Development of a multifibre system for interstitial photodynamic therapy of malignant tumours

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Abstract

Photodynamic therapy is a laser based treatment modality of malignant tumours. In this thesis, a system for interstitial photodynamic therapy has been used and improved. The system consists of a diode laser and a device with six optical fibres for illumination of the tumour and measurement of the light distribution in the tumour. A computer program for dosimetry has been developed. The dosimetry program is based on diffusion theory for light distribution in tissue and uses the finite element method for solving the diffusion equation. Another computer program, including the dosimetry module, to be used during an interstitial PDT session has also been implemented. The whole system was tested at the Lund University Hospital at two different occasions on a total of six mice with malignant tumours.

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1. Introduction

Ever since the discovery of the laser in the 1960's, an increasing number of practical applications for lasers have been found. In the metal industry lasers are used for high precision cutting and drilling, in the electronics industry diode lasers are found in an increasing number of components and devices e.g. CD-players, fibre communication systems and so on. The use of lasers in medicine is in an early stage but is generally regarded as having great potentials. Some applications used clinically are laser surgery, laser Doppler diagnostics of the heart and thermotherapy. An interesting application is the use of laser as a tool for diagnostics and treatment of tumours. At the Department of Physics at the Lund Institute of Technology clinical studies of superficial tumours have been performed for many years [1]. This Master's thesis was made at the Department of Physics at the Lund Institute of Technology. It is part of a project within the medical group concerning the development of a system for interstitial photodynamic therapy, i.e. a system for treatment of deeper lying tumours where the laser light is delivered to the tumours through optical fibres.

The purpose of this Master's thesis is to develop a dosimetry model for light distribution in the tumour during interstitial photodynamic therapy, improve the interstitial photodynamic therapy system and the software controlling the system and to test the model, system and its software during an interstitial photodynamic therapy treatment of mice.

In chapter 2 an introduction to photodynamic therapy is given. The basic principles behind this cancer treatment modality and some of the chemical compounds used in this kind of treatment are discussed. The theory behind tissue optics, i.e. light propagation in tissue, is briefly introduced in chapter 3. This forms the basis for developing the dosimetry model, which is described in chapter 4. Chapter 5 and 6 describes the modifications made on the system and the software used to control the system respectively. The test of the system, the software and the model is discussed in chapter 7. Finally there is a summary of the project in chapter 8.

2. Photodynamic therapy

Photodynamic therapy (PDT) is a form of medical therapy where a chemical compound, called a photosensitiser is added to the human body. When illuminating the tissue with light at a specific wavelength a chemical reaction, involving the photosensitiser, is induced. Some sensitisers have the characteristic to gather in tumour tissue, rather than in healthy tissue. This selectivity and the fact that the photochemical reaction is toxic to the surrounding tissue forms the basis for PDT to be used as a treatment modality of malignant tumours. Within this thesis PDT refers to photodynamic therapy of cancer tumours.

2.1 Photosensitisers

There are several important criteria that has to be fulfilled by a chemical compound to be used as a photosensitiser in PDT. Since it is desirable that the photochemical process occurs in tumour tissue only, it is essential that the sensitiser gathers in tumour tissue to greater extent than in normal tissue. The photochemical process is also dependent on the absorption of light by the photosensitiser. This makes it important for the photosensitiser to absorb light at a wavelength not being completely absorbed by surrounding tissue. Once the light has been absorbed by the photosensitiser, the photochemical reaction should occur in such a way that it efficiently kills the tumour cells.

Traditionally different kinds of porphyrin derivatives e.g. Photofrin have been used as tumour-seeking substances. The chemical structure of porphyrin molecules is similar to that of the haem group of haemoglobin, but lacks the Fe-ion in the centre of the molecule [2,3]. The selective accumulation of porphyrin in tumour cells is due to numerous reasons e.g. lower pH, higher concentration of certain proteins and higher blood flow in malignant cells than in healthy tissue [4]. Porphyrins have a strong absorption band around 405 nm, but it is preferable to use light sources at 630 nm even though porphyrins absorb weaker in this band. This since tissue absorbs considerably less in the red region, whereas the penetration depth of light increases (Figure 3.1).

A different way to accumulate porphyrin in tumour cells is by adding the pro-drug δ-amino levulinic acid (ALA) to the tissue. ALA, by itself not photodynamically active, is part of the haem biosynthesis where haemoglobin is formed in the human body (Figure 2.1) [1].

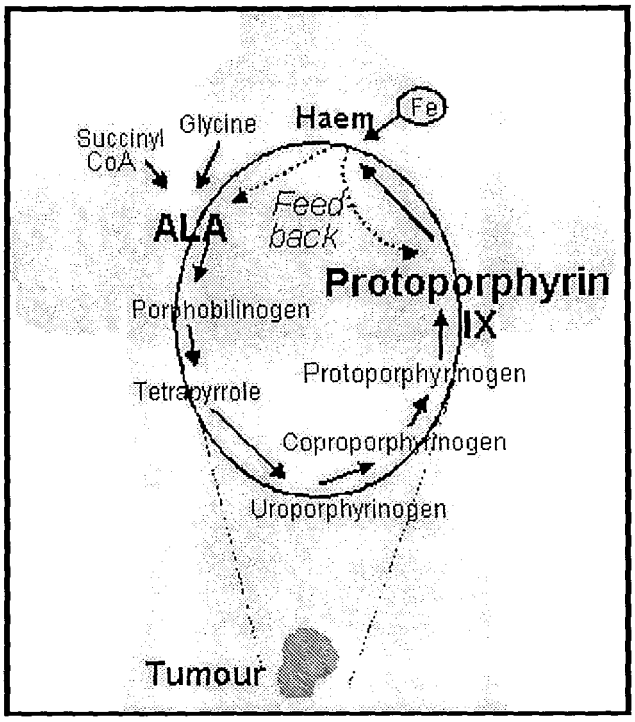

Figure 2.1 The haem biosynthesis in the human body [1].

In the normal case, when no extra ALA has been added, the formation of ALA from glycine and succinyl co-enzyme A is a slow process. The following steps up to the formation of Protoporphyrin IX (PpIX) are quite rapid and not time limiting to the process. The PpIX then converts to haem by a rather slow process [5]. Under normal conditions the process is strictly regulated and no considerable accumulation of PpIX will occur. By adding extra ALA, which is selectively accumulated in tumour cells, an excess amount of PpIX will be formed in these cells because of the slow conversion of PpIX to haem. Since PpIX is photodynamically active it is now possible to perform PDT [6].

Recently much effort has been put into the development of new and better photosensitisers. Desired qualities for new sensitisers are e.g. improved selectivity between healthy and diseased tissue and absorption of light at a longer wavelength, where penetration depth is larger in tissue. One example that has lately experienced a lot of interest is lutetium texaphyrin (Lu-Tex) absorbing light at 732 nm. The longer absorption wavelength is an advantage not only in terms of the larger penetration depth, but also because the existence of less expensive and higher performing diode lasers at this wave-

length. Preliminary studies involving Lu-Tex show good results and clinical trials are about to begin [7,8].

2.2 Basic principles

The photodynamic process is based on the optical excitation of photo-sensitisers transferring their excess energy to other molecules. These molecules are more reactive in their higher energy state and chemical reactions are induced. The chemical reactions are supposed to kill the tumour cells and are of strictly photochemical nature, i.e. not dependent on supplied heat [9].

The photodynamic process, involving porphyrin e.g. PpIX, starts with the absorption of a photon. When absorbing in the Soret band (405 nm) the porphyrin molecule is excited to a singlet state S_2 and absorption in the Q-band (630 nm) leaves the molecule in the first excited singlet state S_1 (Figure 2.2).

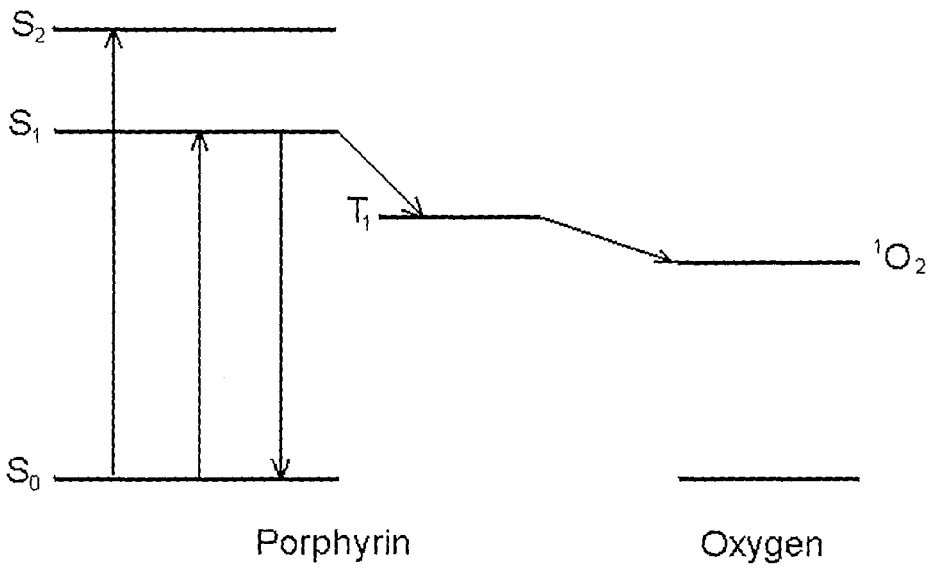

Figure 2.2 Energy level diagram showing the photodynamic process where energy is transferred from porphyrin to oxygen.

From this state porphyrin can relax back to the ground state S_0, emitting fluorescence. Since porphyrin selectively accumulates in tumours this characteristic fluorescence can be used as a diagnostic tool [2-4,10]. Another possibility is that the molecules in the S_1 state relaxes internally to the lowest lying triplet state T_1. This process, called inter-system crossing, is spin forbidden but can still occur with rather high probability if the energy difference between the two states is fairly small [3]. The transition from T_1 to S_0 has a very low probability and T_1 thus forms a metastable state. This increases the possibility of interaction between the porphyrin molecules in the

T_1 state and surrounding molecules. There exist two different processes, both involving oxygen, particularly interesting in PDT. The first one (type I) means that an electron is transferred to an adjacent molecule, thereby forming chemical radicals. The second one (type II), by far the most important in PDT, involves energy transfer, mainly to oxygen, leaving it in an excited singlet state [10,11]. Singlet oxygen, $^1O_2$, is very reactive and highly toxic to its surroundings. Because of its short lifetime in tissue, $^1O_2$ has a short radius of action [8]. This short radius of action and the fact that $^1O_2$ forms to greater extent in tumour tissue, where the photosensitiser has accumulated, guarantees the selective mortality of tumour cells.

2.3 Treatment considerations

Up to now PDT has mostly been used clinically to treat superficial tumours by laser illumination of the skin of the patients. In this kind of treatment it is possible to apply the photosensitiser (e.g. ALA) topically, relying on the diffusion of the substance to all parts of the tumour. A drawback to this method of supplying the sensitiser is the non-uniform distribution of drug in the tumour resulting in poor treatment results for deeper lying parts of the tumour [12]. If the drug instead is supplied systemically (e.g. intravenously or orally) the distribution in the tumour gets more uniform. On the other hand the dose has to be increased and the whole body is exposed to the drug. This could lead to sideeffects like sensitivity to intense sunlight and mild feelings of sickness.

3. Tissue optics

To be able to perform dosimetry, e.g. in connection with PDT, knowledge of the principles behind light propagation in tissue is essential. A complete model has to be able to explain a variety of physical phenomena, e.g. reflectance, absorbance, transmittance and inteference effects. Since tissue is highly inhomogeneous, with many different kinds of structures of various sizes, the problem gets complex and an exact solution is not available.

There exist several models based on different kinds of simplifications [4,13]. Faced with a specific modelling problem one has to consider the properties of importance and choose a model accordingly. If topics relating to the wave nature of light are to be examined, a model based on electromagnetic field theory is to be preferred. If on the other hand, as in our case, the main interest is in studying light transport and absorption, averaged over a volume, a model based on transport theory seems to be an accurate choice. In transport theory light is considered only as a flow of energy and the wave nature of the photon is ignored. The basic principle of transport theory is the conservation of energy in every point in space. Within this thesis only models based on the latter approach have been treated.

3.1 Optical properties

At the interaction of light with tissue transport theory considers two different kinds of events: absorption and scattering. Normally processes where photons change their energy, e.g. inelastic scattering and fluorescence, are not considered, although it is possible to take such effects into account. To be able to fully describe absorption and scattering three parameters are of major importance: the absorption coefficient, the scattering coefficient and the anisotropy factor.

3.1.1 Absorption coefficient

The absorption coefficient, μ_a, describes the probability for absorption of a photon per unit length i.e. a photon travelling a small distance, ds, has a probability of $\mu_a ds$ of being absorbed. Typical values of the absorption coefficient in human tissue range from below one up to more than a hundred cm^{-1} for light in the visible region. The values vary strongly for different kinds of tissue, typically being larger for tissue containing large amounts of blood. Furthermore the absorption varies with the wavelength of light (Figure 3.1).

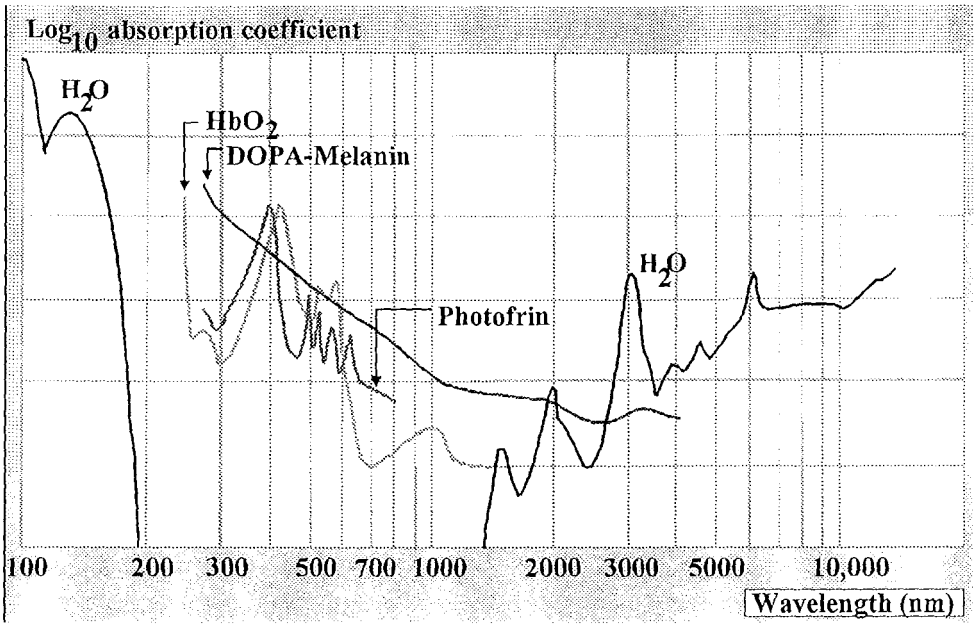

Figure 3.1 Light absorption for different absorbers in tissue, from Boulnois (1985).

Different components in tissue have different characteristic absorption spectra, notice e.g. the two absorption peaks around 550 nm being typical for haemoglobin (HbO_2). Most components in tissue show a decreasing absorption for longer wavelengths, suggesting a longer wavelength to have larger penetration depth. Above approximately 1300 nm water is on the other hand absorbing strongly, diminishing the penetration depth of IR radiation.

3.1.2 Scattering coefficient

The scattering coefficient, μ_s, is defined in a similar way as the absorption coefficient. In this case this means that a photon travelling a small distance, ds, has a probability of $\mu_s ds$ of being scattered, i.e. the scattering coefficient indicates the number of scattering events per unit length. Generally the value of the scattering coefficient is one to three orders of magnitude larger than the value of the absorption coefficient. As in the case of absorption, the scattering varies widely for different kinds of tissue. Highly scattering tissue, like breast tissue, typically contains large amounts of fat. The actual microscopic origin of scattering in cells is a debated issue but among the suggestions are cell nuclei, mitochondria and cell membranes [4]. Scattering in tissue is often treated theoretically in terms of Mie theory. With this theory it is, in combination with knowledge of the sizes of the scattering centres, possible to predict the wavelength dependency of scattering. By adding the scattering and the absorption coefficients one gets the total attenuation coefficient, μ_t. The inverse of this coefficient describes the mean free path for a photon in tissue.

3.1.3 Anisotropy factor

When a scattering event has occurred the propagation direction of a photon may change. The angle between the directions before and after a scattering event is called θ and is in the range 0 to π. An often used parameter in tissue optics is the phase-function, $p(\cos\theta)$, which is the probability distribution for cosine of the scattering angle. This function is defined in the interval $-1<\cos\theta\leq 1$, where it has values between 0 and 1. The anisotropy factor, g, is the expectation value of $\cos\theta$ and varies between -1 and 1. The value of g gives a rough estimation of the preferred direction of scattering. If the scattering is isotropic g will equal zero and if it is highly forward oriented g will be close to unity. In tissue a typical value of g is 0.9, with large variations for different kinds of tissue. Sometimes it is not sufficient to consider just the anisotropy factor, but one needs a more detailed knowledge of the phase-function. An often used analytical function, that has been shown experimentally to be a good approximation, is the Henyey-Greenstein function [4]:

$$p(\cos\theta) = \frac{(1-g^2)}{2(1+g^2-2g\cos\theta)^{3/2}} \tag{3.1}$$

3.2 The transport equation

As stated above, transport theory considers energy balance in a small volume dV. By studying the possible events at the interaction between light and tissue in dV, one ends up with an equation called the transport equation. Depending on the nature of the problem at hand it is possible to choose between a time dependent and a time independent approach. The time dependent approach is appropriate when studying situations such as propagation of short pulses in tissue. Within this thesis we have only considered problems involving continuos light sources and have not been interested in transient behaviours. Consequently the time independent approach has been used exclusively. A complete derivation of the transport equation, although straightforward, involves quite a number of mathematical details and is therefore beyond the scope of this thesis. We will only give a brief summary of the results and short explanations of the terms appearing in the equation.

The quantity normally used to describe the propagation of power, in this case in the form of light, is the radiance L(r,s) [$Wm^{-2}sr^{-1}$]. The radiance is the power flowing through a small area positioned at r. The flow is in the direction s, being perpendicular to the plane containing the area, within a small solid angle around s. Using this quantity the transport equation can be expressed as [13]:

$$\begin{aligned}\mathbf{s}\cdot\nabla L(\mathbf{r},\mathbf{s}) = &-\mu_a L(\mathbf{r},\mathbf{s}) - \mu_s L(\mathbf{r},\mathbf{s}) + \\ &+ \mu_s \int_{4\pi} p(\mathbf{s},\mathbf{s}')L(\mathbf{r},\mathbf{s}')d\omega' + S(\mathbf{r},\mathbf{s})\end{aligned} \tag{3.2}$$

Looking at a small volume dV the term on the left-hand side describes the change of radiance in direction s. The first term on the right-hand side is the amount of light, originally propagating in direction s, absorbed in dV. In the same way the second term represents light being scattered from direction s into some other direction. The third term is the most complicated one and describes light being scattered from all other directions into the direction s. The function p(s,s') is the phase function mentioned in section 3.1.3 above. The angle θ used in equation 3.1 is in this case the angle between the two directions s and s'. Finally the last term on the right-hand side of equation 3.2 is a source term, representing e.g. an optical fibre placed in dV.

In real applications the absorption and scattering coefficients can, although not stated explicitly in equation 3.2, vary over the total volume considered. In addition boundary conditions specific for the problem at hand have to be formulated. To be able to solve the transport equation some sort of simplifications have to be made. There are three major methods for accomplishing this: discretisation methods, expansion methods and probabilistic methods. In the following sections examples of the latter two will be given: diffusion theory as an example of an expansion method and Monte Carlo simulation as an example of a probabilistic method. The discretisation methods are based on the idea of just analysing a few directions of the light flow, thus replacing the complicated integral in the transport equation with a summation, much easier to handle mathematically. Some discretisation methods worth mentioning are e.g. the Kubelka-Munk theory and the Adding-doubling method [13].

3.3 Diffusion theory

The principle behind diffusion theory is to expand the radiance function, appearing in the transport equation, in function series of spherical harmonics (Y_{lm}) [2,13]:

$$L(\mathbf{r},\mathbf{s}) = \sum_{l=0}^{\infty} \sum_{m=-l}^{l} \sqrt{\frac{2l+1}{4\pi}} L(\mathbf{r}) Y_{lm}(\mathbf{s}) \tag{3.3}$$

By just using up to the first degree in the series expansion, i.e. l=1, the radiance can be expressed in the form:

$$L(\mathbf{r},\mathbf{s}) = A(\mathbf{r}) + \mathbf{s} \cdot \mathbf{B}(\mathbf{r}) \tag{3.4}$$

where the first term represents an isotropic distribution of light and the second term is a gradient representing a preferred direction for light. After inserting this into the transport equation and making a few simplifications one ends up with the time independent diffusion equation:

$$-D\nabla^2 \phi(\mathbf{r}) = -\mu_a \phi(\mathbf{r}) + S(\mathbf{r}) \tag{3.5}$$

A new quantity, the fluence rate $\phi(r)$ [Wm^{-2}], have been introduced. The fluence rate is the total power flowing through a small area, regardless of

direction, divided by this area. This is the same as integrating the radiance over all directions. D is called the diffusion coefficient, defined as:

$$D = \frac{1}{3(\mu_a + \mu_s(1-g))} \tag{3.6}$$

Finally S(r) [Wm^{-3}] in equation 3.5 is a source term describing the distribution of light sources in the volume of interest.

The method above is comparable to first order perturbation theory, where an isotropic light distribution is perturbed with a gradient. In perturbation theory in general the perturbation must be small compared to the unperturbed contribution in order to have accurate results. With this point of view it is easy to understand that the actual light distribution must be fairly close to isotropic for the diffusion equation to be valid. Close to a light source light distribution is highly unisotropic and the diffusion equation is not valid. Further away from the source multiple scattering has occurred, the light has become diffuse, and diffusion theory provides accurate results. In the same way a condition for the validity of the diffusion equation is that the scattering coefficient is substantially larger than the absorption coefficient. Otherwise a large portion of the absorption will take place close to the light source, where light has not yet become diffuse.

An analytical solution is obtainable only in some special cases, e.g. a point source in infinite or semi-infinite homogeneous tissue. For more complicated geometries or inhomogeneous tissue numerical methods has to be used. The diffusion equation is in itself an approximation and when using numerical techniques, for obtaining a solution, additional approximations are made. This has to be taken into account when evaluating the model.

3.4 Monte Carlo simulations

In a paper in Med. Phys. November 1983 [14], a new model for tissue optics was presented. The probabilistic model, called Monte Carlo, had previously been used in medicine in the study of ionising radiation. Although this first model had substantial limitations the basic principles have remained the same. These principles, based on statistical methods, will be briefly presented in the following section.

The Monte Carlo model is, in contrast to the diffusion model, not an attempt to obtain an actual solution to the transport equation. Instead the absorption and light distribution is obtained by simulating the paths of multiple photon packages in tissue. The simulation is performed in terms of random walk for the photon packages where direction is changed at scattering events, the photon packages are attenuated at absorption events and terminated when fully absorbed or exiting the tissue.

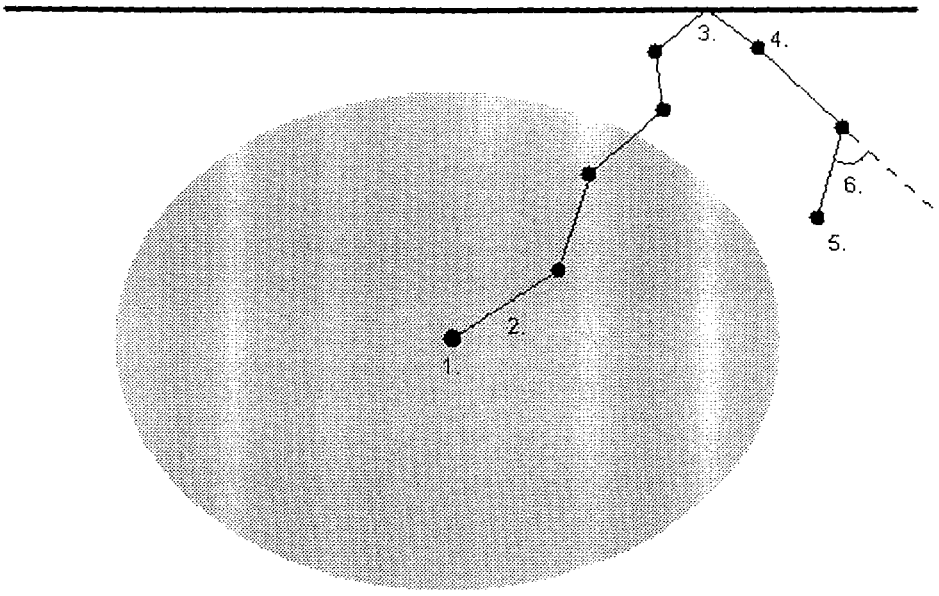

Figure 3.2 The path of a photon package during a Monte Carlo simulation. The shaded area represents tumour tissue and the solid line in the top of the figure represents a boundary between tissue and air.

Following the numbering used in Figure 3.2 the major simulation steps for one photon package are:

1. A photon package is sent from the light source, either through a boundary or inside the tissue. The photon package is assigned a weight describing the energy of the package.

2. Based on the total attenuation coefficient, μ_t, a stepsize is randomly selected and the package is moved this distance to a new location.

3. If the new location is outside the tissue one part of the photon package is lost through the boundary. The remaining part is reflected back into the tissue according to Fresnel reflection and a new location and weight for the package is calculated.

4. Due to absorption the weight of the photon package is attenuated a factor proportional to the absorption coefficient, μ_a.

5. If the weight is smaller than a predefined threshold value the package is terminated with a certain probability or enhanced by a factor. This factor and the probability for termination are chosen in a way that on the average no energy is lost in this step.

6. According to the angular distribution defined by the phase function the photon package is scattered into a new direction. The new direction is defined

by the angle given by the phase function, in combination with the azimuthal angle, randomly selected in the interval 0 to 2π.

7. If the photon package has not been terminated, the simulation continues with step 2.

The process described above is repeated for several photon packages and information about e.g. the absorption in each point is saved. In order to get good statistics in the simulation a large number of photon packages has to be used. An example of output from a Monte Carlo program can be seen in Figure 3.3.

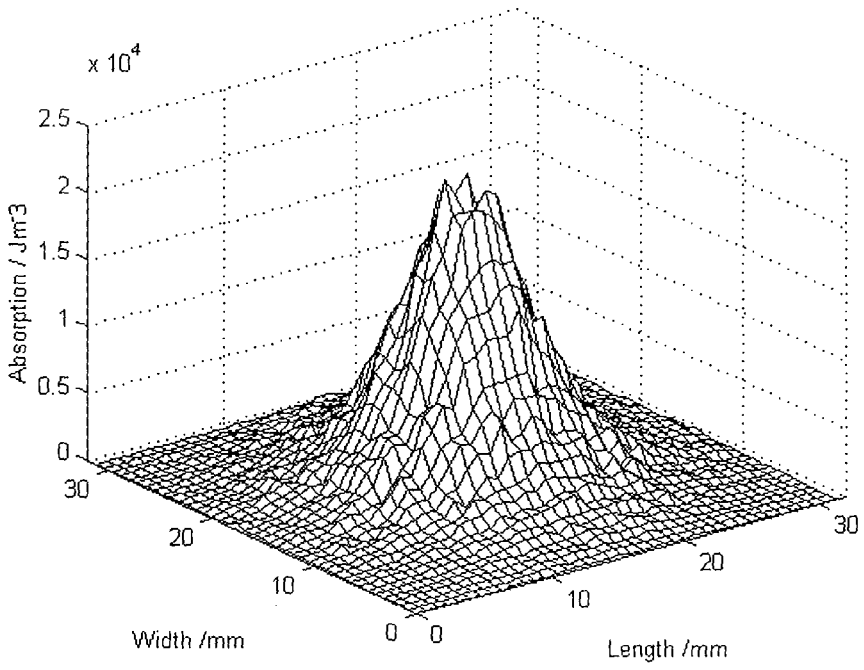

Figure 3.3 The absorbed light dose, in homogeneous tissue, in a plane a few mm from a light source. Near the boundary the curve is not as smooth as it is closer to the source due to too few simulated photon packages.

4. The dosimetry model

A dosimetry model predicting the light dose absorbed in tumour and surrounding tissue is essential when performing PDT. In interstitial PDT all the optical fibres used can be placed independently in the tumour, the illumination time can vary among the fibres and the geometry of the tumour might be complex. All these parameters obviously complicate the situation compared to the treatment of skin cancer by superficial illumination, making dosimetry even more important in interstitial PDT. If the positions of the optical fibres are not carefully selected several undesired situations might occur, e.g. parts of the tumour could be left untreated, healthy tissue surrounding the tumour might be damaged or the treatment time could be longer than necessary. By using a good dosimetry model and thereby planning the treatment in advance, the risk for these situations to occur could be limited. In addition, dosimetry makes it possible to detect damages and changes in tissue during treatment. Appropriate steps in order to minimise the damages, e.g. switching one or several fibres off, can then be taken.

Faced with the actual problem of writing computer code for performing dosimetry at interstitial PDT, decisions have to be made regarding what mathematical model to use. For realistic geometries none of the models mentioned above offers an analytical solution both accurate and simple to obtain, instead some sort of numerical method must be used. Monte Carlo simulations provide accurate results and are rather straight forward to implement. A drawback to the Monte Carlo method is the fact that simulations are quite time consuming. Especially for points in space where the photon flux is low, a large number of photon packages need to be simulated in order to get good statistics, and thereby an accurate solution. The growth of tumours is located at the boundary between malignant and healthy tissue, making this area especially interesting in PDT. Since the photon flux often is low at this boundary Monte Carlo simulations is not a realistic choice for dosimetry if speed in the calculations is of importance. Since diffusion theory gets more accurate at larger distances from the light source, where the photon flux is low, this seems to be a better choice. As mentioned above the diffusion equation can not be solved analytically, other than for a few special cases, thus numerical techniques like the finite element method must be used.

4.1 The finite element method

A numerical technique mostly used in engineering for mathematical modelling of mechanical systems is the finite element method. This method is very versatile and can be used for solving different kinds of partial differential equations for various boundary conditions. The basis for this method is to divide the entire region of interest into smaller elements, so called finite elements [15,16]. An assumption is made of how the solution varies over one

element, e.g. linearly, and a solution for the entire region is then calculated by considering the interaction between the elements. By varying the geometry of the finite elements almost any region of interest can be modelled to sufficient accuracy.

There exist several general finite element programs, both freeware and commercial, on the market. None of the programs we investigated could, however, solve our specific problem, thus these existing programs would have had to be modified for our purpose. Since our experience is that such a modification can be rather complicated and since the dosimetry program had to be incorporated with another computer program controlling the hardware, we chose to implement a finite element method program of our own. The program was implemented as a Windows DLL (Dynamic Link Library) using C++. Our intentions here is not to fully describe the finite element method but rather to give a brief introduction. We choose to do this by describing the steps taken in the implementation of our model.

In order to quickly get a working prototype of the dosimetry program we chose to do the first implementation in Matlab. When having a working program in Matlab we could easily translate the code into C++, apart from a few well-defined problems e.g. representation of large, sparse matrices and an equation solver. In the following section we will describe the procedure when making the Matlab implementation and in section 4.3 we will concentrate on the algorithms and data structures chosen for the C++ implementation.

4.2 Implementation considerations

Our first step when implementing the dosimetry program was to decide the geometry of the tissue volume to be studied. We decided to restrict ourselves to a box where the sides could be of different lengths. This box would contain the tumour, being surrounded by healthy tissue. The next step was to divide the box into smaller finite elements and decide the shape of these elements. In our case cubic elements seemed to be an appropriate choice, since it would be easy to divide the box into these elements and the following calculations seemed to be simpler. The solution to the diffusion equation is only considered at the corners of the finite elements and in between linear interpolation is made. For the finite elements a so called element stiffness matrix is calculated. This matrix describes the interaction of the eight corners in the cube, i.e. to what extent the solution for one corner influences the solutions at the other corners. Since only the corners of the finite elements are considered, the whole volume of interest is described by a large three-dimensional grid of points. These points are numbered in a systematic way and a large matrix, where each row represents a single point, is formed. The matrix element at row i and column j gives the influence of point number j on point number i. All elements in this so called global stiffness matrix can be calculated using the element stiffness matrix and the numbers of neighbouring points. Since only neighbouring points contribute to the matrix, most of the matrix elements will be zero. If we call the global stiffness matrix A and let the

solutions for all the points form a vector X, we get a system of linear equations:

$$AX=B \tag{4.1}$$

where B is a vector containing information about light sources and boundary conditions. The whole light distribution problem is thus reduced to solving a system of linear equations, i.e. obtaining the vector X.

4.3 Data structures and algorithms

Matlab has built-in functions to represent large matrices and to solve systems of linear equations. Thus the program described in the previous section was rather straight forward to implement. Since it is not possible to incorporate a Matlab program with other languages and since Matlab code is rather slow we had to rewrite the program in C++. There were no major difficulties in translating the code apart from the two issues mentioned above, namely how to represent a large matrix where a majority of the elements are zero and how to solve the large system of linear equations in an efficient way.

In matrix A in equation 4.1 each row represents a point in three dimensional grid forming the volume of interest. As an example, suppose that our volume of interest is cubic and each side is divided into 30 elements. This makes a total of 30^3 points in the grid, and thus the matrix will contain $(30^3)^2$ elements. If we use double precision floating point numbers (represented with 8 bytes) to represent the matrix elements the matrix would require $8*(30^3)^2 \approx 5.8$ Gbytes of memory. This is not possible to represent in an ordinary computer so we had to use a structure where only non-zero elements are represented. The most efficient way to implement such a structure depends on whether an assumption about the order in which the elements are to be accessed is made or not. Since we at this point did not know what method to use when solving the system of linear equations no assumption about the accessing order could be made. We used a large array where each element represents one row of the large matrix. Each array element contains the non-zero elements of the corresponding row of the matrix, stored in a structure making fast access to the elements possible (Figure 4.1).

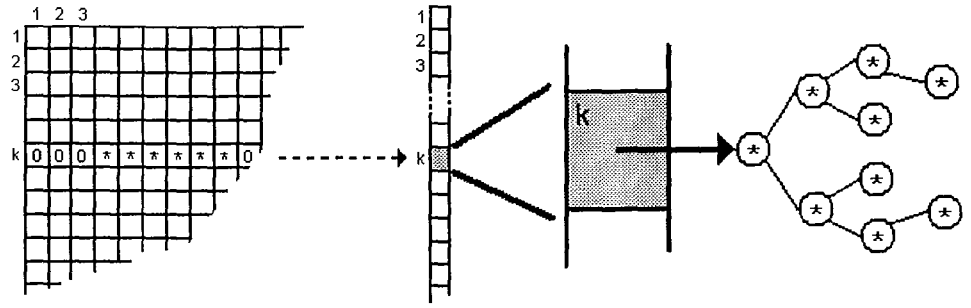

Figure 4.1 A schematic picture showing how a large matrix is represented in the dosimetry program. Each row in the matrix is represented by one element in an array. The array element contains a tree where each non-zero element in the matrix row is represented by a node.

This structure was chosen to be a balanced binary search-tree, which has been proven to be an efficient data structure for situations like ours [17]. This representation of the matrix allows us to allocate memory only for the non-zero elements, which dramatically decreases the memory usage.

A widely used method for solving systems of linear equations is the LU-decomposition, which is the method used in Matlab [17,18]. Briefly described this method splits the original system of linear equations into two systems, easier to solve. Thus equation 4.1 is transformed to:

$$\begin{aligned} LY &= B \\ UX &= Y \end{aligned} \tag{4.2}$$

where L is a lower triangular matrix, U is an upper triangular matrix and Y is a temporary vector. A problem in our case was that even though the original matrix only had a few non-zero elements in each row, the matrices L and U could contain many more non-zero elements. This made the calculations time- and memory-consuming and an alternative method had to be found. We found out that methods often used for solving systems of linear equations, where a large part of the elements are zero, are the iterative methods. Applied to our problem these methods use an initial guess about the vector X and calculate the left hand side of equation 4.1. By comparing the calculated values with the vector B on the right hand side, a new improved guess about the vector X can be made. By iterating this procedure, solutions with increasing accuracy can be found. Different algorithms for making the guesses and iterations exist and we chose to use the Gauss-Seidel algorithm [19]. It is necessary to set a condition for stopping the iteration. In our case we stopped the iteration when the norm of the difference between the calculated and actual right hand side was less than a certain value. It is worth noticing that this introduces an error in the calculations that has to be taken into account when evaluating the dosimetry program.

By using the methods and structures described above a working program was implemented in C++. The program uses e.g. the optical parameters, the

geometry of a tumour and the fibre positions to calculate the light distribution in the volume of interest.

4.4 Evaluation of the dosimetry program

To be able to evaluate the dosimetry program a comparison was made with an analytical solution to the diffusion equation. As mentioned above analytical solutions are obtainable only for a few special geometries, e.g. a point source in infinite homogeneous tissue. In order to imitate these conditions with the dosimetry program, calculations were made for a fairly large homogeneous cube. The cube had to be large to minimise the effect of the boundaries on the light distribution. The analytical solution for the geometries mentioned above is:

$$\phi(\mathbf{r}) = \frac{W\mu_{eff}^2}{4\pi\mu_a}\frac{1}{|\mathbf{r}|}\exp(-\mu_{eff}|\mathbf{r}|) \tag{4.3}$$

$$\mu_{eff} = \sqrt{3\mu_a(\mu_a + \mu_s(1-g))} \tag{4.4}$$

where the optical parameters are defined in section 3.1, W is the source strength and r is the distance from the source.

In the comparison we used the following optical parameters: μ_a=0.05 mm^{-1}, μ_s=10 mm^{-1} and g=0.9. The light source was placed in the centre of a cube with a side length of approximately 25 mm and the source strength was set to 100 mW. The matrix, containing the absorbed light dose, produced by the dosimetry program was loaded into Matlab and the analytical solution was evaluated in the corresponding points. Studies were made at different sections of the cube for the two solutions (Figure 4.2).

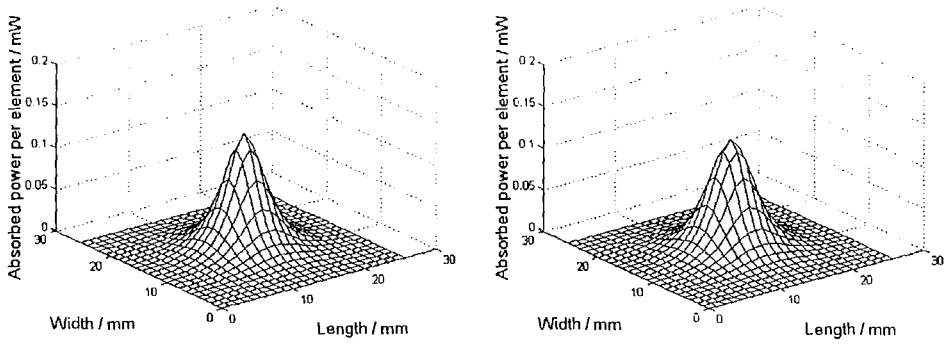

Figure 4.2 The graphs are showing the absorbed power per element for the analytical solution (to the left) and the finite element method solution (to the right). The section showed is a few mm away from the light source.

The difference between the two solutions were studied and we found that they differed by about 5 % or less (Figure 4.3). We have found that the relative difference is largest close to the light source. This is probably due to that the iterative method used for solving the system of linear equations, mentioned in section 4.3, is converging slower where the slope of the curve is steeper. This is not a significant problem since the diffusion equation is not valid close to a light source anyway and the fibres used in the interstitial PDT system will not be placed that close together.

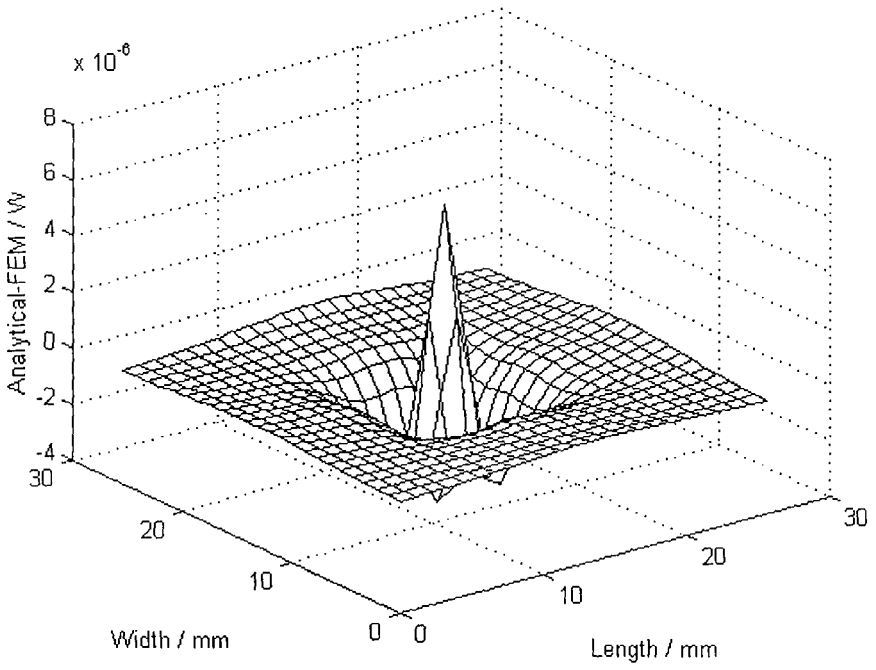

Figure 4.3 The difference between the analytical and the finite element method solutions in the same section as the one showed in Figure 4.2.

In order to test our model for an inhomogeneous volume of interest, a Monte Carlo program was implemented according to the principles described in section 3.4. In this program it is possible to place the light source inside a spherical tumour with variable radius. A comparison was made for the absorbed energy in each element between the Monte Carlo simulation and the finite element program. The absorbed energy was studied in different sections of the volume of interest for both models (Figure 4.4). The optical parameters used for the tumour were: μ_a=0.050 mm^{-1}, μ_s=10 mm^{-1} and g=0.9 and for the tissue surrounding the tumour they were: μ_a=0.025 mm^{-1}, μ_s=5 mm^{-1} and g=0.9. In the Monte Carlo program 1,000,000 photon packages were used in the simulation.

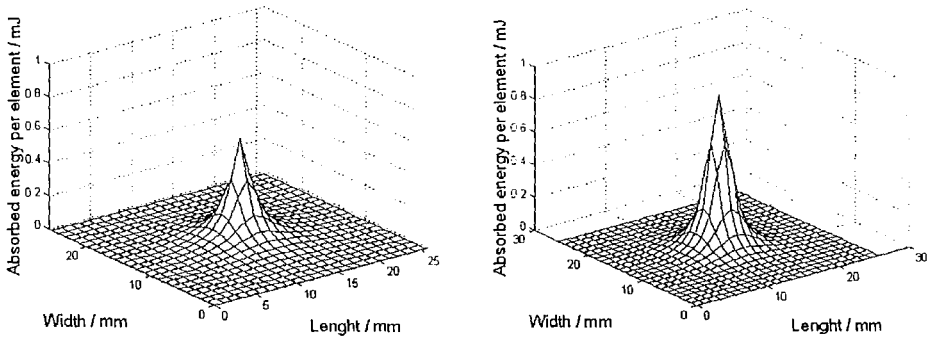

Figure 4.4 The calculated absorbed energy in a section for the Monte Carlo program (to the left) and the finite element program (to the right).

The calculated absorbed energy distributions for the two models are quite similar except close to the light source, where the deviation is up to 50 %. As mentioned above the diffusion equation, which is the basis for our dosimetry model, is not valid close to the source and the deviation is thus expected. To be able to study this in more detail the absorbed energy distribution in the two models along a line through the volume is shown in Figure 4.5.

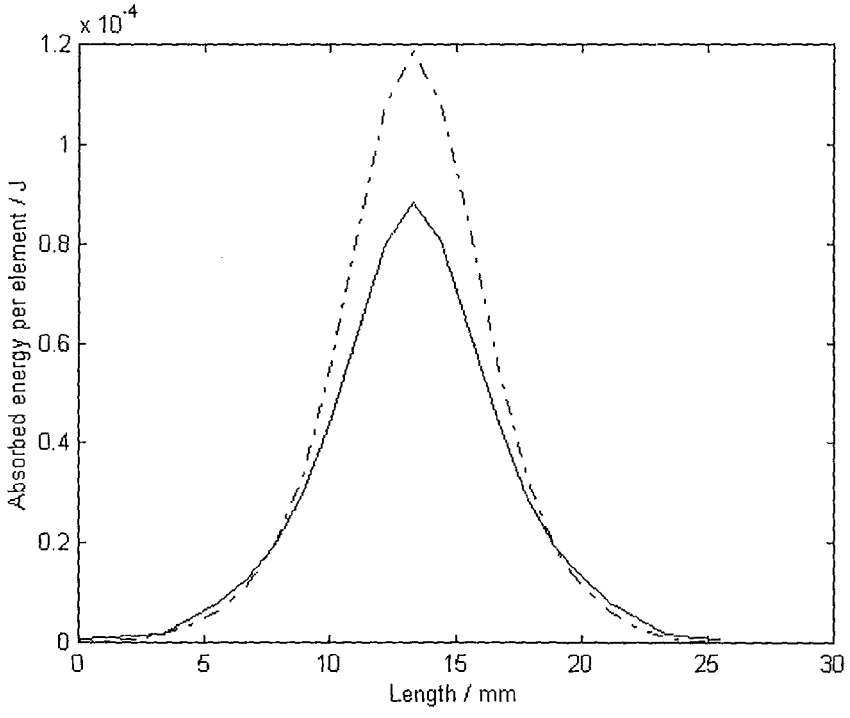

Figure 4.5 The calculated absorbed energy along a line through the volume of interest for the Monte Carlo program (solid line) and the finite element program (dotted line).

5. Hardware

The system for performing interstitial PDT consists of two main parts: a light source and the actual PDT dosimetry system. Both of these parts had been developed prior to this diploma work, but modifications have been made to the latter one. The light source and the dosimetry system will be described in more detail in the following sections. Apart from these two parts the system includes optical quartz fibres, with core diameters of 400 μm, and a personal computer controlling the system. Both the fibres and the computer are standard equipment, wherefore we will not describe them any further.

5.1 The light source

Performing PDT, using ALA as photosensitiser, requires light of wavelengths around 635 nm. It is possible to get light at this wavelength from a dye laser system, but such a system requires a pump laser, e.g. a Nd:YAG laser. Thus the total system gets rather large and clumsy. The light source used within this Master's thesis is an InGaAsP diode laser (Ceralas PDT635) designed for medical use [20] (Figure 5.1).

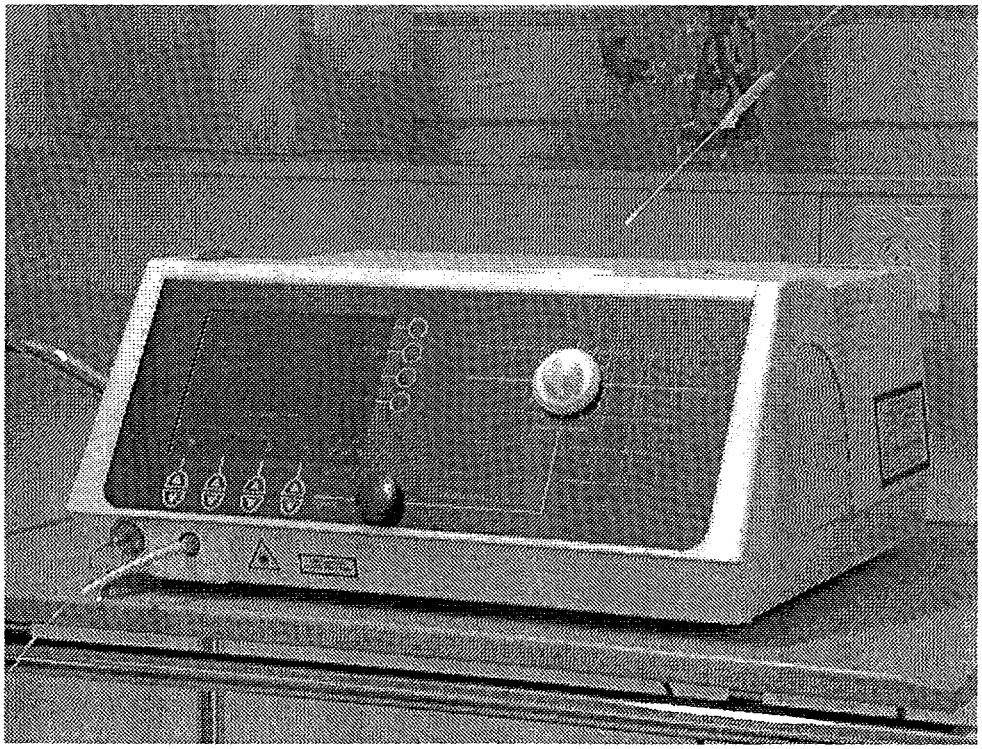

Figure 5.1 The diode laser used for interstitial PDT.

The output power of this laser is variable in the range 0-1.5 W and the wavelength of the light is around 635 nm. In order to deliver light from the laser to the dosimetry system an optical fibre with a core size of 400 μm is connected to the output connector. This fibre must have an numerical aperture of 0.37 to 0.48 to be able to deliver the maximum power of the laser. A great advantage with this laser system, beside its handy dimensions, is the power supply requirements; 230 VAC and 1.7 amperes, which makes it possible to connect the laser to an ordinary wall socket.

5.2 The interstitial PDT dosimetry system

The interstitial PDT dosimetry system was developed at the Division of Physics in Lund. The two main features of the dosimetry system are the possibility to split the laser light, supplied by the diode laser, into three or six output fibres and that it enables monitoring of the light delivered by the dosimetry system to the tumour via the output fibres (Figure 5.2 and Figure 5.3).

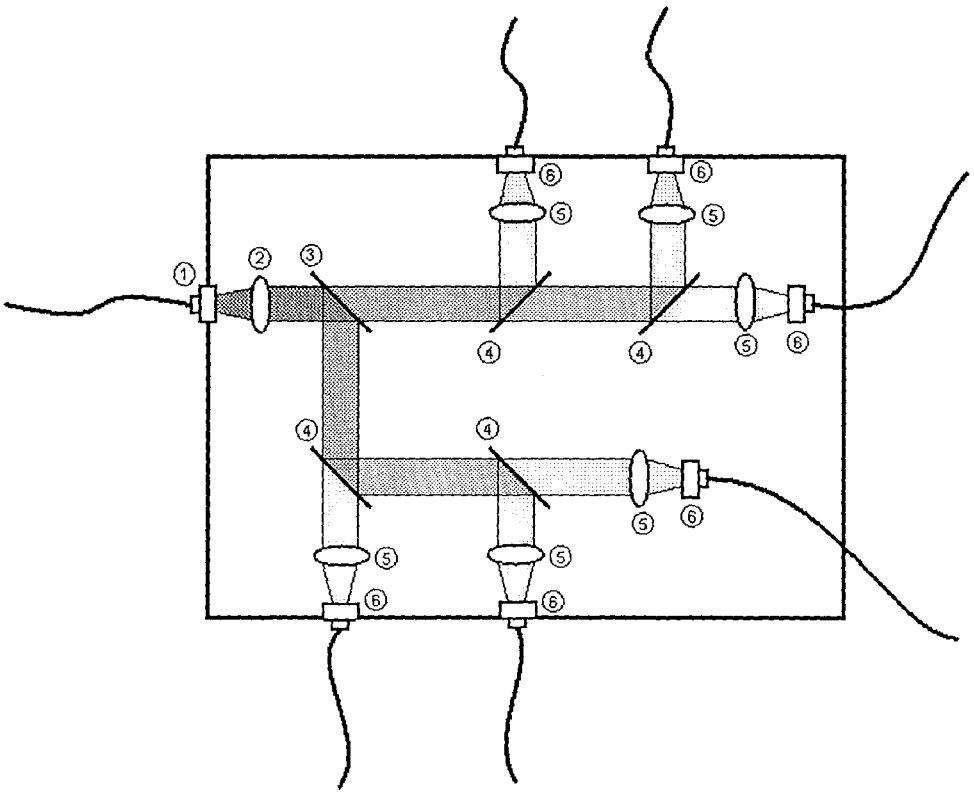

Figure 5.2 A sketch showing the interstitial PDT dosimetry system viewed from above. The laser light enters through a fibre and is divided into six parts and delivered by the dosimetry system through six output fibres.

The light, delivered by the laser through the input connector (marked as 1 in Figure 5.2), is collimated by a lens (2). An optional 50/50 beamsplitter (3)

makes it possible to use either three or six output fibres, which is determined by the size of the tumour to be treated. Additional beamsplitters (4) are used to split the light into equal parts (three or six). Finally, lenses (5) focus each part of the laser light on the output connectors (6) delivering the light to the tumour via the output fibres. In its original appearance the system suffered from substantial light losses due to e.g. mismatch of numerical apertures. Originally the system was designed to use fibres with a core diameter of 200 μm, but when using the diode laser, fibres with a core diameter of at least 400 μm have to be used. In addition there were large difficulties in adjusting the equipment (lenses, output connectors, beamsplitters etc.). Consequently the dosimetry system was modified in terms of new lenses and new output connectors easier to translate in the x-, y- and z-directions.

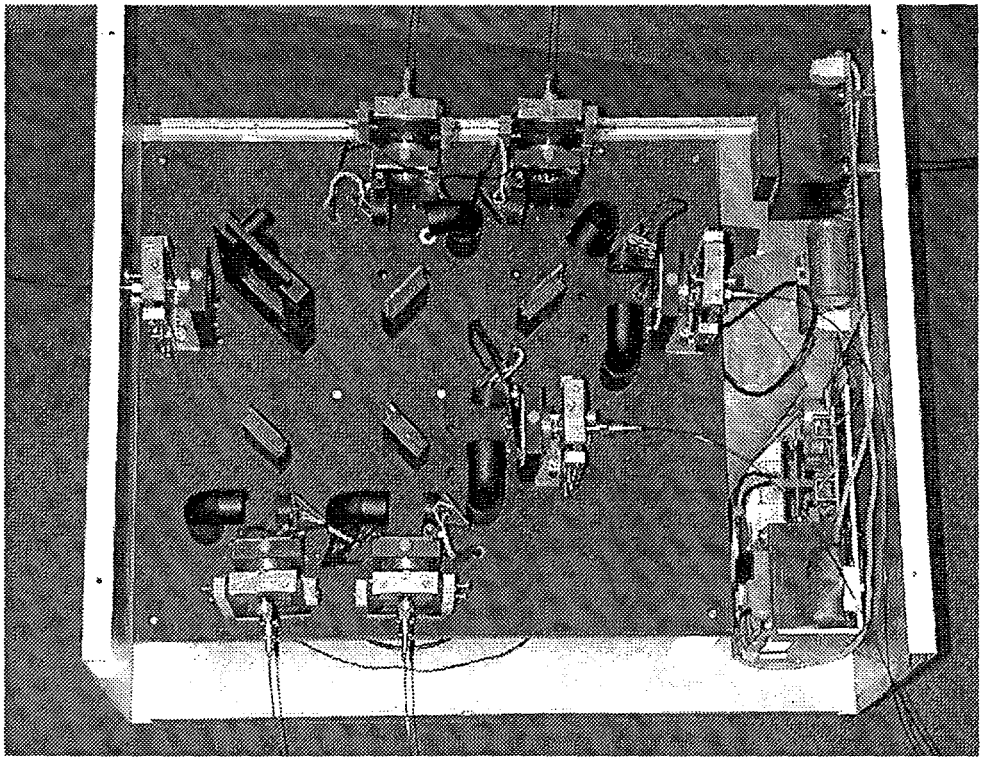

Figure 5.3 Top view of the interstitial PDT dosimetry system with fibres. The leftmost fibre is the fibre delivering light from the diode laser.

Monitoring of the light distributed in the tumour is accomplished by diodes mounted on rotating vertical axles between the lens and the output connector. By turning the axle, the diode is positioned at the end of the output fibre. In this way the laser light is blocked and the light propagating from the tumour (illuminated by the other fibres) through the fibre can be measured. By measuring and blocking the fibres alternately, the influence of each fibre on the light flow at all the other fibres can be estimated in a way similar to tomography (CT). Studying the measured values and how they change with time will hopefully give information about changes in the tissue during treatment, e.g. damage to blood vessels, enabling proper actions to be taken.

6. Software

During an interstitial PDT session it is practical if most of the equipment used can be controlled and automatically operated by a computer. The interstitial PDT dosimetry system in its original version was controlled by a program developed at the Division of Physics in Lund. In order to fit our specifications the program had to be modified, but since such a modification would have been to complicated, we decided to implement a program of our own. LabVIEW, developed by National Instruments, was chosen as programming language because of its ability to communicate with hardware and because of its built-in and easy to use graphical toolbox.

6.1 LabVIEW

LabVIEW is a procedure oriented graphical programming language especially useful when performing data acquisition and controlling instruments. A program written in LabVIEW is called a virtual instrument (VI) and consists of two main parts: the front panel and the block diagram.

The front panel is the graphical user interface receiving input data from the user and presenting the results. LabVIEW has a large number of built-in graphical tools for presenting and receiving data. These tools are designed to imitate input and output devices, such as digital displays, knobs, slides and so on, on real instruments. In LabVIEW an input device is called control and an output device is called indicator.

The block diagram is the source code, where each control and indicator used in the VIs front panel is represented by a block (Figure 6.1). Common structures and operations used in ordinary programming languages, e.g. for-loops, while-loops and if-statements, are also represented this way. These blocks are connected by wires showing the flow of data through the program. A VI can be used as a separate program or as a subprogram in other VIs. If the VI is used as a subprogram the icon of this VI forms a block which can be connected by wires as any other block in the block diagram. Each input and output parameter is represented by a wire connector.

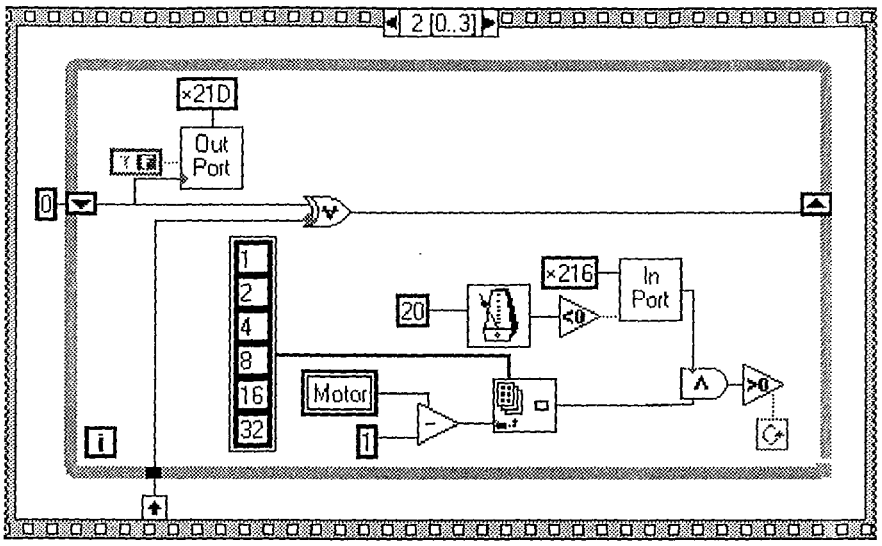

Figure 6.1 An example of a block diagram from LabVIEW. This VI is taken from the interstitial PDT program and is used for closing one of the output fibres.

It is possible to incorporate code written in other programming languages into LabVIEW. We used this feature when connecting the dosimetry program, written in C++, with the interstitial PDT program. Our reason for not writing the dosimetry program in LabVIEW was that extensive mathematical calculations tend to be very slow in LabVIEW, both to implement and to execute. LabVIEW supports at least two different ways to import modules not written in LabVIEW: code interface nodes (CINs) and windows DLLs. When using the CINs, ordinary C functions can be used but the code has to be modified to fit the data structures used in LabVIEW. When we tried using CINs for the dosimetry program we encountered problems with the memory handling in LabVIEW. We also found it very hard to debug the CIN, since it was not possible to run the CIN as a separate program and thereby removing all other sources of errors. By using the DLLs instead these problems were overcome and it was also possible to write the program in an object oriented way, making debugging even easier. When used in LabVIEW a DLL works in the same way as an ordinary VI, i.e. it is represented by a block with input and output connectors. A drawback to using DLLs in LabVIEW is, however, that no other LabVIEW processes can run simultaneously with the DLL, i.e. the multitasking ability of LabVIEW is lost.

6.2 The interstitial PDT program

In the following sections we will briefly describe the functionality and to some extent the implementation of the program we have developed within this project. The description will mainly follow the use of the program as it is to be used during an interstitial PDT treatment.

6.2.1 Defining the tumour

Prior to a tumour treatment the size and type of the tumour has to be determined. This is typically done at least a couple of hours before the actual treatment takes place. At this point it is possible to start the dosimetry calculations by defining the tumour in the interstitial PDT program. First the user is asked to choose tissue types for the tumour and the normal tissue surrounding the tumour (Figure 6.2).

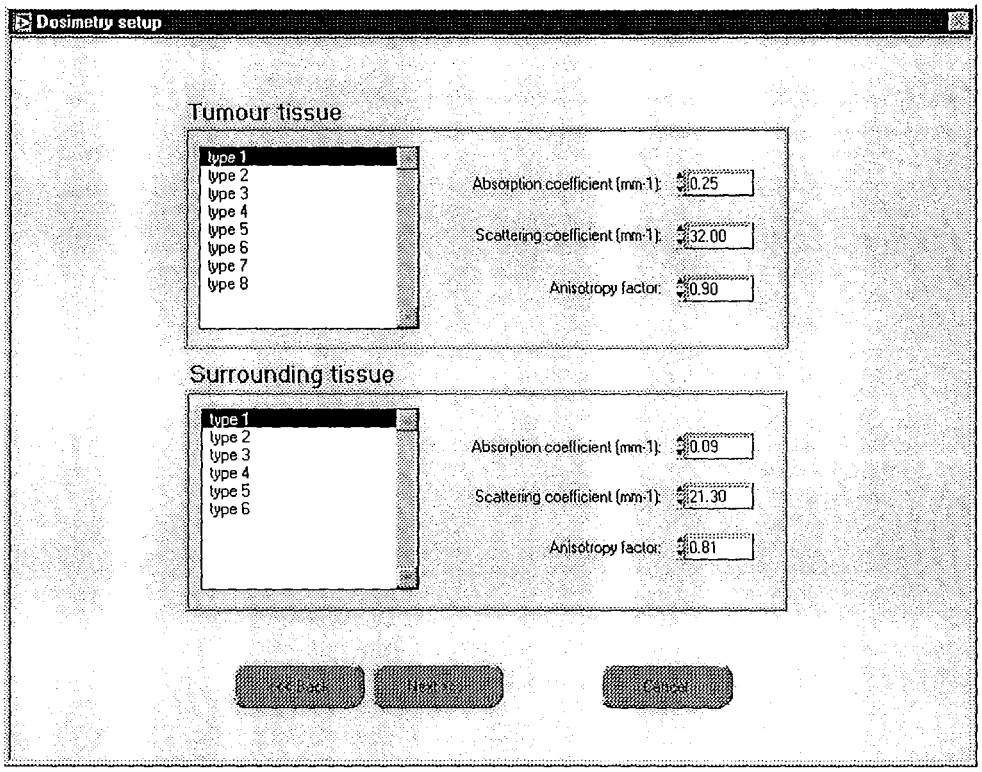

Figure 6.2 A screen shot from the interstitial PDT program where the user can define the tumour type and the type of the surrounding tissue.

The information about tissue types is needed since the optical parameters described in section 3.1 differ between different types of tissue and this will influence the light distribution in the volume of interest. Some common tissue types are stored in two files, Normaltissue.dat and Tumtissue.dat, containing the optical parameters for some normal and tumour tissue types respectively. It is very easy to add new types since the files are plain text files read by the program. In addition the user can set the optical parameters to any desired value. The chosen values are stored in global variables so they can be used later in the program.

Once the optical parameters are set the user is asked to choose a shape, best representing the tumour, from a list of predefined shapes. The program is designed in a way that makes it relatively easy to add new shapes to the list. Depending on the chosen shape different VIs are opened where the user is

asked to enter parameters specific for this shape, e.g. if the shape of the tumour is chosen to be spherical, the radius of the sphere is asked for.

6.2.2 Defining the light sources

When the tumour is defined the user has to decide how many optical fibres to use during treatment. It is possible to set the power delivered from each fibre, since this can vary depending on what laser is used and how well the system is aligned. The next task for the user is to decide the position of each fibre in the tumour (Figure 6.3).

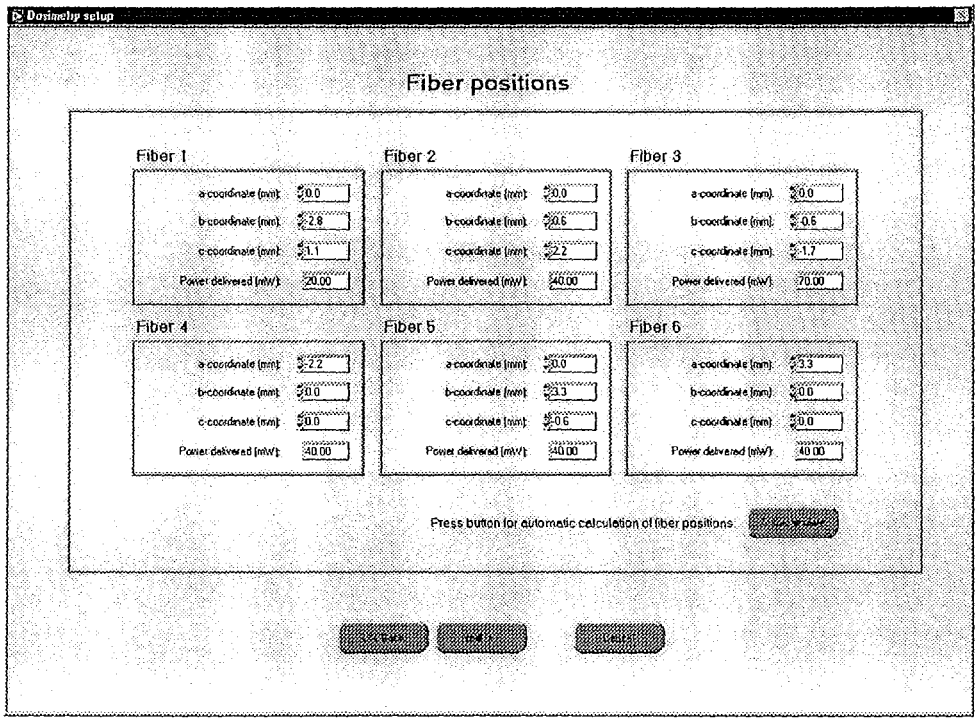

Figure 6.3 A screen shot from the interstitial PDT program where the positions of the fibres are to be determined either by the user or automatically by the program.

The position is defined by three co-ordinates that can be entered either by hand or suggested by the program. When the program is used to suggest the co-ordinates the program calls a DLL written in C++. This DLL contains a function that tries to optimise the total treatment time by placing the fibres properly. Optimising the treatment time is the same as maximising the minimal light dose in the tumour. When trying to find an optimal configuration of the fibres, several different algorithms are used in sequence. Briefly described, the program first identifies the point in the tumour where the light dose is minimal and then moves a fibre closer to this point, hopefully resulting in a more even light distribution. This procedure is repeated until there is no further improvement. Then a routine for local optimisation is used for trying to improve the solution by moving the fibres to neighbouring points. The DLL function is not guaranteed to give the optimal configuration

of the fibres but has proven experimentally to give fairly good results within a reasonable calculation time.

6.2.3 Performing the dosimetry calculations

When the dosimetry calculations are to be performed by the program, the user is asked to enter the name of a file where the results of the calculations will be stored. In this way the calculations can be done in advance and the dosimetry file can be loaded into the program when the treatment takes place. The program calls the DLL containing the dosimetry program and passes information about the tumour and the light sources as parameters. To make the program more flexible the dosimetry calculations are performed for each fibre individually. The light doses from the different fibres are then added to obtain the total light dose. If one fibre for some reason must be excluded during treatment the program can easily calculate the new light dose by just subtracting the effect of the excluded fibre. If there are changes in the optical parameters during a treatment, e.g. due to changes in blood perfusion, the program, as it is, has no possibility to adjust for this. The dosimetry calculations are quite time consuming and the time required depends strongly on the number of elements used in the finite element grid. The program automatically sets the number of elements so the calculations can be performed in a reasonable time, i.e. in the order of a few minutes.

6.2.4 Performing an interstitial PDT treatment

At the time of the actual treatment, the user is first asked to choose a file from a list of the predefined dosimetry files. The program reads the data from the file and stores it as global variables for later use. The user then enters several parameters necessary for the treatment (Figure 6.4).

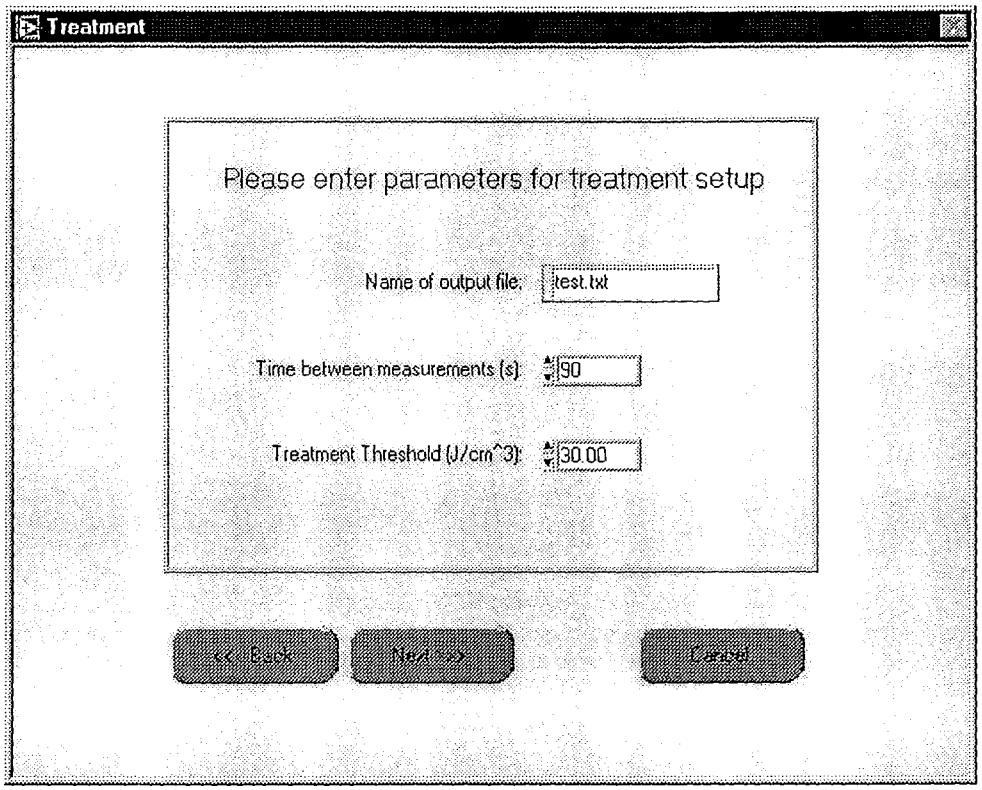

Figure 6.4 A screen shot from the interstitial PDT program where it is possible to enter parameters used by the program during the treatment.

The user is asked to enter the time interval between the computer controlled measurements. In the output file the measured values from the diodes, described in section 5.2, are stored to enable later evaluation of the interstitial PDT session. A threshold value for light absorption is used for calculating the total treatment time required. The threshold value gives the minimum light dose needed for the photodynamic reaction to be effective. The program then guides the user through the preparations for the treatment, e.g. lets the user know when to place the fibres in position and when to turn the laser on. Once the fibres are in position a background acquisition is performed, i.e. a measurement is made when all the output fibres are blocked.

When the background acquisition is completed the fibre gates open up and all the fibres start illuminating the tumour. During treatment interrupts are made, with the interval previously set by the user, to perform measurements with the diodes and then presenting the result to the user (Figure 6.5).

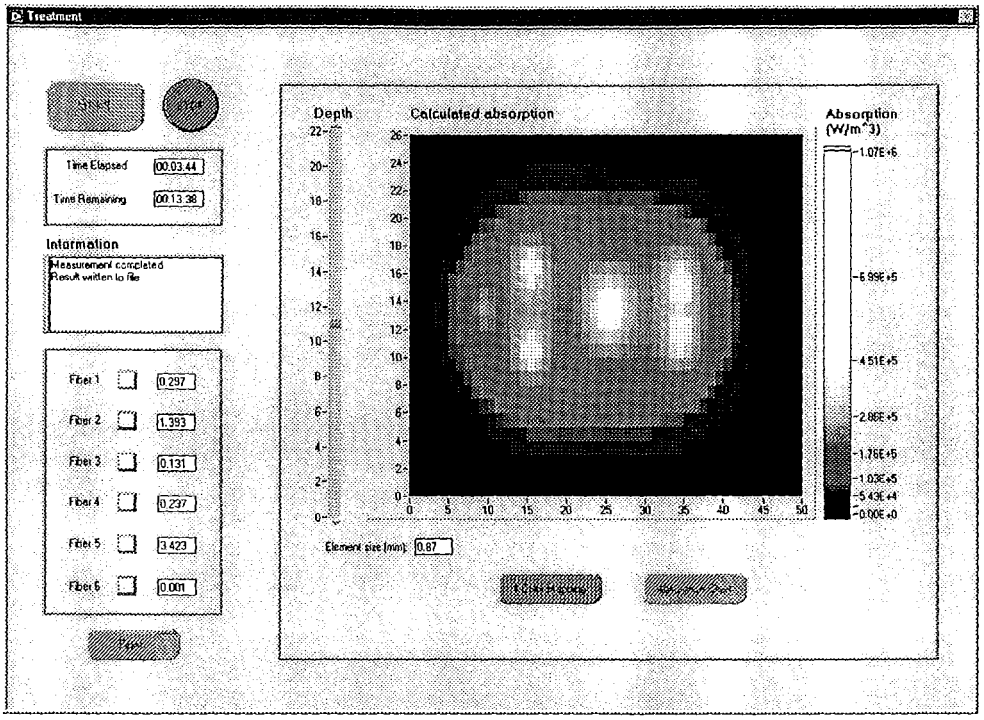

Figure 6.5 A screen shot from the interstitial PDT program showing e.g. the calculated light distribution in the tumour to be treated (to the right) and the latest measured diode signals (to the left).

The user can at any time stop the treatment, i.e. close all the fibres, by pressing the stop button and then restart the session by pressing the start button. The user can continuously monitor the progress of the treatment in a graph showing the parts of the tumour already having received a light dose higher than the predefined threshold (Figure 6.6).

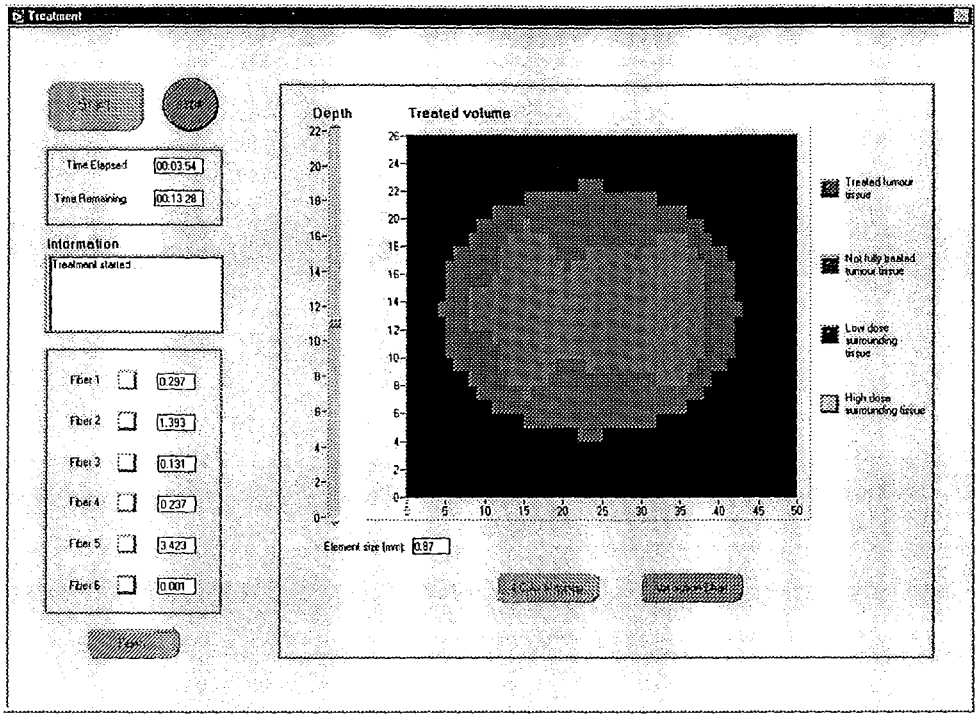

Figure 6.6 A screen shot from the interstitial PDT program showing e.g. what parts of the tumour that have received a light dose larger than the threshold value.

In the same graph it is also possible to study the calculated light distribution in the tumour layer by layer (Figure 6.5). Both the calculated remaining treatment time and the total elapsed time is presented to the user and the user is alerted when the elapsed time is greater than the calculated time.

6.2.5 The structure of the program

The whole program consists of a large number of separate VIs, all being controlled from the main program (Figure 6.7).

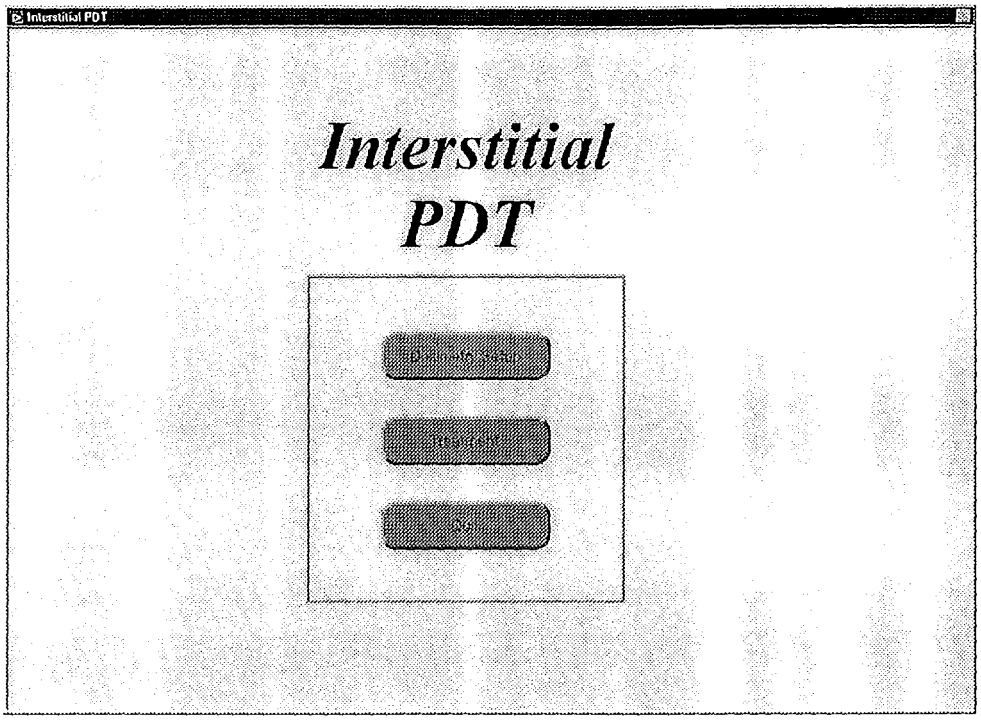

Figure 6.7 A screen shot from the interstitial PDT program showing the main menu of the program.

All calls to VIs from the main program are made dynamically in a way that makes it easy to add new VIs and thereby new features to the program. The program is divided into two separate loops working individually. The first loop handles the preparations for a treatment, i.e. defining the tumour and light sources and performing the dosimetry calculations. The other loop handles the treatment session routines. Communication between different VIs is performed by writing and reading of global variables, i.e. variables that can be accessed by any active VI. The program uses three different directories for system and data files. In the system directory a compiled version of the program and the DLLs mentioned above are found together with the data files used by the program, e.g. files containing information about different tissue and tumour types. Dosimetry files are stored in a separate directory called the setup directory and finally all the output files with the data from the treatment are stored in the output directory as text files.

7. Experiments and results

Two treatment sessions were performed at the Lund University Hospital during this project. On each occasion three naked mice with large tumours on the side of their bodies was injected with ALA and the interstitial PDT system was used for the treatment of the tumours (Figure 7.1).

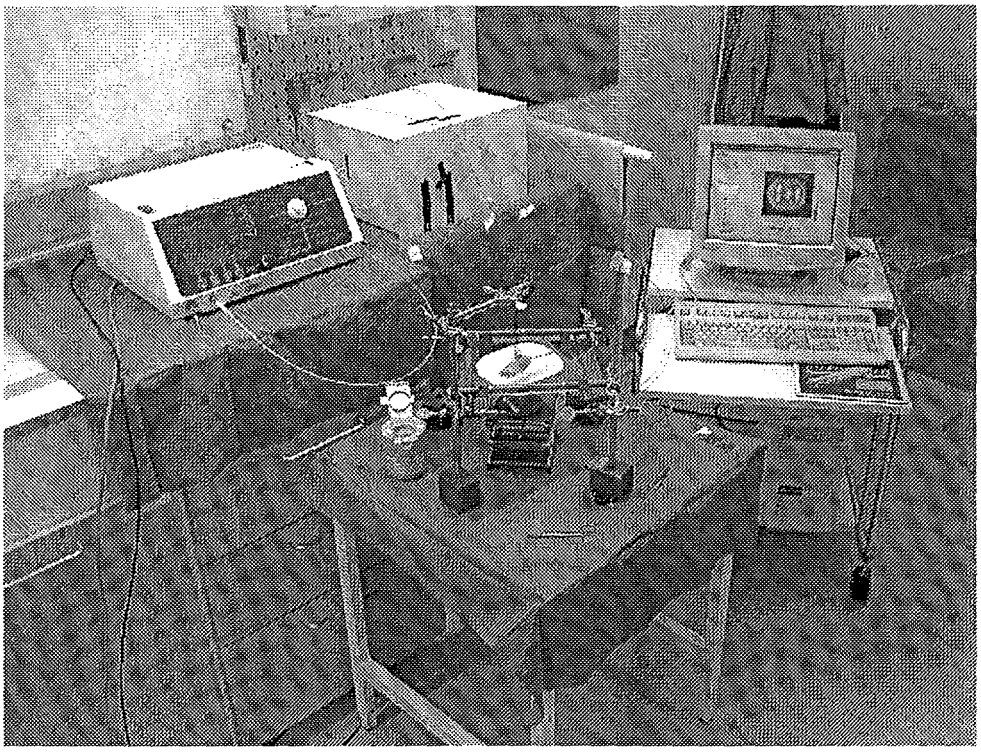

Figure 7.1 The set-up for an interstitial PDT treatment on mice.

We had two main purposes of these sessions. One was to evaluate the dosimetry model by measuring the total treated volume and compare that with the predicted volume. The other purpose was to test and evaluate how well adapted the system was for real treatments.

7.1 Experimental set-up

Prior to the treatment, the size of each tumour was determined and the light distribution was calculated for different fibre configurations (the auto-calculation of the fibre positions was not implemented at the time of these treatments). The system was aligned and the output power from each fibre was optimised. Even though the system had been rebuilt, the light losses were considerable and a maximum total output power, from the six fibres together, of 250 mW was achieved when the laser was delivering 1.5 W. A few days in

advance to the treatments new fibres were cut, new fibre connectors were applied onto the fibres and the fibre tips were polished. Approximately two hours before the treatment a mouse was injected with ALA in a dose of 100 mg per kg body mass. Immediately before the start of the treatment the mice were anaesthetised. The total treatment time was limited to approximately half an hour, which was the time the mice could be kept asleep.

7.2 Results and discussion

The six tumours that were treated varied in size and shape from almost spherical with a radius of 6 mm to oval with a total length of 33 mm. Thus the calculated treatment times also varied extensively, but as mentioned in the previous section the upper limit was set by the time the mice were asleep. This was not regarded as a real problem since we wanted to try different light doses in order to estimate the threshold value anyway. The treatments were interrupted automatically every 90th or 120th second to perform measurements with the diodes. Data from one set of measurements are shown in (Figure 7.2).

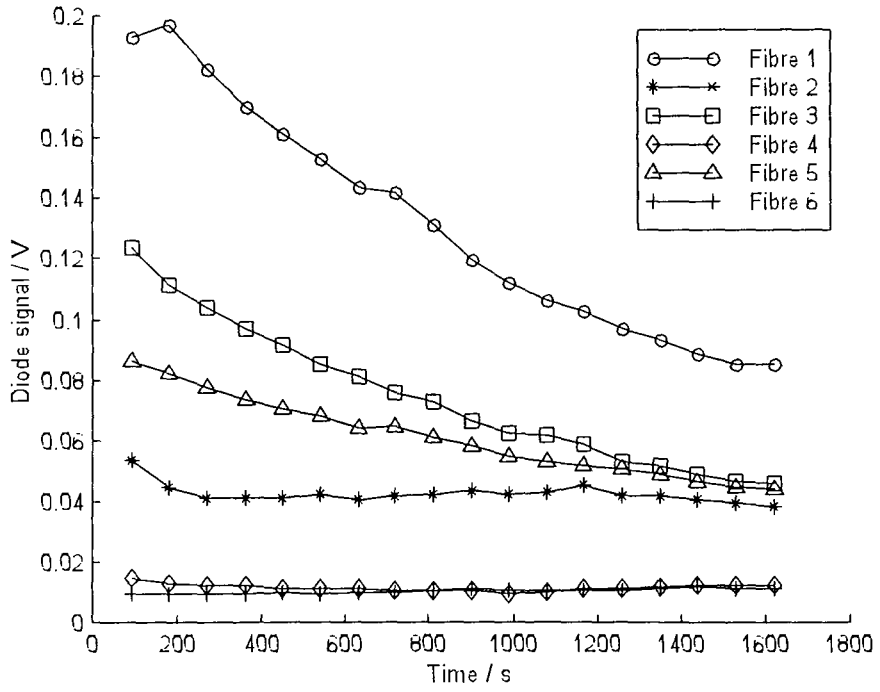

Figure 7.2 Results from a measurement performed on a mouse. Each curve corresponds to the diode signal, given by the light propagating back through one fibre, when illuminating the tumour through the other five fibres.

This figure shows the diode signal levels, measured every 90th second, when one fibre is used for measurement and the other five are used as light sources

in the tumour. On every measuring occasion all six fibres were used for measuring sequentially. The fibres were positioned along the main axis of the ellipsoidal tumour and the most powerful fibre was placed on top. Because of the positions of the fibres and the variation in output power between the fibres it is obvious that the levels of the diode signals differ. The decrease in signal was probably caused by increased absorption, a phenomena that has been observed earlier in connection with PDT [21].

The equipment and the software worked satisfactory during both treatment sessions. A problem encountered during the treatments was, however, that it was very difficult to place the fibres exactly as had been decided prior to the treatment when performing the dosimetry calculations. This difficulty caused the death of one mouse during treatment as one fibre punctured one of the mouse's vital organs when it was to be positioned. Unfortunately it was not possible to evaluate the treatment results on the other five mice as they all died a few days after the treatment. The reasons for this was probably that ALA accumulate not only in tumour tissue, but also in some other tissue types, such as the liver and the intestine. Both these organs are located very close to the tumour in the mice. Thus the photochemical reaction occurred in these organs as well leading to lethal damages. In addition, the tumours of some of the mice were large at the time of treatment and the tumour burden might have contributed to the deaths of the mice.

8. Discussion and conclusions

The purpose of this Master's thesis was to develop a dosimetry model for propagation of laser light in tumour tissue during an interstitial PDT treatment and to improve the hard- and software used for this kind of treatment. The system (dosimetry model, hard- and software) has been tested when performing treatment on mice.

During the treatments performed at Lund University Hospital the system showed good stability and the functions of the controlling program worked as expected. However, some difficulties showed up concerning positioning of the fibres. Fibres with smaller core radius would make it easier to insert the fibres into the tumour since cannulae then could be used. The use of thinner optical fibres would hopefully also decrease the risk for haemorrhage (bleeding). Unfortunately it is not possible to use such fibres in combination with the diode laser mentioned in section 5.1 since the losses in the fibre coupling then would be too large. There is also need for some kind of fibre holder fixing the positions throughout the treatment. To make full use of the dosimetry program, it must be possible to verify the actual positions of the fibres in the tumour. This could perhaps be accomplished by ultrasonic imaging or by magnetic resonance imaging. An alternative to the interstitial PDT dosimetry system would be to use six separate diode lasers directly connected to the output fibres. Using this set-up it is, however, not completely obvious how to use the same fibres both for delivering and measuring light. In the set-up we have been using it would be desirable to use a laser less divergent in order to reduce the light losses at the fibre couplings. An interesting idea including a diode laser array placed in a cavity with a phase conjugating mirror has been developed by a research group at Riso National Laboratory, Roskilde, Denmark [22].

The fact that the mice died in connection with the treatments does not, in our opinion, indicate that the model and method are not working properly. The mice were so small that the tumours became a very large part of the total body volume and were located close to vital organs. In addition the fibres used were thick, especially for small animals, and the fibre holders used were far from ideal. These are probable reasons for the mice's deaths. In the calculations prior to the treatment, no considerations were made to minimise the dose in the vital organs surrounding the tumour. An evaluation of the treatment modality would first require studies of larger animals with tumours located at larger distances from vital organs. Such studies would give the opportunity to make an accurate estimation of the threshold value of the light absorption in order to achieve the desired treatment result. After these studies the dosimetry program could be used for calculating optimal conditions, e.g. fibre positions and treatment time, for performing interstitial PDT on tumours close to vital organs.

The diode signals given during a treatment can give hints about larger changes in the structure, e.g. punctured blood vessels. Thus it would be an easy task to modify the program to automatically take proper actions in such a situation, e.g. close one fibre and recalculate the treatment time. It would also be desirable to make some measurements on tissue samples with known optical parameters to be able to make an absolute calibration of the diode signals.

A problem with the dosimetry model is that real tissue often is quite inhomogeneous, a fact that in principle could be accounted for in the dosimetry program but is very difficult to measure in advance to the treatment. A first step would be to locate larger blood vessels, since blood is absorbing light to a larger extent than other tissue constituents. Perhaps ultrasonic imaging could be a method for accomplishing this.

A hope for the future is that it would be possible to build an integrated system both for diagnostics and treatment. This system should have possibilities for performing fluorescence measurements during treatment in order to make dynamic monitoring of the photosensitiser distribution possible. It would also be of great use if the oxygenation of the tumour could be measured during treatment, since oxygen is essential for the PDT treatment to be effective. This measurement could perhaps be accomplished by looking at the absorption of white light in the tumour. It has been suggested that PDT in association with thermotherapy could have some synergy effects that perhaps could be used in future systems [23]. Thus the system should also have possibilities for performing temperature measurements.

In comparison with other tumour treatment modalities, interstitial photodynamic therapy has the advantages of being rather simple and inexpensive. The equipment can also be made fairly small and mobile. Since the radiation sources are located inside the tumours, the method is harmless to the surrounding organs and tissue when the optical fibres are placed properly. Future photosensitisers with better selectivity between diseased and healthy tissue will make PDT even more effective. The method has the benefit of being a complement rather than an alternative to other methods, such as ionising radiation. The method of interstitial photodynamic therapy is still in an early phase of development, but in our opinion it has potentials of being a useful therapy method.

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