Advanced 3D Monte Carlo Algorithms for Biophotonic and Medical Applications

Lewis McMillan

University of
St Andrews

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Declaration

I, Lewis McMillan, hereby certify that this thesis, which is approximately 32000 words in length, has been written by me, that it is the record of work carried out by me, or principally by myself in collaboration with others as acknowledged, and that it has not been submitted in any previous application for a higher degree.

I was admitted as a research student in September 2015 and as a candidate for the degree of PhD in September 2015; the higher study for which this is a record was carried out in the University of St Andrews between 2015 and 2019.

Date ..... Signature of candidate .....

I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate for the degree of PhD in the University of St Andrews and that the candidate is qualified to submit this thesis in application for that degree.

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Abstract

The Monte Carlo radiation transfer (MCRT) method can simulate the transport of light through turbid media. MCRT allows the simulation of multiple anisotropic scattering events, as well as a range of microphysics such as polarisation, and fluorescence. This thesis concerns the development of several MCRT algorithms to solve various biophotonic and medical problems. Modelling of tissue ablation, autofluorescent signals, and a theoretical quasi-wave/particle MCRT model were developed as part of this thesis.

Tissue ablation can be used to treat acne scarring and Rhinophyma, it can also be used to help enhance topical drug delivery. Currently depth of ablation is not easily elucidated from a given laser or laser power setting. Therefore, a numerical tissue ablation model is developed using MCRT, a heat diffusion model, and a numerical tissue damage model to assess ablation crater depth and thermal damage to the surrounding tissue.

Autofluorescence is the natural fluorescence of biological structures in tissue. Autofluorescence can be used as a biomarker from several diseases including: cardiovascular diseases, Alzheimers and diabetes. However, the origin of the signal is not completely clear. The effect of tissue optics on the signal, which fluorophores contribute to the signal and by how much, and how different locations on the body can effect the signal are all not well understood. This thesis presents a study on the effect of tissue optics on the autofluorescent signal. As part of this study AmoebaMCRT was created to determine the relative concentrations of fluorophores for a given autofluorescent signal.

Finally, we have developed an extension to the MCRT that allows the simulation of quasi-wave/particles. This method relies on the Huygens-Fresnel principle and the tracking of the phase of each individual photon packet. The extension, φMC, allows the modelling of complex beams that require the wave properties of light such as Bessel, and Gaussian beams. We then use φMC to predict which beam, Bessel or Gaussian, preforms "better" in a highly turbid medium.

Acknowledgements

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Contents

Abbreviations

FEM finite element method.

MCRT Monte Carlo radiation transfer.

NM Nelder-Mead.

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Chapter 1

Conclusion

1.1 Summary

To summarise this thesis, MCRT is a powerful technique that can be used to calculate the transport of light (as particles or quasi-wave/particles) through turbid media, whilst modelling multiple anisotropic scattering alongside a variety of microphysics. The only noted downsides to the MCRT method noted in the literature (as well as discussed at length in this thesis) is the computational load required for some problems, and the selection of optical properties. With the growing power of computational devices, the computational load of MCRT becomes less of a factor. Likewise the optical properties of various biological tissues, are increasing being measured with greater precision and accuracy.

Chapter 1 introduced the concept at the heart of this thesis, the Monte Carlo method. The chapter gave examples of how the Monte Carlo method can be used to sample from spectra, and how it is can be used to model various physical events. Chapter 2 followed on from chapter 1's explanation of the Monte Carlo method, by introducing MCRT used in all subsequent chapters. Chapter 2 also covered the theory behind the method and presented details of the implementation of the method into code as well as various computational speedups utilised.

Chapter 3 described the application of the MCRT method to modelling tissue ablation. Details of how the MCRT was coupled up to a numerical model of heat diffusion and thermal damage model was presented. The chapter showed that we can successfully model experimental and theoretical data with our numerical model. The power the model has is that we can predict thermal damage, and ablation crater size for any laser, and configuration thereof, without the need to test on humans or animals. It also allows the testing of different lasers without the purchase of said laser, which could allow clinicians to "try before they buy". The chapter also presented (with tongue firmly in cheek) the application of this numerical model to humane spy disposal.

Chapter 4 presented the modification of the MCRT method, such that it would allow the modelling of the photon packets as quasi-wave/particle packets, in place of the usual particle model MCRT models. This was achieved via a few small changes within the code, based upon well understood theoretical models, namely the Fresnel-Huygens principle. The method was thoroughly validated against several theoretical expressions. The method was also validated against experimental results from collaborators at the University of Dundee. The new method was then used to compare Bessel and Gaussian beams performance in highly turbid media, to see which beam preformed "better".

Chapter 5 presented a model of skin autofluorescence using MCRT. The chapter detailed a five layer skin model created to accurately model the skin effect on light transport. The five layer model included the various chromophores found in the skin such as blood, water, and melanin. The model also includes various naturally occurring fluorophores. Changes in the autofluorescent response of tissue has been shown to be indicative of various diseases. However, details of how each fluorophore contributes to the signal is not well understood. Therefore a study on how tissue optics affects the autofluorescent signal, and how much each fluorophore contributes was undertaken. The MCRT algorithm was also coupled to an optimisation technique to determine relative concentrations of the fluorophores in the skin from a given autofluorescent signal. The technique chosen was the Nelder-Mead method. The Nelder-Mead (NM) method uses simplices in order to move around the search space and find global minima. The method was coupled to the the MCRT algorithm and thoroughly validated against toy models. Finally details of how autofluorescent data from collaborators was fitted to using these techniques.

1.2 Future Prospects

There are several avenues of promising work that can continue on from this thesis.

The code developed as part of the tissue ablation chapter, could easily be adapted for use in modelling photothermal therapy. Photothermal therapy is the use of light to selectively heat up nanoscale materials that have been inserted into tumours. The nanoscale materials, such as gold nanorods, are targeted with a specific wavelength of light (usually near infra-red) which heats up the rods and thus the surrounding tissue, eventually killing the adjacent cells [1, 2]. This could be easily modelled within the code developed as part of chapter 3, with little to no major changes. The code could be used to help optimise photothermal treatment modalities and predict treatment outcomes.

There is also scope to improve the heat transfer model. As mentioned in the chapter, a simple explict model was used as it relatively easy to setup and solve a given problem using this scheme. However, this scheme leads to constraint on the timestep. This could be avoided by using an implicit scheme which is unconditionally stable for any timestep. Another way the heat transfer model could be improved is thought the use of the finite element method (FEM). The FEM allows PDEs to be solved on arbitrary grids, which would reduce the high memory requirement our model needs to achieve good resolution. The FEM would also allow a more accurate skin model to be included within the simulation, making the simulation more accurate.

Finally, the work of chapter 3 could also be extended to include a drug diffusion model. One use of tissue ablation is a an optical drill to create micro holes in the skin. These holes in the skin then allow better penetration of topical drugs. Modelling both the laser tissue ablation process and drug diffusion process in one simulation would allow *in-silico* testing of treatment parameters which could easily be optimised by the model.

The algorithm developed as part of chapter 4's work, φMC, also has several avenues of future research. It should be fairly easy to extend the algorithm to model other beams, such as an Airy beam. It should also be fairly trivial to implement a spatial light modulator (SLM). An SLM is a device that can modulate light that is incident on it including imparting phase to different parts of the incident beam. This allows arbitrary complex beams to be created. The ability to model an SLM would open up the ability to model complex experiments in such things as wavefront shaping. Other types of experiments the algorithm could be used for include: laser speckle imaging, focusing light though turbid media, and complex micromanipulation [3–5].

One obvious avenue of future research would be to improve the five layer skin model presented as part of chapter 5's work. The skin model presented is planar, where as tissue is not planar

in any sense. The first improvement on this could be to introduce a more complex geometrical structure into the voxel model. However, this method would quickly run into a computational wall. To represent the non planar reality of the tissue would require many voxels, such that the RAM required to run any simulation would be prohibitive to running the simulations. Therefore, a different geometrical model would need to be used. A solution to this was briefly investigated: use of a mesh to model the skin's structure. Triangular meshes can be used to approximately model any arbitrary shape or volume. The use of triangular meshes have been used to great effect by other authors in MCRT codes. Due to time constraints this was abandoned for this thesis before a fully working code could be developed. Figure 1.1 shows MCRT being preformed on a gourd, made from a triangular mesh.

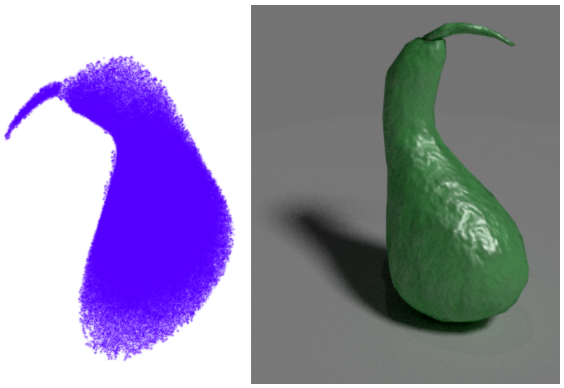

Figure 1.1: *Image on the left shows the fluence of light in a gourd, calculated using MCRT. The optical properties of the gourd in this simulations are similar to that of skin. The optical properties of the medium around the gourd are that of air. Image on the right shows a rendering of the same mesh in blender.*

A meshed skin model would allow objects like hairs, blood vessels, sweat glands, and the uneven boundaries greatly increasing the accuracy of the simulations.

Finally as the data from our collaborators machine was not of a quality such that it could be reproduced using amoebaMCRT, this data could be taken again with a better machine, or other authors could be found that have the requisite data. amoebaMCRT would then be run on this data to determine the amount of that each fluorophore contributes to the signal. Other optimisation techniques other than the NM method could also be explored. Techniques such as simulated annealing, genetic algorithms* or machine learning could be used. It could also be possible for our MCRT code to be used to create a "bank" of spectra that could then be used to train a machine learning algorithm to label peaks, and contributions to those peaks by fluorophores.

*The use of genetic algorithms was explored, however the computational cost of using them was deemed too high.

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