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3-Dimensional quantitative detection of nanoparticle content in biological tissue samples after local cancer treatment

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ABSTRACT

X-ray computed tomography is nowadays used for a wide range of applications in medicine, science and technology. X-ray microcomputed tomography (X μ CT) follows the same principles used for conventional medical CT scanners, but improves the spatial resolution to a few micrometers. We present an example of an application of X-ray microtomography, a study of 3-dimensional biodistribution, as along with the quantification of nanoparticle content in tumoral tissue after minimally invasive cancer therapy. One of these minimal invasive cancer treatments is magnetic drug targeting, where the magnetic nanoparticles are used as controllable drug carriers. The quantification is based on a calibration of the X μ CT-equipment. The developed calibration procedure of the X-ray- μ CT-equipment is based on a phantom system which allows the discrimination between the various gray values of the data set. These phantoms consist of a biological tissue substitute and magnetic nanoparticles. The phantoms have been studied with X μ CT and have been examined magnetically. The obtained gray values and nanoparticle concentration lead to a calibration curve. This curve can be applied to tomographic data sets. Accordingly, this calibration enables a voxel-wise assignment of gray values in the digital tomographic data set to nanoparticle content. Thus, the calibration procedure enables a 3-dimensional study of nanoparticle distribution as well as concentration.

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1. Introduction

In the last decades research activities in the field of biomedical applications of ferrofluids, suspensions of magnetic nanoparticles in appropriate carrier liquids, are increasing, especially in applications to cancer treatment [1–4].

Some promising local cancer therapies are being investigated. The magnetic drug targeting (MDT) is one of these treatments, significantly reducing side effects.

Abbreviations: AAS, atomic absorption spectroscopy; BKFIL-algorithm, back projection of filtered projections algorithm; CCD, charged coupled device; CT, computed tomography; ICP-MS, inductively coupled plasma mass spectrometry; eV, electron volt; LeTo, low energy tomography; MDT, magnetic drug targeting; MeV, mega electron volt; MRX, magnetorelaxometry; PTFE, polytetrafluoroethylene; PUR, polyurethane; VSM, vibrating sample magnetometer; μ CT, microcomputed tomography; X μ CT, X-ray microcomputed tomography

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For the treatment with MDT a chemotherapeutic agent is bound to magnetic nanoparticles which are suspended in an adequate carrier liquid. Then the fluid is injected into an artery which supplies a tumor. An external magnetic field is applied to direct the ferrofluid to the target region and to keep it there for the duration of the treatment. The magnetic nanoparticles carrying drugs accumulate within the tumoral region, so the drugs can act locally and are not spread throughout the body. Therefore, the treatment is expected to be more efficient and to produce fewer side effects than conventional chemotherapy. At present, MDT is being tested on animals [1,2].

One of the crucial parameters for the efficiency of the therapeutic approach described above is the correct distribution of magnetic nanoparticles. The iron oxide nanoparticles have to be spread homogeneously over the tumor volume and be present in an appropriate quantity.

X-ray computed tomography, a 3-dimensional visualization method, is used to study the biodistribution of magnetic nanoparticles within the tumoral tissue. In this paper we present a method

which enables a 3-dimensional quantitative analysis of the nanoparticle content. This method is a calibration procedure which has been applied to a polychromatic X-ray microcomputed tomography instrument.

2. Materials and methods

This chapter briefly describes the X-ray microcomputed tomography ($X_{\mu}CT$) equipment used as well as the principle of magnetorelaxometry measurements. Then, the materials used for the production of the calibration phantom, an elastomer and a ferrofluid, will be described. Further on, the calibration phantom itself will be presented.

2.1. Micro-computed tomography

Since the discovery of X-rays by Conrad Roentgen in 1895 [5], imaging techniques using X-rays have played an increasingly important role in medicine as well as in engineering. X-ray computed tomography is an especially significant imaging method, since this measurement technique produces 3-dimensional representations of opaque structures. The mathematical background for computed tomography stems from a theorem postulated in 1917 by the Austrian mathematician Johan Radon. Radon showed that a 2-dimensional distribution of a variable can be determined if the line integrals of the variable over all viewing angles are known [6].

X-rays are generated by a strong acceleration of charged elementary particles in electromagnetic fields, or by high-energy transitions in the electron shells of atoms and molecules. The energy of X-ray photons ranges from a few electron volts (eV) to several mega electron volts (MeV). This corresponds to a wavelength range of 10–0.01 Å. Because of their high energy, X-ray photons are absorbed by matter much less than visible light. The conversion of X-rays to visible light can be achieved by the interaction of X-ray photons with orbital electrons of a scintillator material. The visible light can be converted to digital data, for example by CCD cameras [7].

The following types of tomography equipment are used most frequently in medical and technical practice. In medical CT-scanners, the unit, consisting of an X-ray source and detector, is rotated around the patient [8].

In laboratory tomography, particularly in micro-tomography, the sample is rotated while the X-ray source and detector have defined positions (see Fig. 1) [9].

For our calibration, a special form of conventional X-ray tomography called microcomputed tomography ($X_{\mu}CT$) was used. The prefix (μ) expresses that the size of the volume elements of the 3-dimensional data set is in the micrometer range. These elements, or volume pixels, are denoted by the abbreviation “voxels” [10].

The $X_{\mu}CT$ -equipment used is named LeTo (Low energy Tomography). It is based on a conventional X-ray tube [11–13]. The maximum acceleration voltage of the polychromatic X-ray source is 50 kV, and the maximum emission current is 1 mA. The cone-shaped beam can

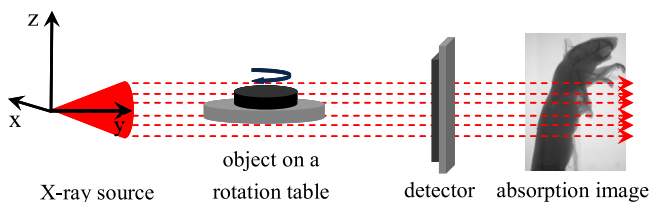


Fig. 1. Principle of a μCT measurement. In contrast to a conventional medical CT-scanner a rotation of the object is performed. Further on the object can be manipulated in x-, y-, and z-directions.

be used to adjust optical magnifications. Due to LeTo's geometrical arrangement, optical magnifications from 1.3 to 5 are possible [9]. In combination with a CCD-camera with 1024×1024 pixels on a chip with $13 \times 13 \mu m^2$ of active area, a spatial resolution of 17–100 μm can be achieved.

Fig. 2 shows some interior equipment of the $X_{\mu}CT$ -apparatus. The aluminum filter on the right side of the photograph is used to reduce the beam hardening. A tumor sample is shown in the center of the figure. The sample is mounted on a manipulator comprised of a Y-translation axis, a rotation axis and an XY-table.

2.2. Magnetorelaxometry (MRX)

Magnetorelaxometry (MRX) is a very sensitive method for magnetic nanoparticle detection with a mass resolution of several hundred nanograms [14,15]. The main advantage of this measuring method is the sensitivity for the particular magnetic nanoparticles used for the local cancer treatment. This specificity concerning the used magnetic nanoparticles is not only given by commonly used techniques like ICP-MS (inductively coupled plasma mass spectrometry) or AAS (atomic absorption spectroscopy), which detect the presence of the elements, even if they are not in the condensed form of magnetic nanoparticles.

MRX is an integral method which detects the magnetic field due to the relaxation of the magnetic moment of magnetic nanoparticles within a sample which has been polarized by a magnetic field for a few seconds [16].

This method is also non-destructive and provides the absolute nanoparticle content value for the validation of the calibration procedure with complex samples for MDT.

2.3. Animal model and magnetic drug targeting

The calibration procedure presented in the following was tested on biological tissue samples, which were tumors treated with magnetic drug targeting. These tumors were grown on New Zealand White rabbits. Therefore VX-2 squamous cell carcinoma was inoculated on the hind limb of a rabbit. As soon as the size of the tumor reaches 20 mm magnetic drug targeting has been performed. For the treatment a chemotherapeutic agent mitoxantrone was bound on the magnetic nanoparticles of the ferrofluid. The magnetic fluid used, is based on magnetite particles covered in starch and suspended in water. The magnetic fluid has been described in [17] in detail.

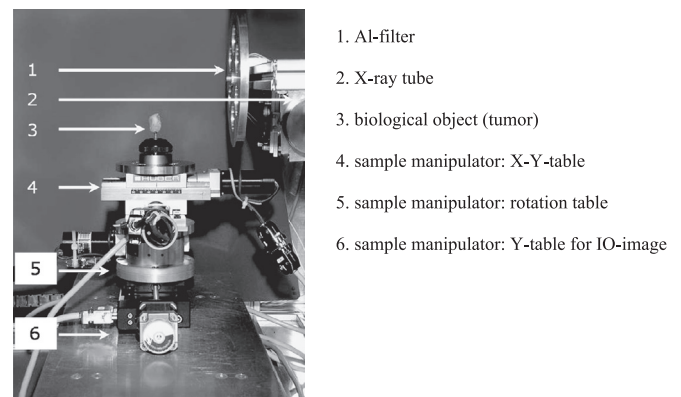


Fig. 2. LeTo – Low energy Tomography. In this photograph, from right to left, there are an aluminum filter (1) for the reduction of beam hardening artifact, X-ray tube (2), and a tumor sample after MDT (3) which is mounted on the sample manipulator (4–6). (1) Al-filter, (2) X-ray tube, (3) biological object (tumor), (4) sample manipulator: X-Y-table, (5) sample manipulator: rotation table, and (6) sample manipulator: Y-table for IO-image.

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