

Advanced 3D Monte Carlo Algorithms for Biophotonic and Medical Applications

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PhD
at the
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Declaration

I, Lewis McMillan, hereby certify that this thesis, which is approximately ***** 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.

Date Signature of supervisor

Date Signature of supervisor

Abstract

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Acknowledgements

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Abbreviations

MCRT Monte Carlo radiation transfer.

NM Nelder-Mead.

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Chapter 1

AmoebaMCRT, modelling autofluorescence in skin for novel biomarkers of cardiovascular disease

1.1 Introduction

1.2 Skin Model

So far in this thesis all tissue models have been simplified, by assuming that tissue is a homogeneous structure with uniform optical properties. However this is not the case in reality. Tissue is very un-homogeneous, with non-uniform optical properties. However to create a 1 to 1 model of tissue in a simulation is impractical due to the resolution required to resolve all the constituent part of the tissue down to the cell level. Therefore we need to make a compromise between reality and what is possible to model efficiently. To this end the section presents a 5 layer model of human skin. Dermatologists usually split the skin into 5 layers: Stratum Corneum, Epidermis*, Papillary Dermis, Reticular Dermis, and Hypodermis, see Fig. 1.1.

Each of these layers have various amounts of chromophores and scatterers. To accurately model these various chromophores and scatterers, and therefore the skin, we must discuss the chemical makeup and spatial structure of the skin.

Stratum Corenum

The top most layer of the skin is the stratum corenum. This layer mostly consists of dead skin cells (keratinocytes). The function of this layer is to be a protection barrier to prevent damage, infection and diffusion of unwanted chemicals.

*The epidermis can be split into several more layers, however these layers are optical similar and are rather small so we model just one layer here.

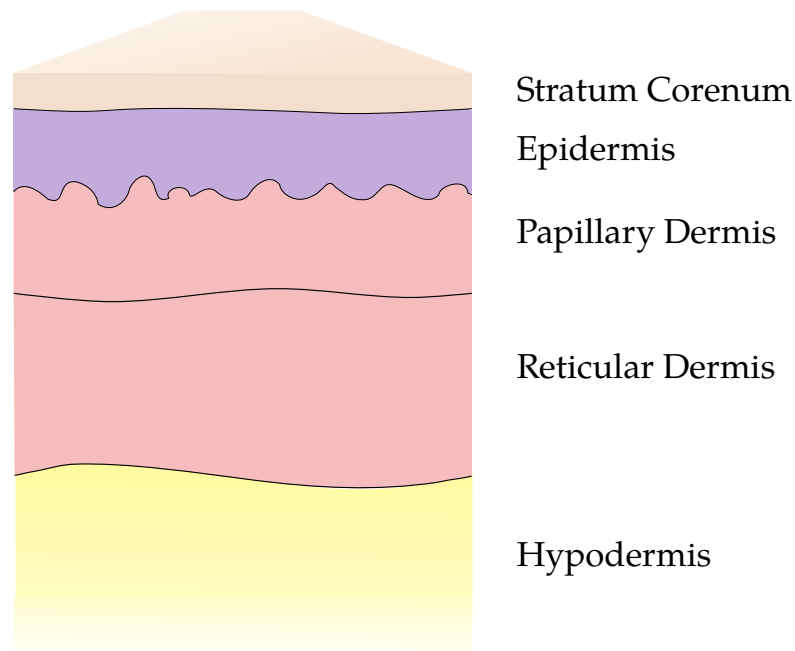


Figure 1.1: Illustration of skin layers in human skin.

Epidermis

Below the stratum corneum is the epidermis. The epidermis consists of several layers that are optically similar so we restrict our model to modelling as one whole layer. The layers that make up the epidermis are the stratum basale, stratum spinosum, stratum granulosum, and the stratum lucidum[†]. The purpose of the epidermis is as before to provide a protective barrier to the underlying layers. The epidermis contains melanin which protects the stem cell keratinocyte which divide to form keratinocyte which form much of the upper layers of the skin. In the stratum basale there is also melanocyte which produce the pigment melanin which is responsible for the color of the skin, and providing some protection from harmful UV light. Other types of cells found in the epidermis are Langerhans cells and Merkel cells which are part of the immune system and nervous system respectively.

Dermis

The dermis is split into three different layers in our model: the papillary dermis, reticular dermis and the hypodermis.

The papillary dermis has blood

The reticular dermis has blood

The hypodermis consists of fat and

[†]The stratum corneum is usually part of the epidermis, however as its optical properties are different than that of the epidermis we model it as a separate layer.

Optical Properties

With a discussion of what makes up the skin, and what molecules contribute to the skins optical properties, this section gives an account of how our skin model, models the optical properties of skin.

To model blood, we first split blood into Deoxygenated and Oxygenated. We mix these two groups using the tissue oxygenation coefficient S . Blood absorption spectra are taken from

$$\mu_{a,oxy/deoxy} = 150 \ln 10 \frac{\epsilon}{64458} \quad (1.1)$$

$$\mu_{a,b}(\lambda) = SO_2 \mu_{a,Oxy} + (1 - SO_2) \mu_{a,DeOxy} \quad (1.2)$$

The next chromophores are bilirubin and β -carotene. The absorption coefficients are calculated using the blah

$$\mu_{a,Bilirubin}(\lambda) = \frac{\epsilon_{bilirubin}}{585} \ln 10 C_{bilirubin} \quad (1.3)$$

$$\mu_{a,\beta-Caro}(\lambda) = \frac{\epsilon_{\beta-Caro}}{537} \ln 10 C_{\beta-Caro} \quad (1.4)$$

To model melanin's absorption coefficient we use Eq. (1.5), taken from...

$$\mu_{a,mel}(\lambda) = 6.66 \times 10^{11} \times \lambda^{-3.33} \quad (1.5)$$

Finally we use a base absorption coefficient to model the absorption due to the other parts of the skin that contribute to its optical properties, but individually do not have a large effect.

$$\mu_{a,b} = 7.84 \times 10^8 \times \lambda^{-3.255} \quad (1.6)$$

Figure 1.2: Absorption coefficients for the various chromophores found in skin.

1.3 Modelling Fluorescence

Fluorescence is the process in which light of a certain wavelength is incident on a molecule, the molecule absorbs the light and re-emits the light at a new longer wavelength.

Figure 1.3 shows an example of Jablonski diagram.

To model fluorescence from multiple fluorophores requires a change of the Monte Carlo radiation transfer (MCRT) code presented thus far. This change is to the interaction portion of the algorithm, so that it will now include the option for a packet to undergo fluorescence. To calculate whether a packet absorbs, scatters or fluoresces, first the probability of each of these events must be calculated. Discussion of scattering and absorption (by the bulk medium) was described in ???. To calculate the probability of fluorescence, we first assume that the quantum yield of the molecule is unity. This is physically unrealistic, however it does not affect the simulations accuracy, as modelling a realistic quantum yield would mean that more packets would be discarded, and thus the signal to noise ratio would be worse than if we assume a quantum yield of unity. To calculate the probability of fluorescence, the absorption coefficient of the fluorescent molecule must be calculated. This is shown in Eq. (1.7):

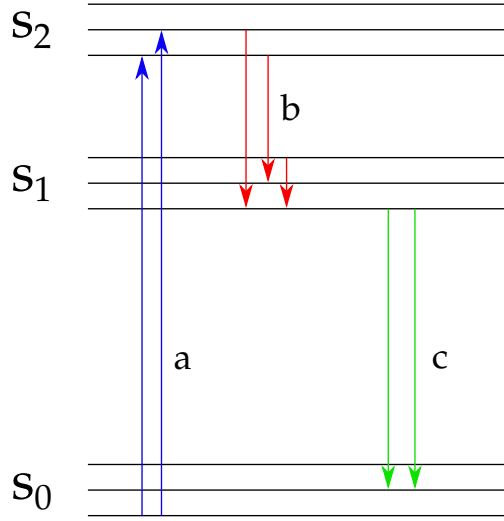


Figure 1.3: Jablonski diagram for PPIX. a) excitation of the ground state via absorption of a photon, b) non-radiative transition, and c) fluorescence.

$$\mu_f = \ln(10) C \varepsilon \quad (1.7)$$

Where C is the concentration of the fluorophore, ε is the extinction coefficient of the fluorophore, and $\ln(10)$ is the natural logarithm of 10[‡].

The next step is to calculate the total attenuation coefficient for a given species as in Eq. (1.8)

$$\mu_{t_i} = \mu_{s_i} + \mu_{a_i} + \mu_{f_i} \quad (1.8)$$

Where as usual μ_a and μ_s are the absorption and scattering coefficients, and μ_f is the fluorescence coefficient as defined in Eq. (1.7). As the absorption coefficient of fluorophores are small in comparison to the medium, and that the absorption coefficient of fluorescent molecules are generally much larger than that of their scattering coefficient, we assume that the scattering coefficient is negligible. Finally we calculate the probability of interacting with a given species using Eq. (1.9)

$$P_i = \frac{\mu_{t,i}}{\sum_{i=1}^N \mu_{t,i}} \quad (1.9)$$

Where P_i is the probability of interacting with the i^{th} species, the numerator is the attenuation coefficient for i^{th} species, and the denominator is the total attenuation coefficient for all the species.

Algorithm 1 shows the process used to determine which species to interact with.

[‡]This factor appears as historically ε was measured in base 10 [1].

```

set  $\mu_{tot}$ ;
set all  $P_i$ 's;
set  $\xi_1$ ;
if  $\xi_1 < P_1$  then
    set  $\xi_2$ ;
    if  $\xi_2 < a_m$  then
        Scatter in medium;
    else
        Absorb in medium;
    end
else if  $\xi_1 < P_1 + P_2$  then
    Species 1 fluoresces;
else if  $\xi_1 < P_1 + P_2 + P_3$  then
    Species 2 fluoresces;
else if  $\xi_1 < P_1 + P_2 + P_3 + \dots + P_n$  then
    Species n fluoresces;
else
    Error;
end

```

Algorithm 1: *An algorithm to determine which species to interact with. P_1 is the probability of interacting with the bulk medium, P_2 to P_n is the probability of interacting with a fluorescent species, a_m is the albedo of the bulk medium, ξ_i is a random number, and μ_{tot} is the total attenuation coefficient of all the species summed.*

This method allows an arbitrary number of fluorophores to be modelled.

1.4 Nelder-Mead Method

The Nelder-Mead (NM) method is an algorithm for unconstrained optimisation. The algorithm is based upon iteratively updating a simplex. A simplex is a structure in $n - dimensional$ space, consisting of $n + 1$ points that are not in the same plane. Therefore in 1D, the simplex is a line, in 2D a triangle, in 3D a tetrahedron, etc.. The Nelder-Mead method is a gradient free method, meaning that it does not require derivative to be calculated and that the search space does not need to be smooth.

The algorithm works by removing the worst vertex of the simplex and replacing it with a ‘better’ vertex calculated via a number of different operations. These operations can be seen in Fig. 1.4.

The first step of the NM method is to sort the initial vertices according to their fitness. For $n = 2$, we define x_w as the ‘worst’ point, x_l and the ‘lousy’ point, and x_b the ‘best’ point, such that $f(x_b) \leq f(x_l) \leq f(x_w)$, where $f(x)$ is evaluating the ‘fitness’ of a point x . With the vertices sorted, the centroid of the simplex is calculated as in Eq. (1.10). The centroid is the mean of all the vertices bar the ‘worst’ point.

The next step is to move the simplex via a reflection. To calculate the new vertex via reflection Eq. (1.11) is used, where α is the reflection factor. If this new point, x_r , is better[§] than the current ‘best’ point then we calculate a new point in the same direction but further using the expansion operation Eq. (1.12), where γ is the expansion factor. If this new point, x_e ,

[§]Here better means the point has a lower fitness score, as we use χ^2 metric to assess the fitness of a point.

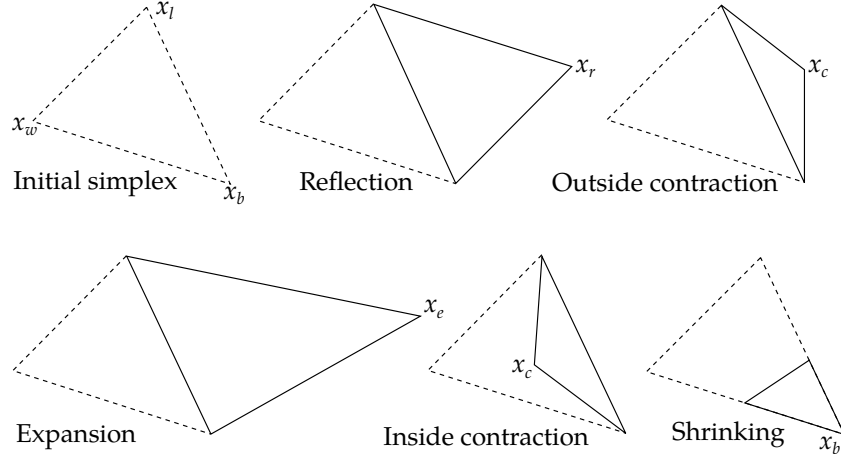


Figure 1.4: Operations that can be performed on a simplex for $n = 2$.

is better than the ‘best’ point then we replace x_w with x_e and start the process again. However if x_e is not better than the ‘best’ point, then we discard it and replace the worst point with x_r the reflected point.

If when calculating x_r , we find that it is worse than the ‘best’ point, we then check if x_r is better than the ‘lousy’ point. If x_r is better than x_l then we replace the ‘worst’ point and start the process again. However if the x_r is worse than x_l , we then compare it to the ‘worst’ point. If x_r is better than the ‘worst’ point then we perform an inside contraction Eq. (1.14), where β is the contraction factor. If this new point, x_{ic} , is better than the ‘worst’ point then we keep it, otherwise we perform the shrink operation, shrinking the whole simplex around the ‘best’ point.

If x_r is not worse than the ‘worst’ point then we perform an outside contraction Eq. (1.13). This computes a new point x_{oc} . If x_{oc} is better than x_w , then we keep it, otherwise again we shrink around the ‘best’ point.

The process described above is summarised in Fig. 1.5. Standard values for the factors are: $\alpha = 1$, $\beta = \frac{1}{2}$, and $\gamma = 2$. Though in practise these values are adjusted for the problem at hand.

$$c = \frac{1}{n} \sum_{i=1, i \neq w}^{n+1} x_i \quad (1.10)$$

$$x_r = c + \alpha(c - x_w) \quad (1.11)$$

$$x_e = c + \gamma(x_r - c) \quad (1.12)$$

$$x_{oc} = c + \beta(x_r - c) \quad (1.13)$$

$$x_{ic} = c + \beta(x_w - c) \quad (1.14)$$

As the Nelder-Mead method has no inbuilt convergence criteria, this must be added. We use two different criteria based upon simplex size, and vertex fitness. The criteria for the simplex size is as; if the size of the simplex (Eq. (1.15)) Where p_i and p_{i+1} are vertices in the simplex that are connected by an edge.

$$size = \sum_{i=1}^{n+1} |p_i - p_{i+1}| \quad (1.15)$$

If the size of the simplex falls below a pre-set value, then we perform a factorial test to see if the simplex should be restarted or if the algorithm should terminate. The factorial test checks the space around the current simplex to ensure that we have converged to a global minima. If the check fails then the algorithm is restarted with the current best point kept, and new vertices generated.

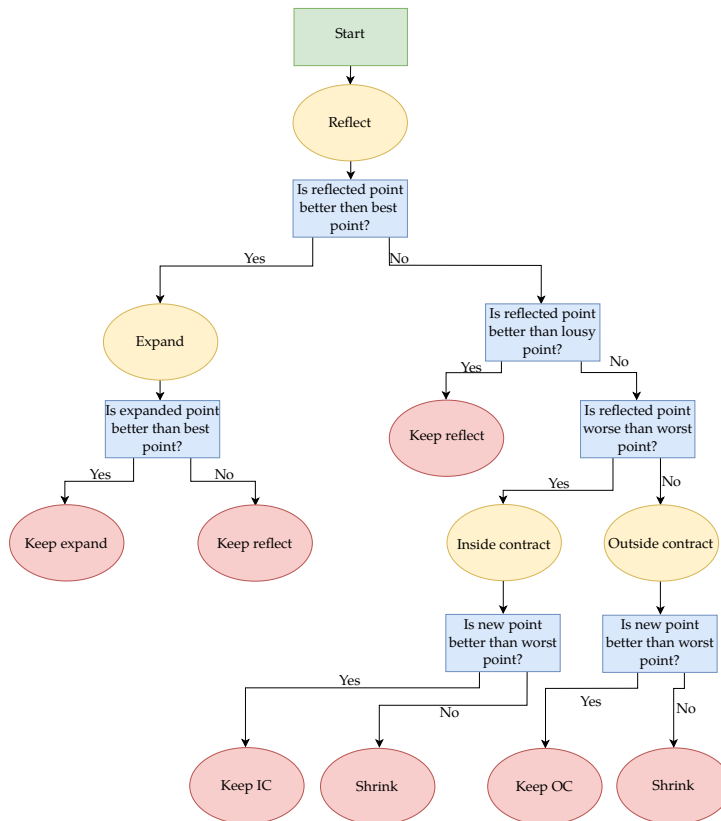


Figure 1.5: Nelder-Mead decision tree

The other convergence criteria is the a check to see if the best point is ‘good enough’. The current best point is compared to a pre-set fitness value. If the best point is better than the pre-set value then the algorithm terminates.

1.5 Validation

The NM method was coded in Fortran, so that it could be easily interfaced with the MCRT code developed as part of this thesis. To test that the method works as intended a number of trial functions were tested, see Table 1.1. This was achieved by selecting an initial simplex, and the method allowed to iterate until it converged. The results of this are shown in Fig. 1.6.

To ensure that the NM method can be used to find the unknown concentrations of the autofluorophores, we test the method with a known model. This model consists of three different fluorophores: NADH (nicotinamide adenine dinucleotide), FAD (flavin adenine dinucleotide), and a fictitious fluorophore that has similar properties to NADH and tyrosine, such that the

Name	Formula	Global Minumum
Sphere	$x^2 + y^2$	$f(0, 0) = 0.$
Rosenbrock	$(a - x)^2 + b(y - x^2)^2$	$f(1, 1) = 0.$
Ackely	$-20 \exp \left[-0.2 \sqrt{0.5 (x^2 + y^2)} \right] - \exp [0.5 (\cos 2\pi x + \cos 2\pi y)] + e + 20$	$f(0, 0) = 0.$
Himmelblau's	$(x^2 + y - 11)^2 + (x + y^2 - 7)^2$	$f(3, 2) = 0.,$ $f(-2.805118, 3.131312) = 0.,$ $f(-3.779310, -3.283186) = 0.,$ $f(3.584428, -1.848126) = 0.$

Table 1.1: Table of standard test functions for numerical optimisation.

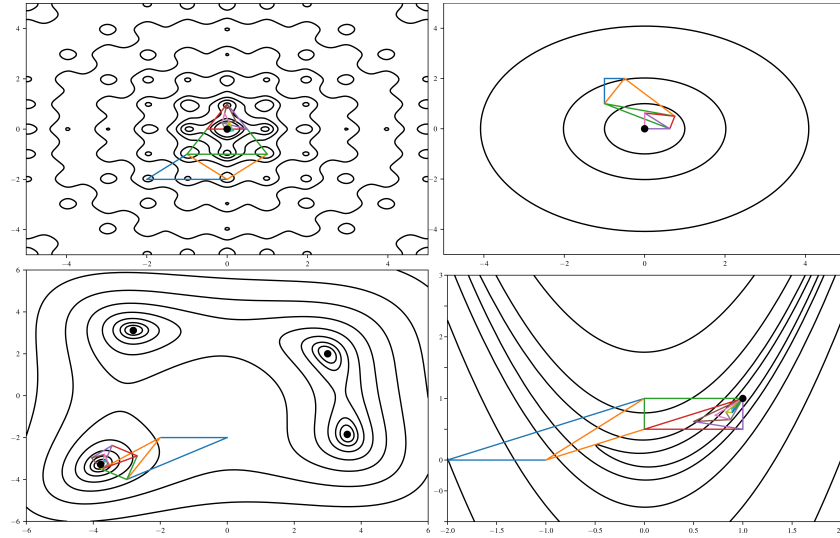


Figure 1.6: Contour plots of test functions with Nelder-Mead simplexes over plotted. Top left is the Ackely function, top right is the sphere function, bottom left is the Himmelblau's function, and the bottom right is the Rosenbrock function. Blue simplex is the initial simplex, and the large black dots represent the Global minima.

excitation spectrum is that of NADH and the emission spectrum is that of tyrosine. The three fluorophores are distributed in the stratum corenum (NADH), epidermis (FAD), and the papillary dermis (fictitious). The concentration in these layers is such that the bulk optical properties are not affected: NADH has a concentration of x , FAD y , and the fictitious fluorophore has a concentration of z .

As many models need to be run in order to determine whether a global maxima has been reached using the NM method and the fluorophore concentration low many packets need to be run. Therefore the MCRT algorithm has to be computationally efficient in order to arrive at an answer within a reasonable time. To this end the 3D skin model is shrunk to a 1D model so that the optical integration routine can efficiently move the photon through the simulated medium. The optical properties of the incident wavelength are also stored so that when a new photon is started the optical properties can easily be adjusted without need for any calculation.

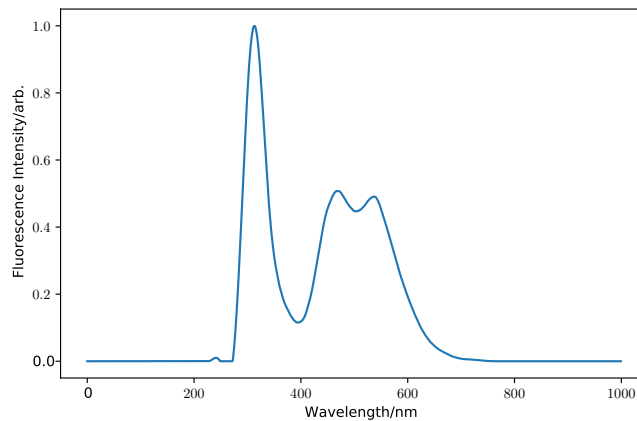


Figure 1.7: Example of toy model for testing NM method. The three peaks correspond to the fictitious fluorophore, NADH, and FAD respectively.

We first run this model through the MCRT to get an output spectrum. We then test the NM method for $n = 2$ and $n = 3$.

1.6 Results

1.7 Discussion

1.8 Conclusion

We have presented our code, AmoebaMCRT, which combines the Nelder-Mead method and MCRT in order to determine the concentrations of naturally occurring fluorophores in human skin.

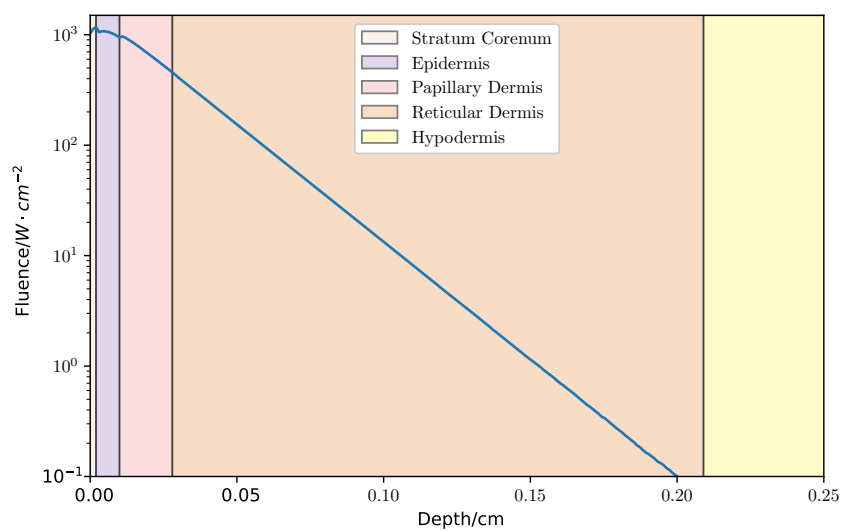


Figure 1.8: Penetration of UV radiation as a function of depth.

Bibliography

- [1] Steven L Jacques. Optical properties of biological tissues: a review. *Physics in Medicine & Biology*, 58(11):R37, 2013.