resolved laser spectrometer, medical diagnostics, transillumination imaging

1. Introduction

Medical applications of laser radiation started to emerge shortly after the introduction of lasers in 1960. The first applications were of thermal nature, where the beam energy was used to coagulate or evaporate tissue (‘the blood-less knife’). Surgical applications have remained very important, as have ophthalmological aspects, in particular the coagulation of retinal excess blood vessels related to diabetic disease. Laser/tissue interactions of thermal and other natures are discussed in [1]. Photodynamic therapy (PDT) is a non-thermal treatment mode effective in eradicating malignant tumours by a combination of tumour-seeking sensitizer substances and laser light [2–5].

Diagnostic utilization of laser radiation has also emerged. During the last 15 years laser spectroscopic techniques have been developed providing powerful means for non-intrusive medical diagnostics of tissue in real time (see, e.g., [6] and [7]). The field includes the early diagnostics and demarcation of malignant tumours, the characterization of blood vessels for guiding interventional angioplastic procedures and scattering spectroscopy for optical mammography etc.

Many medical applications involve continuous lasers, especially when it comes to just delivering a certain heating effect to the tissue. Pulsed lasers with typical pulse lengths of 10 ns are also used, especially for tissue ablation, lithotripsy and for enabling background light rejection by gated viewing in tissue fluorescence imaging. Ultrafast laser pulse generation enabled through mode locking has opened up a new domain of ultrafast spectroscopy. The field has developed particularly fast since the introduction of Kerr-lens mode-locking in titanium-doped sapphire (Ti:Sa) [8] and the possibility to conveniently increase the available pulse energy through chirped-pulse amplification (CPA) [9]. Ultrafast spectroscopy is covered extensively in the literature; see e.g. [10]. The field of femtochemistry [11] has allowed the study of many fundamental processes in biology and medicine, such as photosynthesis and vision. However, ultrafast laser pulses have also allowed new types of study which are more directly connected to practical medicine. Thus, they

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allow convenient studies of light transport through tissue in a similar way as the transport and scattering of longer pulses in the atmosphere have earlier been studied (see e.g. [12]). Light propagation in tissue is important for the development of optical mammography, for light dosimetry in connection with PDT and for species concentration assessments. Ultrashort optical pulses can be used directly or after non-linear conversion, which enables the generation of new wavelengths. Thus, a 'white' optical continuum can be formed by self-phase modulation, allowing multi-spectral propagation studies. High energy pulses in interaction with metal targets can generate hard x-rays of considerable interest for future medical imaging. These latter aspects are the subject of the present paper, which is organized as follows. The next section discusses the short-pulse propagation in tissue with an emphasis on imaging through turbid media. Then, in section 3 white light generation and its use for tissue constituent concentration assessment is discussed. Section 4 describes the generation and characterization of intense x-ray bursts and their potential use in medicine. Finally, prospects for the future are discussed in section 5.

2. Ultrashort laser pulses in scattering media

Multiple light scattering in weakly absorbing media is a common phenomenon observed in clouds, fog and water. While some light is transmitted (there is still daylight on a cloudy day) image contrast disappears (the sun disc is not observed through the cloud). Milk is an even more scattering medium, and the presence of, e.g. a cherry, held by the stem inside a glass of milk, cannot be assessed in normal transillumination. Similarly, red light passes a human hand, but it is not possible to see the shadows of the bones. If the image blurring due to scattering somehow could be defeated, red light tissue transillumination would be attractive for optical mammography without the use of ionizing radiation. Also it would be very interesting to localize haematoma after trauma to the skull. Preceeding such imaging applications, primary studies concerned the study of brain oxygenation [13, 14]. First imaging recordings with scattering rejection through living tissue were reported in 1990 [15]. The basic idea behind imaging through turbid media using time-resolved spectroscopy is to restrict the detection to the photons which travel through the medium without being scattered. This corresponds to the first emerging photons following short-pulse injection as illustrated in figure 1 [16]. The non-scattered 'ballistic' photons are recorded as the transmitter–detector line-of-sight is scanned across the sample. If an object of different absorbing and scattering properties is hidden inside the scattering medium the ballistic signal is changed.

As an illustration, imaging through a sample of newly resected breast tissue placed between two glass plates is demonstrated in figure 2 [17]. A diode laser operating at 815 nm and producing 30 ps pulses at a rate of 10 MHz was used. The single-photon time-correlated detection technique was used. A time dispersion curve through the 3 cm thick sample is shown together with the apparatus function corresponding to the pulse convoluted with the system response. A ductal carcinoma is revealed in the time-gated transillumination image shown, while the image corresponding to the time integrated signal lacks diagnostic value. Many techniques for time gated imaging have been developed, including the use of optical Kerr gating, stimulated Raman amplification and second-harmonic cross correlation. Other techniques, which focus on the distinct phase properties of the non-scattered light, are heterodyne detection and light-in-flight holography. Different aspects of light in scattering media such as tissue are covered in [18]. Time-resolved photon propagation studies have also been performed in green leaves from plants [19]. Very recently studies of photon propagation in strongly scattering media have been extended to the monitoring of gas enclosures, discernable because of the extremely sharp absorptive features of a free gas in comparison with a solid or a liquid [20, 21].

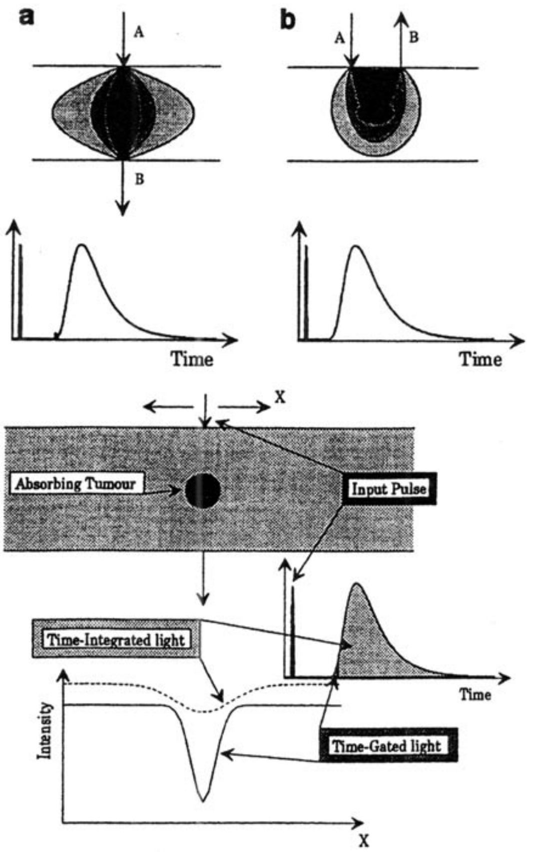

Figure 1. Top: geometries for time-resolved measurements on scattering media. (a) transillumination and (b) backscattering. Bottom: gated viewing through tissue. An enhanced spatial resolution is obtained by selecting the ballistic light only (from [16]).

3. White light generation from intense ultrashort pulses

When high-power laser pulses are focused into a condensed medium such as water, a light continuum is generated through self-phase modulation [22]. The origin of the phenomenon is the dependence of the index of refraction on the light intensity, leading to frequency chirps when the pulse intensity is rising and falling. Following the injection of such pulses into strongly scattering media, such as tissue, the time dispersion of the photons can be studied. The spectral contents and the

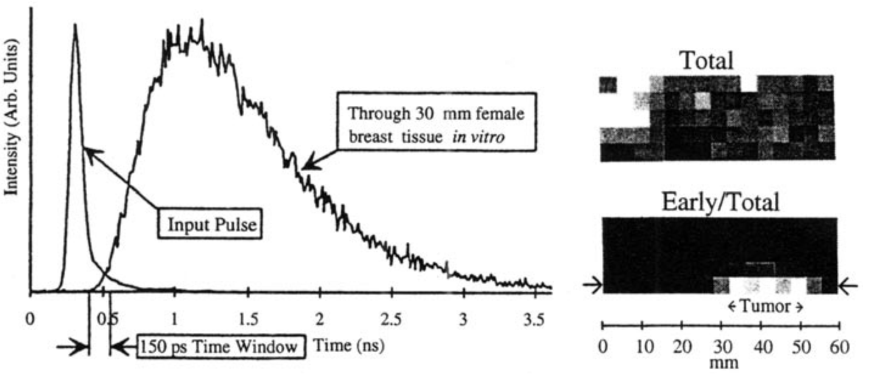

Figure 2. Transillumination images through breast tissue *in vitro*. The presence of a tumour is evident when the first part of the temporal dispersion curve is used. When integration over the whole time dispersion curve is performed no tumour is discernable. On the left in the figure an individual dispersion curve is shown together with the experimental apparatus function (from [17]).

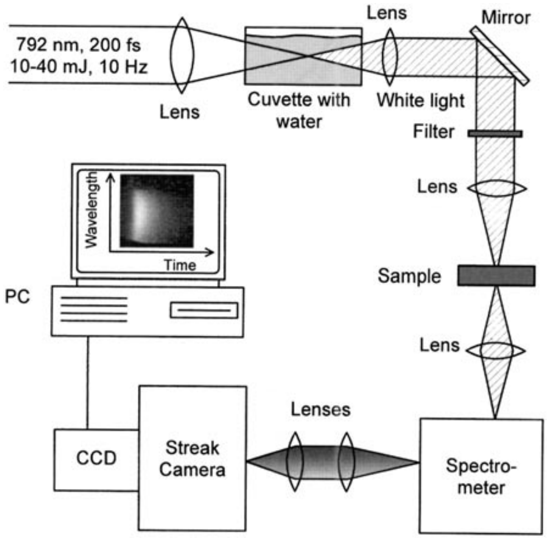

Figure 3. Set-up for time-resolved photon propagation studies using white light (from [23]).

time duration of the radiation can be measured with a streak camera coupled to the exit slit of a spectrometer. A two-dimensional representation of time versus colour is obtained. An experimental set-up for studies of this kind is shown in figure 3 [23].

In the white-light propagation studies, as well as in the laser-produced x-ray work in Lund we have utilized a terawatt CPA laser system based on Ti:Sa. It is part of the Lund High-Power Laser Facility, which is described in [24]. The CPA technique allows to achieve extremely high optical intensities in compact laser systems. An initial, short pulse is temporally stretched before amplification in order to reduce the peak power in the amplifier stage for a given pulse energy, avoiding the need for large beam diameters. Pulse compression is then performed in a grating arrangement to achieve ultrahigh powers. Ti:Sa can readily be pumped by Nd:YAG radiation that is frequency doubled to 532 nm. The material has a wide gain profile and can thus support amplification of ultrashort pulses (down to tens of femtoseconds), which results in lower pulse-energy demands for reaching terawatt power levels at a repetition rate of 10 Hz. Apart from the pulse power, important quality factors describing a terawatt laser are the pulse duration, the focusability and the contrast between the main pulse and possible prepulses or a background level (pedestal).

Nearly transform-limited pulses of 100 fs duration are generated from an Ar^+-laser pumped Kerr-lens mode locked Ti:S oscillator. Pulses at a repetition rate of 76 MHz and at an average power of about 1 W (10 nJ/pulse, 100 kW peak power) are obtained. The 100 fs output pulses from the oscillator are temporally stretched by a factor of about 2500 in a grating and lens arrangement that is double passed. The stretched oscillator pulse is injected into a regenerative Ti:Sa amplifier. This unit is pumped by 65 mJ of green light from a frequency doubled Nd:YAG laser. After 14 double passes and about 10^6 times amplification, the pulse is ejected and further power boosting is performed in a six-pass (butterfly) Ti:S amplifier crystal to reach a level of up to 450 mJ. Two frequency doubled high-energy Nd:YAG lasers pump the amplifier at a total energy level of 1.6 J at 10 Hz. Relay imaging of the pump laser-rod surface using evacuated beam-transport telescopes is used to achieve a more uniform pumping. A beam diameter of 8 mm is used through the final Ti:Sa crystal. The beam is expanded to 50 mm diameter in order to reduce the power density, and the pulse is compressed using two parallel, 11×11 cm^2 gold coated holographic gratings with 1800 grooves mm^{-1} and a first-order diffraction efficiency of about 90%. After double passing the grating arrangement the low-frequency leading-edge light is delayed and the high-frequency trailing edge is catching up to emerge simultaneously from the compressor. In the white-light generation experiments between 10 and 40 mJ of energy was used in 200 fs pulses.

Our experiments allowed the study of transillumination dynamics through tissue at all visible wavelengths simultaneously [23], facilitating feasibility studies and optimum wavelength choice for optical mammography [17]. An example of a two-dimensional recording is shown in figure 4 [25], where a tumour loaded with a tumour-seeking sensitizer (optical contrast agent) is simulated by a cavity containing bensoporphyrine derivative (Quadraologics Vancouver) inside a block of scattering Delrin plastics.

More recently, we have extended this type of measurements to the study of absorption spectra of sensitizers *in situ* in living tissue [26]. A rat tumour model was used, where a human adenocarcinoma, inoculated on the hind leg muscle, produced tumours of about 15 mm diameter.

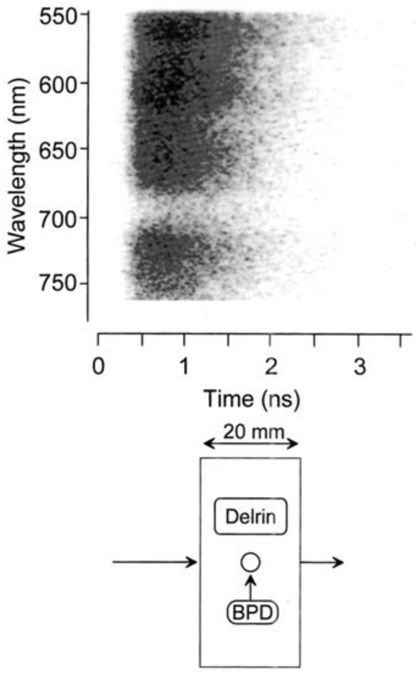

Figure 4. Two-dimensional representation of experimental data on a Delrin sample of scattering plastic containing a cavity filled with the tumour-sensitizing agent bensoporphyrine derivative. The photon temporal dispersion as a function of the wavelength is shown with the absorption band of the bensoporphyrin molecules clearly visible (from [25]).

Optical fibres were used to inject the light into the tissue and to collect scattered light emerging again at a distance of about 8 mm. The rats were injected with dissulphonated aluminum phtalocyanine at a concentration of 2.5 or 5 mg/kg body weight and measurements were performed on both the tumour and normal tissue. From the experimental recordings the absorption and scattering coefficients can be extracted. This allows the plotting of the absorption profile of the sensitizer *in vivo* and an assessment of the tumour/normal tissue uptake ratio. Similar techniques can be used to extract tissue absorption and scattering properties related to optical mammography [27]. A further application is the assessment of the concentration of certain near-IR-absorbing molecules in scattering powders [28].

4. X-ray generation and applications

When short-duration terawatt laser pulses are focused onto a solid target consisting of a material with a high nuclear charge Z, intense x-ray radiation of few ps duration and with energies exceeding hundreds of keV is emitted [29, 30]. A set-up for this type of experiment is shown in figure 5 [31]. Most of our work was performed with 110 fs pulses of 1–2 TW power. The spectral characterization of such a source poses difficulties since pile-up problems due to the intense bursts occur in conventional energy-dispersive spectrometers. By making use of Compton scattering and using long exposure times these problems could be overcome [32]. Crystal spectroscopy using Bragg and Laue geometries is a further method for spectral studies in the hard x-ray region [33, 34]. A spectral recording for tantalum using the Bragg geometry is given in figure 6 [33]. Ultrasharp and single-shot imaging was demonstrated in our early work [30, 35]. Imaging of small animals could be achieved as shown in figure 7 [25]. Feasibility experiments utilizing differential absorption across a K absorption edge have been performed [31]. Here, the K lines of tantalum and gadolinium targets were used to bridge the 50 keV K-absorption edge of gadolinium used as a contrast agent. Figure 8 displays images for rats with Gd- and Ce-based contrast agents, respectively, administered to their stomachs. Tantalum and gadolinium targets were used in the x-ray source. Since the Kα emission lines bridge the gadolinium absorption edge but not the cerium one, different behaviours are seen in the two animals [36].

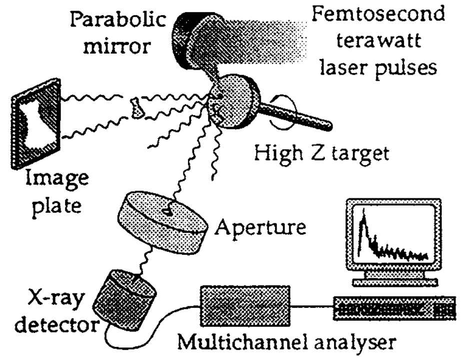

Figure 5. Experimental set-up for the generation of hard x-ray radiation in the interaction of ultraintense laser pulses with a rotating metal target (from [31]).

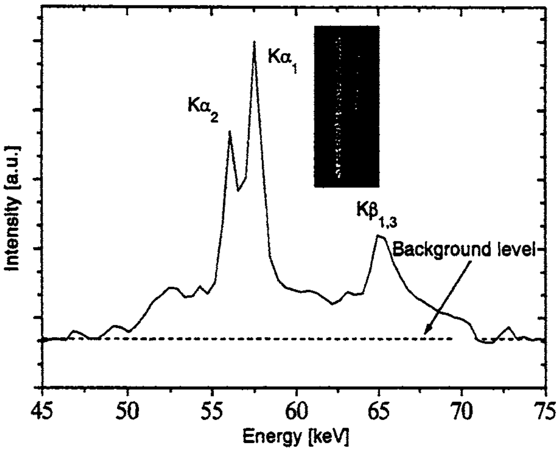

Figure 6. X-ray spectrum for a laser-irradiated tantalum target, recorded around the Kα lines using a crystal spectrometer with a scintillator/ccd detector arrangement (from [33]).

Further, the short temporal duration of the laser-produced x-ray pulses has been utilized in time-gated viewing experiments [37, 38] to suppress Compton-scattered photons, potentially allowing a dose reduction in medical x-ray imaging. Normally, such scattered radiation is suppressed employing anti-scattering grids (tunnel vision), but this leads to an increased patient dose, since the grids also block out useful photons. We have performed extensive modelling and experimental work illustrating possibilities and limitations for time-gated x-ray viewing. Linear imaging using an x-ray streak camera was demonstrated simulating the cases

Figure 7. Image of a sacrificed Wistar-Furth rat, recorded on a normal radiographic imaging plate using a tantalum laser-produced x-ray source filtered by a thin copper sheet to cut off most of the radiation with energy below 25 keV (from [25]).

of mammographic and whole-body applications. Without time resolution a lead obstacle was observed with strongly reduced contrast due to the scattering. By restricting the imaging to the ballistic photons only, contrast is enhanced. Recently, the gated-viewing concept has been combined with tomographic back-projection to yield scatter-reduced two-dimensional images of tissue phantoms (See figure 9) [39, 40].

5. Discussion

The use of short laser pulses and laser-produced continua of electromagnetic radiation in the visible and in the x-ray regions has been described in this chapter. Optical mammography was discussed showing proof-of-principle experiments. Quite an effort has been invested in this field in many laboratories. The clinical practicability of optical mammographs will be connected to the development of effective tumour discrimination mechanisms and improvements in the data-taking speed. Tomographic optical diagnostics of non-compressed breasts is a further desirable feature. For the generation of optical and x-ray continua as described above, a large TW research laser system, operating at a repetition rate of 10 Hz, was used in proof-of-principle experiments. In the white-light generation studies only a fraction af the available pulse energy was used. Actually, a new 1 kHz, 35 fs pulselength laser system based on CPA technology in Ti:Sa and producing close to 3 mJ pulse energy, now available to us at the Lund High-Power Laser Facility, is more suited for the purpose, because of the higher useful average power available. A white-light set-up has the virtue of allowing simultaneous assessment of all relevant wavelengths in the study of absorptive and scattering properties of tissues and optical contrast agents. Based on the results, pulsed diode lasers at optimal wavelengths can be chosen for clinically adapted equipment.

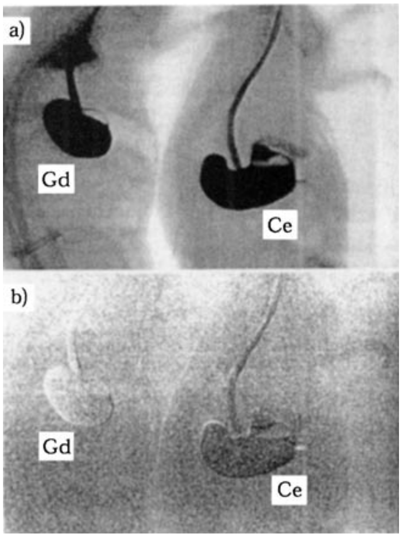

Figure 8. Differential imaging of the stomach regions of two sacrificed Wistar-Furth rats (200 g) given gadolinium- and cerium-containing contrast agents. The upper part of the figure shows direct recordings and the lower part the result of division of images taken for the gadolinium and the tantalum source (from [36]).

Regarding the possibilities of developing a realistic diagnostic system based on laser-produced x-rays, several aspects have to be taken into consideration. A basic question is of course, whether the absorbed dose of x-rays delivered as intense spikes of ultrashort duration has the same biological effect as an equivalent dose of conventional, CW x-ray radiation. Initial experiments on survival rates for Chinese hamster cells show that this is indeed the case (see figure 10) [41]; otherwise the concept would have to be abandoned at once. The x-ray imaging recordings on small animals using the 10 Hz system and employing image plates [42] typically required several minutes of exposure time. Measurements on the x-ray yield from the system upgraded to about 5 TW of pulse power yielded a calibrated output in the Kα lines of tantalum and tin of 10^8–10^9 photons/shot. In order to achieve adequate amounts of radiation for human radiography a laser system with a higher repetition rate than the 10 Hz system employed should be used. Preliminary work with the 1 kHz short-pulse system mentioned above has been performed, showing that hard x-rays allowing thick tissue imaging are generated also from low-energy pulses [43]. The use of artificial prepulses was found to increase the yield a few-fold. However, it is clear that a kHz system with pulse energies above 100 mJ would be needed to approach clinical applications. Such systems are by no means unrealistic.

The attractiveness of a laser-based x-ray source would be in a combination of ultrasharp imaging due to the small source size, differential absorption imaging around the iodine K absorption edge and gated viewing for the suppression of image-blurring Compton-scattered photons. The last two aspects could theoretically lead to a reduction

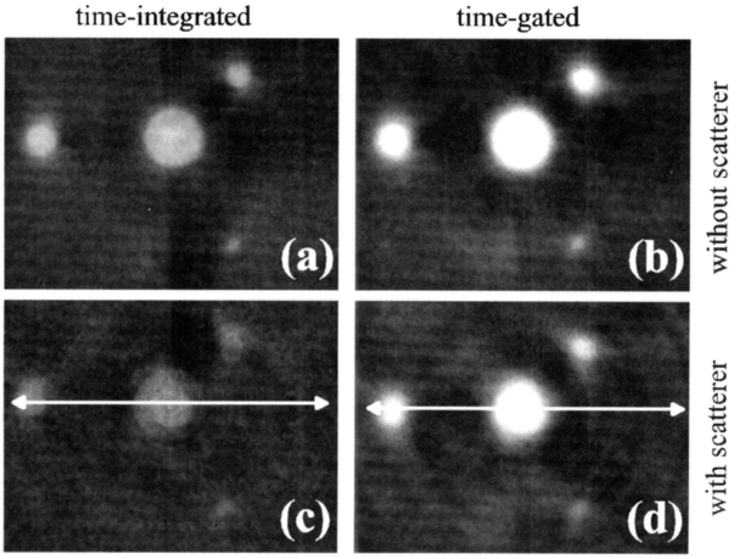

Figure 9. Tomographic reconstruction of a small wire target arrangement surrounded by 4.5 cm of water. Scattering reduction through time gating has been achieved (from [39]).

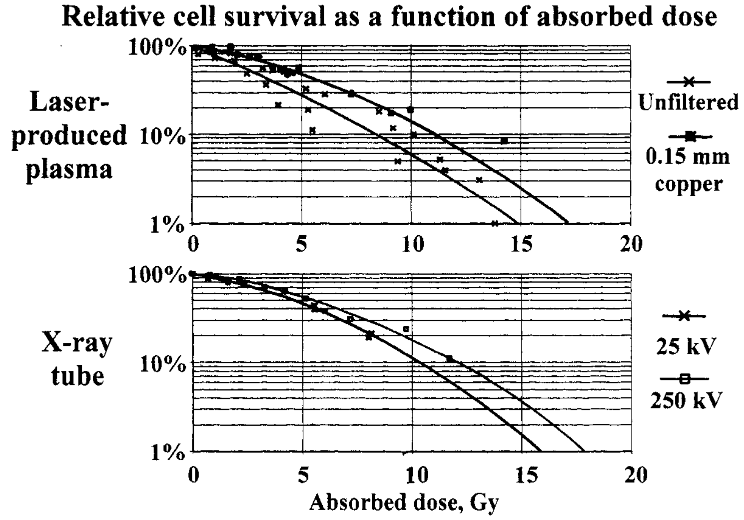

Figure 10. Survival curves for V79-CH cells subject to laser-produced x-rays and conventional ionizing radiation from a 25 kV and a 250 kV conventional x-ray tube. The diagram shows that the radiation from the different sources has a similar influence on a live biological specimen (from [41]).

of the dose of ionizing radiation. Synchrotrons are already being used for differential absorption measurements for dose reduction in angiography using an iodine contrast agent [44, 45]. To make the laser-based source advantageous over synchrotrons or conventional sources, some way to enhance the characteristic line emission over the bremsstrahlung continuum would have to be found. Then an intensity-reducing x-ray monochromator [34] can be avoided. The greatest potential of the laser-based x-ray source seems to be for the gated-viewing reduction of scattered radiation, since even modest reductions in absorbed x-ray doses could mean substantial savings in radiation-damage-induced suffering and costs. Mammographic applications [46] are attractive besides angiographic imaging. A high-average-power source would have to be integrated with a high-efficiency 2D gated x-ray detector, which still needs to be developed.

A new emerging field for possible medical applications of short-pulse intense laser radiation is laser-induced nuclear reactions [47]. High-average-power sources could be useful for the production of radioisotopes for medical diagnostics. Further, compact particle accelerators for tumour irradiation could be envisaged.

Acknowledgments

The author acknowledges a very fruitful interaction with a large number of students and colleagues at home and abroad, in particular F Albert, R Berg, E Anderson, S Andersson-Engels, R Cubeddu, E Förster, M Grätz, K Herrlin, G Hölzer, J Johansson, L Kiernan, C af Klinteberg, I Mercer, A Persson, A Pifferi, A Sjögren, C Tillman and C-G Wahlström. This work was supported in part by the EC Network grant FMRX-

CT96-0080 and the Access to Large-Scale Facility grant ERBFMGECT950020, by the Swedish Medical Research Council, Swedish Natural Science Research Council, Swedish Engineering Sciences Research Council and the Knut and Alice Wallenberg Foundation.

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